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About the cover: Weighted linear regression analysis of all large-epidemiological studies illustrating the increased incidence rate of septic meningitis related to spinal anesthesia from 1940 to 2015. The size of the circles represent the sample size of each epidemiological study included in this systematic review. See article by Zorrilla-Vaca A. et al. (pages 363-77).
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Local anesthetics with additives for single shot nerve block: what are the benefits and risks?

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The use of local anesthetic peripheral nerve blocks for anesthesia and postoperative analgesia has increased significantly in recent years with the advent of ultrasound-guided techniques. While catheter-based techniques are useful for postoperative pain management, they can present challenges related to patient management such as catheter displacement and the potential for increased infection. Adjuvants are frequently added to local anesthetics to promote onset of neural blockade or to prolong analgesia. Adjuvants that have been used include epinephrine, sodium bicarbonate and hyaluronidase to promote onset; clonidine, dexametomidine, dexamethasone, opioids, ketamine, magnesium and adenosine to prolong duration. Those that have been studied widely will be discussed. More recently, the introduction of liposomal solutions which provide a sustained release of local anesthetic have become commercially available. Many randomized controlled trials and meta-analyses have examined the pros and the cons of the use of various adjuvants. However, caution is recommended with use of any perineural adjuvant, as none of these agents, with the exception of epinephrine and hyaluronidase have been licensed for this use in most countries and there is a potential risk of neurotoxicity.

Local anesthetic mixtures with epinephrine have been available for decades. The addition of epinephrine not only prolongs duration of anesthesia but reduces systemic toxicity from local anesthetics due to diminished uptake into the systemic circulation. It has been suggested, however that epinephrine may increase the risk of neurotoxicity. Hyaluronidase, is an enzyme which breaks down intercellular linking cement thereby promoting spread of injected local anesthetics and speed of onset of neural blockade. Sodium bicarbonate is added to local anesthetic solutions with the aim of raising the pH, thereby increasing the fraction of unionized fraction necessary for diffusion through the nerve cell membrane. This was the basis behind the introduction of carbonated local anesthetics. These include clonidine and dexametomidine. Clonidine has historically been used systemically as an adjunct to general anesthesia and also as an additive during neural blockade. Studies have indicated that α-2 adrenoceptor agonists do lead to a prolongation of neural blockade up to 2 hours compared with plain solutions, however the mechanism of action remains unclear. Some studies showed systemic effects consistent with systemic absorption of these agents which would tally with the doses administered.

Comment on p. 304.
Some discussion about the use of opioids in local anesthetic mixtures is warranted. Their use in spinal and epidural anesthesia has been well documented, however most studies concerning their use in perineural block have failed to demonstrate any benefit. Indeed, most studies show an increase in systemic side effects from the opioid.13, 14

Adenosine has been implicated in the mediation of pain through central and peripherally located receptors.15 The prospective randomized controlled trial by Ammar et al.16 published in this issue of Minerva Anestesiologica compared adenosine and magnesium sulphate as adjuvants for transversus abdominis plane block. The results suggest that the addition of adenosine 12 mg to peripheral nerve blocks provided superior analgesia in terms of visual analogue score at 6 and 12 hours and reduced morphine consumption at 48 hours compared to the control group. The mechanism of action is postulated to be action on A2A and A3 adenosine receptors located in peripheral nerves.17 In this study there were no systemic effects using this dose of adenosine.

Magnesium, the other adjuvant used in the trial, is involved in hundreds of different enzymatic processes in vivo.18 These include coagulation, ATP generation, Ca-related activation of excitable cells, reperfusion syndromes in neural and cardiac ischemia and pain modulation. The pain modulation is postulated to be action on the amino acid receptors N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). These receptors are found in abundance in the dorsal horn and are also present in peripheral nerves. Magnesium ions bind to the NMDA receptor, which is a calcium channel preventing activation by glutamate - the neurotransmitter. Once activated, the magnesium ion is displaced allowing influx of calcium ions. This in turn activates intracellular protein kinase to generate more AMPA receptors. AMPA receptors, also activated by glutamate are sodium channels. The proliferation of these channels potentiates synaptic transmission along pain fibers. Local injection of magnesium affects the calcium-magnesium ratio thereby preventing activation and proliferation of these receptors.18 In the study above, workers used 500mg of magnesium sulfate as a mixture. The results with magnesium were similar to the adenosine group in terms VAS at 6 and 12 hours and overall morphine consumption at 48 hours. Again, there were no systemic side effects.

There are new formulations of liposomal bupivacaine, providing sustained release of bupivacaine thereby reducing normal systemic absorption. The studies so far with use in nerve blockade have produce conflicting results but many warrant further research.19

There are several caveats to consider when administering local anesthetics with additives. The first is potential toxicity. Toxicity may result from local injection, systemic absorption or inadvertent intravascular injection.20 Several additives have been implicated in local toxicity, including epinephrine, but it is not clear whether this is due to the additive or the local anesthetic. Many of the additives have been used in doses that would be consistent with normal parenteral administration and therefore effects particularly with regard to the potential of analgesia seen in some studies need to be taken into account. Ammar et al. used adenosine and magnesium in doses unlikely to produce systemic side effects given the dosages and even in the situation of inadvertent intravascular injection and produced demonstrably superior outcomes. Inadvertent intravascular injection can be minimised by the use of ultrasound-guided techniques, however this requires the pre requisite training and skills in this technique. In single shot injection, the clinician wishes to provide long-lasting analgesia but this should not be at the expense of potential side effects. The important message to convey is that very few additives have been shown to improve outcome and many are unlicensed for this use.

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2. Williams BA, Hough KA, Tsui BY, Ibinson JW, Gold MS, Gebhart GF. Neurotoxicity of adjuvants used in
Local anesthetics with additives for single shot nerve block: what are the benefits and risks?


Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.


General anesthesia (GA) comprises unconsciousness, amnesia, control of autonomic reflexes, occasionally skeletal muscle relaxation, and analgesia. Achieving analgesia with opioids seems to be easy as their impact on pain-associated motor and hemodynamic reactions can be complemented by concomitant administration of anesthetics.\(^1\) Additionally, they can readily be antagonized. This attitude, however, neglects the potentially harmful side-effects of intraoperative over- or under-treatment with analgesics.\(^2\)

Although the anesthesiologist’s armamentarium of today includes relaxometry and depth of anesthesia monitors, we are currently just barely able to reliably predict the treatment effect of analgesics given to unconscious patients in the course of surgery. However, in contrast to the other two monitors it is not that simple to develop an appropriate tool that allows administration of sufficient analgesia that prevents patients from either suffering from severe pain upon awakening or from side-effects due to overdose.

As pain requires its conscious sensation, the gold standard for pain assessment is patients’ self-reported pain. During unconsciousness and muscle relaxation we therefore, cannot speak of pain as pain is neither perceived nor do individual pain behaviors occur. Nevertheless, nociception, i.e. the detection of tissue damage or other noxious stimuli by specific sensors with subsequent afferent transmission to subcortical centers still is present.\(^3\) When not counter-balanced by appropriate analgesia it will elicit potentially undesired efferent autonomic reflexes and stress reactions like tachycardia, hypertension, sweating, mydriasis, and lacrimation.\(^4\) It is by observation of these reflexes and, in sedated patients, also pain-associated behavior like grimacing, eye opening or movement that we judge inadequate analgesia. Yet these reactions are far from being specific. As mentioned above, an integral part of GA is the suppression of autonomic reflexes, which at the same time alters those associated with nociception. Administered fluids further interfere with the autonomic nervous system. Moreover, comorbidities (e.g. diabetical neuropathy) or prescribed

**“Arterial stiffness”: a different approach in the pursuit to assess the intraoperative nociception antinociception balance**

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EDITORIAL

Comment on p. 311.

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Methodologically, the use of invasive blood pressure and desflurane can entail additional confounders. Following cannulation, the arterial wall may become spastic and desflurane may induce sympathetic activation. According to the authors, these effects should have been negligible and did most likely not influence their results. Additionally, laryngoscopy and orotracheal intubation, although frequently used as examples of intense noxious stimuli, may elicit autonomic reflexes via distant – not pain-associated roots. They are also not standardized, as intubation is occasionally difficult resulting in a prolonged duration of intense stimulation. The fact that the two stimuli are not comparable is also evidenced in the present study by the higher normalized K-values in both groups post intubation as compared to post laryngoscopy. Moreover, future studies need to elucidate how K performs in more heterogeneous patient groups, under different noxious stimuli and various types of general anesthesia that modify autonomic output (e.g. β-blockers) additionally complicate conventional assessment of intraoperative nociception as well as the development of more advanced methods that facilitate this task. Since all the currently available tools rely on indirect measures of nociception they are more or less affected by patient factors, patient medication, and anesthesia- or surgery-induced interactions.

In their study published in this issue of Minerva Anestesiologica, Yanabe et al. employed a novel mechanic approach to gauge intraoperative nociception by determining arterial stiffness (quantified as the K-value), which, however, requires arterial cannulation. They could previously correlate K with the intraoperative stress response and now investigated the correlation with stress intensity. In 28 paralyzed patients K was calculated during desflurane anesthesia from the photoplethysmography amplitude and arterial pressure before and after laryngoscopy and again before and after a second nociceptive stimulus (i.e. endotracheal intubation). K increased after laryngoscopy from a stable no-nociception state and even more so after intubation. K also was associated with stimulus intensity simulated by two different analgesia regimens (remifentanil plasma concentration 2 vs. 6 ng/mL, respectively), whereby K increased in conjunction with mean arterial pressure and heart rate.

As the researchers also used indirect measures (pain-elicited vasoconstriction and the decrease in plethysmographic amplitude) to assess nociception, the specificity of K in the course of surgery will potentially be similarly poor as that of other analgesia indices. Although patient management was standardized and patients with hypertension, diabetes mellitus, peripheral vascular disease and renal failure were equally distributed between groups, the huge inter-individual variability in K even at baseline indicates that pre-existing factors or concomitant homeostatic alterations matter. Normalization of the analgesia index to reduce inter-patient variability has therefore been conducted as recommended.
ciceptive state. As with other analgesia monitors, detection of intraoperative opioid overdosing has to be addressed, too.

Since there is no gold standard for the assessment of intraoperative nociception and associated reflexes may create different reactions at different effector sites depending on intensity, duration and other confounders it is probably prudent to investigate nociceptive autonomic reflexes at various effect sites. This would allow differentiating antinociception and nociception for our patients undergoing general anaesthesia and genetic variability. Acta Anaesthesiol Scand 1999;43:409-13.


This may also explain the lower response entropy values in the high remifentanil group at similar desflurane concentrations.

Arterial stiffness may have the potential to be used as an analgesia monitor but several questions still have to be answered to clarify its suitability. Nevertheless, researchers in this field can be commended since they strive to seek a technique that reliably assesses the individual nociception — antinociception balance, which is essential to provide optimal analgesia for our patients undergoing GA and has been overdue for a long time.

References


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Colonization, contamination, or infection in perineural catheters: how to discriminate?

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A perineural catheter (PNC) is a percutaneously inserted catheter whose tip is adjacent to a nerve, mostly for the administration of local anesthetics. It is often used to prolong and titrate regional anesthesia. It is currently recommended to improve postoperative analgesia and hemodynamic stability, to accelerate the mobilization after surgery, reducing the dose and collateral effects of systemic medications in several conditions, as after orthopedic and vascular surgery.1

Some authors advocated the risk of infections with this practice.2 A solid evidence on this topic does not exist, and a great variability has been reported across studies. Depending on the catheter insertion site, the incidence of infection is reported to range from 0% to 7% for peripheral catheters3-6 and from 0.8% to 4.2% for epidural catheters.7-9 This may depend on procedure practices as skin disinfection, dressing, number of skin punctures and/or on patient comorbidities. The problem is that PNC infection is not well defined, and definitive criteria to discriminate infection and inflammation are lacking. According with different authors, PNC infection may be defined as the presence of local signs of inflammation, purulent catheter site exudate and systemic signs of infection, or simply as the presence of 2 symptoms out of redness, swelling, and pain.10

Clinical signs of local inflammation at catheter insertion site might be often confused with the presence of infection. We absolutely need a consensus on this topic. Moreover, microbiological data may be difficult to interpret, becoming unclear the distinction between colonization and true infection. Colonization has been reported ranging between 6%11 and 63%,6 and mainly occurring in asymptomatic patients. Mechanism is considered to be the same of short-term central venous catheter, with most of infections which come from skin flora surrounding the insertion site, and grow in the extra-luminal state.

In this setting, in the interesting paper published in this issue of Minerva Anestesiologica, Blumenthal et al. hypothesized that positive catheter tip cultures could depend more on skin contamination during removal than on a true catheter colonization.12 Thus, they suggested that an accurate skin disinfection before perineural catheter removal could significantly affect the microbiological results, reducing the rate of positive tip cultures.

To this aim, 200 patients were randomized to receive (with-group) or not (without-group) a skin disinfection with a sprayed alcoholic solution before removal of the PNC. Results may be summarized in three points:

— no infection was observed;
— a significant reduction of bacterial colo-
Colonization was observed after alcoholic skin disinfection from 28% to 14%; — catheter colonization was not correlated with local signs of inflammation.

Blumenthal et al. arises interesting questions on this topic. What is the meaning of catheter colonization? Is it a useful information to the clinician? Do we need tip cultures? When are they recommended?

We have no data to draw definitive answers. Blumenthal’s results support the concept that laboratory data must be interpreted on clinical basis. Rate of colonization was dramatically reduced by an accurate skin disinfection, and it was independent from local signs of inflammation, mainly depending on contamination during catheter removal. If this were correct, neither positive catheter tip culture nor local signs of inflammation alone can be considered mandatory indications for definitive perineural catheter removal.

The main point is that we need a standardization of several issues regarding PNC, in particular about diagnosis of infection and practices of catheter removal. According with microbiologic diagnostic of catheter related bloodstream infections, skin disinfection before central venous catheter removal is well described, but this practice was not mentioned in studies on PNC. Waiting for a consensus on this procedure, the technique used for removal must be taken into account when interpreting the results of future studies.

In conclusion, author’s data support the hypothesis that colonization rates of perineural catheters do not reflect infectious risk, but largely depend on skin contamination. The subject is new and interesting, and our knowledge is still scarce. A common effort is needed for a standardization of definitions and procedures, and improve our clinical practice.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Meningitis is a serious complication associated with neuraxial techniques and its early diagnosis and effective treatment are essential. In this issue of Minerva Anestesiologica, Zorrilla-Vaca et al.1 performed a systematic review of 234 cases of septic meningitis associated with spinal, epidural and combined neuraxial anesthesia. They analyzed case-by-case all regional anesthesia-associated septic meningitis reports published between 1900 and 2015 in term of epidemiological, microbiological and clinical data. Approximately 60% of new articles were added in this recent review as compared with the two major reviews published before 2005,2, 3 thus demonstrating a linear increase in the number of reported cases of septic meningitis with an estimated annual increase of 0.7 cases per 1 million neuraxial anesthesia and a pooled incidence rate ranging between 0.9 to 1.1 cases per 100,000 epidural or spinal anesthesia respectively. The authors argue that the increase of reported cases over the reviewed timeframe could be explained by advancements in diagnostic, quality of care, awareness and epidemiologic surveillance.1 Their comment is extremely interesting if we consider that nowadays, neuraxial techniques are not limited to spinal, epidural, or combined spinal-epidural administration of drugs, such as anesthetics, analgesics, or steroids: they include lumbar puncture/spinal tap, epidural blood patch, intrathecal chemotherapy, diagnostic epidural or spinal injection of contrast media for imaging, neurological procedures involving spinal canal, lumbar/ spinal drainage catheters and spinal cord stimulation.4 This review gives the chance for some general comments.

Firstly, meningitis following neuraxial anesthesia is mainly iatrogenic and anesthesiologists may play the unpleasant role of infection’s vectors, furthermore this meningitis is a concern not only for less affluent countries, where the pattern of anesthetic morbidity and mortality may vary because of the relative lack of health care facilities, equipment and personal, but also for developed countries. In literature, the possible causes of meningitis and cerebrospinal fluid infection following neuraxial block procedures, include break in sterile technique with direct introduction of bacteria, hematogenous spread with microscopic bleeding in presence of asymptomatic bacteriemia, while a less likely cause is primary contamination of equipment and anesthesia drugs, since sterile packaging has almost eliminated this issue. Actually, droplet infection from patient itself or medical person and needle contamination from incompletely sterilized skin are recognized as the major routes of infection.5 Zorrilla-Vaca

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findings are consistent with these data, since they identified *Streptococcus salivarius* and *Staphylococcus aureus* as the most common bacteria related to spinal and epidural anesthesia respectively.\(^1\) In addition, young women undergoing caesarean section and patients undergoing orthopedic surgery showed an increased frequency of septic meningitis, and this finding may be consistent with neuraxial technique performed with time constraint or outside the operative room: most of the organisms causing iatrogenic meningitis after lumbar puncture are mouth commensals and often clustering of cases by single anesthesiologist is reported.\(^6\) Moreover, it is well documented in literature that often anesthesiologists, and often the senior ones, do not use facemasks when performing lumbar punctures\(^7\) and that negative behaviors learned by junior doctors may be influenced by their seniors, while time constraints negatively influence whole équipel compliance with basic sterile precautions such as hand-hygiene procedures.\(^8\) Furthermore, some procedures can be perceived by health personnel as less hazardous, and vigilance on asepsis relaxed. Therefore, it will never be enough emphasized that the asepsis for spinal and epidural anesthesia should not be less rigorous than for surgery, and there is no reason not to follow the aseptic rules of the operating theatre.\(^5\), \(^9\), \(^10\)

Secondly, more efforts are still needed to make etiologic diagnosis uniform and standard. Meningitis should always be considered as a possible differential diagnosis in patients suspected of having fever, postdural puncture headache, convulsion and altered neurologic status. Suspicion should immediately be followed by collection of blood and cerebro-spinal fluid (CSF) for culture and analysis. Elevated CSF white blood cell count, preponderance of polymorphonuclear cells (PMN\%) and/or positive CSF culture in patients with neurological findings are pathognomonic for meningitis\(^3\), \(^4\), \(^11\), \(^17\) and were the inclusion criteria applied in this review.\(^1\)

Low glucose concentration, low CSF to blood glucose ratio, elevated protein levels and high lactate concentration in CSF could be helpful in differentiating bacterial from other types of meningitis which have different treatment and prognosis.\(^11\)-\(^13\) Moreover, recent ESCMID guidelines added CSF Gram staining, polymerase chain reaction (PCR), and immunochromatographic antigen testing as diagnostic tests which could provide additional information, especially when the CSF culture is negative.\(^12\) However, these last methods are not of widespread application: Zorrilla-Vaca\(^1\) evidenced that barely in 13.1\% cases molecular methods were used to complete the diagnosis, and that articles reporting these data came mainly from developed countries. This finding with no doubt poses a general problem of uneven healthcare facilities access.

Finally, this review highlight the heterogeneity between published data:\(^1\) the wide majority of reports on neuraxial-associated meningitis even in recent years, are case reports or small case-series, while large epidemiologic studies are substantially lacking. This data underline the critical need for increasing the awareness among medical personnel in either developing and developed countries, for stimulating educational improvement in the patient quality care and multicenter surveillance system.

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Evolution of supraglottic airway devices: the Darwinian perspective

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Reading Sir Charles Darwin’s cornerstone publication “On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life”,1 one of the Authors’ conclusions was that evolution is the key of survival.

At time of its publication, the evolution theory was a revolution indeed, and deeply questioning the classic (and religion-influenced) common thoughts and (pseudo-) scientific opinions on the origin of species.

In an ambitious parallel, we could try to re-interpret the evolution theory applied to airway management devices, and particularly supraglottic airway devices (SADs), in light of a Darwinian perspective. Could evolutionary biology be applied to airway management? Could the diversity we observe in airway management tools and devices be considered to be the result of a natural selection going through a branching evolutionary pattern, as for Sir Darwin’s theory?

We might say yes, and the paper from Gordon et al. in this issue of Minerva Anestesiologica might be further support of the Darwinian perspective.2

The first revolution in achieving complete airway control was through tracheal intubation in late 1800s’: it remained the gold standard of practice for more than a century and it is arguably still today a standard of care. Since then, little has changed regarding the principles of intubation, despite evolution of materials, tubes and cuffs, videolaryngoscopy and technology.

Nevertheless, some problems with intubation remained unchanged: difficult intubation is maybe more common than recognized failed SAD placement,3 but maybe less common than failed supraglottic ventilation.4 Intubation leads to a certain morbidity, including minor problems (from the anesthesiologists’ perspective) such as dental injury (from 25 up to 39% in different studies and database),5, 6 various degrees of airway trauma (up to 33% in ASA closed claims)7 postintubation sore throat (14-90% as from some meta-analysis)8 or long terms sequelae such as tracheal stenosis (6-21%).9 One might wonder whether intubation is as safe as we think or wish.10

Dr. Archie Brain was the first to question the existing dogma regarding the primacy of tracheal intubation in the 1980s, initiating the first true revolution (or, in evolutionary perspective, the first real mutation) in airway control, with the concept of the Laryngeal Mask Airway (LMA™). The mutation came about through mixing the features (genes) of a tracheal tube with those of a Goldman nasal mask, eventually resulting into the home-made

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glued prototype of a new airway device, which was trademarked and commercialized less than a decade later.

It took years from development for this mutant species to enter in operation rooms and, above all, in anesthesiologists’ mind, habits, guidelines and trust. But it happened.

In the early 90’s, the LMA™ was the most commonly used device in the event of a failed airway. Following this, new “collateral mutations” occurred, consistent with the branching pathway proposed by Lord Darwin (Figure 1), and many SADs appeared on the market.

Some of them, due to evolutionary pressure, were “aberrant mutations” poorly compatible with survival in the competitive airway devices world, while others evolved as devices with specific features (such as the intubating LMA, iLMA™ - Teleflex Medical, Athlone, Ireland), enabling them to survive.

As for Darwinian evolutionary cycling patterns, around ten years after the first mutation, a new one occurred, and again from Dr. Brain’s (r)evolutionary mind. It was the time of the esophageal seal mutation, which once again changed everything. Gastric access and increased pharyngolaryngeal sealing led to new mutant devices, starting with the ProSeal LMA™ (Teleflex Medical), and followed by i-gel™ (Intersurgical Ltd, Wokingham, UK), Ambu Aura Gain™ (Ambu A/S, Ballerup, Denmark), LMA Supreme™ and LMA Protector™ (Teleflex Medical) and the Laryngeal Tube II™ (VBM Medizintechnik GmbH, Sulz am Neckar, Germany): all collectively part of a revolutionary new brand of second generation SADs.

Time and evolutionary pressure determined the devices that survived and entered in clinical practice, pushing the boundaries of simple airway rescue to advanced airway procedures, such as routine use in laparoscopy and RSI rescue, which were simply considered heretic for the first generation devices.

These new SADs also gained traction in the field of obstetric anesthesia, previously considered strictly off-limits, offering new perspectives also in pediatric patients. Further, they started to be considered a suitable (if not pre-
ferred) airway for the prone position,\textsuperscript{14} and their role in different airway management guidelines morphed,\textsuperscript{15} as the evidence-base grew to showed their reliability and extended safety limits.

After closed claims analyses, which showed how first generation SADs saved patients’ lives through being a bridge to secure the airway after failed intubation,\textsuperscript{16} the 4th National Audit Project, conducted in UK,\textsuperscript{17} raised concerns over the safety of tracheal intubation and emphasized that correctly used SADs, and especially second generation devices, are safer than perhaps we feared. Aspiration was a feature of tracheal intubation and first generation SADs but not of second generation devices, though these were under-used.\textsuperscript{18}

More recently, a new era and a kind of new evolution pattern has begun, so much that some researchers strongly advocate abandoning the vintage first generation devices,\textsuperscript{19} in favor of regular and routine (if not compulsorily) use of the safer and more reliable second generation SADs.

In light of the opportunity to combine features and benefits of tracheal tubes and SADs, another variation (mutation) has recently occurred, that is intubation through high sealing and performing SADs. This last mutation was probably the result of (environmental) pressure coming from the fears of reluctant anesthesiologists and resultant market requests. Of note, Archie Brain’s original idea of supraglottic ventilation was only this — with intubation not a primary goal.

In some authors’ point of view, this could be the third generation devices; however, there is no position for this term in the current taxonomy for devices with large variations in construction, materials, performance, and features.\textsuperscript{20}

Reliable intubation through a SAD provides the great potential of devices with an intrinsic B-plan in the event of difficult/failed intubation, but currently fiberoptic guidance is always recommended in national guidelines \textsuperscript{15} and might widen SADs applications in specific fields such as obese patient intubation \textsuperscript{21} or for protected extubation.\textsuperscript{20}

Simple does not mean easy, so new tasks, skills and dexterity are required for the anesthesiologists to glean the very best from the supraglottic approach. Evidence indicates that a SADs specific learning curves exists, that not all patients and conditions are suitable for SADs placement \textsuperscript{3} and that cuff pressure monitoring is highly desirable if not compulsory.\textsuperscript{13, 22} On other hand, there is elusive evidence of the device(s) associated with the lowest occurrence of aspiration and the best patient outcomes.

Mutations (variations) and development in the performance of airway devices also produce a situation in which a mutation (change) is required in the anesthesiologists’ mindset. If we look at airway management from a different perspective, some concerns should arise: we still use the tracheal tube in the assumption that it works better in preventing aspiration, which is a relatively rare phenomenon, occurring most commonly in emergency patients.\textsuperscript{17, 19} We therefore accept the cost of increased sore throat, postoperative hoarseness and airway trauma which might someway compromise patients’ well-being and surgical outcome, especially for day-surgery procedures.\textsuperscript{23} On the other hand, we do not regularly use second generation SADs to avoid the rare possibility of aspiration, particularly in elective setting\textsuperscript{17, 19} where they might usefully provide the benefits of effective performance and reduced airway morbidity,\textsuperscript{18, 24, 25} when used correctly.

In this issue of Minerva Anestesiologica, Gordon \textit{et al.}\textsuperscript{2} do provide an exhaustive review of SADs, of their applications, different features, limitations and benefits, which could help to improve our knowledge and stimulate review of our practice.

Or might we really consider to change our practice? Anesthesiologists are resistant to changes, probably because they are exposed to hours of boredom and seconds of terror, leading to a natural desire for devices in which they have a high confidence through familiarity, and subsequent trust. Does this drive our (over)reliance on the use of the tracheal tube and first generation SADs.

We should consider, or rather embrace evolution: this would also enable us to improve our knowledge and training, and consequentially, our trust in alternatives to intubation.
With the potential for new benefits, improved outcomes and new opportunities, the evolution of the SAD still has a distance to run — and perhaps more importantly, so does the anesthesiologist’s embracing of these developments.

Perhaps we should remember Lord Darwin’s conclusions, that it is not the strongest species that survive, but rather the promptest to evolve and adapt to their environment.

References

The application of ultrasound in the treatment of critically ill patients has become part of everyday life in intensive care medicine. In the early nineties, pioneers of critical care ultrasound (CCUS) began to diagnose acute deteriorations of pulmonary function caused by pleural effusions. Rapid progress was made to widen the view, when Daniel Lichtenstein et al. established their concept of lung ultrasound, making pneumothorax and pulmonary edema accessible for ultrasound diagnosis. Basic and clinical science soon added more evidence and the process of lung ultrasound in the critical care setting culminated in international consensus guidelines. Almost ten years earlier, a protocol of focused echocardiography made imaging of the heart available for non-cardiologic intensivists and many other applications of CCUS evolved, such as estimating intracranial pressure by sonography of the optic nerve sheath diameter or compression sonography of peripheral veins in the context of suspected thromboembolism. Today, the application of CCUS for rapid diagnosis of the reason of hemodynamic and respiratory failure, for procedural guidance, and for detection of venous thrombosis is well-established.

In this issue of Minerva Anestesiologica, Vieillard-Baron and Mayo elegantly demonstrate the usefulness of CCUS by presenting three case reports embedded in a concise review of the literature. The authors have to be congratulated for using this unorthodox, yet easy-to-follow approach, which offers the reader further stimuli for improving rapid diagnostic strategies in challenging patients.

Meanwhile, apart from the well-established applications of CCUS, some questions remain. First of all, to the best of our knowledge, randomized controlled trials verifying the hypothesis that CCUS may improve outcome or related parameters of patients treated in the intensive care unit are lacking. Although two randomized controlled trials have been initiated to answer this question (NCT03296891 and NCT03093987, respectively), the design of these trials confronts the investigators and the intensive care community with a serious task: on the hand, the outcome of critically ill patients depends on many variables, thus rendering the interpretation of such trials extremely difficult. Dettmer et al. described the parameters age, vasopressor requirement, thrombocytopenia, pre-existing kidney disease, failed ventilator liberation, and acute kidney injury as strong predictors of the primary outcome in critically ill patients with prolonged mechanical ventilation. Most of these parameters may not be significantly in-
fluenced by the use of CCUS. On the other hand, which diagnostic tools should be used in the control group? Only traditional tools including physical examination, chest radiography, and laboratory tests or even advanced hemodynamic monitoring such as transpulmonary thermodilution? How shall we deal with the ethical dilemma that a majority of frontline intensivists is committed to the benefit of CCUS during the treatment of critically ill patients and would not like to miss this tool in their everyday practice?

Another open question is the issue of how to best teach intensivists the skills and competencies that are necessary to perform CCUS? Many national societies already published their recommendations for training and competency. However, these guidelines are always based on expert opinions and are far from being validated in prospective clinical trials. Recently, some progress has been made about the possible format of a CCUS-course and the optimal number of practice studies required to achieve competency, whereas it remains elusive how to maintain a high skill level for longer periods especially among residents. Moreover, how should we deal with valued and experienced critical care practitioners who have been working on the intensive care unit for decades and are able to treat their patients at the highest level without using critical care ultrasound? Is it really possible to determine the use of CCUS as mandatory based upon the available literature data?

In their review article, Vieillard-Baron and Mayo are not able to give an answer to the above-mentioned questions. However, they demonstrate how focused CCUS may be used as a powerful adjunct to traditional diagnostic pathways on the intensive care unit by presenting three typical cases. This approach shows how sonography can guide patient management and help to avoid more harmful, cost-intensive and time-consuming diagnostic modalities or at least to use them more specific.

Possible future directions might be strengthening international and interdisciplinary efforts to: 1) standardize diagnostic protocols in order to increase the quality and comparability of results; 2) refine learning and teaching strategies; and 3) perform (more) randomized controlled trials to prove the positive effects of CCUS on patient management. We congratulate Minerva Anesthesiologica and the authors for featuring this important topic, as we enjoy and appreciate this technique in our everyday practice on the intensive care unit. We hope this article might stimulate others to expand the use of CCUS and to take part in future scientific developments.

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Comparison between adenosine and magnesium sulphate as adjuvants for transversus abdominis plane block: a prospective randomized controlled trial

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ABSTRACT

BACKGROUND: Various adjuvants have been employed during different nerve blocks. We aimed to evaluate the effect of adding adenosine versus magnesium sulphate to bupivacaine on the quality and duration of transversus abdominis plane (TAP) block.

METHODS: Participants were randomized to TAP block using either 20 mL of bupivacaine hydrochloride 0.375% + 12 mg adenosine in 2 mL of saline 0.9% (adenosine group), 20 mL of bupivacaine hydrochloride 0.375% + 500 mg magnesium sulphate in 2 mL saline 0.9% (magnesium group) or 20 mL of bupivacaine hydrochloride 0.375% + 2 mL saline 0.9% (control group). Primary outcome measure included postoperative pain as assessed by Visual Analog Scale (VAS) for pain scoring on movement and secondary outcomes included analgesia duration, postoperative morphine need and any adverse effects.

RESULTS: VAS in adenosine and magnesium groups was significantly less than in control group at 6 and 12 hours post-operatively whereas it was comparable in adenosine and magnesium groups at all time points. Analgesia duration was significantly longer in adenosine and magnesium groups in comparison to the control group and it was relatively longer in the magnesium group when compared to adenosine group (401 vs. 447 vs. 320 minutes in adenosine, magnesium and control groups, respectively; P=0.003).

CONCLUSIONS: Both adenosine and magnesium improved the quality and duration of TAP block, but the duration was relatively longer with magnesium.

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Key words: Adenosine - Bupivacaine - Magnesium - Abdominal muscles - Autonomic nerve block.

A major proportion of pain developed by patients undergoing abdominal surgeries is attributed mainly to somatic pain signals derived from the abdominal wall. Components of the anterior abdominal wall (skin, muscles and parietal peritoneum) are supplied by sensory neurons derived from the anterior rami of spinal nerves T6 to L1, which include the intercostal nerves (T6 to T11), subcostal nerve (T12) and ilioinguinal and iliohypogastric nerves (L1). These neurons pass through a neurofascial plane between the internal oblique and transversus abdominis muscles. Transversus abdominis plane (TAP) block is designed...
to target these neurons in this neurofascial plane through the lumbar triangle of Petit. This triangle is bounded anteriorly by the external oblique muscle, posteriorly by the latissimus dorsi muscle, whereas the base is formed by the iliac crest.2

Adenosine plays a significant effect in the central and peripheral mediation of pain.3 Spinal antinociceptive effect of adenosine A1 receptors have been revealed whereas adenosine A2A and A3 receptors have been implicated in peripheral mediation of pain.3-5 Elevation of adenosine levels by suppression of adenosine kinase has provided analgesia to animals.6, 7 Intrathecal injection of adenosine has provided analgesia in neuropathic and postoperative pain models in rats.8

Magnesium has been shown to provide analgesia in different experimental pain models in rats.9 In another study, neuropathic pain model in rats was obtunded through magnesium-mediated suppression of N-methyl-d-aspartate (NMDA) receptors.10 A lot of experimental and clinical trials have shown improved analgesia by combining local anesthetics with magnesium in different regional anesthetic techniques.11-13 However, other trials have reported failure of magnesium in providing analgesia.14

Different adjuvants have been employed to increase duration and improve quality of the local anesthetic action in various peripheral nerves and regional block techniques. However, to date, there is no universal agreement on the best adjuncts or drug combinations yet.

We hypothesized that addition of both adenosine and magnesium would have comparable adjuvant effect.

Materials and methods

The current trial was performed between December 2015 and November 2016 after institutional review board approval was gained and a written informed consent was got from every patient. The study was registered with the Pan-African Clinical Trials Registry (PACTR201511001360267). ASA I or II adult male patients subjected to Lichtenstein Tension-Free Mesh Repair for primary inguinal hernia were enrolled in the trial. Exclusion criteria included morbid obesity (Body Mass Index ≥35 kg/m²), significant heart disease (valve lesions, coronary artery problem or cardiomyopathy), refusal of the participants to provide informed consent, allergy to the study drug, preexisting clotting disorders or abdominal wall sepsis at the block site. The participants were randomized through sealed opaque envelopes to get TAP block using either 20 mL of bupivacaine hydrochloride 0.375% + 12 mg adenosine in 2 mL saline 0.9% (adenosine group), 20 mL of bupivacaine hydrochloride 0.375% + 500 mg magnesium sulphate in 2 mL saline 0.9% (magnesium group) or 20 mL of bupivacaine hydrochloride 0.375% + 2 mL saline 0.9% (control group). Randomization was performed centrally by an independent statistician. The participants and clinicians responsible for data collection were blinded to the studied drugs. The injectate in all groups was prepared and coded by an independent anesthesiologist not involved in TAP performance, patient care or collection of data and handled it to the clinical staff who were made blinded to the studied drugs. Discussion with the participants about the use of the 100-mm linear Visual Analog Scale (VAS) for pain evaluation was done preoperatively (0 mm means no pain, and 100 mm the severest pain).

The patients received 1-2 mg of midazolam IV as a premedication and 500 mL of physiological saline 0.9% about 20 min before anesthetic induction. All patients were monitored by continuous electrocardiogram, pulse oximetry, capnography and non-invasive blood pressure.

General anesthesia was induced by using fentanyl 3 µg/kg and propofol 1.5-2 mg/kg. Followed by administration of rocuronium bromide 0.8 mg/kg for tracheal intubation. Maintenance of anesthesia was achieved by 1 MAC of isoflurane and fentanyl 1 µg/kg/h, and no patient needed any additional narcotics during surgery. A single-injection TAP block was done in all patients immediately after anesthetic induction guided by an ultrasound probe (4-10 MHz of a Hewlett-Packard 77020A
ultrasound monitor [Andover, MA, USA]). The puncture site was disinfected with an alcoholic povidone-iodine solution. With the patient in the supine position, the ultrasound probe was positioned transversally, anterior to the midaxillary line, in a transverse plane to the lateral abdominal wall between the lower costal margin and iliac crest. The needle was then positioned in plane and directly under the ultrasound probe, and then advanced to the potential space between the internal oblique and transversus abdominis muscles. Thereafter, the injectate was administered giving rise to expansion of the TAP, that appeared as a hypoechoic space. Meticulous aspiration was carefully done before injection to exclude any inadvertent intravascular injection. Reversal of neuromuscular block was accomplished by using neostigmine (0.05 mg/kg) + atropine (0.02 mg/kg). After extubation, patients were transferred to the recovery room where consciousness and vital data were assessed till they fulfilled criteria for safe discharge.

Postoperatively, morphine was given intravenously in boluses of 0.02 mg/kg when needed as a patient-controlled analgesia (PCA) when VAS score at movement was >30 mm or upon patient request with a lock-out interval of 10 minutes and a maximum 4-hour dose of 20 mg. Ondansetron 4 mg IV was given to any patient developing nausea and or vomiting. The primary outcome included VAS for postoperative pain scoring on movement at 1, 2, 6, 12, 24, and 48 hours postoperatively. The secondary outcomes included analgesia duration, postoperative morphine requirement and frequency of nausea, vomiting, somnolence or any other adverse effects. Analgesia duration was defined as the time elapsed from injection of local anesthetic till first need of postoperative rescue analgesic in the form of IV morphine using PCA.

Statistical analysis

With a 2-sided type I error of 5% and study power at 80%, 25 patients in each group was considered enough to demonstrate a 25% difference between groups in VAS scoring on movement at 6 hours postoperatively based on preliminary results in our institution. Continuous variables are reported as mean and standard deviation or median (interquartile range) and categorical variables are expressed as numbers. Qualitative variables were tested using $\chi^2$ test.

Kolmogorov–Smirnov test was used to verify normality of the data. Data were evaluated with the intention to treat basis using two-way analysis of variance (ANOVA). This was followed by least significant difference (LSD) test, if a difference between groups had been detected. Friedman repeated-measures ANOVA on ranks was used to analyze non-parametric data. $P<0.05$ was considered statistically significant (SigmaStat, Systat Software, Richmond, VA, USA).

When statistical significance was established ($P<0.05$), Bonferroni’s test was performed to isolate the source of significance.

Results

Eighty-one consecutive patients were considered eligible. Two patients were excluded because of not meeting inclusion criteria and four patients declined to participate. Therefore, 75 patients were enrolled and equally randomized into three equal groups (Figure 1). The three groups were matched regarding the demographic and operative criteria (Table I). VAS on movement was comparable between groups at 1 and 2 hours postoperatively; however, VAS in adenosine and magnesium groups was significantly less than in control group at 6 and 12 hours postoperatively. Later on, VAS in adenosine and magnesium groups was matched with that in the control group at 24 and 48 hours postoperatively. Adenosine and magnesium groups were comparable regarding VAS at all time points. All three groups have reported VAS media values <40 at all time points (Table II). Analgesia duration was significantly longer in adenosine and magnesium groups in comparison to the control group and it was relatively longer in the magnesium group when compared to the adenosine group (Table II).
Postoperative 48-hour morphine need in the adenosine and magnesium groups was significantly less than in the control group whereas it was relatively less in the magnesium group when compared to the adenosine group (Table II). Frequency of nausea and or vomiting was significantly more in the control group than in either adenosine or magnesium group.

