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EDITORIAL

Drug interaction is the cornerstone of modern anesthesia practice

Chien-Kun TING *

Department of Anesthesiology, Taipei Veterans General Hospital, National Yang-Ming University, Taipei, Taiwan

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In the study by Weber and Prasser published in this issue of *Minerva Anestesiologica*, 60 patients underwent elective otolaryngeal or ear surgery for investigating a propofol-sufentanil interaction model to determine the optimal concentration of either drug for adequate anesthesia and rapid recovery, by evaluating both clinical endpoints and electroencephalography findings. They concluded that sufentanil has a dose-dependent synergistic effect on the clinically observed outcomes and parameters from three depths of hypnosis (DoH) devices (Bispectral Index [BIS], Narcotrend Index, and cAAI) in patients hypnotized with propofol.

Anesthesiologists are required to have an in-depth knowledge of pharmacology; we use the synergy between hypnotics and analgesics to suppress consciousness and nociception. Under general anesthesia, a set of desirable clinical endpoints should be achieved, including lack of awareness, lack of movement, adequate muscle relaxation, acceptable blood pressure, and body homeostasis maintenance. No single drug is universally satisfactory for achieving these endpoints. For practical purposes, anesthesia in the modern age involves the administration of at least two drugs — an opioid and a sedative hypnotic. This concept of multiple drug use was first described by Lundy in 1926, who used the term balanced anesthesia. Balanced anesthesia involves the use of desirable drug combinations by reducing the required doses of individual drugs to minimize the side effects. Currently, balanced anesthesia is one of the most worldwide used techniques for general anesthesia.

Drug interactions are usually considered in the dose or concentration domain, and there are many ways to study drug interaction. The dose–response relation curve is based on the standard sigmoid Emax model. In their study, Weber and Prasser used the modified Observer’s Assessment of Alertness and Sedation Scale (mOAA/S) to measure the clinical endpoints and defined loss of responsiveness to verbal command (LORverb) by the transition from mOAA/S level 3 to 2; noxious (painful) stimulation (LORnox), corresponding to mOAA/S level 0, served as the primary endpoint of this study. The mOAA/S Scale was firstly developed to measure the level of alertness in subjects who are sedated. Probit regression analysis was used to determine the dose–response relation curve for the two different clinical endpoints.

There is experimental evidence showing that conscious recall of intraoperative events is only the tip of an iceberg. Three DoH devices were used in the study of Weber and Prasser to avoid awareness and facilitate rapid recovery. The BIS index was first introduced in 1992 by Aspect Medical Systems. The main component of the BIS monitor is bispectral analysis, which evaluates the phase relations from a single channel EEG signal measured from the patient’s forehead. Although
BIS-guided anesthesia and ETAG-guided anesthesia may be equivalent with regard to avoidance of intraoperative awareness,\textsuperscript{8} BIS-guided total intravenous anesthesia plays an important role in reducing the risk of intraoperative awareness.\textsuperscript{9, 10} In 2000, Monitor Technik produced the Narcotrend monitor based on the concept described by Loomis \textit{et al.}\textsuperscript{11} The Narcotrend monitor classifies the state of anesthesia into five stages (A to F); they were further subdivided into three sub-stages by Kugler.\textsuperscript{12} Analogous to BIS, the newer versions of the monitor also display the index value (0 to 100).\textsuperscript{7} The first AEP commercial monitor was introduced by Danmeter in 2001. AEP-Monitor/2 is not only based on AEP, but also analyses the spectral EEG parameters.\textsuperscript{7} Different DoH devices have different algorithms, which leads to a different index value; this is compatible with Weber and Prasser's finding that specific devices have their own dose–response curves.

Drug interactions can be described by shifts in dose–response curves, where one drug influences the dose–response curve for another drug. Weber and Prasser tried to analyses drug interaction using dose–response curves in the three DoH devices. Nonlinear regression was used to determine the curves. The method suggested by Hannam and Anderson\textsuperscript{13} was applied to determine whether the interaction is synergistic or additive. If the curve was noted to shift to the left, it was considered to indicate synergy. The other approach to study interaction between two drugs is to plot dose pairs together to form a line which shows a particular level of effect. These isoeffect lines are called isoboles. Isobolograms can be easily constructed and analyzed. Numerous published studies have used this methodology, and their conclusions are comparable to those of studies using more complex methodologies; however, the limitation of isobolograms is that the result is only applicable to the effect level investigated. To gain a full understanding of the interaction between two drugs for all effect levels, it is possible to overlay a series of isoboles ranging from the minimal effect to the maximal effect attainable (Emax).\textsuperscript{14}

The response surface is a three-dimensional graph with two drugs (A and B) on the horizontal $x$ and $y$ axes and the effect on the vertical $z$ axis. The surface is based on the shift in dose-response curves and the isobologram; it describes effects for the complete set of doses for the endpoint in question. Responses may be either continuous, such as BIS and blood pressure, or quantal, such as sedation scale scores, awake/sleep, and movement/immobility. There was a breakthrough in response surface modeling after 2000, owing to not only the advancements in computing technology that made the complex calculation possible\textsuperscript{15} but also the increasing demand for precise anesthesia. This concept was first introduced by Box and Wilson,\textsuperscript{16} and was first introduced into the field of anesthesia by Greco \textit{et al.}\textsuperscript{14} in 1995. The response surfaces create models of all possible combinations of two or more drugs for a given effect. Further, they characterize the entire spectrum of the drug effect, which is an important advantage of this approach in anesthesia and clinical pharmacology. This approach reduces the complex physiology to a few mathematical elements.\textsuperscript{2}

Drug interaction is the cornerstone of modern anesthesia practice. Understanding the synergism, additive effects, and even antagonism among anesthetics, especially hypnotics and opioids, may aid in making anesthesia more effective, minimizing side effects from the use of a single anesthetic, and improving the safety of patients. On the other hand, comprehending the underlying physiological mechanisms regulating the depth of hypnosis, by monitoring electroencephalography findings, can aid in formulating cost-effective and safer anesthetic protocols.

The study successfully addresses synergistic effect of sufentanil on the hypnotic effect of propofol both in their primary and second outcome by TCI effective site concentration (Marsh model). The findings provided some evidence that sufentanil could be beneficial in loss of consciousness of propofol, but problems with study design prevented the authors from fully addressing this issue. A comprehensive examination of opioid-propofol interaction requires a different study design. Future studies should consider reliable new methods such as response surface so that the findings can be generalized.
References


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Intravenous dexmedetomidine: can it modulate the effects of inflammation, or is it only an antinociceptive agent?

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The stress response was first described by Sir David Cuthbertson,1 after observing metabolic disturbances in patients with limb injuries. The term describes a systemic response that involves a network of interrelated hormonal, metabolic, inflammatory and immunological changes observed in patients following injury.2 The surgical stimulus, changes secondary to the surgical procedure or to intraoperative nociception trigger two initial pathways: the release of cytokines (principally IL-1β, IL-6 and tumor necrosis factor-α [TNF-α])3 and inflammatory mediators from the damaged tissues, and the stimulation of afferent neurons (C and A fibers).4 Both pathways lead to activation of the central effectors of the stress response, i.e., the locus coeruleus-noradrenergic or sympathetic systems situated in the brainstem, and the hypothalamic release of corticotrophin-releasing hormone, which activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis.5 The renin–angiotensin–aldosterone system is also activated, partly as a result of increased sympathetic activity. The overall metabolic effect of the hormonal changes is increased catabolism of energy storage molecules (proteolysis, lipolysis and hyperglycemia, which mobilizes substrates to provide energy sources), and retention of sodium and water to maintain fluid volume. Although the primary role of this response is to promote healing and recovery, this sustained hypermetabolic and hyperdynamic state following surgery has been associated with worse prognosis and increased risk of postoperative complications.6 Thus, it triggers pathophysiological events related to postoperative morbidity (e.g. cardiac ischemia and hemodynamic instability, renal and pulmonary decompensation, increased catabolism, impaired immunity, or hypercoagulability syndrome), undermines progress, recovery and surgical outcomes, delays rehabilitation, prolongs hospitalization and impairs functionality.6

Fast-track or “enhanced recovery” programs are based on these concepts.7 Their main goal is to control postoperative pain and inflammation by effective multimodal opioid-sparing analgesic regimens aimed at limiting adverse outcomes secondary to organ dysfunction in the context of surgical stress.6

Recent years have seen an increase in the use of alpha2 adrenoreceptor agonist drugs. Specifically, intravenous dexmedetomidine is often used as a perioperative adjunct to general anesthesia due to its hypnotic and sedative effects on
the central nervous system, its short half-life, and its analgesic effects in opioid-free anesthesia.\textsuperscript{8,9} Recently it has also been used as a coadjuvant with local anesthetics in regional anesthesia for nerve plexus blocks.\textsuperscript{10} Several theories have been put forward to explain its central and peripheral action.\textsuperscript{11} Different experimental trials in animal models and humans have suggested an effect on various inflammatory mediators. However, the results remain controversial.\textsuperscript{12,13} For example, a previous study of tourniquet-induced ischemia-reperfusion injury found no significant differences in oxidative stress when dexmedetomidine was used.\textsuperscript{14}

In this issue of Minerva Anestesiologica, Kim et al. report that IL-6 and lactate was significantly lower in an IV dexmedetomidine group vs. controls after the release of the ischemia tourniquet in total knee arthroplasty surgery.\textsuperscript{15} Nevertheless, these results should be viewed with caution. The results showed significant differences with respect to baseline, but not with respect to the control group, in which differences in MDA and TNF values did not reach significance, even though lactate and IL-6 levels were lower than controls. Lower doses of remifentanil were found in the dexmedetomidine group compared to controls, a finding echoed in previous studies.\textsuperscript{16}

The foregoing study has important limitations. The time of ischemia is the main factor affecting the increase in mediators, and sampling was systemic, not in the ischemia area. A recent meta-analysis recommended reducing time of ischemia in knee arthroplasty to avoid poor outcomes and complications derived from inflammatory mediators, even though this increases perioperative blood transfusion requirements and reduces surgical vision in the field due to bleeding.\textsuperscript{17,18} In addition, the antinociceptive action of dexmedetomidine could influence the minor differences in mediators levels between groups by improving central control of nociceptive stimuli.\textsuperscript{15} The mechanisms of action of dexmedetomidine are currently unknown. Evidence is emerging on its effects on electroencephalogram and its sites of action in the central nervous system, but its effect on peripheral receptors and central modulation of inflammatory mediators remains unclear.\textsuperscript{9,19} Further multicenter studies with a larger patient groups are needed to confirm or refute the results of this study. Other new benefits of dexmedetomidine need to be discovered through basic research. There is still a long way to go.

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Predicting extubation success: instrumental assessment, clinical tests and cave diving

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Ability to identify the moment when our patient is ready for extubation is a daily challenge for anesthetists in operating theatre, and especially in intensive care unit. Extubation readiness is a complex issue deriving from combination of anatomical and functional readiness to extubation, and many parameters need to be addressed by the all team in aim to obtain a successful and durable extubation. The same definition of extubation failure is variable and covering a quite wide time window. As a result, extubation failure is claimed to occur in up to 10% to 30% of ICU patients with implications on mortality, with peculiar characteristics in specific patients subsets. Hence, there is strong need of clinical and research studies, as the one published by Lombardi et al. in this issue of Minerva Anestesiologica.

The premises of their study, as declared by the same authors, are not encouraging: the panorama of available clinical and instrumental options is quite crowded, but with no test showing reliable and sufficient specificity, sensitivity and predictive value. Reasons for such a poor performance lie in the multifactorial bases behind extubation success or failure: fluid balance, cardiovascular performance, oxyphoretic status, nutritional status, neurological function may affect the result of weaning and extubation concurrently with pulmonary function and airway patency status. Not forgetting the possibility of co-existence of a difficult airway, which might be a further factor delaying or influencing the decision to extubate. The “psychological” issue is, basing on recent evidence, just a piece of the puzzle of human factors which might delay extubation or determine its failure, including the handover/handout process, the lack of communication or changing poor piece of information, and inadequacy of teamwork.

The research by Lombardi et al. highlights better performances for Rapid Shallow Breath Index and cough in their ability to predict a successful extubation, but at same time the Authors provide some important messages. First of all, no single test is out-performing other tests, which clearly shows we do not have a magic bullet. Second point is the very acute concept expressed by authors that might be some tests more than others highly associated with successful extubation, but they are not able to prevent or predict an extubation failure. Last but not least, they clearly demonstrate that if on one hand there would be large benefit from a better performing test, on the other we are far from such an achievement as we first need to find out standard definitions, pre-ordinated procedures, and we need to define time-spams for specific events (such as extubation failure and need to re-intubate) prior to search for the ideal test. Once we will have this starting point, available tests will be opportunely evaluated, scored and allocated, and opportunely integrated with contribution of newer technologies (such as diaphragm and airway ultrasound, or neurally adjusted ventilation assist).
A further crucial step will be adequate integration and combined interpretation of functional parameters and clinical tests (assessing neurological, hemodynamic, pulmonary and muscular function) with anatomical ones, including airway patency evaluation and eventual co-existence of difficult airways. In this last setting, an extubation failure might also lead to critical accidents with severe difficulty, if not failure, to provide adequate airway management.3, 8-11

The assessment of anatomical readiness for extubation remains of paramount importance, and in this sense the same cuff leak test shows a series of limitations in terms of reproducibility and predictive value,1, 12 with particular reference to observations in a large meta-analysis that a positive cuff test does not always call for re-intubation, the patient’s ability and adequacy to breath spontaneously remaining preserved despite airway caliber reduction.13 Conversely, tests such as direct fiberoptic inspection of the airway before extubation (which might also be useful for secretions clearance)14 and the search for postextubation stridor still do remain probably under-used.15

Some specific settings, such as postoperative course of head and neck or cervical spine surgery, strongly call for an airway inspection as part of an extubation strategy,16 while never forgetting that the same presence of an endotracheal tube, yet for short periods, produces anatomical and functional changes in human larynx.17 As elegantly demonstrated by Lombardi et al.,2 we are still missing such an integrated test, m-Bwap Score remaining the unique model considering both weaning parameters and clinical parameters to predict extubation failure, any information upper airways patency being unfortunately lacking. In any case, certainty or yet suspect of an anatomically difficult extubation, independently on any other non-anatomical parameter readiness, should address to adequate planning and availability of devices and strategies to provide a safe extubation.1, 10

Which could then be a reasonable solution? For sure we do need to improve amount and quality of research on the extubation issue aiming to obtain single or multiple tests and/or scores with adequate sensitivity, specificity and predictive value, with harmonization of either anatomical and functional issues and large inter-individual reproducibility. Meantime, we should probably use better what we have and we should focus on what we could more easily improve, with special reference to human factors, including adequate preparedness, teamwork, communication, including optimization and standardization of the handover/handout process and hopefully with integration of checklists and cognitive aids.18 We should start thinking in terms of extubation strategy independently on success, failure and means to achieve it. Strategy meant not as the sole procedure itself, but always forecasting a pre- and post-extubation safety pathway, including (but not limited to):

- bedside promptly available airway cart during extubation so to be ready to deal with an airway emergency (e.g. videolaryngoscope, scalpel-bougie-tube, etc.);1, 10, 11, 14, 16
- “safe” extubation strategy using an airway exchange catheter (AEC) or similar whenever a “difficult” extubation is expected (parameters of difficult intubation, repeated airway instrumentation attempts, head and neck surgery, airway surgery, prolonged intubation, etc.);1, 11, 16
- endoscopic examination (flexible bronchoscope or rhinoscope) either before and/or after extubation (also including Bailey’s manoeuvre);19
- preliminary front of neck access by cricothyrotomy or tracheotomy as optional strategy whenever it might represent the only guarantee for safety;1, 20
- postextubation monitoring, both instrumental (standard monitoring — considering late value of pulse oxymetry — and CO2 detection, search for post-extubation stridor) and visual by nurses/doctor.1

Last but not least, we should never forget, even when we would have a bunch of perfect tests, our starting point, which is clinical experience. Sensitivity and specificity of clinical evaluation seem to be poor,2 and this is expectedly due to complexity of extubation failure/success question. Nevertheless, we believe that experience remains and will remain extremely important both now and with (hopefully not far) future perfect tests.
To underline the importance of skills and experience, we would recall the recent case of the cave accident in Tham Luang, Thailand, with an entire young football team and its coach imprisoned in a partly submerged cave for 17 days. Though being something apparently so far from the extubation issue, it lights up some important thoughts on our discipline and on complex relationship with evidence-based medicine, protocols and guidelines. The real heroes of the Thailand accident were professional divers from military elite corps, including the courageous Thailand diver Samal Gunan who lost his life during one of the rescue attempts. Between them, there was also a hero with double function: a professional cave diver with more than 30-years-experience who eventually was also a doctor. To be precise, an anesthetist. Richard Harris, from Adelaide, Australia, wrote in his curriculum vitae that he “loves challenges, such as taking care of critical patients in hostile and remote environments.” and he demonstrated it in the Tham Luang accident. His task in the rescue mission was probably the hardest, as he was called to triage for the whole group of prisoned, to identify their clinical conditions and to establish rescue sequence and to initiate the amazing operation ended in salvation of all people.

Thinking at the incredible work of everybody involved in this massive rescue operation, apart from unavoidable emotional involvement, we do have proof of incredibly efficient system requiring extreme coordination, communication and many more non-technical challenges together with arrangement of highly sophisticated tools and devices (such as masks, rebreathers, tanks, ropes and diving equipment). The responsibility of Dr. Harris, in the darkness of the cave, must have been tremendous, and he performed his job brilliantly probably using precise triage guidelines and protocols, despite he was using a diving suit and not a white coat. For sure, he did also use a lot of good sense, clinical judgment to come to crucial decisions. For sure he did all this using also, if not mainly, his practical and long-lasting experience, both as cave diver and as anesthetist.

So, during our rescue mission for a safe and successful extubation, we congratulate the study by Lombardi et al. and we do encourage further and methodologically correct studies. We do also invite our colleagues to know the available tests so to use them in their better performances, and to develop and produce extubation strategies, protocols and checklists.

Never forgetting our white coats, the role of clinical experience and suggested devices, which should always be applied aside with available tests and shared (and adequately recognized) during the teamwork efforts leading to the perfect extubation.

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The availability of ultrasound in anesthesia has opened up a vista of regional anesthesia possibilities, allowing the innovation of new blocks and approaches. Recently, there has been great enthusiasm for the development of interfascial blocks, despite a low level of understanding regarding the actual characteristics, structure and behaviors of the various fasciae involved. For most practicing anesthetists the array of blocks and approaches described within a given area can be bewildering, literally by inserting the needle a couple of centimeters either medially or laterally to reach a given fascial plane they have come across a different acronym!

One such block is the Erector Spinae Plane block (ESP) reviewed in this issue of Minerva Anestesiologica and first described in 2016 by Forero. The ESP block involves depositing local anesthetic under ultrasound guidance deep to the erector spinae muscle but just superficial to the tip of the transverse process. This is generally described employing a cranio-caudad or caudal-cranial needle direction. This sounds simple and indeed is.

At ultrasound workshops the erector spinae muscle is often referred to as a distinct entity, yet in fact these muscular structures are actually a very complicated network of small muscles linking up the ribs and transverse processes. The muscle group is made up of the erector spinae muscles (made up of ileocostalis, longissimus and spinalis muscles), transversospinal muscles (consisting of semispinalis, multifidus, and rotatores muscles), and the deepest component is formed by the levatores rostrum muscles. This bilateral potential space between the erector spinae muscle complex and the transverse processes extends from the nuchal fascia to the sacrum also called the erector spinae plane. The length of this potential space and, therefore, the possibility for extensive dermatomal coverage may make it a highly versatile addition to the regional anesthesia armamentarium. It is, hence, not surprising that we have seen case reports describing the ESP block for everything from carotid endarterectomy, through to thoracotomy and laparotomy.

Ultrasound is now shining a light on where we are actually placing our needles. Ultrasound guided regional anesthesia, however, can be difficult to master and can also be a deterrent for the uptake of such techniques. A major potential advantage of the ESP block is its simplicity and unlike nerve blocks fascial plane blocks do not have the potential difficulty of nerve identification. The ESP also has a very simple sono-anatomical end point (the tip of the transverse pro-
cess) to aim for. Previously, landmark paravertebral blocks possibly resulted in accidental fascial blocks (such as the ESP or retrolaminar blocks) as evidenced by the disappearance of the need for multilevel injections following the introduction of ultrasound guidance.

As it is a more superficial block, ESP may prove to be safer than ultrasound-guided paravertebral or epidural block, though the number of cases published are relatively small. So far only one incidence of pneumothorax whilst performing an ESP block has been described. Rare, but catastrophic complications of central techniques such as an epidural abscess or spinal cord damage are viewed with trepidation by patients and are potentially avoided. A further distinct advantage is the lack of sympathectomy which may benefit patients where hypotension may be detrimental. Also useful is the fact the injection site is distant to the surgical site which means if a catheter is placed preoperatively it is dose not interfere with the operative site. In addition, if the block is performed postoperatively any air or disruption of planes postabdominal surgery will not affect the ultrasound imaging and placement of needle or catheter.

However, there are a number of important and unanswered questions: What is the spread of the local anesthetic, and what is the actual mode of action? Is there a faster absorption and higher maximal plasma concentrations of local anesthetic during ESP similar to what has been described in children having ultrasound delivered ilioinguinal blocks?2 Is there a greater risk of myotoxicity which, whilst uncommon, is more likely with interfascial blocks?5

Cadaveric studies have shown that there is local anesthetic spread via the gaps between the small muscular slips that form this complex muscle structure into the paravertebral and epidural spaces over 2-5 levels, and anterolaterally into the intercostal spaces over 5-9 levels.4 However, at this point it is hard to recommend widespread use of the ESP as more work is required to assess the actual mode of action, and how the local anesthetic spreads within patients, and how this spread may be affected by block performance in the awake or anesthetized patient. Is there a difference between left and right ESP spread, and does the pressure changes of laparoscopy affect the spread of local anesthetics? Equally, in order to advocate the ESP block for daily practice, we need comparisons to more established regional techniques within a standard multimodal analgesic package. For example, how do bilateral ESP catheters compare to an epidural for post laparotomy analgesia? Would the ESP block be more appropriate where minimal access surgery is used? Can it reliably help to facilitate an opioid free recovery, given its reliance on spreading to the paravertebral space? Further investigations are also required to elucidate if specific conditions and patients will be better served by the ESP e.g. multiple fractures,7 extensive chest wall lesions, as a rescue block for a failed thoracic epidural, or in obese patients where a clear ultrasound view of the paravertebral space is difficult.

There are distinct advantages such as the simplicity of the ESP and the greater dermatomal coverage when compared to other techniques e.g. paravertebral or quadratus lumborum blocks. However, there is good clinical evidence that an established ultrasound delivered paravertebral block (with or without a catheter) remains the most appropriate block for major postoperative pain such as a thoracotomy. Perhaps more effort should be made to investigate as to why this technique is currently underutilized in other clinical settings despite its reliability? Is it really only an erroneously perceived technical difficulty? The promise of the ESP being a simple and easy to learn ultrasound technique makes it very attractive. However, at this point the ESP block remains the poor man’s paravertebral block and only time and research will tell.

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**ORIGINAL ARTICLE**

**Stimulating versus non-stimulating catheter for lumbar plexus continuous infusion after total hip replacement**

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**ABSTRACT**

BACKGROUND: This study was aimed to investigate whether stimulating catheters for continuous lumbar plexus block reduce local anesthetic consumption after hip arthroplasty if compared with traditional non-stimulating catheters.

METHODS: Seventy-two ASA I-III, 18-82-year-old, undergoing primary hip replacement (THA) for osteoarthritis with spinal anesthesia were randomized into two groups: Stim group (stimulating catheter, N.=36) and Nonstim group (non-stimulating catheter, N.=36). After surgery, 15 mL of mepivacaine 1% were administered in both groups through the catheter. An electronic pump was connected to deliver ropivacaine 0.2% (3 mL/h, bolus 3 mL, lock out 15 min) for the first 72 h. Patients were given ketorolac 30 mg IV every 8 h, acetaminophen 1g IV every 8 h and oxycodone 10 mg per os for rescue analgesia. Primary outcome was postoperative local anesthetic consumption. Numerical Rating Scale (NRS), complications, both quadriceps and obturator strength measurements, and opioid requirement were also registered. Mixed effect models (random intercept) were built for repeated measures over time. A difference between groups was considered statistically significant if P<0.05.

RESULTS: Local anesthetic consumption and NRS were comparable between groups. Patients in the Nonstim group required significant more rescue opioid analgesia compared with the Stim group during the first 36 h (P=0.002). Quadriceps and adductor muscle strength was equally preserved in the two groups.

CONCLUSIONS: The study showed comparable local anesthetic consumption, pain scores and muscle strength preservation between the two groups. The stimulating catheter allowed a significant, although underpowered, reduction in opioid consumption.


KEY WORDS: Lumbosacral plexus - Nerve block - Catheters - Arthroplasty, replacement, hip.
provides higher level of pain relief, allowing lowered opioid requirements.\(^6\) Moreover, it has been demonstrated that the use of LPB decreases bleeding and the need for transfusions during total hip arthroplasty (THA).\(^7\)

The main limit to a more widespread use of LPB is the fear of complications and their potential severe consequences.\(^3\) The use of ultrasound has been proposed in order to improve reliability reducing adverse events. Unfortunately, the depth of the structure (up to 11 cm) makes the vision difficult in many patients with the currently available ultrasound resolution.\(^9, 10\) Therefore, for LPB, the superiority of ultrasound guidance versus traditional technique based on landmarks and nerve stimulation is still debated.\(^11\)

We have recently demonstrated that using a stimulating catheter for LPB significantly decreases the minimum effective local anesthetic volume (MEV) to achieve a primary block via the catheter compared to non-stimulating one.\(^12\)Whether the stimulating catheter also provides superior analgesia after THA is still being questioned.

In this prospective, randomized, blinded investigation our primary endpoint was to investigate if the use of stimulating catheters for continuous LPB might reduce local anesthetic consumption after THA if compared with the infusion via traditional non-stimulating catheters. Secondary endpoints were postoperative analgesia measured by the Numerical Rating Scale (NRS), the assessment of quadriceps and obturator strength, the opioid requirement, and the incidence of complications.

**Materials and methods**

The Institutional Review Board (IRB) of the IRCCS Policlinico, Milan, Italy (principal investigator Gianluca Cappelleri) approved the study. A registration number (NCT02162121) was achieved prior to all enrollments. In the period between May 2014 and October 2016, 72 patients American Society of Anesthesiologists (ASA) physical status I-II, 18-82-year-old, undergoing primary hip replacement (THA) for osteoarthritis were enrolled. A written informed consent was obtained from all participants during the anesthesiologist visit.

Exclusion criteria were: ASA status >III, dysplasia, rheumatoid arthritis, any contraindication to regional anesthesia, diabetes, opioid chronic consumption, patient refusal and any neurological deficit.

In the operating room, after the placement of an infusion line and the application of the standard monitoring including three-lead ECG, non-invasive blood pressure cuff and pulse-oximeter, a spinal anesthesia was performed on the patient turned on the non-operated leg. Levobupivacaine 0.5% solution 15 mg was injected through a 25G needle (Pencan, Bbrawn, Geisingen Germany). With the same lateral position and both legs flexed a single author (GC), skilled in regional anesthesia, performed all lumbar plexus blocks. The surface landmarks were identified by drawing a vertical line at the level of the superior border of the posterior iliac crests (intercrystal line) and another horizontal line in the midline by palpating the lumbar spinous processes. An ultrasound scan with a 3-5 MHz curve probe (Sserve, Sonosite, Washinton, USA) was performed in order to identify the L3 or L4 transverse process position and its depth. An insulated 18G 10 cm Tuohy needle from a continuous peripheral nerve block set (Stimulong 100, Pajunk, Geisingen, Germany) was inserted perpendicularly to the plane of the skin, four cm laterally to the intersection of these two lines, with the bevel oriented cranially, aiming the L3 or L4 transverse process. A combination of loss-of-resistance and nerve stimulation techniques was applied to localize the psoas muscle and lumbar plexus. The peripheral nerve stimulator was initially set at 1 mA, 2 Hz, 1 ms. The needle was advanced until quadriceps muscle contraction was elicited or until bone contact (transverse process) was encountered. In the latter case, the needle was withdrawn, redirected caudally to walk off the transverse process and advanced 2 cm until quadriceps muscle contraction was elicited. The final position of the stimulating needle was considered acceptable when quadriceps muscle contraction was still present with a current output ≤0.5 mA.

At this point patients were randomized into two groups: the first group received the stimulating catheter (Stim group =36 patients), while
the second group received a traditional non-stimulating catheter (Nonstim group =36 patients). Randomization was performed using a computer-generated sequence of numbers and sealed envelope technique. When the lumbar plexus was correctly localized, an investigator not involved in the management of the patients opened the envelope to reveal the group allocation to the anesthesiologist. A single 22-G stimulating catheter end-hole type was used in both groups.

In the Stim group the current output was shifted to the stimulating catheter as previously set when attached to the needle and then the catheter was advanced 3-5 cm past the needle tip, while maintaining the same quadriceps contraction strength. If the muscle contraction decreased or disappeared suggesting the catheter tip dislocation far from the LPB target, the catheter was withdrawn, a small adjustment (rotation or advancement) in the position of the needle was made and the catheter reinserted until maintaining muscle contractions. In case of failure in achieving this with small adjustments of the needle and the catheter, the needle was removed and reinserted using a different angulation. The placement was considered satisfactory when the quadriceps contraction was maintained with a final current output from the catheter ≤0.5 mA.

In the Nonstim group the catheter was inserted through the needle and blindly advanced 3-5 cm beyond the needle tip without further adjustments.

In both groups the catheters were kept closed until the end of surgery. In the Post Anesthesia Care Unit (PACU), when the dermatomeric level of neuraxial block was below L3 as revealed by the pinprick test, a blinded investigator, not involved in catheter management, performed a lumbar plexus block by injecting 15 mL of mepivacaine 1% through the catheter. LPB was considered successful if 20 minutes after LA injection the patient experienced a decreased sensation to touch in the ipsilateral knee region and/or weakness upon the knee extension of the thigh compared to before the LA injection through the catheter and with the contralateral side. In case of failure, the catheter was judged dislodged and the patient excluded from further analysis. The lumbar catheter was then connected to an electronic pump (Micrel device, Athens, Greece) scheduled to deliver a solution of ropivacaine 0.2% (basal rate 3 mL/h, 3 mL bolus, lock out 15 min, max 15 mL/h). In both groups catheters were removed after 72h postoperatively. Postoperative analgesia also included ketorolac 30 mg intravenously (IV) every 8h, acetaminophen 1g IV every 8h and oxycodone 10 mg per os for rescue analgesia.

Postoperative assessments included the Numerical Rating Scale (NRS, 0= no pain, 10= worst imaginable pain) for pain both at rest and on movement, local anesthetic consumption, opioid-requirement and complications, and was performed every 12 h for the first 72 h by an investigator unaware of the group allocation. Patients also received functional examination to assess the physical performance on both quadriceps and obturator muscles using an electronic handheld manometer (Imada DS2-500N, Beijing, China). The quadriceps and adductor strength was assessed as the maximum voluntary isometric contraction (MVIC) at 24, 48 and 72 h postoperatively and compared to baseline (preoperatively). We used standardized, recommended procedures to obtain valid measurements.10 Quadriceps strength was evaluated in seated position with the knees flexed at 90°. The dynamometer was placed on the ipsilateral anterior tibial perpendicular to the tibial crest just proximal to the medial malleolus. For hip adductor evaluation, each patient was turned supine with the leg held at 30° off midline and the dynamometer placed over the medial femoral epicondyle (adductor tubercle). For all measurements, subjects were asked to reach their maximum effort contracting the target muscle(s). The MVIC was registered on the dynamometer display as a peak. Each patient performed three attempts for each investigated muscle on both the operated and non-operated side. We reported the average of these three attempts.

Statistical analysis

Statistical analysis was performed with the dedicated software Stata 11.1 (Copyright 2009 StataCorp. LP, StataCorp, 4905 Lakeway Drive, College Station, TX 77845, USA).

Continuous variables were reported as mean±SD and compared with the Wilcoxon Rank-Sum Test.
Categorical variables were reported as number/total (percentage) and compared with the Pearson $\chi^2$ test.

Mixed effect models (random intercept) were built for repeated measures over time in order to better investigate the group effect on local anesthetic consumption, NRS, quadriceps and adductor muscle strength.

Differences between groups were considered statistically significant if $P<0.05$.

In assessing sample size we relied on our previous personal observation of a mean local anesthetic dose of 200 mL with 70 mL SD of ropivacaine 0.2% during the first 24 postoperative hours. For the present superiority study, keeping alpha 0.05 and power 80% we aimed at observing at least a 50 mL local difference between groups. This yielded a total sample size of 62 (31/group) patients, which we increased to 72 (36/group) taking into account possible dropouts.

Results

Seventy-two patients were enrolled in the study. Two patients in the Stim group denied their consent immediately after surgery, six patients (four in Nonstim group and two in Stim group) had their lumbar catheter dislodged after the first 24h: therefore 64 of 72 patients were included in the final per-protocol analysis (Figure 1). Demographic data are showed in Table I.

Time of catheter placement required 290±205 sec in the Stim group and 264±256 sec in the Nonstim group (P=0.414). All patient showed a successful block after the first mepivacaine bolus as defined per protocol.

Local anesthetic consumption (Ropivacaine 0.2%) in the Stim group at 24h was 110±42 mL compared with 116±55 mL in Nonstim group (P=0.902), while at 48h it was 184±62 mL in Stim group versus 209±73 mL in Nonstim group (P=0.422). At 72 h, patients in the Stim group required 273±71 mL versus 273±72 mL in the Nonstim group (P=0.768). The relevant mixed effect model indicated no group effect on local anesthetic doses (P=0.353).

Patients in Stim group required less opioid rescue in the first 24 h compared with Nonstim group. At 6 h they received oxycotin with a mean of 3.333±4.781 mg versus 5.0±5.080 mg in Nonstim group (P=0.172), at 12 h the Stim group received 1.515±3.641 mg versus 4.687±5.070 mg in Nonstim group, (P=0.002), while at 24 h the Stim group received 0.312±1.767 mg versus 4.062±4.989 mg in Nonstim group (P=0.005). Only one patient of the Nonstim group required 10 mg of oxycotin at 36 h, while no patient required opioids on the following assessment in both groups.

No difference was found in NRS for pain at each of the evaluated time points (Figure 2). The relevant mixed effect model indicated no group effect on NRS (P=0.644).

No difference was recorded in both quadriceps
The superiority of stimulating versus non-stimulating catheters is debated in literature.\textsuperscript{12-14} This is crucial especially when the use of ultrasound is still debated as single guidance and nerve stimulator technique still remains a valid option, as for deeper blocks. The rationale for the present investigation derives from the evidence of an important reduction of the minimum effective anesthetic volume (MEAV50) when the first bolus is administered through the catheter.\textsuperscript{9} In our previous investigation we found that the use of a stimulating catheter halves the MEAV50 of mepivacaine 1.5\%, while increasing the success rate in patients undergoing lumbar plexus block.

The results of this randomized controlled trial do not seem to fully confirm those findings. The similar analgesic profile, between stimulating and non-stimulating catheters, in our present investigation could be attributed to the mild level of pain registered in our population after total hip replacement performed on patients undergoing a multimodal approach to pain treatment. The average NRS during the first 72 hours were below 4/10 in both groups (Figure 3), and no patient required opioid rescue after 36 hours: this pain model could mask significant differences between the two techniques.

Comparing our previous investigation,\textsuperscript{9} we should also underline that pain in the sciatic region was not investigated in the present study: although the majority of the innervation of the hip is provided by the lumbar plexus, complete unilateral block of the lower extremity would have been provided by adding a proximal sciatic

The present study demonstrated comparable local anesthetic consumptions and pain scores during the first 24, 48 and 72 hours after total hip replacement when a stimulating catheter is positioned for postoperative continuous infusion of LPB instead of a non-stimulating catheter. Patients with the stimulating catheter received significantly less opioids resulting in an effective opioid-sparing analgesia.

**Table II.**—The strength reduction in the operated quadriceps and adductor muscles compared to baseline.

<table>
<thead>
<tr>
<th>Strength reduction from baseline</th>
<th>Stimulating group</th>
<th>Non-stimulating group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadriceps POD1</td>
<td>34±27</td>
<td>47±37</td>
<td>0.042</td>
</tr>
<tr>
<td>Quadriceps POD2</td>
<td>49±31</td>
<td>59±91</td>
<td>0.412</td>
</tr>
<tr>
<td>Quadriceps POD3</td>
<td>68±27</td>
<td>65±52</td>
<td>0.061</td>
</tr>
<tr>
<td>Adductor POD1</td>
<td>36±24</td>
<td>58±48</td>
<td>0.055</td>
</tr>
<tr>
<td>Adductor POD2</td>
<td>61±52</td>
<td>63±48</td>
<td>0.868</td>
</tr>
<tr>
<td>Adductor POD3</td>
<td>71±51</td>
<td>63±41</td>
<td>0.352</td>
</tr>
</tbody>
</table>

POD1, POD2, POD3: postoperative day one, two and three. Data are expressed as percentages.

and adductor muscle strength compared with baseline in the two groups, except for quadriceps muscle strength in the first postoperative day (Table II). The relevant mixed effect model indicated no group effect on quadriceps (P=0.593) and adductor (P=0.644) strength.

**Discussion**

The present study demonstrated comparable local anesthetic consumptions and pain scores during the first 24, 48 and 72 hours after total hip replacement when a stimulating catheter is positioned for postoperative continuous infusion of LPB instead of a non-stimulating catheter. Patients with the stimulating catheter received significantly less opioids resulting in an effective opioid-sparing analgesia.
nerve block to our protocol. Nevertheless, the multimodal approach applied to postoperative analgesia in the present investigation showed a satisfactory level of pain control in our patients throughout the period of the study, together with preserved adductor and quadriceps muscle strength in both groups. The only notable result in muscle strength was observed during the first postoperative day: Nonstim group showed a greater reduction of quadriceps muscle strength in the operated lower limb when compared to baseline. Nevertheless, the result is not consistent in the following days and does not involve adductor strength as well: we would therefore consider this result as non-clinically relevant. The results of our study show that continuous LPB added to a multimodal protocol provide effective analgesia in patients undergoing hip replacement together with adductor and quadriceps muscle strength preservation, regardless of the stimulating or nonstimulating technique. We kept the volume of ropivacaine 0.2% infused at 3 mL/h with a 3 mL bolus every 15 min, allowing a maximum rate of 15 mL/h through the lumbar plexus catheter for postoperative infusion. We chose the basal rate according to previous clinical experience and also based on previous literature observations: although the optimal local anesthetic concentration, basal rate, bolus volume, and lockout period in the lumbar plexus remain undetermined, Ilfeld et al. found that 42% of the ropivacaine group, in their population undergoing primary hip arthroplasty, required to have their basal infusion halved to enable ambulation. This suggests that an initial basal rate of 8 mL/h was too high for many patients when using 0.2% ropivacaine. Therefore, a low rate of infusion should preserve muscle strength and early mobilization, while frequent boluses can help in titrating more effectively the adequate local anesthetic volume for each patient. Nevertheless no difference was found in local anesthetic requirement between groups. By contrast, the number of patients requiring opioid rescue analgesia in the first 24 hours was significantly reduced in Stim group. This finding confirms a potential superiority of the stimulating catheter technique in achieving a true opioid sparing analgesia. No patient required opioids after 36h in both groups, only 6/32 patients of the Stim group required opioids within the first 12 hours, versus 13/32 in Nonstim group up to 36 hours. Although opioid requirement was not our primary endpoint, this relevant result suggests the need for further powered investigation (Figure 4).

**Limitations of the study**

The study presents some limitations. First of all, the difference in local anesthetic consumption was selected as the primary endpoint, while we found a significant difference only in the requirement of opioid rescue analgesia. This choice could have induced an alpha error. Secondly, the low-dose of local anesthetic bolus through the catheter, although clinically appropriate, could have masked major differences between groups. Moreover, a multimodal approach to postoperative pain was administered to our study population: although the protocol was adequate in our clinical context, as proved by the low pain levels in both groups, it could have masked a significant difference in terms of local anesthetic consumption between groups.

The method applied to judge the success of block might represent another limitation: LPB was achieved in all patients by injecting a bolus...
of mepivacaine 1% 15 mL through the catheter just after regression of spinal below the level of L3. We did not apply a strict definition for block success but we considered a reduction of touch sensation or a thigh weakness compared to contralateral as a corrected catheter placement. We did not register any failure block as defined per protocol, and therefore we considered all blocks successful and catheters appropriate for postoperative analgesia that was our main purpose. Although a more rigorous definition of success could have lead to a higher failure, our results are representative of the usual clinical practice.

Conclusions

In conclusion, the placement of a stimulating catheter versus a non-stimulating one does not seem fully justified in terms of postoperative analgesic efficacy in our population undergoing primary hip arthroplasty. In the context of a multimodal approach to pain, both types of catheter placement techniques allowed low levels of pain scores together with motor strength preservation in the adductor and quadriceps muscles and low opioid consumption. Nevertheless, the infusion of ropivacaine 0.2% via a stimulating catheter allowed an underpowered significant reduction in rescue oxycontin requirements.

What is known

- Continuous lumbar plexus block represents an effective analgesic technique after hip replacement.
- The use of stimulating catheters significantly decreases the minimum effective local anesthetic volume to achieve a primary lumbar plexus block via the catheter compared to the non-stimulating ones.

What is new

- The present study did not find any difference between stimulating and non-stimulating catheters with regards pain scores, local anesthetic consumption, and muscle strength reduction after hip replacement.
- In a multimodal pain approach, patients with stimulating catheters required less opioid for postoperative analgesia compared with the non-stimulating ones.

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.

Multi-parametric functional hemodynamic optimization improves postsurgical outcome after intermediate risk open gastrointestinal surgery: a randomized controlled trial

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ABSTRACT

BACKGROUND: Perioperative goal directed therapy (pGDT) using flow monitoring has been associated with improved outcomes. However, its protocols are often based on stroke volume only: as a target for fluid loading, inotropic support and vasopressors (via mathematical coupling of systemic vascular resistance). In this trial, we have tested the multi-parametric pGDT protocol based on esophageal Doppler variables (corrected flow time, peak velocity) in intermediate-to-high risk patients undergoing gastrointestinal surgery.

METHODS: Intermediate-to-high risk patients undergoing gastrointestinal surgery were randomized to standard care (control) or multi-parametric pGDT (intervention). Postoperative complications and death rate as well as hospital length of stay were assessed as primary and secondary outcomes.

RESULTS: Overall, 140 patients (intervention, N.=71, and control, N.=69) were included and randomized out of 197 eligible. Higher vasoactive/inotropic drug use and lower fluid balance were observed in the intervention group leading to favorable hemodynamic profile. The pGDT intervention was associated with improved primary outcome (28 days mortality and morbidity defined as occurrence of any defined complication) — 20 patients (28.2%) versus 32 (46.4%) in the control group (P=0.036); RR 0.61 (95% CI: 0.39-0.95), P=0.03. No differences in mortality and hospital length of stay were observed between groups.

CONCLUSIONS: In this monocentric trial the multi-parametric pGDT protocol based on domain specific functional hemodynamic parameters was associated with lower rate of postoperative complications in intermediate-to-high risk patients undergoing scheduled gastrointestinal procedures.

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Key words: Cardiac output - Fluid therapy - Hemodynamics - Intraoperative monitoring - Postoperative complications.

In year 2018 it was exactly 30 years since the seminal paper by Shoemaker has been published in Chest journal.1 Since then the perioperative goal directed therapy (pGDT) has gained much attention. Up to today there have been more than 60 studies published (single-centric in majority but several multi-centric as well) concerning the hemodynamic treatment in the perioperative period. The evidence for (or signal of) improved postoperative outcomes (i.e. mortality,
morbidity and postoperative length of stay) has been further supported by numerous meta-analyses. However, recent surveys among practicing anesthesiologists demonstrated, that pGDT is still far from being an everyday practice. In addition, several recent studies failed to prove the benefit: the Challand’s group has demonstrated, that maximizing stroke volume (as indicated by the NICE recommendation) may have detrimental effect in aerobically fit patients undergoing open gastrointestinal surgery. Later on, the largest multi-centric study published on the topic so far — the OPTIMISE trial — has failed in its primary outcome of decreased morbidity and mortality after surgery using low invasive LiDCOrapid system to maximize stroke volume plus a fixed dose of dopexamine.

The goal of maximizing stroke volume replaced in many trials the previous attempts to use more specific predictors of preload reserve (i.e. corrected flow time [FTc], or dynamic variations of stroke volume/pulse pressure induced by mechanical ventilation) first to simplify the algorithm and second because its non-limited use. However, the “maximization” approach may lead to unnecessary fluid loading as pointed by Challand and not to “optimization” of the preload. Actually this approach is limited by the assumption that any change in stroke volume during surgery is purely preload dependent, what may not be the case in situations with change of afterload and/or inotropy. Quite surprisingly, the same flow parameter (SV) is used in the same protocol as a target of inotropic support (often in a form of predefined cardiac index or oxygen delivery values). In order to avoid this single-parameter (i.e. SV) use we have prepared a multi-parametric pGDT esophageal Doppler protocol based predominantly on variables more specific for different cardiovascular system domains: preload reserve (FTc), inotropy (peak velocity [PV]) and afterload (systemic vascular resistance [SVRI]).

The aim of this trial was to test the hypothesis that such multi-parametric pGDT protocol improves the postoperative complications rate in population of intermediate-to-high risk surgical patients undergoing open abdominal surgery.

Materials and methods

The prospective randomized trial was performed between April 2014 and June 2016 on the Department of Anesthesiology and Intensive Care and Department of Surgery, University hospital Ostrava, Czech Republic. The protocol of the study was approved by the local Ethical committee (ref. no.: 220/2014) and all participants signed informed consent prior to inclusion. The study was registered under ClinicalTrials.gov identifier: NCT02104687. All intermediate to high-risk patients (American society of anesthesiology score of 2 or 3) scheduled for open abdominal gastrointestinal surgery with presumed length of more than 120 minutes or with expected blood loss of more than 15% of blood volume were assessed for eligibility. Patients younger than 21 years, pregnant women, those undergoing emergency procedures and those having overt signs of sepsis were excluded from the study. Use of esophageal Doppler monitor CardioQ (Deltex TM Medical Limited, Chichester, UK) precluded inclusion of patients undergoing esophageal surgery and those with known esophageal pathology.

Randomization and outcome measures

Participants were randomly assigned to either control or intervention groups at presence to the operating room (1:1 randomization scheme; using the sealed opaque envelopes stored in a premade container). The treating anesthetist, attending anesthesia nurse and eventually the independent hemodynamic monitoring operator (in the control group) were aware of the patient’s group allocation. This information was concealed for all other participants and study team members as well as ICU and ward staff.

One-month postoperative morbidity, assessed as occurrence of any of organ or infectious complication or death, was the study’s primary outcome measure. The postoperative complications were based on standard definitions for cardiovascular, respiratory, abdominal, renal and central nervous complications as well as relevant infections similar to previous studies. Besides, postoperative mortality, the length of ICU and hospital stay were assessed as secondary outcome measures. Patients were routinely screened for the primary and sec-
ondary outcomes by a study group member unaware of patient’s group allocation on daily basis. Groups were further compared according to their intraoperative hemodynamic profile (20 minutes intervals), intraoperative and early postoperative (daily up to three days) fluid balance and inotropic/vasoactive drugs use. Laboratory parameters of oxygen debt (i.e. lactate serum level, base excess and oxygen saturation in the vena cava superior [ScvO₂]) and inflammatory markers (leukocytes, C-reactive protein, procalcitonin, interleukin 6) were also measured and compared for intergroup difference.

Anesthesia, hemodynamic monitoring and protocol care

All patients underwent standard preoperative preparation; those restricted in oral fluid intake received intravenous supplementation (2 mL/kg/h; Plasmalyte, Baxter). Propofol served as induction agent; sufentanil and cisatracurium were used throughout the procedure to achieve adequate analgesia and muscle relaxation. The anesthesia maintenance was performed using sevoflurane in O₂-air mixture. All patients received a crystalloid maintenance infusion of 1.5 mL/kg/h (Plasmalyte, Baxter). Volume controlled mode of ventilation (tidal volume: 8 mL per kilogram of ideal body weight, positive end expiratory pressure 5 cmH₂O, FiO₂ 0.4-0.5) was used to maintain normocapnia. If epidural catheter was placed the analgesic loading dose of sufentanil 20 μ in 10 mL of saline was administered before skin closure. If possible, patients recovered from anesthesia and were extubated in the operating room; afterwards they were admitted to the postoperative ICU for the immediate post-surgical care.

Besides standard intraoperative monitoring (3-lead ECG, pulse oximetry, diuresis) all patients received central venous catheter for central venous pressure (CVP) monitoring and their radial artery was cannulated for invasive blood pressure assessment (IBP) and mean arterial pressure (MAP) measurements. The CardioQ esophageal Doppler probe was inserted in all patients immediately after anesthesia induction into the distal esophagus and the position was corrected according to the manufacturer’s recommendations in order to obtain the best descend-ing aortic Doppler flow signal. The search for optimal signal was repeated during the surgically procedure as needed. In the intervention group the treating anesthetist was aware of the values measured by the CardioQ monitor. Contrary, in the control group the hemodynamic monitoring was performed by an independent operator and concealed to the treating anesthetist. All hemodynamic variables were sampled externally in 20 minutes intervals for further analysis.

The hemodynamic optimization in the intervention group (study goal cardiac index [CI] in the range of 2.5-3.8 L/min/m²) was based on parameters acquired from the CardioQ monitor: fluid boluses (300 mL of Plasmalyte), dobutamine (1-µg/kg/min increments), noradrenaline (0.02-µg/kg/min increments) or isosorbide dinitrate (1-µg/kg/min increments) infusions were all administered according to the protocol scheme (Figure 1). In the control group, the intraoperative hemodynamic care (use of fluids, inotropes or vasoactive agents) was purely on the treating anesthetist decision based on the knowledge of standard parameters (i.e. heart rate, IBP, CVP, diuresis, clinical findings).

Statistical analysis

The study sample size was estimated according to previous studies coming from Czech milieu

Figure 1.—Study optimization protocol. CI: Cardiac Index; Ftc: corrected flow time; PV: peak velocity; SVRI: index of systemic vascular resistance.
and our institutional data analysis both showing a usual morbidity in target population of 60%. In order to reach the presumed effect of the pGDT protocol given the results of Hamilton’s meta-analysis published at the moment of study design preparation (odds ratio for postoperative morbidity 0.43 [0.34-0.53]) — a sample of 64 patients per group would yield a power of 80% with type I error rate of 5%. We have decided to include 150 patients in total in order to cover potential drop offs.

The statistical analysis was performed in cooperation with the Institute of biostatistics and analyses, Masaryk University, Brno, Czech Republic. After testing normality of data distribution, intergroup differences were assessed using standard parametric or non-parametric tests (t-test, Mann-Whitney test). The χ² or Fisher exact tests were used to test categorical variables. Relative risk (RR) and its 95% confidence interval (CI) were also calculated for primary outcome and its denominators (mortality and morbidity). A P value below 0.05 was deemed statistically significant. Results are displayed as median (5th; 95th percentile) or mean and standard deviation based on their distribution, categorical data are given as number (percentage).

Results

During the study period, 197 patients were assessed for eligibility, 45 patients did not meet the inclusion criteria, two patients have declined to participate (Figure 2). Enrolled participants (N=150) were equally randomized into intervention (N=75) and control (N=75) group. After inclusion in 10 patients (four in the intervention and six in the control) the surgical procedure was cancelled due to inoperability, leaving 71 (intervention) and 69 patients (control) for the final analysis. Both groups were comparable in terms of baseline demographic parameters, chronic health care conditions and surgical procedures performed (Table I).

The intervention group showed better results in terms of the study’s primary outcome (28 days morbidity defined as occurrence of any defined complication) — 20 patients (28.2%) versus 32 (46.4%) in the control group (P=0.036); RR 0.61 (95% CI: 0.39-0.95), P=0.03. Abdominal and gastrointestinal complications were the major driver of this finding (Table II). There was no difference in mortality: one patient died in each group, P=0.99. The ICU (4 [2; 7] versus 4 [2; 17] days; P=0.339) and hospital length of stay (9 [6; 21] versus 11 [6; 40] days; P=0.301) were comparable between groups. However, the overall occupancy of hospital bed was 116 days shorter in the intervention group (796 vs. 912 days).

The hemodynamic optimization in the intervention group was associated with significantly improved flow parameters during the procedure (Figure 3, Table III). The average cardiac index values were higher in almost all time-points throughout the procedure starting after the 20minutes – Figure 3, panel A. This finding was not based solely on the improved fluid loading (FTc differed only for short period after the start of procedure) (Figure 3B), but more importantly on the increased contractility (PV) (Figure 3C) and decreased systemic resistance (Figure 3D). No major differences were observed in standard parameters (MAP [Figure 3E] or heart rate [Figure 3F]). The intervention was coupled with increased use of inotrope (44 [62%] vs. three [4%]; P=0.001) and decreased noradrenalin administration (18 [25%] vs. 38 [55%]; P=0.001).

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**Figure 2.**—Study flow chart according to CONSORT statement.
### Table I.—Baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intervention group (N=71)</th>
<th>Control group (N=69)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F/M ratio</td>
<td>32/39 (45%/55%)</td>
<td>24/45 (35%/65%)</td>
<td>0.231</td>
</tr>
<tr>
<td>Age, years</td>
<td>66±11</td>
<td>65±10</td>
<td>0.434</td>
</tr>
<tr>
<td>Height, cm</td>
<td>171.1±8.1</td>
<td>171.2±9.4</td>
<td>0.867</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.3±13.4</td>
<td>81.2±16.8</td>
<td>0.493</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.5±4.4</td>
<td>27.8±4.8</td>
<td>0.142</td>
</tr>
<tr>
<td>ASA 2/3/4</td>
<td>37/30/4 (52%/42%/6%)</td>
<td>33/33/3 (48%/48%/4%)</td>
<td>0.779</td>
</tr>
</tbody>
</table>

#### Type of surgery

- Hemicolectomy: 16 (22.5%) vs. 20 (29.0%)
- Rectum resection: 40 (56.3%) vs. 33 (47.8%)
- Pancreas resection: 10 (14.1%) vs. 15 (18.5%)
- GIT reconstruction: 5 (7.0%) vs. 3 (4.3%)
- Laparoscopic procedure: 48 (67.6%) vs. 36 (52.2%)
- Operation time, min: 191±57 vs. 188±70
- Epidural catheter: 52 (73.2%) vs. 46 (66.7%)
- Body temperature (end of surgery): 36.5 (36.4-36.6) vs. 36.5 (36.4-36.6)
- Possum score (physiologic): 19.2±5.4 vs. 18.4±4.7
- Possum score (operative): 16.5±5.0 vs. 17.3±5.7

#### Chronic conditions

- Acute myocardial infarction: 3 (4.2%) vs. 5 (7.2%)
- Ischemic heart disease: 6 (8.5%) vs. 7 (10.1%)
- Heart failure: 1 (1.4%) vs. 3 (4.4%)
- Atrial fibrillation: 8 (11.3%) vs. 7 (10.1%)
- Hypertension: 44 (62.0%) vs. 44 (63.8%)
- Chronic obstructive pulmonary disease: 4 (5.6%) vs. 7 (10.1%)
- Diabetic mellitus: 19 (26.8%) vs. 17 (24.6%)
- Chronic kidney disease: 5 (7.0%) vs. 3 (4.3%)

Continuous data are displayed as mean±SD or median (interquartile range). Categorical data are number of patients (percentage).

Statistical significance was tested by Mann-Whitney or t-test and Fisher’s exact test.

### Table II.—Postoperative outcomes.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intervention group (N=71)</th>
<th>Control group (N=69)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. of patients with any considered complication or death</td>
<td>20 (28.2%)</td>
<td>32 (46.4%)</td>
<td>0.036*</td>
</tr>
<tr>
<td>Total N. of complications (per patient)</td>
<td>41 (0.6%)</td>
<td>80 (1.16%)</td>
<td>0.022*</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1.4%)</td>
<td>1 (1.4%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Artificial ventilation &gt;24 hours</td>
<td>3 (4.2%)</td>
<td>4 (5.8%)</td>
<td>0.717</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>–</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>–</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>–</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>4 (5.6%)</td>
<td>7 (10.1%)</td>
<td>0.363</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (1.4%)</td>
<td>0 (0.0%)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Ileus</td>
<td>11 (15.5%)</td>
<td>22 (31.9%)</td>
<td>0.028*</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1 (1.4%)</td>
<td>3 (4.3%)</td>
<td>0.362</td>
</tr>
<tr>
<td>Reoperation</td>
<td>1 (1.4%)</td>
<td>4 (5.8%)</td>
<td>0.205</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>8 (11.3%)</td>
<td>13 (18.8%)</td>
<td>0.242</td>
</tr>
<tr>
<td>Acute psychosis</td>
<td>2 (2.8%)</td>
<td>3 (4.3%)</td>
<td>0.678</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>2 (2.8%)</td>
<td>3 (4.3%)</td>
<td>0.486</td>
</tr>
<tr>
<td>Abdominal infection</td>
<td>2 (2.8%)</td>
<td>7 (10.1%)</td>
<td>0.095</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (2.8%)</td>
<td>4 (5.8%)</td>
<td>0.438</td>
</tr>
<tr>
<td>Wound infection</td>
<td>2 (2.8%)</td>
<td>5 (7.2%)</td>
<td>0.271</td>
</tr>
<tr>
<td>Catheter infection</td>
<td>1 (1.4%)</td>
<td>3 (4.3%)</td>
<td>0.362</td>
</tr>
<tr>
<td>Infection, uncertain source</td>
<td>1 (1.4%)</td>
<td>2 (2.9%)</td>
<td>0.617</td>
</tr>
</tbody>
</table>

#### Secondary outcomes

- Hospitalization duration, days: 9 (6; 21) vs. 11 (6; 40)
- ICU hospitalization duration, days: 4 (2; 7) vs. 4 (2; 17)

Continuous data are median (5th; 95th percentile), categorical data are number of patients (percentage). Statistical significance were tested by Mann-Whitney and Fisher’s exact test.

*Statistically significant difference.
The use of vasodilator was non-frequent and occurred only in the intervention group (seven patients (9.9%) vs. none; P=0.013). Unlike many previous pGDT studies we have observed no major difference in fluid input and output, though the final intraoperative balance was lower in the intervention patients (Table III).

Postoperatively (within the first three postoperative days) no gross differences were observed in the care, besides the slightly higher use of noradrenalin in the control group (four patients [6.1%] vs. nine [13.2%]; three [4.6%] vs. 11 [16.2%] and one [1.9%] vs. eight [12.5%] on days 1, 2 and 3; P<0.05 for days 2 and 3). Postoperative use of norepinephrine was significantly associated with complication development with odds ratio 7.85 (95% CI: 2.49-24.7), 13.69 (95% CI: 3.01-62.3), and 5.81 (95% CI: 1.19-28.45) at 24, 48, and 72 hours respectively. The fluid balance was comparable between groups as well as its constituents (i.e. fluid inputs and outputs). Lactate serum levels were slightly more elevated in the control group at three and 12 hours after surgery (0.84±0.25 mmol/l vs. 0.98±0.38 mmol/l, P=0.02; and 1.15±0.61 vs. 1.43±0.84 mmol/l, P=0.071 in the intervention versus control groups, respectively), but fully normalized afterwards. The ScvO₂, pH, and base excess values were without major differences. The inflammatory response was also of similar extent based on comparable leukocyte counts 48 hours postoperatively in intervention and control group (9.1 [5.7; 17.8] vs. 10.1 [6.2; 15.8] million/mL; P=0.793) and levels of C-reactive protein (171.0 [38.0; 283.0] vs. 148.5 [60.0; 291.0] mg/L; P=0.401), procalcitonin (0.40 [0.15; 6.18] vs. 0.31 [0.12; 6.66] µg/L; P=0.643) and interleukine-6 (64.0 [15.5; 498.0] vs. 54.0 [9.4; 443.0] ng/L; P=0.934).

Figure 3.—Development of intraoperative hemodynamic parameters. Comparison of intervention (black) and control (grey) groups in six most important hemodynamic variables: A) Cardiac Index (CI, L/min/m²); B) corrected flow time (FTc, ms); C) peak velocity (PV, m/s¹); D) index of systemic vascular resistance (SVRI, dyn.s/cm⁵/m²); E) mean arterial pressure (MAP, mmHg); F) heart rate (HR, bpm).
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Intervention group (N=71)</th>
<th>Control group (N=69)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average intraop mean arterial pressure, mmHg</td>
<td>81±10</td>
<td>79±9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Average intraop heart rate, bpm</td>
<td>69±12</td>
<td>68±13</td>
<td>0.493</td>
</tr>
<tr>
<td>Average intraop cardiac index, L/min/m²</td>
<td>2.82±0.61</td>
<td>2.45±0.61</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Average intraop corrected flow time, ms</td>
<td>333±30</td>
<td>329±35</td>
<td>0.020*</td>
</tr>
<tr>
<td>Average intraop peak velocity, m/s</td>
<td>63±19</td>
<td>56±15</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Average intraop systemic vascular resistance index, dyn.s/cm²/m²</td>
<td>2278±629</td>
<td>2648±827</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Fluids input, mL</td>
<td>2529±1180</td>
<td>2905±1367</td>
<td>0.108</td>
</tr>
<tr>
<td>Plasmalyte, mL</td>
<td>2432±1065</td>
<td>2758±1096</td>
<td>0.099</td>
</tr>
<tr>
<td>Erythrocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. patients (%)</td>
<td>8 (11%)</td>
<td>11 (16%)</td>
<td>0.467</td>
</tr>
<tr>
<td>Volume, mL</td>
<td>641 (279)</td>
<td>566 (245)</td>
<td>0.231</td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. patients (%)</td>
<td>3 (4%)</td>
<td>8 (12%)</td>
<td>0.126</td>
</tr>
<tr>
<td>Volume, mL</td>
<td>602±11</td>
<td>491±134</td>
<td>0.066</td>
</tr>
<tr>
<td>Diuresis, mL</td>
<td>561±285</td>
<td>551±367</td>
<td>0.496</td>
</tr>
<tr>
<td>Blood losses, mL</td>
<td>411±398</td>
<td>407±448</td>
<td>0.378</td>
</tr>
<tr>
<td>Fluid balance, mL</td>
<td>1563±896</td>
<td>1961±1044</td>
<td>0.036*</td>
</tr>
<tr>
<td>Dobutamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. patients (%)</td>
<td>44 (62%)</td>
<td>3 (4%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Start of administration, min</td>
<td>55±32</td>
<td>143±81</td>
<td>0.044*</td>
</tr>
<tr>
<td>Rate, µg/kg/min</td>
<td>6±4</td>
<td>5±1</td>
<td>0.106</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. patients (%)</td>
<td>18 (25%)</td>
<td>38 (55%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Start of administration, min</td>
<td>134±54</td>
<td>96±58</td>
<td>0.012*</td>
</tr>
<tr>
<td>Rate, µg/kg/min</td>
<td>0.108±0.045</td>
<td>0.384±1.237</td>
<td>0.003*</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. patients (%)</td>
<td>7 (10%)</td>
<td>0 (0%)</td>
<td>0.013*</td>
</tr>
<tr>
<td>Start of administration, min</td>
<td>59±24</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Rate, µg/kg/min</td>
<td>1.02±0.68</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>132.0±18.49</td>
<td>132.9±20.02</td>
<td>0.989</td>
</tr>
<tr>
<td>3 h postop</td>
<td>116.8±16.70</td>
<td>115.3±19.49</td>
<td>0.691</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>7.43±0.06</td>
<td>7.42±0.05</td>
<td>0.480</td>
</tr>
<tr>
<td>3 h postop</td>
<td>7.27±0.55</td>
<td>7.37±0.10</td>
<td>0.953</td>
</tr>
<tr>
<td>pO₂, kPa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>18.2 (16.7-19.4)</td>
<td>18.7 (17.4-19.8)</td>
<td>0.06</td>
</tr>
<tr>
<td>3 h postop</td>
<td>13.1 (11.9-14.5)</td>
<td>13.4 (12.2-14.6)</td>
<td>0.513</td>
</tr>
<tr>
<td>pCO₂, kPa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>4.9 (4.4-5.1)</td>
<td>4.8 (4.4-5.1)</td>
<td>0.981</td>
</tr>
<tr>
<td>3 h postop</td>
<td>5.0 (4.6-5.5)</td>
<td>5.0 (4.6-5.5)</td>
<td>0.607</td>
</tr>
<tr>
<td>HCO₃, mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>25.1 (24.7-25.8)</td>
<td>25.5 (24.7-26.3)</td>
<td>0.288</td>
</tr>
<tr>
<td>3 h postop</td>
<td>23.7 (22.5-24.5)</td>
<td>22.9 (21.5-24.1)</td>
<td>0.016</td>
</tr>
<tr>
<td>BE, mmol/L</td>
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<td></td>
<td></td>
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<tr>
<td>Preop</td>
<td>0.35±2.39</td>
<td>0.31±2.72</td>
<td>0.681</td>
</tr>
<tr>
<td>3 h postop</td>
<td>-1.40±2.99</td>
<td>-1.46±2.77</td>
<td>0.520</td>
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<td>Lactate, mmol/L</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>0.88±0.31</td>
<td>0.99±0.39</td>
<td>0.154</td>
</tr>
<tr>
<td>3 h postop</td>
<td>0.84±0.25</td>
<td>0.98±0.38</td>
<td>0.020</td>
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<td>ScvO₂, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>84.29±6.53</td>
<td>83.51±8.17</td>
<td>0.697</td>
</tr>
<tr>
<td>3 h postop</td>
<td>84.81±7.15</td>
<td>83.25±6.62</td>
<td>0.115</td>
</tr>
</tbody>
</table>

Continuous data are mean±SD or median (interquartile range). Categorical data are number of patients (percentage). Statistical significance was tested by t-test, Mann-Whitney test and Fisher’s exact test.