Table I.—Patients, demographic and operative criteria.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adenosine group (N=25)</th>
<th>Magnesium group (N=25)</th>
<th>Control group (N=25)</th>
<th>P value</th>
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<tbody>
<tr>
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<td>Weight, kg</td>
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<td>170±14</td>
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<td>Anesthesia time, min</td>
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<td>114±21</td>
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<td>1.7±0.9</td>
<td>1.8±0.9</td>
<td>0.512</td>
</tr>
<tr>
<td>IV fentanyl, μg</td>
<td>97±32</td>
<td>96±31</td>
<td>95±30</td>
<td>0.432</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. Statistical significance was set at P<0.05.

Table II.—Characters of TAP block and postoperative pain in all groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adenosine group (N=25)</th>
<th>Magnesium group (N=25)</th>
<th>Control group (N=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS on movements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 hour postop</td>
<td>3.8 (0.0-6.0)</td>
<td>3.7 (0.0-6.0)</td>
<td>4.0 (0.0-7.0)</td>
<td>0.354</td>
</tr>
<tr>
<td>2 hours postop</td>
<td>4.0 (2.0-6.0)</td>
<td>4.0 (1.0-7.0)</td>
<td>4.0 (2.0-6.0)</td>
<td>0.344</td>
</tr>
<tr>
<td>6 hours postop</td>
<td>13.0 (9.0-18.0)</td>
<td>14.0 (10.0-18.0)</td>
<td>32.0 (22.0-43.0)</td>
<td>0.004*</td>
</tr>
<tr>
<td>12 hours postop</td>
<td>15.6 (10.0-23.0)</td>
<td>14.0 (8.0-22.0)</td>
<td>27.8 (2.0-38.0)</td>
<td>0.030*</td>
</tr>
<tr>
<td>24 hours postop</td>
<td>21.0 (15.0-27.0)</td>
<td>22.3 (14.0-29.0)</td>
<td>25.0 (17.0-33.0)</td>
<td>0.603</td>
</tr>
<tr>
<td>48 hours postop</td>
<td>2.0 (0.0-3.0)</td>
<td>1.0 (0.0-2.0)</td>
<td>2.0 (0.0-3.0)</td>
<td>0.512</td>
</tr>
<tr>
<td>Analgesia duration, min</td>
<td>402±74</td>
<td>447±84</td>
<td>320±72</td>
<td>0.003*</td>
</tr>
<tr>
<td>Postop 48-hour morphine need, mg</td>
<td>9.5 (2.5-15.8)</td>
<td>4.9 (1.3-8.0)</td>
<td>23.1 (11.2-29.2)</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD, or median (interquartile range). TAP: transversus abdominis plane; VAS: Visual Analog Scale. *Statistically significant difference between groups (P<0.05).
Adenosine provides central through peripheral anti-inflammatory effect through impact of intrathecal injection of adenosine analogs on levels of substance P in cerebrospinal fluid was evaluated in animals and the investigators concluded that intrathecal administration of adenosine analogs succeeded in providing analgesia to animals through lowering cerebrospinal fluid level of substance P. The impact of intrathecal administration of adenosine on neuropathic pain model was evaluated in another experimental trial in rats and the investigators reported reduction of hypersensitivity through central release of norepinephrine and encouraged central administration of adenosine for management of chronic neuropathic pain.

Regarding magnesium, many studies have reported that addition of magnesium to local anesthetics resulted in a favorable outcome with respect to quality and efficiency of local anesthetics in different regional block techniques. Addition of 6 mL of 25% magnesium to lidocaine for intra-venous regional analgesia (IVRA) in upper extremity operations provided accelerated block onset and less tourniquet pain with no side effects.

Buvanendran et al. reported that intrathecal administration of magnesium 50 mg during labor analgesia gave out to prolongation of the action of intrathecal fentanyl analgesia with no adverse effects. Ghatak et al. added 50 mg of magnesium to bupivacaine for epidural block and reported that addition of magnesium provided acceleration of onset of epidural block without adverse effects. In another trial, 250 mg of magnesium was added to bupivacaine for interscalene nerve block and resulted in prolongation of analgesia duration. Gunduz et al. reported that addition of 150 mg magnesium to prilocaine provided longer axillary brachial plexus blockade without any complications.

In a recent trial, addition of 150 mg magnesium to bupivacaine during TAP block resulted in lower postoperative pain scores, longer duration of analgesia and lesser demands for rescue analgesics.

Another recent trial reported that 500 mg magnesium addition to bupivacaine in TAP block showed better postoperative analgesia in the form of longer duration, lesser analgesic requirements and nausea or vomiting. In our study, we used the same dose of magnesium like this recent trial.

Discussion

The results of the present trial have shown that local use of adenosine and magnesium as adjuvants for TAP block resulted in lower VAS on movement, longer analgesia duration, lesser morphine requirement and lower frequency of nausea and or vomiting. However, analgesia duration was longer and morphine requirement was less in the magnesium group when compared to the adenosine group which can be attributed to the relatively shorter duration of adenosine action.

Regarding adenosine, a lot of human trials have reported antinociceptive action of IV adenosine. These trials addressed that adenosine provides central antinociceptive action through central A1-receptor stimulation and peripheral anti-inflammatory effect through A2A and A3 receptors stimulation. Gan et al. addressed that perioperative administration of IV adenosine resulted in better postoperative recovery, as evidenced by lower pain scores and narcotic need.

Intrathecal administration of adenosine analogs has been tried for long term treatment of inflammatory and neuropathic painful conditions. However, few studies have tried adenosine for blocking peripheral nerves. The impact of intrathecal injection of adenosine analogs on levels of substance P in cerebrospinal fluid was evaluated in animals and the investigators concluded that intrathecal administration of adenosine analogs succeeded in providing analgesia to animals through lowering cerebrospinal fluid level of substance P.

Figure 2.—Adverse effects in all groups. *Significant difference between groups (P<0.05).
In our study, we used bupivacaine in a concentration of 0.375% according to a previous trial hoping to have a better analgesic profile. Also, we used adenosine in the dose of 12 mg according to a previous study in our institution.

Contrary to our findings, addition of 50 mg of magnesium to ropivacaine during caudal block in children failed to provide additional analgesia which may be attributed to a relatively inadequate magnesium dose used in that trial.

It should be emphasized that both adenosine and magnesium may cause vasodilatation, bradycardia and inhibition of cardiac contractility which may result in adverse effects on hemodynamics. The doses of adenosine and magnesium in our trial were safe and without adverse effects on hemodynamics. However, we still do not know where the optimal dose of either adenosine or magnesium may lie, which may give a limitation to the current trial.

Conclusions

Both adenosine and magnesium can be considered as good adjuvants to improve quality and duration of TAP block but the duration was relatively longer with magnesium. Further research work is needed to decide whether larger doses of adenosine or magnesium can safely result in greater potentiation of analgesia and reduction of postoperative narcotic requirements.

Key messages

— Addition of both adenosine and magnesium to bupivacaine during TAP block provides higher quality and duration of the block with lesser narcotic requirement and postoperative nausea and or vomiting.

— Magnesium provides relatively longer analgesia duration and less narcotic consumption than adenosine.

— Adenosine or magnesium addition to bupivacaine during TAP block does not significantly affect incidence of shivering, somnolence, hypotension or bradycardia.

— The 0.375% concentration of bupivacaine, 500 mg dose of magnesium or 12 mg dose of adenosine can be considered safe for TAP block.

References


15. Fukunaga AF, Alexander GE, Stark CW. Characterization of the analgesic actions of adenosine: Comparison of ad-
ADENOSINE VS. MAGNESIUM SULPHATE IN TAP BLOCK

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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A new arterial mechanical property indicator reflecting differences in invasive stimulus intensity induced by alteration of remifentanil concentration during laryngoscopy

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ABSTRACT

BACKGROUND: Reliable analgesia monitoring is not available for general anaesthesia cases. In 2003, we introduced a method to characterise arterial mechanical properties, which we termed arterial stiffness (K). However, it is unclear whether differences in K actually indicate changes in the intensity of a noxious stimulus. Thus, we examined the relationship between stress intensity and the value of K.

METHODS: Thirty patients under general anesthesia were randomly divided into two remifentanil concentration groups (2 and 6 ng/mL). After a steady concentration of remifentanil was achieved for at least 3 minutes, laryngoscopy was performed. After completion of laryngoscopy, once the K value returned to near-baseline, laryngoscopy with endotracheal intubation was performed, and the value of K after the procedure was recorded and analyzed.

RESULTS: In total, data were obtained for 28 of 30 patients. The values of K before the laryngoscopy were not significantly different between the groups (2 ng/mL group: 13.1 [8.5-33.1] mmHg/%; 6 ng/mL group: 11.6 [4.3-31.4] mmHg/%; P=0.53). After laryngoscopy, K was approximately 2 times greater in the 2 ng/mL group than in the 6 ng/mL group (39.0 [13.6-115.9] mmHg/% vs. 19.0 [5.5-85.1] mmHg/%, P=0.02). After intubation also, K was approximately 2 times greater in the 2 ng/mL group (52.0 [27.7-122.0] mmHg/% vs. 24.3 [7.2-94.9] mmHg/%, P=0.04).

CONCLUSIONS: The value for arterial stiffness (K) non-proportionally changes in response to stimulus intensity; therefore, it has the potential to be used as an indicator of nociceptive stimulation intensity.


Key words: Photoplethysmography - Anesthesia, general - Monitoring, intraoperative.

It is widely known that surgical procedures elevate the stress response, and analgesics such as opioids can suppress this response. Although measurement of the effects of cerebral hypnotic drugs and muscle relaxation is common in clinical practice, analgesia monitoring is not available for
general anesthesia cases. As alternatives, hemodynamics indices such as heart rate and blood pressure are widely used in clinical situations. However, hemodynamic indices are affected not only by administration of analgesics, but also by the administration of cardiovascular agents. Therefore, a reliable and specific method for monitoring analgesia during general anesthesia is needed.

It is well known that the skin vasomotor response can be monitored sensitively using a photoplethysmogram (PPG) or laser Doppler skin blood flow meter, or by measurement of skin conductance. Particularly, the amplitude of PPG has attracted the attention of clinicians due to its diffusion properties in clinical contexts. However, PPG provides information about blood flow, not direct information about the character of the artery, which is the effector of skin vasomotor response. Thus, theoretically, PPG cannot distinguish whether the blood flow change is induced by circulatory changes or by the skin vasomotor response. In 2003, our group introduced a method to graphically indicate the pressure-volume relationship of peripheral arteries using the Lissajous curve between the arterial waveform and PPG waveform. Moreover, we succeeded to approximate the character of the Lissajous curve using a mechanical impedance model and determined the arterial mechanical properties using two coefficients, which we termed arterial stiffness (K) and arterial viscosity (B). The values of K and B indicate the change in the viscoelastic properties of the arterial wall; therefore, they are theoretically independent of circulatory changes. In 2009, we showed that the value of K could be used as a sensitive stress response monitor during general anesthesia.

However, it is unclear whether differences in K actually indicate changes in the intensity of a noxious stimulus. Thus, in the present study, we examined the relationship between stress intensity and the value of K.

Materials and methods

Patients

After obtaining approval from our institutional ethical review board and receiving written informed consent, 30 patients scheduled for elective surgery under general anesthesia between 2015 January and 2015 June were enrolled. Patients who met any of the following exclusion criteria were not enrolled: atrial fibrillation, impairment of upper arm blood flow or nervous disorder, or cerebral vascular disease.

Measurements

Patients were randomly divided into two plasma remifentanil concentration groups (2 and 6 ng/mL). When using simple body-weight based dosing, the plasma concentration of remifentanil is affected by differences in age, sex, and body morphology. Therefore, we chose remifentanil doses based on the plasma concentration estimated by the pharmacokinetic model of Minto. Prior to induction of anesthesia, a photoplethysmography probe (TL-271T, Nihon Kohden, Tokyo, Japan) was attached to the thumb of the measuring upper limb. An electrocardiogram (ECG), processed encephalogram (EEG; Entropy, GE Healthcare UK Ltd., Buckinghamshire, UK), and neuromuscular blocking agent monitor (NMT - Neuromuscular Transmission, GE Healthcare UK Ltd., Buckinghamshire, UK) were equipped before induction of anaesthesia. A non-invasive blood pressure cuff was placed onto the upper arm, contralateral to the PPG probe. The arterial pressure and PPG waveforms were monitored using a bedside monitor (BSS-9800, Nihon Kohden) and recorded on a personal computer; then, the values for K were calculated using an online personal computer.

In all patients, anesthesia was induced with 2-4 µg/mL of propofol using a target controlled infusion pump (TE-371, Terumo, Tokyo, Japan). After loss of response to verbal commands and decrease of the RE (response entropy on EEG) to <70, 1 mL of 2% lidocaine was injected at the puncture site and a 22-gauge catheter was placed into the radial artery on the same limb as the PPG probe for invasive arterial pressure monitoring. The measurements from both the invasive and non-invasive blood pressure monitoring were compared for

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validation of measurement value, and smooth backflow was confirmed. Additionally, all patients were cannulated within three attempts, at most. After validating the invasive blood pressure monitoring, propofol was ceased and administration of 4% desflurane with 6 L/min of oxygen, 0.5 to 1.0 mg/kg of rocuronium, and the planned dose of remifentanil to achieve the predefined plasma concentration (2 or 6 ng/mL) commenced. Before induction, we calculated the initial dose of remifentanil using pharmacokinetic simulation to achieve the target plasma concentration. Throughout the measurement period, we adjusted the dose of remifentanil by pharmacokinetic simulation to maintain the target plasma concentration. The concentration of desflurane was constantly maintained during the measurement period. In some cases, an epidural catheter was inserted before induction, but no drugs were infused into the epidural space until the measurement period was complete. All patients showed no response to train-of-four stimulation during the measurement period. After a steady concentration of remifentanil was achieved for at least 3 minutes, laryngoscopy was performed, and the values for K before and after the procedure were recorded and analyzed. After completion of laryngoscopy, once the K value returned to near-baseline, endotracheal intubation was performed, and the value of K after the procedure was recorded and analyzed. All laryngoscopy and endotracheal intubation procedures were performed by a trained anesthesiologist (Y.K.). If the laryngoscopy was difficult during the first attempt with a Macintosh laryngoscope, a second attempt (laryngoscopy and endotracheal intubation) would be performed with a McGRATH™ MAC video laryngoscope (Medtronic, Dublin, Ireland). All endotracheal intubations were successful on the first attempt.

The K value was calculated based on the arterial mechanical impedance model. The details of the calculation have been described by Nakamura et al. To summarize, we described a Lissajous curve between the arterial waveform and PPG waveform to graphically demonstrate the status of the peripheral artery (Figure 1). Changes in the form of the Lissajous curve are correlated to changes in nociceptive stimulation intensity. We approximated the character of the Lissajous curve using the mechanical impedance model and determined the arterial mechanical properties using two coefficients, arterial stiffness (K) and arterial viscosity (B). Specifically, the values of K and B were calculated with both the arterial pressure and PPG amplitude at time $t$ using the following formula:

$$dP_b(t) = KdP_f(t) + BdP_f(t)$$

and

$$dP_b(t) = P_b(t) - P_b(t_0), \quad dP_f(t) = P_f(t) - P_f(t_0), \quad \text{and} \quad dP_f(t) = P_f(t) - P_f(t_0)$$

where $t_0$ is the start time of displacement, and $P_b(t)$, $P_f(t)$, and $P_f(t)$ are arterial pressure, PPG amplitude, and the first derivative of PPG waveform at time $t$, respectively. Each K and B is determined as a value in each heartbeat by performing least square fitting of the formula.

Figure 1.—An example of the change in a Lissajous curve induced by nociceptive stimulation.

The loops represent the Lissajous curve between the arterial waveform and photoplethysmogram waveform of a heartbeat. When the values at the beginning and end of the heartbeat are similar, the Lissajous curve forms a loop. When nociceptive stimulus occurs, the loop drops. We believe that the Lissajous curve has the potential to graphically express several peripheral arterial conditions, one of which being a nociceptive reaction. In this study, we focused on the ability of the curve to indicate the strength of the nociceptive reaction using the coefficients acquired by applying a mechanical impedance model to the curve.
for all the data obtained in each heartbeat. Specifically, we estimated the arterial waveform from the PPG amplitude. K and B are the conversion coefficients from the measured PPG amplitude to the estimated arterial waveform. In our previous study, only K seemed to be a promising candidate as an indicator of nociceptive stimulation intensity; therefore, we only analyzed K in this study.\textsuperscript{11}

Statistical analysis

Data are shown as the median (range). The average value at 1.5 minutes before laryngoscopy was treated as the value before laryngoscopy. The peak values of the period from the event (laryngoscopy or endotracheal intubation) to 1.5 minutes after each event were treated as the values after laryngoscopy and after intubation. The changes in the K value after laryngoscopy (nK\textsubscript{ls}) and after endotracheal intubation (nK\textsubscript{ei}) were normalized by dividing them by the K value before laryngoscopy in each case. Statistical analysis was performed using Mann-Whitney’s U-Test between groups, using Wilcoxon’s signed rank test in a group, and using Pearson’s correlation analysis between events, with 5% set as the level of significance. Prior to the study, a power analysis was performed using G*power 3.1.0 program (http://www.gpower.hhu.de/). To obtain a 0.80 power with an estimated difference between two different remifentanil concentrations of 100%, the sample size of each group was calculated as 12. We set the sample size at 15 patients for each group to keep the detection power consistent if measurement errors occurred in approximately 25% of cases.

Results

In total, 30 patients were included in this study; however, the data for two patients in the 2 ng/mL group were not collected due to an operational error of the recording device. The background data for all 30 patients are shown in Table I. There were no significant differences in the patients’ background. Additionally, there were no patients with peripheral vascular disease or renal failure. Further, there were no

\begin{table}
\centering
\begin{tabular}{lcccc}
\hline
\multicolumn{2}{c}{} & \textbf{Remifentanil concentration} & \multicolumn{2}{c}{P value} \\
\hline
\multicolumn{1}{l}{} & \multicolumn{1}{l}{2 ng/mL} & \multicolumn{1}{l}{6 ng/mL} & \multicolumn{1}{l}{} \\
\hline
\textbf{Age, years} & 62.4±9.7 & 58.4±9.1 & 0.27 \\
\textbf{Sex (M/F)} & 9/4 & 6/9 & 0.11 \\
\textbf{Height, cm} & 165.1±9.3 & 161.4±9.7 & 0.32 \\
\textbf{Weight, kg} & 64.0±13.5 & 59.1±8.8 & 0.25 \\
\textbf{ASA PS (1/2/3)} & 5/8/0 & 4/11/0 & 0.75 \\
\textbf{Hypertension, N. (yes/no)} & 2/13 & 7/15 & 0.08 \\
\textbf{Diabetes mellitus, N. (yes/no)} & 3/13 & 3/15 & 0.84 \\
\hline
\end{tabular}
\caption{Patients’ background data.}
\end{table}

\begin{table}
\centering
\begin{tabular}{lcccc}
\hline
\multicolumn{2}{c}{} & \textbf{Remifentanil concentration} & \multicolumn{2}{c}{P value} \\
\hline
\multicolumn{1}{l}{} & \multicolumn{1}{l}{2 ng/mL} & \multicolumn{1}{l}{6 ng/mL} & \multicolumn{1}{l}{} \\
\hline
\textbf{Time from arterial cannulation to Pre-LS measurement (s)} & 547±175 & 463±93 & 0.14 \\
\textbf{Average response entropy during the measurement period} & 63±12 & 47±5 & 0.0006 \\
\textbf{Fluid infusion during the measurement period (mL)} & 424±165 & 409±164 & 0.80 \\
\textbf{Difficult airway} & 2/13 & 2/15 & 0.87 \\
\textbf{Baseline MBP (mmHg)} & 69.1±10.2 & 64.8±10.9 & 0.29 \\
\textbf{Post-LS MBP (mmHg)} & 91.7±21.0 & 69.0±12.0 & 0.003 \\
\textbf{Post-ET MBP (mmHg)} & 111.5±23.7 & 75.3±10.4 & 0.0001 \\
\textbf{Baseline HR (bpm)} & 73.5±14.7 & 67.8±10.8 & 0.26 \\
\textbf{Post-LS HR (bpm)} & 80.5±19.5 & 68.0±9.6 & 0.05 \\
\textbf{Post-ET HR (bpm)} & 97.0±21.9 & 75.4±10.6 & 0.005 \\
\textbf{Baseline PPG amplitude} (\%) & 11.8±8.1 & 9.8±11.5 & 0.6 \\
\textbf{Post-LS PPG amplitude} (\%) & 9.2±6.0 & 15.9±12.9 & 0.09 \\
\textbf{Post-ET PPG amplitude} (\%) & 8.6±5.3 & 15.4±11.9 & 0.06 \\
\hline
\end{tabular}
\caption{Comparison of the time and measurement data (excluding K) between the two groups.}
\end{table}

ET: endotracheal intubation; HR: heart rate; LS: laryngoscopy; MBP: mean blood pressure; PPG: photoplethysmogram.
laryngoscopy and endotracheal intubation, and heart rate after endotracheal intubation.

Figure 2 shows the value of arterial stiffness K at each measurement point. The values of K before the laryngoscopy were not significantly different between the groups (2 ng/mL group: 13.1 [8.5-33.1] mmHg/%, 6 ng/mL group: 11.6 [4.3-31.4] mmHg/%; P=0.53). In contrast, K after the laryngoscopy was approximately 2 times greater in the 2 ng/mL group (39.0 [13.6-115.9] mmHg/% vs. 19.0 [5.5-85.1] mmHg/%, P=0.02). K after intubation was also approximately 2 times greater in the 2 ng/mL group (52.0 [27.7-122.0] mmHg/% vs. 24.3 [7.2-94.9] mmHg/%, P=0.04). Although the values of K after laryngoscopy and after intubation were not significantly different in the 2 ng/mL group (P=0.12), there was a significant difference between the two values in the 6 ng/mL group (P=0.02).

Figure 3 shows the nKls and nKei of both groups. nKls in the 2 ng/mL group was also significantly greater than that in the 6 ng/mL group (2.5 [1.3-5.6] vs. 1.4 [1.0-2.5], P=0.002), and so was the nKei (3.4 [1.7-9.3] vs. 1.9 [1.0-4.7], P=0.002). Similarly, the values of K, nKls, and nKei were not significantly different in the 2 ng/mL group (P=0.08), but there was a significant difference in the 6 ng/mL group (P=0.01).

Figure 4 indicates the correlation of the K values between post-laryngoscopy and post-endotracheal intubation, which were significantly correlated (r=0.67, P=0.0001). Furthermore, the log of the K values showed a stronger correlation than the original K values (r=0.86, P<0.0001).

Figure 3.—Normalized K after laryngoscopy and intubation. The normalized values of arterial stiffness K after laryngoscopy and after endotracheal intubation are presented. Normalized K values after laryngoscopy (nKls) were calculated by dividing the K value after laryngoscopy by the K value before laryngoscopy in each case. Normalized K values after endotracheal intubation (nKei) were calculated by dividing the K value after endotracheal intubation by the K value before laryngoscopy in each case. The dotted box represents values at remifentanil effect-site concentrations of 2 ng/mL and the blank box represents values at remifentanil effect-site concentrations of 6 ng/mL.
The K values after laryngoscopy and after endotracheal intubation had a significant positive correlation. This result implies that K is affected similarly by these two sequential stimulations. The response to the second nociceptive stimulus can be suppressed by additional administration of analgesics when K is affected by the initial stimulus. However, the value of K showed a greater difference between two events in patients who showed a high K value during laryngoscopy. The reason is that the dynamic range of the plethysmogram is 10 times higher or more, which is too great to detect the difference. In patients with a high K value, K mainly reflects the change in amplitude of the plethysmogram. Therefore, we used the logarithm of the K value. By using the logarithm, it was clear that K was correlated between the events, which indicated that intra-individual differences were efficiently suppressed.

Although the logarithm of K can suppress intraindividual differences, the logarithm of K was not effective for suppressing inter-individual differences. The logarithm of K showed a smaller deflection of the distribution, and the size of distribution itself did not change. The large distribution is due to the high dynamic range of plethysmogram, and it is difficult to solve with-

Discussion

Our results indicate that K values differ according to the plasma concentration of remifentanil, which reflects differences in the intensity of surgical nociceptive stimuli during general anesthesia. In a previous study, we found that the arterial stiffness K highly correlated with both the stimulation intensity and the pain score. However, that study was performed in awake subjects. Therefore, it was still unclear if the arterial stiffness K reflects the intensity of the stimulation during general anesthesia. In this study, we confirmed that arterial stiffness K has a sufficient dynamic range to be used as an indicator of the intensity of the nociceptive stimulation during general anesthesia. However, the distribution of K in the same estimated plasma concentration group is too broad. One reason is the difference in the sensitivity to opioids. Another reason is that the amplitude of the plethysmogram can be influenced by multiple factors. However, the normalized K value was more clearly affected by the stimulation of laryngoscopy and endotracheal intubation. This indicates that arterial stiffness K can be a sensitive parameter for monitoring nociceptive stimulation after normalization relative to the controlled value.

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Although the logarithm of K can suppress intraindividual differences, the logarithm of K was not effective for suppressing inter-individual differences. The logarithm of K showed a smaller deflection of the distribution, and the size of distribution itself did not change. The large distribution is due to the high dynamic range of plethysmogram, and it is difficult to solve with-
out normalizing. The most widely used method for monitoring analgesia with plethysmography is the surgical plethysmographic index (SPI).\textsuperscript{16} Huiku \textit{et al.} performed histogram transformation of previously obtained data from a database of many patients.\textsuperscript{16} Using this method, the interindividual differences in the measurements was smaller, however it cannot be confirmed that the control value represents the patient’s relaxed value. Therefore, we normalized the measurements using the manually obtained values when the patients were in a relaxed state. In this way, the normalized K can be considered to indicate interindividual differences in the response to invasive stimuli of the same intensity.

\textbf{Limitations of the study}

This study had limitations. First, we administered two different concentrations of analgesics as an alternative to two procedures which have two different nociceptive intensities. Although a reliable and precise indicator of nociceptive stimulation intensity was not yet established, Huiku \textit{et al.} used the anesthesiologists’ assessment as the indicator of intensity of nociception.\textsuperscript{16} The potential problem with this method is that the anaesthesiologist may estimate the intensity of nociception by observing a change in heart rate and plethysmogram amplitude, which were used to calculate the developed index. In other words, using the score assessed by the anesthesiologist, the study evaluated the assessment reflecting the anesthesiologist’s prediction of the intensity, and not the actual intensity of the nociceptive stimulation. Therefore, we used two analgesic concentrations, which is objectively thought to induce different reactions to nociceptive intensity.

Second, this study was performed before surgery. During surgery, many factors may affect the response to nociceptive stimulation, and consequently, the measurements. Therefore, the strength of K as a nociceptive stimulation intensity indicator should be evaluated during surgery. In our previous study, we did not prove that changes in K actually represent changes in nociceptive stimulation intensity. Therefore, we executed this study in a well-controlled situation to make the differences in stimulation intensity more apparent. The performance of the prediction of nociceptive stimulation intensity during surgery should be evaluated in future studies.

Third, the K value can be affected by patient factors, such as coexisting disease, age, sex, or body size. Unfortunately, the sample size was not sufficiently large to analyze the influence of these factors on the K value. Further study is needed to elucidate these influences.

Fourth, in the present study, the P values of some comparisons were near the threshold of significance. This may be because the interindividual differences were wider than we presumed. Therefore, larger studies are needed to validate our results.

Finally, this study’s aim was to reveal the characteristics of the value of K and the normalized K. Although a previous study indicated that K is a better indicator of the amplitude of photoplethysmography, we did not compare the advantages of K to that of the other analgesic monitor candidates. Therefore, further investigation is needed to compare the utility of K to that of other candidates as indicators of analgesia under general anesthesia.

\textbf{Conclusions}

The results demonstrate that K values differ in patients with different estimated plasma concentrations of remifentanil during general anesthesia. The K values after laryngoscopy and after intubation had a significant positive correlation. Moreover, the normalized K value was more clearly affected by the stimuli of laryngoscopy and endotracheal intubation. This indicated that arterial stiffness K can be used as a sensitive monitor of nociceptive stimulation after normalizing relative to a control value. When the logarithm was used, K showed a clear correlation between laryngoscopy and endotracheal intubation, which suggests that the intraindividual difference was efficiently suppressed. These results indicate that the value of K non-proportionally changes in response to the intensity of the stimulus; therefore, it has the potential to be used as an indicator of nociceptive stimulation intensity.
A NEW ARTERIAL MECHANICAL PROPERTY INDICATOR REFLECTING DIFFERENCES IN STIMULUS INTENSITY

Key messages

— Although measurement of the effects of cerebral hypnotic drugs and muscle relaxation is common in clinical practice, analgesia monitoring, which can be used for titration of analgesics, is not available for use in general anaesthesia cases.

— Our proposed method can graphically indicate the pressure-volume relationship of a peripheral artery using the Lissajous curve between the arterial waveform and photoplethysmogram waveform, and can indicate the arterial stiffness “K” of the peripheral artery as an index, which can be used as an indicator of nociceptive stimulation intensity.

— Our proposed indicator K showed increased values at more intense nociceptive stimulation simulated by lower remifentanil concentrations; this indicates that K has the potential to be an indicator of analgesic requirement.

— The logarithm of K represented similar response intensity in two sequential stimulations, which indicates that the logarithm of K has high reproducibility.

References


Confl icts of interest:—Nihon Kohden Corporation provided the bedside monitor and the data acquisition software used in this study. This study conception, design, trial management, data collection, data analyses, and the writing of the manuscript, have been executed completely independently of Nihon Kohden Corporation and any other external organizations.

Congresses:—This study was presented at the 16th World Congress of Anesthesiologists, 28 August-2 September 2016, Hong Kong, China.
Influence of skin disinfection prior removal of perineural catheter on bacterial colonization, contamination and local inflammation: a prospective randomized study

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ABSTRACT

BACKGROUND: There is a wide variation of perineural catheter (PNC) colonization rates in the literature. The impact of skin disinfection on PNC colonization and inflammation is not clear. The objective of this prospective, randomized clinical study was to investigate the influence of alcoholic skin disinfection before PNC removal on the detection of bacteria on PNC.

METHODS: Two hundred patients receiving a PNC for orthopedic surgery were randomized to receive (with-group) or not (without-group) a skin disinfection with a sprayed alcoholic solution before removal of the PNC. Bacterial colonization and contamination of the PNC and clinical signs of inflammation and infection of the PNC insertion site were evaluated. Skin disinfection with a sprayed alcoholic solution and sterile removal of the distal and subcutaneous part of the PNC was performed after 72 hours or earlier if signs of infection occurred with semiquantitative culture and enrichment culture of both parts.

RESULTS: Alcoholic skin disinfection before PNC removal significantly reduced bacterial colonization with a reduction from 28% to 14% and from 32% to 17% for the tip and the subcutaneous part of the PNC, respectively (P<0.05). Clinical signs of inflammation at the PNC insertion site were similar (73%) in the two groups. The detection of colonization in 54 (27%) out of 200 PNC did not correlate with clinical signs of inflammation independently of the number of bacteria isolated. Redness was noted in 71% and 68% of patients in the without- and with-alcoholic skin disinfection-group respectively. Local pain on pressure was present in 28% and 19% in the without- and with-group respectively.

CONCLUSIONS: Alcoholic skin disinfection before PNC removal reduced the detection of PNC colonisation by 50%. There was no correlation between clinical signs of inflammation and PNC colonization.


Key words: Anesthesia, conduction – Inflammation - Catheter-related infections.

Continuous peripheral nerve blocks through perineural catheters (PNC) are commonly used for postoperative analgesia after orthopedic surgery 1 to reduce the need for postoperative opioids and to minimize the incidence of their side-effects. Besides nerve damage, infectious complications of PNC are a major concern, particularly in surgery using prosthetic material.

Comment in p. 292.
There is still little data dealing with PNC local inflammation and infection in the literature.\textsuperscript{2-8} The reported incidence of infectious complications ranges between 0% and 3.2%\textsuperscript{9} and PNC colonization rate varies between 6.2% and 63%.\textsuperscript{5} The role of PNC contamination by commensal bacteria of the skin during removal remains unclear. This is in contrast to the semiquantitative culture method for identifying intravenous catheter-related infections. The semiquantitative culture technique distinguishes colonization with possible associated infection (≥15 colonies\textsuperscript{10} or ≥5 colonies\textsuperscript{11}) from contamination by skin flora during withdrawal of the catheter.

The aim of this study was to investigate primarily the influence of alcoholic skin disinfection before PNC removal on the detection of bacteria on the subcutaneous part of the PNC and on the tip. Furthermore, as a secondary outcome, the correlation of bacterial colonization with PNC associated local inflammation or infection was evaluated. We hypothesized that PNC can be contaminated by skin flora during its withdrawal and therefore alcoholic skin disinfection before PNC removal would reduce the detection of bacteria on the different parts of the PNC.

Materials and methods

After obtaining institutional local ethics committee approval (Gesundheitsdirektion des Kantons Zürich, Kantonale Ethik-Kommission; Chairman Prof. N. Herzog, EK-0011/05; Clinical Trials.gov NCT02599181), 200 patients between 2012-2013, scheduled for elective orthopedic surgery including placement of a PNC, were prospectively included after written informed consent. Patients were then randomized according to a computerized random list and allocated into two arms: the WITH-group in which they received a skin disinfection before PNC removal, and the WITHOUT-group in which disinfection before removal of the PNC was not performed. Exclusion criteria were ASA>3, diabetes mellitus, medication with immunosuppressant drugs or any other immune-compromising illness, PNC removal before 72 hours postoperatively and PNC removal not according to the study protocol. The PNC (interscalene, infraclavicular, femoral, sciatic, popliteal) were placed preoperatively for intraoperative anaesthesia and postoperative analgesia. In the preanesthetic area, PNC were placed under standardized sterile conditions: Hairy skin subsequently covered by the catheter dressing was shaved. The anesthesiologist, wearing a facemask and a cap, then performed surgical hand disinfection and was clothed with sterile gown and gloves. Skin disinfection was performed with a two-layer application of an alcoholic povidone-iodine solution (Betaseptic\textsuperscript{®}, Mundipharma, Basel, Switzerland). Three minutes later, the area of the puncture point was surrounded with sterile drapes. After local anesthetic skin infiltration, the nerves were identified with nerve stimulator technique.\textsuperscript{12-16} After subcutaneous tunneling through an 18-gauge intravenous catheter for 4-5 cm, the PNC was connected to a micro filter (200 nm). The procedure was completed by single skin disinfection with the same alcoholic povidone-iodine solution and covering the puncture site and the PNC with transparent adhesive tape (Optiseal® IV3000\textsuperscript{®}, Smith & Nephew, Solothurn, Switzerland). The initial block was performed with 40 ml ropivacaine 0.5% (200 mg) through the PNC. Preoperatively, all patients received antibiotic prophylaxis with 1.5 g intravenous cefuroxim that was repeated twice postoperatively at 8-hours interval.

Postoperatively, six hours after the initial bolus, a local anesthetic infusion line was connected to the micro filter of the PNC. All patients received patient-controlled perineural analgesia. The PNC were observed twice daily by one of the authors (S.B. or M.M.) unaware of patient’s group assignment for clinical signs of local inflammation and local or systemic infection. Local inflammation was defined as redness, swelling or pain on pressure at the PNC insertion site. Local infection was defined as the appearance of pus at the PNC insertion site. Systemic infection was defined as fever >38°C or the occurrence of shivering. The adhesive dressing was changed only if the PNC became dislodged or if blood or secre-
tions made visualization of the puncture site impossible. For the dressing change, the anesthesiologist wore a facemask, a cap and sterile gloves.

PNC were removed after 72 hours or earlier if there was any sign of local or systemic infection. The patients according to previous randomization were allocated to either the group “with” or “without” alcoholic skin disinfection before PNC removal. Removal of the PNC was performed on the ward by an anesthesiologist wearing a facemask and a cap. In the “without” group, the skin was disinfected with a sprayed alcoholic solution (propanol-biphenol) (Kodan®, Schulke & Mayr, Zurich, Switzerland). After three minutes, when the skin was dry the anesthesiologist wearing sterile gloves and using sterile tweezers withdrew the distal part of the PNC (directed to the tip of the PNC) for 1 cm at the insertion site and then cut distally from the tweezers with a sterile pair of scissors. The distal part of the PNC was then totally withdrawn with the sterile tweezers, and with the sterile pair of scissors cut in two parts: the tip (defined as the most distal 2 cm) and the subcutaneous part, which were placed in separate dry sterile containers. The remaining proximal part of the PNC was thrown away.

The sterile containers containing the PNC were stored at 4 °C and were sent to the laboratory the same day for microbiological analysis of the PNC. The PNC was rolled onto sheep blood agar plates (Becton Dickinson BD, Basel, Switzerland) similar to the semiquantitative culture method for intravenous catheters and thereafter immediately transferred to a liquid enrichment medium (thioglycolate medium, BD Basel Switzerland). Sheep blood agar was incubated for two days and thioglycolate for five days. In case of growth in the enrichment media only, an aliquot of the liquid was subcultured on solid media. Reports were considered to be positive if any growth was present. Identification of the isolated bacteria and susceptibility testing were performed according to standard methods. All patients were observed for clinical signs of local infection at the PNC insertion site and for clinical signs of systemic infection one week after PNC removal.

Statistical analysis

The reported incidence of PNC colonization rates (=the primary outcome) vary from 6.2% to 63%. A reduction of the detection of PNC colonization by 20% in the group with skin disinfection was considered significant. Based on these data, a power analysis indicated that a sample size of 59 patients per group was sufficient to have an 80% power at the 95% significance level. To increase the power we decided to assess 100 PNC in each group to compare the two different PNC removal techniques with regard to detection of bacterial colonization of PNC.

To assess the correlation of bacteria on the PNC with clinical signs of inflammation, the sensitivity, specificity, positive and negative values were calculated on the basis of the following three categories: 1) any growth of bacteria including enrichment; 2) more or equal to 5 colonies; and 3) more or equal to 15 colonies with the semiquantitative culture technique.

Patient and PNC characteristics were analyzed with the Mann-Whitney U test. Categorical data were analyzed with a cross-tabulation analysis and calculated using the Chi square-test or the Fisher’s Exact Test when appropriate, continuous and categorical data were expressed as mean±SD. For all statistical analysis a P value <0.05 was considered significant. For statistical analysis the software SPSS for windows, version 19 (SPSS inc. Chicago, IL, USA) was used.

Results

Two-hundred-four patients were prospectively enrolled. Because of protocol violation four patients were excluded and 200 patients were included: 100 in the WITH-group and 100 in the WITHOUT-group disinfection before removal of the PNC. A flow diagram of the CONsolidated Standards of Reporting Trials is shown in Figure 1. There was no difference in demographic and PNC related data between the two groups (Table I).

Alcoholic skin disinfection before PNC removal significantly reduced the overall detec-
The detection rate of any bacterial growth on the PNC from 35% in the without-group to 19% in the with-group. The reductions of the detection rate from 28% to 14% for the tip (P<0.05) and from 32% to 17% for the subcutaneous part of the PNC were also significant (P<0.05) and are shown in Figure 2. If the tip was colonized, the subcutaneous part was mostly colonized as well, but not vice versa.

At the time of PNC removal, 73% of patients had clinical signs of local inflammation at the PNC insertion site and there was no difference among the two groups. The detection of colonization in 54 (27%) out of 200 PNC did not correlate with clinical signs of inflammation (Figure 3). This finding was independent of the number of bacteria isolated. Redness was present in 71% of patients in the without-group and in 68% of patients in the with-group. Local pain on pressure was found in 28% and 19% of patients in the without-group and with-group, respectively. Local swelling was detected in 3% and 5% of patients in the with-group and without-group, respectively.

The correlation of any detected bacteria...
The identification and distribution of the microorganisms are summarized in Table III. In 44 (80%) out of the 54 positive PNC only one organism was detected, with coagulase negative staphylococci being the most frequent organisms in both groups. Additional single organisms identified were Propionibacterium acnes, Staphylococcus aureus, Enterobacter species and Corynebacterium species. PNC was colonized in 19% (10 out of 54) with more than 1 organism, with significant higher incidence in the WITHOUT-group. The same bacteria were cultured from the tip and the subcutaneous part from 37 out of 54 PNC, but clinical signs of infection have never been shown.

No clinical signs for local infection with pus or systemic infection with fever were detected in either group during the time the PNC were in place, at PNC removal or one week after its removal.
contamination by skin flora with the cutoff of ≥5 or ≥15 colonies.10, 11 Applying those cutoffs for PNc, the rate of colonization is reduced by 50% compared to the detection rate of any bacterial growth as well in the with- as in the without group (Figure 3). Furthermore the spectrum of the detected species was broader in the group without skin disinfection.

In the group with alcoholic skin disinfection before PNc removal only 9% of the PNc showed a colonization of ≥15 colony forming units suggesting that the higher detection rate of bacteria in the group without disinfection is mainly due to the contamination by skin flora.

The first article specifically dealing with infectious complications of PNc was published by Cuillon et al. in 2001. They reported that 57% of 208 femoral catheters were colonized with one or more organisms after 48 hours. More recently, Neuburger et al. observed an incidence of colonization of 63% when 169 PNc with clinical signs of infection were analyzed.5 These two studies found an incidence of colonized PNc that was about twice of that found in our investigation. In contrast to these two studies, the results of Capdevila’s3 large multicenter study published in 2005 are in accordance with the data in the WITHOUT-group of the present study. Analyzing 969 out of 1416 PNc, the authors reported a 29% incidence of colonized PNc, but the authors did not state whether there was any specific reason for the culture.3 Compère et al. found the lowest incidence of colonized PNc with 6.2% in their

<table>
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<th>TABLE II.—Sensitivities, specificities, positive predictive values (ppv), negative predictive value (npv) of the detection of any growth of bacteria (including enrichment), of ≥5 or ≥15 colonies by semiquantitative culture of the PNC for detection of clinical signs of local inflammation.</th>
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<tr>
<td>WITH skin disinfection before PNC-removal</td>
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<td>Sens.</td>
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<td>Any growth of bacteria on the tip or the subcutaneous part</td>
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<td>Any growth of bacteria on the tip</td>
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<td>Growth of ≥5 colonies on the tip and/or the subcutaneous part</td>
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<td>Growth of ≥15 colonies on the tip and/or the subcutaneous part</td>
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<td>Growth of ≥5 colonies on the tip</td>
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<td>Growth of ≥15 colonies on the tip</td>
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<td>Growth of ≥5 colonies on the subcutaneous part</td>
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<tr>
<th>TABLE III.—Microorganisms isolated from 54 PNC in the groups WITH and WITHOUT skin disinfection before PNC-removal.</th>
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<tr>
<td>1 organism / PNC</td>
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<tr>
<td>Coagulase – negative staphylococci</td>
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<tr>
<td>Propionibacterium acnes</td>
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<tr>
<td>Staphylococcus aureus</td>
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<tr>
<td>Others</td>
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<tr>
<td>Enterobacter aerogenes, Enterobacter cloacae, Corynebacterium sp.</td>
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<tr>
<td>&gt;1 organism / PNC</td>
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<tr>
<td>Coagulase-negative staphylococci</td>
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<tr>
<td>Staphylococcus aureus</td>
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<tr>
<td>Enterococcus sp.</td>
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<tr>
<td>Others</td>
</tr>
<tr>
<td>Bacillus cereus, Morganella morganii, Citrobacter koseri, Clostridium sp., Streptococcus sp.</td>
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*P<0.05

1In nine out of ten cases, coagulase – negative staphylococci were detected together with other bacteria

Discussion

The detection of any growth of bacteria on PNC was influenced by the technique of PNC removal. Alcoholic skin disinfection before PNC removal halved the bacterial growth compared to the rate without skin disinfection. The semiquantitative culture method distinguishes intravenous catheter — related infections due to colonization of the catheter from a contamination by skin flora with the cutoff of ≥5 or ≥15 colonies.10, 11 Applying those cutoffs for PNC, the rate of colonization is reduced by 50% compared to the detection rate of any bacterial growth as well in the with- as in the without group (Figure 3). Furthermore the spectrum of the detected species was broader in the group without skin disinfection. In the group with alcoholic skin disinfection before PNC removal only 9% of the PNC showed a colonization of ≥15 colony forming units suggesting that the higher detection rate of bacteria in the group without disinfection is mainly due to the contamination by skin flora.

The first article specifically dealing with infectious complications of PNC was published by Cuillon et al. in 2001. They reported that 57% of 208 femoral catheters were colonized with one or more organisms after 48 hours. More recently, Neuburger et al. observed an incidence of colonization of 63% when 169 PNC with clinical signs of infection were analyzed.5 These two studies found an incidence of colonized PNC that was about twice of that found in our investigation. In contrast to these two studies, the results of Capdevila’s3 large multicenter study published in 2005 are in accordance with the data in the WITHOUT-group of the present study. Analyzing 969 out of 1416 PNC, the authors reported a 29% incidence of colonized PNC, but the authors did not state whether there was any specific reason for the culture.3 Compère et al. found the lowest incidence of colonized PNC with 6.2% in their
2009 investigation. A similar detection rate of 10.4% was found by Aveline and coworkers. This was in line with our WITH-group with disinfection and a cutoff of ≥15 colonies (see above). The differing results of the above mentioned studies could be explained by different study designs. In the Cuvillon study,2 all femoral catheters were removed and analyzed after 48 hours. Capdevila did not mention the indication for the microbiological analysis3 and Neuburger sent all catheters with clinical signs of inflammation or infection for culture.5 The Compère7 and Aveline8 studies were designed to evaluate the PNC colonization rate and all the PNC were analyzed.

Then the PNC have been removed under different conditions: only Neuburger defined how the skin was prepared with alcoholic solution before the PNC were removed under aseptic conditions,5 a procedure similar to ours.

Finally, in the studies mentioned above, the definitions of positive PNC colonization were not comparable and different laboratory methods developed for analyzing intravascular catheters were used for PNC culture: Cuvillon et al.2 cut 3 cm of the distal portion of the PNC, using the same semiquantitative culture method used in our study10 and defined more than 15 colony-forming units as positive. Neuburger et al.5 declared culture results of the PNC tip with more than 5 colonies to be positive.11 The groups of Capdevila,3 Compère7 and Aveline8 mentioned PNC colonization to be positive as the growth of at least one microorganism on quantitative culture17 regardless of the colony-forming units on the distal part of the PNC.

We defined the most distally located 2 cm of the PNC as the tip, since we hardly ever advance the PNC more than 2-3 cm over the tip of the needle, what is comparable to the technique described in the Compère study.7 Capdevila3 and colleagues advanced the PNC 3-15 cm, Aveline et al.8 did not mention how far PNC were threaded over the needle, but both groups sent the distal 5 cm to analysis. In the work by Neuburger et al.5 it was neither defined how far the PNC were advanced nor how many centimeters they sent as the tip for analysis.

Interestingly, there was no difference of colonization rate between the tips and the subcutaneous parts, neither in the with-group, nor in the without-group. Since this was the first time, that the tip and the subcutaneous part of PNC have been analyzed separately, the interpretation of this finding is difficult. Since the study was not designed to answer this question, it was most likely underpowered to find a difference between the tip and the subcutaneous part.

The predominance of coagulase-negative staphylococci in the microbiological analysis was not surprising. This organism was the most frequent organism identified in former studies.3, 5, 7, 8 This is in accordance to studies that revealed Staphylococcus epidermidis as the most frequently isolated bacteria from epidural catheters.18-22 This organism has been generally regarded as a pathogen with little clinical significance,2 which is reflected by the difference between high PNC colonization rates but few clinical infectious complications,2, 5, 23 a finding that has been confirmed with epidural catheters as well.9, 20, 22 There is no correlation of the detection of any bacteria and the clinical signs of inflammation at the insertion site of the PNC; the sensitivities and negative predictive values were low, even without disinfection. On the other hand, the specificities and positive predictive values indicated a high rate of false positive results of detection of bacteria without any signs of local inflammation.

These findings suggest that routine PNC culture is clinically irrelevant in the vast majority of cases. Furthermore, PNC colonization rate is not a valid surrogate marker for clinical signs of local inflammation at the PNC insertion site. The high incidence of local inflammatory signs could be attributable to a local response to the PNC as a foreign body.

The colonization rate of 9% (cutoff ≥5 colonies) in our WITH-group compared to the results of Neuburger et al.5 (63%, cutoff ≥5 colonies), who also disinfected the skin before PNC removal with an alcoholic disinfectant, showed an impressive difference of the colonization rate. In their study the cellular immunosuppression following trauma24
may be responsible for increased PNC colonization. Additionally, in our study, PNC were removed after a mean duration of three days, whereas the PNC in the Neuberger study were in place for a median of four days. Longer PNC duration has been identified by Capdevila as a risk factor for local inflammation and infection.\(^{23}\)

**Limitations of the study**

One limitation of the present study is that we did not compare different types of skin disinfectants. Whether the type of skin disinfectant would have influenced our results remains speculative and could be investigated in future studies. We are aware of the widespread use of chlorhexidine as skin disinfectant, an agent not available in our department. Another possible limitation of our investigation is that we performed skin disinfection before PNC removal with spray disinfection. However, this technique has been proven to be at least as effective as swab disinfection.\(^{25}\) Additionally our study was either not designed to identify a PNC location with increased (or decreased) incidence of PNC colonization or the issues of different co-morbidities. Moreover, this study was not blinded; it was an open label investigation. In order to reduce a possible bias the outcome assessors (physician and microbiologist) were blinded to the group the patients were assigned.

This work shows that skin disinfection prior PNC removal greatly reduced the incidence of bacterial colonization and contamination and emphasizes that in clinical practice the performance of PNC culture is only recommended when obvious clinical signs of infection such as local pus, fever or shivering are present.

**Conclusions**

This investigation demonstrated that skin disinfection prior PNC removal can halved the incidence of bacterial colonization. Moreover, there is no correlation between clinical signs of inflammation and PNC colonization. Local signs of inflammation alone seem not to be a strong indication for perineural catheter removal. Therefore, the technique used for PNC removal must be taken into account when interpreting the results of future studies of PNC colonization and when also PNC removal for semiquantitative culture is performed in the case of signs of infection.

**Key messages**

- Alcoholic skin disinfection before PNC removal halves the incidence of PNC colonization.
- There is no correlation between clinical signs of inflammation and PNC colonization.
- Local signs of inflammation alone seems not to be a mandatory indication for perineural catheter removal.
- In clinical practice performance of PNC culture is only recommended in case of obvious signs of infection.

**References**


Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.
Authors’ contributions.—Stephan Blumenthal: Ethical Committee, Manuscript, Data Sampling. Reinhard Zbinden: laboratory testing, manuscript; Sascha Mandic: data sampling, anesthesia; Christoph Alexander Rüst: statistical analysis; José Aguirre: manuscript, anesthesia; Alain Borget: manuscript, anesthesia.
Patterns of changes in functional and neurocognitive status in elderly patients after transcatheter vs. surgical aortic valve replacements

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ABSTRACT

BACKGROUND: Replacement of severely stenotic aortic valve may influence cognitive and physical functioning. The aim of this study was to compare cognitive and functional status after surgical (SAVR) vs. transcatheter aortic valve replacements (TAVR) in the elderly with severe aortic stenosis (AS).

METHODS: It was a prospective observational study with over 6 months of follow-up. Eighty ≥70-year-old patients with AS underwent TAVR (N.=40) or SAVR (N.=40). Mini Mental State Exam (MMSE), activities daily living (ADL) score and instrumental activities daily living (IADL) score were used to assess the cognitive status, fundamental functioning and complex independent living skills, respectively. The tests were conducted at baseline and 6 months after the procedure. Additionally, MMSE was carried out at discharge.

RESULTS: Baseline MMSE score was lower in the TAVR vs. SAVR group (P=0.001). In the SAVR group, there was a transient in-hospital decline in mean MMSE score (P=0.020), absent in the TAVR group. Baseline ADL and IADL scores were lower in TAVR patients. Both groups experienced mild improvement. The average increase among those with improved IADL score was larger after TAVR (2.37 vs. 1.37 after SAVR; P=0.029). A systolic blood pressure (SBP) decrease <60 mmHg as well as larger periprocedural shift in SBP (expressed by a difference between maximum and minimum SBP) during TAVR were associated with the decline in the ADL (P=0.001) and IADL scores (P=0.043).

CONCLUSIONS: Cognitive patterns differed between the TAVR and SAVR patients. A transient MMSE decline did not alter the 6-month status. TAVR might improve functionality. Periprocedural SBP decrease and larger changes in SBP are risk factors for functionality deterioration after TAVR.


Key words: Aortic valve stenosis - Transcatheter aortic valve replacement - Activities of daily living - Cognition - Quality of life - Cognitive Dysfunction.

Aortic valve stenosis (AS) is the most common acquired valvular heart disease. 1, 2 Its prevalence increases with age, reaching 2.5% at 75 years and 8.1% at 85 years of age.1, 2 It reduces both the length and the quality of life.3, 4 Transcatheter aortic valve replacement (TAVR) improves survival compared to stan-
standard medical therapy and is non-inferior to surgical aortic valve replacement (SAVR) in high-risk operable patients. However, in the elderly, the quality of life expressed by independence in everyday activities is at least as important as the clinical outcomes. Results of a quality-of-life substudy in Cohort A in the PARTNER trial showed that TAVR significantly improved the physical and mental health scores between baseline and 1 year after either TAVR or SAVR. Yet, changes in the neurocognitive status were not evaluated in the study.

To our knowledge, there is no head-to-head study analyzing changes in both neurocognitive and functional status with objective tools such as mini mental state examination (MMSE), activities daily living (ADL) and instrumental activities daily living (IADL) in this population. In the light of the large amount of data confirming higher prevalence of cerebral embolism in patients undergoing TAVR than in patients undergoing SAVR, comparative analysis is crucial.

The primary goal of this study was two fold: to compare the influence of SAVR and TAVR on the changes in neurocognitive and functional status in elderly people with severe AS during 6 months after procedure.

Materials and methods

Patients selection

Between September 2012 and October 2014 78 TAVR and 463 SAVR were performed in our Institution. Forty consecutive patients in each group were enrolled into the observational prospective study if they met all inclusion criteria: severe AS, elective valve replacement, ≥70 years of age. Exclusion criteria were: chronic kidney disease ≥stage 4, complex cardiac surgery, malignant tumor diagnosis in the last 5 years. Severe AS was defined as a mean aortic gradient >40 mmHg, peak velocity >4 m/s or aortic valve area <1 cm². All patients were considered symptomatic. Clinical outcomes were defined according to the Valve Academic Research Consortium (VARC-2) recommendations. Informed consent was obtained from all patients. The study was approved by the local ethics committee (no 1335/2012, no 1492/2015).

TAVR and SAVR interventions

The Heart Team evaluated patients with severe AS and identified those suitable for SAVR or TAVR. Patients with at least moderate mitral regurgitation (MR) were included if insufficiency did not require intervention. TAVR was conducted using the bioprosthesis Sapien XT (N.= 21), CoreValve (N.=18) or Engager (N.=1) via femoral (N.=29), subclavian (N.=5), apical (N.=4) or direct aortic route (N.=2). The type of prosthesis was chosen according to the aortic root anatomy. Femoral access was the route of first choice. In case of anatomical difficulties, other routes were chosen. SAVR was conducted using bioprosthesis (N.=37) or mechanical valve (N.=3) via full sternotomy (N.=39) or ministernotomy (N.=1). Perioperative haemodynamic data were reported on hand-written medical charts.

All but one TAVR procedures were conducted under general anesthesia with intubation and muscle relaxation. All patients received volatile anaesthetic agent (either sevofluran or isoﬂurane). All surgical patients were subjected to extracorporeal circulation.

Neurocognitive and functional status assessment

Mini Mental Text Exam (MMSE), a 30-point test, was used for the assessment of cognitive function. It is a widely used tool for the evaluation of cognitive function and its changes over time. It examines such functions as registration, attention and calculation, recall, language, ability to follow simple commands and orientation. Functional status was assessed using the ADL and IADL scores for discrimination changes in basic and complex skills over the follow-up period. The ADL score, ranging from 0 to 6 points, reflects performance in six basic functions: bathing, dressing, toileting, transferring, continence and feeding. The
IADL Score, ranging from 8 to 24 points, evaluates eight complex independent living skills.

The tests were conducted at baseline (within 24 hours before procedure) and 6-9 months after the procedure by two trained co-authors of the study. MMSE was additionally conducted at discharge.

**Statistical analysis**

Continuous data were represented as mean±standard deviations. Categoric variables were expressed as numbers (percentages). Normality was assessed using the Shapiro-Wilk Test. The means of normally distributed data for two independent groups were compared using Student’s t-test. The Mann-Whitney U-Test was used where appropriate. Univariate and multivariate logistic regression analyses were undertaken to assess the predictors of decline in the tests. A P value of <0.05 was considered statistically significant, and all reported p-values were two-sided. Receiver Operating Characteristic (ROC) curves were used to determine the area under the curve (AUC) for periprocedural systolic blood pressure change as predictor of decline in the tests. Optimal cut-off points were based on the largest Youden’s index (sensitivity + specificity – 1) and presented with classical test parameters: sensitivity, specificity. Statistical analyses were conducted using IBM SPSS version 21.

**Results**

**Study population**

Eighty patients with symptomatic severe AS were recruited for the study. Forty underwent TAVR and forty underwent SAVR. Thirty-eight patients in each group were assessed at discharge and 35 patients in each group attended the follow-up visit after a mean time of 246 (165-419) days from TAVR and 233 (172-350) days from SAVR. The TAVR patients were older (P<0.001), and had higher perioperative risk according to the logistic EuroSCORE (P<0.001). All baseline characteristics are summarized in Table I.

| Table I.—Patients’ baseline and periprocedural characteristics. |
|-------------------------|-------------------------|-------------------------|
| Baseline               | TAVR (N.=40) | SAVR (N.=40) | P value |
| Age                     | 80.13±5.26  | 74.45±3.95  | <0.001  |
| Female sex              | 31 (77.5)   | 27 (70)     | 0.45    |
| Arterial hypertension   | 33 (82.5)   | 33 (82.5)   | 1       |
| BMI                     | 27.58±6.25  | 28.18±4.41  | 0.626   |
| Smoking                 | 5 (12.5)    | 4 (10)      | 0.725   |
| Diabetes mellitus       | 13 (32.5)   | 14 (35)     | 0.813   |
| Coronary artery disease | 24 (60)     | 9 (22.5)    | <0.001  |
| History of MI           | 5 (12.5)    | 2 (5)       | 0.235   |
| AF                      | 19 (47.5)   | 11 (27.5)   | 0.065   |
| History of cardiac surgery | 9 (22.5) | 0 (0)       | 0.001   |
| PCI                     | 9 (22.5)    | 1 (2.5)     | 0.007   |
| Neurological drug therapy | 8 (20)   | 1 (2.5)     | 0.014   |
| Carotid artery stenosis >50% | 6 (15) | 2 (5)       | 0.136   |
| Stroke                  | 5 (12.5)    | 3 (7.5)     | 0.456   |
| Pulmonary disease       | 7 (17.5)    | 3 (7.5)     | 0.176   |
| Poor mobility           | 11 (27.5)   | 5 (12.5)    | 0.094   |
| eGFR (mL/min/1.73 m²)   | 57.04±15.95 | 66.60±17.04 | 0.011   |
| Anaemia                 | 18 (45)     | 19 (47.5)   | 0.825   |
| NYHA class I            | 0           | 3 (7.5)     | 0.077   |
| NYHA class II           | 8 (20)      | 17 (42.5)   | 0.030   |
| NYHA class III          | 30 (75)     | 19 (47.5)   | 0.012   |
| NYHA class IV           | 2 (5.0)     | 1 (2.5)     | 0.562   |
| LogEuroSCORE            | 17.88±12.64 | 7.4±3.25    | <0.001  |
| Aortic valve area (cm²) | 0.62±0.16   | 0.71±0.2    | 0.062   |
| Mean aortic gradient (mmHg) | 57.39±15.36 | 58.19±20.63 | 0.706   |
| LVEF (%)                | 61.55±11.03 | 60.55±9.76  | 0.673   |
| At least moderate MR    | 15 (37.5)   | 5 (12.5)    | 0.010   |
| Periprocedural          |              |              |         |
| Duration of procedure (min) | 198.65±56.73 | 261.25±43.29 | <0.001  |
| RBC transfusion (units) | 0.8±2.20    | 2.18±2.66   | 0.014   |
| Periprocedural SBP <60 mmHg | 9 (22.5)  | 27 (70)     | <0.001  |
| drop <60 mmHg           |              |              |         |
| ΔSBP (mmHg)             | 82±27       | 106±23      | <0.001  |
| Duration of SBP drop <60 mmHg (min) | 10±4 | 27±23 | 0.001 |
| General anesthesia with muscle relaxation | 39 (97.5) | 40 (100) | 0.323 |
| Anesthesia with sevoflurane | 15 (37.5) | 22 (55) | 0.190 |
| Benzodiazepines during procedure | 0 (0) | 6 (15) | 0.012 |
| ICU stay (days)         | 4.93±4.43   | 2.98±2.48   | 0.001   |

Data are expressed as mean±SD or N. (%).
**Clinical outcomes**

There was one in-hospital death and one post-discharge death in each group. Acute kidney injury as defined by the VARC-2 criteria, was more common after SAVR (P=0.022). Surgical patients more frequently experienced deep hypotonia (defined as systolic blood pressure decrease [SBP]<60 mmHg, P=0.001) of a longer duration. Also shift in SBP (difference between maximum and minimum SBP) was larger during SAVR (P<0.001). All SBP drops <60 mmHg in TAVR patients occurred during rapid pacing and/or balloon inflation. The TAVR patients required longer stay in the intensive care unit (ICU, P<0.001). No patients underwent pacemaker implantation after SAVR, as opposed to 8 TAVR patients (P=0.002). Postoperative new-onset atrial fibrillation was more prevalent after SAVR (P<0.001). The clinical outcomes details are displayed in Table II.

**Neurocognitive status**

Mean baseline MMSE score was significantly lower in the TAVR patients than in the SAVR patients (24.50±4.10 vs. 27.08±2.64, P=0.001). There was a significant deterioration in the mean MMSE score to 25.79±2.31 (P=0.020) at discharge after SAVR, which was not observed after TAVR (Figure 1A). However among the TAVR patients there were still individuals who suffered from an in-hospital decrease in MMSE of at least one point. Most of them maintained or improved their results in the postdischarge period (12 out of 16; P=0.02). So did most of the SAVR patients (20 out of 21; P<0.001), with no differences between the groups in the follow-up (P=0.194). In-hospital decrease in the MMSE score did not influence the risk of decline from baseline to the follow-up in either group (P=0.138 for TAVR; P=0.464 for SAVR). Thus, the follow-up results were similar to those at baseline in both therapeutic groups and remained significantly lower after TAVR when compared to SAVR (24.23±3.23 vs. 27.34±2.73, respectively; P<0.001). The number of patients who maintained or improved the baseline results in the follow-up was similar in each group (18 out of 35 TAVR patients vs. 19 out of 35 SAVR patients; P=0.811).

Univariate analysis showed a trend for association between longer ICU stay and decline in the MMSE score over the hospitalization period in TAVR patients (OR 1.38; 95% CI 0.99-1.92; P=0.061). The correlation between the duration of ICU stay and decline in the MMSE score became significant after adjustment for sex, age and baseline MMSE score (OR 1.55; 95% 1.05-2.29; P=0.028).

In the SAVR group, patients with higher baseline MMSE score were more prone to the decline during hospitalization (OR 1.37, 95% CI 1.01-1.87; P=0.04). Multivariate regression adjusted for age and sex confirmed this observation (P=0.048).

Neither baseline nor periprocedural risk factors were found to contribute significantly to the decline in the MMSE score over the whole study.

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**Table II.**—Clinical outcomes.

<table>
<thead>
<tr>
<th>Event</th>
<th>TAVR</th>
<th>SAVR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (&lt;72 h)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Death (in-hospital)</td>
<td>1 (2.5)</td>
<td>1 (2.5)</td>
<td>1</td>
</tr>
<tr>
<td>Death (follow-up)</td>
<td>2 (5.7)</td>
<td>2 (5.7)</td>
<td>1</td>
</tr>
<tr>
<td>MI (in-hospital)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>MI (follow-up)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Stroke (in-hospital)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Stroke (follow-up)</td>
<td>1 (2.9)</td>
<td>0</td>
<td>0.307</td>
</tr>
<tr>
<td>Pacemaker (in-hospital)</td>
<td>7 (17.5)</td>
<td>0</td>
<td>0.006</td>
</tr>
<tr>
<td>Pacemaker (follow-up)</td>
<td>8 (22.9)</td>
<td>0</td>
<td>0.002</td>
</tr>
<tr>
<td>New onset AF (in-hospital)</td>
<td>2 (5)</td>
<td>15 (37.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New onset AF (follow-up)</td>
<td>2 (5.7)</td>
<td>16 (45.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>19 (47.5)</td>
<td>29 (72.5)</td>
<td>0.022</td>
</tr>
<tr>
<td>RRT</td>
<td>0</td>
<td>2 (5)</td>
<td>0.152</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>4.93±4.43</td>
<td>2.98±2.48</td>
<td>0.001</td>
</tr>
<tr>
<td>Rehospitalization (follow-up)</td>
<td>16 (45.7)</td>
<td>16 (45.7)</td>
<td>1</td>
</tr>
<tr>
<td>CV rehospitalization (follow-up)</td>
<td>14 (40.0%)</td>
<td>15 (44.1%)</td>
<td>0.729</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or n/N, (%). AF: atrial fibrillation/flutter; CV: cardiovascular; ICU: intensive care unit; MI: myocardial infarction; RRT: renal replacement therapy. AF: atrial fibrillation/flutter; eGFR: estimated glomerular filtration rate; ICU: Intensive Care Unit; LVEF: left ventricle ejection fraction; MI: myocardial infarction; MR: mitral regurgitation; neurological drug therapy (antidepressants, benzodiazepines and/or antipsychotic drugs); PCI: percutaneous coronary intervention; RBC: red blood cell; SBP: systolic blood pressure; Δ SBP: difference between maximum and minimum systolic blood pressure during procedure.
Risk factors for the decline in the ADL performance after TAVR were presence of SBP decrease <60 mmHg during procedure (OR 40; 95% CI 4.71-333.33; P=0.001), longer duration of SBP drop <60 mmHg (OR 1.37; 95% CI 1.10-1.73, P=0.006), larger shift in SBP during procedure (OR 1.04; 95% CI 1.0-1.08, P=0.039) and at least moderate MR at baseline (OR 7.87; 95% CI 1.21-47.61; P=0.024). After adjustment for sex, age and baseline ADL score all above risk factors remained significantly associated with decline in ADL: SBP decrease <60 mmHg (P=0.01), longer duration of SBP drop <60 mmHg (P=0.007), higher amplitude of maximum SBP change during procedure (P=0.046) and at least moderate MR at baseline (P=0.024).

To determine possibility to predict decline in the test based on periprocedural SBP shift ROC curve was generated. It was confirmed that larger SBP change is, the larger is the risk of decline in the test with AUC of 0.774 (0.554-0.933). A cut-off point of 83 mmHg was calculated for decline prediction with 88% sensitivity and 59% specificity.

Assessment of risk factors for the decline after SAVR could not be done as the performance was excellent, with only one person experiencing a decline in the ADL score.

**IADL**

Mean baseline IADL score was lower in the TAVR group (18.83±4.48 vs. 22.28±1.99 in SAVR; P=0.001). By the end of the study, it increased up to 19.57±2.84 after TAVR (P=0.710) and to 23.00±1.86 after SAVR (P=0.071). The difference between the groups remained significant (P<0.001) (Figure 1C). Fewer TAVR patients maintained or improved their IADL score (22 out of 35 in TAVR vs. 30 out of 35 in SAVR; P=0.029), but their benefit was more pronounced than after SAVR (increase of 2.37 after TAVR vs. 1.37 after SAVR; P=0.029).

As in the ADL test results, the decline in the IADL score after TAVR was associated with periprocedural SBP decrease <60 mmHg (OR 6.67; 95% CI 1.12-40; P=0.037), larger shift...
in SBP (OR 1.03; 95% CI 1.06-1.0, P=0.04) and at least moderate MR (OR 5.10; 95% CI 1.21-21.28; P=0.026). On contrary to ADL, there was only trend for association between duration of SBP drop <60 mmHg and IADL test results (P=0.081). Additional risk factors were procedure duration (min) (OR 1.02; 95% CI 1-1.04; P=0.045) and rehospitalization for cardiovascular causes (OR 5.43; 95% CI 1.22-24.39; P=0.027). After adjustment for age, sex and baseline IADL score, the following risk factors remained significant: periprocedural SBP decrease <60 mmHg (P=0.042), at least moderate MR (P=0.043), duration of the procedure (P=0.012) and rehospitalization for cardiovascular causes (P=0.041). And there was only trend for larger shift in SBP (P=0.078).

However, ROC curve analysis showed dependence of performance in IADL on SBP shift with AUC of 0.720 (0.535-0.904) and cut-off point of 78 mmHg with 80% sensitivity and 59% specificity.

No factors were found to be significantly correlated with the IADL score changes after SAVR.

Discussion

TAVR has become an alternative treatment in high-risk older patients with rates of survival and improvement of symptoms similar to those of SAVR.5, 6 What has become an issue of concern is an increased risk of stroke and silent cerebral ischemia after the TAVR procedure.5, 9 For the elderly population, life extension may be at least as essential as maintaining mental and physical independence, which might be seriously affected by a high burden of neurologic injury.

To the best of our knowledge, to date there have been few head-to-head studies comparing the influence of TAVR and SAVR on both mental and physical status.13, 14 In most of those studies, tests based on a subjective measurement of health status were used, such as Medical Outcomes Study Short-Forms. Only two studies comparably evaluated changes in the neurocognitive status.15, 16 Our study is the first to use comprehensive cognitive and functional status assessment within objective basic geriatric scales: MMSE, ADL and IADL. The comparison of these two therapeutic groups is challenging as there will always be baseline differences between them unless qualification criteria change. Currently, TAVR, by definition, is dedicated to patients of higher risk profile being still a procedure of second choice.

In the present study we found that elderly patients after TAVR, despite their higher risk profile, gain benefits comparable to those of SAVR in terms of neurocognitive status and at least comparable benefits in terms of functional status over a 6-month period.

One of the main results of this study is the reported lack of influence of the transient decline in neurocognitive function shortly after valve replacement on outcomes assessed over six months in both groups. By the end of the follow-up, the MMSE results were stable after both SAVR and TAVR. However, neurocognitive patterns differed between the groups (Figure 1A) with a more pronounced, albeit transient, decline in the surgical group and more common but comparably deep postdischarge decline after TAVR. Acknowledging differences in baseline risk profiles, the more prevalent but mild postdischarge decreases after TAVR might reflect a naturally occurring cognitive decline. If so, longer follow-up period could indicate worse outcomes in nonsurgical patients. On the other hand, Ghanem et al. proved a stable 2-year cognitive performance in over 90% of study patients after TAVR, despite a high intrinsic risk for cognitive deterioration.17

Our results are in agreement with the study by Knipp et al. who studied the cognitive function of patients with severe AS undergoing transapical TAVR or SAVR and followed them for up to three months.15 However, a few differences between the studies should be noted: 1) in the study by Knipp et al., TAVR was conducted only via transapical route; 2) the LogEuroSCORE was lower in our TAVR patients and higher in our SAVR patients; 3) the follow-up period was twice longer in our study. These differences indicate that the findings apply to broad population and for a longer period.
Despite that, a significant amount of data remains inconsistent with the literature. For example, Alissar et al. showed cognitive improvement after both TAVR and SAVR with even greater increase after SAVR; Zimpler et al. showed that early neurocognitive deficits following SAVR in elderly patients are persistent. These differences might be caused by the use of various assessment tools. Furthermore, ICU stay, reported in our study to be a risk factor for MMSE decline after TAVR, was longer in case of TAVR patients compared to SAVR, while for example PARTNER 2 cohort A study showed reverse outcomes. This might be related to the fact that the PARTNER 2 cohort A study included not high risk patients but those with intermediate risk. Another cause could be a significantly higher number of pacemakers implanted that could affect ICU stay.

We also reported a mild improvement of functioning after both TAVR and SAVR. Although the increase in the ADL score was insignificant, the difference between the groups narrowed (Figure 1B), therefore our study might indicate that patients with the greatest degree of disability may gain benefits from TAVR. One should note that the ADL score evaluates the very basic living skills and a one-point gain or loss reflects a considerable change in the patient’s independency. As nearly all surgical patients obtained maximum baseline score, we could only show the maintenance but not the improvement in the ADL score after SAVR. Complex skills also improved in both groups (Figure 1C). Interestingly, among patients who maintained or improved their IADL score, the average increase was significantly higher after TAVR. This indicates that there is a subgroup of TAVR patients who are likely to improve.

Identifying risk factors for the decline in tests, association between periprocedural SBP decrease <60 mmHg, its duration and magnitude of SBP drop with ADL and IADL outcomes was proved. The TAVR patients who experienced periprocedural SBP decrease <60 mmHg which occurs in relation to rapid pacing and/or balloon inflation were over 40 times more prone to a decline in the ADL score and over 6 times more prone to a decline in the IADL score, compared to the patients without the SBP decrease. The risk of decline in IADL score was increasing along with duration of deep hypotension during TAVR. Finally, we showed that irrespective of deep hypotension the magnitude of SBP shift affects TAVR patients performance. These findings indicate a relation between hemodynamic status and patients outcomes and emphasize extreme hemodynamic sensitivity of these population. Several studies failed to prove a relation between the presence and the number of new ischemic lesions, as well as neurologic and cognitive functions after TAVR. However, other studies show that in a substantial proportion of patients, rapid ventricular pacing is associated with microcirculatory arrest and a delayed recovery of microflow. We suggest that it is global ischemia due to low blood pressure and its rapid shifts that contributes to these deficits. Cerebral embolism should still be regarded as a conceivable cause of the decline in these functions, however it might also be the coexistence of cerebral ischemic lesions along with the decrease in SBP that finally leads to mental and physical dysfunctions.

We did not find any association between poor performance and SBP decrease during SAVR. Several causes might be responsible for the discrepancy, such as: 1) lower load of cerebral ischemic lesions after SAVR; 2) better baseline functional and cognitive status; 3) use of extracorporeal circulation that maintains cardiac output and prevents hypoperfusion even in the presence of hypotension. To prove it we showed that it is haemodynamic instability expressed by periprocedural shift in SBP that correlated with worse cognition.

Given the high rate of cerebral incidence and the inconclusive results of studies comparing the influence of TAVR and SAVR on neurocognitive and functional status, there is a need for a large comprehensive trial. To date, the greatest amount of data originated from PARTNER Cohort A, and although the data included mental status and physical assessment using the SF-12 test, it did not cover neurocognitive evaluation. Identification of risk factors associated with the decline in cognition and
functionality will be a valuable information to physicians and patients for informed decision-making.

Limitations of the study

Our study had several limitations. First of all, it had a small sample size, which may affect the statistical power of the analysis. Second of all, it was a single-center study, whose findings should be generalized with caution. On the other hand, it is well within range of comparable studies in this field and adds to the scarce data on the subject. There were also multiple differences in basic characteristics between the groups. As was mentioned in the Discussion, the differences might affect natural changes in the neurocognitive status of the elderly. Furthermore, data concerning perioperative delirium, that could affect cognitive performance, were not reported. Additionally, we did not find association of neither SBP drop nor SBP change with neurocognitive functions that could be expected due to their association with functional performance. This might be related to the fact that MMSE results were already moderately decreased at baseline and further deterioration would need more profound insult. Learning and practice effect due to repetition of MMSE at a short time interval could affect results. Finally, data regarding blood pressure fluctuations were retrieved from hand-written charts which if replaced with electronic charts could have been more precise.

Conclusions

We have demonstrated a comparable influence of TAVR and SAVR on neurocognitive and functional status over six months, but with a different trajectory of changes. In-hospital neurocognitive impairment, which was more pronounced in the surgical patients, did not affect the 6-month cognitive outcomes in either group. Both modes of treatment have a potential to maintain or improve physical status. Perioperative blood pressure decrease may deteriorate physical performance after TAVR.

Key messages

— TAVR patients compared to SAVR patients present significantly lower mental and physical status.
— Comparable number of TAVR and SAVR patients maintain or improve their neurocognitive functions after valve replacement, but significantly less TAVR patients maintain their physical status.
— The neurocognitive function of TAVR patients may be altered by periprocedural blood pressure changes and/or drops of systolic blood pressure <60 mmHg during rapid pacing and balloon extension.

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Authors’ contributions.—Marta Załęska-Kocięcka designed the study and was a guarantor of the manuscript. Anna Skrobisz, Maciej Grabowski, Maciej Dąbrowski, Sebastian Woźniak, and Anna Mierzyńska made substantial contributions to conception and design, acquisition and interpretation of data. Janina Stepińska, Anna Konopka, and Marek Banaszewski contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. Katarzyna Piotrowska had full access to all of the data in the study and takes responsibility for the accuracy of the data analysis.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Role of flexible fiberoptic laryngoscopy in predicting difficult intubation

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ABSTRACT

BACKGROUND: The ability to precisely predict which intubations will be difficult during administration of anesthesia is an important part of preoperative preparation. This study’s goal is to accurately identify patients who will be difficult to intubate using the number of tracheal rings observed preoperatively by fiberoptic laryngoscopy.

METHODS: We enrolled 994 adult patients in our study who required general anesthesia and orotracheal intubation for their elective surgeries. All patients received a Mallampati Test, a Wilson Risk-Sum Score, and fiberoptic laryngoscopy before operation. Each patient’s age, Body Mass Index (BMI), and neck circumference was recorded preoperatively. Logistic regression analysis was applied to evaluate the association between the recorded risk factors and a potentially difficult intubation. The three preoperative assessments were compared using three parameters: positive predictive value, sensitivity, and specificity.