3 h postop: blood taking three hours after the surgery has ended; start of administration: time elapsed from the case initiation till the start of agent administration.

*Statistically significant difference.
Discussion

In this single-center randomized trial we have demonstrated the postoperative clinical outcome benefit (measured by rate of postoperative complications) of pGDT protocol based on esophageal Doppler derived domain-specific targets — corrected flow time, peak velocity and systemic vascular resistance in intermediate-to-high risk surgical patients undergoing open abdominal procedures.

Our results correlate with the previous findings of multiple studies on this topic\(^9, 11, 14\) and also with the results of the most recent meta-analysis on the topic encompassing 95 studies and almost 11,659 patients.\(^{15}\) However they are in disparity with those in which sophisticated and domain-specific targets were replaced with more simplistic view of stroke volume maximization driven fluid loading and/or stroke volume/cardiac index based targets of oxygen delivery.\(^{5, 16-18}\) From this point of view the traditional approach which enables tailoring fluids, vasoactive substances and inotropes seems to be more efficient. There may be several other reasons for this finding. Our patients were not tested in terms of cardiac performance prior the surgery so we cannot directly compare their fitness to population of Challand study.\(^{6}\) However, all our patients were able to perform activities with 4 METs equivalent (\(i.e\.\) climbing two flights of stairs) and given their co-morbidities and ASA score we have graded them as intermediate- to high-risk and linked probably more to the aerobically fit population in the Challand study.\(^{6}\) Inclusion of open procedures and absence of enhanced recovery program may be other reasons. However, the POSSUM score and postoperative outcomes in control groups are comparable among described studies.\(^{5, 9, 11, 16}\)

Over the decades the view on pGDT and perioperative fluid therapy has evolved significantly. Starting from liberal and restrictive cook-book recipes, over the high maintenance plus goal directed bolus treatment we have evolved to goal directed dynamic response driven fluid restriction. Maintenance fluids were minimized in our trial as proposed by Chappel \textit{et al.}\(^{19}\) In our study the total average volume infused (bolus and maintenance) was 2432 mL (intervention group), compared to almost four liters in Challand,\(^6\) Salzwedel\(^9\) or in multiple other studies as demonstrated by Rollins and Lobo in their meta-analysis.\(^{20}\) Quite interestingly the fluid loading showed similar characteristics between both groups, \(i.e\.\) fluid volume and its timing (demonstrated by FTc evolution) (Figure 3). This was already described by both Challand\(^6\) and Pearse\(^8\) leading to the notion that the “standard” care starts to resemble the pGDT fluid interventions pathways especially when risk of hypovolemia is reduced by decreased rate of bowel preparation, limiting of the fasting period and use of pre-operative intravenous replacement.

Besides, crystalloids were the only fluids used for volume therapy in our study. Yates \textit{et al.}\ has demonstrated that crystalloids may be used for perioperative pGDT equally to the usual colloid loading without risk of significant fluid extravasations.\(^21\) Our study supports this finding by demonstrating that crystalloids are useful for intraoperative management and that their loads may be significantly decreased by reducing the maintenance fluids. More importantly it seems they are easily mobilized during the postoperative course leading to even lower 24 hours balance (2.6 liters in our interventions group) which is close to the enhanced recovery “zero balance” dogma.\(^{22}\)

In contrast to the fluid loading, the use of both vasopressors and inotropes differed significantly between intervention and control groups. Also, it differed significantly from previous “pragmatic” studies\(^8\) with fixed dopexamine use or fluid optimization trials without inotropic support targets.\(^6, 17, 18\) In our trial the inotropes were titrated according to their effect on the peak velocity. This led to their higher use (44 patients; 62\%) as compared to previous studies which used predominantly the stroke volume/cardiac output thresholds (Benet \textit{et al.},\(^11\) 2\%, Salzwedel \textit{et al.}\(^9\) 41\%). In contrast the primary cardiovascular medication used in the control group was noradrenalin (resembling the Salzwedel’s trial)\(^9\) demonstrating that unlike fluids the clinical judgment of vasoactives/inotropes needs is insufficient. Higher use of norepinephrine (especially in the postoperative course) may be linked to imbalance in regional oxygen delivery and increased number of postoperative complications. These
Limitations of the study

No matter how positive our findings are, one should never forget that monocentric studies are prone for significant bias. We have tried our best to perform the study as far as possible in line with the best research principles. The robust methodology and meticulous approach to interventions delivery as well as postoperative assessment is on one side important strength of our trial. On the other, the same may be observed as a major drawback when general (non-research) implementation is considered. The future development of monitoring software coupled with automated analysis, guides and prompts may significantly help to overcome this problem. Besides, the baseline quality of care in the institution and non-standardization of the decisions in the protocol may significantly affect the outcomes in the control group. From this point of view the postoperative outcome are not significantly different from those reported by many other authors from Western Europe. Moreover, they are for sure descriptive for the central/eastern Europe region (and possibly many others) where pGDT and enhanced recovery programs are still far from being standard of care.

Conclusions

This study has demonstrated that a complex pGDT protocol based on domain specific functional hemodynamic parameters of preload reserve, inotropy and afterload may be associated with lower rate of postoperative morbidity in intermediate-to-high risk patients undergoing scheduled gastrointestinal procedures.

What is known

• Perioperative goal directed therapy is associated with improved postoperative outcomes in high risk surgical patients.
• Esophageal Doppler has been used in multiple trials to guide fluid therapy using corrected flow time and stroke volume.
What is new

- Multi-parametric approach using not only stroke-volume and flow-based variables, but also parameters of afterload and inotropy (such as peak velocity) may further improve the perioperative goal directed protocol.
- In this study, such multi-parametric approach was associated with a decreased complications rate in scheduled gastrointestinal intermediate-to-high risk patients.

References


Conflicts of interest.—Jan Benes is a consultant for Edwards Lifesciences, Inc. and CNSystems Medizinsystems AG. All other authors declare not to have any competing interest.

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Authors’ contributions.—Pavel Szturz designed the study. Pavel Szturz, Pavel Folwarczny, Roman Kula, and Jan Neiser performed the patient management and participated actively on the writing of the manuscript. Pavel Ševčík helped design the study and managing the financial sources, participating actively in patients’ management, and writing the manuscript. Jan Benes revised the study design, actively participated on the results interpretation and drafted the manuscript. All authors have read and approved the final version of the text.

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**Effect of adding nalbuphine to intrathecal bupivacaine with morphine on postoperative nausea and vomiting and pruritus after elective cesarean delivery: a randomized double blinded study**

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**ABSTRACT**

BACKGROUND: The use of intrathecal morphine may result in serious side effects in parturients undergoing cesarean delivery. Nalbuphine, is a mu receptor antagonist and a kappa receptor agonist. Combinations of opioid agonist and agonist antagonist can decrease the incidence of opioid related side effects. We aimed to investigate the effect of adding nalbuphine, to intrathecal morphine on postoperative nausea and vomiting and pruritus after a cesarean delivery.

METHODS: Eighty parturient undergoing elective cesarean delivery under spinal anesthesia were randomized into two similar groups. Group 1: received 10 mg of 0.5% hyperbaric bupivacaine with 0.2 mg morphine. Group 2: received as a group 1 plus 0.5 mg nalbuphine, with total volume 2.5 mL in both groups. Measurements: Data on the severity of nausea and vomiting were collected using a numerical rating scale and visual analogue scale was used to quantify pruritus. Onset and duration of sensory blockade, Visual Analog Scale for pain, the first time to ask for rescue analgesia and total rescue analgesic consumption were recorded.

RESULTS: Nausea and vomiting and pruritus severity scores and number of patients developed nausea and vomiting and pruritus were significantly lower (P<0.001) in group 2. Onset and duration of sensory block, time to first request for rescue analgesia, Visual analog Scale for pain and paracetamol consumption showed no statistically differences between both groups (P>0.05).

CONCLUSIONS: We concluded that the addition of nalbuphine to intrathecal bupivacaine plus morphine significantly reduced the incidence and severity of postoperative nausea and vomiting and pruritus without affecting analgesic potency.

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KEY WORDS: Injections, spinal - Morphine - Nalbuphine - Postoperative nausea and vomiting - Pruritus.
result in serious side effects. These side effects may lead to patient discomfort and prolonged hospital stay thus limiting the usefulness of IT morphine.

Nalbuphine is a mu receptor antagonist and a kappa receptor agonist. When added as an adjunct to intrathecal local anesthetics, it provides good analgesia with decreased incidence and severity of mu receptor side effects. Administered intramuscular (IM) or intravenous (IV), nalbuphine in doses up to 0.15 mg/kg is considered equipotent to morphine in its analgesic and respiratory effects. However, at larger doses (0.4 mg/kg), there is a ceiling effect on both respiratory depression and analgesic effectiveness.

The addition of nalbuphine to morphine intrathecally can improve postoperative pain management in patients undergoing knee surgery under spinal anesthesia. Although its safety and advantages over other opioids had been ensured in involving animals as well as human, only a few studies are available with regard to intrathecal nalbuphine.

We hypothesized that adding nalbuphine to intrathecal morphine could decrease the incidence of morphine related side effects in parturient undergoing cesarean delivery. The primary endpoint of this study was to investigate the effect of adding nalbuphine to intrathecal morphine on postoperative nausea and vomiting (PONV) in women undergoing cesarean delivery under spinal bupivacaine anesthesia. The secondary endpoints were to evaluate its effect on postoperative pruritus and quality of postoperative analgesia.

Materials and methods

This prospective, randomized, double blinded study was performed in Women Health Hospital, Assiut University, Faculty of Medicine (July 2016-August 2017), after obtaining approval from the local ethics committee under the number 17100394 on 10 July 2016 and registered in ClinicalTrials.gov ID: NCT02716129 with initial release 15 March 2016, and written informed patient consent was obtained after thorough explanation.

Eighty parturients (ASA physical status I-II) undergoing elective cesarean delivery under spinal anesthesia were included in this study. Patients with infection at the site of injection, coagulopathy or other bleeding diathesis, pre-existing neurologic deficits, history of hypersensitivity to any of the given drugs, inability to communicate with the investigator and history of chronic opioid use were excluded from the study.

Randomization

The patients were divided randomly (permutated blocks) by a computer generated program (Random Allocation Software [RAS]) into group 1 and group 2, which were placed in a sealed envelopes prior to study initiation and opened prior to anesthesia by a physician who prepared the solutions with equal volume and identified it with the patient number, according to the envelope drawn. The physician, who was responsible for the anesthesia and the responsible investigator, remained blind to the chosen group until the end of the study.

Anesthesia technique

On arrival in the operating room, a peripheral IV cannula 18 G was inserted and each patient was preloaded with 10 mL/kg Ringer’s lactate solution. Standard non-invasive monitors were applied including, non-invasive blood pressure (NIBP), ECG, and pulse oximetry. Intrathecal block under strict aseptic conditions was performed in sitting position at L3-4 or L4-5 interspinous space with 25G Quinke spinal needle using 0.5% hyperbaric bupivacaine. Urinary catheter was inserted to all the parturient. Patients who did not develop sensory block up to T4 and Bromage’s grade 4 motor blocks were excluded from the study.

Study groups

Eighty patients were randomized into two groups:

- group 1 (morphine group): 40 patients of this group received intrathecal 10 mg of 0.5% hyperbaric bupivacaine with 0.2 mg morphine in 0.5 ml volume with total volume 2.5 mL;
- group 2 (morphine plus nalbuphine group): 40 patients of this group received intrathecal 10
mg of 0.5% hyperbaric bupivacaine with 0.2 mg morphine plus 0.5 mg nalbuphine in 0.5 mL volume with total volume 2.5 mL.

Data collection

Patient data, such as age, sex, weight, height, BMI, gestational age, gravidity and duration of the procedure were recorded. Cardio-respiratory parameters, such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and respiratory rate (RR) were recorded before IT injection of the drug, every 15 minutes for the first two hours postoperative and then every six hours for the first postoperative 24 hours.

Some variables were identified to be measured:
- the onset of sensory blockade (from the end of injection to loss of pinprick sensation at T4 dermatome) and duration of sensory blockade (two-segment regression time from the highest level of sensory blockade);
- pain score: patients were asked to rate their pain by using a visual analog pain scale (VAS pain score) (0 for no pain to 10 for the worst pain imaginable) every 2 h for 24 h after surgery; patients were not being awakened during sleep (VAS is considered to be <4), the first time to ask for analgesics or when VAS was >4 and total rescue analgesic consumption were recorded.

Evidence of side effects was evaluated:
- any side effects in the form of postoperative nausea and vomiting, pruritus, hypotension (MBP >20% below baseline), bradycardia (HR<60 beats/min.) and respiratory depression (RR<8 breath/min or arterial oxygen saturation <90%), were recorded for 24 hours;
- nausea and vomiting: data on the severity of nausea and vomiting was collected face to face using a numerical rating scale (NRS nausea and vomiting severity score), based on Edmonton Symptom Assessment System. The numerical scale is a rating scale from 0 to 10 (0 meaning that the symptom is absent and 10 that it is of the worst possible severity), and the parturient herself selected the number associated with his severity;
- itching: a Visual Analog Scale (VAS Pruritus Severity Score) was used to quantify pruritus.

The patient draws a line anywhere on the scale that best represents the severity of his itching (0=No itching and 10=Worst possible itching).

- sedation score: Using Ramsay Sedation Scale; 1= patient is anxious and agitated or restless, or both, 2= patient is cooperative, oriented, and tranquil, 3= patient responds to commands only, 4= patient exhibits a brisk response to light glabellar tap or loud auditory stimulus, 5= patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus, 6= patient exhibits no response.

Postoperative management

Vomiting (NRS>4) in the presence of stable hemodynamic was managed with 4 mg ondansetron, pruritus (VAS>4) was treated with 4 mg dexamethasone, for the event of bradycardia patient was receiving IV atropine, hypotension was treated with IV fluids and ephedrine and respiratory depression was managed with naloxone and appropriate supportive ventilation for the patient.

Breakthrough pain with VAS<4, the patient was managed with 1 gm of paracetamol intravenous infusion. Morphine 0.1 mg/kg IV was given as a rescue analgesia when VAS was ≥4 with maximum of three doses with a minimum 8 hour interval between the two consecutive injections.

Sample size calculation

Based on a previous study which estimated the incidence of morphine induce nausea and vomiting as 56%, the sample size was evaluated in order to detect 20% reduction in the incidence of nausea and vomiting after adding nalbuphine to intrathecal morphine using $\chi^2$ in a two tailed study with $\alpha=0.05$ and $\beta=20%$. Seventy six patients were needed in both groups with a ratio of sample size in group 1 to group 2 =1, two patients were added to each group to compensate for dropouts.

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 20) software. Per-protocol population was analyzed and descriptive values were expressed as mean±SD or number (%). Independent Student’s
Results

Eighty patients were included in this study, three patients were excluded; one patient did not develop T4 sensory block and two patients had postpartum hemorrhage and required surgical intervention. Seventy seven patients were completed the study; 38 patients in group 1 and 39 patients in group 2; in accordance with the consort flow diagram as shown in Figure 1.

Patients’ characteristics and operative data showed no statistically significant differences between the two groups with regard to age, weight, BMI, height, gestational age, gravidity and duration of the operation (Table I). Vital signs were comparable as regards their HR, SBP, DBP, MBP and RR with not statistically significant differences between both groups as shown in Table I. There was no patient observed in both groups with a respiratory rate <8 breaths/min.

Nausea and vomiting severity score (NRS) and pruritus severity score (VAS) were significantly lower (P<0.001) in group 2 when compared to group 1. The number of parturient who developed nausea and vomiting and the number of parturient who developed pruritus was significantly lower in group 2 (P<0.001). We did not observe any parturient who required treatment for nausea and vomiting or pruritus in group 2, while in group 1, 12 patients (31.5%) treated for nausea and vomiting or pruritus.

Table I.—Parturient characteristics and vital signs of patients.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (N.=38)</th>
<th>Group 2 (N.=39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.45±4.8</td>
<td>22.85±5.8</td>
<td>0.623</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85.1±10.1</td>
<td>83.05±8.5</td>
<td>0.337</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.6±9.7</td>
<td>165.0±8.6</td>
<td>0.445</td>
</tr>
<tr>
<td>BMi</td>
<td>29.6±4.5</td>
<td>30.2±3.8</td>
<td>0.561</td>
</tr>
<tr>
<td>Gestational age (week)</td>
<td>37 (6)</td>
<td>37 (5)</td>
<td>0.524</td>
</tr>
<tr>
<td>Gravidity</td>
<td>Primigravida</td>
<td>12 (31.5%)</td>
<td>0.721</td>
</tr>
<tr>
<td></td>
<td>Multigravida</td>
<td>26 (68.5%)</td>
<td></td>
</tr>
<tr>
<td>Duration of C.S. (min)</td>
<td>51.45±6.6</td>
<td>53.55±6.1</td>
<td>0.151</td>
</tr>
<tr>
<td>Vital signs</td>
<td>Heart (beat/min)</td>
<td>83.1±12.0</td>
<td>0.087</td>
</tr>
<tr>
<td></td>
<td>Systolic blood pressure (mmHg)</td>
<td>108.6±9.1</td>
<td>106.4±8.4</td>
</tr>
<tr>
<td></td>
<td>Diastolic blood pressure (mmHg)</td>
<td>72.4±6.0</td>
<td>71.1±5.5</td>
</tr>
<tr>
<td></td>
<td>Mean arterial blood pressure (mmHg)</td>
<td>84.1±6.8</td>
<td>82.9±6.9</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate (breaths/min)</td>
<td>16.2±2.5</td>
<td>15.4±2.1</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD, median (range), and number (%). P>0.05 not statistically significant.
undergoing caesarean section are exposed to drug induced hemodynamic and surgical stimuli, such as uterine manipulation and opioid administration for postoperative analgesia.

22 Rawal et al. studied the behavioral, motor, electroencephalographic and histopathologic changes following intrathecal nalbuphine in sheep and they found that the changes were similar to that of those who received saline implying that intrathecal nalbuphine is safe in human population.

Table II.—Nausea and vomiting severity score, pruritus severity score, number of patients developed and required treatment for pruritus and vomiting.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (N.=38)</th>
<th>Group 2 (N.=39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity score (NRS)</td>
<td>7.05±2.7</td>
<td>1.4±1.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Number of patient developed nausea and vomiting (%)</td>
<td>21 (55.2%)</td>
<td>2 (5.1%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Number of patient required treatment (%)</td>
<td>12 (31.5%)</td>
<td>0 (0%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity score (VAS)</td>
<td>5.6±2.01</td>
<td>1.4±1.7</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Number of patient developed pruritus (%)</td>
<td>23 (60%)</td>
<td>3 (7.7%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Number of patient required treatment (%)</td>
<td>16 (42.1%)</td>
<td>0 (0%)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD, number and percentage (%). NRS: Numerical Rating Scale. VAS: Visual Analog Score. *Significant P<0.05.

Table III.—Onset and duration of sensory block, Ramsay Sedation Scale, time to 1st analgesic request visual analog pain score (VAS) and paracetamol consumption.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (N.=38)</th>
<th>Group 2 (N.=39)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory block onset (min)</td>
<td>2.12±0.49</td>
<td>1.98±0.32</td>
<td>0.140</td>
</tr>
<tr>
<td>Sensory block duration (hours)</td>
<td>20.2±3.4</td>
<td>21.1±2.9</td>
<td>0.636</td>
</tr>
<tr>
<td>Ramsay Sedation Scale</td>
<td>2.5±0.82</td>
<td>2.6±1.03</td>
<td>0.214</td>
</tr>
<tr>
<td>Time to 1st analgesic request (hours)</td>
<td>18.3±3.2</td>
<td>18.7±3.7</td>
<td>0.613</td>
</tr>
<tr>
<td>VAS pain score</td>
<td>1.9±1.16</td>
<td>1.5±1.14</td>
<td>0.131</td>
</tr>
<tr>
<td>Paracetamol consumption (gm)</td>
<td>0.30±.47</td>
<td>0.20±.41</td>
<td>0.322</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. P>0.05 not statistically significant. VAS: Visual Analog Score.

required IV ondansetron for treatment of vomiting (NRS>4) and 16 patients (42.1%) required IV dexamethasone for treatment of pruritus (VAS>4) as shown in Table II.

Onset and duration of sensory block, time to 1st analgesic request, VAS pain score values, Ramsay Sedation Scale and postoperative paracetamol consumption as a rescue analgesic showed no statistically significant differences between both groups (P>0.05) as shown in Table III. The postoperative VAS pain score during the first 24 hours was <4 in both groups (1.9±1.16 and 1.5±1.14). Paracetamol was given as a rescue analgesic and the parturient did not need morphine.

Discussion

Postoperative nausea and vomiting is multifactorial in origin, especially in pregnant and puerperal women. In addition to general and pre-existing risk factors, such as elevated gonadotropin and progesterone serum levels, parturient undergoing caesarean section are exposed to drug induced hemodynamic and surgical stimuli, such as uterine manipulation and opioid administration for postoperative analgesia.

Our data revealed that, patients who received intrathecal morphine and nalbuphine as an additive to bupivacaine had significantly lower incidence of postoperative nausea and vomiting and pruritus with a significantly lower severity score compared to patients who received intrathecal morphine alone as an additive to bupivacaine. Both groups were comparable as regard onset and duration of sensory block, time to first rescue analgesic request, VAS pain score values and rescue analgesic consumption.

Is intrathecal nalbuphine safe in human population?

Rawal et al. studied the behavioral, motor, electroencephalographic and histopathologic changes following intrathecal nalbuphine in sheep and they found that the changes were similar to that of those who received saline implying that in-
Intrathecal nalbuphine was devoid of neurotoxic effects. Later in 1992, study by Lin, involving human population, observed that both nalbuphine 0.4 mg and morphine 0.4 mg as an additive to intrathecal tetracaine provided prolonged duration of analgesia than the control group, but, lesser side effects in the nalbuphine group. Gupta et al. confirmed that intrathecal nalbuphine does not cause significant side effects, even at the dose of 2 mg.

Is intrathecal nalbuphine safe during pregnancy?

Culebras et al. found that intrathecal nalbuphine in patients undergoing elective cesarean section provided early postoperative analgesia without maternal respiratory depression and the neonatal APGAR scores, arterial blood gas values were also not affected. Subsequently, in 2002, Yoon et al., concluded that the incidence of pruritus was significantly lower in patients undergoing cesarean section under spinal anesthesia with intrathecal nalbuphine as an additive to 0.5% bupivacaine compared to intrathecal morphine. A study by Gomaa et al. concluded that intrathecal nalbuphine produced lesser side effects such as pruritus, nausea and vomiting compared to intrathecal fentanyl in cesarean section patients.

In this study, adding nalbuphine to intrathecal morphine significantly decreased the incidence of PONV to 5.1% compared to 55.2% in intrathecal morphine without nalbuphine. The need for ondansetron as antiemetic or dexamethasone for treatment of pruritus was significantly reduced in parturients receiving nalbuphine plus morphine during the first 24 hours postoperative. Two articles have evaluated the effect of adding nalbuphine to intrathecal morphine on side effects related to morphine in patients undergoing lower abdominal and lower limb surgeries. Moustafa et al. added single dose of 1 mg nalbuphine to intrathecal 0.2 mg morphine with bupivacaine and Kumar et al. studied the effect of three different doses of intrathecal nalbuphine (0.5, 1 and 1.5 mg) with intrathecal morphine, compared to 0.2 mg morphine plus 0.5 mg nalbuphine in our study. Both Moustafa and Kumar concluded that intrathecal addition of nalbuphine to morphine decreases opioid related pruritus and nausea and vomiting without affecting postoperative analgesia.

The onset and incidence of minor opioid related side effects after intrathecal morphine administration do not depend on its dose, occurring with even very small doses of morphine. Accordingly, they can be considered as a patient-dependent effect of the drug, suggesting the presence of a primary dose independent excitatory component that might be related to the theory of the bimodal activation of opioid receptors. Interpatient variability may also be related to pharmacogenetic factors in the patients, that can lead to treatment failure or to life-threatening adverse drug reactions among patients with identical doses of the same drug.

Gehling et al. in their meta-analysis have looked at the efficacy and side effects of intrathecal opioids after caesarean section and they observed that patients receiving morphine < 0.3 mg in addition to spinal anesthesia showed a significantly increased risk of nausea, vomiting, pruritus, and a slightly lower risk of respiratory depression compared with placebo patients treated with systemic opioids (P>0.05). Wong et al. observed that intrathecal morphine 0.2 mg provided better analgesia but with more nausea compared with morphine 0.1 mg.

Several studies concluded that the addition of different doses of nalbuphine (0.5, 0.6, 1 and 1.5 mg) to intrathecal bupivacaine cause prolongation of duration of sensory block and postoperative analgesia and less requirement of analgesics in postoperative period without increasing the side effects or complication in surgeries under spinal anesthesia. Our study did not evaluate the effect of adding nalbuphine to intrathecal bupivacaine without morphine and did not estimate the analgesic potency of nalbuphine compared to morphine, because the primary endpoint of this study was to investigate postoperative morphine related side effects.

Combinations of morphine and nalbuphine in IV patient controlled analgesia (PCA) can decrease the incidence of opioid related pruritus and nausea and vomiting, without affecting the analgesia and PCA requirement, and the antipruritus effect is ratio dependent. This may provide a novel combination strategy of opioid
agonist and agonist antagonist for postoperative pain management after gynecologic surgery.\textsuperscript{32} The reduction in the incidence of opioid related nausea might result from blocking the excitatory effects of opioids.\textsuperscript{33} Nalbuphine is a mixed opioid agonist antagonist and low-dose nalbuphine may act like an ultra-low dose of naloxone, this can decrease the opioid-related side effects, with unchanged analgesic and opioid requirements.\textsuperscript{32} Several studies have reported that IV nalbuphine can reduce morphine-related effects.\textsuperscript{34}

Limitations of the study

This study did not provide the optimal concentration of nalbuphine added to intrathecal bupivacaine with morphine, however the single intrathecal nalbuphine dose (0.5 mg) was investigated based on its safety during pregnancy in other studies.\textsuperscript{24, 25} Although the population to be analyzed in a superiority trial is the intention to treatment (ITT) according to the guidelines for the analysis of the controlled clinical trials (ICH-E9), we used the per-protocol population instead of ITT.

Conclusions

Based on our data, we concluded that, the addition of 0.5 mg nalbuphine to intrathecal bupivacaine plus 0.2 mg morphine significantly reduced the incidence and severity of postoperative morphine related nausea and vomiting and pruritus without affecting the analgesic potency of morphine after cesarean delivery.

What is known

- Intrathecal morphine provides effective postoperative analgesia and increases the risk of nausea, vomiting and pruritus.
- Nalbuphine is a mu receptor antagonist and a kappa receptor agonist; although its safety and advantages over other opioids had been ensured, only a few studies are available with regard to adding nalbuphine to intrathecal morphine.

What is new

- The addition of nalbuphine to intrathecal morphine is associated with reduction in the incidence and severity of postoperative nausea, vomiting and pruritus in parturient undergoing cesarean delivery under spinal bupivacaine anesthesia.
- It also does not affect the onset and duration of sensory block, VAS pain score values and postoperative analgesic consumption.

References

12. Gunion MW, Marchionne AM, Anderson CT. Use of the


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

Utilization of echocardiography in Intensive Care Units: results of an online survey in Germany

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ABSTRACT

BACKGROUND: In patients with hemodynamic instability echocardiography has been recommended as the preferred modality to evaluate the underlying pathophysiology. However, due to the fact that recent scientific data on the utilization of echocardiography in German Intensive Care Units (ICU) are scarce, we sought to investigate current practice.

METHODS: A structured, web-based, anonymized survey was performed from May until July 2015 among members of the German Interdisciplinary Association of Critical Care and Emergency Medicine (DIVI) consisting of 14 questions. Descriptive data analysis was performed.

RESULTS: One hundred four intensivists participated in the survey. Two-thirds of participants (66%) used echocardiography regularly for hemodynamic monitoring and stated that it changed the therapy in 26-50% of the cases irrespective of the time performed after ordering the examination. Transthoracic (TTE) were more frequently used than transesophageal (TEE) examinations. Twenty-six percent of the participants held an echocardiography certificate with a formal examination, 27% completed a structured training without an examination and almost half of the questioned ICU personnel (47%) did not complete a comprehensive training.

CONCLUSIONS: The results of this survey demonstrate a widespread utilization of echocardiography as part of routine diagnostic on frequent number of operative ICUs. However, there might be a lack of structured echocardiographic training especially for anesthesiologists.

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KEY WORDS: Echocardiography - Intensive Care Units - Hemodynamics - Education.

Patients admitted to the Intensive Care Unit (ICU) are frequently presenting with circulatory shock.1, 2 Diagnosing the underlying pathophysiology is of utmost importance for taking appropriate measures that aim to increase cardiac output (CO) and thus oxygen delivery (DO2). In this context, goal directed therapy has been shown to improve patient outcome.3 In the
last decade, echocardiography has been recognized as a useful diagnostic and monitoring tool in perioperative medicine. As early as in 1996, a multiplane transesophageal echocardiographic examination has been recommended in cases of unexplained life-threatening hemodynamic instability. Cahalan et al. already introduced and used focused TTE in the late eighties and recommended Intensive Care Unit (ICU) staff to obtain focused ultrasound skills. In the following years, Jensen and Sloth were able to demonstrate the feasibility of focused transthoracic (TTE) echocardiography to visualize and optimize determinants of cardiac output.

In critically ill patients with hemodynamic instability, echocardiography has now been recommended as the preferred modality to evaluate the underlying pathophysiology as opposed to more invasive technologies. Strategies to train non-cardiologists have been published since then promoting a widespread use of echocardiography. According to a recent multicenter cross-sectional study, transesophageal (TEE) echocardiography and TTE were available in 85.7% (TEE) and 95.0% (TTE) in German, Austrian and Swiss ICUs. In another survey regarding the hemodynamic assessment in cardiosurgical ICUs 44.7% of the responders stated that TEE was used. A physician experienced in performing TEE examinations was available in 72% of the time around-the-clock.

However, little is known about the frequency TTE and TEE are applied on ICUs as well the qualification of the examiners. We thus aimed to investigate the utilization of echocardiography as part of routine diagnostic in ICUs in Germany and to assess current training, certification and indication practices.