RESULTS: The risk factors which were determined to be predictive for difficult intubation were: BMI, neck circumference, Mallampati Test, Wilson Risk-Sum Score, and fiberoptic laryngoscopy (P<0.05). Fiberoptic laryngoscopy as a predictive factor in the preoperative setting had a higher sensitivity, specificity, and positive predictive value than did the Mallampati Test or the Wilson Risk-Sum Score (P<0.05).

CONCLUSIONS: Fiberoptic laryngoscopy is a more accurate and convenient preoperative method to predict difficult intubation.

Difficult tracheal intubation is defined as intubation that requires repeated attempts, regardless of tracheal pathology.1 Whether a tracheal intubation is difficult can be affected by several variables: patient factors, utilization of proper equipment, and anesthesiologist expertise. Difficult tracheal intubation can lead to serious adverse outcomes during the administration of general anesthesia, including brain injury, cardiopulmonary arrest, unnecessary surgical interventions, airway trauma, and even death.2 Adequate preoperative planning, however, can reduce the risk of having a difficult tracheal intubation and the resulting consequences significantly.3

The American Society of Anesthesiologists (ASA) provides guidelines for how to preoperatively evaluate the condition of a patient’s airway, including considering the medical history of the patient, physical examination, and additional tests (e.g., radiography, computed tomography scans, fluoroscopy).1 Many clini-
cal factors and tests have been used to predict which patients might have a difficult intubation, including modified Mallampati Test, Wilson Risk-Sum Score, and thyromental distance.

The Mallampati Test was first proposed by Mallampati in 1985 and was modified by Samsoom et al. in 1987. This test can be performed quickly at the bedside to predict potential difficult intubations in surgical patients undergoing general endotracheal anesthesia. The Mallampati Test is frequently used because of its simplicity and rapidity. The Wilson Risk-Sum Score was first proposed by Wilson in 1988. This test includes the patient's weight, head and neck movement, jaw movement, receding mandible, and prominent maxillary incisors. The Wilson Risk-Sum Score is also commonly used to predict difficult intubation and is favored by some physicians because it encompasses a wide array of patient parameters. However, while both the Mallampati and the Wilson Risk-Sum Score are commonly used in preoperative assessments, studies have shown that both have high-false positive rates. There is thus a great clinical need for an accurate method to adequately predict difficult intubation.

Recently, new techniques (such as radiography, computed tomography sans, and magnetic resonance imaging) have been proposed to assess the anatomical features of the upper airway and identify airways that could be difficult to intubate. However, these diagnostic tests are not recommended as routine screening tools because they expose the patient to harmful radiation and can be exorbitantly expensive. Ultrasonography also be explored as a technique to predict difficult intubation because it is not invasive, harmless, and not expensive. Yao et al. used ultrasonography to measure tongue thickness and then calculated the ratio to thyromental distance in order to predict difficult intubation. However, all of these techniques indirectly assess the structure of the airway by measuring the anatomical structures surrounding it. Additionally, these techniques often require combining data from multiple techniques in order to improve their predictive power. An alternative predictive procedure that directly assesses the airway and the structures around it should be explored.

Flexible fiberoptic laryngoscopy has been shown to be the most accurate method to examine laryngeal disorders directly since it was first proposed by Sawashimain 1968. This technique is currently generally accepted and widely used. Selner et al. found that physicians spend less than five minutes performing this examination, after analyzing over 1700 individual examinations. Few to no side effects were observed. Additionally, this examination is not costly to the patient. Using this technique, Rosenblatt et al. used a flexible fiberoptic intubating bronchoscope to observe the anatomy of the upper airway. In up to one fourth of patients with potentially difficult airways, the previously established airway management plan was changed after observations with the fiberoptic bronchoscope. Our study prospectively investigated the feasibility of using fiberoptic laryngoscopy to predict difficult intubations. To test the accuracy of fiberoptic laryngoscopy versus other techniques, we compared it with the Mallampati Test and the Wilson Risk-Sum Score, evaluating for positive predictive value (PPV), sensitivity, and specificity.

**Materials and methods**

This study was conducted by the Department of Otolaryngology and Anesthesiology in our hospital. Approval from the Ethics Committee and informed consent from all patients were obtained. We enrolled 994 patients (ASA I-III) 21-67 years of age who required general anesthesia and orotracheal intubation for elective surgery. Exclusion criteria included age younger than 18 or laryngeal lesions hindering normal intubation (e.g. massive space occupying lesions, abnormal anatomy) (Table I).

Information regarding the patient’s age, gender, neck circumference, and BMI were recorded by a doctor in our department. In order to avoid experimental results being af-
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Inclusion criteria, exclusion criteria, history, and standard airway examination.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Recorded history</th>
<th>Standard airway examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA classification I-III</td>
<td>Age &lt;18 years</td>
<td>Age</td>
<td>Mallampati Test</td>
</tr>
<tr>
<td>Age ≥18 years</td>
<td>The laryngeal lesions hindering normal intubation (e.g., massive space occupying lesions, abnormal anatomy)</td>
<td>Gender, Neck circumference, BMI</td>
<td>Wilson Risk-Sum</td>
</tr>
<tr>
<td>Scheduling general anesthesia and orotracheal intubation for elective surgery</td>
<td></td>
<td>Fiberoptic laryngoscopy</td>
<td></td>
</tr>
</tbody>
</table>

Fiberoptic laryngoscopy was performed by an expert technician with the patient in a semi-recumbent position (the head of the examining chair raised 30 degrees). All patients received topical nasal decongestant and an anesthetic before the examination. The technician stood on the right side of the patient during the procedure. First, the patient was instructed to close his or her mouth and breathe gently through the nose. The fiberoptic laryngoscope (3.6 mm diameter, Olympus, Japan) was then advanced into one naris close to the vocal cords until it produced an irritating cough in the patient. The camera lens was then maneuvered to maximally expose the number of subglottic tracheal rings. The number of exposed tracheal rings observed in each patient was recorded.

In order to explore the relationship between the number of exposed subglottic tracheal rings and a predicted difficult intubation, we collected data from 400 patients over half a year. The 400 patients were divided into four groups according to Cormack and Lehane’s classification. The number of exposed tracheal rings for each patient in each group was recorded. By calculating the mean and standard deviation for each group, the classification in relation to the number of observed tracheal rings was determined. The glottic and subglottic view was noted as follows (Figure 2): Grade 1, seven or more tracheal rings visible; Grade 2, 5 to 6 tracheal rings visible; Grade 3, 3 to 4 tracheal rings visible; Grade 4, 2 or fewer tracheal rings visible. Patients with grade 3-4 were designated as predicted difficult intubation.

Figure 1.—Mallampati Test.

Figure 2.—Fiberoptic laryngoscopy (The amount of subglottic tracheal rings can be observed).
All patients were pre-medicated with intramuscular atropine and phenobarbital sodium. Midazolam (2-3 mg), propofol (2 mg/kg), sufentanil (20-25 µg), and atracurium (50 mg) were used for anesthesia induction, according to international standards. Laryngoscopy was performed by an anesthesiologist blinded to the assessments of the preoperative examination. The anesthesiologist used a Macintosh laryngoscope blade size 3 or 4 with the patient’s head in the “sniffing position.” The laryngoscopic view was classified according to Cormack and Lehane as follows: grade 1, full view of glottis; grade 2, only posterior commissure visible; grade 3, only epiglottis visible; grade 4, epiglottis invisible. Grade 3-4 were designated as predicted difficult intubation.

Statistical analysis

Statistical analysis was performed with SPSS 17.0 (SPSS Inc., Chicago, IL, USA) and MedCalc version 15.2 (MedCalc Software, Maria-kerke, Belgium) for Windows. Logistic regression analysis was applied to evaluate the association between the risk factors.

Table II.—Score assignment for the risk factors in logistic regression analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1: Age (year)</td>
<td>0</td>
</tr>
<tr>
<td>X2: BMI (kg/m²)</td>
<td>&lt;26</td>
</tr>
<tr>
<td>X3: Neck circumference (cm)</td>
<td>&lt;42</td>
</tr>
<tr>
<td>X4: Mallampati Test</td>
<td>Class I or II</td>
</tr>
<tr>
<td>X5: Wilson’s Score</td>
<td>&lt;2</td>
</tr>
<tr>
<td>X6: Fiberoptic laryngoscopy</td>
<td>Grade 1 or 2</td>
</tr>
<tr>
<td>Y: Difficult intubation</td>
<td>No</td>
</tr>
</tbody>
</table>

(Cormack and Lehane view grade 3 and 4)

Table III.—The risk factors and difficult intubation.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>B</th>
<th>SE</th>
<th>df</th>
<th>Wald value</th>
<th>P value</th>
<th>Exp (B)</th>
<th>95% CI for Exp (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.967</td>
<td>0.940</td>
<td>1</td>
<td>1.059</td>
<td>0.304</td>
<td>2.631</td>
<td>0.417–16.613</td>
</tr>
<tr>
<td>BMI</td>
<td>2.570</td>
<td>1.150</td>
<td>1</td>
<td>4.999</td>
<td>0.025</td>
<td>13.069</td>
<td>1.373–124.379</td>
</tr>
<tr>
<td>Neck circumference</td>
<td>3.029</td>
<td>0.929</td>
<td>1</td>
<td>10.621</td>
<td>0.001</td>
<td>20.673</td>
<td>3.344–127.796</td>
</tr>
<tr>
<td>Mallampati Test</td>
<td>2.982</td>
<td>0.936</td>
<td>1</td>
<td>10.139</td>
<td>0.001</td>
<td>19.727</td>
<td>3.147–123.647</td>
</tr>
<tr>
<td>Wilson’s Score</td>
<td>3.072</td>
<td>0.912</td>
<td>1</td>
<td>11.350</td>
<td>0.001</td>
<td>21.581</td>
<td>3.614–128.889</td>
</tr>
<tr>
<td>Fiberoptic laryngoscopy</td>
<td>3.685</td>
<td>0.833</td>
<td>1</td>
<td>19.556</td>
<td>0.001</td>
<td>39.834</td>
<td>7.781–203.933</td>
</tr>
</tbody>
</table>

Results

In this study, 994 adult patients aged 21 to 67 years and comprised of 486 males and 508 females were enrolled. After a direct laryngoscopy to predict which patients would have a difficult intubation, the incidence of actual difficult intubations in 994 cases was 3.82% (N.=38).

Scores for the risk factors in logistic regression analysis are shown in Table II. The factors measured were age, gender, neck circumference, and BMI. The association between these risk factors and actual difficult intubation are shown in Table III. The risk factors which were predictive of difficult intubation were BMI (P=0.025), neck circumference (P=0.001), Mallampati Test (P=0.001), Wilson Risk-Sum Score (P=0.001), and fiberoptic laryngoscopy (P=0.001), but not age (P=0.304).

The results of the three predictive assessments and the predicted versus proven difficult intubations are shown in Table IV. In the 956 proven easy intubation cases, the Mallampati Test predicted 516 cases, Wilson Risk-Sum Score predicted 808 cases, and the fiberoptic laryngoscopy predicted 946 cases. In the 38 proven difficult intubation cases, the Mallampati Test predicted 24 cases, the
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Table IV.—Predictions of the three tests compared with laryngoscopic classifications.

<table>
<thead>
<tr>
<th>Predictive test</th>
<th>Proved EI Predicted EI</th>
<th>Proved DI Predicted DI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mallampati Test</td>
<td>516</td>
<td>440</td>
</tr>
<tr>
<td>Wilson’s Score</td>
<td>808</td>
<td>148</td>
</tr>
<tr>
<td>Fiberoptic laryngoscopy</td>
<td>946</td>
<td>10</td>
</tr>
</tbody>
</table>

EI: easy intubation (Cormack and Lehane view grade 1 and 2); DI: difficult intubation (Cormack and Lehane view grade 3 and 4).

Figure 3.—Receiver Operator Characteristics (ROC) curves of the three predictive methods and their areas under curves (AUCs; value and its 95% confidence interval).

Table V.—The AUCs of three predictive tests and the differences compared with Fiberoptic laryngoscopy.

<table>
<thead>
<tr>
<th>Test</th>
<th>AUC (95% CI)</th>
<th>Difference (95% CI)</th>
<th>Z value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiberoptic laryngoscopy</td>
<td>0.91 (0.89-0.92)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mallampati Test</td>
<td>0.59 (0.56-0.62)</td>
<td>0.32 (0.23-0.40)</td>
<td>7.23</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Wilson’s Score</td>
<td>0.76 (0.73-0.78)</td>
<td>0.15 (0.06-0.24)</td>
<td>3.29</td>
<td>&lt;0.0010</td>
</tr>
</tbody>
</table>

Table VI.—Positive predictive value (PPV), sensitivity and specificity of three predictive assessments.

<table>
<thead>
<tr>
<th>Test</th>
<th>PPV (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mallampati Test</td>
<td>5.17</td>
<td>63.16</td>
<td>53.97</td>
</tr>
<tr>
<td>Wilson Risk-Sum Score</td>
<td>12.94</td>
<td>57.89</td>
<td>84.52</td>
</tr>
<tr>
<td>Fiberoptic laryngoscopy</td>
<td>76.19*</td>
<td>84.21**</td>
<td>98.95*</td>
</tr>
</tbody>
</table>

*P<0.01 versus Mallampati Test; **P<0.05 versus Mallampati Test and Wilson’s Score.

Wilson Risk-Sum Score predicted 22 cases, and the fiberoptic laryngoscopy predicted 32 cases. Figure 3 shows the ROC curves of the three predictive methods. The AUCs of these methods and the differences compared against fiberoptic laryngoscopy are shown in Table V. The AUCs of fiberoptic laryngoscopy, Mallampati Test and Wilson Risk-Sum Score were 0.91, 0.59 and 0.76. The AUC of fiberoptic laryngoscopy was significantly higher than Mallampati Test and Wilson risk-Sum Score. Table VI summarizes the PPV, sensitivity, and specificity of the three methods. The PPV, sensitivity, and specificity of the Mallampati Test were 5.17%, 63.16%, and 53.97%, respectively. The PPV, sensitivity, and specificity of the Wilson Risk-Sum Score were 12.94%, 57.89%, and 84.52%, respectively. The PPV, sensitivity, and specificity of the fiberoptic laryngoscopy were 76.19%, 84.21%, and 98.95%, respectively. The PPV, sensitivity, and specificity of the fiberoptic laryngoscopy were significantly higher compared to the Mallampati Test and the Wilson Risk-Sum Score. Fiberoptic laryngoscopy had the highest PPV, sensitivity, and specificity compared to the other methods.

Discussion

Difficult intubation remains a leading cause of death during general anesthesia, although its incidence is relatively low.19, 20 If a patient has a medical history of confounding factors that could make intubation difficult (including obstructive sleep apnea, neck masses, or con-
genital malformations), the incidence of difficult intubation often increase significantly.\textsuperscript{21-24} However, if an experienced anesthesiologist can assess the condition of the airway accurately and prepare the appropriate anesthetic management plan preoperatively, the risk of death during general anesthesia will be drastically reduced. Therefore, a preoperative accurate prediction of difficult intubation is critically important. Currently, there are several bedside tests to identify difficult airways, but none have sufficient accuracy.\textsuperscript{25}

Among these tests, the Mallampati Test and the Wilson Risk-Sum Score are the most convenient and popular methods to preoperatively assess the condition of the airway. Both have been found to be inaccurate in predicting difficult intubation when used alone.\textsuperscript{26-28} In our study, the Mallampati Test had 63.16% sensitivity and 53.97% specificity, and the Wilson’s Risk-Sum Score had 57.89% sensitivity and 84.52% specificity. Ezri \textit{et al.}\textsuperscript{29} and Aktas \textit{et al.}\textsuperscript{30} found the sensitivity of Mallampati Test to be 56%, similar to our result. Kim \textit{et al.}\textsuperscript{31} reported the Wilson’s risk-sum score had 47.1% sensitivity and 91.5% specificity. In addition, one of the greatest disadvantages of these two tests is that they do not apply to patients without locomotor activity. As a result, it is necessary to explore a more convenient and accurate assessment that has fewer restrictions.

Shiga \textit{et al.}\textsuperscript{26} demonstrated that bedside tests had poor accuracy when used alone; however, combination of multiple bedside tests could improve their predictive power, though likely not enough for consistent accuracy. Difficult intubation is affected by multiple factors. In our study, we found that the risk factors which predicted difficult intubation were BMI and neck circumference. Therefore, a single test may not predict difficult intubations consistently.\textsuperscript{32} A better way to predict difficult intubation is necessary.

Karla \textit{et al.}\textsuperscript{33} showed that fiberoptic laryngoscopy is a viable option in preoperative assessment. It can evaluate laryngeal and subglottic anatomical structures directly.\textsuperscript{34} Rosenblatt \textit{et al.}\textsuperscript{17} found that a preoperative endoscopic laryngeal examination was correlated with planned airway management in 26% of patients. However, there have been few studies assessing the utility of fiberoptic laryngoscopy in predicting difficult intubation.

Fiberoptic laryngoscopy is an essential examination in many otolaryngology practices. This operation is not overly uncomfortable and is easily performed with only a topical nasal decongestant and an anesthetic. The operation can be performed while the patient is either conscious or unconscious. Notably, the patient is also in a position roughly similar that under which general anesthesia is administered during an operation. All of these factors make fiberoptic laryngoscopy an attractive method to preoperatively predict difficult intubation.

Fiberoptic laryngoscopy is still not the standard of care, nor is it universally accepted as a necessary and accurate preoperative assessment. We sought to demonstrate quantitatively the accuracy of preoperative fiberoptic laryngoscopy in order to assuage skeptics and demonstrate its utility. In our study, we predicted airway condition by utilizing fiberoptic laryngoscopy to observe the number of exposed subglottic tracheal rings. We correlated the number of observed subglottic tracheal rings with a prediction about difficult intubation. We then assessed the accuracy of this prediction compared to the actual difficulty of the intubation. Our results indicated that fiberoptic laryngoscopy as a preoperative predictor of difficult intubation had a higher PPV, sensitivity, and specificity than either the Mallampati test or the Wilson Risk-Sum Score.

Other techniques similar to the fiberoptic laryngoscopy have been tested. However, when compared to fiberoptic laryngoscopy, we assert that these techniques are inferior. Rosenblatt \textit{et al.}\textsuperscript{17} found that fiberoptic bronchoscopy could be used as a preoperative endoscopic airway examination due to its ability to detect anatomical abnormalities. However, this method relies on the subjective judgment of the technician, without any quantified indicators. Fiberoptic laryngoscopy predicts difficult intubations by quantifying the extent of the subglottic view through defined conventional
assessments. It is not restricted by the skill or experience of the technician, and is therefore predicted to be more accurate. Yamamoto et al.\textsuperscript{35} and O’Budde et al.\textsuperscript{36} used indirect laryngoscopy to predict difficult intubation with a higher accuracy than the Mallampati Test or the Wilson Risk-Sum Score. While this is a useful method, the technical expertise required to perform this operation may be restrictively high. In addition, this examination can lead to a high rate of excessive gag reflex, as reported by Yamamoto et al.\textsuperscript{35} and Arne O’Budde et al.\textsuperscript{36} Notably, fiberoptic laryngoscopy does not have these limitations. In our study, no patients reported feeling poorly after the procedure. Additionally, fiberoptic laryngoscopy can observe the upper airway easily, while indirect laryngoscopy cannot reveal the anatomical structures successfully.

Recently, video laryngoscopy has been increasingly used in endotracheal intubation. Its application does reduce the incidence of difficult intubation. However, it is only used as an auxiliary tool during intubation, rather than a preoperative prediction method. Moreover, many underprivileged hospitals have not been able to utilize this technology because of excessive economic and technological constraints. Although fiberoptic laryngoscopy and video laryngoscopy both expose the laryngeal structure directly, the ranges of exposure are different. Video laryngoscopy relies on lifting the root of the tongue and epiglottis to expose the glottis, while fiberoptic laryngoscopy can go across the epiglottis to reveal the glottis without lifting any structures. Direct laryngoscopy applies the same principle as video laryngoscopy, even though it cannot expose the laryngeal structures directly.

Our data suggests that fiberoptic laryngoscopy has higher accuracy compared to the traditional methods. The greatest disadvantage of traditional methods is that they cannot visually observe laryngeal structures. As it is a type of endoscopy, fiberoptic laryngoscopy not only visualizes laryngeal occupying lesions, but also shows the structure of upper airway. In this study, we found that there was significant correlation between prediction by fiberoptic laryngoscopy and actual intubation difficulty. When the number of tracheal rings exposed by fiberoptic laryngoscope was less than four, the incidence of difficult intubation increased accordingly. Our results showed that fiberoptic laryngoscopy also had high sensitivity (84.21\%) and specificity (98.95\%). We therefore conclude that fiberoptic laryngoscopy is a more accurate preoperative method to predict difficult intubation.

Limitations of the study

This study was designed as a pilot study to determine if fiberoptic laryngoscopy might be a useful tool to preoperatively assess airway condition. There have some limitations in this study, such as the involved patients were only adults, with no children or teenagers. The sample size was a bit small because of the incidence of difficult intubation in the population is low. The advantage of fiberoptic laryngoscopy is likely underestimated as few patients in this study ended up having difficult intubations. A larger sample size will be enrolled in future studies. In addition, we did not compare the fiberoptic laryngoscopy with the emerging assessments, such as radiography, magnetic resonance imaging and ultrasonography, because of the economic constraints of our study. Our results strongly indicate that fiberoptic laryngoscopy is the most accurate and feasible method to predict difficult intubations during administration general anesthesia. If widely utilized, fiberoptic laryngoscopy could decrease the number of deaths due to complications during anesthesia.

Conclusions

Fiberoptic laryngoscopy is the most accurate and convenient preoperative method to predict difficult intubation.

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Key messages

— Difficult intubation is a leading cause of death during general anesthesia.
— Accurate preoperative prediction of difficult intubation can effectively reduce the risk of death during anesthesia.
— Fiberoptic laryngoscopy can visualize the anatomical structure of the upper airway easily and directly.
— Fiberoptic laryngoscopy is an accurate preoperative method to predict difficult intubation.

References


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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Heterogenic control groups in randomized, controlled, analgesic trials of total hip and knee arthroplasty

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ABSTRACT

INTRODUCTION: Postoperative analgesic interventions are often tested adjunct to basic non-opioid analgesics in randomized controlled trials (RCTs). Consequently, treatment in control groups, and possible assay sensitivity, differs between trials. We hypothesized that postoperative opioid requirements and pain intensities vary between different control groups in analgesic trials.

EVIDENCE ACQUISITION: Control groups from RCTs investigating analgesic interventions after total hip and knee arthroplasty were categorized based on standardized basic analgesic treatment. Morphine consumption 0 to 24 hours postoperatively, and resting pain scores at 6 and 24 hours for subgroups of basic treatments, were compared with ANOVA. In an additional analysis, we compared pain and opioid requirements in trials where a non-steroidal anti-inflammatory drug (NSAID) was administered as an intervention with trials where NSAID was administered in a control group.

EVIDENCE SYNTHESIS: We included 171 RCTs employing 28 different control groups with large variability in pain scores and opioid requirements. Four types of control groups (comprising 78 trials) were eligible for subgroup comparisons. These subgroups received “opioid” alone, “NSAID + opioid”, “acetaminophen + opioid”, or “NSAID + acetaminophen + opioid”, respectively. Morphine consumption and pain scores varied substantially between these groups, with no consistent superior efficacy in any subgroup. Additionally, trials administering NSAID as an intervention demonstrated lower pain scores and opioid requirements than trials where NSAID was administered in a control group.

CONCLUSIONS: Analgesic treatment in RCT control groups varies considerably. Control groups receiving various combinations of opioid, NSAID and acetaminophen did not differ consistently in pain and opioid requirements. Pain and opioid requirements were lower in trials administering NSAID as an intervention compared with trials administering NSAID in a control group.

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Key words: Postoperative pain - Hip replacement arthroplasty - Knee replacement arthroplasty - Non-steroidal anti-inflammatory agents - Opioid analgesics.
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We further hypothesized that some of the analgesic effects observed in placebo-controlled trials of an intervention, may be due to bias and non-optimal use of placebos. In an additional analysis we therefore compared pain and opioid requirements in trials where a non-steroidal anti-inflammatory drug (NSAID) was administered as an intervention with trials where a NSAID drug was administered in a control group.

Evidence acquisition

The protocol was registered in the PROSPERO database prior to any data-analysis (registration no. CRD42016050987).

Literature search

The databases from two systematic reviews regarding procedure-specific pain management after THA and TKA were screened for relevant trials. The original searches were performed in PubMed, Embase, and The Cochrane Library, with the last search for THA: August 22nd, 2014, and for TKA: September 9th, 2016. The search-strings were sensitive to detect relevant trials regarding THA and TKA, respectively, and can be seen at the PROSPERO homepage (www.crd.york.ac.uk/PROSPERO/) with trial identifier 9382 (THA) and 14940 (TKA).

Inclusion criteria

Eligible trials were RCTs that compared analgesic interventions with placebo/no treatment in participants of 18 years or more. Thus, current analgesic regimens usually encompass one or more non-opioid (basic) analgesics in addition to opioids, aiming to enhance pain relief, and to reduce opioid-related adverse effects. Accordingly, new interventions for postoperative pain treatment are often investigated as adjuncts to other analgesics (e.g. intervention + basic acetaminophen and rescue opioid versus placebo + basic acetaminophen and rescue opioid).

It must be speculated if the analgesic efficacy of an intervention, examined on top of one or several other analgesics, is directly comparable with the effects observed in trials of the intervention alone. Nevertheless, results from both categories of trials are most often included on an equal basis in meta-analyses. This may confound the interpretation of the pooled results.

Considerable differences in basic analgesic regimens have been demonstrated in trials after both total hip (THA) and knee arthroplasty (TKA). This may reduce the baseline pain level in the control groups of the trials, which in turn will reduce the maximal obtainable pain-relieving effect of the intervention. Our hypothesis was that the composition of basic analgesic treatment would be reflected in postoperative opioid requirements and pain intensities in the control groups.

The aim of the present analysis was therefore to compare opioid requirements and pain intensities in control groups receiving different basic analgesic treatments. Data were systematically extracted from published RCTs regarding pain management after THA and TKA (examples of theoretical comparisons are provided in Figure 1).

Figure 1.—Comparison of basic analgesic treatments. Illustrates how basic analgesic regimens were compared. Control group A received an NSAID, and control group B received acetaminophen. Our hypothesis was that the control group with the lowest morphine requirements and pain scores administered the most effective basic analgesic treatment.
undergoing either THA or TKA. Trials were included if they administered a standardized, basic analgesic treatment in the intervention and control group equally. Any subgroup of a standardized oral or IV basic analgesic treatment that reported primary outcomes in three or more trials was included for statistical comparative analyses. Trials where the control group received invasive procedures were not included in subgroup analysis, as this could potentially decrease pain levels and confound the comparison of basic regimens.

**Outcomes**

Primary outcomes were cumulated opioid consumption 0 to 24 hours postoperatively, and pain at rest at 6 and 24 hours postoperatively in control groups.

**Data extraction**

Two authors independently screened trials for inclusion and extracted data into a Microsoft Excel spreadsheet. Databases were subsequently compared, and discrepancies discussed. In case of no description of basic analgesic treatment, the relevant corresponding authors were contacted for elaboration. If the corresponding author did not respond, the particular trial was categorized as “opioid”.

**Risk of bias (quality) assessment**

All trials were assessed for risk of bias by two authors independently, according to the Cochrane Handbook of Systematic Reviews of Interventions, i.e. sequence generation, allocations concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias.

**Strategy for data synthesis**

Postoperative 0-24 hour opioid consumption was converted to the equivalent dose of IV morphine (Supplementary Table I, online content only). Pain scores, e.g. VAS 0-10 and VRS 0-10, were converted to a 0-100 mm scale. Results expressed as median and IQR/range were converted to mean and standard deviation according to The Cochrane Handbook v. 7.7.3.5 or Hozo et al., as appropriate. Standard deviation was calculated from P values in articles representing no spread according to The Cochrane Handbook v. 7.7.3.3. If the P value was expressed as P<0.05, the conservative approach P=0.05 was used.

**Subgroup analysis**

Control groups from the included RCTs were categorized after type of basic analgesic regimen. Each control group category with primary outcomes reported in three or more trials was included for subgroup analysis. Data for each primary outcome were aggregated to point estimates reported as mean and standard deviation.

In an additional analysis, we extracted data from trials where a NSAID was administered as an intervention after THA or TKA, and from trials where a NSAID was administered in control groups as the only basic analgesic (similar treatments in intervention- and control groups). The two groups: NSAID-intervention vs. NSAID-control were compared with an unpaired t-test.

**Evidence synthesis**

The search resulted in 8329 trials for THA and 8626 for TKA. We included 171 RCTs that compared a postoperative analgesic intervention with a control group. Basic analgesic regimens comprised NSAIDs, acetaminophen, gabapentinoids, steroids, peri-, intra-, and extra articular injections, femoral-, lumbar-, and sciatic nerve blocks, and continuous epidural analgesia, or combinations of two or more of
### TABLE I. —Baseline characteristics for included trials investigating total hip arthroplasty. Trials are categorized according to basic analgesic treatment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment in control group</th>
<th>Treatment in intervention group</th>
<th>N. controls</th>
<th>Anesthesia</th>
<th>Summarized risk of bias</th>
<th>Rescue IV morphine mg (0-24 h)</th>
<th>VAS pain score 1-100 (6 h)</th>
<th>VAS pain score 1-100 (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rescue opioid + NSAIDs</td>
<td>Rectal diclofenac sodium 100 mg during surgery + rescue opioid</td>
<td>Intrathecal morphine</td>
<td>15</td>
<td>SA</td>
<td>High</td>
<td>12.7±12.8</td>
<td>42±19</td>
<td>15±19</td>
</tr>
<tr>
<td>Murphy (2003) 43</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liu (2011) 41</td>
<td>Oral celecoxib 200 mg ×2 + placebo + rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>41</td>
<td>SA</td>
<td>Unclear</td>
<td>27±17.7</td>
<td>67±23</td>
<td>59±18</td>
</tr>
<tr>
<td>Marino (2009) 42</td>
<td>IM ketorolac 30 mg at 0 and 6 h + rescue opioid</td>
<td>Cont. femoral nerve block</td>
<td>75</td>
<td>SA</td>
<td>High</td>
<td>62.6±50.1</td>
<td>–</td>
<td>33±22</td>
</tr>
<tr>
<td>Rescue opioid + acetaminophen</td>
<td>Oral acetaminophen 500 mg ×4 + placebo + rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>46</td>
<td>GA</td>
<td>Unclear</td>
<td>16.8±6.4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Chen (2010) 45</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mathiesen (2008) 46</td>
<td>Oral acetaminophen 1 g ×3 + placebo + rescue opioid</td>
<td>Pregabalin</td>
<td>38</td>
<td>SA</td>
<td>Low</td>
<td>47±28</td>
<td>19±18</td>
<td>12±16</td>
</tr>
<tr>
<td>Andersen (2007) 44</td>
<td>Oral acetaminophen 1 g ×4 + placebo + rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>18</td>
<td>SA</td>
<td>Unclear</td>
<td>26.5±10.8</td>
<td>34±30</td>
<td>–</td>
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<tr>
<td>Rescue opioid + NSAIDs + acetaminophen</td>
<td>IV lornoxicam 8 mg ×2 + oral acetaminophen 500 mg ×4 + rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>21</td>
<td>SA</td>
<td>High</td>
<td>16±8.5</td>
<td>20±20</td>
<td>10±13</td>
</tr>
<tr>
<td>Pandazi (2013) 50</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Remérand (2009) 51</td>
<td>IV acetaminophen 1 g ×4 + IV ketoprofen 50 mg ×4 + placebo + rescue opioid</td>
<td>IV ketamine</td>
<td>75</td>
<td>GA</td>
<td>Unclear</td>
<td>19±12</td>
<td>–</td>
<td>15±12</td>
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<tr>
<td>Kardash (2008) 48</td>
<td>Oral acetaminophen 650 mg ×4 + oral ibuprofen 400 mg ×4 + placebo + rescue opioid</td>
<td>IV dexamethasone</td>
<td>25</td>
<td>SA</td>
<td>High</td>
<td>28.8±16.5</td>
<td>34±24</td>
<td>19±18</td>
</tr>
<tr>
<td>Murphy (2012) 49</td>
<td>Oral acetaminophen 1 g ×4 + oral diclofenac 75 mg ×2 + placebo + rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>46</td>
<td>SA</td>
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<td>37±12.7</td>
<td>55±34</td>
<td>52±34</td>
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</table>

(To be continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment in control group</th>
<th>Treatment in intervention group</th>
<th>N. controls</th>
<th>Anesthesia</th>
<th>Summarized risk of bias</th>
<th>Rescue IV morphine mg (0-24 h)</th>
<th>VAS pain score 1-100 (6 h)</th>
<th>VAS pain score 1-100 (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen (2014) 47</td>
<td>IV parecoxib 40 mg ×2 + oral acetaminophen 500 mg ×4 + placebo + rescue opioid</td>
<td>Intraarticular injection</td>
<td>48</td>
<td>GA</td>
<td>Unclear</td>
<td>5.9±2.7</td>
<td>53±20</td>
<td>38±6</td>
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</table>

Rescue opioid

<table>
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<tr>
<th>Study</th>
<th>Treatment in control group</th>
<th>Treatment in intervention group</th>
<th>N. controls</th>
<th>Anesthesia</th>
<th>Summarized risk of bias</th>
<th>Rescue IV morphine mg (0-24 h)</th>
<th>VAS pain score 1-100 (6 h)</th>
<th>VAS pain score 1-100 (24 h)</th>
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</thead>
<tbody>
<tr>
<td>Fletcher (1995) 25</td>
<td>Placebo + rescue opioid</td>
<td>IV ketorolac</td>
<td>20</td>
<td>GA</td>
<td>High</td>
<td>32.5±17.9</td>
<td>31±22</td>
<td>23±22</td>
</tr>
<tr>
<td>Manoir (2006) 30</td>
<td>Placebo + rescue opioid</td>
<td>Oral morphine</td>
<td>20</td>
<td>GA</td>
<td>Unclear</td>
<td>33±24.6</td>
<td>40±31</td>
<td>35±22</td>
</tr>
<tr>
<td>Stevens (2007) 38</td>
<td>Placebo + rescue opioid</td>
<td>Fascia iliaca block</td>
<td>22</td>
<td>SA</td>
<td>High</td>
<td>41.5±12.3</td>
<td>34±9</td>
<td>21±0.4</td>
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<tr>
<td>Martinez (2007) 32</td>
<td>Placebo + rescue opioid</td>
<td>IV parecoxib</td>
<td>21</td>
<td>GA</td>
<td>Unclear</td>
<td>47±27</td>
<td>25±23</td>
<td>20±23</td>
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<tr>
<td>Martinez (2014) 33</td>
<td>Placebo + rescue opioid</td>
<td>IV ketamine</td>
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<td>GA</td>
<td>Low</td>
<td>–</td>
<td>–</td>
<td>18±22</td>
</tr>
<tr>
<td>Peduto (1998) 36</td>
<td>Placebo + rescue opioid</td>
<td>IV propacetamol</td>
<td>47</td>
<td>GA</td>
<td>High</td>
<td>17.6±27.4</td>
<td>29±27</td>
<td>16±21</td>
</tr>
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<td>Manoir (2003) 23</td>
<td>Placebo + rescue opioid</td>
<td>IV nefopam</td>
<td>90</td>
<td>GA</td>
<td>High</td>
<td>27.3±19.2</td>
<td>29±20</td>
<td>25±17</td>
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<tr>
<td>Akin (2002) 20</td>
<td>Placebo + rescue opioid</td>
<td>I.m. piroxicam</td>
<td>20</td>
<td>GA</td>
<td>High</td>
<td>30.2±18.2</td>
<td>22±7</td>
<td>10±8</td>
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<tr>
<td>Camu (2002) 22</td>
<td>Placebo + rescue opioid</td>
<td>Oral valdecoxib</td>
<td>61</td>
<td>SA</td>
<td>High</td>
<td>31.6±14.8</td>
<td>–</td>
<td>–</td>
</tr>
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<td>Grace (1995) 36</td>
<td>Rescue opioid</td>
<td>Intrathecal morphine</td>
<td>30</td>
<td>SA</td>
<td>Unclear</td>
<td>36±19.6</td>
<td>4±10</td>
<td>5±15</td>
</tr>
<tr>
<td>Malan (2003) 29</td>
<td>Placebo + rescue opioid</td>
<td>IV parecoxib</td>
<td>65</td>
<td>GA or SA</td>
<td>High</td>
<td>57.5±30.4</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Segstro (1991) 37</td>
<td>Placebo + rescue opioid</td>
<td>Rectal indomethacin</td>
<td>22</td>
<td>GA</td>
<td>Low</td>
<td>58.3±24.1</td>
<td>38±28</td>
<td>28±19</td>
</tr>
<tr>
<td>Anis (2011) 21</td>
<td>Rescue opioid</td>
<td>Lumbar plexus block</td>
<td>20</td>
<td>GA</td>
<td>High</td>
<td>13.8±3.8</td>
<td>90±15</td>
<td>50±15</td>
</tr>
<tr>
<td>Mendieta Sanchez (1999) 34</td>
<td>Placebo + rescue opioid</td>
<td>Intrathecal morphine</td>
<td>15</td>
<td>SA</td>
<td>High</td>
<td>23.4±7.6</td>
<td>23±12</td>
<td>14±9</td>
</tr>
<tr>
<td>Milligan (1993) 35</td>
<td>Rescue opioid</td>
<td>Subarachnoidial diamorphine</td>
<td>30</td>
<td>SA</td>
<td>High</td>
<td>31±18.7</td>
<td>25±26</td>
<td>1±2</td>
</tr>
<tr>
<td>Grace (1994) 27</td>
<td>Rescue opioid</td>
<td>Intrathecal morphine</td>
<td>30</td>
<td>SA</td>
<td>High</td>
<td>34±5.8</td>
<td>0±23</td>
<td>–</td>
</tr>
<tr>
<td>Fernandez-Liesa (2000) 24</td>
<td>Placebo + rescue opioid</td>
<td>Intrathecal methadone 4 mg</td>
<td>15</td>
<td>SA</td>
<td>High</td>
<td>21±28.3</td>
<td>22±4</td>
<td>11±18</td>
</tr>
<tr>
<td>Wu (2011) 40</td>
<td>Placebo + rescue opioid</td>
<td>IV dexmedetomididine</td>
<td>20</td>
<td>Unclear</td>
<td>High</td>
<td>56.1±9.4</td>
<td>15±4</td>
<td>12±3</td>
</tr>
<tr>
<td>Laitinen (1992) 28</td>
<td>Placebo + rescue opioid</td>
<td>IV diclofenac</td>
<td>18</td>
<td>SA</td>
<td>High</td>
<td>20±20</td>
<td>20±20</td>
<td>24±18</td>
</tr>
</tbody>
</table>

Postoperative consumption of rescue opioids and pain scores for the control group are presented as mean±SD. Rescue opioids were converted to IV morphine equivalents. The summarized risk of bias was determined according to Cochrane. GA: general anesthesia; SA: spinal anesthesia.
these analgesics or analgesic techniques. A total of 28 different basic analgesic regimens were employed in the control groups of these 171 trials.

Subgroup analysis

Four types of control groups were eligible for subgroup analysis. These subgroups administered “opioid” alone, “NSAID + opioid”, “acetaminophen + opioid”, and “NSAID + acetaminophen + opioid”, respectively, as basic analgesic treatment. In total 78 trials used one of these four types of control groups; 32 after THA and 46 after TKA.

The summarized risk of bias was low in eight, unclear in 39, and high in 31 of the 78 trials included in subgroup analysis.

Baseline variables, summarized risk of bias, cumulated 0-24 hour opioid requirements, and pain scores at 6 and 24 hours postoperatively of each included control group are presented in Tables I and II.

Opioid consumption

The 78 trials included in the subgroup analysis revealed major heterogeneity in consumption of IV morphine equivalents 0-24 hours postoperatively, ranging from 5.9 to 62.6 mg after THA, and from 5.5 to 116 mg after TKA.

For trials regarding both THA and TKA, we demonstrated an overall significant difference in morphine consumption among the 4 subgroups, but no consistent additive effect of the different analgesics was demonstrated (Table III, Figure 2).

Total hip arthroplasty

Control groups that received “NSAID + acetaminophen + opioid” consumed less IV morphine equivalents in the 0-24 h postoperative period compared to control groups that received “NSAID + opioid”, “acetaminophen + opioid”, or “opioid”, (P≤0.001). Further, control groups that received “acetaminophen + opioid” and “opioid” consumed significantly less morphine compared to control groups that received “NSAID + opioid” (P<0.001) (Supplementary Table II).

Total knee arthroplasty

Control groups that received “NSAID + acetaminophen + opioid” consumed more IV morphine equivalents in the 0-24-hour postoperative period compared with those receiving “opioid” (P=0.013), less IV morphine equivalents compared with those receiving “acetaminophen + opioid” (P<0.001), and insignificantly more IV morphine equivalents compared with those receiving “NSAID + opioid” (P=0.074). Furthermore, control groups that received opioid alone consumed less IV morphine equivalents compared with those receiving acetaminophen + opioid (P<0.001) (Supplementary Table II).

Aggregated data

From the aggregated data of patients undergoing either THA or TKA, significantly lower morphine consumption was demonstrated in control groups that received “NSAID + acetaminophen + opioid” compared with “opioid” (P=0.019), “NSAID + opioid” (P=0.001), and “acetaminophen + opioid” (P<0.001). Moreover, the “opioid” consumption was lower for control groups that received opioid compared with those receiving either “NSAID + opioid” (P=0.002) or “acetaminophen + opioid” (P<0.001) (Table III, Figure 2).

Pain scores

Mean postoperative pain intensities displayed a large degree of heterogeneity amongst the 78 trials included in subgroup analysis; at 6 hours at rest (VAS range: THA: 0-90 mm; TKA: 10-80 mm), and at 24 hours at rest (VAS range: THA: 1-59 mm; TKA: 6-57 mm).

For both THA and TKA we demonstrated overall significant differences in pain intensities among the four types of control groups, but no consistent additive effects of NSAIDs or acetaminophen were demonstrated (Table III). Further, there was no type of control group that...
Table II.—Baseline characteristics for included trials investigating total knee arthroplasty.

<table>
<thead>
<tr>
<th>Total knee arthroplasty</th>
<th>Treatment in control group</th>
<th>Treatment in intervention group</th>
<th>Patients in control group</th>
<th>Anesthesia</th>
<th>Summarized risk of bias</th>
<th>Rescue IV morphine mg (0-24 h)</th>
<th>VAS pain score 1-100 (6 h)</th>
<th>VAS pain score 1-100 (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rescue opioid + NSAIDs</td>
<td>Rectal indomethacin 100 mg ×2 + rescue opioid</td>
<td>Femoral or psoas nerve block</td>
<td>20</td>
<td>SA</td>
<td>High</td>
<td>47.5±14.2</td>
<td>38±26</td>
<td>34±19</td>
</tr>
<tr>
<td>Cole (2000) 80</td>
<td>Oral diclofenac 50 mg ×3 + placebo + rescue opioid</td>
<td>Intrathecal morphine</td>
<td>18</td>
<td>SA or GA</td>
<td>Unclear</td>
<td>38.5±17.8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fu (2009) 81</td>
<td>Celecoxib 200 mg ×2 + placebo + rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>40</td>
<td>SA</td>
<td>Unclear</td>
<td>28±29.1</td>
<td>67±16</td>
<td>50±11</td>
</tr>
<tr>
<td>Zhang (2011) 84</td>
<td>Oral celecoxib 200 mg ×2 + placebo + rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>26</td>
<td>GA</td>
<td>Unclear</td>
<td>30±5.5</td>
<td>50±7</td>
<td>43±10</td>
</tr>
<tr>
<td>Allen (1998) 79</td>
<td>IV ketorolac 15/30 mg ×4 + sham block + rescue opioid</td>
<td>Femoral and sciatic nerve block</td>
<td>12</td>
<td>SA</td>
<td>High</td>
<td>–</td>
<td>54±21</td>
<td>27±10</td>
</tr>
<tr>
<td>Zhang (2007) 85</td>
<td>IV lornoxicam 0.3 mg/h for 48 h + rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>30</td>
<td>GA</td>
<td>Unclear</td>
<td>17±7</td>
<td>21±8</td>
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</tr>
<tr>
<td>Rescue opioid + acetaminophen</td>
<td>Oral acetaminophen 1 g ×4 + rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>23</td>
<td>GA</td>
<td>Unclear</td>
<td>74±23.8</td>
<td>26±17</td>
<td>24±21</td>
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<tr>
<td>Essving (2010) 87</td>
<td>Oral acetaminophen 1 g ×4 + placebo + rescue opioid</td>
<td>IV tramadol</td>
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<td>SA</td>
<td>Low</td>
<td>72±27.2</td>
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<tr>
<td>Stiller (2007) 89</td>
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<td>IV ketamine</td>
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<td>GA</td>
<td>Unclear</td>
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<tr>
<td>Cengiz (2014) 86</td>
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<td>Oral nimodipine</td>
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<td>Unclear</td>
<td>45±24</td>
<td>50±27</td>
<td>34±21</td>
</tr>
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<td>Casey (2006) 85</td>
<td>Acetaminophen 1 g ×4 + placebo + rescue opioid</td>
<td>Oral duloxetine</td>
<td>24</td>
<td>SA or GA</td>
<td>Unclear</td>
<td>19.8±13.7</td>
<td>10±24</td>
<td>10±24</td>
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<tr>
<td>Rescue opioid + NSAIDs + acetaminophen</td>
<td>Oral acetaminophen 1 g ×4 + oral rofecoxib 50 mg 30 min before operation and each morning + rescue opioid</td>
<td>Cont. femoral nerve block</td>
<td>20</td>
<td>SA and sedation</td>
<td>High</td>
<td>19±15</td>
<td>31±24</td>
<td>15±12</td>
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<tr>
<td>Seet (2006) 94</td>
<td>Oral acetaminophen 1 g ×4 + oral meloxicam 15 mg ×1 (2 h after surgery) + placebo + rescue opioid</td>
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<td>29</td>
<td>SA</td>
<td>Unclear</td>
<td>116±59.1</td>
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(To be continued)
Table II.—Baseline characteristics for included trials investigating total knee arthroplasty (continues).

<table>
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<tr>
<th>Total knee arthroplasty</th>
<th>Treatment in control group</th>
<th>Treatment in intervention group</th>
<th>Patients in control group</th>
<th>Anesthesia</th>
<th>Summarized risk of bias</th>
<th>Rescue IV morphine mg (0-24 h)</th>
<th>VAS pain score 1-100 (6 h)</th>
<th>VAS pain score 1-100 (24 h)</th>
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</thead>
<tbody>
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<td>IV acetaminophen 1 g × 3 + IV diclofenac 75 mg × 2 + placebo + rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>40</td>
<td>SA</td>
<td>Low</td>
<td>26±11.8</td>
<td>50±11</td>
<td>30±11</td>
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<tr>
<td>Vendittoli (2006) 96</td>
<td>Acetaminophen 500 mg × 4 + celecoxib 200 mg × 2 + rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>20</td>
<td>SA</td>
<td>High</td>
<td>50.3±25.4</td>
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<td>33±19</td>
</tr>
<tr>
<td>Yuenyongviwat (2012) 97</td>
<td>Oral acetaminophen 1 g × 4 + oral meloxicam 7.5 mg × 2 + IM diclofenac 50 mg after operation + placebo + rescue the opioid</td>
<td>Local infiltration analgesia</td>
<td>30</td>
<td>SA</td>
<td>Unclear</td>
<td>5.5±1.9</td>
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<tr>
<td>Jenstrup (2012) 91</td>
<td>Oral acetaminophen 1 g × 4 + oral ibuprofen 400 mg × 4 + placebo + rescue opioid</td>
<td>Adductor canal block</td>
<td>37</td>
<td>SA and sedation</td>
<td>Low</td>
<td>56±26</td>
<td>42±24</td>
<td>21±20</td>
</tr>
<tr>
<td>Frassanito (2015) 90</td>
<td>IV acetaminophen 1 g × 4 + IV ketorolac 30 mg × 2 + placebo + rescue opioid</td>
<td>IV magnesium</td>
<td>20</td>
<td>SA</td>
<td>Unclear</td>
<td>14.4±10.7</td>
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<tr>
<td>Kardash (2007) 92</td>
<td>Oral acetaminophen 650 mg × 4 + oral celecoxib 100 mg × 2 + sham block + rescue opioid</td>
<td>Femoral or obturator nerve block</td>
<td>20</td>
<td>SA and sedation</td>
<td>Unclear</td>
<td>–</td>
<td>–</td>
<td>27±13</td>
</tr>
<tr>
<td>Rescue opioid</td>
<td>Placebo + rescue opioid</td>
<td>Femoral nerve block</td>
<td>41</td>
<td>SA</td>
<td>Unclear</td>
<td>29.8±14</td>
<td>40±14</td>
<td>38±13</td>
</tr>
<tr>
<td>Chan (2012) 56</td>
<td>Placebo + rescue opioid</td>
<td>3-in-1 femoral nerve block</td>
<td>12</td>
<td>GA</td>
<td>Unclear</td>
<td>42±11</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ng (2001) 70</td>
<td>Placebo + rescue opioid</td>
<td>Intrathecal morphine</td>
<td>15</td>
<td>SA</td>
<td>High</td>
<td>22.8±11.3</td>
<td>43±25</td>
<td>46±22</td>
</tr>
<tr>
<td>Kunopart (2014) 66</td>
<td>Rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>21</td>
<td>SA</td>
<td>Unclear</td>
<td>18.8±8.4</td>
<td>61±21</td>
<td>44±32</td>
</tr>
<tr>
<td>Leownorasate (2014) 67</td>
<td>Rescue opioid</td>
<td>Cont. local infiltration analgesia</td>
<td>17</td>
<td>SA or GA</td>
<td>High</td>
<td>19±13.1</td>
<td>68±10</td>
<td>43±9</td>
</tr>
<tr>
<td>Ong (2010) 5</td>
<td>Rescue opioid</td>
<td>Intraarticular injection</td>
<td>27</td>
<td>SA</td>
<td>Unclear</td>
<td>58.6±27.3</td>
<td>72±21</td>
<td>55±29</td>
</tr>
<tr>
<td>Mauerhan (1997) 68</td>
<td>Placebo + rescue opioid</td>
<td>Transdermal fentanyl patch</td>
<td>20</td>
<td>SA</td>
<td>Unclear</td>
<td>24.9±20.1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sathitkarmmane (2014) 74</td>
<td>Placebo + rescue opioid</td>
<td>IV nefopam or IV ketamine</td>
<td>24</td>
<td>GA</td>
<td>Low</td>
<td>56.8±5.9</td>
<td>41±7</td>
<td>36±6</td>
</tr>
</tbody>
</table>

(To be continued)
opioid and higher pain scores compared with those receiving acetaminophen + opioid (P<0.001).

**Combined interpretation of morphine consumption and pain scores**

Despite statistical significant differences for each outcome, we could not designate a super-

**consistently demonstrated lower pain scores compared to the other control groups.**

For aggregated data of 6- and 24-hour pain scores (THA and TKA), no significant difference in pain intensity was demonstrated between patients that received NSAID + acetaminophen + opioid, and patients that received opioid (P=0.564). Both of these groups had lower pain scores compared with those receiving NSAID + opioid and higher pain scores compared with those receiving acetaminophen + opioid (P<0.001).

**Table II.—Baseline characteristics for included trials investigating total knee arthroplasty (continues).**

<table>
<thead>
<tr>
<th>Total knee arthroplasty</th>
<th>Treatment in control group</th>
<th>Treatment in intervention group</th>
<th>Patients in control group</th>
<th>Anesthesia</th>
<th>Summarized risk of bias</th>
<th>Rescue IV morphine mg (0-24 h)</th>
<th>VAS pain score 1-100 (6 h)</th>
<th>VAS pain score 1-100 (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busch (2006) 55</td>
<td>Rescue opioid</td>
<td>Local infiltration analgesia</td>
<td>32</td>
<td>SA or GA</td>
<td>High</td>
<td>43±9.3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Jacobson (1998) 65</td>
<td>Rescue opioid</td>
<td>Intrathecal diamorphine</td>
<td>7</td>
<td>SA</td>
<td>Unclear</td>
<td>21.5±6</td>
<td>52±40</td>
<td>32±30</td>
</tr>
<tr>
<td>Ozen (2006) 73</td>
<td>Rescue opioid</td>
<td>3-in-1 femoral nerve block</td>
<td>15</td>
<td>GA</td>
<td>High</td>
<td>40.3±11.8</td>
<td>14±15</td>
<td>7±12</td>
</tr>
<tr>
<td>Hirst (1996) 61</td>
<td>Sham femoral nerve block + rescue opioid</td>
<td>Femoral nerve block</td>
<td>11</td>
<td>GA</td>
<td>Unclear</td>
<td>35±23.2</td>
<td>–</td>
<td>29±27</td>
</tr>
<tr>
<td>Edwards (1992) 57</td>
<td>Rescue opioid</td>
<td>3-in-1 femoral nerve block</td>
<td>18</td>
<td>GA</td>
<td>High</td>
<td>30.2±9.7</td>
<td>64±21</td>
<td>56±17</td>
</tr>
<tr>
<td>Badner (1996) 54</td>
<td>Placebo + rescue opioid</td>
<td>Intraarticular injection</td>
<td>27</td>
<td>GA</td>
<td>Unclear</td>
<td>81±30</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Huang (2008) 62</td>
<td>Rescue opioid</td>
<td>Oral celecoxib</td>
<td>40</td>
<td>SA</td>
<td>High</td>
<td>19.7±9.6</td>
<td>74±4</td>
<td>43±3</td>
</tr>
<tr>
<td>Hubbard (2003) 63</td>
<td>Placebo + rescue opioid</td>
<td>IV parecoxib</td>
<td>63</td>
<td>SA</td>
<td>Unclear</td>
<td>43.5±15.9</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Inan (2007) 64</td>
<td>Placebo + rescue opioid</td>
<td>IV lornoxicam</td>
<td>20</td>
<td>GA</td>
<td>Unclear</td>
<td>41±11</td>
<td>17±22</td>
<td>11±15</td>
</tr>
<tr>
<td>Niruthisard (2013) 71</td>
<td>Placebo + rescue opioid</td>
<td>Oral pregabalin</td>
<td>25</td>
<td>SA or GA</td>
<td>Unclear</td>
<td>18.4±15.8</td>
<td>24±22</td>
<td>27±22</td>
</tr>
<tr>
<td>McNamme (2001) 69</td>
<td>Rescue opioid</td>
<td>Femoral and sciatic nerve block</td>
<td>24</td>
<td>SA</td>
<td>Unclear</td>
<td>36±4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Garcia (2010) 58</td>
<td>Placebo + rescue opioid</td>
<td>Intraarticular injection</td>
<td>25</td>
<td>SA</td>
<td>Unclear</td>
<td>20.6±7</td>
<td>80±5</td>
<td>20±15</td>
</tr>
<tr>
<td>Guara Sobrinho (2012) 59</td>
<td>Placebo + rescue opioid</td>
<td>Intrathecal ketamine</td>
<td>20</td>
<td>SA</td>
<td>Unclear</td>
<td>14.5±2.4</td>
<td>55±31</td>
<td>32±28</td>
</tr>
<tr>
<td>Abrisham (2014) 52</td>
<td>Placebo + rescue opioid</td>
<td>Transdermal fentanyl patch</td>
<td>20</td>
<td>GA</td>
<td>Unclear</td>
<td>–</td>
<td>67±16</td>
<td>57±14</td>
</tr>
<tr>
<td>Tugay (2006) 76</td>
<td>Rescue opioid</td>
<td>Femoral nerve block</td>
<td>8</td>
<td>GA</td>
<td>Unclear</td>
<td>45±22</td>
<td>35±24</td>
<td></td>
</tr>
<tr>
<td>Silvanto (2002) 75</td>
<td>Placebo + rescue opioid</td>
<td>IV diclofenac</td>
<td>16</td>
<td>SA</td>
<td>Unclear</td>
<td>–</td>
<td>16±12</td>
<td></td>
</tr>
<tr>
<td>Zhu (2016) 78</td>
<td>Placebo</td>
<td>IV parecoxib</td>
<td>62</td>
<td>GA</td>
<td>High</td>
<td>–</td>
<td>34±12</td>
<td>21±12</td>
</tr>
</tbody>
</table>

Trials are categorized according to basic analgesic treatment. Primary outcomes: Postoperative consumption of rescue opioids and pain scores for the control group are presented as mean±SD. Rescue opioids were converted to IV morphine equivalents. The summarized risk of bias was determined according to Cochrane.

GA: general anesthesia; SA: spinal anesthesia.
HETEROGENIC CONTROL GROUPS IN THA AND TKA TRIALS

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NSAIDs administered as an intervention versus as a basic analgesic treatment

From the review databases, we identified 13 trials that administered NSAID as an intervention for THA and TKA (Table IV). Then, we identified nine trials that administered NSAID in a control group for THA and TKA. The summarized risk of bias for these 22 trials was low in one, unclear in eight, and high in 13 of these trials. Subsequently, we compared pain and opioid requirements from the 13 trials where NSAID was administered as an intervention with the nine trials where NSAID was administered in a control group (Table V, Figure 3).

Discussion

We identified a large variation in the composition of multimodal basic analgesic treat-

Table III.—Subgroup data for primary outcomes.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Rescue opioid</th>
<th>Rescue opioid + NSAID</th>
<th>Rescue opioid + acetaminophen</th>
<th>Rescue opioid + NSAID + acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>THA 0-24 h rescue IV morphine, mg</td>
<td>33.6±24</td>
<td>45.7 mg±44.1</td>
<td>29.7 mg±22.7</td>
<td>20.8 mg±15.5</td>
</tr>
<tr>
<td>N.=593</td>
<td>N.=131</td>
<td>N.=102</td>
<td>N.=215</td>
<td></td>
</tr>
<tr>
<td>6-h VAS pain score 1-100 mm</td>
<td>27±26</td>
<td>60±25</td>
<td>24±23</td>
<td>45±29</td>
</tr>
<tr>
<td>N.=440</td>
<td>N.=56</td>
<td>N.=56</td>
<td>N.=140</td>
<td></td>
</tr>
<tr>
<td>24-h VAS pain score, 1-100 mm</td>
<td>21±20</td>
<td>39±25</td>
<td>12±16</td>
<td>28±24</td>
</tr>
<tr>
<td>N.=472</td>
<td>N.=131</td>
<td>N.=38</td>
<td>N.=215</td>
<td></td>
</tr>
<tr>
<td>TKA 0-24 h rescue IV morphine, mg</td>
<td>36.1±21.8</td>
<td>34.1±21.8</td>
<td>61.2±31.1</td>
<td>42.4±44.5</td>
</tr>
<tr>
<td>N.=504</td>
<td>N.=104</td>
<td>N.=125</td>
<td>N.=196</td>
<td></td>
</tr>
<tr>
<td>6-h VAS pain score 1-100 mm</td>
<td>49±26</td>
<td>46±24</td>
<td>33±26</td>
<td>43±21</td>
</tr>
<tr>
<td>N.=432</td>
<td>N.=128</td>
<td>N.=125</td>
<td>N.=97</td>
<td></td>
</tr>
<tr>
<td>24-h VAS pain score, 1-100 mm</td>
<td>35±23</td>
<td>37±16</td>
<td>17±21</td>
<td>25±16</td>
</tr>
<tr>
<td>N.=442</td>
<td>N.=128</td>
<td>N.=97</td>
<td>N.=137</td>
<td></td>
</tr>
<tr>
<td>Aggregated data for THA and TKA</td>
<td>34.7±23</td>
<td>40.6±36.4</td>
<td>47±31.7</td>
<td>31.1±34.4</td>
</tr>
<tr>
<td>0-24 h rescue IV morphine, mg</td>
<td>N.=1097</td>
<td>N.=235</td>
<td>N.=227</td>
<td>N.=411</td>
</tr>
<tr>
<td>6- and 24-h VAS pain score, 1-100 mm</td>
<td>33±26</td>
<td>43±24</td>
<td>24±24</td>
<td>34±25</td>
</tr>
<tr>
<td>N.=893</td>
<td>N.=222</td>
<td>N.=158</td>
<td>N.=294</td>
<td></td>
</tr>
</tbody>
</table>

Cumulated consumption of rescue opioids and pain scores for subgroups categorized according to basic analgesic treatment for total hip and knee arthroplasty. Aggregated morphine consumption and 6- and 24-h pain scores for are presented. Aggregated number of patients are calculated based on mean number of patients for 6-/24-h measures for each procedure. Data are reported as mean±SD.

Figure 2.—Subgroup data regarding primary outcomes. Cumulated 0-24 morphine consumption and pain scores for subgroups of basic analgesic treatments for both THA and TKA. We demonstrated no consistent trends for a superior basic analgesic treatment. In the upper right corner is a demonstration on the hypothesis-based expected distribution of pain levels amongst subgroups. Values are presented as mean and 95% confidence intervals.

Figure 3.—Subgroup data regarding primary outcomes. Cumulated 0-24 morphine consumption and pain scores for subgroups of basic analgesic treatments for both THA and TKA.
### Table IV.—Baseline characteristics for trials administering NSAIDs as an intervention.

<table>
<thead>
<tr>
<th>Study</th>
<th>Tested intervention</th>
<th>Patients in active group</th>
<th>Anesthesia</th>
<th>Summarized risk of bias</th>
<th>Rescue IV morphine mg (0-24 h)</th>
<th>VAS pain score 1-100 (6 h)</th>
<th>VAS pain score 1-100 (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip arthroplasty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akin (2002)</td>
<td>IM piroxicam 20 mg before and during surgery</td>
<td>40</td>
<td>GA</td>
<td>High</td>
<td>16.3±18.2</td>
<td>6±11</td>
<td>3±6</td>
</tr>
<tr>
<td>Dahl (1995)</td>
<td>Oral ibuprofen 800 mg ×1 immediately postoperative</td>
<td>48</td>
<td>SA</td>
<td>High</td>
<td>–</td>
<td>13±12</td>
<td>–</td>
</tr>
<tr>
<td>Fletcher (1995)</td>
<td>IV ketorolac 60 mg pre/postoperative</td>
<td>40</td>
<td>GA</td>
<td>High</td>
<td>34.3±19.6</td>
<td>25±20</td>
<td>32±24</td>
</tr>
<tr>
<td>Laitinen (1992)</td>
<td>IV diclofenac 75 mg followed by 5 mg/h for 15 h</td>
<td>20</td>
<td>SA</td>
<td>High</td>
<td>–</td>
<td>11±23</td>
<td>8±18</td>
</tr>
<tr>
<td>Malan (2003)</td>
<td>IV parecoxib 20-40 mg ×2</td>
<td>116</td>
<td>SA or GA</td>
<td>High</td>
<td>40.4±30.4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Martin (2007)</td>
<td>IV parecoxib 40 mg ×1-2</td>
<td>41</td>
<td>GA</td>
<td>Unclear</td>
<td>25.5±11.9</td>
<td>17±21</td>
<td>14±23</td>
</tr>
<tr>
<td>Segstro (1991)</td>
<td>Suppository indomethacin 100 mg x4</td>
<td>25</td>
<td>GA</td>
<td>Low</td>
<td>24±12.9</td>
<td>28±10</td>
<td>10±13</td>
</tr>
<tr>
<td>Total knee arthroplasty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huang (2008)</td>
<td>Oral celecoxib 400 mg preoperative and 200 mg ×2</td>
<td>40</td>
<td>SA</td>
<td>High</td>
<td>15.1±8.7</td>
<td>66±3</td>
<td>38±4</td>
</tr>
<tr>
<td>Hubbard (2003)</td>
<td>IV parecoxib 20 mg ×2</td>
<td>126</td>
<td>SA</td>
<td>Unclear</td>
<td>34±18</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Inan (2007)</td>
<td>IV lornoxicam 16 mg before surgery and 8 mg ×2</td>
<td>20</td>
<td>GA</td>
<td>Unclear</td>
<td>26±10</td>
<td>18±14</td>
<td>10±16</td>
</tr>
<tr>
<td>Silvanto (2002)</td>
<td>IV diclofenac 50 mg ×3 or ketoprofen 100 mg ×3</td>
<td>48</td>
<td>SA</td>
<td>Unclear</td>
<td>–</td>
<td>11±13</td>
<td>22±10</td>
</tr>
<tr>
<td>Zhu (2016)</td>
<td>IV parecoxib 40 mg ×2</td>
<td>60</td>
<td>GA</td>
<td>High</td>
<td>25±8</td>
<td>18±8</td>
<td>–</td>
</tr>
</tbody>
</table>

Postoperative consumption of rescue opioids and pain scores for the intervention groups are presented as mean±SD. None of the patients received other basic analgesic treatment. The summarized risk of bias was determined according to Cochrane.

GA: general anesthesia; SA: spinal anesthesia.

### Table V.—Intervention versus basic analgesic treatment with NSAIDs. Consumption of rescue opioids and pain scores for trials administering an NSAID as an intervention versus trials administering an NSAID as a basic analgesic treatment in control groups. Aggregated consumption of rescue opioids and aggregated 6- and 24-hour pain scores are presented.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Rescue opioid + NSAIDs as an intervention</th>
<th>Rescue opioid + NSAIDs as a basic treatment</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip arthroplasty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-24 h rescue IV morphine, mg</td>
<td>27.9±22.5</td>
<td>45.7±44.1</td>
<td>-17.80 [-25.67, -9.93]</td>
</tr>
<tr>
<td>N.=396</td>
<td></td>
<td>N.=131</td>
<td></td>
</tr>
<tr>
<td>6-h VAS pain score 1-100 mm</td>
<td>16±18</td>
<td>60±25</td>
<td>-44.00 [-50.98, -37.02]</td>
</tr>
<tr>
<td>N.=214</td>
<td></td>
<td>N.=56</td>
<td></td>
</tr>
<tr>
<td>24-h VAS pain score, 1-100 mm</td>
<td>14±21</td>
<td>39±25</td>
<td>-25.00 [-30.34, -19.66]</td>
</tr>
<tr>
<td>N.=166</td>
<td></td>
<td>N.=131</td>
<td></td>
</tr>
<tr>
<td>Total knee arthroplasty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-24 h rescue IV morphine, mg</td>
<td>29.1±17.5</td>
<td>34.1±21.8</td>
<td>-5.00 [-9.89, -0.11]</td>
</tr>
<tr>
<td>N.=186</td>
<td></td>
<td>N.=104</td>
<td></td>
</tr>
<tr>
<td>6-h VAS pain score 1-100 mm</td>
<td>30±23</td>
<td>46±24</td>
<td>-16.00 [-21.42, -10.58]</td>
</tr>
<tr>
<td>N.=168</td>
<td></td>
<td>N.=128</td>
<td></td>
</tr>
<tr>
<td>24-h VAS pain score, 1-100 mm</td>
<td>23±13</td>
<td>37±16</td>
<td>-14.00 [-17.40, -10.60]</td>
</tr>
<tr>
<td>N.=168</td>
<td></td>
<td>N.=128</td>
<td></td>
</tr>
<tr>
<td>Aggregated data for THA and TKA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-24 h rescue IV morphine, mg</td>
<td>27.7±21.1</td>
<td>40.6±36.4</td>
<td>-12.90 [-17.85, -7.95]</td>
</tr>
<tr>
<td>N.=597</td>
<td></td>
<td>N.=235</td>
<td></td>
</tr>
<tr>
<td>6- and 24-h VAS pain score, 1-100 mm</td>
<td>20±22</td>
<td>43±24</td>
<td>-23.00 [-26.99, -19.01]</td>
</tr>
<tr>
<td>N.=314</td>
<td></td>
<td>N.=222</td>
<td></td>
</tr>
</tbody>
</table>

Data are reported as mean±SD, if not otherwise specified.
Interpretation of subgroup analysis

We observed no consistent differences in morphine consumption or pain scores between control groups receiving NSAID, acetaminophen and opioid, alone or in combination. Thus, we could not confirm our hypothesis, that different, mono- or multimodal analgesic regimens in control groups from different RCTs would demonstrate relevant differences and additive effects in morphine requirements and pain intensities.

When reviewing the published literature, the multimodal analgesic approach is a widely accepted paradigm, which has just recently been supported by evidence from a large systematic review with network meta-analysis. Specific mono-analgesic treatments with NSAIDs or acetaminophen have been investigated in a number of RCTs and meta-analyses, with a broad consensus that both analgesics are superior to placebo. One review demonstrated superior effects of NSAIDs compared to acetaminophen, but with the disadvantage of a higher risk of adverse events, whereas comparable analgesic effects of the analgesics were demonstrated in two other reviews.

However, in our study the distribution of pain levels seemed unrelated to the basic analgesic treatment. Despite the limitations of this study (primarily large distribution of standard deviations), the results calls for high quality upscale RCTs that investigate the separate- and additive effects of different, non-opioid analgesic treatments.

We also observed that patients receiving an NSAID as an active intervention had lower morphine requirements and pain levels, compared with patients in control groups that received equal doses of an NSAID as a basic analgesic treatment. This finding may in part be explained by bias in the included trials. Lack of, or insufficient blinding of participants and personnel (which was demonstrated in the two original systematic reviews for a large number of the included trials), will typically degrade the placebo effect, as patients and clinicians may recognize the nature of the placebo treatment. Therefore, patients in these trials may
have lower expectancy towards the treatment effect, and thereby a tendency towards higher perceived pain levels reflected in higher pain scores and opioid requirements. This has been demonstrated in other fields of musculoskeletal pain, such as lower back pain trials.

For the subgroup analysis data were missing for morphine consumption in 14% of trials, for 6-hour pain scores in 28%, and for 24-hour pain scores in 23%. Thirty-two percent of included trials reported only one of the outcomes, morphine consumption or pain scores, in a way that was compatible to our analysis. This outlines that global consensus-driven standardization of outcome reporting would benefit both meta-analyses and analyses like the present.

**Strengths and limitations of the study**

This pre-protocolled analysis is based on an extensive amount of original literature and was conducted in a systematic approach. In spite of the procedure-specific nature of the review, trials displayed heterogeneity in outcomes possibly due to factors such as cultural differences, specific hospital settings, accepted level of pain, and baseline characteristics. The included RCTs were generally characterized by high risk of bias, which reduces the strength of the results. Most often, sample sizes were small inducing a risk of overestimated intervention effects and maybe of affecting baseline pain levels, although this has not been investigated. We included studies from two reviews with inclusion criteria sensitive to provide an exhaustive list of RCTs in the search periods. It is a limitation that we did not update the original search for THA from August 22nd, 2014 to September 9th, 2016.

We allowed aggregation of THA and TKA data, because mean pain levels and opioid consumptions in the control groups of the two reviews that forms the basis of the present analyses were similar to an agreeable extend (6-hour pain scores at rest: 31 and 38 mm, 24-hour pain at rest: 23 and 33 mm, and 0-24-hour IV morphine consumption: 31 and 33 mg, for THA and TKA, respectively).

For this investigation we used the most frequent reported outcomes in RCTs regarding immediate postoperative pain. Only limited data were available after the first 24 hours. The opioid sparing effect and pain scores were presented as median and interquartile range in some of the included trials, indicating a non-parametric distribution. Also, the large distribution of standard deviations for the aggregated means indicate large inter-individual variability and reduces the robustness of the results. For analyses, it was necessary to convert these results to mean and standard deviation. Further, it was necessary to convert different opioids to IV morphine equivalents. Although these conversions were done by validated methods, it may have caused imprecision of the results of the review.

**Conclusions**

For RCTs investigating postoperative pain management after THA or TKA, control groups revealed major heterogeneity in basic analgesic treatment. Different control groups receiving basic analgesic treatment with either opioids, NSAIDs and/or acetaminophen or no basic treatment, did not differ consistently regarding postoperative pain levels and opioid consumptions. Further, active-groups that received NSAID as an intervention displayed lower pain scores and opioid requirements compared with control groups that received NSAID as a basic analgesic treatment.

**Key messages**

— Control groups in randomized, controlled trials of postoperative pain management are heterogenic regarding basic analgesic treatment, opioid consumption and pain scores.

— Pain levels and opioid consumption in control groups of postoperative pain management trials did not consistently correlate to basic analgesic treatment (opioids, NSAIDs and/or acetaminophen or no basic treatment).
— When active groups received NSAIDs as an intervention, they displayed lower pain scores and opioid requirements, than did control groups receiving comparable NSAID treatment as basic analgesic treatment.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.


For supplementary materials, please see the online version of this article at www.minervamedica.it.
Epidemiology of septic meningitis associated with neuraxial anesthesia: a historical review and meta-analysis

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ABSTRACT

INTRODUCTION: Neuraxial anesthesia in the form of spinal and epidural are two of the most frequent forms of regional anesthesia. We aimed to describe and compare the relevant epidemiological, clinical and microbiological characteristics of all reported cases of septic meningitis associated with the use of spinal and epidural anesthetics.

EVIDENCE ACQUISITION: We performed a systematic review of septic meningitis associated with neuraxial anesthesia. We included all relevant case-reports and observational studies in which authors described septic meningitis in association with spinal, epidural or combined neuraxial anesthesia using local anesthetics.

EVIDENCE SYNTHESIS: A total of 234 cases of septic meningitis were reported following review of 71 case-report articles and 22 epidemiological studies. In total, there have been 199, 25 and 10 reported cases of septic meningitis associated to spinal, epidural and combined neuraxial anesthesia, respectively. The lack of use of surgical masks was the most common risk factor (41, 16.7%). Streptococcus salivarius was the most common bacteria (17.0%) related to spinal anesthesia and Staphylococcus aureus (26.7%) was the most common one related to epidural. The time to symptom onset was significantly reduced in spinal (median time, 24 hours IQR [8-72] vs. 96 hours IQR [84-240]; P=0.003) compared to epidural anesthesia. The overall mortality rate is 15.3% and 13.3% for reported cases related to spinal and epidural anesthesia, respectively.

CONCLUSIONS: While the true incidence remains speculative, this review suggests that given increasing indications for spinals and epidurals, septic meningitis remains an important associated with neuraxial anesthesia.

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Key words: Anesthesia, spinal - Anesthesia, epidural - Anesthesia, conduction - Anesthesiology - Meningitis - Infection.

Introduction

Septic meningitis is considered a rare but serious infection wherein a pathogen crosses the blood-brain barrier, thereby leading to meningitis. Depending upon the virulence of the specific microorganism, the patient comorbidities and the detection or treatment methods involved, septic meningitis carries high risk of long term neurologic impairment and substantial mortality. ¹ Regional anesthesiologists
designed to directly penetrate the blood-brain barrier such as spinal or epidural techniques, offer a unique opportunity for pathogens to gain direct access to the leptomeninges. Given the invasive nature of these procedures and their growing list of indications, which include abdominal, obstetric and orthopedic procedures, it may be surprising that more cases of septic meningitis are not reported.2

Prior to 2005, there were only two major reviews that summarize the global occurrence of septic meningitis associated with spinal and epidural anesthesia.2,3 Since that time advancements in spinal and epidural needle and kit design, knowledge of aseptic technique and barrier precautions and the potential for alterations in the global microbial profile have provided an opportunity to perform a contemporary evaluation of the infectious risk of these two regional techniques and additionally describe clinical and microbiological data in more detail. To that end, our group conducted a historical review of the literature to investigate the available evidence and provide a consolidated account of both the clinical frequencies and reported incidence of septic meningitis after spinal and epidural anesthesia. By writing this article we hope to increase awareness of the risk of meningitis in efforts to decrease this serious infectious complication of regional anesthesia.

Evidence acquisition

We conducted this systematic review in accordance with recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.4 The protocol for this review has been registered at PROSPERO International Prospective Register of Systematic Reviews (no. CDR42015027296).

Search strategy and selection criteria

The available literature was systematically searched within six main electronic databases (PubMed, EMBASE, Literature of Latin America and Caribbean [LILACS], Scopus, Cochrane Library, Google Scholar, ISI Web of Science) to identify all articles reporting the association of septic meningitis in spinal, epidural and combined spinal-epidural (CSE) anesthesia from database inception to December of 2015. The electronic search strategy used the terms “meningitis,” “bacterial meningitis,” “septic meningitis,” “meningocerebralitis” and the combination of each term with the terms “spinal anesthesia,” “epidural anesthesia,” “peridural anesthesia,” and “subarachnoid anesthesia.” The search strategy was translated in accordance with appropriate database Boolean operators. We also searched all cross-references for articles not captured in our initial search strategy. There was no restriction on study design and therefore our search included case reports, case series, retrospective and prospective studies. Publications were excluded if they did not assess the association between septic meningitis and neuraxial anesthesia. Other infectious complications associated with spinal and epidural anesthesia, such as the intradural or epidural abscesses, subdural empyema, discitis, osteomyelitis, and spondylitis were not reviewed in this paper. There were no language restrictions.

For the purposes of this review, septic meningitis was defined as: 1) presence of neurological findings including nuchal rigidity, headache, photophobia, and/or altered mental status as well as 2) elevated cerebrospinal fluid (CSF) white blood cell count (WBC/mL), preponderance of polymorphonuclear cells (PMN%) and/or positive CSF culture. The lack of positive culture did not preclude formal diagnosis given the potential for periprocedural or treatment-specific antimicrobials present at the time of diagnosis.

Data extraction

The title and abstract were screened by two reviewers (A.Z.V. and R.H.) independently for inclusion criteria. The full texts of the selected articles were retrieved and each reference list was screened to identify additional publications that were excluded in the initial search. Any discrepancies in the selected studies were resolved by consensus of two addi-
tional reviewers (M.M. and L.R.L.). Selected articles were stratified into two groups: 1) case reports or case series, in which incidence rates were not provided so we only used this type of articles to count the absolute frequency of septic meningitis (single cases and outbreak investigation studies); and 2) epidemiological studies, including prospective and retrospective studies in which incidence rates of septic meningitis associated with spinal or epidural anesthesia were estimated (these articles were the unique articles used to calculate the pooled incidence of septic meningitis). Data was obtained from group 1 when available, including sociodemographic information such as age, sex, country, and region as defined by the World Health Organization, clinical information such as the type of anesthetic, time to onset of symptoms of meningitis, CSF data such as WBC/mL, PMN%, culture data, the indication for procedure, the outcome, and the time to recovery or death. Lastly, microbiological information, such as the microorganism isolated and the suggested method for inoculation, was extracted. Similarly, data was obtained from group 2, including the country, the study time frame, the number of technique specific anesthetics, the number of cases of septic meningitis, and the reported incidence rate (per 100,000 spinal or epidural anesthetics).