Materials and methods

A structured web-based, anonymized survey was performed from May until July 2015 among members of the German Interdisciplinary Association of Critical Care and Emergency Medicine (DIVI).

The survey consisted of 14 questions: questions 1-3 inquired information about the type of hospital, the number of ICU beds and the focus (i.e. surgical, anesthesiological, etc.) of the respective ICU. Questions 4 and 5 assessed how many TTE and TEE examinations were performed and by whom they were conducted. Questions 6 and 7 dealt with the documentation of the examination. Questions 8-10 assessed echocardiographic training and certification as well as whether the ICU or hospital had direct access to a physician who had completed a formal training in echocardiography. Question 11 examined the period of time it usually takes from ordering an echocardiogram until it was actually performed, in case the examination was done by physicians of a different clinical discipline. Finally, the use and impact of echocardiography in hemodynamic unstable patients and clinical decision making (questions 12 and 13) and the participants wish to have a more intensive training in echocardiography (question 14) were asked. The complete questionnaire form can be found in the enclosed Supplementary Digital Material 1, Supplementary Text File 1.

The study was approved by the committee on research ethics at the institution in which the research was conducted and any informed consent from human subjects was obtained as required.

Statistical analysis

For statistical analysis Excel 2016 (Microsoft Corporation, Redmond, USA) and SPSS version 22 (IBM, Armonk, NY, USA) were used. Analyses of construct validity were carried out using chi² testing after transforming continuous to categorical variables. Figures were created using Prism 5.0 (GraphPad Software, San Diego, CA, USA) and Excel 2016.

Results

In total, physicians of 104 German ICUs participated in the survey. Most ICUs belonged to university hospitals (36%) (non-university maximum care hospitals =21%, community hospitals =25%, acute hospitals =13%, no data available =6%). For the most part, ICUs consisted of 11 to 20 beds (48%) [1 to 10 beds =18%, >20 beds =23%, no data available =10%] and were led by departments specialized in anesthesiology (Figure 1).
Use of echocardiography as part of diagnostic routine

TTE examinations were conducted more often than TEE (Figure 2) and mainly performed by cardiologists (TTE: 45%; TEE: 42%) and anesthesiologists (TTE: 37%, TEE: 51%) (Figure 3, 4). Echocardiographic images were stored directly on the ultrasound machine (42%) or in a picture archiving and communication system (PACS) (40%) (no storage at all = 0%, no data available = 8%). In addition, 45% of the participants reported that a paper-based report and 44% that an electronic report was stored in their IT system (no report at all = 3%; no data available = 8%). In 79% previous echocardiographic findings were electronically accessible.

Training and qualification in echocardiography

Figure 5 gives an overview about the level of training and qualification in echocardiography from three different perspectives: 1) as reported
by the participant about her/his individual level of training and qualification; 2) regarding physicians on the ICU; and 3) regarding physicians in the hospital. Forty-seven percent of the intensivists who regularly performed echocardiography examinations had not completed a structured training nor acquired an (inter-)national board qualification certificate, i.e. they only had basic knowledge or were “in training.” Twenty-seven percent had completed a structured training without a formal examination, i.e. they had completed a training in focused assessed transthoracic echocardiography and in focused assessment with sonography in trauma (FATE/FAST training) or had participated in a one-day training thoracoabdominal sonography (AFS module cardiac sonography). Twenty-six percent had received an echocardiography certificate by the European Association of Cardiovascular Imaging and the European Association of Cardiothoracic Anaesthesiology (EACVI/EACTA), by the German Society of Anaesthesiology and Intensive Care Medicine (DGAI) or by the German Society of Ultrasound in Medicine and Biology (DEGUM). Twenty-two percent of the ICU staff and of all department staff had not completed a structured training or acquired an (inter-)national board qualification certificate, whereas 23% and 25%, respectively, completed a structured training without an examination and 54% and 52% of the ICU staff and all department staff received board qualification certificate.

In 70% of the responding ICUs and in 83% of the responding hospitals at least one physician with an (inter-)national board qualification certificate in echocardiography was available. Nevertheless, in 20% (ICU) and in 5% (hospitals) supervision by a physician with echocardiographic verification was not ensured (no data available =10% ICU / 12% hospitals).

Influence of echocardiography on therapeutic decisions

When a different clinical department than the one who ordered the echocardiography performed the examination, most echocardiographs were performed within the first 12 hours (Figure 6A). Forty-six participants of the 70 responders to this question stated that echocardiography changed the therapy in more than 25% of patients (Figure 6B). Even when the examinations were performed more than 12 hours later after they had been initially ordered, they still changed the therapy regimen over a wide range of cases. Sixty-six percent of the participants (N.=51) responded that echocardiography was part of their routine hemodynamic monitoring (not part of standard routine =23%; no answer =10%). Sixty-three participating physicians (82%) stated that they would like to have a more intensive training in echocardiography; seven (9%) did not see a need for further qualification (no answer =9%).

No association was found between size type/size of hospital and number of conducted echocardiographies as well as level of acquired certi-
fication and impact of echocardiography integration in routine patient assessment and expressed need for training, suggesting that echocardiography, both TTE and TEE, have already become widely applied methods throughout many types of institutions.

Discussion

We conducted a survey on the current utilization of TTE and TEE as well as formal qualification and certification of physicians regarding their use of echocardiography in ICUs in Germany. To our knowledge, this is the most comprehensive nationwide investigation of this topic, covering all subspecialties of intensive care. Interestingly, despite the interdisciplinary character of the hosting society (DIVI), most responding ICUs in this survey were led by anesthesiologists. This may reflect the clinical importance of echocardiography even in disciplines not primarily familiar with echocardiography. In this context, the introduction of focused “hemodynamic” echocardiography particular by anesthesiologists may have driven their interest to take part in this survey far more. This survey reveals the importance of focused hemodynamic echocardiography, demonstrated by a high amount of consecutive therapeutic implications, as well as the interdisciplinary need of a structured training program. The focus should be on the focused hemodynamic transthoracic examination in particular since the authors believe that its non-invasive nature makes it ideal for initial training and the use in critically ill patients. Thirty-four percent of participants stated not performing echocardiography as a standard hemodynamic diagnostic procedure, and 82% claimed the need for more intensive training. That strongly suggests that a lack of echocardiographic education may be the reason for not conducting this decisive examination.

From 2008 to 2013, the utilization of TTEs and TEEs on German cardiac surgical ICUs had increased as a result of a widespread availability of ultrasound machines and available guideline recommendations, all contributing to recognizing the advantages of bedside ultrasonography. It is likely that the same applies to non-cardiac surgical, mixed ICUs. Since the introduction of echocardiography in intensive care medicine, anesthesiologists and intensive care practitioners used TEE due to its assumed higher image quality in mechanically ventilated patients compared to TTE. Interestingly, this survey now reveals that the majority of echocardiographic examinations are TTEs and the non-invasive transthoracic view is the more frequently used practice. Most survey participants stated that echocardiographs were a regular part of their hemodynamic assessment. According to our survey, an echocardiography performed at an earlier point of time changed the current therapy in 26-50% of all patients, and even a late echocardiography still had an impact on the therapeutic regimen in a wide range of cases. Therefore, we believe that an echocardiographic examination should be performed as early as possible in order to optimize DO₂. Similar results have been published as early as 1998 by Benjamin et al.4 Here, the results of an additionally performed TEE changed the therapy derived by pulmonary artery catheter in 52% of the patients. It is important to state that this accounted for the acute postoperative setting and is in line with current recommendations for intensive care treatment.7, 15

Previously published results showed that a short and intensive training can enable physicians to obtain a basic image quality that is sufficient to guide therapy using TEE or TTE.16, 17 However, a consentient echocardiographic curriculum among German intensive care practitioners and their corresponding societies is still missing. Nevertheless, first efforts to structure a formal training for internal medicine intensivists have currently been published.18 Until now, the only structured qualification in TTE for anaesthesists in Germany is a one-day course without a formal examination in contrast to the training in TEE which consists of a seminar, implementation performed under supervision and an oral examination. Not surprisingly, most physicians stated that they did not hold a certificate and 27% only took part in a course without a formal examination. This insufficient, “hemodynamic focused” training could partly explain the request detected in our survey for further training in echocardiography. We therefore believe that
the training and qualification process, especially in TTE has to be broadened. For this purpose, 2D imaging techniques for left and right ventricular function and morphometry, as well as the color Doppler for semiquantitative valve assessment should be trained together with a quick examination for the detection of pericardial effusion. This could be a way to increase the number of instantaneously performed echocardiographs and to decrease the time difference between ordering and actually performing the examination. Even if 70 participants (83%) stated that there was a physician available with a completed training and qualification in echocardiography at the ICU and the hospital, respectively, only 28 participating ICUs claimed that examinations were conducted within two hours. This could be not only a wasted potential but also a risk since echocardiography has the potential to differentiate between a multiplicity of diagnoses and shock forms and early interventions can improve outcome.\(^8, 19\) Furthermore, false diagnoses and conclusions could harm our patients.\(^20\) Therefore, efforts should be intensified to train and qualify as many intensivists as possible. This should not be limited to consultants but also be extended to residents and even chairs of departments as 34% and 35% of the latter had only a basic knowledge without any certification. Moreover, these findings point towards a need of shared curriculum that is supported by all stakeholders of intensive care on a ward level. In anesthesiology, for instance, the echocardiography curriculum has recently been extended to TTE.\(^21\) In our opinion, a such approach should be fostered by the commitment of further medical societies to endorse a common core curriculum.

Most examinations were archived, either by saving the echocardiograms direct on the ultrasound machine or in a PACS, and in the majority a written report was prepared. We hypothesize that physicians who perform these examinations believe in the high value of a structured report within the clinical decision making. Thus, reporting one’s finding have also to be included in the training process.

In order to integrate the data into the current international context, it is possible to summarize that the important role of echocardiography in an acute and intensive care setting is not only seen in Germany but also in other European countries. Quintard et al. reported that almost 90% of French intensivists considered echocardiography essential for the hemodynamic assessment.\(^22\) A recent study on hemodynamic monitoring in intensive care units in Switzerland reported that echocardiography was only frequently used as part of the hemodynamic management in 41% and 57% never performed an echocardiography themselves, whereas 6% used it always, 12% frequently and 25% sometimes.\(^23\) The authors interpreted the discrepancy by a trend towards a more invasive circulatory monitoring in Switzerland. Yet 59% of the Swiss intensivists believed fully and 39% selectively that intensive medicine specialists should be able to perform an echocardiography.\(^23\)

In the context of broad acceptance and dissemination of echocardiography and the increasing perception of its importance and therapeutic consequences, hemodynamic focused echocardiography may also be used as an initial examination in intensive care units and can be regarded as an integral part of intensive care admission. To what extent a therapeutic implications or new approaches of hemodynamic optimization can be derived from this is currently not clear, since there is currently no work on routine echocardiography screening on admission to the intensive care unit. But surely hemodynamic focused echocardiography can be an indicator for a complete cardiological echocardiography. However, based on current guidelines and previous studies, we already know that hemodynamically focused echocardiography is feasible in critically ill patients and has a positive influence on the outcome of the patient.\(^17\) Since the authors believe further investigation is necessary, we have integrated hemodynamically focused echocardiography into the standard admission procedure of our intensive care units.

Limitations of the study

The study has some limitations. The survey was available by online access for members of the DIVI so that a double selection bias could have influenced the results: only DIVI members had
access to the questionnaire and as a self-selecting bias only the primed and echocardiography-interested physicians may have answered. Another limitation was the self-assessment of the participants with only estimations of the number of examinations and the percentage change in therapy. Additionally there was a bias for the participating hospitals, because more than one physician per hospital could have answered the questionnaire, leading to an overrepresentation of some estimations and answers. Finally, more university ICU’s and ICU’s led by anesthesiologists took part in this survey so that the here present result cannot be generalized to all ICU especially non-operative, non-university ICU’s.

Conclusions
In conclusion, echocardiography is a widespread used diagnostic modality in German ICUs which regularly changes the therapeutic regimen even when it is performed later than indicated. Although most ICUs and hospitals have certified personnel to perform echocardiographic examinations, there seems to be a lack of structured training. ICU societies should work in this field together to establish and standardize a structured training.

What is known
- Echocardiography previously has been found to improve patient outcome in cases of hemodynamic instability and goal-directed therapy plays an important role in the subsequent therapy.

What is new
- Echocardiography is already a widely used monitoring tool in intensive care units in Germany, but a structured broad educational program seems to be missing.
- Early hemodynamic focused echocardiography may imply changes in therapy, but even if echocardiography is used after more than 12 hours it still has a high influence on therapy regimen over a wide range of cases.

References


Conflicts of interest.—Felix Balzer received funding unrelated to this study by Medtronic and ClearFlow, Inc.; Matthias Heringlake receives honoraria for lectures and scientific advise by Covidien/Medtronic; Orion Pharma, Amomed Pharma, Tenax Therapeutics, Fresenius Medical, and Baxter Medical not related to this study; Heinrich V. Groesdonk reports personal fees from GE Healthcare, outside the submitted work; Michael Sander reports personal fees from Masimo, personal fees from Ratiopharm, grants and personal fees from Edwards Life Sciences, grants and personal fees from Getinge Group, grants and personal fees from AMOMED, personal fees from Medtronic, outside the submitted work; Sascha Treskatsch received funding for experimental research from B. Braun federation and EACTA as well as honoraria for lectures from Edwards, Carinopharma, OrionPharma and Smith&Nephews, all not related to this study.

Authors’ contributions.—Felix Balzer and Ralf F. Trauzeddel contributed equally to this study and manuscript.


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ORIGINAL ARTICLE

Investigating propofol-sufentanil interaction using clinical endpoints and processed electroencephalography: a prospective randomized controlled trial

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ABSTRACT

BACKGROUND: Propofol and sufentanil target controlled infusion technology is used with increasing frequency. Drug interaction modelling, using clinical endpoints and processed electroencephalography helps determine optimal drug concentrations to assure adequate anesthesia.

METHODS: Sixty patients were randomized to receive a constant concentration of sufentanil (0.25 ng/mL (Group S0.25), 0.5 ng/mL (Group S0.5)), 0 ng/mL (Group S0). Propofol was administered in steps of 0.5 µg/mL, up to 4 µg/mL. Processed EEG (Bispectral Index, Narcotrend Index) and auditory evoked potentials (composite A-Line autoregressive Index; cAAI), were recorded simultaneously. Sufentanil-propofol interaction was assessed by Probit — and nonlinear regression analysis.

RESULTS: Sufentanil had a dose-dependent synergistic effect on the effect-site concentration of propofol (µg/mL) associated with a 50% probability (EC50) of loss of responsiveness to verbal command (S0: 2.84 µg/mL, R2 0.773; S0.25: 1.95 µg/mL, R2 0.862; S0.5: 1.48 µg/mL, R2 0.887) and noxious stimulation (S0: 3.46 µg/mL, R2 0.626 µg/mL; S0.25: 2.17 µg/mL, R2 0.535; S0.5: 1.69 µg/mL, R2 0.597). Non-linear regression analysis revealed a synergistic sufentanil effect on the propofol EC50 for BIS (S0: 3.36 µg/mL, R2 0.79; S0.25: 2.77 µg/mL, R2 0.86 µg/mL; S0.5: 2.6 µg/mL, R2 0.84); Narcotrend Index (S0: 3.57 µg/mL, R2 0.66; S0.25: 2.91 µg/mL, R2 0.70; S0.5: 2.02 µg/mL, R2 0.51) and cAAI (S0: 3.42 µg/mL, R2 0.59; S0.25: 3.00 µg/mL, R2 0.63; S0.5: 3.14 µg/mL, R2 0.59).

CONCLUSIONS: Sufentanil has a synergistic effect on the clinically observed hypnotic properties of propofol. These findings apply also to the depth of hypnosis measured by the Bispectral Index, Narcotrend Index and cAAI.

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KEY WORDS: Propofol - Sufentanil - Drug interactions - Electroencephalography.

Opioid-hypnotic drug interaction modelling analysis helps to determine the optimal concentrations of either drug to assure both adequate anesthesia and rapid recovery.1 Depending on the particular drug combination, hypnotic-opioid drug interactions have been found to be either additive, supra-additive (synergistic), or infra-additive.2 Based on clinical effects opioid-drugs and propofol have been reported to interact either synergistic or additive.2 Propofol-opioid interaction has also been investigated using electroencephalographic
(EEG) monitoring of depth of hypnosis (DoH), leading to conflicting results, describing either additive or no effect of opioid drugs on hypnosis provided by propofol.

When delivering general anesthesia, hypnotic drugs should ideally be administered at concentrations not significantly higher than required to achieve loss of consciousness. Opioid drugs should be added to inhibit the autonomic and somatic responses to surgical stimulation. A good understanding of the hypnotic-opioid drug interaction helps to titrate both drugs to their optimal concentration.

Effect site target controlled infusion (TCI) of propofol and sufentanil, provides a rapid achievement of stable and inter-individually comparable user defined effect site drug concentrations, making it a perfect, clinically applicable research model to investigate propofol-sufentanil interaction.

The primary outcome parameter of this prospective randomized controlled trial was the impact of sufentanil on propofol requirements to achieve loss of consciousness, using probit regression analysis. As a secondary outcome parameter, non-linear regression analysis was performed to investigate sufentanil-propofol interaction, simultaneously measured by three different DoH monitors, the Bispectral Index Monitor (Aspect Medical Systems Inc., Norwood, MA, U.S.A.) and the Narcotrend™ monitor (MT Monitortechnik GmbH & Co. KG, Bad Bramstedt, Germany), both based on processed EEG and the mid latency auditory evoked potential derived AEP Monitor/2™ (Danmeter A/S, Odense, Denmark)

Materials and methods

This double-blind prospective randomized controlled trial, approved by the institutional review board of the University Hospital Regensburg, Germany (ZKS 04/202, November 15, 2004) was conducted at the University Hospital Regensburg in accordance with the principles of good clinical practice and the Helsinki Declaration.

Patients aged between 18 and 60 years, ASA physical status I or II, scheduled for elective oto-laryngeal or ear surgery requiring general anesthesia were eligible for enrolment. Primary exclusion criteria were known allergies to either propofol or sufentanil, chronic conditions and medication known to affect the central nervous system, significant hearing impairment, a body mass index higher than 30 and insufficient knowledge of German language to give written informed consent.

After having given written informed consent the study patients were randomly allocated to one of three study groups, defined by the effect site TCI concentration of sufentanil applied. The pharmacokinetic model developed by Gepts et al. was used.

Patients were randomized to three groups of 20, characterized by sufentanil effect site concentrations ($C_{\text{Sufentanil}}$), which remained unchanged throughout the whole study period:
- Group S0.25: $C_{\text{Sufentanil}}$ 0.25 ng/mL;
- Group S0.5: $C_{\text{Sufentanil}}$ 0.5 ng/mL;
- Group S0: No sufentanil, control group, receiving saline infusion instead.

Propofol was delivered using the fast $ke_0$ 1.21/min. version of the pharmacokinetic model developed by Marsh et al., providing a rapid equilibration between the central compartment and the effect site. TCI was started at an effect site concentration ($C_{\text{Propofol}}$) of 0.5 µg/mL, which was subsequently raised by 0.5 µg/mL every five minutes up to a maximum of 4 mcg mL$^{-1}$, resulting in a total registration period of 45 minutes.

Both TCI models were integrated into an Orchestra Base Prime™ TCI workstation (Fresenius Vial Infusion Technology, Bad Homburg, Germany).

All study interventions took place during induction of anesthesia, in the quiet environment of an anesthesia induction room, prior to tracheal intubation. Decreases in mean arterial blood pressure of more than 30% of baseline or absolute values of less than 60 mmHg were treated with volume expansion or low-dose noradrenaline as appropriate. The single anesthesiologist responsible for patient care in all participants of this study (C.P.) is an experienced user of the TCI workstation and the three DoH-devices.
Study procedures

Patients were attached to standard monitoring used during induction of anesthesia (ECG, pulse-oximetry and noninvasive blood pressure at five-minute intervals). Before starting the application of sufentanil and or propofol, study patients were connected to three DoH monitors according to the manufacturers’ recommendations.

A BIS Vista monitor (software version 1.02) was used to calculate the Bispectral Index (BIS) of hypnotic depth, ranging from 100 (fully awake) to 0 (very deep hypnosis). BIS data were downloaded directly from the monitor for subsequent statistical analysis.

A Narcocontrol EEG monitor (software version 4.6) was used to calculate the EEG-derived Narcocontrol Index (NII), a dimensionless scale from 0 (very deep hypnosis) to 100 (wakefulness). Narcocontrol EEG data were transferred to a personal computer for subsequent analysis with the Narcocontrol software package (MT Montoretechnik, Bad Bramstedt, Germany).

AEP were recorded using the AEP Monitor/2 (software version 1.61). A dimensionless index, called composite A-line Autoregressive Index (cAAI), ranging from 60 (patient fully awake) to 0 (very deep hypnosis) is calculated from the AEP or the EEG, depending on the signal-to-noise (SNR) ratio. AEP Monitor/2 data were transferred to a personal computer for subsequent analysis with the AAI Graph software package (Danmeter A/S, Odense, Denmark).

DoH was also assessed clinically at 1 minute intervals by an investigator who was blinded to group allocation and the screens of the three DoH devices, using the modified Observer’s Assessment of Alertness and Sedation Scale (mOAA/S) (Table I). The two clinical endpoints loss of responsiveness to verbal command (LORverb), defined by the transition from mOAA/S level 3 to 2 and noxious (painful) stimulation (LORnoxi), corresponding to mOAA/S level 0, served as the primary end-points of this study.

EEG/AEP data recorded in the 5th minute of each concentration-step of propofol, allowing to achieve steady state effect-site concentrations, were used for subsequent non-linear regression analysis of propofol effect on the EEG/AEP indices of DoH.

The study period ended after five minutes on a Cpropofol of 4 µg/mL, resulting in a total data registration period of 45 minutes.

Statistical analysis

Continuous data were tested for normality by means of a D’Agostino and Pearson Normality Test before either parametric or non-parametric tests were applied.

For each study-group probit regression analysis was performed to calculate the 5%, 50% and 95% effective Cpropofol (EC5, EC50, and EC95, respectively), together with their 95% confidence intervals (CI), based on each concentration step of Cpropofol required to achieve LORverb and LORnoxi. Nonlinear regression analysis was used to investigate the relationship between DoH-index values and Cpropofol by fitting the data in a sigmoidal dose response model. Specifically, the Cpropofol resulting in a half-maximal effect on the DoH-index (EC50) was calculated.

Due to a lack of published data relating to our primary research question no formal sample size calculation was performed. Based on the availability of research staff and the assumed number of patients that were eligible for inclusion we chose to recruit 20 patients in each study group.

Probit regression analysis was performed using MedCalc™ (Version 17.6, MedCalc, Ostend, Belgium). All other analyses were performed using Prism 7 for Mac OS X (Version 7.0c, GraphPad Software Inc., La Jolla, CA, U.S.A.). P values <0.05 were considered significant.

Results

A total of 60 patients were included (for patient characteristics see Table II). All patients completed the study.

Table I.—Modified Observer’s Assessment of Alertness and Sedation Scale (mOAA/S).

<table>
<thead>
<tr>
<th>Score</th>
<th>Responsiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 (alert)</td>
<td>Responds readily to voice with normal tone</td>
</tr>
<tr>
<td>4</td>
<td>Responds slowly to voice with normal tone</td>
</tr>
<tr>
<td>3</td>
<td>Responds after calling loudly or repeatedly</td>
</tr>
<tr>
<td>2</td>
<td>Responds after mild prodding or shaking</td>
</tr>
<tr>
<td>1</td>
<td>Does not respond to mild prodding or shaking</td>
</tr>
<tr>
<td>0</td>
<td>Does not respond to pain</td>
</tr>
</tbody>
</table>
At the time of LOR_{verb} the EC_{50} (median (95% CI)) for propofol was 2.84 (2.66 to 3.02) µg/mL in group S_0, 1.95 (1.79 to 2.01) µg/mL in group S_{0.25} and 1.48 (1.34 to 1.63) µg/mL in group S_{0.5}. The EC_{50} for LOR_{nox} was 3.46 (3.26 to 3.71) µg/mL in group S_0, 2.17 (2.01 to 2.34) µg/mL in group S_{0.25} and 1.69 (1.50 to 1.75) µg/mL in group S_{0.5}. More detailed information regarding LOR_{verb} and LOR_{nox} is given in Table III, Figure 1.

The propofol EC_{50}s describing the effects of different C_{propofol} on BIS, Narcotrend-Index and cAAI were as follows: The EC_{50} for the BIS was 3.36 (3.26 to 3.47) µg/mL in group S_0, 2.77 (2.69 to 2.90) in group S_{0.25} and 2.88 (2.80 to 3.00) in group S_{0.5}. The EC_{50} for the Narcotrend-Index was 2.91 (2.78 to 3.05) in group S_0, 2.61 (2.52 to 2.70) in group S_{0.25} and 2.57 (2.41 to 2.74) in group S_{0.5}. The EC_{50} for the cAAI was 3.42 (3.26 to 3.62) in group S_0, 3.00 (2.84 to 3.17) in group S_{0.25} and 3.14 (2.97 to 3.33) in group S_{0.5}.

Table II.—Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Group S_{0.25}</th>
<th>Group S_{0.5}</th>
<th>Group S_0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>40±10</td>
<td>41±11</td>
<td>38±13</td>
</tr>
<tr>
<td>Bodyweight (kg)</td>
<td>79±12</td>
<td>81±14</td>
<td>76±13</td>
</tr>
<tr>
<td>BMI</td>
<td>25.4±3.03</td>
<td>25.8±2.7</td>
<td>24.3±2.95</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>7/13</td>
<td>6/16</td>
<td>6/14</td>
</tr>
</tbody>
</table>

Data presented as mean±SD.

Table III.—Probit regression analysis.

<table>
<thead>
<tr>
<th></th>
<th>R²</th>
<th>P</th>
<th>Ec_{50} C_{prop} (95% CI)</th>
<th>Ec_{50} C_{prop} (95% CI)</th>
<th>Ec_{50} C_{prop} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOR_{verb}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group S_0</td>
<td>0.773</td>
<td>&lt;0.0001</td>
<td>1.91 (1.49 to 2.17)</td>
<td>2.84 (2.66 to 3.02)</td>
<td>3.77 (3.50 to 4.20)</td>
</tr>
<tr>
<td>Group S_{0.25}</td>
<td>0.862</td>
<td>&lt;0.0001</td>
<td>1.25 (0.88 to 1.47)</td>
<td>1.95 (1.79 to 2.10)</td>
<td>2.64 (2.43 to 3.02)</td>
</tr>
<tr>
<td>Group S_{0.5}</td>
<td>0.887</td>
<td>&lt;0.0001</td>
<td>0.93 (0.57 to 1.12)</td>
<td>1.48 (1.34 to 1.63)</td>
<td>2.04 (1.85 to 2.39)</td>
</tr>
<tr>
<td>LOR_{nox}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group S_0</td>
<td>0.626</td>
<td>&lt;0.0001</td>
<td>2.38 (1.85 to 2.67)</td>
<td>3.46 (3.26 to 3.71)</td>
<td>4.54 (4.17 to 5.24)</td>
</tr>
<tr>
<td>Group S_{0.25}</td>
<td>0.853</td>
<td>&lt;0.0001</td>
<td>1.45 (1.07 to 1.67)</td>
<td>2.17 (2.01 to 2.34)</td>
<td>2.90 (2.68 to 3.28)</td>
</tr>
<tr>
<td>Group S_{0.5}</td>
<td>0.897</td>
<td>&lt;0.0001</td>
<td>1.09 (0.74 to 1.27)</td>
<td>1.69 (1.50 to 1.75)</td>
<td>2.13 (1.95 to 2.47)</td>
</tr>
</tbody>
</table>

Probit dose-response regression analysis of study groups S_{0}, S_{0.25} and S_{0.5}, showing the required effect site concentrations of propofol (C_{prop}), together with their 95% confidence intervals, associated with 5%- (EC_{50}), 50%- (EC_{50}) and 95%- (EC_{95}) probabilities to achieve loss of responsiveness to verbal command (LOR_{verb}) and noxious stimulation (LOR_{nox}). R² represents Nagelkerke R².

Table IV.—Nonlinear regression analysis (EC_{50} propofol).

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
<th>Ec_{50} C_{prop} (95% CI)</th>
<th>Hill Slope (95% CI)</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS</td>
<td>S_0</td>
<td>3.36 (3.26 to 3.47)</td>
<td>-0.42 (-0.46 to -0.37)</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>S_{0.25}</td>
<td>2.77 (2.69 to 2.86)</td>
<td>-0.41 (-0.45 to -0.38)</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>S_{0.5}</td>
<td>2.61 (2.52 to 2.70)</td>
<td>-0.37 (-0.40 to -0.34)</td>
<td>0.84</td>
</tr>
<tr>
<td>NI</td>
<td>S_0</td>
<td>3.57 (3.41 to 3.74)</td>
<td>-0.39 (-0.45 to -0.33)</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>S_{0.25}</td>
<td>2.91 (2.78 to 3.05)</td>
<td>-0.40 (-0.46 to -0.35)</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>S_{0.5}</td>
<td>2.02 (1.82 to 2.22)</td>
<td>-0.29 (-0.35 to -0.24)</td>
<td>0.51</td>
</tr>
<tr>
<td>cAAI</td>
<td>S_0</td>
<td>3.42 (3.26 to 3.62)</td>
<td>-0.44 (-0.59 to -0.37)</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>S_{0.25}</td>
<td>3.00 (2.84 to 3.17)</td>
<td>-0.44 (-0.52 to -0.38)</td>
<td>0.63</td>
</tr>
<tr>
<td></td>
<td>S_{0.5}</td>
<td>3.14 (2.97 to 3.33)</td>
<td>-0.43 (-0.51 to -0.36)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Propofol effect site concentrations (EC_{50} with 95% confidence intervals), per study group and DoH-monitor, needed to achieve a 50% reduction of the max. value of the DoH-Index. Correlation coefficient R²; Hill Slopes, describing the steepness of the curve.
to 2.86) μg/mL in group S\textsubscript{0.25}, and 2.61 (2.52 to 2.70) μg/mL in group S\textsubscript{0.5}. The EC\textsubscript{50} for the Narcotrend Index was 3.57 (3.41 to 3.74) μg/mL in group S\textsubscript{0}, 2.91 (2.78 to 3.05) μg/mL in group S\textsubscript{0.25}, and 2.02 (1.82 to 2.22) μg/mL in group S\textsubscript{0.5}. The EC\textsubscript{50} for the cAAI was 3.42 (3.26 to 3.62) μg/mL in group S\textsubscript{0}, 3.00 (2.84 to 3.17) μg/mL in group S\textsubscript{0.25}, and 3.14 (2.97 to 3.33) μg/mL in group S\textsubscript{0.5}. More detailed information is given in Table IV, Figure 2.

There were no episodes of hypotension requiring the administration of vasoactive drugs or any other adverse events in any patient.

Discussion

The results of this prospective randomized controlled trial provide evidence of a synergistic effect of sufentanil on the hypnotic effect of propofol. This applies to both the clinically observed hypnotic effect and the effect on processed EEG and AEP.

Comparing our results to other published studies reporting propofol-sufentanil interaction is difficult and differences in outcomes must be interpreted with great caution. Different TCI models, each with its own set of parameters, not surprisingly lead to different pharmacokinetic effects. Various factors are known to influence the performance of TCI models, among them patient age,\textsuperscript{12} the speed of drug infusion,\textsuperscript{13} and device specific modifications of TCI models which have been integrated into commercially available TCI systems.\textsuperscript{6,8}

Forestier et al.\textsuperscript{14} conducted a study on propofol (Diprifusor TCI model)\textsuperscript{15} and sufentanil (Gepts TCI model)\textsuperscript{7} titration in patients undergoing coronary artery surgery. To be sufficiently anesthetized, patients on 0.5 ng/mL sufentanil, required an average propofol concentration of 1.56 μg/mL. This is comparable to the results of our study, where patients on a C\textsubscript{sufentanil} of 0.5 ng/mL had a propofol EC\textsubscript{50} of 1.48 μg/mL for LOR\textsubscript{verb} and 1.69 μg/mL for LOR\textsubscript{nox}.