Quality appraisal

There are no accepted criteria for assessing quality of case reports. Studies included in group 2 were assessed based upon the presence of a clear and consistent diagnosis of septic meningitis and associated comorbidities. High risk of bias was considered either when the diagnosis was inconsistent or incomplete or when ten percent or more of the data were missing.

Statistical analysis

Descriptive data of quantitative variables were presented as pooled mean with standard deviation (SD) or as pooled median with interquartile range (IQR, 25-75%), depending on the data distribution. Qualitative data of nominal variables were presented as frequency with percentage. Patients were grouped based on the type of anesthesia (i.e., spinal or epidural anesthesia). To obtain the incidence rate of septic meningitis after spinal or epidural anesthesia, we added all of the cases from the second section and divided that number by the total number of spinal or epidural anesthesia performed in the time interval of the study. This process was done for each year, beginning in 1952, allowing us to create an observable trend. Using the statistical software Stata version 13 (Stata, College Station, TX USA), we constructed box plots were constructed to visually observe the significant difference from the bivariate analysis. In addition, patients were grouped based on the recovery status (full or partial recovery versus death) after meningitis and compared to the type of regional anesthesia (spinal, epidural or combined) using the Kaplan-Meier survival method. For patients with complete or partial recovery, the Pearson correlation coefficient was calculated to examine the relationship between age and the reported follow-up interval. Additionally, we use Spearman correlation coefficient to assess the correlation between the reported incidence rates and the years. To estimate a meta-analyzed incidence rate we could only use studies between 1990 and 2015, which obtained an incidence of more than 0 cases per 100,000 anesthesia. Meta-regression analysis was used to determine the linear trend of incidences reported along the past century. All meta-analysis statistical procedures were performed using the Stata software, version 13.0.

Evidence synthesis

Literature search results

The electronic search yielded 18,199 total citations. After the exclusion of 878 duplicates and 16,630 articles based upon predetermined criteria, 691 studies remained. Subsequent full-text screening resulted in the exclusion of an additional 609 articles (Figure 1), resulting in 89 articles. Review of cross-references revealed that additional four articles were missed in the initial search strategy.
more than 30% missing data were typically cases reported as part of large epidemiologic studies. We excluded 98 cases due to the high risk of bias and low level of documented evidence from a large outbreak in Bangladesh. In that outbreak there were only 21 cases described in detail.

**Overall impact of septic meningitis related to regional anesthesia**

There were 234 cases of septic meningitis related to neuraxial anesthesia. In total, 26 deaths were reported and nine patients suffered residual medical or neurological impairment. The greatest number of reported cases was from Europe (113, 48.3%), followed by South-East Asia (52, 22.2%), Eastern Mediterranean (33, 14.1%) and the Americas (33, 14.1%). In 114 (61%) cases, CSF cultures grew at least one pathogen, of which Gram positive bacteria were the most common microorganism isolated (i.e., *Streptococcus* spp., *Staphylococcus* spp., *Enterococcus* spp., diphtheroids) with 74 isolates (64.9%), gram negative bacteria were present in 30 isolates (26.3%) and *Aspergillus* spp. was reported as the causative agent in 10 patients (8.8%).

**Septic meningitis associated with spinal anesthesia**

Up to 2015, a total of 199 patients have been reported to have septic meningitis associated with spinal anesthesia among 48 case-report cases.

Of the 93 publications that met the inclusion and exclusion criteria for data extraction and final analyses, 71 publications were either single case reports (59, 83%), case-series (5, 7%) or outbreak investigation reports (7, 10%) and 22 publications were epidemiologic studies that estimated the incidence of septic meningitis after either spinal anesthesia (N.=19) or epidural anesthesia (N.=5) procedures.

**Quality assessment**

All case reports included had a correct diagnosis after taking into consideration other similar entities such as the aseptic meningitis, postdural headache, idiopathic meningitis and chemical meningitis. The median percentage of missing data in the articles included was 20% (lack of clinical variables such as CSF or microbiological data). In 147 cases, missing data did not exceed 30%; those suffering

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**Figure 1**—PRISMA flow chart of the selection of studies. See “Methods” and “Results” for details for search strategies and excluded references.

**Figure 2**.—Worldwide distribution of the cases of septic meningitis associated with regional anesthesia.

*Countries with internal points have no reports of meningitis cases related to regional anesthesia.*
articles (Supplemental Digital Content), and 19 large epidemiologic studies. The cases were reported from 24 widely distributed countries (Figure 2, Appendix I): including India (25, 12.6%), Sweden (24, 12.1%), Bangladesh (21, 10.6%), Egypt (18, 9%), Turkey (14, 7%), and the USA (13, 6.5%). Table I outlines the age, gender and other relevant demographic information for reported cases of septic meningitis. The median age was 32 years old (IQR, 26-42 years) and 64% were female patients. The frequency of septic meningitis from spinal anesthesia was most common in obstetrical (66, 45.8%) and orthopedic surgeries (28, 19.4%). Survival outcome was reported in 157 patients (56 articles), of which

| Table I.—Sociodemographic and clinical data of the reported septic meningitis related to spinal, epidural and combined anesthesia. |
|---|---|---|
| Variable | Spinal anesthesia (N=199) | Epidural anesthesia (N=25) | Combined anesthesia (N=10) |
| Articles (N=67), N. (%) | Value | Articles (N=16), N. (%) | Value | Articles (N=10), N. (%) | Value |
| Median age, a years [IQR] | 40 (72.7) 32 [26-42] | 13 (81.3) 46 [22-77] | 9 (90) 32 [19-39] |
| Female sex, b N. (%) | 43 (78.2) 71 (64.0) | 13 (81.3) 12 (80.0) | 8 (80) 8 (88.9) |
| WHO region, c N. (%) | Europe 37 (55.2) 40 (52.5) | Americas 9 (13.4) 24 (12.1) | Eastern Mediterranean 7 (6.4) 32 (16.1) | South-Eastern of Asia 4 (6) 51 (25.6) | Western Pacific 1 (1.5) 1 (0.5) | Africa 1 (1.5) 1 (0.5) |
| Procedure indication, d N. (%) | Obstetrical analgesia 20 (29.9) | Orthopedic 18 (26.9) | Urologic 9 (13.4) | Herniorrhaphy 8 (11.9) | Hemorroidectomy 4 (6) | Vascular 4 (6) | Appendicectomy 2 (3) | Other 5 (7.5) |
| Median WBC/mL, [IQR] | 37 (67.3) | 1,659 [669-6,755] | 10 (62.5) | 24 (19.4) | 8 (50.0) | 5 (3.5) | 3 (18.8) | 3 (18.8) |
| Median PMN%, [IQR] | 37 (67.3) | 1,659 [669-6,755] | 10 (62.5) | 24 (19.4) | 8 (50.0) | 5 (3.5) | 3 (18.8) | 3 (18.8) |
| Symptoms onset (hours), f median [IQR] | 41 (74.6) | 24 [8-72] | 10 (66.7) | 96 [84-240] | 8 (88.9) | 17 [14-36] |
| Outcome, g N. (%) | Recovery 40 (59.7) | Partial recovery 7 (10.4) | Death 9 (13.4) |

* IQR, interquartile range; WHO, World Health Organization; CSF, cerebrospinal fluid; PMN, polymorphonuclear leukocytes; WBC, white blood cells; only included in the analysis: 107 results for spinal cases, 15 results for epidural, and 9 results for combined cases; only included in the analysis: 111 results for spinal cases, 15 results for epidural, and 8 results for combined cases; only included in the analysis: 199 results for spinal cases, 25 results for epidural, and 9 results for combined cases; only included in the analysis: 144 results for spinal cases, 16 results for epidural, and 9 results for combined cases; only included in the analysis: 128 results for spinal cases, 13 results for epidural, and 8 results for combined cases; only included in the analysis: 123 results for spinal cases, 15 results for epidural, and 8 results for combined cases; only included in the analysis: 157 results for spinal cases, 15 results for epidural, and 10 results for combined cases.
125 (79.6%) had full recovery, 8 (5.1%) had partial recovery, and 24 died yielding a mortality rate of 15.3% (95% confidence interval [CI] 9.7-20.5%).

Of the 53 articles summarizing 162 patients with microbiological information, only 97 (59.9%) samples of CSF grew pathogens (Table II).5-21, 23-29, 32, 34-39, 41-51, 67, 69, 72, 89 The most common microorganism cultured was *Streptococcus salivarius* (26, 16.0%), followed by *Serratia marcescens* (13, 8.5%) and *Pseudomonas* spp. (16, 9.9%). Sixty-five cultures showed no microorganism growth. In 20 of these patients (13.1%) the diagnosis was approached by molecular methods, including polymerase chain reaction (PCR), and in the other 34 patients (22.2%) analysis of WBC and PMN data in cerebrospinal fluid (CSF) provided the formal diagnosis. It is important to note that most of the articles reporting CSF data and PCR results were published in the last two decades and came from developed countries.

A suspected risk factor for inoculation was documented in 89 cases (44.7%); the most common being the potential lack of aseptic precautions, including the failure to use surgical masks (39, 19.6%), contamination of needles (19, 9.5%), poor hand hygiene (19, 6.6%), and multiple use of vials (8, 4%). Other risk factors included preexisting bacteremia (2, 1%),8, 86 post-tsunami effect (5, 2.5%),19 and others as summarized in Appendix II.

There has been a positive linear trend of the number of reported cases related to spinal anesthesia over the last two decades ($r=0.683$, $P<0.001$) (Table III; Figure 3A).

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Spinal anesthesia (N.=199)</th>
<th>Epidural anesthesia (N.=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Articles, (ref)</td>
<td>Case-patients (N.=162) reported, N. (%)</td>
</tr>
<tr>
<td>Not growth</td>
<td>5, 11, 17, 18, 24, 27, 38, 41, 42, 44, 46, 75, 76</td>
<td>65 (40.1)</td>
</tr>
<tr>
<td>Gram positive bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulase-positive <em>Staphylococcus</em></td>
<td>24, 29, 38</td>
<td>6 (3.7)</td>
</tr>
<tr>
<td>Coagulase-negative <em>Staphylococcus</em></td>
<td>8, 29</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td><em>Streptococcus salivarius</em></td>
<td>13, 15, 21, 23, 25, 26, 32, 34-37, 39, 42, 44, 51, 82</td>
<td>26 (16.0)</td>
</tr>
<tr>
<td>S. mitis</td>
<td>9, 24, 44, 49</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>S. sanguis</td>
<td>10, 48</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>6, 67</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>S. viridans</td>
<td>74</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>S. oralis</td>
<td>43, 85</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>S. bovis</td>
<td>67</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>S. agalactiae</td>
<td>86</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>S. vestibularis</td>
<td>7</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>S. cremoris</td>
<td>44</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>S. uberis</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S. milleri</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>Streptococcus spp.</em></td>
<td>69</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>14, 47</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>Corynebacterium xerosis</td>
<td>50</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>28</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Bacillus spp.+<em>Aspergillus</em> spp.*</td>
<td>19</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Abiotrophia detectiva</td>
<td>45</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Gram negative bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>16, 20</td>
<td>13 (8)</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.*</td>
<td>12, 24, 38, 72</td>
<td>16 (9.9)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>73</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Fungi</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Aspergillus</em> spp.*</td>
<td>19, 38</td>
<td>10 (6.2)</td>
</tr>
</tbody>
</table>

*Microorganisms isolated in mortalities.
Figure 3.—Epidemiology of cases reported of septic meningitis related to spinal, epidural and combined anesthesia world-wide, 1900-2015. A) The absolute frequency of septic meningitis related to spinal (dark), epidural (gray), and combined (light color) anesthesia each year; B) represents the cumulative frequency (continuous curve which correspond to the right vertical axis) and incidence rate per year (dashed curve which correspond to the left vertical axis) of septic meningitis associated with spinal anesthesia.
Septic meningitis associated with epidural anesthesia

Through 2015, a total of 25 cases of septic meningitis have been reported among 16 articles (Supplemental Digital Content). The majority of cases were published as case report articles (11, 68.8%) and five cases of septic meningitis (31.3%) among epidemiologic studies (Table IV).65, 66, 69, 90

Outcome was assessed in 15 cases of septic meningitis related to epidural anesthesia, of which 12 cases (80%) had full recovery, one (6.7%) had partial recovery, and two died, resulting a mortality rate of 13.3%. There were two suspected risk factors reported: preexisting bacteremia prior to the procedure and poor hand hygiene. Microbiological data was available in 12 out of 15 cases.

The most common microorganism isolated from CSF culture was Staphylococcus aureus (4, 26.7%), and there was a more limited variety of pathogens compared to spinal anesthesia (Table II).

A positive linear trend in the number of reported septic meningitis cases associated with epidural anesthesia published over time was observed (Table IV and in Figure 3A [gray area]) (r=0.372, P=0.002). Based upon the pooled data from epidemiological studies, the incidence of septic meningitis associated with epidural anesthesia is 0.9 cases (95% CI: 0.3-1.5 cases) per 100,000 epidural anesthesia.

**Table IV.**—Large studies describing incidence of septic meningitis associated to epidural anesthesia/analgesia.

<table>
<thead>
<tr>
<th>Study, ref</th>
<th>Interval time of the study</th>
<th>Country</th>
<th>Epidural anesthesias</th>
<th>Case-patients with septic meningitis</th>
<th>Incidence rate of septic meningitis, per 100,000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palot et al., 1994,90</td>
<td>1988-1992</td>
<td>France</td>
<td>288,351</td>
<td>3</td>
<td>1 (0-2.2)</td>
</tr>
<tr>
<td>Auroy et al., 2002,65</td>
<td>1998-1999</td>
<td>France</td>
<td>35,293</td>
<td>1</td>
<td>2.8 (0-8.4)</td>
</tr>
<tr>
<td>Vernis et al., 2004,91</td>
<td>2004†</td>
<td>France</td>
<td>59</td>
<td>0</td>
<td>0 (NA)</td>
</tr>
<tr>
<td>Moen et al., 2004,66</td>
<td>1990-1999</td>
<td>Sweden</td>
<td>450,000</td>
<td>5</td>
<td>1.1 (0.1-2.1)</td>
</tr>
<tr>
<td>Pitkanen et al., 2013,69</td>
<td>2000-2009</td>
<td>Finland</td>
<td>185,000</td>
<td>1</td>
<td>0.5 (0-1.6)</td>
</tr>
<tr>
<td>Overall incidence rate</td>
<td>-</td>
<td>-</td>
<td>958,703</td>
<td>10</td>
<td>1.0</td>
</tr>
<tr>
<td>Pooled estimate‡ (95% CI)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.9 (0.3-1.5)</td>
</tr>
</tbody>
</table>

ND: not described.
†Year of publication, it is not the interval time of the study because it was not described in the publication; ‡include only the large studies with more than hundred epidural anesthesia.
**Septic meningitis associated with CSE anesthesia**

Through 2015, a total of 10 case reports of septic meningitis associated with CSE were noted (Supplemental Digital Content).²⁹⁻¹⁰⁰ Our search did not yield a single epidemiological study assessing the incidence of this complication after CSE anesthesia.

Microbiological data was obtained in all 10 cases. *Streptococcus salivarius* was isolated in two cases (20%), with non-hemolytic *Streptococcus* and *Staphylococcus epidermidis* isolated in one case apiece. The six additional cases resulted in negative CSF culture results (Table II). All but one case reported on formal CSF analysis, with the median WBC level of 5,055 leukocytes/mL (IQR 3,240–5,700), and the predominance of polymorphonuclear cells (median PMN 88.5%, IQR 83–92%). In all cases, patients made full recovery.

There were fewer cases of meningitis related to CSE published over time (Table III and Figure 3A [light area]), as compared to the spinal or epidural anesthesia. There has been a significant linear decline in the reported number of cases over that same time frame (*r*=-0.159, *P*=0.04).

**Clinical characteristics between cases of septic meningitis associated with neuraxial anesthesia**

**Symptom onset and recovery time**

The onset of neurologic symptoms was significantly faster in association with spinal anesthesia (median 24 hours, IQR 8–72) compared to cases associated with epidural anesthesia (median 96 hours, IQR 84–240 hours), *P*=0.003 (Figure 5). We found no significant difference in the time to recovery between meningitis cases associated with spinal or epidural anesthesia (*P*=0.072; Figure 6).

**Discussion**

**Summary of findings**

To our knowledge, this is the first article to summarize the available evidence surrounding septic meningitis associated with the provision of neuraxial anesthesia. According to our results: 1) early data was available in the form of only case-reports or limited case series with individual cases of septic meningitis being both widely distributed and affecting diverse patient populations; 2) there has been a significant linear increase in the number of reported cases over time (Table III and Figure 3A [light area]), as compared to the spinal or epidural anesthesia. There has been a significant linear decline in the reported number of cases over that same time frame (*r*=-0.159, *P*=0.04).
cases of septic meningitis after neuraxial anesthesia with a pooled incidence rate of around 1.1 and 0.9 cases per 100,000 spinal and epidural anesthetics respectively.

Our estimates suggest an annual increase of 0.7 reported cases of septic meningitis per one million neuraxial anesthetics performed over the reviewed timeframe in this study. This observed increase may have several explanations. Over the intercedent period, there have been considerable modifications in consensus definition of septic meningitis, diagnostic advancements in laboratory analysis, and alterations in both reporting metrics and provider awareness. In addition, there has been a considerable expansion in the indications for neuraxial anesthesia and the broader incorporation of the varied techniques into formal clinical education. Lastly, reimbursement has started to become tied to rates of hospital associated infection, providing further reason for more heightened and uniform surveillance practices. Given these factors, it is certainly possible that the true incidence of septic meningitis associated with neuraxial anesthesia has remained unchanged while reporting has substantially increased.

What appears to be true is that the methodology for reporting has become more robust. All included epidemiological studies were dated towards the latter portion of the 1900’s, whereas prior study was limited to almost exclusively case-reports. Based upon a pooled analysis of these epidemiological studies, the incidence of septic meningitis associated with spinal anesthesia differed substantially from previous published estimates. In a 2008 review by Schulz-Stubner et al., data from nine epidemiological studies reported an incidence rate of 3.7 cases per 100,000 spinal anesthesia, well above the rate of 1.1 cases per 100,000 spinal anesthetics we found over the last twenty-five years (95% CI: 0.8-1.8 cases). While the reason for the discrepancy between these findings is not clear, it may be due to interval improvement in procedure-specific barrier precautions, aseptic skin preparation and general provider awareness.

While a number of included studies failed to identify a perceived risk factor for acquiring meningitis, the largest percentage of those reported outlined basic sterile precautions associated with the procedure itself and curiously older case reports tended to report such risk factors indicating the real social impact of the problem. Interestingly, we noted a relative delay in symptom onset for cases associated with epidural anesthesia compared to spinal counterparts. This introduces consideration of an alternative source of inoculation based upon the use of indwelling catheters, which are commonly associated with epidural technique. While providers often employ sterile precautions upon insertion, similar strategies may not be universally observed upon repeatedly accessing long term epidural catheters. Overall the relatively low percentage of reporting of specific risk factors suggests that there may remain substantial barriers to effective evaluation of this important complication.

There are distinct differences between the virulence of the two most common pathogens observed in spinal and epidural anesthesia, Streptococcus salivarius and Staphylococcus aureus. While S. salivarius is a commensal and indigenous microorganism usually present in the oral cavity and typically not considered a primary pathogen in surgical procedures, S. aureus is frequently isolated from surgical site infections and likely originates from the patient’s own skin colonization. Simply identification of these two seemingly unrelated organisms among those most commonly isolated in this patient population suggests multiple primary methods for inoculation. As previously stated, S. salivarius can arise from inappropriate use of barrier precautions in the form of face masks, S. aureus is more likely to result from improper site cleansing, underuse of procedure drapes, multiuse vials, and repeated catheter site exposure.

Certainly, reports of streptococci as the causative bacteria of many septic meningitis cases following regional anesthesia suggests that droplets play an important role in transmission from the oropharynx to the CSF. Such evidence would lend support for the use of surgical masks. Many institutions sup-
port the use of surgical masks including but not limited to the the Healthcare Infection Control Practices Advisory Committee (HIPAC) and the Centers for Disease Control and Prevention (CDC) increased their efforts against this type of complications. In 2006 the American Society of Regional Anesthesia and Acute Pain Medicine (ASRA) also started to recommend the use of surgical masks. Our study also observed that fungi were more likely a causative factor in catastrophic situations (e.g., tsunami), and gram-negative bacteria in situations of multiple-use practices.

Conclusions

While the true incidence remains speculative (1.1 cases per 100,000 cases), this review suggests that given increasing indications for spinals and epidurals, septic meningitis remains an important complication associated with neuraxial anesthesia. This review serves to outline the available information regarding both the reported incidence and clinical characteristics of septic meningitis associated with neuraxial anesthesia. Clearly, the available literature has improved substantially in this area after being isolated to simple case-reports early on and evolving into large epidemiological analysis. Given the greater acceptance and application of both spinal and epidural anesthesia, heightened awareness of this serious complication is important. Diffusion of historical lessons like the one presented in this review only serve to further promote advancement in the quality of care delivered to patients.

Key messages

— In total 234 cases of septic meningitis associated with neuraxial anesthesia have been reported since the introduction of this anesthetic technique.
— Streptococcus salivarius and Staphylococcus aureus were the most common bacteria related to spinal and epidural anesthesia respectively.
— Overall incidence of septic meningitis is 1.1 cases (0.7-1.5) per 100,000 spinal anesthetics, within an annual increase of 0.7 reported cases of meningitis per 1 million spinal anesthetics.
— Septic meningitis remains an important and possibly underrepresented complication associated with neuraxial anesthesia.
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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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### Appendix

**APPENDIX I.**—Geographic distribution of septic meningitis after regional anesthesia (spinal, epidural and combined) reported in the literature between 1900-2015.

<table>
<thead>
<tr>
<th>Country</th>
<th>Spinal anesthesia (N.=199)</th>
<th>Epidural anesthesia (N.=25)</th>
<th>CSE anesthesia (N.=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indian</td>
<td>25 (12.6%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sweden</td>
<td>24 (12.1%)</td>
<td>5 (20%)</td>
<td>-</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>21 (10.6%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Egypt</td>
<td>18 (9%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Turkey</td>
<td>14 (7%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>USA</td>
<td>13 (6.5%)</td>
<td>5 (20%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Finland</td>
<td>11 (5.5%)</td>
<td>1 (4%)</td>
<td>-</td>
</tr>
<tr>
<td>Israel</td>
<td>10 (5%)</td>
<td>1 (4%)</td>
<td>-</td>
</tr>
<tr>
<td>Spain</td>
<td>10 (5%)</td>
<td>2 (8%)</td>
<td>-</td>
</tr>
<tr>
<td>France</td>
<td>8 (4%)</td>
<td>5 (20%)</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>7 (3.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>UK</td>
<td>7 (3.5%)</td>
<td>-</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Cuba</td>
<td>7 (3.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sri-Lanka</td>
<td>5 (2.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Romania</td>
<td>4 (2%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tunisia</td>
<td>4 (2%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Brazil</td>
<td>3 (1.5%)</td>
<td>-</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Germany</td>
<td>2 (1%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Australia</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bosnia</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Canada</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hungary</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pakistan</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Poland</td>
<td>-</td>
<td>4 (16%)</td>
<td>-</td>
</tr>
<tr>
<td>Senegal</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Singapore</td>
<td>-</td>
<td>1 (4%)</td>
<td>-</td>
</tr>
<tr>
<td>Denmark</td>
<td>-</td>
<td>1 (4%)</td>
<td>-</td>
</tr>
<tr>
<td>Korea</td>
<td>-</td>
<td>-</td>
<td>1 (10%)</td>
</tr>
</tbody>
</table>

CSE: combined spinal-epidural anesthesia.

**APPENDIX II.**—Risk factors related to the cases of septic meningitis after regional anesthesia (spinal, epidural and combined) reported between 1900-2015.

<table>
<thead>
<tr>
<th>Factor reported</th>
<th>Spinal anesthesia (N.=199)</th>
<th>Epidural anesthesia (N.=25)</th>
<th>CSE anesthesia (N.=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not found</td>
<td>110 (55.3%)</td>
<td>23 (92%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Lack of surgical masks usage</td>
<td>39 (19.6)</td>
<td>-</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Contamination of needles</td>
<td>19 (9.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Inadequate aseptic technique*</td>
<td>13 (6.5%)</td>
<td>1 (4%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Contamination of drug batches or saline bottles</td>
<td>7 (3.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Previous bacteremia</td>
<td>2 (1%)</td>
<td>1 (4%)</td>
<td>-</td>
</tr>
<tr>
<td>Multiple use of vials or solutions contaminated</td>
<td>8 (4%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Repeated attempts</td>
<td>1 (0.5%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Skin colonization</td>
<td>-</td>
<td>-</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Extradural blood patch</td>
<td>-</td>
<td>-</td>
<td>1 (10%)</td>
</tr>
</tbody>
</table>

*Lack of aseptic precautions on the puncture site, sterilization of equipment or poor hand hygiene.*
Rational approach to transfusion in liver transplantation

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ABSTRACT

For over 50 years patients with liver cirrhosis were considered to be at markedly increased risk of bleeding. This dogma was seemingly supported by abnormalities in standard laboratory tests (SLTs), such as the prothrombin time, that were interpreted as indicating a bleeding diathesis. However, publications from the last decade have revealed SLTs to be poor predictors of bleeding and it is now understood that stable patients with cirrhosis have a rebalanced haemostatic system and preserved thrombin generation. Viscoelastic tests (VETs), such as ROTEM® or TEG™ allow dynamic assessment of the entire coagulation process and provide a better illustration of the interactions between pro- and anticoagulants as well as platelets. Despite their documented success in reducing transfusion rates in liver transplantation more than 30 years ago, the adoption of VETs has been met with some resistance and has only recently gained significant momentum. Bleeding risk should be assessed in every patient undergoing invasive intervention and must consider markers of disease severity, underlying coagulation incompetence, anaemia and surgical factors. The recognition that bleeding in this patient cohort is predominantly linked to mechanistic factors such as portal hypertension, rather than primary coagulopathy, has led to a paradigm shift in their perioperative management. Cognizant of their detrimental effect, the use of large volumes of fresh frozen plasma to correct derangements in SLTs has given way to more refined haemostatic management with specific factor concentrates guided by VETs, coupled with measures to minimize portal venous pressure and meticulous surgical hemostasis.

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Key words: Blood coagulation - Blood transfusion - Blood coagulation factors.

The management of coagulation in patients with end-stage-liver-disease (ESLD) undergoing liver transplantation (LT) remains controversial. Despite very low transfusion rates (20%) during LT reported by some centres, these results are not being replicated widely, perhaps due to differences in patient populations, surgical techniques and transfusion triggers.

Liver transplantation has historically been regarded as a mass transfusion operation. The first patient undergoing liver transplantation died of uncontrolled bleeding on the operating table. Early studies of blood product use in LT reported red cell transfusion rates of 28.5 units in adult and 11 RBC units in paediatric transplants. Although the definition of massive transfusion varies widely, it is universally agreed that it is strongly associated with adverse outcomes including reduced long-term survival. Patient blood management (PBM) initiatives have consequently endeavoured to reduce transfusion by promoting the screening and treatment of anemia, optimization of...
coagulation and minimisation of perioperative blood loss.

The expansion of liver transplant programmes, surgical advances, better organ quality through donation after brainstem death and improved understanding of pathophysiological contributors to bleeding, have helped to drive down transfusion.5

This has been underpinned by the rising use of point-of-care coagulation monitoring such as viscoelastic tests, which have played a seminal role in enhancing our understanding of the coagulation system in ESLD and have become an essential element of goal-directed coagulation management in LT. Mechanical factors related to portal hypertension, rather than coagulopathy, are now understood to be the fundamental triggers for bleeding complications. A host of measures to mitigate the risk of bleeding and optimize coagulation, such as surgical, anaesthetic and pharmacological interventions continue to be the subject of study, with variable impact on outcomes. This raises the question — what is the optimal management of bleeding in this patient group?

Hemostasis in end-stage liver disease

The liver plays a pivotal role in the synthesis of plasma coagulation factors; end-stage liver disease (ESLD) is consequently associated with complex alterations of haemostatic processes. Historically, the presence of a bleeding diathesis secondary to coagulopathy was inferred from derangements in SLTs such as prolonged PT and raised INR in patients with severe liver disease. This was believed to result from diminished liver synthetic function leading to a reduction in procoagulant proteins such as the vitamin-K dependent factors II, VII, IX and X.

The current model of coagulation (Figure 1)6 consists of initiation, propagation and amplification phases and has replaced the historic coagulation cascade. ESLD-associated changes in the coagulation system affect primary and secondary hemostasis as well as fibrinolysis. Platelets, the principal effectors of primary hemostasis, as well as erythrocytes and granulocytes may be reduced by hypersplenism secondary to increased portal venous pressures in cirrhotic liver disease. This is balanced, however, by an increase in the platelet-adhesion protein von Willebrand Factor (vWF), which may be increased by up to 200%, and a concurrent reduction in vWF’s enzymatic cleavage by ADAMTS13.7-9

Secondary hemostasis also remains preserved overall due to a concurrent reduction in both procoagulant factors and anticoagulant drivers such as protein C and S. Fibrinolytic activity and clot instability due to increased levels of tissue plasminogen activator (t-PA) may be present. Clinically significant fibrinolysis is, however, infrequently seen due to elevated levels of the acute-phase reactant plasminogen activator inhibitor (PAI-1).10 Levels of PAI-1 are markedly elevated in cholestatic liver disease and also in patients with acute liver disease, and consequently fibrinolysis is rare.

Assumptions that these alterations give rise to an increased bleeding risk have not been substantiated. Reports of up to 80% transfusion-free LT rates, normal or elevated endog-
enous thrombin potential (ETP) and increased thromboembolic complications in cirrhotic patients have cast serious doubt on the concept of an auto-anticoagulated state. Improved understanding of the pathophysiological processes indicate that lower levels of procoagulant factors are offset by reduced hepatic production of anticoagulant proteins, and that the haemostatic system is therefore “re-balanced.” While stable cirrhotic patients have preserved coagulation capacity, evidence suggests that this delicately balanced state is much more prone to decompensation by physiological stressors, increasing the risk of both bleeding and thrombosis.

Evidence increasingly supports the theory that vascular mechanics have a much greater impact on bleeding risk in this patient group than defects in the hemostatic system. Congestion of the splanchnic circulation, secondary to elevated portal pressures, leads to the development of portal hypertensive gastropathy and varices. Further rises in portal venous pressure, particularly in the presence of infection, may precipitate variceal rupture and upper gastrointestinal (GI) bleeding. This may be triggered or perpetuated by liberal fluid management to correct hypotension or, commonly, transfusion of fresh frozen plasma (FFP) to correct an elevated INR, leading to plasma volume expansion and consequently raised PVP.

Effects of blood product transfusion

The multiple adverse effects of blood product transfusion are well recognized and evidence from the literature indicates a strong association with increased morbidity and mortality. In LT, transfusion of 2 units of red cells (RBC) has been linked with an increased rate of surgical site infections and transfusion of 6 or more units (an accepted definition of massive transfusion in LT) is associated with decreased survival. De Boer et al. identified a dose-dependent prognostic relationship between transfusion and survival. In their study, one-year mortality was increased with a hazard ratio of 1.37/unit platelet and 1.07/unit RBC transfused. The study by Li et al. evaluating long-term survival in living donor liver transplants indicated that massive transfusion (6 or more RBC) adversely affected long-term survival at 3- and 5-years.

The underlying mechanisms for adverse outcomes after transfusion are uncertain and may be linked to transfusion reactions, immune modulation and transmission of blood-borne infections. The incidence of bacterial infection from blood products is variably quoted as 1:2000 to 1:10,000 and primarily implicates platelet transfusion, due to their storage at room temperature (20 °C). Transmission of viral infection is uncommon with an incidence of 1:450,000 (hepatitis B) to 1:50 million (hepatitis C or HIV). Hemolytic transfusion reactions may be immediate or delayed and are caused by donor membrane antigens reacting with antibodies in recipient plasma.

Transfusion-associated circulatory overload (TACO) is pulmonary edema secondary to congestive heart failure. Transfusion-related acute lung injury (TRALI) is non-cardiogenic pulmonary edema, most frequently associated with FFP administration. It is caused by donor antibodies forming complexes with recipient leucocytes, which become entrapped in the lung, leading to capillary leak and impaired oxygenation. As donor antibodies are found primarily in the plasma of females who have a prior history of pregnancy, FFP is only sourced from male donors. FFP transfusion is positively correlated with a higher rate of nosocomial infections and pulmonary complications in long-term follow-up studies and may be related to modulation of the immune system. Such transfusion-related immunomodulation (TRIM) is caused by non-specific immune mediators in stored blood.

It should be noted that most studies evaluating the impact of transfusion on outcome after LT are observational and therefore not powered to assess causal links between blood loss, transfusion rate, morbidity and mortality. Nonetheless, judicious use of blood products, which are an expensive and scarce resource, will serve to minimize risks associated with transfusion. Over the past decade, this has been championed by PBM programmes which aim...
to reduce transfusion and associated adverse outcomes through a multifaceted, multidisciplinary approach. PBM focuses on detection and optimization of preoperative anemia, intraoperative measures to minimize bleeding, guided coagulation management using near-patient testing and use of restrictive transfusion thresholds.

Risk assessment and prediction of bleeding

Bleeding risk should be individually evaluated in every patient with ESLD undergoing an invasive procedure. The notion that severity of illness correlates with intraoperative blood loss is corroborated by evidence from the literature. MELD score has been shown to be a marker of bleeding in a mixed LT population (split-liver, piggy-back, caval preservation technique, living donor) while preoperative anemia and thrombocytopenia are independent predictors of increased intraoperative blood loss and adverse outcomes. Surgical factors such as previous abdominal operations or retransplantation present significant additional risk with respect to major bleeding.

Evaluation of the integrity of hemostatic processes is a key element in bleeding risk assessment. Traditionally, this was based on standard laboratory tests (SLTs) such as prothrombin time (PT), activated partial thromboplastin time (aPTT) and platelet count. A prolonged PT is associated with reduced syntheses of vitamin-K-dependent factors (II, VII, IX and X), while diminished levels of V, IX, XI and XII are associated with a raised aPTT. Despite causing prolongation of the aPTT, isolated factor XII deficiency, first reported in 1955, is not associated with an increased risk of clinical bleeding. In fact, the eponymous Mr. Hageman, who gave his name to factor XII, suffered from recurrent thromboembolic events, rather than bleeding complications — explained by factor XII-mediated activation of plasminogen to plasmin, which contributes more to fibrinolysis than haemostasis. This illustrates the potential misinformation provided by SLTs and their utility in predicting bleeding in cirrhotic patients has since continued to be challenged. In 1981, Ewe’s prospective observational study assessing spontaneous liver bleeding time, PT and platelet count in cirrhotic patients undergoing laparoscopic liver biopsies found that even a PT ratio of 10% did not correlate with a prolonged liver bleeding time while conversely, approximately 40% of patients with a PT ratio of 100% exhibited prolonged localized bleeding.

SLTs were not designed to guide coagulation therapy in acquired bleeding disorders, and do not reflect the balance of pro- and anticoagulant proteins that exists in vivo. Assays such as PT and aPTT are terminated after less than 5% of thrombin is activated and lack full activation of key anticoagulant drivers such as protein C. Tripodi et al. evaluated in vitro thrombin generation capacity in cirrhotic patients and healthy controls. ETP was reduced in cirrhotic patients when tested with a conventional thrombin generation assay. However, this difference disappeared upon activation of the potent anticoagulant protein C by addition of thrombomodulin (TM) to the test assay. Activated protein C inhibits factor Va and VIIIa; its production is diminished in cirrhotic liver disease, compensating for reduced procoagulant factor synthesis and resulting in preserved thrombin generation overall.

A recent meta-analysis of SLTs also failed to demonstrate their utility in guiding hemostatic therapy. Notably, of the 1123 publications screened for this review, only three studies were prospective and none were randomized, starkly highlighting the lack of well-designed studies supporting the use of SLTs.

Evidence supporting the potential role of viscoelastic tests (VETs) such as rotational thromboelastometry (ROTEM®) or thrombelastography (TEG™) as a more suitable alternative to SLTs is mounting. TEG was first described in 1948 as a method for the assessment of coagulation in whole blood and its first clinical use in liver transplantation published in 1985. TEG-guided blood product administration was associated with a 33% reduction in infusion volume while blood coagulability was maintained without an increase in red cell transfusion. Although the adoption of VETs in
the wider medical arena has been slow, hampered by scepticism and high capital costs, their routine clinical use in LT is now firmly established and considered standard of care.

While SLTs assess only the initiation process, which represents a small percentage of overall thrombin production, VETs reflect initiation, propagation and amplification phases as well as fibrinolytic processes and are therefore able to provide a more global assessment of coagulation. They are usually performed at or near the bedside, using small samples of whole blood.

In a randomized controlled trial of preprocedural prophylaxis in cirrhotic patients, De Pietri et al. demonstrated a highly significant reduction in blood transfusion using a TEG-guided transfusion algorithm when compared with SLTs (16.7% vs. 100%, P<0.0001). In the TEG group, a prolonged reacting time prompted treatment with FFP, and a maximal amplitude <30 mm triggered transfusion of platelets. In the SLT group the trigger for FFP transfusion was an INR≥1.8 and platelet count <50 nL for platelet transfusion. Postprocedural hemoglobin concentration was significantly higher in the TEG group than the SLT group, while there was no difference in bleeding episodes (1 the SLT group, none in the TEG group).

The utility of other TEG parameters such as the first derivative of the velocity curve (V-curve) in predicting bleeding during transplantation has recently been demonstrated. In this retrospective study of 198 patients undergoing LT, patients were stratified into low-blood-loss (LBL: median 205 mL) and high blood loss (HBL: median 874 mL) groups. In the HBL group, the V-curve showed a lower maximum velocity of clot generation, a lower area under maximum velocity curve (AUC), and a higher time-to-maximum velocity than in the LBL group. This holds potential for stratification of bleeding risk based on a preoperative blood sample.

A further advantage of VETs is their short turnaround time relative to SLTs. In a comparison of ROTEM with SLTs in pediatric surgery (where ROTEM was performed in the lab) SLT results were available after a median of 53 minutes while 10-minute ROTEM values were available after 23 minutes. VET measurement at or near the bedside achieves further reduction in turnaround times.

Studies also suggest that ROTEM parameters such as the A5 (amplitude after 5 minutes) correlate well with maximum clot firmness (MCF) and may be an effective early indicator of critically low platelet and fibrinogen levels during liver transplantation.

How can we avoid bleeding?

Management of bleeding and hemostasis varies substantially between centres, and is dependent on geographical variations in patient cohorts, local protocols and the personal experience of individual clinicians. Management priorities should focus on techniques to minimise blood loss and goal-directed optimization of coagulation.

The impact of surgical technique on bleeding and transfusion requirements remains contested. The advent of the piggyback technique held promise for reducing blood loss as it necessitates only a single IVC anastomosis, with a shorter resultant warm ischemia time. While this hypothesis is supported by some case control studies, a Cochrane review failed to show a reduction in transfusion requirements or any impact on outcome. Nevertheless, careful surgical technique and attention to surgical haemostasis is fundamental to reducing blood loss.

Patients with ESLD and portal hypertension are prone to significant increase of their body fluid volume. The data of that study indicated that both total body volume and distribution was abnormal, as well. Cirrhotic patients contain 37% of their total body volume in the splanchnic circulation, compared to <30% in healthy individuals. Moreover, there is a difference in total vascular compliance, while this value in healthy volunteers ranges from 0.5-1 mL/mmHg/kg body weight, this parameter is significantly higher (1.5-2.5 mL/mmHg/kg body weight) in cirrhotic patients. An infusion bolus of 500 mL increases the mean arte-
trial pressure (MAP) in healthy persons by 5 mmHg.\(^{42}\) However, in cirrhotic patients an infusion is less effective for correction of MAP. The fluid is mainly pooled in the splanchnic system,\(^{12}\) which mainly increase the portal pressure and increase the risk of bleeding from collateral veins during surgery, transplant and non-transplant surgery, as well. Modulation of splanchnic circulation with splanchnic vasconstrictors may decrease the portal pressure.\(^{43,44}\)

Mechanical factors related to portal hypertension are increasingly understood to be important precipitants for bleeding in patients with ESLD. A study by Giannini et al. assessing alterations in PVP depending on FFP volume transfused, reported increases in PVP of 15 mmHg and 26 mmHg with FFP volumes of 1.5 L FFP and 2.5L FFP, respectively.\(^{45}\) Such rises in PVP may be associated with a greatly increased risk of variceal bleeding.

A randomized controlled trial comparing blood loss during liver resection with liberal (>5 cm H\(_2\)O [=3.6 mmHg]) and restrictive management of CVP (<5 cm H\(_2\)O)\(^{46}\) demonstrated median blood loss of 1000 mL and 200 mL, respectively. Similarly, in a RCT assessing liberal CVP vs low CVP (defined in this study as <5 mmHg or 40% lower than baseline),\(^{47}\) a low CVP strategy led to a 50% reduction in blood loss. It must be emphasised that mean pressure in the low CVP group was above 5 mmHg at all of the five predefined measurement time points and that CVP differed between groups at time points 1 (1 hour after start of operation), 2 (2 hours after start of operation) and 3 (30 minutes after portal vein cross-clamping) only. Notably, CVP did not differ significantly at 30 minutes post-reperfusion (“liberal CVP” group 10 mmHg vs. “low CVP” group 9 mmHg), the period recognized to be the most vulnerable phase for graft dysfunction.

Other strategies to lower PVP include phlebotomy\(^{48}\) and forced diuresis or venodilation using pharmacological agents.\(^{47,49-51}\) Massicotte et al. studied the effect of phlebotomy and phenylephrine infusion on PVP and CVP in patients undergoing liver transplantation.\(^{48}\)

The median CVP decreased from 13 mmHg to 7 mmHg after phlebotomy but subsequent restoration of the MAP using phenylephrine led to an increase of CVP to 11 mmHg. Similarly, PVP decreased from 18 mmHg to 9 mmHg after venesection, but remained 9 mmHg following phenylephrine infusion. This study, alongside numerous others published over the past 15 years, has challenged the utility of static pressures such as CVP in assessing volume status, particularly in the presence of vasopressor therapy, and it is accepted that cardiac filling pressures are poor predictors of fluid responsiveness.\(^{52}\) Massicotte’s study concludes, therefore, that a lower PVP target would likely be more effective in minimizing perioperative blood loss as it is the prevailing PVP rather than CVP that determines bleeding in these patients.

Reductions in PVP during liver transplantation have also been achieved using pharmacological agents such as arginine-vasopressin\(^{44}\) and its synthetic analogue terlipressin.\(^{53}\) Reductions in PVP are effected through splanchnic vasoconstriction leading to reduced portal vein flow without reduction of central venous and mean arterial pressures or cardiac output.

Management of patients with portal hypertensive variceal disease must therefore focus on maintaining low PVP, with lesser attention paid to CVP, achieved using a restrictive fluid management strategy\(^{12}\) combined with judicious pharmacological therapy.

**How can we treat bleeding?**

Treatment of coagulopathy may either be by empirical administration of FFP based on SLTs or goal-directed administration of specific factors guided by point-of-care tests such as VETs. Indeed FFP is sometimes (mis)used as volume replacement to avoid dilutional coagulopathy, however, in the context of heavy and sustained bleeding, where there is a need to maintain intravascular volume, this has some justification. The majority of data supporting the use of FFP originates from the trauma setting, where the use of high FFP-to-RBC ratios in massive transfusion have shown improved
survival regardless of INR on admission.\textsuperscript{54} Studies advocating a fixed FFP: RBC ratio date back to 2003, where a computer-simulated model indicated an optimal ratio of 2:3.\textsuperscript{55} Since 2007 several retrospective studies have suggested better survival with 1:1 ratios \textsuperscript{56-59} and this survival benefit was more recently corroborated by the PROMMTT (Prospective, Observational, Multicenter, Major Trauma Transfusion) Trial.\textsuperscript{60} In this study of over 1200 patients, 60% of in-hospital deaths occurred within the first three hours after admission. Multivariate analysis indicated that high (>1:1) FFP: RBC ratios were independently associated with decreased 6-hour mortality (HR=0.31) but this protective effect diminished over time, with no difference in survival seen beyond 24 hours. Similarly, the PROPPR Trial,\textsuperscript{61} which compared fixed ratios of FFP: platelets: RBC of 1:1:1 with 1:1:2, found no difference in 24-hour and 30-day survival.

In the context of ESLD and LT, the volume load associated with the use of FFP appears counterproductive. Chowdary \textit{et al.} demonstrated that the use of 12 mL/kg FFP failed to correct a prolonged aPTT and/or PT in 80% of patients and 100% correction was only achieved using 30 mL/kg.\textsuperscript{62} This dose translates into volumes of approximately 2400 mL for the average 80 kg patient, which, in the absence of bleeding may lead to significant increases in portal venous pressure and a consequent increase in bleeding risk. The 2004 Guidance from the British Committee for Standards in Haematology stated\textsuperscript{63} that the indications for FFP are very limited and recommended its use only for plasma exchange for thrombotic thrombocytopenic purpura.

A feasible alternative to FFP may be the use of coagulation factor concentrates. The most commonly used factors in patients with ESLD are fibrinogen concentrates (FC), prothrombin complex (PCC) and factor XIII, which may be used to treat bleeding in the presence of normal VET parameters. Factor VIII concentrates tend to be reserved for patients with complex coagulation defects such as hemophilia with superimposed cirrhosis.

Virus-inactivated factor concentrates are now commercially available, eliminating the risk of transmission of infection. Nonetheless, concerns still exist about the safety profile of specific coagulation factor concentrates, in particular with respect to thrombotic risk.

The first report of PCC use in liver transplantation dates back to 1994.\textsuperscript{64} In this study PCC was administered to a target PT ratio of 60% following pretreatment with AT III at a dose of 30 I.E./kg (in most cases 2000 I.E.). There were no reported thrombotic events in this study.

Newer PCC formulations currently available\textsuperscript{65} for clinical use include three-factor (II, IX, X) and four-factor (II, VII, IX, X) concentrates. These preparations also contain the vitamin-K dependent anticoagulants protein C and S to balance procoagulability and are formulated with heparin to prevent factor activation. They appear to be associated with an improved safety profile and a recent comprehensive review of the use of PCC did not find an association with increased risk of thrombosis\textsuperscript{66} in the absence of additional prothrombotic risk factors. Although there is presently limited data detailing the use of PCC in patients with liver disease, the results of ongoing studies are hoped to inform future practice. For instance, the PROTON study, a double blind, multicenter, placebo-controlled randomized trial aims to assess the impact of PCC on blood transfusion rates in cirrhotic patients with a prolonged INR (≥1.5) undergoing LT. This study, in which patients will be randomized to either placebo or PCC prior to surgery,\textsuperscript{67} started recruitment in 2013 and its results are awaited with interest.

The data on fibrinogen use in liver transplantation remains scarce. Figures from efficacy studies in non-transplant patients with acquired hypofibrinogenemia\textsuperscript{68} indicate that the administration of 4 g of FC increased the serum fibrinogen level from 0.65 to 2 g/L. As evidence from several studies strongly suggests that hypofibrinogenemia is associated with severe bleeding in cirrhotic patients,\textsuperscript{69-71} recommendations suggest a target fibrinogen level of >1.5 g/L in this patient cohort if there is active bleeding.\textsuperscript{72}

Trials of ROTEM-guided coagulation factor administration in liver transplantation\textsuperscript{73} have
shown significant reductions in blood product administration. In a single centre study by Kirchner et al., approximately 58% of patients received fibrinogen and 35% PCC, resulting in a 37% transfusion-free transplant rate; 85% received no FFP and 71% received no platelets. The incidence of thrombotic complications was comparable in patients receiving coagulation factor concentrates with patients receiving standard blood products.73

Preemptive treatment with fibrinogen liver transplantation is not recommended as indicated in the RCT by Sabate et al.74 comparing prophylactic FC with saline. Targeting a preoperative fibrinogen level of 2.9 g/L in the intervention group, a median FC dose of 3.54 g was administered. There was no difference in transfusion rates between groups and while thrombotic events in the saline group were more common, this was not statistically significant. However, analysis of ROTEM data revealed that the EXTEM MCF and the FiBTEM MCF were similar between groups and were not indicative of hypocoagulability (EXTEM MCF 45 mm in FC group, 46 mm in saline group).

Considering the fine balance between coagulopathy and prothrombotic risk, it would seem prudent to avoid the administration of coagulation factors in the absence of bleeding and to use VETs to guide appropriate dosing. In general, there is now a move away from pre-emptive or prophylactic correction of abnormal values, towards using VET to correct specific defects only if there is active or significant bleeding.

Antifibrinolytic therapy

Routine use of prophylactic antifibrinolytic agents was common in the early history of LT, as the massive blood loss was relatively common, and any potential risk of thrombosis associated with the use of antifibrinolytics was small in comparison. However, the risk-benefit balance has altered now that massive bleeding is less frequent, and there is a move away from prophylactic therapy towards selective (high risk patients) or treatment only. Prediction is difficult as hyperfibrinolysis-induced bleeding may become most pronounced in the post reperfusion stage of the operation and depends to a great extent on the quality of the donor liver, which is not reflected by the preoperative condition of the recipient. Treatment with antifibrinolytic therapy is increasingly recommended only when there is evidence of microvascular ooze and/or documented fibrinolysis (CLI>15%) on TEG/ROTEM.75

In the presence of good graft function, fibrinolysis is usually self-limiting after reperfusion and does not always require treatment.75 The decision to treat should be based on the presence of diffuse bleeding, severity of fibrinolysis and the stage of the operation. Fibrinolysis occurring during dissection and the early anhepatic phase of surgery is more likely to require treatment, as it is unlikely to resolve spontaneously, and tends to increase in severity. After reperfusion of a marginal graft, fibrinolysis is more common, and can be severe, and some centers routinely give tranexamic acid prior to reperfusion when a DCD graft is used.76

Conclusions

Transfusion practices in patients undergoing liver transplantation have been challenged in recent years due to improved understanding of the pathophysiological rebalancing of coagulation and recognition that bleeding is predominantly related to portal hypertension. This has resulted in a change from the massive transfusion and requirement of boots in the OR of earlier days, to a more gentle environment with moderate or even zero transfusion rate.

Comprehensive bleeding risk assessment must include consideration of preoperative factors such as MELD score, anemia and thrombocytopenia, while intraoperative blood loss should be minimized by means such as maintenance of low portal pressures augmented by pharmacological agents and restrictive fluid regimes. Perioperative transfusion and management of coagulopathy should be guided by viscoelastic tests, as recommended in the recent ESA guidelines, and this may best
be achieved using specific factor concentrates. Contrary to the trauma population, the liberal use of FFP in this patient group is not supported by the evidence and indeed is associated with adverse outcomes.

Key messages

— Hemostasis in patients with ESLD is rebalanced and does not need any kind of treatment, since there are no signs of bleeding.
— Transfusion of any blood product is accompanied by serious adverse events. For that reason we should be reluctant with applying blood products. They should only used in case of absolute necessity.
— Risk assessment and coagulation management should be based on VETs (TEG or ROTEM), rather than on SLT. VETs assess the whole coagulation process (initiation, propagation and amplification) and the turnaround time is significantly shorter compared to SLT.
— Modulation of the splanchnic circulation with the aim to decrease PVP with terlipression or arginine-vasopression could be considered to lower the blood loss. Fluid overload should be strictly avoided.

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Supraglottic airway devices: indications, contraindications and management

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Abstract

Supraglottic airway devices (SADs) have become an essential tool in airway management. Over the past three decades, these devices have been increasingly adopted as an alternative to face mask ventilation and/or endotracheal intubation. The range of proposed uses and features has increased significantly. They are used in pre- and in-hospital settings, elective and emergency anesthesia, in spontaneously breathing and ventilated patients, as conduits for intubation, as a bridge to extubation and for airway rescue. With SADs, serious complications such as aspiration and loss of airway are rare and largely preventable. Adequate operator experience, familiarity with the selected device, attention to details and careful patient selection are fundamental to safety and proficiency. In this review, we explore the increasing proposed uses for SADs and discuss possible complications and the management of these.

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Key words: Airway management - Intubation, intratracheal - Complications.
UK are administered with SADs. However, recent evidence shows that SADs are sometimes inappropriately used, with inadequate patient or device selection, and/or suboptimal techniques.

In this perspective, we explore the expanding indications for SADs use and discuss the possible complications and management.

**Indications**

*Primary airway management device*

**Operating room**

Most anesthesiologists are familiar with basic SAD use, such as ambulatory anesthesia for short procedures with maintenance of spontaneous ventilation. Here, we will focus on the use of SADs in more complex patient groups — obese patients, obstetric patients and those receiving laparoscopic surgery. In such settings, the use of second generation SADs (with enhanced safety features over first-generation devices) and adequate patient selection, operator’s experience and optimal technique assume even greater importance. In a meta-analysis comparing the use of an SAD and ETT in patients undergoing laparoscopic surgery, the authors found no difference in rates of first attempt success, gastric insufflation, regurgitation or aspiration. The ETT group had a higher incidence of laryngospasm, cough at removal, dysphagia, dysphonia, sore throat and hoarseness. A Cochrane review looking at two studies comparing the LMA® Proseal™ to a tracheal tube in the obese showed a failure rate of 3-5% with the LMA® Proseal™. There was no significant difference in the proportion of successful placements at first attempt. The leak fraction was increased in some patients but ventilation was not affected. Endotracheal cuff pressures were not measured in one of the two studies included in the review. There was significant improvement in intraoperative and postoperative oxygenation and reduced postoperative coughing. In Obstetrics, there has been a trend towards increased use of SADs as rescue devices in failed intubations for cesarean sections, with continued use of the device until completion of surgery. Over 4700 elective and urgent caesarean sections using LMA as the primary airway device have been described without significant complications. However, with absent definitive data, endotracheal intubation remains the standard of care for primary airway management in caesarean sections.

SADs can offer significant advantages in the pediatric population. For children, first-generation SADs are widely used and the somewhat limited evidence suggests that they have a high success rates with low risk of complications. In infants, a recent randomized controlled trial compared SAD to ETT use in minor elective procedures. Incidence of perioperative respiratory adverse events was significantly lower in those who received SAD versus ETT.

**Emergency resuscitation and prehospital care**

Emergency endotracheal intubation outside the operating room is associated with significant challenges, including higher incidence of difficult intubation due to environmental factors, possible lack of laryngoscopy experience, rapidly deteriorating clinical scenarios and higher risk of regurgitation. SADs may offer important advantages in this setting, with higher success rates over face mask ventilation and endotracheal intubation, and their use is contemplated in international resuscitation guidelines. The esophageal-tracheal Combitube® has been widely used in the prehospital setting in the USA with a high insertion success rate with paramedics although not as high as ETT placement (70% vs. 84%). A retrospective study looking at prehospital Combitube airway complications found that 13 of the 69 complications in 280 patients most likely resulted from trauma associated with the Combitube insertion.

Recent North American data from 10,455 out of hospital cardiac arrests showed that patients who received ETT had a higher rate of survival to discharge with satisfactory
functional status compared to those who had SADs. However, this association had multiple confounding factors. The optimal airway management strategy in this context depends on the precise circumstances and on the operator experience.

**Neonatal resuscitation**

Several studies report that SADs appear to offer a safe and effective alternative to mask ventilation and ETT in term or near term infants in the setting of delivery room resuscitation. SADs may be easier to use and more effective than face mask, although further large trials are needed.

Conduit for endotracheal intubation

Some SADs are designed to facilitate ETT placement through their ventilation tube, either blindly or with the aid of flexible fiberoptic guidance. These devices include the i-Gel®, the LMA® Fastrach™, LMA® ProtectorTM, air-Q®, Baska Mask®, the intubating laryngeal tube iLTS-D®, and the Ambu® Aura-iTM and Aura GainTM. The SADs with integrated fiberoptics for visualized intubation are discussed later under the section types and features.

Intubation via SADs not designed for this purpose is fraught with challenges and should be carefully considered. Impediments to success include presence of bars in the pharyngeal bowl, internal diameter and length of the ventilation tube of the SAD. Importantly, the 15 mm connector may be glued to the mask (i.e., LMA® Classic™) or removable (i.e., air-QTM). The added length created by a glued connector does not allow the tip of a standard 26-27cm ETT to reach distal to the vocal cords.

Even in experienced hands, blind introduction of an ETT through an SAD has a high failure rate and is not recommended. Visualized intubation via an SAD can be performed with a flexible bronchoscope. Alternatively an Aintree Intubating Catheter (Cook® Medical Inc., Bloomington, IN, USA), specifically designed to accommodate a small-diameter flexible bronchoscope can be used to advance an appropriately sized ETT through an SAD.

**Airway rescue**

Arguably the SADs most vital role is its use in a “cannot intubate, cannot oxygenate” scenario. Rescue ventilation via SAD has become a widely recognized important step in guidelines for management of difficult airways by several international societies in both adults and children. A “cannot intubate, cannot oxygenate” situation should not be declared until a supraglottic airway device has been attempted and successful ventilation through an SAD may avoid emergency surgical airway. All anesthesiologists should be familiar with their chosen SAD for airway rescue. Since they are relatively low cost and most are easy to learn to use, we should use them regularly so that we are comfortable with their insertion technique and features in emergencies.

**Use in extubation**

Bailey and others described changing the endotracheal tube for an SAD to ensure smooth extubation. The SAD can be inserted with the patient still deeply anesthetized before or after removal of the ETT and can reduce cardiovascular instability and coughing associated with extubation. This technique should be considered an advanced airway technique. It is potentially hazardous in a patient known to have a difficult airway, risk of aspiration and severe laryngeal edema, or severe laryngeal/bronchospasm. It is however, a useful tool when laryngeal anatomy or vocal cord movement requires assessment at the end of surgery, exchanging the ETT for SAD, initiating spontaneous ventilation and examination with a flexible bronchoscope through the SAD.

**Use in the percutaneous dilatational tracheostomy**

SADs are used to ventilate patients on intensive care units during percutaneous dilatational tracheostomy as an alternative to endo-
tracheal tube ventilation. A Cochrane review including eight RCTs concluded that evidence is too limited to draw conclusions on the efficacy or safety of SADs versus ETTs for this procedure.  

Contraindications and complications

Aspiration risk

Aspiration and loss of the airway are probably anesthesiologists’ biggest concerns with SAD use. Large observational studies and meta-analyses report aspiration rates of 1-3 per 10,000 cases — comparable to the rates with facemask ventilation or endotracheal intubation. This incidence may be underestimated, with many cases unpublished or unrecognized. In the NAP4 UK audit involving nearly 3 million general anesthetics, the majority of serious SAD-related complications were aspiration and these included the worst outcomes.

Data for aspiration risk for individual SAD types is limited. In an observational study of 700 scheduled caesarean sections using the LMA® Supreme™, no patients aspirated. There are published case reports of aspiration using the i-Gel® and the LMA® Proseal™ and it has been suggested that if the LMA® Proseal™ is not positioned carefully, it may increase the aspiration risk. Given the low frequency of recognized aspiration, adequately powered trials comparing SADs vs. ETTs are difficult to perform. Devices incorporating gastric channels could theoretically lower the risk of aspiration, and large, well designed trials would be needed to determine this particular aspect. Table I summarizes those situations at higher risk of complications. NAP4 highlighted the importance of careful case selection and skilled delivery of anesthesia techniques for induction, maintenance and emergence to avoid SAD complications. Both first and second-generation devices were used in the airway complications reported but there were notably many cases where junior anesthesiologists were using first-generation SADs.

<table>
<thead>
<tr>
<th>TABLE I.—Risk factors associated with complications with SAD use - adapted from NAP4 (Cook et al.).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factors</strong></td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>History of gastroesophageal reflux/nausea/vomiting</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
</tr>
<tr>
<td>Predicted difficult airway</td>
</tr>
<tr>
<td>Surgical factors</td>
</tr>
<tr>
<td>Urgent surgery</td>
</tr>
<tr>
<td>Lithotomy or head down position</td>
</tr>
<tr>
<td>Patient position for surgery limits airway access, e.g. prone</td>
</tr>
<tr>
<td>Anesthetic factors</td>
</tr>
<tr>
<td>Junior anesthesiologist</td>
</tr>
<tr>
<td>Inadequate preoperative airway assessment</td>
</tr>
<tr>
<td>Light anesthesia</td>
</tr>
<tr>
<td>Bliting on emergence</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE II.—Predictors of difficulty with supraglottic airway device insertion or ventilation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce mouth opening</td>
</tr>
<tr>
<td>Small mouth</td>
</tr>
<tr>
<td>Supraglottic, extraglottic, subglottic or glottis pathology, particularly edema</td>
</tr>
<tr>
<td>Fixed cervical spine flexion</td>
</tr>
<tr>
<td>Manual in line neck stabilization</td>
</tr>
<tr>
<td>Insertion during application of cricoid pressure</td>
</tr>
<tr>
<td>Increased BMI</td>
</tr>
<tr>
<td>Increased intra-abdominal pressure</td>
</tr>
<tr>
<td>Abnormal dentition</td>
</tr>
<tr>
<td>Edentulous</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Limited airway access during ventilation</td>
</tr>
<tr>
<td>Chest wall anomalies, e.g. severe COPD or spinal deformity</td>
</tr>
<tr>
<td>Laryngospasm or bronchospasm</td>
</tr>
</tbody>
</table>

Expected difficulty with SAD insertion or ventilation

Table II outlines the predictors of difficulty with SAD insertion and ventilation. In these situations, an alternative management plan should be considered.

Expected difficult intubation

SADs should be used with caution in patients who are expected to be difficult to intubate. NAP4 highlighted the risks of “failing to plan for failure.” Where SADs were used to avoid a suspected difficult intubation, outcomes were poor when the airway was lost and a back-up plan had not been considered.
or could not be executed. Elective, controlled flexible bronchoscopic intubation may be a more sensible option.

**Patient position**

Patient position can both increase aspiration risk and limit access to the airway should problems arise. The Trendelenburg, lithotomy and prone position increase intra-abdominal pressure and splint the diaphragm making respiratory complications more likely. SAD use has been described in all three positions, and SAD insertion as a rescue for accidental extubation of prone patients has been proposed by some authors. For all the above circumstances, if an SAD is selected, use of second generation devices, a reliable plan B with appropriate access to equipment and staff for airway rescue are recommended.

**Duration of use**

There are no randomized studies comparing SADs with ETTs for long periods. There is no evidence to suggest that longer durations of SAD use is associated with increased risk of complications, and a maximal duration of use has not been determined for SADs. If prolonged use is contemplated, cuff pressure should be monitored and kept as low as possible and a second generation device is recommended to decrease gastric insufflation. Case reports have described safe use for over nine hours.

**Other complications**

The NAP4 report documented four cases of postobstructive pulmonary edema requiring ICU care as a result of biting the SAD on emergence from anesthesia. A bite block is recommended if not already integrated in the chosen SAD.

Minor complications include sore throat, dysphonia, dysphagia and cough. All are said to occur less frequently with SAD use than ETT use. There is a reduced incidence of sore throat when SAD cuff pressures are maintained <60 cmH2O. An overinflated cuff may also distort the airway, and cause hypopharyngeal and tongue edema. More rare but serious complications include recurrent laryngeal, hypoglossal, lingual or mental nerve injury; trauma to teeth, lips, pharyngeal mucosa, tongue, uvula, epiglottis or laryngeal apparatus and compression of the common carotid artery or internal jugular vein with reduced cerebral perfusion or venous congestion respectively. Extremely rare events include pharyngeal rupture, pneumomediastinum or mediastinitis.

**Management**

**Insertion**

A description of insertion technique accompanied the release of the LMA® and newer SAD models. Several different insertion techniques have since been described. The standard insertion technique with full cuff deflation results in failure rates five times lower than other techniques. The general principle for insertion aims to simulate swallowing a food bolus. With adequate anesthesia depth, the lubricated mask is advanced along the hard palate, soft palate and pharyngeal wall until resistance is felt. Clinicians need to be familiar with the specific insertion techniques recommended for the chosen SAD. The SAD should be secured in a manner that maintains it in this position.

**Types and features**

More than 40 SADs are currently available for adults and designs are constantly evolving. Ventilation failure rates range from 0 to 41% with most devices having failure rates between 0-5%. Suboptimal performance varies with the device, the appropriateness of the selected size, inflation, securement and operator experience. Statutory requirements for safety and quality focus on manufacturing standards and potential for patient harm rather than performance. After device marketing, manufacturers are not required to demonstrate efficacy or quality of performance and since most devices perform adequately, hundreds or thousands of uses would be needed to make meaningful comparisons. Rather than discuss
### Table III.—Features of more commonly used Supraglottic Airway Devices

<table>
<thead>
<tr>
<th>Device</th>
<th>Generation *</th>
<th>Inflated cuff</th>
<th>Gastric drain</th>
<th>Integrated bite block</th>
<th>Special features</th>
<th>ETT passage considered in design</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMA Classic (LMA North America)</td>
<td>1st</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Aperture bars to prevent epiglottic airway obstruction</td>
<td>No bars limit view and deviate ETT passage, inadequate stem length, 15 mm connector glued and narrow</td>
</tr>
<tr>
<td>LMA Flexible (LMA North America)</td>
<td>1st</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Aperture bars to prevent epiglottic airway obstruction</td>
<td>No bars limit view and deviate ETT passage, inadequate stem length, 15 mm connector glued and narrow</td>
</tr>
<tr>
<td>Fastrach LMA (LMA North America)</td>
<td>1st</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Fastrach ETT-soft moulded tip for atraumatic passage</td>
<td>Yes</td>
</tr>
<tr>
<td>LMA Pro-seal (LMA, North America)</td>
<td>2nd</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Second posterior cuff</td>
<td>No difficulty advancing ETT due to alignment of airway channel</td>
</tr>
<tr>
<td>LMA Supreme (LMA, North America)</td>
<td>2nd</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Two drainage channels</td>
<td>No difficulty advancing ETT due to alignment of airway channel</td>
</tr>
<tr>
<td>LMA Protect (LMA, North America)</td>
<td>2nd</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Integrated fiberoptic bundles and viewer screen</td>
<td>Yes</td>
</tr>
<tr>
<td>LMA Ctrach (LMA, North America)</td>
<td>2nd</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Epiglottic elevating bar</td>
<td>No</td>
</tr>
<tr>
<td>Ambu Aura-Once (Ambu, Denmark)</td>
<td>1st</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ambu Aura-i (Ambu, Denmark)</td>
<td>2nd</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Depth markers</td>
<td>Yes</td>
</tr>
<tr>
<td>Ambu AuraGain (Ambu, Denmark)</td>
<td>2nd</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Depth markers</td>
<td>Yes</td>
</tr>
<tr>
<td>Laryngeal tube LT (VBM Medical, Germany)</td>
<td>1st</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Proximal cuff to stabilize during CPR</td>
<td>No</td>
</tr>
<tr>
<td>Laryngeal tube LTSII &amp; LTSD (VBM Medical, Germany)</td>
<td>2nd</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Proximal cuff to stabilize during CPR</td>
<td>No</td>
</tr>
<tr>
<td>iLTSD (VBM Medical, Germany)</td>
<td>2nd</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Proximal cuff to stabilize during CPR, specific ETT and stabilizer available</td>
<td>Yes</td>
</tr>
<tr>
<td>i-Gel (Intersurgical, Europe)</td>
<td>2nd</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Self-pressurizing cuff available</td>
<td>Yes</td>
</tr>
<tr>
<td>Air-Q (Mercury Medical, North America)</td>
<td>2nd</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Removable 15 mm connector</td>
<td>Yes</td>
</tr>
<tr>
<td>Air-Q Blocker (Mercury Medical, North America)</td>
<td>2nd</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Removable 15 mm connector</td>
<td>Yes</td>
</tr>
<tr>
<td>Baska Mask (BVLM, Australia)</td>
<td>2nd</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Increased airway pressure increases seal pressure. Traction on “tail” can angulate tip of mask</td>
<td>No</td>
</tr>
<tr>
<td>TotalTrack (MedComflow, Spain)</td>
<td>2nd</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Integrated fiberoptic system with LCD screen. Aspiration system for internal mask secretions</td>
<td>No</td>
</tr>
</tbody>
</table>

LMA: laryngeal mask airway; ETT: endotracheal tube; LTS: laryngeal tube suction; CPR: cardiopulmonary resuscitation.

*The term third generation SAD is not used to avoid confusion.*

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GORDON

SUPRAGLOTTIC AIRWAY DEVICES

March 2018
the potential implications of studies comparing types of SAD, this paper summarizes the features of some commonly used devices in Table III.5, 6, 42 Important features to note include quality of the esophageal seal allowing ventilation with higher peak airway pressures, a gastric channel permitting stomach decompression, the angle of curvature especially in those devices with rigid shafts, the thickness and shape of the cuff; the material used for SAD construction (PVC, silicone or elastomere) and existence of an integrated bite block. More recent SAD designs incorporate channels to direct gastric content away from the airway and integrated cuff pressure measurement e.g. the LMA® Protector Airway. The Video Laryngeal Mask Totaltrack™ allows simultaneous ventilation and visualization of intubation which can prove useful in patients predicted to both be difficult intubations and prone to rapid oxygen desaturation.44

Troubleshooting

SAD malposition is relatively common, and largely related to inadequate insertion technique, depth of anesthesia or size selection. In one study, fibroptic assessment of 108 patients with LMAs showed that 40% were malpositioned.45 Malposition can lead to significant leaks causing inadequate ventilation, gastric insufflation, aspiration and airway obstruction. Potential problems include downfolding of the epiglottis, folding of the cuff, and the tip of the SAD sitting between the vocal cords.46

Table IV summarizes the tests that can be employed to ensure correct placement (possible in second generation SADs).4

Conclusions

Since their introduction in the 1980s, SADs have emerged as essential airway management tools. Over the years, the variety of devices, their features and the proposed uses have expanded significantly. They are used in hospital settings, prehospital care, elective and emergency anesthesia, in spontaneously breathing patients and for positive pressure ventilation, as conduits for intubation, to bridge extubation and for airway rescue. There are multiple potential complications but most are rare. Aspiration and loss of airway are amongst the most serious. Clinicians should not become complacent about their use. Although considered a low skill technique, adequate practice, familiarity with the specifics of the chosen device, and careful patient selection are important to ensure safety and proficiency. These considerations can help reduce the incidence of SAD complications and promote further development and use of these highly successful airway inventions.

**Table IV.**—Tests that allow to check adequate positioning and performance of second generation Supraglottic Airway Devices.4

<table>
<thead>
<tr>
<th>Placement Test</th>
<th>Question</th>
<th>Procedure</th>
<th>Results with correct placement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric tube (bubble test)</td>
<td>Is SAD adequately deep in postcricoid region?</td>
<td>Seal drainage tube with drop of gel then PPV</td>
<td>No bubbles detected in the drop of gel</td>
</tr>
<tr>
<td>Suprasternal notch tap test</td>
<td>Is SAD adequately deep in postcricoid region?</td>
<td>Seal drainage tube with drop of gel and apply pressure to suprasternal notch with a finger</td>
<td>Gel moves synchronously with suprasternal pressure</td>
</tr>
<tr>
<td>Insertion of gastric tube</td>
<td>Is the tip of the device folded?</td>
<td>Insert gastric tube via SAD drainage tube</td>
<td>No resistance encountered</td>
</tr>
<tr>
<td>Performance Test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal leak pressure test</td>
<td>What is the maximum peak pressure to ventilate without a leak?</td>
<td>Set APL valve to 30 cmH₂O, set gas flow to 3L/min, note the pressure at which an audible leak occurs</td>
<td>&gt;25 cmH₂O or +8 cmH₂O above peak airway pressure under normoventilation</td>
</tr>
<tr>
<td>Maximum minute volume ventilation</td>
<td>Can you achieve the maximum minute ventilation with the SAD?</td>
<td>Perform four maximum breaths in 15 s and calculate the minute ventilation</td>
<td>&gt;12L in adults or &gt;2x resting minute ventilation</td>
</tr>
</tbody>
</table>

SAD: supraglottic airway device; APL: adjustable pressure limiting.
Key messages

— Proposed uses of SADs are expanding and designs are constantly evolving.

— As we extend the boundaries for safe practice with supraglottic devices, the NAP4 audit has taught us the importance of careful case selection, operator experience and vigilance to airway management at each stage of anesthesia.

— Regular SAD use will develop and maintain familiarity and skill, increasing the likelihood of better outcomes in emergency settings.

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Dupta B,omez-amachandranooka trametz.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Lung ultrasonography and echocardiography in the Intensive Care Unit: a combined and practical approach

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ABSTRACT

This article describes some practical applications of critical care ultrasonography that are of interest to the frontline intensivist. Instead of presenting a standard state of the art review article, we present 3 typical clinical cases where combined echocardiography, lung ultrasonography, and other ultrasonography techniques were helpful to the critical care team. The manuscript includes a variety of figures and video clips that illustrate the utility of critical care ultrasonography in guiding diagnosis and management of the critically ill patient.

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Key words: Ultrasonography - Echocardiography - Critical care - Lung.

Critical care ultrasonography (CCUS), as defined in the ACCP/SRLF Statement, has strong utility for the assessment of respiratory and circulatory failure. This is reflected by its incorporation into critical care training programs, its widespread use by frontline intensivists at the international level, and by the large number of studies that have been published in the field. Echocardiography, by the transthoracic (TTE) or the transesophageal (TEE) route, allows for the rapid evaluation of systolic and diastolic function of the ventricles, the assessment for need of fluids, and categorization of shock state in order to guide management strategy. Lung ultrasonography can be combined productively with echocardiography to evaluate respiratory failure.

The aim of this manuscript is to inform the reader of the utility of the combining echocardiography with lung ultrasonography for management of cardiopulmonary failure in the Intensive Care Unit (ICU). Rather than writing another standard “state of the art” paper, we present three true life cases of the type frequently encountered in critically-ill patients; pulmonary edema, difficulty with weaning from mechanical ventilatory support, and pulmonary embolism with shock, framed in order to demonstrate the use of ultrasonography in the ICU. All of the cases are associ-
The patient had severe persistent hypoxemia following intubation while being bag ventilated with FIO₂ of 1.0. A team member performed immediate limited bilateral lung ultrasonography by scanning anterior rib interspaces on the right and left.

Case 1: acute pulmonary edema

This 19-year-old female presented with severe dyspnea. According to family members, she had a non-specific prodrome for several days before admission of malaise and fever. She developed abrupt shortness of breath and mental status change which required transport to the emergency department. She had been in excellent health up to the present illness. The critical care team was called for immediate consultation.

Vital Signs: Blood pressure (BP) 70/40 mmHg, respiratory rate (RR) 42 cycles/min, Temp 39 °C, heart rate (HR) 135/min, O₂ saturation 90% on high flow nasal oxygen.

The patient was lethargic with labored breathing. Lung examination showed bilateral rhonchi and wheezing. There was no audible murmur. The examination was otherwise normal.

The critical care team prepared for a high risk urgent endotracheal intubation (UEI).

**Question 1**

How is ultrasonography useful during urgent endotracheal intubation (UEI)?

A major potential complication of UEI in this patient was aspiration of gastric contents. Ultrasonography is useful for rapid identification of gastric content that alerts the ICU team to the possibility that a patient may be at risk for massive aspiration event. Examination for gastric contents was performed while the UEI team set up for a high risk intubation sequence. The results of the gastric ultrasonography are shown in Figure 1 and Supplementary Video 1A, online content only.

Figure 1 and Supplementary Video 1A demonstrate a large volume of fluid in the stomach. The team leader decided that the patient could tolerate nasogastric tube insertion on an emergency basis. One liter of gastric fluid was suctioned from the stomach before induction followed by successful intubation.

The patient had severe persistent hypoxemia following intubation while being bag ventilated with FIO₂ of 1.0. A team member performed immediate limited bilateral lung ultrasonography by scanning anterior rib interspaces on the right and left.

**Question 2**

How is ultrasonography useful for evaluation of refractory hypoxemia following successful endotracheal intubation?

One consideration for refractory post intubation hypoxemia is inadvertent tube placement into the right mainstem bronchus with the inflated endotracheal tube cuff blocking air entry into the left lung. This can be detected using lung ultrasonography to identify lung sliding. Lung sliding with bag ventilation indicates that there is air entry into the lung i.e. proper tube placement. In addition it would immediately exclude the possibility of pneumothorax, however unlikely. The results of the lung ultrasonography are shown in Supplementary Video 1B, C.

Supplementary Video 1B demonstrates lung sliding on the right side coincident with bag ventilation; video 1C demonstrates absent lung sliding on the left side. Following pullback of the endotracheal tube using real time ultrasonography control, there was bilateral lung sliding indicating that the endotracheal tube is now well positioned. There was no pneumo-
question 3

How is ultrasonography useful for rapid evaluation of acute respiratory failure?

It is superior to chest radiography and similar in performance to chest computerized tomography for detection of pneumothorax, normal aeration pattern, alveolar/interstitial pattern, alveolar consolidation, and pleural effusion.8, 9 Due to its immediate availability, it was the best initial imaging modality in this case. The team immediately performed a more comprehensive lung ultrasonography. The results of the lung ultrasonography are shown in Figure 2 and Supplementary Video 1D.

Figure 2A and Supplementary Video 1D, which was representative of a pattern found in multiple interspaces, demonstrates a profuse B pattern. This finding is consistent with a severe alveolar or interstitial process. This may occur due to primary lung injury (e.g. ARDS); due to elevation of left atrial pressure (cardiogenic pulmonary edema); or, less commonly, due to both processes simultaneously. Figure 2B and Supplementary Video 1E was taken with a high frequency linear vascular probe, in order to examine the morphology of the pleural line. The pleural line is irregular supporting the diagnosis of edema following primary lung injury as the mechanism for the B line formation.10 The profuse pattern B line pattern is more consistent with cardiogenic pulmonary edema, so the ICU team considered the possibility of a dual diagnosis. Figure 2C and Supplementary Video 1F shows translobar alveolar consolidation of the left lower lobe.11 Given the clinical presentation, the team considered pneumonia leading to sepsis and ARDS with high probability, but considered also the possibility of cardiogenic pulmonary edema.

question 4

How is echocardiography useful for evaluation of hemodynamic failure?

Echocardiography has utility for evaluation of shock for several reasons:

— it may occasionally identify an imminently life threatening process that, if left untreated, will cause early death of the patient;
— it allows prompt categorization of the shock state (cardiogenic, obstructive, hypovolemic, or vasoplectic with their subcategories);
— it guides a management strategy that is derived from the categorization;
— it allows identification of coexisting causes for hemodynamic failure;
— it is useful for serial examinations to
track evolution of the disease process, response to therapy, and additional complications.