Schraag et al.\textsuperscript{16} investigated propofol-sufentanil interaction using the Marsh model\textsuperscript{9} for propofol and a pharmacokinetic dataset for sufentanil published by Hudson.\textsuperscript{17} The authors reported a 10-20% reduction in propofol EC\textsubscript{50} to achieve loss of consciousness when sufentanil was added at an analgesic concentration. According to the authors, propofol-sufentanil interaction modelling showed evidence of additivity rather than

![Figure 2.—Nonlinear regression analysis of propofol effect on DoH Indices.](image-url)
synergy. They furthermore concluded that this rather small difference in propofol EC50 for loss of consciousness is likely due to a kind of opioid-hypnotic interaction which they assumed to be fundamentally different from the interaction observed for noxious stimulation. In our study, we observed reductions of propofol EC50 of approximately 50% for both LORverb and LORnox (Table III, Figure 1) when sufentanil was administered, clearly suggesting synergy. Whether or not this synergy is due to the same kind of drug interaction at both clinical endpoints (LORverb and LORnox) remains subject to speculation.

Chen et al.,19 in their 2014 paper, describing an attempt to define the optimal combination of sufentanil/propofol effect site concentrations for burn dressing changes and wound management, chose an approach exactly opposite to ours. Propofol was kept constant at an effect-site concentration of 1.2 µg/mL (Marsh model), assuming this should be a dose inducing conscious sedation. Csufentanil generated by the pharmacokinetic dataset published by Bovill et al.,19 was varied between 0.1 and 0.5 ng/mL. All patients remained conscious. In our study, a Cpropofol of 1.2 µg/mL was associated with a 0% probability of LORverb when on a Csufentanil of 0.25 ng/mL and a 15% probability when on a Csufentanil of 0.5 ng/mL (Figure 1).

Sebel et al.20 reported that the BIS was a good predictor of patient reactions to skin incision, as long as propofol was used as the primary hypnotic. In their study co-administration of sufentanil confounded the use of the BIS as a measure of DoH. These findings were later confirmed by Lysakowski et al.,4 who investigated the effect of sufentanil 0.2 ng/mL on the hypnotic effects of propofol. While they found an additive effect of sufentanil on the clinically observed propofol effect, this enhancement could not be confirmed by the BIS. As opposed to these two studies, we observed both clinical and EEG related enhancement of propofol effect by sufentanil.

We also investigated propofol-sufentanil interaction by using the composite A-line Autoregressive Index cAAI. Vereecke et al. showed that the cAAI was significantly better correlated with propofol effect site concentration than the BIS.10 Therefore we decided to apply cAAI-technolology as an alternative approach to investigate propofol-sufentanil interaction. In our study, adding sufentanil to propofol resulted in a reduction of the propofol EC50 for the cAAI, but this reaction was much less pronounced than for the two EEG-derived DoH indices BIS and NI. In addition, we could not demonstrate a dose dependent effect of sufentanil. We have no explanation for this (unexpected) finding. It is furthermore important to mention that a cAAI value of 30 (=EC50) may not necessarily mean the same as BIS or NI values of 50 (=EC50), which are associated with surgical anesthesia. According to the manufacturer, the target range of the cAAI to provide surgical anesthesia is 15-25.21

When we designed our study, we intuitively thought in terms of impact of sufentanil on propofol effect. We are aware that, at least to a certain degree, it may be propofol effect on sufentanil action instead. Experimental data suggest an inhibition of sufentanil metabolism by propofol, resulting in higher plasma concentrations, leading to increased sufentanil effect.22

When interpreting drug interaction there is currently no consensus how to define additivity and synergy (supra-additivity).23 We applied the definition published by Hannam and Anderson,24 suggesting that a leftward shift of the dose-response curve provides evidence of synergy.

As a consequence of our study design, we can only report data collected during the induction period. It could be seen as a shortcoming of our study that we could not draw any conclusions regarding propofol-sufentanil interaction during surgery. We would like to argue instead, that conducting the entire study in the quiet environment of an anesthesia induction room, reducing the impact of environmental confounders to a minimum, is rather the unique strength of the study design than a shortcoming. We cannot exclude the possibility that the observed interaction could change under surgical conditions.

Intuitively, we all know that sufentanil has some impact on the potency of propofol to provide hypnosis. Recently, researchers applied response surface modeling (RSM) to investigate opioid-hypnotic drug interaction.25 RSM is a very sophisticated approach, but in our opinion rather fundamental science than clinical research. This study was designed as a clinical study for prac-
ticing anesthesiologists. We were able to provide sufentanil/propofol dose-response curves that may help anesthesiologists to have a better understanding of sufentanil/propofol interaction. In accordance with the current guidelines regarding the use of DoH-monitoring published by the United Kingdom’s National Institute for Health and Care Excellence (NICE), we highly recommend the use of DoH-monitors during propofol/sufentanil anesthesia, not forgetting that specific devices have their own dose-response curves.

Conclusions

The results of this prospective randomized controlled trial provide evidence of a synergistic effect of sufentanil on the hypnotic properties of propofol, assessed both clinically and using BIS, NI or cAAI. When using the BIS, Narcotrend Index or cAAI, EC50 values for Cpropofol are device specific.

What is known

- Hypnotic drugs like propofol and opioid drugs like sufentanil are known to interact in a dose-dependent fashion.
- Propofol effect on DoH can be assessed by processed electroencephalography (EEG) or auditory evoked potential (AEP) monitoring.

What is new

- Addition of sufentanil to propofol results in a dose-dependent reduction of the effect site concentration of propofol required to achieve loss of responsiveness to verbal command and noxious stimulation.
- Sufentanil- and propofol effect site concentration effects on the DoH assessed by monitoring devices based on processed EEG or AEP result in device specific dose-response relationships.
- Pharmacodynamic data found with a specific pharmacokinetic model may not necessarily be (exactly) the same when the drug is delivered using a different pharmacokinetic model.

References

8. Cortinez LJ. What is the ke0 and what does it tell me about propofol? Anaesthesia 2014;69:399–402.

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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Authors’ contributions.—Frank Weber designed the study, analyzed the data and wrote the manuscript. Christopher Prasser helped design the study, conducted the study, helped analyze the data and write the manuscript.


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Effects of dexmedetomidine on inflammatory mediators after tourniquet-induced ischemia-reperfusion injury: a randomized, double-blinded, controlled study

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ABSTRACT

BACKGROUND: Tourniquet use during total knee arthroplasty (TKA) produces ischemia-reperfusion injury (IRI), with systemic release of inflammatory cytokines and reactive oxygen species upon tourniquet release. We conducted a randomized, placebo-controlled, double-blind trial to examine whether dexmedetomidine (DEX) as an adjunct during general anesthesia in patients undergoing unilateral TKA could attenuate the rise in inflammatory cytokines and oxidative stress.

METHODS: Sixty-eight patients were randomized to either the control or DEX group. DEX was administered at a loading dose of 0.5 μg/kg, followed by an infusion of 0.4 μg/kg/h. We measured serum levels of malondialdehyde (biomarker of oxidative stress) and proinflammatory cytokines (interleukin-6 [IL-6] and tumour necrosis factor-α [TNF-α]) preinduction (baseline), 60 and 90 min post-tourniquet release. We also assessed hemodynamics, intraoperative remifentanil consumption, and postoperative pain scores and analgesic consumption.

RESULTS: Malondialdehyde was higher than baseline after tourniquet release in both groups (P≤0.001), but the levels were similar between groups at all times. TNF-α was significantly higher than baseline at 60 min post-tourniquet release only in the control group (P=0.009). Serum IL-6 increased significantly above baseline at 60 and 90 min post-tourniquet release in both groups (P<0.001). At 90 min, IL-6 was significantly lower in the dexmedetomidine group than in the control group (P=0.049). Remifentanil consumption, heart rate, and pain scores were significantly lower in the dexmedetomidine group.

CONCLUSIONS: Our results suggest that dexmedetomidine as an adjunct to general anesthesia attenuated the rise in proinflammatory cytokines, providing protective effects in tourniquet-induced IRI.


KEY WORDS: Dexmedetomidine - Inflammation - Ischemia - Tourniquets.

Total knee arthroplasty (TKA) is a common surgical procedure for treating older patients with advanced osteoarthritis, a condition present in 60% of adults over the age of 65. Ischemia-reperfusion injury (IRI) occurs during TKA as a consequence of using a tourniquet to prevent bleeding, maximize visualization of the surgical field, and facilitate cementing of bone implants. Tourniquet use reduces oxygen delivery to muscle cells, altering their metabolism and subsequently...
initiating transcription of IRI-related genes. Following tourniquet deflation, reperfusion results in systemic release of inflammatory cytokines and reactive oxygen species, leading to acute muscle cell damage and remote organ injury. Systemic inflammation triggered by tourniquet induced-IRI and the surgical stress response affect functional mobility outcomes after TKA.

Dexmedetomidine is a potent α2-adrenoceptor agonist that has sedative, analgesic, and anxiolytic effects. Anti-inflammatory effects of dexmedetomidine have been recently highlighted. Preclinical murine IRI models demonstrated its protective effects against IR-induced organ injury, including modulation of proinflammatory cytokine production. In human whole blood in vitro, dexmedetomidine suppressed lipopolysaccharide-induced production of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). In human clinical studies, the effects of dexmedetomidine on inflammatory responses have been somewhat inconsistent, but studies in patients undergoing cardiac surgery and non-cardiac major abdominal surgery reported that dexmedetomidine reduced proinflammatory cytokine levels, which led to attenuated inflammatory responses and improved mortality. In a previous study of tourniquet-induced IRI, the use of dexmedetomidine as an adjuvant to sevoflurane anesthesia did not show any protective benefits on oxidative stress. However, the inflammatory response effects of dexmedetomidine, which is used as an adjuvant to anesthesia during surgery using a tourniquet, have not been heretofore evaluated.

We hypothesized that intraoperative dexmedetomidine would suppress the inflammatory responses associated with tourniquet-induced IRI. To explore this issue, we assessed serum levels of proinflammatory cytokines and malondialdehyde (MDA), a biomarker of oxidative stress, in older adults undergoing TKA.

Materials and methods

This study was approved by the institutional ethics review committee of Severance Hospital, Korea (No. 4-2015-0794) and registered at ClinicalTrials.gov (NCT02648958). A total of 68 patients were enrolled between January 2016 and July 2017 at Severance Hospital. The patients were aged between 20 and 80 years, had American Society of Anesthesiologists’ physical status class I–III, and were scheduled to undergo elective TKA. Patients with following conditions were excluded: rheumatoid arthritis, heart block greater than first degree, left ventricle ejection fraction <40%, use of antioxidants within 24 h before surgery, diabetes mellitus, hepatic or renal disease, chronic administration of anti-inflammatory drugs, or allergy to study drugs. Written informed consent was obtained from all patients before enrolment.

Perioperative management

In the operating room, routine monitors were applied. A 20-G radial artery catheter was inserted to monitor arterial blood pressure. Anesthesia was induced with thiopental (5 mg/kg) and remifentanil; rocuronium (0.6 mg/kg) was used to facilitate intubation. Anesthesia was maintained with desflurane and remifentanil to achieve a Bispectral Index score of 40-60 and maintain the systolic arterial pressure within 20% of baseline. When the heart rate (HR) was <50 beats/min or the systolic pressure was <80 mmHg, the anesthesiologist administered atropine (0.5 mg) or ephedrine (6 mg), respectively. Intraoperative fluid administration with Plasmalyte (Plasma solution A, CJ pharmaceutical, Seoul, Korea) was managed according to the decision of attending anesthesiologist. During surgery, a pneumatic tourniquet was applied to the relevant extremity in all patients and inflated to a pressure of 320 mmHg. In all patients, one surgeon performed cemented TKA to maintain a uniform surgical stimulus.

Before the end of surgery, fentanyl 1 µg/kg was administered to reduce postoperative pain. Concurrently, intravenous patient-controlled analgesia (PCA) was begun, consisting of fentanyl 1200 µg plus ramosetron 0.3 mg (total volume including saline, 240 mL) delivered as a 4 mL/h background infusion and 2-mL demand doses with a 10-min lockout period. This was continued for 48 h after surgery. Pain at rest were evaluated at 1-6 h, 6-12 h, 12-24 h, and 24-48 h postoperatively using an 11-point verbal numerical rating scale (VNRS) ranging from 0= no pain to 10= worst imaginable pain. Tramadol 50 mg was administered for a pain VNRS≥5 or upon patient request.
When physical therapy was performed at 12–24 h and 24–48 h postoperatively, patients were asked to rate their worst pain intensity on movement.

Interventions

The day before surgery, enrolled patients were randomly assigned to either saline group (control group) or dexmedetomidine group (DEX group) in a 1:1 ratio using computer-generated random number codes. Assignments were concealed in sealed envelopes. Randomization was not stratified or blocked. Study drugs were prepared in identical 50-mL syringes by a nurse anesthetist who was blinded to group assignment. The DEX group received dexmedetomidine 0.5 μg/kg before induction of general anesthesia, followed by a dexmedetomidine infusion at 0.4 μg/kg/h until 10 min before the end of surgery. The control group received a volume-matched normal saline bolus and infusion as placebo. The surgeon, patients, attending anesthesiologists responsible for patient care, and nurses were all blinded to group assignments during the study period.

Evaluation of inflammatory response and oxidative stress

Blood samples for MDA, TNF-α, and IL-6 were obtained before induction of anesthesia (baseline) and 60 and 90 min after tourniquet deflation. Each blood sample was centrifuged to separate the serum, which was then stored at -70°C for subsequent analysis of MDA, TNF-α, and IL-6. Serum MDA was analysed using high-performance liquid chromatography. TNF-α and IL-6 were determined using enzyme-linked immunosorbent assay kits (Quantikine® high-sensitive immunoassay; R&D Systems, Minneapolis, MN, USA). All blood samples for biochemistry assays were obtained through the arterial line. Arterial blood gas analysis, including lactate, was performed at baseline and 60 and 90 min after tourniquet deflation using a blood gas analyser (GEM Premier 3000, Instrumentation Laboratory, MA, USA).

Statistical analysis

Sample size was estimated using MDA levels as the primary endpoint. In a previous study, 14 mean±SD of MDA levels was 5.1±1.3 nmol/mL at 2 h after tourniquet release during lower extremity surgery. We considered a 20% reduction of MDA levels to be clinically relevant. With a significance level of 5% and power of 90%, 31 subjects were required in each group. We factored in a 10% dropout rate and enrolled 34 patients in each group. Data are shown as the number of subjects, mean±SD, or median (interquartile range). Groups were compared on normally distributed data with an independent t-test, non-normally distributed data with the Mann-Whiney U Test, and categorical variables with the χ² test or Fisher exact test as appropriate. Variables with repeated measures were analyzed using a linear mixed model with patient indicator as a random effect, and group, time, and group-by-time interaction as fixed effects. The group-by-time interaction assesses whether the change over time differs between groups. Repeated measure ANOVA was used for intra-group comparisons with p values that were adjusted by the Bonferroni correction for multiple comparisons. A P value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY, USA) and SAS 9.2 (SAS Institute Inc, Cary, NC, USA).

![CONSORT diagram](image-url)
Results

A total of 86 patients scheduled for TKA under general anesthesia were assessed for eligibility during their preoperative anesthesia consultation: 68 were enrolled and 18 were excluded (2 declined to participate and 16 did not meet the inclusion criteria) (Figure 1). Finally, the study cohort comprised 67 patients because one of the 68 was excluded due to repetitive tourniquet application during surgery. The patients’ characteristics and the clinical parameters were comparable in both groups, except intraoperative remifentanil consumption which was significantly higher in the control group than in the DEX group (Table I).

There were no significant differences in levels of MDA, TNF-α, or IL-6 between the two groups at baseline (Table II). Serum MDA increased significantly at both 60 and 90 min after tourniquet release compared with baseline; this increase occurred in both the control group (P<0.001, P=0.001, respectively) and the DEX group (both P<0.001). Serum TNF-α increased after tourniquet release but was significantly higher at 60 min after tourniquet release than baseline only in the control group (P=0.009). Serum IL-6 increased significantly at both 60 and 90 min af-

### Table I.—Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Control (N.=34)</th>
<th>DEX (N.=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>66.2±8.6</td>
<td>65.1±7.4</td>
<td>0.563</td>
</tr>
<tr>
<td>Sex; male</td>
<td>4 (11.8)</td>
<td>4 (12.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>Weight; kg</td>
<td>61.9±8.1</td>
<td>59.9±6.7</td>
<td>0.284</td>
</tr>
<tr>
<td>Body Mass Index; kg/m²</td>
<td>25.9±3.1</td>
<td>25.0±2.6</td>
<td>0.192</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (59)</td>
<td>16 (49)</td>
<td>0.396</td>
</tr>
<tr>
<td>History of knee surgery</td>
<td>9 (27)</td>
<td>9 (27)</td>
<td>0.941</td>
</tr>
<tr>
<td>Duration of tourniquet; min</td>
<td>79.2±16.8</td>
<td>75.2±12.7</td>
<td>0.284</td>
</tr>
<tr>
<td>Duration of surgery; min</td>
<td>90.8±19.8</td>
<td>85.9±15.9</td>
<td>0.267</td>
</tr>
<tr>
<td>Duration of anesthesia; min</td>
<td>129.6±22.0</td>
<td>125.3±20.4</td>
<td>0.414</td>
</tr>
<tr>
<td>Infused crystalloid solution; mL</td>
<td>618.1±254.7</td>
<td>674.9±277.4</td>
<td>0.366</td>
</tr>
<tr>
<td>Total dose of remifentanil; mg</td>
<td>0.51±0.20</td>
<td>0.32±0.12*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postoperative hospital stay; days</td>
<td>3.2±0.5</td>
<td>3.1±0.7</td>
<td>0.780</td>
</tr>
</tbody>
</table>

Data are mean±SD or number of patients (%). DEX: dexmedetomidine. *P<0.05 compared with control group.

### Table II.—Lactate and inflammatory mediators.

<table>
<thead>
<tr>
<th></th>
<th>Control (N.=34)</th>
<th>DEX (N.=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA; nmol/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.82±0.65</td>
<td>2.74±0.61</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>60 min after tourniquet release</td>
<td>3.89±0.67*</td>
<td>3.49±0.64†</td>
<td>0.256</td>
</tr>
<tr>
<td>90 min after tourniquet release</td>
<td>3.67±0.88*</td>
<td>3.42±0.70†</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>TNF-α; pg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.50±0.92</td>
<td>1.47±0.87</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>60 min after tourniquet release</td>
<td>2.25±1.38†</td>
<td>1.57±0.90</td>
<td>0.110</td>
</tr>
<tr>
<td>90 min after tourniquet release</td>
<td>1.81±0.96</td>
<td>1.51±0.98</td>
<td>0.788</td>
</tr>
<tr>
<td>IL-6; pg/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.11±0.88</td>
<td>1.10±0.94</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>60 min after tourniquet release</td>
<td>4.03±2.30†</td>
<td>3.14±2.07†</td>
<td>0.484</td>
</tr>
<tr>
<td>90 min after tourniquet release</td>
<td>8.10±3.65†</td>
<td>5.96±2.69* †</td>
<td>0.049</td>
</tr>
<tr>
<td>Lactate; mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.14±0.45</td>
<td>0.97±0.30</td>
<td>0.260</td>
</tr>
<tr>
<td>60 min after tourniquet release</td>
<td>1.49±0.51†</td>
<td>1.17±0.30* †</td>
<td>0.008</td>
</tr>
<tr>
<td>90 min after tourniquet release</td>
<td>1.40±0.60†</td>
<td>1.11±0.28†</td>
<td>0.060</td>
</tr>
</tbody>
</table>

Data are mean±SD. *P<0.05 compared with control group; †P<0.05 compared with baseline. DEX, dexmedetomidine; IL-6, interleukin-6; MDA, malondialdehyde; TNF-α, tumour necrosis factor-α.
DEXMEDETOMIDINE AND TOURNIQUET-INDUCED INFLAMMATION

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significantly different between the two groups. The number of patients who required pharmacological intervention because of intraoperative hypotension was not different between the control group (21%) and DEX group (36%). Atropine was administered to three patients in the DEX group.

Pain scores at rest were significantly lower in the DEX group than in the control group at 12-24 h and 24-48 h postoperatively (Table III). Pain scores on movement were significantly lower in the DEX group than in the control group at 24-48 h postoperatively. The cumulative PCA volume infused until 48 h after surgery and the number of patients requiring rescue analgesics were similar in the two groups.

Discussion

In this randomized, double-blind, placebo-controlled trial, dexmedetomidine, as an adjuvant to general anesthesia, attenuated the rise of pro-inflammatory cytokines after tourniquet-induced IRI. The rise in IL-6 levels was significantly suppressed by dexmedetomidine infusion at 90 min after tourniquet release, when compared with placebo. Furthermore, intraoperative dexmedetomidine reduced postoperative resting pain and movement pain for 12-48 h and 24-48 h, respectively, after TKA.

TKA is the most common surgical treatment for mitigating pain and restoring functional mobility in older patients with chronic pain associated with osteoarthritis. Despite high success rates for pain, functional outcomes depend on postoperative restoration of lower extremity muscle strength. A 12% reduction in quadriceps volume at two weeks after TKA has been demonstrated by magnetic resonance imaging.15 Muscle atrophy after TKA, which is the major cause of functional mobility impairments, may be affected by several factors, including age, obesity, postoperative physical activity, and systemic inflammation triggered by tourniquet induced-IRI.3 In addition, the surgical stress response involves metabolic, inflammatory, and immune reactions. Therefore, perioperative anesthetic management that reduces the immuno-modulatory effects of inflammation may be of clinical benefit in older adults undergoing TKA.

Dexmedetomidine attenuates inflammation
and surgical stress responses. Although the precise mechanisms of its anti-inflammatory effects are not well understood, several possible mechanisms have been postulated, including modulation of cytokine production by macrophages and monocytes, inhibition of apoptosis, and central sympatholytic effects with subsequent relative predominance of cholinergic anti-inflammatory pathways. Previous animal and clinical studies showed that dexmedetomidine reduced levels of proinflammatory cytokines, such as TNF-α and IL-6, leading to attenuation of the acute phase inflammatory response and reduced mortality. In our study, serum TNF-α peaked at 60 min after tourniquet release, at which time it was significantly higher than baseline only in the control group. In the DEX group, TNF-α increased only slightly at 60 min after tourniquet release and thereafter returned to baseline. IL-6 increased up to 90 min after tourniquet release, and dexmedetomidine significantly suppressed IL-6 levels at that time point when compared with placebo. While the timing of the IL-6 peak depends on the type of surgery, serum IL-6 usually peaks 6-24 h after joint replacement surgery. Although we measured proinflammatory cytokines only up to 90 min after tourniquet release, our results suggest that dexmedetomidine reduced the acute phase inflammatory response after TKA.

Tourniquet-induced ischemia followed by reperfusion is accompanied by an increase in reactive oxygen species, leading to muscle cell damage. One of the major secondary oxidation products in lipid peroxidation is MDA, which is considered a good indicator of free radical damage in pathologies associated with oxidative stress. Our results showed that dexmedetomidine did not reduce serum MDA levels after tourniquet-induced IRI. This finding is consistent with the results of some animal studies, which demonstrated that dexmedetomidine did not reduce MDA levels but improved inflammatory response and histologic injury. In a previous clinical study of lower extremity surgery using a tourniquet, standard dose of dexmedetomidine (loading dose 1 μg/kg, infusion 0.7 μg/kg/h) as an adjuvant to sevoflurane anesthesia did not show any protective benefits on oxidative stress, as measured by MDA levels and total antioxidant capacity.

### Table III

<table>
<thead>
<tr>
<th>Pain scores at rest</th>
<th>Control (N=34)</th>
<th>DEX (N=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6 h</td>
<td>6.0 (4.0-7.3)</td>
<td>5.0 (2.0-6.3)</td>
<td>0.242</td>
</tr>
<tr>
<td>6-12 h</td>
<td>4.5 (3.0-6.5)</td>
<td>4.0 (2.0-6.0)</td>
<td>0.343</td>
</tr>
<tr>
<td>12-24 h</td>
<td>4.0 (2.8-5.0)</td>
<td>2.0 (2.0-4.0)*</td>
<td>0.031</td>
</tr>
<tr>
<td>24-48 h</td>
<td>4.0 (2.0-5.0)</td>
<td>1.0 (0.0-3.0)*</td>
<td>0.006</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain scores on movement</th>
<th>Control (N=34)</th>
<th>DEX (N=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12-24 h</td>
<td>6.0 (5.0-8.0)</td>
<td>5.0 (4.0-7.0)</td>
<td>0.076</td>
</tr>
<tr>
<td>24-48 h</td>
<td>6.0 (4.5-6.5)</td>
<td>4.0 (2.0-5.0)*</td>
<td>0.007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PCA volume used; mL</th>
<th>Control (N=34)</th>
<th>DEX (N=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6 h</td>
<td>38.1±11.5</td>
<td>36.4±9.4</td>
<td>0.601</td>
</tr>
<tr>
<td>6-12 h</td>
<td>70.4±19.8</td>
<td>68.0±17.0</td>
<td>0.677</td>
</tr>
<tr>
<td>12-24 h</td>
<td>125.5±29.2</td>
<td>127.5±28.7</td>
<td>0.836</td>
</tr>
<tr>
<td>24-48 h</td>
<td>217.0±23.7</td>
<td>218.0±16.7</td>
<td>0.898</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients requiring rescue analgesics</th>
<th>Control (N=34)</th>
<th>DEX (N=33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-6 h</td>
<td>10 (29)</td>
<td>11 (33)</td>
<td>0.729</td>
</tr>
<tr>
<td>6-12 h</td>
<td>9 (27)</td>
<td>11 (33)</td>
<td>0.539</td>
</tr>
<tr>
<td>12-24 h</td>
<td>8 (24)</td>
<td>9 (27)</td>
<td>0.725</td>
</tr>
<tr>
<td>24-48 h</td>
<td>7 (21)</td>
<td>7 (21)</td>
<td>0.950</td>
</tr>
</tbody>
</table>

Data are mean±SD, median (IQR), or number of patients (%).
DEX: dexmedetomidine; PCA: patient-controlled analgesia.
*P<0.05 compared with control group.
tourniquet release, whereas we measured MDA, TNF-α, and IL-6 until 90 min after tourniquet deflation in older patients who might be vulnerable to ischemia reperfusion injury in the current study. Alternatively, the moderate dose of dexmedetomidine used in this study may be insufficient to suppress oxidative stress. Although dexmedetomidine dose-dependently attenuated intestinal injury in a preclinical murine IRI model, large doses of dexmedetomidine may contribute to adverse hemodynamic effects and are not suitable for clinical application.

In this study, the lactate levels after tourniquet release were significantly higher than baseline in both groups, indicating that anaerobic glycolysis occurred during the tourniquet-induced ischemic period. Dexmedetomidine significantly reduced the lactate level at 60 min after tourniquet release compared with placebo. In previous clinical studies, dexmedetomidine has been reported to decrease lactate levels in patients undergoing liver transplantation and increase lactate clearance in septic shock patients probably by adrenergic modulation,21,22

The anesthetic and analgesic-sparing effects of dexmedetomidine are well known. In this study, the remifentanil dose required to maintain similar Bispectral Index values was significantly lower in the DEX group. A recent meta-analysis showed that intraoperative dexmedetomidine was associated with less postoperative pain, reduced opioid consumption, and a lower risk for opioid-related adverse events. In this study, while the infused PCA volume and frequency of rescue analgesics were similar in both groups, resting pain scores for 12-48 h after TKA were lower in DEX group compared to control group. Although the mechanism of prolonged analgesic effects of dexmedetomidine has not been fully elucidated, one possible explanation is that activation of α2-adrenoreceptors modulates transmission of nociceptive signals in the central nervous system.24 Another potential explanation involves the interaction between proinflammatory cytokines and pain, whereby proinflammatory cytokines modulate pain sensitivity and pain influences the production and release of cytokines.25 It is also possible that the antinociceptive action of dexmedetomidine may have contributed to the anti-inflammatory effects in this study. Regardless of the exact mechanism, we also observed reduced pain on movement at 24-48 h postoperatively, which may have particular clinical importance by facilitating postoperative physical activity.

Use of dexmedetomidine in the perioperative period has been associated with attenuated hemodynamic responses to surgical stimuli and attenuated tourniquet-induced hyperdynamic responses.26 In this study, although arterial pressures did not differ between groups, HR was slower in the DEX group at most intraoperative times. We specifically selected a moderate dose of dexmedetomidine in this study of older adults (aged 50 to 80 years) to avoid the side effects usually associated with higher doses and older age, including bradycardia, hypotension, and hypertension.27

Limitations of the study
There were some limitations in this study. First, cytokine responses and oxidative stress were not prominent even in the control group, compared with previous studies of patients undergoing cardiac and major non-cardiac surgery.10-12 The characteristic cytokine profiles in our study were attributed to the duration of ischemia and magnitude of tissue damage associated with TKA, which is not major surgery. Second, we measured serum levels of MDA, TNF-α, and IL-6 in systemic blood. As concentrations of these substances are usually greater at the surgical site than in the systemic circulation, the serum changes in cytokine concentrations may not exactly reflect anti-inflammatory effects of dexmedetomidine at the surgical site. Finally, this trial was not designed to detect difference in functional outcomes or incidence of adverse effects. Further studies are needed to investigate the effects of anti-inflammatory effects of dexmedetomidine on clinical impact, such as functional mobility.

Conclusions
Our study showed that, in unilateral TKA using a tourniquet, dexmedetomidine did not reduce MDA formation but did attenuate inflammatory
responses. This result suggests that dexmedetomidine exerts protective effects in IRI associated with extremity surgery using a tourniquet under general anesthesia.

What is known

- Dexmedetomidine has anti-inflammatory effects that lead to improved mortality in patients undergoing cardiac surgery and major abdominal surgery.
- Tourniquet use during total knee arthroplasty produces ischemia-reperfusion injury, with systemic release of inflammatory cytokines and reactive oxygen species upon tourniquet release.

What is new

- Using dexmedetomidine as an adjunct to general anesthesia attenuated the rise in pro-inflammatory cytokines, providing protective effects against tourniquet-induced ischemia-reperfusion injury.
- Dexmedetomidine administration reduced postoperative resting pain and movement pain after total knee arthroplasty.

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.

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Authors’ contributions.—Seung H. Kim: data acquisition, data management, interpretation of data and statistical analysis, drafting of manuscript; Do-Hyeong Kim: data management, interpretation of data and statistical analysis; Seokyung Shin: data acquisition, data management, technical support, interpretation of data; Seon J. Kim: data acquisition, data management, technical support, interpretation of data; Tae L. Kim: data acquisition, data management, technical support; Yong S. Choi: conception and design, obtaining funding, data acquisition, interpretation of data and statistical analyses, manuscript revision, supervision.


Evaluation of an active decision support system for hemodynamic optimization during elective major vascular surgery

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ABSTRACT

BACKGROUND: Active decision support systems implementing goal directed therapy may be an approach to reduce disparities in outcome between different health care providers. We assessed feasibility of and adherence to an active decision support system (ADSS) comprising fluids, vasopressors, and dobutamine to optimize hemodynamics during high-risk vascular surgery.

METHODS: In this prospective observational trial a closed-loop goal-directed therapy protocol, employing the minimally-invasive LiDCOrapid device, was used to actively provide advice to the anesthesiologist during surgery. All given suggestions and all interventions were recorded. Every intervention without or against the given advice had to be justified. The primary outcome parameters were the number of interventions done according to the ADSS and its duration of use. Reasons for non-compliance served to describe its limitations.

RESULTS: The active decision support system was employed in 32 patients for 137 hours. Median (IQR) use of the ADSS as percentage of surgery time was 100% (94-100%) with 743 interventions being executed. 634 interventions were done according to ADSS proposals. Reasons to act against or without advice were: hemodynamic instability (6%), foreseeing a surgical event (2%), medical reasons (2%), awaiting hemodynamic improvement (1%) and orders by senior physician or surgeons (1%). In five patients the anesthesiologist decided to modify intervention thresholds of the underlying protocol.

CONCLUSIONS: High rates of compliance underline clinical acceptability and feasibility of this ADSS during vascular surgery. It may therefore facilitate the work of anesthesiologists and reduce disparities in patient outcomes due to different healthcare providers. Particularly, rapidly developing hemodynamic perturbances as well as co-factors the ADSS as of now does not anticipate are current limitations. These findings may serve to further improve this stand-alone real-time ADSS.