As lung ultrasonography is combined productively with echocardiography in the evaluation of acute respiratory failure, the team performed an immediate echocardiography in order to look for immediately life threatening cause for the shock state, to categorize the pattern of hemodynamic failure, and to guide management strategy.

The results of the echocardiography are shown in Figure 3 and Supplementary Video 1G-K. They show severe mitral regurgitation in association with a mitral valve vegetation. The acute valve failure was due to disruption of valve function related to endocarditis with rapid onset of severe cardiogenic pulmonary edema. The blood cultures grew Strep species. It is likely that the left lower lobe pneumonia resulted in bacteremia that infected mitral valve. The anterior leaflet of the mitral valve has morphological features suggesting mitral stenosis that may have predisposed to endocarditis. The mitral stenosis had not yet resulted in any symptoms in this otherwise healthy young woman. There is mild aortic regurgitation without evidence of vegetation, although TTE does not rule out this possibility. Transesophageal echocardiography would have been required for definitive evaluation of the aortic valve.

Based upon the echocardiography results and severe cardiopulmonary failure, the patient had emergency mitral valve replacement. The aortic valve required replacement as well, as intraoperative findings indicated that there was aortic valve endocarditis that was not visible on TTE. The patient was discharged from the hospital without further incident two weeks later.

This case is an example of the utility of combining lung ultrasonography and echocardiography for rapid assessment of cardiopulmonary failure. It allowed prompt identification of a life threatening process at point of care, identification of the source of sepsis in the form of a pneumonia, and consideration of a dual diagnosis for the lung findings (ARDS and cardiogenic pulmonary edema). By extending the examination to a whole body ultrasonography approach,12 the ICU team was able to avoid a potentially life threatening complication of urgent endotracheal intubation (massive aspiration of gastric contents) and to identify the cause of refractory hypoxemia post endotracheal intubation (right main-stem intubation).

Case 2: weaning from mechanical ventilatory support

This 73-year-old male had been on mechanical ventilatory support for nine days. He required endotracheal intubation following failure of non-invasive ventilatory support for bacteremic left lower pneumococcal pneumonia that was associated with hemodynamic failure requiring several days of vasopressor support. He had a history of severe COPD and ischemic heart disease that required coronary stenting three months before admission. The patient had clinical improvement, so the ICU team placed the patient on a spontaneous breathing trial with pressure support of 5 cmH₂O and PEEP of 5 cmH₂O. They observed that the patient became tachypneic, hypertensive, and tachycardic with a rapid shallow breathing index of 140. They placed the patient back on assist control ventilation pending another attempt at a spontaneous breathing trial (SBT).
Vital signs: BP 120/70 mmHg, RR 16 cycles/min, Temp 39 °C, HR 82/min normal sinus rhythm, O₂ saturation 97%, TV 500 cc, FIO₂ 0.35 PEEP 5 cmH₂O, BMI 21.

The patient was alert and cooperative.

The lungs were clear and there was no peripheral edema. Compared to admission, the ICU team observed that the patient had lost muscle mass.

The laboratory values were within normal limits.

**Question 1**

How is ultrasonography useful for assessing the patient when there is consideration of weaning from mechanical ventilatory support?

Examination of cardiac, diaphragmatic, lung, and pleural function with ultrasonography may be helpful to the intensivist while weaning the patient from mechanical ventilatory support. Before and during a SBT, ultrasonography may identify findings that suggest that the extubation will fail; and that, if remedied, may improve the likelihood of successful extubation.

The ICU team performed echocardiography followed by diaphragmatic, lung, and pleural ultrasonography.

**Echocardiography**

Supplementary Video 2A, online content only shows the parasternal short axis view of the heart. There is reduced left ventricular (LV) function and a systolic wall motion abnormality involving the anterior septum and anterior wall of the left ventricle.

These findings suggest risk of precipitating ischemic dysfunction during the SBT. Spontaneous breathing is a form of exercise that increases the need for cardiac output which may precipitate ischemia with cardiogenic pulmonary edema in this patient with significant coronary artery disease. In order to reduce risk of cardiac ischemia, the ICU team decided to give the patient 50 mg of metoprolol in order to attenuate tachycardia, and planned to use the nitroglycerine drip both for tight control of blood pressure and as an anti-ischemic medication should the need arise. The patient was already on both aspirin and clopidogrel.

Figure 4A, B shows the mitral valve (MV) diastolic inflow and tissue Doppler imaging (TDI) of the lateral mitral annulus before the SBT respectively. The MV inflow and annular velocity are consistent with grade 3 diastolic function with an E/e' ratio of 15 consistent with elevation of left atrial pressure (LAP).

These Doppler measurements permit the intensivist to identify and grade diastolic function as well as to estimate left atrial pressure. The reader is referred to a useful algorithm in the 2016 ASE/EACVI Statement on Evaluation of LV Diastolic Function. The algorithm calls for measurements that are not always practical in the critically ill patient on mechanical ventilatory support, instead being designed for the stable patient studied in an echocardiography laboratory. The algorithm...
is appropriately simplified for frontline use by the intensivist to include the MV inflow and lateral annular TDI velocity. Measurement of these variables before the performance of the SBT may be useful to identify patients at high risk of weaning failure. In the present case, the mitral inflow pattern with elevated E/A ratio and elevated E/e’ before the SBT was suggestive of an elevation of left atrial pressure with risk that the SBT could precipitate cardiogenic pulmonary edema. A number of studies have reported on the utility of Doppler measurements for identifying the patient who may fail the weaning trial due to changes in diastolic function that may occur during a SBT. While these studies suggest that Doppler measurements have utility in predicting failure of SBT, what lacks is any study that guides a management strategy determined by the Doppler measurement.

Based upon the echocardiography examination, the ICU team decided to give an empiric dose of intravenous furosemide in order to reduce the risk of cardiogenic pulmonary edema that might be precipitated by the change in loading conditions implicit to spontaneous breathing. Reevaluation several hours following initiation of diuresis suggested a significant decrease in LAP as indicated by the E/A ratio reversal (Figure 4C).

**Ultrasonography of the diaphragm**

Figure 5 shows measurement of the right hemidiaphragmatic excursion which was 0.9 cm during SBT with pressure support of 0 cm H₂O and PEEP 5 cm H₂O.

Ultrasonography allows visualization of the diaphragm with the right hemidiaphragm more easily imaged than the left. This allows measurement of diaphragmatic excursion, expressed in centimeters, and diaphragmatic thickening, expressed as thickening fraction. Both parameters may have utility in predicting the outcome of extubation. Unilateral or bilateral diaphragmatic paralysis is readily identified with ultrasonography. It is uncommon as an isolated cause for weaning failure in the medical patient, being more relevant in the post cardiac surgery case. The presence of bilateral diaphragmatic excursion excluded diaphragmatic paralysis in this patient, so the ICU team focused on determining if there was diaphragmatic dysfunction.

The ICU team identified reduced diaphragmatic excursion that was in the range that has been reported to be associated with weaning failure. Absent more specific diagnosis, the cause of the dysfunction was considered to be multifactorial: disuse atrophy, chronic de-conditioning due to severe COPD antecedent to the present illness, and possible critical illness polyneuromyopathy, none of which were immediately reversible. The results of the diaphragmatic ultrasonography indicated that the patient had high risk for extubation failure, but they did not absolutely contraindicate an attempt at extubation. The ICU team decided that they would place the patient on non-invasive ventilatory support immediately following any extubation in an attempt to unload the dysfunctional diaphragm.

**Lung and pleural ultrasonography**

Figure 6A and Supplementary Video 2B show the lung ultrasonography pattern found at multiple sites over the thorax excepting the left lateral lower thorax. There is a generalized...
A line pattern with lung sliding, indicating normal aeration pattern and no presence of pleural effusion. Figure 6B and Supplementary Video 2C show the lung ultrasonography pattern found over the distribution of the left lateral lower thorax. There was a small non-translobar consolidation involving the lateral segment of the left lower lobe.

The combined lung and pleural ultrasonography results identify no factor that would contraindicate another SBT. Chest radiography is not required, as lung ultrasonography is superior to chest radiography for detection of findings that are relevant to this clinical situation. Chest CT scan would have no additional utility; as the results would be similar to the ultrasonography, added to which are the problems related to radiation exposure and out of ICU transportation of the patient. The finding on ultrasonography of a large pleural effusion in a marginal patient would lead to consideration of a high volume thoracentesis in order to improve likelihood of successful extubation. Although intuitively attractive, there is limited literature to support the utility of removing a pleural effusion on outcome of extubation. This remains a clinical decision. The patient had no pleural effusion. The finding of a residual left lower lobe consolidation was anticipated, given the initial diagnosis of bacteremic left lower lobe pneumonia. Ultrasonography is an effective means of identifying alveolar consolidation, and can be used to track the improvement of the pneumonia by serial scanning. The consolidation pattern in this patient may take a while to resolve completely, but is not sufficient to discourage another attempt at a SBT.

Soummer et al. reported that lung ultrasonography has some utility for predicting weaning failure by identification of lung de-recruitment that may occur during the SBT. Lung ultrasonography performed at the start and at the end of the SBT may be used to detect loss lung aeration that occurs during the SBT regardless of its cause. The use of a validated Lung Ultrasonography Score (LUS) has been reported to allow quantification of lung aeration for a variety of applications. The use of lung ultrasonography relates to the observation that the spontaneous breathing after a period of mechanical ventilation may result in changes in lung aeration. The LUS Score is determined by assigning numerical values to patterns lung ultrasonography (A lines, B lines, consolidation). The numerical values of four different lung ultrasonography patterns assessed at 12 defined lung regions are summed with the total giving the final LUS. An A pattern is scored as 0, scattered B line pattern as 1, profuse B line pattern as 2, and consolidation as 3. The maximal LUS is therefore 36. The higher the LUS, the less well aerated is the lung. The LUS is calculated before and during the SBT. An increase in LUS, especially above 17, that occurs with SBT predicts failure of extubation, although there is an indeterminate range of rise where the test does not have strong predictive value.

Lung ultrasonography was performed be-
fore and 30 minutes into the SBT. This patient had a low LUS at the start of the SBT with a value of 3. This is consistent with a well aerated lung. Under the challenge of SBT, the ICU team re-measured the LUS. The lung ultrasonography examination performed during the SBT showed A line pattern at 8 examination points. Figure 6C and Supplementary Video 2D shows a new scattered B line pattern that was found at three examination points. The left lower lateral consolidation was unchanged. The LUS during SBT was therefore six. This represents a minor loss of aeration during SBT and is associated with a high probability of successful extubation. The maintenance of a predominant A line pattern (indicated by the low LUS) indicated that there was minimal loss of aeration during the SBT, and that the change in loading conditions had not precipitated cardiac ischemia with elevation of LAP. This would have resulted in a profuse B line pattern and not as a limited number of scattered B lines in a few areas.

During the SBT, the ICU remained alert for changes in cardiac loading conditions that might precipitate cardiac ischemia in this predisposed patient. The patient had some augmentation of heart rate that responded to 5 mg of metoprolol by intravenous infusion. The standing dose of metoprolol was increased as well. An increase in blood pressure occurred early in the SBT which was promptly controlled with nitroglycerine that was prepared for immediate infusion before the SBT. Due to concerns related to the reduced diaphragmatic function detected by ultrasonography combined with severe COPD, the patient was extubated to non-invasive ventilation. Over the course of several days, the patient was changed to nocturnal NIV and transferred to the pulmonary rehabilitation service. Cardiology service was involved for ongoing assessment and treatment of the ischemic heart disease.

This case represents a typical example of the utility of combining ultrasonography and echocardiography during the weaning process. In many patients, the weaning process is straightforward and would not warrant this level of ultrasonography examination. In this case, the ICU team identified the patient as being a “difficult to wean” patient; hence the use of multimodality ultrasonography. In our experience, the relevant echocardiography measurements can be made in a short period of time, particularly as this type of patient will already likely have had a comprehensive examination earlier in the hospitalization. The lung, pleural, and diaphragmatic ultrasonography examination are performed as a single sequence and take a few minutes to accomplish by the intensivist who is competent in critical care ultrasonography. Calculation of a formal LUS is laborious, particularly as it requires examination of the posterior thorax. An alternative method is to use a simplified LUS without examination of the posterior thorax, or even a qualitative assessment of aeration before and during the SBT. These have not been validated in the literature, but are a pragmatic approach in the busy ICU.

Case 3: pulmonary embolism

This 29 year old female presented following a cardiac arrest at home. Following successful cardiopulmonary resuscitation by the prehospital team, the patient was admitted to the ICU with persistent hypotension on high dose epinephrine infusion. She was on mechanical ventilatory support in assist control mode and was making no spontaneous respiratory effort.

Vital Signs: BP 90/50 mmHg, RR 16 cycles/min Temp 36 °C, HR 120/min normal sinus rhythm, O₂ Saturation 90%, TV 450cc, FIO₂ 0.6.

Cardiac and pulmonary examination were normal.

Laboratory: PaCO₂ 45 mmHg, PaO₂ 60 mmHg, base deficit 14 mmol/L with high lactate level.

Question 1

How is ultrasonography useful for to rule out an imminently life threatening cause for this patient’s shock state?

The combination of echocardiography and lung ultrasonography are useful for rapid
identification of an imminently life threatening cause for the shock state such as tension pneumothorax, pericardial tamponade, or massive pulmonary embolism. Although not applicable to this case, the identification of life threatening hemorrhage related to trauma is another example where immediate ultrasonography has major application, as exemplified by the use of the extended FAST (focused assessment with sonography in trauma) examination that is in widespread use by trauma specialists.

The ICU team performed an immediate TTE, lung ultrasonography, and examination for deep venous thrombosis (DVT).

Supplementary Video 3A, online content only shows the lung ultrasonography pattern found at multiple sites. There were A lines with lung sliding throughout indicating normal aeration pattern. Supplementary Video 3B shows a TTE image of the apical four chamber view of the heart. There is massive dilation of the right ventricle. Supplementary Video 3C shows a thrombus in the left common femoral vein.

The lung ultrasonography ruled out tension pneumothorax as a cause of the shock state and suggested the possibility of pulmonary embolism which typically does not show major abnormality on lung ultrasonography. The TTE examination was consistent with the diagnosis of hemodynamically significant pulmonary embolism, with the confirmatory result of a deep vein thrombosis (DVT) in the common femoral position. Due to the severe shock state, the ICU team decided to administer fibrinolytic therapy on an urgent basis. At this juncture, use of the fibrinolytic agent without confirmatory imaging would have been reasonable; given the delay inherent to performance of a computerized tomography pulmonary angiography. As an alternative, the ICU team performed immediate TEE seeking confirmation of the diagnosis.

Supplementary Video 3D and Figure 7A show a mid-esophageal four chamber view with TEE. There was right ventricular dilatation. Supplementary Video 3E and Figure 7B show a transgastric view at 0° with paradoxical septal motion. This confirmed the presence of an acute cor pulmonale. Supplementary Video 3F and Figure 7C show a thrombus in the right pulmonary artery. This established a definitive diagnosis of pulmonary embolism.

The safety of TEE is well established when performed in critically ill patients on mechanical ventilatory support. Given its ease of use and excellent image quality, it was deployed in this case as a routine imaging modality, given the risks related to fibrinolytic therapy. Clinical studies have reported that TEE has a high specificity and a moderate sensitivity for detection of pulmonary embolism. The moderate sensitivity of TEE relates to difficulty with imaging the left pulmonary artery and the inability of TEE to detect lobar PE. Based upon this result, the ICU team administered fibrinolytic therapy on an emergency basis. In this patient, the ultrasonography examination also detected

Figure 7.—Transesophageal echocardiography in a patient in shock with a massive pulmonary embolism. A) Transverse mid-esophageal view, visualizing the severe RV dilatation with a compression of the left ventricle; B) transverse transgastric short axis view, visualizing the typical septal flattening (or paradoxical septal motion); C) transverse upper-esophageal view at the great vessel, visualizing a thrombus adherent to the anterior wall of the right pulmonary artery at the lobar bifurcation (arrow). RV: right ventricle; LV: left ventricle; RPA: right pulmonary artery; SVC: superior vena cava.
a DVT of the left femoral vein. A DVT is visualized in only 30-50% of cases of pulmonary embolism.17

Question 2

How is echocardiography useful for following the efficacy of fibrinolysis on the right ventricular (RV) function?

The efficacy of fibrinolytic therapy can be assessed by performing serial echocardiography with focus on RV function. In this case, fibrinolytic therapy was a relative contraindication to repeat TEE, so the ICU team used TTE to follow response to therapeutic intervention (Figure 8).

The RV ejection flow was abnormal before fibrinolysis (Figure 8A). The pulmonary acceleration time below 100 ms is consistent with pulmonary hypertension, the low velocity-time integral (VTI) reflects a low RV stroke volume (normal is approximately 16 cm), and the biphasic VTI is consistent with massive acute obstruction of the pulmonary circulation.

Four hours following fibrinolytic therapy, there was complete normalization of the ejection flow pattern measured by spectral Doppler and reduction in the RV dilation (Figure 8B). Coincident with this, there was improvement in the overall hemodynamic status of the patient.18

Conclusions

Both echocardiography and lung ultrasonography have been well described as having utility for guiding the diagnosis and management of the critically ill patient. Both techniques can be performed rapidly, safely, repeatedly, and in goal directed fashion at point of care by the intensivist in charge of the case. Rather than compartmentalizing the two techniques, we favor integration of echocardiography with lung ultrasonography; given that pulmonary and cardiac function are so closely connected. Other aspects of critical care ultrasonography are included into the imaging strategy by using a whole body ultrasonography approach to assessment of critical illness. While the utility of the whole body approach is intuitively obvious, as reflected in the three cases that we have presented in this article; there is not yet a definitive study that shows that there is improvement in hard endpoints of patient outcome. Individual case descriptions may be convincing, but we encourage research activity to more formally demonstrate clinical effect.2

Key messages

— Echocardiography, lung ultrasonography and other general ultrasonography (diaphragm evaluation, abdominal, vascular) are very helpful in critically-ill patients.
— When combined, they help managing patients.
— Typical cases where critical care ultrasonography is useful are pulmonary edema, weaning failure from the ventilator and circulatory failure.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.


For supplementary materials, please see the online version of this article at www.minervamedica.it.
Right patient selection and management in veno-venous extracorporeal carbon dioxide removal

Dear Editor,

We read with interest the article by Hilty et al.\textsuperscript{1} recently published in Minerva Anestesiologica, which investigated the clinical use of low-flow veno-venous extracorporeal carbon dioxide removal (ECCO\textsubscript{2}R) in two acute hypercapnic respiratory failure (AHRF) scenarios. In mechanically ventilated (MV) patients, ECCO\textsubscript{2}R was effective in supporting the maintenance of lung protective ventilation, while correcting severe respiratory acidosis. In awake spontaneously breathing (SB) patients, ECCO\textsubscript{2}R allowed avoiding the need for invasive mechanical ventilation when patients failed non-invasive ventilation (NIV). However, eight out of 14 MV patients died due to treatment withdrawal and four out of six SB patients progressed to hypoxic respiratory failure and required the upgrade to high-flow extracorporeal circulation before recover or lung transplantation.

In our opinion, this article highlights some important considerations as to the right management of ECCO\textsubscript{2}R in patients suffering from AHRF.

First, it is crucial to select the right patient population that may benefit from ECCO\textsubscript{2}R. The interpretation of the results is limited by the mixed patient conditions and the coexistence of different pathophysiological mechanisms leading to severe hypercapnia, which would have required specific management prior to ECCO\textsubscript{2}R institution. However, pre-cannulation treatment was not clearly described in the study and the indications for ECCO\textsubscript{2}R were in our opinion too generic. In addition, the inclusion of potentially high-risk patients with chronic lung transplant rejection could have blunted the benefit of ECCO\textsubscript{2}R, however, baseline risk scores are not reported. Moreover, MV patients were included after being intubated for median 8.3 days, and therefore they may have been too sick to benefit from ECCO\textsubscript{2}R.

Other potential contraindications to ECCO\textsubscript{2}R (e.g., hemodynamic instability, immunocompromised condition, high body mass index)\textsuperscript{2} may have been present in some patients but were not clearly described.

Second, important information is lacking to understand whether the ventilatory strategy was really protective. Driving pressure values within 48 hours were always significantly higher than the values suggested to be safe in acute respiratory distress syndrome patients,\textsuperscript{3} who were 64% of MV patients included in the study. Additionally, ventilatory settings and arterial blood gases before the institution of ECCO\textsubscript{2}R were poorly described and so was the neuro-muscular blockade and esophageal pressure utilization after cannulation. Finally, peak airway pressure may be an inaccurate estimate of plateau pressure in obstructive lung diseases.

Third, some technical issues deserve mention. The authors reported that they could not reach the targeted ECCO\textsubscript{2}R blood flow (400 mL/min) in SB patients due to negative intrathoracic pressure. However, five out of six of SB patients were ventilated with NIV. Furthermore, the observation that post-membrane partial pressure of CO\textsubscript{2} could be a sensitive parameter for monitoring membrane system status could be questioned by the concept that CO\textsubscript{2} clearance in the artificial lung depends on several factors, among which pre-membrane CO\textsubscript{2} (PvCO\textsubscript{2}) has a crucial role.\textsuperscript{4} Even if PvCO\textsubscript{2} was measured, it is not reported, and transmembrane CO\textsubscript{2} gradient did not decrease significantly within 48 hours.

In conclusion, in our opinion the interesting study hypotheses were not supported by an adequate study design and the lack of crucial information makes it difficult to interpret the study results.

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Patient selection for extracorporeal CO₂ removal: a task as challenging as for ECMO therapy

Dear Editor,

We would like to thank Pettenuzzo and Del Sorbo for their insightful comment ¹ on our article exploring the feasibility of low flow veno-venous extracorporeal CO₂ removal (ECCO₂R) in acute hypercapnic respiratory failure.²

The patient population included in our study reflects the typical case mix present in a universitary intensive care unit affiliated with a lung transplantation unit. Despite the resulting population heterogeneity, this approach was chosen in order to enable a feasibility assessment of ECCO₂R that is closely rooted in reality, as well as verification in a broad population of our preliminary indications for therapy that were, based on previous literature, focused on parameters regarding respiratory failure.³ We were thus able to identify a subpopulation where further risk stratification is necessary to avoid treatment futility, namely mechanically ventilated patients mainly suffering from acute respiratory distress syndrome (ARDS). Based on these results, as is stated in our article, we agree with Pettenuzzo and Del Sorbo that the indications for ECCO₂R need to be refined – especially in patients whose outcome depend on successful bridging to recovery. The PRESERVE score as a tool for assessment of recovery potential in ARDS patients where veno-venous extracorporeal membrane oxygenation (ECMO) therapy is considered,⁴ has recently been validated in our population of ARDS patients treated with ECMO.⁵ Preliminary results from our ongoing research suggest that the PRESERVE score may further be a useful tool for selection of patients suffering from hypercapnic respiratory failure in ARDS for treatment with ECCO₂R, representing a more sensible approach than the use of isolated criteria. Our protocol, in an attempt to position the use of ECCO₂R as a rescue therapy, further favored the inclusion of patients at the limit of lung protective mechanical ventilation, resulting in a median peak inspiratory pressure of 31 mbar and tidal volume of 5.2 mL/kg, corresponding to the original ARDS network guidelines. As a consequence of low overall lung compliance the resulting median driving pressure was 25 mbar before initiation of ECCO₂R. Given the most recent results including the study by Amato et al. and referenced by Pettenuzzo and Del Sorbo,⁶ that were published since the conclusion of our study, we agree that driving pressure (ΔP=Pplat-PEEP) should be considered in the inclusion criteria for ECCO₂R in mechanically ventilated patients in the future. We suggest considering ECCO₂R treatment in patients suffering from hypercapnic respiratory failure with pH≤7.25 and/or PaCO₂≥9 kPa, where in mechanically ventilated patients an inability is reached to maintain VT≥6 mL/kg, Pplat≤30 mbar and ΔP≤15 mbar, and to base this expert decision on similar criteria as applied in considering ECMO therapy, possibly including the PRESERVE score in ARDS patients in order to avoid futile treatment.

In awake spontaneously breathing patients, mortality in our population was low but an eventual upgrade from ECCO₂R to full ECMO was necessary in a majority of patients. This is unsurprising considering that more patients in the respective group suffered from cystic fibrosis awaiting lung transplantation than other indications such as exacerbated chronic obstructive pulmonary disease. Arguably, in these patients ECMO duration was reduced by up to 4.3 days. If using ECCO₂R to delay more invasive ECMO treatment results in a benefit for patients remains to be examined in future studies. Due to the low number of patients, our study does not allow to draw conclusions regarding success of bridge to recovery in awake spontaneously breathing patients such as patients with exacerbated chronic obstructive pulmonary disease.

As Pettenuzzo and Del Sorbo point out, spontaneous breathing increases variability in airway and intrathoracic pressure. Even though NIV has the capac-

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4. © 2018 EDIZIONI MINERVA MEDICA
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ity to add between 5 and 15 mbar of positive airway pressure, this would not be sufficient to counteract negative pleural pressure induced by forced inspiratory maneuvers in spontaneous breathing during respiratory failure. We thus believe that the most likely explanation for our observation that target flow rates were more difficult to achieve in these patients is the association with negative inspiratory pressure during inspiration, while of course another factor is increased mobility in awake patients. We are not aware of previous studies reporting pleural pressure measurements during awake ECMO or ECCO₂R treatment. However, our subjective experience with ECCO₂R is similar to veno-venous ECMO treatment in awake versus in mechanically ventilated patients, supporting this hypothesis. Apart from blood flow rate, efficiency of the gas exchange membrane further determines system efficiency. \( \text{PvCO}_2 \), as determined in Table III in our article, as the sum of post membrane PCO₂ and pre to post membrane ΔPCO₂ neither changed over the course of membrane system lifetime, nor between one and 48 hours of ECO₂R treatment (P>0.05). The influence of membrane efficiency, \( \text{PvCO}_2 \) and blood flow rate on post membrane PCO₂ is complex, thus real-life data is needed to discern its value in a clinical setting. By demonstrating consistency in \( \text{PvCO}_2 \) during the later stages of treatment, our data suggests that post membrane CO₂ dependence on \( \text{PvCO}_2 \) becomes less relevant and thus is a good surrogate measurement of membrane efficiency during that period of treatment. Technological development has since enabled measurement of CO₂ concentration within the membrane sweep gas outlet, further eliminating inaccuracies introduced by difficulties in assessing total CO₂ content in blood samples, which will be reflected in future studies.

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Vol. 84 - No. 3 MINERVA ANESTESIOLOGICA
ing and far to be solved controversy for the best performing SAD, strongly calling for research standardization. However, we must be absolutely aware with the difficulty of testing and standardization of procedures and methods, such as operators’ experience, type and duration of surgery and anesthesia depth monitoring; the last one being of paramount importance if we want to compare ease of insertion, sealing performance and pharyngeal side effects.

If we compare, for example, results from Kriege et al.1 with recent paper from L’Hermite,2 we might find out that in the second paper, the insertion time for LMA-Supreme™ (LMA-S) (Teleflex Medical, Athlone, Ireland) was 30 sec and the sore throat incidence was 21.5%, compared to 18 seconds and 12% in the first paper on same endpoints; the time to insertion of AuraGain™ (AG) (Ambu A/S, Ballerup, Denmark) in Kriege’s study 1 was similar to that of LMA-S in L’Hermite’s Study.2 Conversely, a fresh cadaver study from Lopez3 showed similar performance for AG, LMA-S and I-gel™ (Intersurgical, Wokingham, UK) in terms of insertion, including adjusting maneuvers, and sealing capabilities, but pointing out different cuffs design and tips stiffness and consequential implications in the course of insertion.

Kriege et al.1 compared two deeply different devices: AG is currently the only second-generation SAD with an inflatable cuff designed for tracheal intubation, thus PVC made and with a more than 90° airway conduit shape with eccentric gastric access designed to address endotracheal tube towards laryngeal inlet. LMA-S is PVC made, with close to 90° airway conduit shape and coaxial gastric access, resulting in increased rigidity and impossibility to provide direct intubation. Cuff thickness is different and its relation to airway/gastric conduit is such to result in a lower inflated/deflated ratio compared to other SADs and that is obviously conditioning insertion. Same conclusion comes from cuff shapes, LMA-S’s tip being elongated and known to be more keen to flipping 7 but to enter deeply than other SADs in upper esophageal sphincter,3,4 which could for instance grant higher sealing and aspiration protection but may condition postoperative dysphagia, especially if no neuromuscular blocking agents and no anesthesia depth monitor is used.2

More open questions come from cuff pressure monitoring, correct size choice parameters, anesthetic plan adequacy for insertion and for maintenance, removal endpoints and complication assessment criteria: for all these reasons, we believe that the final answer to the seek of best device is far to come.

In the crowded parade of SADs, many classification attempts have been made,5 but this is probably not the right way to follow, as any classification, due to technological evolution and market pressure, would get out of date almost immediately. Probably we should simply change the point of view, shifting any classification in advanced or basic SADs, based on specific targets and clinical endpoints expected from the device we are using. The real point might be choosing our SAD not for its absolute advantage but for tailored indication in the patient: if we expect more aspiration risk it could be wiser to address our choice to a device physically “plugging” the upper esophageal sphincter such as LMA-S; if we expect more comfort and need for intubation we could choose AG and (should future studies confirm its performance) the recently launched silicone-cuff LMA Protector™ (Teleflex Medical, Athlone, Ireland); if we are worried about cuff pressure in specific clinical setting we could choose I-gel™. If we have to deal with obese patients we will move necessarily our choice to second generation advanced SADs,6 while if we need to cover endoscopic procedures not renouncing to advantages of complete airway control, we could choose LMA-Gastro™ (Teleflex Medical, Athlone, Ireland).7

Rather than a competition to find out the absolutely best device, we should develop tools to address the choice of best device for a certain procedure in a certain patient, and we should have opportunity to choose in our SADs portfolio and to become proficient with different devices, probably starting to include below this lines also first generation devices if not for minimal procedures.8

Interestingly, in Kriege’s 1 results, novices were better performing with LMA-S than with AG, which we would interpreter not as a study bias but as a further clue that single SAD performance on specific issue is highly depending on design and constructive features, not necessarily conditioning overall performance, but affecting specific issues such as insertion.

We expect that a more sophisticated device would increase the learning curve and might even prove to be more difficult to insert or to manage but in front of increased performance. This is what we are personally experiencing with LMA Protector™, which is entirely silicon made and bulkier if compared with LMA-S thus resulting in longer learning curve also in hands of experienced users.

In anesthetic era when SADs are becoming not only rescue but definitively routine airways, with extended indications and increasing performance, excellently performed studies like Kriege’s 1 do highlight the need to find not a best SAD but the best SAD for our patient.

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We still lack an effective method to identify the best supraglottic airway device

Dear Editor,

We appreciate the interest by Pavoni et al.\(^1\) regarding our published trial\(^2\) and are thankful for the opportu-
nity to further comment on this important topic. Today, the varieties of supraglottic airway devices (SGA) are confusing and the number is constantly increasing. For the common anesthesiologist, it has become nearly impossible to fully appreciate the different builds, features and materials used for all different types of SGAs. How can the anesthesiologist decide which SGA to use? It is now generally accepted that so-called second-generation SGAs offer benefits and safety over the classic (first generation) laryngeal mask airway in a range of scenarios.\(^3\)\(^6\)

The comments of Pavoni et al.\(^1\) are in full agreement with our opinion. It is surprising that most manufacturers of SGAs seem to ignore many of these critical questions that Pavoni et al.\(^1\) ask. Often new models are pushed on the market before the existing tools are fully characterized. Study results with a specific device are transferred to other devices and models without understanding the significant differences in build, shape and material used. A published analysis of a product by one manufacturer under certain conditions cannot be directly translated to the product of another manufacturer. Additionally, it cannot be assumed that study results are still valid if a manufacturer decides to change material, build or shape of an SGA without changing the name of the device or informing the practitioner about these changes. Study results of a specific group of patients, for example normal weight, middle-aged females, can also not be transferred such as those that are cachectic, edentulous and elderly.

It is not easy to guarantee transferability of studies in the field of airway management since there are many factors which could influence performance of the specific device. Cook et al. had already identified this problem in 2003 and proposed a structured analysis of novel airway devices, similar to the developmental process of drugs.\(^7\) Additionally, the pharmaceutical industry has to prove in well-designed studies, and a predefined manner, that the pharmacologic agent is actually accomplishing its therapeutic goal. Indication, side effects and safety have to be evaluated and described. This approach is more difficult in trials focusing on airway management because of the significant role of the individual anesthesiologist’s expertise. In the field of airway management evaluation of devices and tools are largely driven by investigator-initiated studies. This often results in smaller studies that are performed by airway enthusiasts who have a high level of clinical expertise.

Our observed insertion time for the LMA Supreme is comparable to other publications which confirms our observation.\(^8\)\(^9\) Faster time for insertion of the LMA Supreme may be attributed to its shape and material, in contrast to the more flexible and bulky structure of the Ambu Gain.

The question is what device is commercially available that has an acceptable success rate with minimal risk of airway injury? We agree with Pavoni et al.\(^1\) that the choice for an optimal SGA is dependent on different points of view and does not follow any classifications.\(^10\)

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The decision of if and what kind of SGA is used strongly depends on specific patient characteristics (e.g. pediatric vs. adult, existing reflux) and situations (e.g. ophthalmic surgery vs. laparoscopic abdominal surgery). One has to ask if it is really mandatory to use an SGA for example, for a laparoscopic abdominal surgery in a morbidly obese patient? Even with all the advantages of SGAs, the endotracheal tube is a very well accepted device that is successfully used to ventilate patients.

Brain described in his first publication a short- and long-term learning curve for successful LMA usage. Brimacombe seconded this observation that the optimal use of this device, resulting in a significant reduction of adverse events, is achieved after two years and more than 750 applications. The learning curve of successful insertion of the laryngeal mask is also dependent upon the specific device that is being used. Consequently, the key to a successfully using an SGA largely depends on the clinical expertise and experience of the user.

In conclusion, extensive, randomized, controlled multicenter studies are needed to characterize specific SGAs and to identify potential advantages, limitations and disadvantages. Study results from clinical trials like ours can be extremely helpful to design these much-needed large-scale trials. The specialty of anaesthesiology has not developed an efficient way to focus research efforts to identify the devices and tools that we are looking for.

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Thyroid surgery under bilateral superficial cervical block and hypnosis

Dear Editor,

Recently, there has been a renewed interest in hypnosis for surgery. Anaesthetists participate in introducing hypnosis to their practice and to the treatment of pain. The induction of hypnosis is rather simple and fast procedure, during which the patient is guided through suggestions to focus his attention on general well being, deep relaxation, eyelid heaviness and regular breathing. In a meta-analysis, Tefikow et al. demonstrated that
hypnosis exerts a beneficial effect on pre- and post-surgical stress, drug consumption, postoperative pain and duration of surgery.

We present a case of hemithyroidectomy performed under superficial cervical block and hypnosis.

After obtaining written consent for publication, a 76-year-old patient was scheduled for hemithyroidectomy. Her medical history included morbid obesity, obstructive sleep apnea syndrome (OSA) with oral device, arterial hypertension, sinus tachycardia and a degenerative disc disease. Her current treatment included valsartan/hydrochlorothiazide 80 mg/12.5 mg, pregabalin 75 mg, zopiclone 7.5 mg. Her surgical history included a right hip replacement, cataract surgery, abdominal plasty, cesarean section, and tonsillectomy.

At the pre-anesthetic consultation, she was informed of the advantages and disadvantages of different techniques of anesthesia. She choose regional anesthesia under hypnosis. She was informed about shifting to general anesthesia at any time.

Before surgery a peripheral venous catheter was inserted. The patient was monitored with pulse oximetry, non-invasive blood pressure and electrocardiography. An ultrasound guided bilateral superficial cervical plexus block under hypnosis, was performed. Needle insertion was located at the posterior border of the Sternocleidomastoid muscle at a line crossing the cricoid cartilage. To block the plexus and the transverse cervical branch on each side, 10 mL of 0.75% ropivacaine were used.

Ericksonian hypnotic process was used. The patient was invited to detach from her environment and enter to a modified state of consciousness. A moderate degree of sensory isolation was needed. Sonor activity level and alarm volumes were reduced. Whispered conversation was used and unnecessary one was eliminated. This detachment was achieved under Buddhist music.

The hypnotic process was started during the cervical plexus block to allow sufficient depth. Hypnotic focused analgesia and sedation was achieved with different sets of suggestions. Interactive trance and acceptance of suggestions, ratification of trance, direct and indirect permissive suggestions, as well as hypnotic saturation were included.

The patient was positioned the head in slight hyperextension for surgery. Routine dermal preparation of the surgical site was carried. Conventional incision was used. The patient was asked to show any discomfort by face signals.

During thyroid dissection, a 4-cm-large cyst at the lower pole with numerous adhesions resulted in prolonged operative time. Monitoring of recurrent nerves was provided by an Avalanche® neuro-monitor. By inviting the patient to speak regularly, hypnosis allowed additional monitoring. The patient experienced no intraoperative pain or discomfort. Postoperative analgesics were limited to paracetamol.

Hypnosedation as a complementary technique, can be used in many surgeries to replace drugs sedation.

In a survey in thirty French university hospitals, Chabridon et al. reported, that all practiced hypnoanalgesia and two thirds proposed hypnosedation, in invasive procedures. Hypnosis was able to avoid the deleterious consequences of general anesthesia with assisted ventilation. The risk of intraoperative hypoxemia in case of cervical block and drug sedation was avoided too. Postoperatively the patient showed high satisfaction. Thus, hypnosis seems to have found its place as anesthetic adjuvant for thyroid surgery.

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A case of ultrasound-guided Serratus Plane block for postoperative analgesia in video-assisted thoracoscopic lobectomy in a patient with previous axillary dissection surgery

Dear Editor,

We read the brief technical report by Piracha et al. about the effectiveness of the ultrasound-guided deep serratus plane block (US-DSPB) as analgesic technique for anterior chest wall pain. The serratus anterior muscle (SAM) originates on the surface of the first 8 ribs and attaches to the medial border of the scapula. Blanco described the superficial serratus plane, which is a fascial space between the anterior surface of the SAM and the posterior aspect of the latissimus dorsi muscle (LDM), and the deep plane, which exists between the SAM and external intercostal muscle (EIM) at approximately the level of the fifth and sixth ribs. The recent literature suggested that several branches of the intercostal nerves traverse both of these anatomical planes. Fusco et al. reported the efficacy of the ultrasound-guided superficial serratus plane block (US-SSPB) in association to PECS 1 block as anesthetic technique for breast cancer surgery. However, for patients presenting with scar tissue post-mastectomy, US-SSPB may not provide adequate anesthetic spread and a US-DSPB could be preferred. We described a 65-year-old woman, ASA 2, underwent video-assisted thoracoscopic VATS lobectomy. Her medical history included prior ipsilateral axillary dissection surgery. For patients preoperative analgesia for postmastectomy pain syndrome. Reg Anesth Pain Med 2017;42:259-62.

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**TOP 50 MINERVA ANESTESIOLOGICA REVIEWERS**

Top 50 reviewers August 2017-January 2018

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