KEY WORDS: Decision support techniques - Hemodynamics - Vascular surgical procedures.

Disparities in outcome between different health care providers have become a critical issue within anesthesiology.¹ To reduce these disparities and improve overall outcome the trend goes towards more standardized evidence-based care.², ³ The implementation of clinical decision support systems is a viable approach to standardize delivery of health care founded on current evidence.⁴, ⁵

There is a distinction between passive and active decision support systems (ADSS).⁶ In passive decision support systems the health care providers must take the initiative to apply and interpret written guidelines and various document
templates. ADSS, in contrast, support providers by interrupting their workflow and presenting information that might not necessarily be in the scope of their attention. ADSS range from simple alarms, over alerts for drug interactions to complex clinical advice.

Goal-directed therapy (GDT) to optimize hemodynamics aims to specifically adjust cardiac pre- and afterload as well as contractility in a timely manner to improve oxygen delivery by giving fluids, inotropic and/or vasoactive agents. Despite recent set-backs regarding the impact of GDT on mortality, GDT has been associated with a reduction in postoperative complications, renal failure, respiratory failure, wound infections and hospital length of stay.

Protocols employing GDT are mainly passive decision support systems as they merely provide written guidance. In these settings, GDT may be delivered at the discretion of caregivers. Thus, reasons of non-adherence to the protocol may be difficult to recognize. Indeed, reasons for non-adherence to a GDT protocol were not reported in previous studies.

In the setting of an ADSS, the reasons for non-adherence can easily be elucidated by an observer. ADSS that support the provider by interrupting work-flow and proposing administration of fluid in conjunction with pharmacologic agents to improve intraoperative hemodynamics are not yet available.

We developed an ADSS based on an institutional GDT-protocol that incorporates fluids, vasopressors and dobutamine. It is based on real-time data acquired by the minimally-invasive LiDCOrapid™ device (LiDCO, Lake Villa, IL, USA). We implemented our ADSS during major vascular surgery to expose the system to complex hemodynamic perturbances. Aortic or peripheral vascular surgeries are high-risk surgeries since they are associated with an increased incidence risk of major postoperative cardiac complications specifically when performed in sick patients.

The goal of our study was to determine feasibility and adherence to the underlying ADSS to optimize hemodynamics during elective major vascular surgery based on the principles of GDT comprising fluids, vasopressors and inotropes. The primary outcomes were the number of interventions done according to the ADSS and the duration of its use. Reasons for non-compliance to a clinically employed ADSS to discover its limitations were also recorded, which, to our knowledge, has not yet done before.

Materials and methods

This prospective feasibility study was approved by our local ethics committee (Medical University of Vienna, ref: 1967/2014). Written informed consent was obtained from all patients enrolled between February and July 2015. Patients were included if they were scheduled for elective major vascular surgery such as peripheral arterial surgery and open abdominal aortic surgery except for carotid artery surgery. Further exclusion criteria were patients under 18 years of age and absence of sinus rhythm at induction of anesthesia. Apart from recording the number of interventions conducted according to the ADSS as well as the duration of use of the ADSS any feasibility issues encountered with the ADSS, such as problems to maintain goal values for MAP and CO during anesthesia, potentially counter-productive or potentially hazardous advices, were also to be described.

Monitoring and anesthetic technique

Patients were monitored with an electrocardiogram, pulse oximetry, end-tidal PCO$_2$, Bispectral Index (BIS) and a temperature probe. Prior to induction of anesthesia a 20-g catheter was inserted in the radial artery to also measure invasive blood pressure. We took blood gases (including lactate and blood glucose) before induction and on arrival at the post-anesthesia care unit and, if required, during the course of surgery.

Premedication consisted of midazolam 0.1 mg/kg PO one hour prior to surgery. Anesthesia was induced with IV-administration of 1-2 mg of midazolam, fentanyl 2 µg/kg and propofol 1.5 mg/kg. Rocuronium 0.5 mg/kg was used to facilitate oral endotracheal intubation. Phentylephrine 0.04 mg bolus were given when necessary to control blood pressure during induction. Blood transfusions were administered if hemoglobin level was below 7 g/dl in hemodynamically stable patients and 8 g/dL in patients with preexisting cardiovascular disease. If indicated (e.g. for abdominal aortic surgery), a cell-saver was used. Blood collected...
via cell-saver was returned immediately after collection and subsequent processing.

From skin incision to wound closure additional fluids, vasopressors or inotropes were given subject to the recommendations by our ADSS.

Volume-controlled ventilation with a constant tidal volume of 8 mL/kg ideal body weight and a positive end-expiratory pressure of 5 cmH₂O was applied targeting an end-tidal PCO₂ of 32-36 mmHg. Anesthesia was maintained with oxygen-enriched air and sevoflurane 1.5-2.0% end-tidal concentration as well as fentanyl bolus as required. A forced-air warming system and a fluid warmer were used for each operation.

LiDCOrapid device

The Conformité Européen-marked LiDCOrapid device is a minimally-invasive technology using uncalibrated pulse contour analysis to continuously monitor cardiac output (CO) and respiratory variations in stroke volume (SVV). The device was connected via the monitoring screen (Infinity Delta; Drägerwerk AG, Lübeck, Germany) according to the manufacturer’s recommendations. All measured parameters were automatically stored beat-by-beat in the internal database of the device.

The set-up of our active clinical decision support system

In order to assess adherence and the reasons for breach during anesthesia a second study anesthesiologist attended the anesthesiologist in charge. The study anesthesiologist was the active component imitating a computerized voice alarm in our ADSS protocol. The study anesthesiologist was responsible for interpreting the parameters of the LiDCOrapid device and gave advice strictly following the ADSS protocol without commenting the ADSS’s recommendations or in any other way interfering with anesthesia and decision-making of the anesthesiologist in charge.

The anesthesiologist in charge was instructed to follow the advice. However, he could dismiss the recommended advice, when there was any medical reason. The study anesthesiologist took note of all proposed interventions and if they were followed or not. The anesthesiologist in charge had to justify every dismissed advice as well as every intervention, which was not according to protocol. The study anesthesiologist and the anesthesiologist in charge were both residents proficient in vascular anesthesia. Both had the same hierarchy level. Therefore, any bias resulting from different hierarchy levels can be excluded. A senior anesthesiologist supervised the operating room and was aware that an ADSS was applied, which he was asked not to interfere with. Additionally, estimated net blood loss (excluding re-transfused blood from the cell-saver), urine output, volumes of crystalloids and colloids as well as administration of blood products was noted. We also recorded hospital length of stay together with pre- and postoperative serum creatinine levels.

The protocol behind our clinical decision support system

Our institutional GDT protocol was designed to improve hemodynamics during major vascular surgery (Figure 1), by adopting and modifying a protocol already in use in vascular surgery that has been shown to be superior to standard care. In contrast to the previously published protocol no background fluid rate was applied. For initial administration of a fluid bolus we used a threshold value for SVV>13% that has been shown to predict fluid responsiveness in vascular surgical patients. A fluid challenge consisted of 250 mL of Ringer’s lactate solution (RL) rapidly administered IV within two minutes (Figure 1). Baseline MAP and CO values were assessed prior to anesthesia induction. If preoperative measures of MAP from the ward were available, these were taken as the corresponding baseline values. The threshold values for ADSS interventions were 70% of baseline MAP and 80% of baseline CO (Figure 1). By calculating the threshold values from baseline MAP and CO values, we respected the individual preoperative hemodynamic state of each patient in our ADSS protocol.

Statistical analysis

As our intention was to study feasibility, operator compliance and limitations of the ADDS we simply summarized the features in the form of descriptive statistics. Variables are either presented
as mean and standard deviation (SD) or median (IQR [range]) for normally and non-normally distributed data, respectively. The published recommendations for sample size in feasibility studies investigating intervention efficacy in a single group is 20 to 25. We decided to include 31 patients in this study due to the heterogeneity of vascular pathologies in our study population and to account for potential drop-outs.

Results

Thirty-one patients with ASA physical status II to III were included. There were no missing data. The mean age of the patients was 65±10 years. Patient characteristics are provided in Table I.

Adherence to the protocol

Between skin incision and skin closure the ADSS was used for a total of 137 hours and 24 minutes. The median (Q1-Q3) duration of ADSS use as a percentage of surgery time per case was 100% (94-100%, Table II). Compliance with the ADSS was lacking when the following situations occurred: 1) return of spontaneous breathing to wards the end of anesthesia (n.=8); 2) periods of arrhythmia (n.=2); 3) acute severe bleeding (n.=1); 4) ST-segment changes (n.=1); or 5) the order of a consultant to dismiss the ADSS (n.=1).

During use of the ADSS, 743 interventions were executed. 634 (85%) interventions were effectuated as proposed by the ADSS. Among these, 294 (46%) were fluid bolus, 239 (38%) concerned the administration of vasopressors and 101 (16%) dobutamine (Table III). The anesthesiologist in charge performed 104 (14%) therapeutic decisions without (79; 11%) or against (25; 3%) the advice given by the ADSS (Table IV). Reasons to act against or without advice were: hemodynamic instability (6%), foreseeing a sur-
kg/min) was administered although the ADSS protocol curbs the maximal dose at 4.00 µg/kg/min (Table II).

Feasibility issues encountered with the ADSS protocol

In three patients the baseline MAP values before induction of anesthesia were 77, 61, and 115 mmHg respectively. Since the anesthesiologist in charge judged that the intervention threshold of 70% below baseline MAP would either be too low or too high, the critical limit initiating treatment for hypotension was set at 60 mmHg for these patients. Similarly, high CO baseline values were measured before induction of anesthesia in another two patients namely 10.0 and 9.9 L/min. The lowest acceptable CO range was set at 5-6 L/min in these patients.

Postoperative outcomes

Additional postoperative fluid resuscitation was needed in four patients because of hypotension (N.=2), postoperative bleeding (N.=1) or preceding long-lasting surgery with persistent volume depletion (N.=1). Postoperative acid-base status did not show major derangements (Table V). One patient with previous heart transplantation and low left ventricular ejection fraction died postoperatively due to sepsis with multiple organ failure. Extremely prolonged hospital stay (153 days) was observed in another patient with a complicated postoperative course resulting from an underlying wound infection (Table V).

### Table I.—Baseline characteristics (N.=31).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>65±10</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (71%)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (29%)</td>
</tr>
<tr>
<td>BMI &gt;30 kg/m²</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>ASA physical status</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>7 (23%)</td>
</tr>
<tr>
<td>III</td>
<td>24 (77%)</td>
</tr>
<tr>
<td>Pre-existing conditions</td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8 (26%)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>12 (39%)</td>
</tr>
<tr>
<td>Post-myocardial infarction</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>28 (90%)</td>
</tr>
<tr>
<td>Treatment with oral beta blockers</td>
<td>18 (58%)</td>
</tr>
<tr>
<td>History of cancer</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Underlying vascular disease</td>
<td></td>
</tr>
<tr>
<td>Peripheral arterial occlusive disease</td>
<td>17 (55%)</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>10 (32%)</td>
</tr>
<tr>
<td>Peripheral arterial aneurysm</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
</tr>
<tr>
<td>Femoral endarterectomy patch angioplasty</td>
<td>9 (29%)</td>
</tr>
<tr>
<td>Aortic-bifemoral bypass surgery</td>
<td>11 (35%)</td>
</tr>
<tr>
<td>Femoro-popliteal bypass surgery</td>
<td>8 (26%)</td>
</tr>
<tr>
<td>Femoro-distal bypass surgery</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Cross-over femoro-femoral bypass surgery</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or number of patients (percentage). BMI: Body Mass Index.

### Table II.—Duration of use of active decision support system, dosage of catecholamines, fluid balance and Bispectral Index values during ADSS (N.=31).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (Q1-Q3 [range])</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery duration, hh:mm</td>
<td>04:41 (03:41-06:22 [02:10-11:55])</td>
<td>05:12 ± 02:16</td>
</tr>
<tr>
<td>Duration of use of ADSS, hh:mm</td>
<td>04:19 (03:21-05:00 [10:00-11:55])</td>
<td>04:37 ± 02:19</td>
</tr>
<tr>
<td>Duration of ADSS protocol use as a percentage of surgery duration, %</td>
<td>100 (94-100 [0-100])</td>
<td>91±22</td>
</tr>
<tr>
<td>Norepinephrine, µg/kg/min</td>
<td>0.04 (0.03-0.08 [0-0.13])</td>
<td>0.05±0.04</td>
</tr>
<tr>
<td>Dobutamine, µg/kg/min a</td>
<td>0.54 (0-2.12 [0-8.42])</td>
<td>1.36±1.83</td>
</tr>
<tr>
<td>Bispectral Index (N.=30)</td>
<td>43 (40-47 [3-80])</td>
<td>43±7</td>
</tr>
<tr>
<td>Total fluid balance per patient, mL b</td>
<td>1970 (765-5565 [-150-10,075])</td>
<td>3330±3120</td>
</tr>
</tbody>
</table>

* To account for the factor time the dosage was calculated as median dose over each 30-minute epoch starting from incision for each patient. Thereafter, the mean dose of all median doses was calculated over the duration of surgery for each patient. Data are shown as median and mean for all patients; b total fluid balance is calculated as “total fluids given by anesthesiologist in charge” — (urine output + net blood loss) during the entire time in operating room.

ADSS: active decision support system.
Table III.—Type of intervention executed by the anesthesiologist in charge as recommended by the active decision support system.

<table>
<thead>
<tr>
<th>Type of intervention</th>
<th>Total</th>
<th>Per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid administration because of high SVV (&gt;13%)</td>
<td>200</td>
<td>3.5 (0-11 [0-30])</td>
</tr>
<tr>
<td>Fluid administration because of fluid responsiveness (increase in SV&gt;10% following fluid administration)</td>
<td>94</td>
<td>1 (0-5 [0-16])</td>
</tr>
<tr>
<td>Vasopressors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>143</td>
<td>5 (2-7 [0-17])</td>
</tr>
<tr>
<td>Decrease</td>
<td>96</td>
<td>2 (1-5 [0-13])</td>
</tr>
<tr>
<td>Dobutamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>58</td>
<td>1 (0-4 [0-7])</td>
</tr>
<tr>
<td>Decrease</td>
<td>43</td>
<td>1 (0-2 [0-8])</td>
</tr>
<tr>
<td>Total N. of interventions</td>
<td>634</td>
<td>16 (13-27 [5-76])</td>
</tr>
</tbody>
</table>

Data are shown as number of interventions and median (Q1-Q3 [range]) per patient.

Table IV.—Interventions executed by the anesthesiologist in charge and their background.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Description</th>
<th>Example</th>
<th>N. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic interventions (fluids, vasopressors or inotropes) following advice given by ADSS</td>
<td>Advice implemented as given by ADSS</td>
<td>Administration of fluid, adapting vasopressors or inotropes</td>
<td>634 (85%)</td>
</tr>
<tr>
<td>Therapeutic interventions following advice given by ADSS but with minor deviation</td>
<td>Advice executed with minor deviation</td>
<td>Fluid bolus given slower than within 2 minutes</td>
<td>5 (0.7%)</td>
</tr>
<tr>
<td>Therapeutic interventions without recommendations by ADSS</td>
<td>Acted without advice foreseeing a surgical event</td>
<td>Surgical events: vascular de-/clamping, acute bleeding</td>
<td>17 (2%)</td>
</tr>
<tr>
<td>Therapeutic interventions without recommendations by ADSS</td>
<td>Special order of senior anesthesiologist or senior surgeon</td>
<td>Request of senior physician to adapt blood pressure, to adapt catecholamines, to continuously give fluid</td>
<td>14 (2%)</td>
</tr>
<tr>
<td>Therapeutic interventions without recommendations by ADSS</td>
<td>Clinical necessity for double interventions during hemodynamic instability</td>
<td>Urged to simultaneously administer vasopressors and fluids because of severe hypotension, urged to adapt catecholamines after an intervention</td>
<td>48 (6%)</td>
</tr>
<tr>
<td>Therapeutic interventions against recommendations by ADSS</td>
<td>Dismissed advice to await hemodynamic improvement</td>
<td>Delayed start or adaption of catecholamine dose, wait for pharmacological effects to set in (e.g. opioids), end of surgery, erroneously high SVV because of immediate vascular de-/clamping or irregular heartbeats</td>
<td>11 (1%)</td>
</tr>
<tr>
<td>Therapeutic interventions against recommendations by ADSS</td>
<td>Medical reasons to dismiss given advice by ADSS</td>
<td>No further increase or decrease of dobutamine when ST-segment changes appeared on the ECG</td>
<td>14 (2%)</td>
</tr>
<tr>
<td>Total number of recorded interventions encompassing fluids, vasopressors and inotropes</td>
<td></td>
<td></td>
<td>743 (100%)</td>
</tr>
</tbody>
</table>

Table V.—Patient outcome after major vascular surgery using an active decision support system for hemodynamic optimization (N. =31).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Preoperative</th>
<th>Immediately after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH value</td>
<td>7.42 (7.41-7.44 [7.38-7.47])</td>
<td>7.36 (7.33-7.39 [7.17-7.42])</td>
</tr>
<tr>
<td>Arterial base excess, mmol/L</td>
<td>0.2 (-1.0-1.1 [-3.8-3.9])</td>
<td>-1.7 (-2.7 to -0.15 [-7.3-1.8])</td>
</tr>
<tr>
<td>Arterial lactate, mmol/L</td>
<td>0.9 (0.7-1.0 [0.4-1.8])</td>
<td>1.2 (0.9-2.0 [0.6-5.0])</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9 (0.7-1.2 [0.5-6.9])</td>
<td>0.9 (0.7-1.3 [0.35-4.8])</td>
</tr>
<tr>
<td>Length of hospital stay after surgery, days</td>
<td>12 (10-17 [6-153])</td>
<td>1</td>
</tr>
</tbody>
</table>

In-hospital death, N.

Data are presented as median (Q1-Q3 [range]) or numbers.
Discussion

In this trial median (IQR) duration use of ADSS in percent of surgery duration was 100% (94-100%). During ADSS use 85% of all interventions were executed according to the ADSS protocol. This reflects excellent adherence but also a higher rate of non-compliance in relation to a closed-loop system that merely governed intraoperative fluid administration. To our knowledge this is the first study assessing the reasons for dismissing the advice of an ADSS protocol. Threshold values for MAP and CO that had been considered as being too low or too high were adapted in five patients.

As an ADSS can never reflect clinical reality there will always be situations (14% of all interventions in our study) in which anesthesiologists have to act against the current recommendation and overrule the ADSS. Particularly when foreseeable or unexpected hemodynamic changes occur such as vascular clamping, de-clamping or acute bleeding, that require simultaneous administration of fluids, vasoactive drugs and occasionally inotropes thereby breaching the serial order of actions as determined by the ADSS protocol. Other reasons for dismissing the ADSS advice were ST-segment changes that might potentially be aggravated or were even induced by dobutamine. The maximal dobutamine dose was set at 4 µg/kg/min in the present ADSS protocol. Other GDT protocols have maximum doses of dobutamine ranging from 0.5 to 20 µg/kg/min. ADSS advice was also dismissed when it was deemed necessary to wait for the onset of action of previously administered drugs or because of an erroneously increased SVV due to immediate vascular clamping or de-clamping, spontaneous breathing or irregular heartbeats. These limitations to the use of SVV should be considered in an ADSS protocol.

Most interventions (46%) concerned the administration of fluids. The steps of other passive GDT protocols are usually in series beginning with fluid resuscitation, followed by an evaluation of the need for vasoactive drugs and inotropes. In 6% of the interventions done without the ADSS, vasopressors and fluid were given simultaneously during hemodynamic perturbances. With the exception of unstable hemodynamics, a serial approach may, however, be justified as each action may simultaneously impact others.

To our knowledge, there are no studies yet comparing different orders of the serial steps of a GDT protocol.

Some GDT protocols maintain crystalloid fluids at a continuous rate of 1-2 mL/kg/h in addition to fluid bolus. We decided to install no background fluid rate to expose the system to real fluid deficiency but integrated a threshold value for SVV>13% that has been shown to predict fluid responsiveness in vascular surgical patients.

As mentioned above, adaptation of goals for either MAP or CO became necessary in five patients. Exceedingly low baseline MAP values may be due to premedication or the NPO-status. In these cases, we set our lower threshold for MAP at 60 mmHg, which is in line with other studies. On the other hand, excessively high MAP or CO values may relate to the stressed or anxious state of some patients when entering the operating room. Therefore, we suggest that preferably MAP values determined preoperatively at the surgical ward should be taken as baseline values. In contrast to MAP, measuring CO preoperatively on the ward, however, is impracticable. Determination of CO values at baseline (i.e. before induction) as in our ADSS protocol may be attractive since they relate to the individual hemodynamic conditions in the awake patient without any interference by fluids, anesthetics or vasopressor agents. Most GDT protocols start to measure CO only after anesthesia induction and use a fixed threshold for cardiac index or oxygen delivery index.

LiDCOrapid™ is an uncalibrated pulse contour analysis system that is automatically calibrated according to patients’ age, weight and height. Although frequently employed for intraoperative closed-loop goal-directed fluid management, uncalibrated pulse contour analysis systems are known to be less accurate after major hemodynamic alterations than calibrated systems such as lithium dilution or transpulmonary thermodilution. Calibrated systems can be recalibrated if required. For example, when SVR declines after anesthesia induction, uncalibrated pulse contour analysis systems will underestimate CO. Other specific conditions

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study the closed-loop system ordered fluids earlier and more abundant as compared to cases solely managed by an anesthesiologist.

Conclusions

In conclusion, adherence to our modified ADSS was satisfactory since 85% of all interventions were in conformity with the ADSS. Main reasons for non-adherence were hemodynamic instability (6%), foreseeing a surgical event (2%), medical reasons (2%), awaiting hemodynamic improvement (1%) and orders by senior physician or surgeons (1%). In terms of feasibility, adaptations of goals for either MAP or CO were necessary in five patients who exhibited extreme levels.

The described reasons for non-adherence and feasibility issues in our study help to recognize the limitations of the current ADSS and to further develop enhanced computer-embedded ADSS in the future designed to reduce disparities in patient outcome due to different health care providers.

What is known

- Assisted decision support systems are a possible way to offer more standardized care in medicine.
- Complex assisted decision support systems have not yet been implemented in routine patient care.

What is new

- Assisted decision support systems can be designed to support anesthesiologists during major vascular surgery.
- Assisted decision support systems are always limited by their algorithm and the reliability of input data and every advice must be evaluated in this context by an experienced anesthesiologist.
- In our study, mainly sudden changes in hemodynamics and surgical interventions were not immediately recognized and responded to by the active decision support system. It, therefore, required additional interventions by the anesthesiologist in charge.

during vascular surgery like aortic clamping or de-clamping reduce the reliability of uncalibrated pulse contour analysis. Thus calibrated pulse contour analysis systems may actually be more suitable for this purpose.

One challenge of implementing an ADSS is that physicians may feel restricted in their professional autonomy. Yet clinical decision support systems are an effort to standardize care and do not implicate that the physician always has to follow the given advice.

This trial is a single center feasibility study that has no comparison group to test for differences in outcome. However, use of closed-loop assisted systems based on a GDT-protocol has previously been linked to more stable hemodynamics resulting from prolonged preload-independent states intraoperatively and better outcome.

Currently, there are no established set-ups to test adherence and feasibility of ADSS that are frequently computer-based. We assigned a study anesthesiologist aside the one who was in charge of the patient to get a direct feedback about effectuated advises. The role of the study anesthesiologist was simply to convey the situation-driven instructions of the GDT-protocol similar to a voice alarm without neither commenting the current clinical situation nor the particular advice that was given. There was a strict advice not to interfere with anesthesiological management whatsoever. However, as a human subject the study anesthesiologist will always have a more subjective assessment than a computer, which gives the ADSS advice. Nevertheless, our human-based ADSS setting may still give valuable results to understand the current limitations of the ADSS.

Incorporating the administration of fluids together with vasopressors and inotropes if indicated is an advancement of previously published computer-embedded closed-loop systems that basically focused on fluid management only without actively interfering with vascular tone and myocardial contractility. Not simultaneously controlling vascular tone and not integrating the effect of a fluid challenge on SVV may lead to volume overload, particularly with running background infusions. In a simulation

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References


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Authors’ contributions.—Arabella Fischer and Johannes Menger contributed equally to this paper.

Prediction of extubation failure in Intensive Care Unit: systematic review of parameters investigated

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ABSTRACT

INTRODUCTION: Extubation failure (EF) refers to the inability to maintain spontaneous breathing after removal of endotracheal tube. The aim of this review is to identify the best parameter to predict EF in adult intensive care patients.

EVIDENCE ACQUISITION: We searched for publications in PubMed (2000-2016). Studies of patients intubated and mechanically ventilated for more than 24 hours were included and divided in groups basing on the extubation method. 2x2 tables were performed to evaluate the sensitivity, specificity and the predictive values only for those parameters investigated in more than three studies. Studies were divided in groups, basing on time required to define EF (<24 hours, <72 or >72 hours), and EF percentage was calculated for each group.

EVIDENCE SYNTHESIS: On 443 potentially studies, 26 were included. Rapid Shallow Breathing Index (RSBI) and cough strength parameters were found in more than three studies. RSBI or cough strength parameter showed a sensitivity of 20-88.8% or 55.5-85.2%, a specificity of 68.5-94.8% or 24-49%, a positive predictive value (PPV) of 39.5-66.6% or 24-49% and a negative predictive value of 98-82% or 89.5-96.4%, respectively. EF rate was 12.5%, 15.3% and 22% in patients evaluated within 24 hours, 72 hours and over 72 hours, respectively.

CONCLUSIONS: This review shows that all parameters used to predict EF have a low PPV. Therefore, the limitation of use of such predictive tests may prolong unnecessarily the intubation and increase the unfavorable outcome. A prospective study involving all variables could be useful to predict the EF in ICU.


KEY WORDS: Respiration, artificial - Airway extubation - Cough.

Introduction

To decide whether and when to extubate mechanically ventilated patients after weaning is a constant challenge for the intensivist. Extubation failure (EF) is defined as inability to sustain spontaneous breathing after removal of the artificial device such as endotracheal or tracheostomy tube, and need for reintubation within a prespecified time window ranging from 24 hours1 to one week.2-6

Reintubation rates are about 10% to 15%7 in Intensive Care Unit (ICU) patients at low risk for EF, exceeding 25% to 30%7 in high-risk patients.
Predicting EF is a crucial challenge, since there is evidence that failure is associated with poor patient outcomes, independently of underlying illness severity, leading to prolonged mechanical ventilation, longer in ICU stay and higher mortality rates (25% to 50%). Nowadays many physicians base the extubation decision on clinical practice criteria without specific protocols. However, clinical criteria alone revealed a sensitivity and a specificity of 57% and 31% to predict EF, respectively. Many causative factors, which may occur simultaneously, contribute to explain postextubation clinical difficulties and the uncertainty about pathophysiology of extubation success. Factors predicting extubation success are studied individually or in scoring systems (Table I). However, the reliability of these parameters and tests is uncertain, with conflicting results. In literature parameters were studied individually or by using score systems. Nowadays it seems that no parameter, used as single test, could predict EF with adequate sensitivity and specificity. The aim of this systematic review was to identify which could be the best parameter to predict the EF in adult ICU patients.

### Evidence acquisition

We performed a systematic review. We searched PubMed for clinical terms referring to topics of interest: extubation failure parameters in ICU; extubation success parameters; predict extubation outcome; predictive values of extubation. We also searched on extubation with or without Spontaneous Breathing Trial (SBT) and finally terms that the authors sometimes use as a syn-onym for extubation such as “extubation failure” and “weaning outcomes.” The search was limited to publications from 2000 to 2016 to identify all possible international and national articles published in English or Italian. We included studies, based on a single parameter of EF, in adult patients (>18 years) who were mechanically ventilated over 24 hours and we selected prospective and retrospective studies, case series of 10 or more patients. We excluded case reports, ongoing studies, abstracts, reviews and articles that investigated a series of scoring systems. Studies focused on patients with tracheostomy, neuro or cardiac surgical patients, patients with neurodegenerative illness such as Guillain Barre Syndrome and myasthenia were also excluded.

The date of publication, study design and population, number of patients recruited, primary outcome, parameter method, conclusion stated in the included studies were recorded.

We analyzed the methodological quality of

### Table I.—Parameters to predict successful or unsuccessful extubation in ICU.7 9-15

<table>
<thead>
<tr>
<th>Parameter Category</th>
<th>Parameter</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood gas parameters</td>
<td>PH &gt; 7.35; P/F &gt; 150; PaCO2 &lt; 45 mmHg</td>
<td></td>
</tr>
<tr>
<td>Clinical parameters</td>
<td>GCS &gt; 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive fluid balance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hb &gt; 10 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BNP increasing</td>
<td></td>
</tr>
<tr>
<td>Ventilatory parameters</td>
<td>CPAP 5 cmH2O</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PS 5-7 cmH2O</td>
<td></td>
</tr>
<tr>
<td>Respiratory mechanics parameters</td>
<td>Vt &gt; 5 mL/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RSBI &lt; 10512</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PEF &lt; 60 L/min</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P0.1/MIP &lt; 0.3</td>
<td></td>
</tr>
<tr>
<td>Airway protection parameters</td>
<td>Moderate or abundant endotracheal secretions cough: absent or weak</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SV &gt; 2.5 mL/h</td>
<td></td>
</tr>
<tr>
<td>Airway patency parameters</td>
<td>CLt &lt; 110 mL</td>
<td></td>
</tr>
</tbody>
</table>

P/F: oxygen arterial pressure/inspiratory oxygen fraction; PaCO2: carbon dioxide pressure; CPAP: continuous positive pressure ventilation; BNP: brain natriuretic peptide; PS: pressure support; Vt: tidal volume; RSBI: Rapid Shallow Breath Index; PEF: peak expiratory flow; P0.1: airway occlusion pressure; MIP: maximal percentage of increase; SV: secretion volume; CLt: cuff leak test.

Figure 1.—Flow chart of papers screening.
Table II.—Relevant parameters found in the literature.16-38

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Authors and date</th>
<th>Study design and population</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vd/Vt</td>
<td>González-Castro A; 2011 Dec16</td>
<td>Prospective observational cohort study; 100 patients</td>
<td>General ICU</td>
</tr>
<tr>
<td>Cough strength</td>
<td>Kutchak FM; 2015 Jul-Aug17</td>
<td>Cross-sectional study: 135 patients</td>
<td>Neurological ICU</td>
</tr>
<tr>
<td></td>
<td>Smailes ST; 2013 Marc18</td>
<td>Prospective observational study: 125 patients</td>
<td>Medical ICU</td>
</tr>
<tr>
<td></td>
<td>Huang CT; 2013 Aug19</td>
<td>Retrospective study: 119 patients</td>
<td>Medical and Surgical ICU</td>
</tr>
<tr>
<td></td>
<td>Su WL; 2010 Apr20</td>
<td>Prospective study: 150 patients</td>
<td>Surgical and medical ICU</td>
</tr>
<tr>
<td>RSBI</td>
<td>Segal LN; 2010 Mar23</td>
<td>Prospective observational study: 72 patients</td>
<td>Medical and surgical ICU and cardiology ICU</td>
</tr>
<tr>
<td></td>
<td>Liu Y; 2010 Nov24</td>
<td>Prospective observational study: 113 patients</td>
<td>Medical intensive care unit</td>
</tr>
<tr>
<td></td>
<td>Danaga AR; 2009 Jun25</td>
<td>Prospective observational study: 73 patients</td>
<td>Surgical and medical ICU</td>
</tr>
<tr>
<td></td>
<td>Teixeira C; 2008 Dec26</td>
<td>Prospective study: 73 patients</td>
<td>Medical and surgical ICU</td>
</tr>
<tr>
<td>Vert</td>
<td>Seymour; 2008 Jan-Feb27</td>
<td>Prospective cohort study: 88 patients</td>
<td>Surgical ICU</td>
</tr>
<tr>
<td></td>
<td>Hernandez G; 2007 May28</td>
<td>Prospective observational study: 93 patients</td>
<td>Medical and surgical ICU</td>
</tr>
<tr>
<td>Occlusion pressures</td>
<td>Fernandez R; 2004 Feb29</td>
<td>Prospective observational multicenter study: 130 patients</td>
<td>Medical ICU</td>
</tr>
<tr>
<td></td>
<td>Bruton A; 2002 Mar-Apr30</td>
<td>Prospective study: 27 patients</td>
<td>Medical and surgical ICU</td>
</tr>
<tr>
<td>SBT trial</td>
<td>Cekmen N; 201131</td>
<td>Prospective, randomized, controlled trial; 40 patients</td>
<td>General ICU</td>
</tr>
<tr>
<td></td>
<td>Cohen J; 2009 Feb32</td>
<td>Prospective randomized controlled trial: 180 patients</td>
<td>Medical and Surgical ICU</td>
</tr>
<tr>
<td>WOB</td>
<td>Banner MJ; 2012 Feb33</td>
<td>Prospective study: 97 patients</td>
<td>Surgical ICU</td>
</tr>
<tr>
<td></td>
<td>Teixeira C; 2009 Dec34</td>
<td>A prospective cohort study in 2 medical-surgery ICU; 51 patients</td>
<td>Medical and surgical ICU</td>
</tr>
<tr>
<td>US</td>
<td>DiNino E; 2014 May35</td>
<td>Prospective observational study: 63 patients</td>
<td>Medical ICU</td>
</tr>
<tr>
<td></td>
<td>Jiang JR; 2004 Jul36</td>
<td>Prospective, observational study: 55 patients</td>
<td>Medical ICU</td>
</tr>
<tr>
<td>HRV</td>
<td>Huang CT; 2014 Jan37</td>
<td>Prospective observational study: 77 patients</td>
<td>Medical ICU</td>
</tr>
<tr>
<td>Gastric juice PCO2/ PaCO2</td>
<td>Uusar A; 2000 Jul38</td>
<td>Observational study: 68 patients</td>
<td>Medical ICU</td>
</tr>
</tbody>
</table>

Vd: dead volume; Vt: tidal volume; MEP: maximal expiratory pressure; Pmax: maximal inspiratory pressure; GCS: Glasgow Coma Scale; CPF: cough peak flow; CPF: involuntary cough peak flow; WCT: white card test; Hb: hemoglobin; exubation outcome; RC: reflex cough; VC: voluntary cough; CART: classification and regressive tree; RSBI30: RSBI recorded at 30 min of SBT; RSBI120: RSBI recorded at 120' of SBT; f respiratory frequency; MPI: maximal percentage of increase; smRSBI: serial measurement of RSBI PI: percentage of increase; PEF: peak expiratory flow; RSBI: Rapid Shallow Breath Index; VeRT: minute ventilation recovery time; RT: recovery time; RT50%/delta Ve: RT needed to divide Ve to half the difference between End-SBT-Ve and basal Ve; EF: extubation failure; RR: respiratory rate; Ve: minute ventilation; P0.1: occlusion pressure; SMIP: sustained
### Table: Parameters and Methods

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Parameters method</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>Vd/Vt</td>
<td>Vd/Vt=0.94 is a potent predictor of ES</td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>Others: RR, HR, Vt, P/F</td>
<td></td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>RC=PEF</td>
<td>PEF&lt;80 L/min and GCS are independent predictors of EF</td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>Others: MIP, MEP, GCS</td>
<td></td>
</tr>
<tr>
<td>EF= reintubation in ≤7 days</td>
<td>VC=CPF</td>
<td>CPF&gt;60 L/min and endotracheal secretions contribute to ES</td>
</tr>
<tr>
<td>EF= reintubation in any time during the study period</td>
<td>Cough effective and volume secretion</td>
<td>Cough effectiveness is the only variable independently predicting EO</td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>Others: RR, Ve, Vt, RSBI, Pimax, GCS</td>
<td></td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>RC=CPFi</td>
<td>CPFi&gt;58.5L/min is a good predictor of SE</td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>Others: RR, Ve, Vt, MIP, MEP, GCS, Sputum, RSBI</td>
<td></td>
</tr>
<tr>
<td>EF= reintubation or NIV in ≤48 h</td>
<td>RSBI-1;RSBI-30;RSBI-120</td>
<td>RSMRBI in patients with first f/VT ≤105 is unable to predict EF</td>
</tr>
<tr>
<td>EF= reintubation in ≤7 days</td>
<td>VERT</td>
<td>VERT&gt;5 min is correlated with EF</td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>RT50 deltaVe</td>
<td>RT%DeltaVe &gt;7 min is correlated with EF</td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>Others: VERT</td>
<td></td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>P0.1</td>
<td></td>
</tr>
<tr>
<td>EF= reintubation in ≤24 h</td>
<td>Others: RSBI, RSBI*P0.1</td>
<td></td>
</tr>
<tr>
<td>EF= reintubation in ≤24 h</td>
<td>SMIP</td>
<td>SMIP&gt;57.5 pressure time is significantly related to EO</td>
</tr>
<tr>
<td>UW= reintubation in ≤48 h</td>
<td>Others: peak MIP, Vt</td>
<td></td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>SBT mode: T-piece with 4 L/min oxygen vs. CPAP with PEEP&lt;.5 cmH2O, FIO2 &lt;0.4.</td>
<td></td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>RSBI during PSV and ATC</td>
<td>SBT with ATC is at least as effective as PSV in predicting patients able to maintain spontaneous breathing</td>
</tr>
<tr>
<td>EF= reintubation in ≤24 h</td>
<td>WOB</td>
<td>WOB&gt;10 J/min can predict ES</td>
</tr>
<tr>
<td>EF= reintubation or NIV in ≤48 h</td>
<td>Others: RR, RSBI, P/F, Vt, MV, Vd/ Vt, Crs</td>
<td>WOB variation is able to predict EO: EF=0.35±0.08 J/L vs. ES=0.22±0.11 J/L</td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>Others: RR, RSBI, P/F, Vt, MV, HR, PA, Mip, Crs</td>
<td></td>
</tr>
<tr>
<td>EF= reintubation in ≤48 h</td>
<td>Tdi</td>
<td>Δtdi%≥30% can be used to predict EO during PS and SBT</td>
</tr>
<tr>
<td>EF= reintubation in ≤24 h</td>
<td>Others: RSBI, PIM</td>
<td>MD&gt;1.1 cm can predict ES</td>
</tr>
<tr>
<td>EF= reintubation in ≤24 h</td>
<td>HRV pre-PSV, during PSV, postextubation</td>
<td>Incapability to increase HRV suggested a higher probability of EF</td>
</tr>
<tr>
<td>EF= reintubation in ≤24 h</td>
<td>DeltaPg-aCO2</td>
<td>After the stress test DeltaPg-aCO2&lt;12 mmHg is the best predictor of SE</td>
</tr>
</tbody>
</table>

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**Note:** 
- P0.1: airway occlusion pressure; MIP: maximal inspiratory pressure; f: respiratory frequency; PSV: pressure support ventilation; SBT: spontaneous breathing trial; CPAP: continuous positive pressure ventilation; PEEP: end expiratory pressure; FIO2: inspiratory oxygen fraction; ATC: Automatic tube compensation; UW: unsuccessful weaning; Wob: work of breathing; MV: minute ventilation; P/F: oxygen arterial pressure-inspiratory oxygen fraction; HR: heart rate; PA: arterial pressure; Crs: compliance of respiratory system; Tdi: Diaphragm thickness; NIV: noninvasive ventilation; LD: liver displacement; SD: splen displacement; MD: measured displacement; HRV: Heart rate VARIATION; Pco2: carbon dioxide pressure; SIMV: synchronized intermittent mandatory ventilation; SB: spontaneous breath; CV: vital capacity; PF: peak flow; FW: failed weaning; EF: extubation failure; ES: extubation success.
these studies using the “Quality Assessment of Diagnostic Accuracy Studies” (QUADAS) system only for those parameters investigated in three or more articles. This tool combines features derived from empirical evidence and expert opinion into a checklist of 14 items assessing risk of bias, applicability, and reporting quality, each of which should be scored a “yes,” “no” or “unclear”. On a total of 14 questions, a score of at least 10 “yes” was considered of high quality, while a score under 10 positive answers was considered low quality.10,11

We then performed 2x2 tables only for those parameters studied in three or more articles. Contingency tables were performed for results of three of the four papers on RSBI and for results of five of the seven papers on cough strength. Data used to achieve tables were extrapolated by original papers data or using inverse formulas, starting from the value of sensitivity and specificity of investigated parameter and the number of succeeded or failed patients extubation.

In literature, timing to define EF or success is variable: we divided articles by three time periods, <24 hours, <72 hours and ≥72 hours. Finally, we calculated the rate of EF for each group.

Evidence synthesis

The search yielded 443 potentially relevant publications. Figure 1 shows the screening methodology used in this review. The 26 eligible manuscripts organized on the bases of the parameter analyzed are listed in Table II.16-38

Cough strength parameter was studied in seven articles and RSBI in four manuscripts. The following parameters: dead space, volume minute recovery time, occlusion pressures, the changing of RSBI using different trial of spontaneous breathing, work of breathing, Ultra Sound (US) heart variation rate, gastric juice PCO2/PaCO2 and finally entropy of spontaneous peak flow and Tidal Volume, were studied in no more than two manuscripts, therefore we did not consider them.

We performed 2x2 tables for only three of the four studies on RSBI and five of the seven studies on cough strength. In the three excluded papers data were presented as median and interquartile range12 or mean and standard deviation13,14 and authors did not explain the values of sensitivity and specificity of the investigated parameter. Table III shows the predictive values of the parameters analyzed. RSBI was recorded as an absolute value,15 expressed as a percent change of RSBI during two hours or 30 minute of SBT,14,39 or RSBI times P0.1.40 We calculated a positive predictive value (PPV) of 40-67% for RSBI while a PPV of 24-49% for cough strength used as parameters to predict EF. Cough strength was evaluated as effectiveness of cough by evaluating the phlegm moving into the endotracheal tube,9,12 as involuntary and voluntary cough peak flow (CPFi)12,16,41 and as reflex cough peak expiratory flow.13,17,18

Table IV17-19,21-26,39 shows the Quadas Score for articles on cough strength and RSBI. We calculated a Quadas Score of 13 in two articles, a score of 12 in one, a score of 11 in six, a score of 10 in one and finally a score of 8 only in one article, under the cut-off for high quality. The reduction of the score in many studies correlates with error of applicability due to the fact that the low sensitivity and specificity of standard reference is not adequate for comparing the studied target condition.2,16,19 Additionally, the absence of blinding between the index test results and the reference standard contributed to reduce the total score due to review bias.

As regards the timing to define EF, we found that the EF rate was 13% for the patients evaluated within 24 hours, 15% for the patients evaluated until 72 hours from the extubation while 22% for patients followed for more than 72 hours.

Discussion

This systematic review combines data from three and five studies for RSBI and cough strength respectively, which could have better strength than the individual studies and demonstrates that all investigated parameters are factors related to reintubation but unable to be reliably used in clinical practice as unique predictor of EF. Deciding timing of extubation of a mechanically ventilated patient is a crucial decision in ICU, because it is associated with risks and complications. The SBT is described to be a good predictor for patients’ readiness for removal of mechanical ventilation and weaning.
outcomes, but is not a good predictor to evaluate the possibility of reintubation after removal of endotracheal tube or the ability to maintain airway patency.\textsuperscript{9} Currently there is no a gold standard parameter to identify the risk of EF. Furthermore there is no uniform consensus on the threshold value for each studied parameter. Our results show that RSBI and cough strength are not reliable enough to predict EF, because of a low PPV and sensitivity (Table III).

The low predictiveness of the studied parameters in the literature is due to the fact that different design and definitions are used. Differences can be found in the patients’ sample size, in the study setting (medical \textit{vs.} medical-surgical \textit{vs.} cardiac ICU \textit{vs.} Intensive Respiratory Care Unit) and weaning protocol.

Even if RSBI is actually the most used index to predict EF, there is still no consent on the right timing in which the calculation of the index has been found most reliable, since in clinical practice RSBI can be obtained with different methods.\textsuperscript{14, 39, 40} In similar way different approaches were adopted for studies on cough strength. In five studies\textsuperscript{9, 15, 16, 20} the patients were instructed to cough maximally, while another study\textsuperscript{13} used a mechanical stimulation to induce a cough reflex. Evaluating of Cough Peak Flow (CPF), recorded with different types of flowmeters,\textsuperscript{12, 41} is also used for assessment of cough strength. Finally, phlegm movement in the endotracheal tube has also been analyzed.\textsuperscript{9, 12}

Moreover the predictiveness of the EF parameters could depend on the kind of SBT trial. In several studies, authors concluded that the use of pressure support ventilation (PSV) or continuous positive airway pressure (CPAP) as a method of SBT can overstate the percentage of weaning success, reducing the predictive performance of EF parameters.\textsuperscript{21, 22}
We rework the data proves that when these parameters are analyzed to predict EF their PPv is very low (Table III). This means that the presence of effective cough or a low RSBI are highly associated with successful extubation, but are not able to prevent EF.

In the last five years some authors tried to elaborate different models including various parameters to predict extubation outcome, such as cough strength and amount of endotracheal secretions, cough effectiveness is the only variable independently predicting EF.

Table IV.—Table of Quadas Score.17-19, 21-26, 39

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Authors and date</th>
<th>Outcome</th>
<th>Parameters method</th>
<th>Conclusion</th>
<th>Quadas Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough strength</td>
<td>Kutchak FM; 2015 Jul-Aug17</td>
<td>EF= reintubation in ≤48 h</td>
<td>RC=PEF Others: RSBI, MIP, MEP, GCS</td>
<td>PEF&lt;80 L/min and GCS are independent predictors of EF</td>
<td>11/14</td>
</tr>
<tr>
<td></td>
<td>Smailes ST; 2013 Marc18</td>
<td>EF= reintubation in ≤48 h</td>
<td>VC=CPF Others: endotracheal secretion, RSBI</td>
<td>CPF&gt;60 L/min and endotracheal secretions contribute to EF</td>
<td>11/14</td>
</tr>
<tr>
<td></td>
<td>Huang CT; 2013 Aug19</td>
<td>EF= reintubation in ≤7 days</td>
<td>Cough effective and volume secretion Others: RR, Ve, Vt, RSBI, Pimax, GCS</td>
<td>Cough effectiveness is the only variable independently predicting EF</td>
<td>11/14</td>
</tr>
<tr>
<td>Beuret P; 2009 Jun21</td>
<td>EF= reintubation in ≤48 h</td>
<td>VC=PEF</td>
<td>PEF&lt;35 L/min is the sole factor significantly associated with EF</td>
<td>8/14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smina M; 2003 Jun22</td>
<td>EF= reintubation in ≤72 h</td>
<td>VC=PEF Others: RSBI, secretions, Hb</td>
<td>PEF&gt;60 L/min is a potent predictor of EF</td>
<td>11/14</td>
</tr>
<tr>
<td></td>
<td>Khamiees M; 2001 Oct39</td>
<td>EF= reintubation in ≤72 h</td>
<td>VC Others: WCT, RSBI, P/F, Hb, HR, RR, PA, Secretion</td>
<td>Cough strength and volume secretion, others: r/sBi, Hb, may be important PEO</td>
<td>11/14</td>
</tr>
<tr>
<td>RSBI Segal LN; 2010 Mar23</td>
<td>EF= reintubation in ≤24 h</td>
<td>MPI of RSBI at any time point during the 2-h SBT Others: Pl of RSBI assessed at 30 min</td>
<td>MPI of RSBI (increase ≥20% over 2-h period) predict SE</td>
<td>13/14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liu Y; 2010 Nov34</td>
<td>EF= reintubation in ≤48 h</td>
<td>CART system P0.1 × RSBI30, RSBI1</td>
<td>CART algorithm selected 3 discriminators (P0.1 × RSBI30, RSBI1, RSBI30), predict EF</td>
<td>13/14</td>
</tr>
<tr>
<td></td>
<td>Danaga AR; 2009 Jun25</td>
<td>EF= reintubation in ≤48 h</td>
<td>RSBI</td>
<td>RSBI≥76.5 breaths/min/L predict EF</td>
<td>12/14</td>
</tr>
<tr>
<td></td>
<td>Teixeira C; 2008 Dec36</td>
<td>EF= reintubation or NIV in ≤48 h</td>
<td>RSBI≥1-1; RSBI≤30; RSBI&gt;10</td>
<td>smRSBI in patients with first FVT ≤105 is unable to predict EF</td>
<td>10/14</td>
</tr>
</tbody>
</table>

PEF: peak expiratory flow; RSBI: Rapid Shallow Breath Index; GCS: Glasgow Coma Scale; CPF: cough peak flow; CPFi: involuntary cough peak flow; EF: extubation failure; ES: extubation success; EO: extubation outcome; VC: voluntary cough; Pimax: maximal inspiratory pressure; RR: respiratory rate; Ve: minute ventilation; MIP: maximal expiratory pressure; MEP: maximal inspiratory pressure; WCT: white card test; PEO: predictive extubation outcome; P0.1: airway occlusion pressure; CART: classification and regressive tree; RSBI≥30: RSBI recoded at 30' of SBT; RSBI120: RSBI recorded at 120' of SBT; f: respiratory frequency; Vt: tidal volume; MPI: maximal percentage of increase; Pl: percentage of increase; smRSBI: serial measurement of RSBI; SE: successful extubation; EF: extubation failure; NIV: noninvasive ventilation; HR: heart rate.

Interestingly EF rate was 22% for patients evaluated above 72 hours. Our result shows an higher EF rate compared to the extubation rates reported in literature (15-20%).2, 5, 7, 12, 41 The reason could be that the longer the time interval used to define EF is, higher the odds of failure. According with other studies16 we did not find significant difference in APACHE Score, age of patients or mean days of mechanical ventilation. From our results this difference does not depend on days of mechanical ventilation. In all analyzed studies except two,15, 16 predictive parameters were investigated on their power to predict extubation success. Publications findings showed a good PPV for each parameter so that the authors established that they were strong predictor for a successful extubation. Conversely, our reworking of data proves that when these parameters are analyzed to predict EF their PPV very low (Table III). This means that the presence of effective cough or a low RSBI are highly associated with successful extubation, but are not able to prevent EF.

In the last five years some authors tried to elaborate different models including various parameters to predict extubation outcome, such as cough strength and amount of endotracheal secretions, cough effectiveness is the only variable independently predicting EF.
as the Integrative Weaning Index\textsuperscript{23} or the Artificial Neural Network.\textsuperscript{24} We could argue that these studies lack of clinical parameters evaluation. Similarly, other authors focused only on the diaphragmatic strength as a parameter to predict the extubation outcome using new methodic as Ultrasound or Neurally Adjusted Ventilatory Assist ventilation (NAVA). Study conducted using a NAVA catheter have led to the elaboration of new indices used as surrogates of work of breathing that seem to have a good predictive power on extubation success.\textsuperscript{25, 26} Furthermore, the diaphragm thickness\textsuperscript{27} and the indirect movement of the abdominal organs due to the diaphragm movement by US had been considered new indices with an high predictive power of extubability.\textsuperscript{28} The US limit is that the technique is highly operator-dependent.\textsuperscript{27}

EF is often attributed to impaired gas exchange, respiratory muscle fatigue and an imbalance between respiratory load and ventilator demand. However, other clinical parameters play important roles: positive fluid balance, upper airway obstruction and the inability to clear the respiratory secretions and compromised mental status with GCS<10.\textsuperscript{29, 30} For these reasons a possible perspective is to combine weaning parameters, used to investigate the respiratory system with other parameters used to investigate mental status, airway protection, patency of airways and fluid balance.

Actually the unique model that considers either weaning parameters and clinical parameters to predict success of extubation is the modified Burns Score (m-BWAP).\textsuperscript{31} This tool evaluates parameters of patient’s weaning from the ventilator systematically and examines all parameters related to pulmonary function, gas changes, physiological condition. In a retrospective study, a m-BWAP Score > 0 was associated with successful extubation outcome.\textsuperscript{31} However m-BWAP Score lacks of information regarding on the patency of upper airways. The literature shows that upper airways obstruction due to endotracheal intubation, laryngeal edema and laryngeal injuries, granulation and vocal cord dysmotility occurs in about 5 to 15% of patients.\textsuperscript{32, 33} The cuff leak test which is used to detect the amount of airway passage between the tube and suspected swelling laryngeal structures, shows controversial results\textsuperscript{34, 36} and expert opinion suggests the use of direct visual control techniques.\textsuperscript{36} A future possibility could be to integrate this score with parameters evaluating upper airways obstructions, to predict the EF in a prospective observational study.

Limitations of the study
There are several limitations in this review. First, we excluded articles published in languages different from English or Italian\textsuperscript{37} and those studies based on weaning methods to predict the EF.\textsuperscript{19, 38} We also excluded articles lacking original data. Studies including patients with neurodegenerative illnesses were excluded because they could overestimate the EF percentage.

Finally, another limit of this study could be that we analyzed articles showing different study design, population setting and outcomes.

Conclusions
This review shows that all parameters used to predict EF have a low PPV. Therefore, the limitation of use of such predictive tests may prolong unnecessarily the intubation and increase the unfavorable outcome. A prospective study involving all variables could be useful to predict the EF in ICU.

Key messages
• Extubation failure (EF) is defined as inability to sustain spontaneous breathing after removal of the artificial airway and need for reintubation within a prespecified time window ranging from 24 hours to one week.
• Multiple causative factors contribute to explain the clinical difficulties raised by extubation and the persistent uncertainties about the pathophysiology of EF. At the moment there is no reliable parameter for extubation decision.
• The review shows that Rapid Shallow Breath Index and cough strength are not reliable enough to predict EF, because of low positive predictive value and sensitivity.
• Actually, m-Bwap Score is the unique model considering both weaning parameters and clinical parameters to predict EF but lacks information about the patency of upper airways.
• The cuff leak test detecting the patency of upper airways, shows controversial results and expert opinion suggests the use of direct visual control techniques.

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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.


Erector spinae plane block: a systematic qualitative review

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ABSTRACT
INTRODUCTION: The erector spinae plane (ESP) block is an interfascial block proposed to provide analgesia for chronic thoracic pain. It consists in an injection of local anesthetic in a plane between the transverse process and the erector spinae muscles group.

EVIDENCE ACQUISITION: We performed a systematic review of literature following the PRISMA Statement Guidelines. The bibliographic search was conducted on September 2018. We included articles indexed in MEDLINE, EMBASE, Cochrane Library and Google Scholar. Search terms included the following: “erector spinae plane block” OR “ESP block” OR “erector spinae block.” We identified 367 studies and after removal of 206 duplicates and exclusion of 18 records we manually searched 140 studies.

EVIDENCE SYNTHESIS: We identified four randomized controlled trials, but the endpoints were heterogeneous preventing a statistical analysis; we performed then a qualitative review of the literature. Studies showed lower use of opioids and a longer time to first analgesic requirement in the ESP group. In one study, ESP block was found to be as effective as epidural analgesia. ESP block has a wide range of clinical indications. Its mechanism of action is still not thoroughly understood. Only two reports presented complications caused by the block.

CONCLUSIONS: Although data suggests that ESP block is an easy and safe technique, more studies are needed to assess safety, complications rates and efficacy of this technique. In particular, we need well designed RCTs comparing ESP block to gold standard regional anesthesia technique. Nevertheless, ESP block is already a viable option for anesthesiologists all over the world.

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KEY WORDS: Nerve block - Spinal anesthesia - Thoracic wall - Conduction anesthesia.

Introduction

In the last decade the interest in regional anesthesia and in particular in interfascial plane blocks has increased exponentially.1 The idea of providing complete anesthesia for abdominal and thoracic surgery while avoiding both opioids and neuraxial techniques is fascinating.

Until a few years ago nerve and interfascial blocks were performed as landmark techniques, but the routine introduction of anesthesiology-dedicated ultrasound machines in the operating theaters favored their development. Ultrasound-guided regional anesthesia techniques have evolved from being used as the prerogative of locoregional anesthesia experts, to widely used in safe and well consolidated clinical practices. Consequently, many interfascial blocks are now
used for providing abdominal (as for example the transversus abdominis plane block, the rectus sheath block, the quadratus lumborum block) and/or thoracic analgesia (for example pectoral nerves block, serratus block).

In this framework, Forero et al. proposed in 2016 an interfascial block to provide analgesia to patients suffering from thoracic chronic pain consisting of an injection of local anesthetic inside the erector spinae plane (ESP). As stated by the authors in their original work, the discovery of this technique was casual, but subsequent observations showed that this “casual” technique had a wide range of possible indications not only to thoracic area but varying from chronic to acute traumatic pain, from thoracic to orthopedic surgery, from children to elderly patients. In this study, our aim is to review the technique, the indications and possible complications of the ESP block and furthermore we try to trace directions for future research.

Evidence acquisition

A review protocol was written before conducting this study and published on a prospective register of systematic reviews, PROSPERO, with identifier CRD42017084275.

We performed a systematic review of the medical literature following the PRISMA Statement Guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses) for the identification, screening, and inclusion of articles (Figure 1). The bibliographic search was conducted on September 5th, 2018 by one of the authors (ADC). In this review we included articles indexed by MEDLINE, EMBASE, Cochrane Library or Google Scholar. Search terms included the following: “erector spinae plane block” OR “ESP block” OR “erector spinae block.” We did not apply any restrictions on publication type, status, language or publication period in our search. Furthermore, we searched other relevant studies by consulting references and citations.

The articles so identified were then divided in two groups:

- randomized controlled trials (RCTs), non-randomized controlled trials or observational studies involving at least 10 participants per arm to assess the block characteristics. We aimed to check the following aspects: 1) pain scores; 2) opioid consumption; 3) time to first analgesic requirement; 4) sensory block duration; 5) opioid related adverse effects (postoperative nausea and vomiting (PONV), pruritus and sedation); 6) patient satisfaction; 7) block-related complications. RCTs quality were evaluated with Jadad score while other studies quality with at least 10 participants per arm was evaluated with NOS score;

- all other studies such as studies with less than 10 participants per arm, non-full articles (e.g., society abstracts), letters to editors, editorials, case reports, case series, special articles, expert reports and reviews were included in group 2 and used to describe and discuss the techniques, review their indications, and identify any advantages or complications of these techniques.

The quality of evidence was evaluated using the Oxford Center for Evidence-Based Medicine 2011 Levels of Evidence methodology.

Evidence synthesis

We identified 367 unique articles during our bibliographic research that were eligible according
to our protocol criteria. Two hundred and six were duplicate articles and were excluded, all other 158 full-text articles were read and examined. Among the examined articles, 18 were not pertinent to ESP block and were excluded and 14 articles were excluded because they did not provide novel information, the remaining 126 articles were then eligible for this review.

We found four papers (RCTs) classified in group 1 (Table I). Considering the low number of the RCTs and the heterogeneity of the data, a meta-analysis was not performed. Instead, we conducted a qualitative review of the studies.

Overview and main findings of group A papers are summarized in Table II and III. All the remaining 122 papers were classified in group 2 and analyzed with the aim to describe the overview of ESP anatomy and to discuss technique, indications, advantages and complications.

Group 1 results

**Opioid consumption and opioid related side effects**

Three of the studies compared single shot ESP block and general anesthesia to general anesthe-

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**Table I.---Overview table of group 1 papers.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Groups</th>
<th>Study design</th>
<th>Level of evidence</th>
<th>Jadad Score</th>
<th>Surgery</th>
<th>N. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krishna (2018)</td>
<td>GA with bilateral ESP blocks</td>
<td>RCT</td>
<td>1b</td>
<td>3/5</td>
<td>Elective cardiac surgery with cardiopulmonary bypass</td>
<td>110</td>
</tr>
<tr>
<td>Gürkan (2018)</td>
<td>GA with unilateral ESP block</td>
<td>RCT</td>
<td>1b</td>
<td>2/5</td>
<td>Elective unilateral breast cancer</td>
<td>50</td>
</tr>
<tr>
<td>Tulgar (2018)</td>
<td>GA with bilateral ESP block</td>
<td>RCT</td>
<td>1b</td>
<td>3/5</td>
<td>Laparoscopic cholecystectomy</td>
<td>32</td>
</tr>
<tr>
<td>Nagaraja (2018)</td>
<td>GA with continuous thoracic epidural analgesia (TEA)</td>
<td>RCT</td>
<td>1b</td>
<td>2/5</td>
<td>Adult elective cardiac surgical patients underwent median sternotomy</td>
<td>50</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial.

**Table II.---Comparison between endpoints from group A papers.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Local anesthetic</th>
<th>Pain score</th>
<th>Opioid consumption</th>
<th>Time to first analgesic requirement</th>
<th>Sensory block duration</th>
<th>Opioid-related adverse effects</th>
<th>Patient satisfaction</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krishna (2018)</td>
<td>3 mg/kg 0.375% ropivacaine</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Gürkan (2018)</td>
<td>20 mL 0.25% bupivacaine</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Tulgar (2018)</td>
<td>20 mL of 0.375% bupivacaine</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
<tr>
<td>Nagaraja (2018)</td>
<td>TEA:15 mL of 0.25% bupivacaine</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td></td>
</tr>
</tbody>
</table>

Crosses mark reported endpoints.

**Table III.---Comparison between results from group A papers.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Pain</th>
<th>Opioids</th>
<th>Time to analgesic</th>
<th>Opioid adverse effects</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Postop</td>
<td>6 h</td>
<td>12 h</td>
<td>24 h</td>
<td>Intraop</td>
</tr>
<tr>
<td>Krishna (2018)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>=</td>
</tr>
<tr>
<td>Gürkan (2018)</td>
<td>=</td>
<td>=</td>
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<td>=</td>
<td>+</td>
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<td>Tulgar (2018)</td>
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</tr>
<tr>
<td>Nagaraja (2018)</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>+</td>
</tr>
</tbody>
</table>

+: favors ESP block groups; =: no differences between the two groups.
sia alone. Singh et al., 8 instead, compared continuous bilateral ESP block to continuous thoracic epidural analgesia (TEA) for postoperative pain management in cardiac surgery.

All four RCTs5-8 presented in this review analyzed both opioid side effects and consumption. In three studies5,7,8 opioids consumption was lower in ESP block groups compared to control groups. In particular Krishna et al.5 found a significantly lesser fentanyl requirement during intraoperative (149.43±4.97 vs. 721.98±18.82 µg) and postoperative period (P=0.001). Difference in opioids usage was significant for eight hours from the extubation but no difference was recorded in the following hours.

Gürkan et al.6 found a lesser morphine consumption at every timing during the first 24 hours in the ESP group compared to control group (5.76±3.8 vs. 16.6±6.92 mg) but no data about intraoperative opioids was reported. In the study of Tulgar et al.7 fentanyl dosage (6.66 ±11.44 vs. 32.33±22.69 µg) and tramadol dosage (60±52 vs. 99±48 mg) were lesser in ESP group compared to the control group, however the difference was not significant after the first twelve postoperative hours. Conversely, Nagaraja et al.8 reported as not statistically significant both intraoperative (330±82.92 vs. 364.4±105.39 µg) and postoperative difference in fentanyl dose.

All studies reported that no statistically significant complications occurred, however, only two7,8 presented specifically opioid related complications such as nausea and vomiting.

Pain scores

The Numerical Rating Scale (NRS) or the Visual Analog Score (VAS) were used in all the four studies for pain evaluation. Krishna5 found lesser pain corresponding to a lower NRS score in ESP group at every NRS point measurement (every two hours for the first twelve hours). Gürkan6 found no statistical difference in terms of NRS scores (every six hours for the first twenty-four hours). Tulgar et al.7 registered NRS both at rest and on movement every three hours for the first twenty-four hours, however NRS resulted statistically lower in ESP group only for the 0-3 hour time frame. Nagaraja et al.8 assessed pain for the first two days, comparable VAS scores were recorded for the first twelve hours while VAS scores were significantly lower in TEA group at 24, 36, and 48 hours; however it is important to note that the average of VAS score in every group was ≤4 both at rest and during cough.

Time to first analgesic requirement

Only Krishna et al.5 reported the time to first analgesic (six hours in the control group vs. 10 hours in the ESP group). However, no statistical analysis was conducted.

Sensory block duration and patient satisfaction

Patient satisfaction and sensory block duration or extension were not formerly analyzed in any of the group 1 studies.

Block-related complications.

All studies reported no block related complications.

Group 2 results

Overview of ESP anatomy

Although a comprehensive discussion of this topic falls outside the purpose of our review, we will here try to highlight the fundamental anatomical aspects to understand how ESP block could provide analgesia. An extensive and interesting review of the anatomy of the dorsal anatomical region, in particular of the thoracolumbar fascia, can be found in the work by Willard et al.9 At the beginning we present the path of the spinal nerves2 and after that we give an overview of ESP and muscles.

Every upper thoracic spinal nerve splits into two rami, a dorsal one and a ventral one, at its exit from the intervertebral foramen. The dorsal ramus transits posteriorly through the costotransverse foramen (a window bordered superiorly by the transverse process, inferiorly by the underlying rib, laterally by the superior costotransverse ligament, and medially by the lamina and facet joint) and ascends into the erector spinae muscle than, it divides into lateral and medial branches. The medial branch continues to ascend through the rhomboid major and trapezius muscles into a superficial location before ending in a posterior
cutaneous branch. The ventral ramus travels laterally becoming the intercostal nerve, firstly running deep to the internal intercostal membrane and then moving into a plane between the internal and innermost intercostal muscle on the inner face of the rib. The lateral cutaneous branch arises from the intercostal nerve next to the angle of the rib and this branch then ascends into a superficial location.

There are three groups of muscles involved in this block: erector spinae muscles group, transverso-spinal muscles group and levatores rostrum. Erector spinae muscles are not a single muscle, but a really complex muscular group formed by iliocostalis muscles, longissimus muscles and spinalis muscles. These muscles link bone components of the back to each other: the spinous process to spinous process, rib to rib and transverse process to transverse process. Deep to this group of muscles, we find the transverso-spinal group of muscles connecting the transverse processes to the spinous processes (semispinalis, multifidus, rotatores), and deeper still are the levatores rostrum, originating from the transverse processes and inserting into the ribs. Together, all these muscles act as a geometrical structure that would facilitate the spread of local anesthetic.

Another interesting aspect is well explained in a letter by Hamilton et al. In a simplified view, the erector spinae muscles can be visualized as two paired elliptical cylinders, one on each side of the vertebral column. Each “cylinder” is surrounded by a retinacular fascial sheath, separating it from the other muscle compartments of the thoracoabdominal cavity. This fascial sheath (which extends cranially from the nuchal fascia to the sacrum caudally) is characterized by multiple perforations in its anterior wall and is anteromedially intermittently tethered to bony structures such as the spinous processes and transverse processes of the vertebrae it crosses.

Technique

As already stated, ESP block was first described by Forero et al. Practically, it consists of an ultrasound guided local anesthetic injection between the erector spinae muscle and the underlying transverse process. Operatively, the authors described the following procedure: with patient in a sitting position and after identification of the target vertebral level, a high-frequency linear ultrasound transducer is placed in a craniocaudal orientation 3 cm lateral to the spinous process. Three muscles are identified superficial to the hyperechoic transverse process shadow as follows: trapezius, rhomboid major, and erector spinae (Figure 2). A needle is then inserted in a cephalad-to-caudad or in caudad-to-cephalad direction until the tip lays in the interfascial plane between rhomboid major and erector spinae muscles; the correct position of the needle is confirmed by a linear spread of fluid between the muscles upon injection.

However, the same group of authors found the injection in the sheath plane deep to erector spinae muscle (using the transverse process as target) to be preferable, and they now recommend only this approach. Another important reason to use this approach of deep injection is that the rhomboid major muscle has its inferior border at T6, which makes its use as a sonographic landmark impossible at lower levels.

Of note, some authors argued that an injection targeted at the transverse process could miss the erector spinae sheath and prevent the spread of local anesthetic. However, Chin et al. still propose the transverse process as a safe and easy-to-identify target, as long as a linear spread of injectate travelling in both a cranial and a caudal direction from the point of injection is visualized.
As for the position of the patient, ESP block has been overwhelming executed in sitting position; however, it has been successfully performed also in patients in prone\textsuperscript{15, 16} and lateral\textsuperscript{17} position.

On a final note, ESP block has been described as a single shot technique, however its use as a continuous technique has been reported both in adult\textsuperscript{16-20} and in pediatric\textsuperscript{17} patients.

**Mechanism of action and spread of local anesthetics**

Since the first publication of Forero \textit{et al.} in 2016\textsuperscript{2} eleven studies have investigated the mechanism of action and spread of local anesthetic after the ESP block both in cadavers and in clinical patients.\textsuperscript{21-26} Five of these studies were performed on fresh unembalmed cadavers,\textsuperscript{27-31} a total of 28 cadavers were involved. The investigators performed the ESP block in prone position in a cranial-to-caudal direction, using a high frequency linear probe with an in-plane technique. In the original publication Forero \textit{et al.} have supposed that the spread of local anesthetic to the paravertebral space occurred through the costotransverse foramen (Figure 3), which acted as a “gate” through which the anesthetic reached the ventral rami of the spinal nerves. In two separate studies involving a total of 14 cadavers\textsuperscript{27, 31} it was found that both the ventral and dorsal rami were involved by the spread of dye, but it was not so clear that the costotransverse foramen was the “gate,” and in particular it was not possible to verify a clear channel through which the dye diffuses towards the paravertebral space. Recently Ivanusic \textit{et al.} have published an extensive study on ten cadavers.\textsuperscript{30} Surprisingly, the authors report that only one case out of 20 ESP block performed showed an involvement of the ventral rami. The authors claim that the deep muscles of the spine, the transverso-spinal group of muscles, prevent the spread of dye through the costotransverse foramen. They propose a different mechanism of action, no longer similar to a paravertebral block, but rather similar to a combination of multiple intercostal blocks, thanks to the extensive lateral and longitudinal diffusion that they found in their study. Adhikary \textit{et al.} stated that this mechanism of action may act as an additional mechanism of action for analgesia of the anterolateral thoracic and abdominal wall.\textsuperscript{28}

Despite the study of Ivanusic \textit{et al.}, all of the others clinical and cadaver studies that were investigated with the use of radiological instruments have shown that the spread of the contrast agent does reach the neural foramina or the paravertebral/epidural space.\textsuperscript{21-26}

In all of the cadaveric studies there is an evidence of extended diffusion of dye both in craniocaudal and in medial-to-lateral directions. Adhikary \textit{et al.}\textsuperscript{28} reported after anatomical dissection an extended craniocaudal extent of dye staining until 14 vertebral levels deep to erector spinae muscles group. Ivanusic \textit{et al.}\textsuperscript{30} found that when the ESP block was performed at the fifth thoracic vertebra with 20 mL of dye the extent of dye staining deep to erector spinae muscles was toward the first to sixth thoracic vertebra in 75% to 100% of injections. Instead the extent of dye deep to erector spinae muscles from the seventh to the twelfth thoracic vertebra only appeared in 30% to 10% of injections. In the study of Vidal \textit{et al.}\textsuperscript{27} it was found that the block had a mean of 4.6 intercostal spaces stained, with a maximum of seven and a minimum of three, these results are similar to those reported by Yang \textit{et al.}\textsuperscript{31}

In the study of Ivanusic \textit{et al.}\textsuperscript{30} during the anatomical dissection the dye was found in some cases beyond the angle of the rib, in particular the author stated that the costal attachments of the iliocostalis muscle created a sort of boundary that could limit the lateral spread of the dye. Similar to the craniocaudal extent the dye spread lat-

![Figure 3.—View of the costotransverse foramen after removal of erector spinae muscle group.](image-url)
erally at or above the injection level, instead the dye was found deep to the iliocostalis muscles between the first to the sixth thoracic vertebra in 45% to 85% of injections. Adhikary et al.28 have evaluated the spread of dye both with anatomical dissection and magnetic resonance imaging and found that lateral spread of dye was found as far as 10 cm from the midline near the level of injection between the fifth and the seventh thoracic vertebra.

At this time there is not a clinical study designed to evaluate the sensorial distribution of the ESP block, De Cassai et al.32 have reported a brief review to evaluate how many milliliters of local anesthetic was necessary for the sensory block of one dermatome. They found that is needed about 3.4 mL to cover one dermatome, however further studies are needed to answer this question.

**Local anesthetic dose and volume**

The ESP block is suitable for both short and long-acting local anesthetics. The maximum volume of local anesthetic injected in the ESP performed unilaterally was 35 milliliters33 in a patient that suffered post-thoracotomy pain syndrome. When ESP was performed bilateral the maximum volume of LA was 60 mL29, 34 The ESP block was described with single shot or continuous technique. In one case report the catheter was maintained for more than sixty days.35 Catheter could be used in continuous infusion or with intermittent bolus18, 35-38 ranging from 5 mL35 to 20 mL.18, 38 When this regional anesthesia technique was used with continuous catheter the infusion rate ranged from 5 mL/h39 to 14 mL/h.40

ESP block was used also in pediatric population in single shot technique, the volume of local anesthetic ranged from 0.2 mL/kg41 to 0.5 mL/kg42-44 when catheters were positioned the infusion rate ranged from 2 mL/h45 to 4 mL/h.46 A brief overview of local anesthetics and volumes used for the block are reported in Table IV.2, 5, 6, 8, 12, 15-20, 22-24, 30, 33, 35, 36, 38-43, 46-59

**Clinical indications**

ESP block has been used for a wide range of indications varying from carotid endarterectomy to hip surgery. A brief overview of clinical indication is reported in Table V.2, 5-8, 12, 15-17, 19-25, 29, 33, 35-40, 42-45, 47-51, 53-68 while an extensive overview is available as online supplement together with the extended bibliography (Supplementary Digital Material 1: Supplementary Table I).

**Complications**

Only two papers54, 68 reported complication linked to ESP block (pneumothorax).

However, we have to highlight also an involuntary motor block47 caused by low thoracic ESP block and failure of the technique as possible complications associated with the block.

<table>
<thead>
<tr>
<th>Local anesthetic</th>
<th>Concentration</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>0.5%</td>
<td>20 mL24, 30</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.25%</td>
<td>15 mL2, 16 (a), 20 mL2, 6, 12, 15, 19, 30, 47, 48 0.5 mL/kg42, 49 (a), 30 mL43, 50</td>
</tr>
<tr>
<td></td>
<td>0.375%</td>
<td>20 mL7, 30 mL51</td>
</tr>
<tr>
<td></td>
<td>0.5%</td>
<td>10 mL52, 20 mL22, 35, 53 (b)</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>0.25%</td>
<td>8 mL17 (a), 20 mL54</td>
</tr>
<tr>
<td></td>
<td>0.375%</td>
<td>20 mL18</td>
</tr>
<tr>
<td></td>
<td>0.75%</td>
<td>20 mL15 (b)</td>
</tr>
<tr>
<td></td>
<td>0.375%</td>
<td>20 mL36, 57</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>0.125%</td>
<td>30 mL20</td>
</tr>
<tr>
<td></td>
<td>0.2%</td>
<td>0.3 mL/kg58</td>
</tr>
<tr>
<td></td>
<td>0.25%</td>
<td>0.2 mL/kg41 (a), 10 mL46 (a)</td>
</tr>
<tr>
<td></td>
<td>0.375%</td>
<td>3 mg/kg6 (a), 10 mL59, 20 mL40</td>
</tr>
<tr>
<td></td>
<td>0.5%</td>
<td>10 mL39, 20 mL23, 36 (a), 25 mL33</td>
</tr>
<tr>
<td></td>
<td>0.75%</td>
<td>20 mL18</td>
</tr>
</tbody>
</table>

(a): pediatric patient; (b): used for anesthetic purposes.
Table V.—ESP block indications, 2, 5-8, 12, 15-17, 19-25, 29, 33, 35-40, 42-45, 47-51, 53-68

<table>
<thead>
<tr>
<th>Indications</th>
<th>Statement of evidence</th>
<th>RCT</th>
<th>Case series</th>
<th>Case report</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute and chronic pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute neuropathic pain</td>
<td>5</td>
<td></td>
<td>+15, 50</td>
<td></td>
</tr>
<tr>
<td>Acute vertebral fracture</td>
<td>5</td>
<td></td>
<td>+12, 60</td>
<td></td>
</tr>
<tr>
<td>Acute burn injury</td>
<td>5</td>
<td></td>
<td>+61</td>
<td></td>
</tr>
<tr>
<td>Chronic neuropathic pain</td>
<td>4</td>
<td></td>
<td>+2, 57</td>
<td></td>
</tr>
<tr>
<td>Chronic thoracic pain, cancer</td>
<td>4</td>
<td>+24, 31</td>
<td>+19, 35</td>
<td></td>
</tr>
<tr>
<td>Chronic thoracic pain, surgery</td>
<td>4</td>
<td>+33</td>
<td>+62</td>
<td></td>
</tr>
<tr>
<td>Chronic abdominal pain, surgery</td>
<td>5</td>
<td></td>
<td>+21</td>
<td></td>
</tr>
<tr>
<td>Chronic shoulder pain</td>
<td>5</td>
<td></td>
<td>+22</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiothoracic surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracic surgery, open</td>
<td>4</td>
<td></td>
<td>+51</td>
<td>+17, 45, 58</td>
</tr>
<tr>
<td>Thoracic surgery, VATS</td>
<td>4</td>
<td></td>
<td>+63</td>
<td>+23</td>
</tr>
<tr>
<td>Pneumothorax surgery</td>
<td>4</td>
<td></td>
<td>+56</td>
<td></td>
</tr>
<tr>
<td>Thoracic wall surgery</td>
<td>4</td>
<td></td>
<td>+12, 16</td>
<td></td>
</tr>
<tr>
<td>Lung transplant</td>
<td>5</td>
<td></td>
<td>+64</td>
<td></td>
</tr>
<tr>
<td>Rib surgery/fractures</td>
<td>4</td>
<td></td>
<td>+37</td>
<td></td>
</tr>
<tr>
<td>Breast surgery</td>
<td>1b</td>
<td>+6</td>
<td>+60</td>
<td>+54</td>
</tr>
<tr>
<td>Esophagogastroplasty</td>
<td>5</td>
<td></td>
<td></td>
<td>+20</td>
</tr>
<tr>
<td>TA-TAVI, LVAD</td>
<td>4</td>
<td></td>
<td>+48</td>
<td></td>
</tr>
<tr>
<td>Carotid endarterectomy</td>
<td>4</td>
<td></td>
<td>+55</td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>1b</td>
<td>+5, 8</td>
<td>+36</td>
<td></td>
</tr>
<tr>
<td><strong>Abdominal surgery</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrectomy, laparoscopy/open</td>
<td>4</td>
<td></td>
<td>+65</td>
<td></td>
</tr>
<tr>
<td>Renal transplantation</td>
<td>5</td>
<td></td>
<td>+65</td>
<td></td>
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<tr>
<td>Hepatic resection</td>
<td>4</td>
<td></td>
<td>+66</td>
<td></td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>5</td>
<td></td>
<td>+65</td>
<td></td>
</tr>
<tr>
<td>Percutaneous nephrolithotomy</td>
<td>5</td>
<td></td>
<td>+59</td>
<td></td>
</tr>
<tr>
<td>Cesarean section</td>
<td>5</td>
<td></td>
<td>+47</td>
<td></td>
</tr>
<tr>
<td>Bariatric surgery</td>
<td>4</td>
<td></td>
<td>+67</td>
<td></td>
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<tr>
<td>Inguinal hernia</td>
<td>4</td>
<td></td>
<td>+49</td>
<td></td>
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<tr>
<td>Cholecystectomy</td>
<td>1b</td>
<td>+7</td>
<td>+42</td>
<td></td>
</tr>
<tr>
<td>Ileostomy closure</td>
<td>5</td>
<td></td>
<td>+53</td>
<td></td>
</tr>
<tr>
<td>Ventral hernia</td>
<td>4</td>
<td></td>
<td>+29</td>
<td></td>
</tr>
<tr>
<td>Abdominoplasty</td>
<td>5</td>
<td></td>
<td>+40</td>
<td></td>
</tr>
<tr>
<td>Duodenal web</td>
<td>5</td>
<td></td>
<td>+44</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amputation</td>
<td>5</td>
<td></td>
<td>+39</td>
<td></td>
</tr>
<tr>
<td>Hip surgery</td>
<td>4</td>
<td>+25, 38</td>
<td>+43</td>
<td></td>
</tr>
<tr>
<td>Vertebral surgery</td>
<td>4</td>
<td></td>
<td>+68</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

ESP block seems to be a hot topic in regional anesthesia, with more than 130 papers published in less than three years, however this review points out that our knowledge about this block is only at the beginning: only four RCTs of limited quality have been completed and published so far.

Researchers are rapidly trying to fill this knowledge gap; to date, seventeen RCTs involving ESP block are registered on ClinicalTrials.gov. These studies will investigate various open questions regarding ESP block: clinical indications and effectiveness (NCT03652103, NCT03398564, NCT03515434, NCT03413163), equivalence with other interfascial blocks (NCT03619447, NCT03508544, NCT03508531, NCT03593642) and other locoregional technique (NCT03471442, NCT03504371), the use in pediatric population (NCT03627897) and effects of adjuvants on the block (NCT03476642). We will wait with curiosity the results of these studies.

Current evidence suggests that the ESP block has an important effect on perioperative wellness when compared to general anesthesia alone, constantly reducing the opioids consumption and that compared to the thoracic epidural
it performs at least as well in perioperative analgesia.

The ESP block is an easy to perform and to learn technique with unique features compared to other interfascial blocks. Target point is a bone structure\(^2\) making the block execution really safe (only two pneumothoraces have been reported so far)\(^{54, 68}\) and it is the nearest interfascial block (excluding retrolaminar block) to the neuraxis.

The ESP block is executed close enough to neuraxis to spread in paravertebral and epidural space but at the same time far away to be executed also in suboptimal hemostatic conditions. Although there is still debate in the scientific community about the constancy and reliability of spread into paravertebral and epidural space\(^3\) this is a fascinating possibility that needs more formal investigation.

As stated above, complications have been sporadically reported. However, we can suppose that other complications can be associated to the ESP block, in particular: local anesthetic systemic toxicity, hematomas, splanchnic organs punctures, epidural or paravertebral injection.

Failure of the technique is possible especially when it is used as a unique anesthetic technique or visceral innervation is involved. At the end of the day ESP block mimics the effect of a paravertebral block but it is not a paravertebral block; and as Ueshima clearly showed,\(^69\) this possibility has to be taken into account.

How the block works is a question without a definitive answer yet. The wide spread inside the ESP is clearly not sufficient to justify the clinical effects on visceral pain reported by many authors. The supposed spread inside paravertebral space, whereby the ESP block was assimilated to a paravertebral block was called into question in the study by Ivanusic et al.\(^30\)

This study supposes an alternative mechanism to explain the clinical efficacy of the ESP block that involves the spread of LA to the lateral cutaneous branches of the intercostal nerves instead of to the ventral rami through the costo-transverse foramen.

While the exact pathways have yet to be defined, we think that the ESP block involves both the ventral and dorsal rami of the spinal nerves.

We think that on the basis of our clinical experience and on the clinical studies that reported clear involvement of epidural and paravertebral spread of LA by radiological images,\(^21, 22, 25\)

Limitations of the study

Our review has some major limitations that we have to discuss. First of all, this is a qualitative review because of the limited quality of the RCTs available. Furthermore, the heterogeneity of end-point of these studies makes performing a meta-analysis quite difficult. The short time frame since block description can be seen as the major limit of our work. However, we believe that it is important to summarize actual knowledge to understand the wide range of clinical usage of the ESP block, possibly its efficacy, and to point out objectives for future research directions.

Conclusions

The ESP block was first described less than three years ago. Since then, many steps have been taken to understand and explain the potentials of this technique, revealing different indications, mechanisms of action and effectiveness in both adult and pediatric populations.

Nowadays research is focusing into two directions: on one side CT, MRI and cadaveric studies are needed to understand the exact mechanism and the site of action of the block that it is still not thoroughly understood. On the other side clinical studies are expanding clinical indications and investigating the safety and effectiveness of the block.

However, to date, only four RCTs are available in literature and our knowledge is based mostly on case report and case series. For this reason, it is not possible to make a solid recommendation for a routine use of ESP block, but the next RCT studies on the efficacy, safety and non-inferiority of the ESP block compared to the paravertebral block or epidural anesthesia will tell us if the ESP block will definitely address this question. However, the growing number of studies and the increasing worldwide use of this anesthetic technique in all parts of the world, suggest that the ESP block is de facto another option available in the anesthesiologist’s armamentarium.
**Key messages**

- ESP block is an easy-to-perform and relatively safe technique. It consists of an ultrasound guided local anesthetic injection in a plane between the erector spinae muscle and the underlying transverse process.
- ESP block has an important effect on perioperative wellness when compared to general anesthesia alone.
- While the exact pathway has not yet been clearly defined, it seems reasonable to say that the ESP block involves both the ventral and dorsal rami of the spinal nerves.
- Our knowledge about this block is still very limited and further research is needed.

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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.

Authors’ contributions.—Alessandro De Cassai has conceived and designed the presented study alongside Tommaso Tonetti, and he has also performed literature search and data analysis, and written the manuscript. Daniele Bonvicini has made substantial contributions to data interpretation, written and edited the manuscript. Christelle Correale has helped with data processing and manuscript editing. Ludovica Sandei has written and edited the manuscript. Serkan Tulgar has supervised the study.

Comment in: Roberts S, Engelhardt T. Erector spinae plane block: the only block you need to know or the poor man’s paravertebral? Minerva Anestesiol 2019;85:233-5. DOI: 10.23736/S0375-9393.19.13578-X.


For supplementary materials, please see the HTML version of this article at www.minervamedica.it
EXPERTS’ OPINION

Postpartum chronic pain

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ABSTRACT

Postpartum chronic pain is a clinical reality which affects 6.1% to 11.5% of women after delivery and affects their recovery. The large range of incidence observed in the literature relies on criteria used to define chronic postpartum pain. The features depend on the type of delivery. Cesarean delivery which rate is increasing worldwide seems currently associated with lower risk of chronic postpartum pain, specifically chronic pelvic pain. Further chronic scar pain which often involves a neuropathic component is often of mild intensity. In opposite, after vaginal delivery, chronic pelvic pain and perineal pain have an important negative impact on women’s mood and quality of life. As for any chronic pain, individual risk factors account more than degree of tissue trauma. From actual reports in the field, better pain education of both women and health care providers might help to reduce the problem.

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Key words: Chronic pain - Postpartum period - Cesarean section.

Childbirth is a major event in life, associated with both physical and psychological changes which may affect the woman quality of life. Although childbirth may be considered as a natural process, some deliveries necessitate instrumentation and/or surgical intervention and the possibility of persistent pain secondary to the physical trauma of delivery should not be ignored. A growing recognition of the burden of chronic postsurgical pain (CPSP) has risen. Its emerging importance has been supported by CPSP inclusion in the upcoming version of the International Classification of Diseases (ICD-11) under the joint efforts of IASP (International Association for the Study of Pain) and WHO (World Health Organization).1 CPSP interferes rehabilitation in a time when Enhanced Recovery After Surgery (ERAS) programs are promoted including after delivery.2 CPSP is often associated to chronic use of analgesics like opioids and there is currently a growing concern about persistent opioid use after not only major but also minor surgical procedures including cesarean deliveries.3 Also, as the initial event is obvious, CPSP prevention is now considered an indicator of the quality of health cares. The awareness about long term maternal physical and emotional health problems (two major contributors to chronic pain) after childbirth is increasing since the first 2004 report of CPSP after cesarean section,4 with recent study including a 5-years follow-up.5 The present review about postpartum chronic pain is aimed to summarize current knowledge in the field.

Postpartum chronic pain: did the prevalence change over time?

In 1998, Crombie6 underlined that 22.5% of the patients attending Pain Clinics attributed their pain to a previous surgery. Since then, numerous studies have been published which results can be summarized as following: “CPSP occurs in one or
two of 10 surgical patients and becomes an intolerable pain condition after one of every 100 operations,” an incidence which has not changed over time. Any surgical procedure and tissue trauma can cause long-lasting pain. The large range of CPSP incidence observed in the literature relies on surgical techniques, patients population and criteria used to define CPSP. The use of a common updated definition should help to reduce divergences in CPSP incidence. A retrospective study found 6.1% of women with significant pain related to delivery at 2.3 year. A recent systematic review (15 studies including 4475 patients) about “wound CPSP” after cesarean section (CS) revealed a clinically relevant and stable incidence since 2002 estimated at 15.4% at three months and at 11.5% at six months and later. Among patients with CPSP after CS, 9.6% (95% CI: 0.0 to 21.0%) had severe pain. According to this report, chronic postpartum pain after CS represents a significant human and socio-economic problem. However, as already pointed out, a puzzling feature of CPSP relates to the CPSP incidence found in studies compared to the number of patients seen in pain clinics. In his first report, Crombie mentioned abdominal and perineal surgeries as major causes of pain in respectively 47% and 38% of patients attending the Pain Clinics although no mention was made to the type of procedure. Today, findings from the recently developed “transitional pain services” or “extended acute pain services” mention thoracic and orthopedic surgeries as being the most common procedures associated to CPSP. Whether there is no doubt about the existence of chronic pain after delivery, the aforementioned observations point out the fact that women are reluctant to report pain in the context of childbirth considered as a happy event in life, a fact already noticed. Further, some publications suggest that when women consult specialists in urology or pain medicine because of severe perineal pain, the interval between birth and the consultation is often long: mean interval from genital tract trauma (i.e. childbirth or other surgery) to consultation for pain is eight months, range three months to 20 years. That observations underline some educational problem about questioning and reporting postpartum pain in both health care providers and patients.

Postpartum chronic pain: any difference according to the type of delivery?

Chronic postpartum pain has been more often assessed after cesarean than vaginal delivery. CS is one of, if not, the most common surgical procedure performed over the world as estimated number was 22.9 millions in 2012. In CPSP related to CS, scar pain predominates and very often presents with neuropathic character. The Pfannenstiel incision commonly used for caesarean delivery carries a high risk of nerve entrapment. A neuropathic component was found in 24.5% of the patients with chronic scar pain using the Douleur Neuropathique 4 (DN4) tool. However, the neuropathic aspect of CPSP after CS is less stable than that after other surgeries and its intensity is generally low (pain score >3/10 in only 2% of the patients) what is surprising because neuropathic CPSP is usually associated to severe pain and poor quality of life. Deep visceral pain i.e. new onset of chronic pelvic pain (incidence range from 2.9% to 11%) also may occur which strongly decreases the women’s quality of life. Finally, it is interesting to note that women who had CS are more likely to report low back pain (8.5-26.5% at 1 year) than women who had a vaginal delivery (adjusted odd ratio 1.40; 95% CI: 1.05-1.85).

Studies assessing chronic pain after vaginal delivery report 2% to 10% of women with pain at six months and later, almost exclusively in mothers who had an assisted vaginal birth. It is here worth noting that chronic postpartum pain intensity is usually higher when it is related to vaginal delivery than to caesarean delivery and more severely affects the woman’s quality of life and mood. The nature of persistent pain after vaginal delivery is poorly characterized: perineal area and buttocks are often mentioned as well as the presence of deep abdominal and pelvic pain. Some 27.6% of women present late dyspareunia defined as pain during intercourse at one year after childbirth. No relation is found between late postpartum dyspareunia and the mode of delivery i.e. spontaneous versus instrumental, episiotomy or lacerations.

Because the rate of caesarean delivery is currently increasing in developed countries for several reasons like maternal age and comor-
bidity, the impact of the mode of delivery on later woman’s global health and quality of life deserves attention. An old study reported similar outcomes at two years after either planned vaginal or planned caesarean delivery. Recent studies found caesarean delivery associated with a reduced risk of chronic pain (odd ratio: 0.12), specifically a reduced risk of chronic pelvic pain by comparison with vaginal delivery (odd ratio: 0.48 and 0.65, for elective and emergency caesarean delivery, respectively). Emergency versus elective caesarean delivery does not affect the risk of 1-year chronic postpartum pain. However, the global health-related quality of life at five years after birth of a first child was lower in women who had undergone emergency CS than women who had vaginal delivery (instrumental or not) or CS on request. Further, emergency CS tends to increase the intensity of chronic pelvic pain. Finally, it is interesting to note that whether history of CS is not increasing the risk of CPSP after a second caesarean delivery, it represents a significant risk factor for the development of CPSP after hysterectomy performed later in life.

**Postpartum chronic pain: risk factors and preventive strategies**

The degree of tissue trauma is a risk factor for the severity of acute postpartum pain but does not seem to account for the risk to develop severe chronic pain after delivery. That means that factors involved in the development of chronic pain after tissue trauma are “individual-related” and rely on both exaggerated reaction to tissue trauma and failed neuroadaptation in different pain dimensions. From a clinical point of view, in risk stratification for the development of CPSP, “pain predicts pain” i.e. some individuals may be predisposed to severe pain. Both preoperative pain at surgical site or elsewhere (e.g. fibromyalgia, low back pain, chronic headaches…) and acute postoperative pain severity are strong predictors of CPSP. A history of pain is a significant risk factor for CPSP after delivery, both in retrospective studies and prospective ones. Pre-delivery history of pain was the only factor associated with increased chronic pelvic pain. Also, previous history of a peripheral neuropathic event was a significant risk factor for neuropathic CPSP after CS. Acute postoperative pain intensity as well as the time spent in severe postoperative pain is a risk factor for CPSP. After childbirth, acute postpartum pain severity, independent of the type of delivery, significantly increased risk of postpartum depression and an increased risk of persistent pain at two months. In a recent systematic review assessing the association between acute and chronic pain after surgery, movement-evoked acute pain emerged as a predictor of CPSP intensity. Despite no CS study was included in that systematic review, two recent prospective studies report higher pain intensity on movement within 24h post-CS as a risk factor for CPSP up to six months after delivery. Similar findings (i.e. recalled pain) emerged from previous retrospective studies. Acute postpartum pain treatment remains too often suboptimal despite the development of Enhanced Recovery programs where pain control plays a major role in recovery. A multicenter study in 2008 found 10.9% of women with severe pain within 24h after CS. In 2015, similar observations were reported. Although not considered as a major procedure, CS ranked ninth for pain severity among 179 different surgical procedures. Further, worst pain intensity and pain at mobilization were significantly higher after CS compared with three different types of hysterectomy. These aforementioned findings question the quality of postoperative pain management in obstetric population. Here also, there is clearly a need for education of both patients and health care providers.

The subacute period of recovery has emerged as a “key period” for the chronification of postoperative/trauma pain because of the increased involvement of psycho-social factors, including the “psychological burden” of pain in some patients. Today, a paradigm shift from intensity-focused pain measurement to patient functional recovery-assessment has risen. It is mandatory to better understand the interference of pain with functional recovery, particularly in obstetric population where women want to recover faster. Two recent publications have focused on the question. In one study, vaginal delivery and CS populations expressed similar pain scores while show-
Postpartum chronic pain is a clinical reality which affects 6.1% to 11.5% of women after delivery. The incidence has remained stable over time. The features of chronic postpartum pain depend on the type of delivery. Cesarean delivery is associated with scar pain which often involves a neuropathic component generally of mild intensity. Cesarean delivery is also associated to a lower risk of chronic pain, specifically chronic pelvic pain, than vaginal delivery.

Chronic pain after vaginal delivery include chronic pelvic pain and/or perineal pain. When present, pain is often severe and affects woman’s mood and quality of life.

Individual-related factors, more than degree of tissue trauma, are involved in the development of chronic postpartum pain: pre-delivery history of pain and higher pain intensity particularly on movement within 24 h post-delivery stand as important risk factors.

Peripartum pain control is important to prevent chronic pain after delivery. Effective postoperative regional analgesic techniques (intra-wound infiltration, parietal block) was susceptible to reduce CPSP after CS (odd ratio 0.46; 95% CI: 0.26-0.78) (Table I). 9, 10, 12, 17, 19-22

Conclusions

Postpartum chronic pain is a clinical reality which features depend on the type of delivery. Chronic pelvic pain and perineal pain have higher negative impact on women mood and quality of life. As for any chronic pain, individual risk factors account more than degree of tissue trauma. From actual reports in the field, better pain education of both women and health care providers might help to reduce the problem.

Key messages

- Postpartum chronic pain is a clinical reality which affects 6.1% to 11.5% of women after delivery. The incidence has remained stable over time.
- The features of chronic postpartum pain depends on the type of delivery. Cesarean delivery is associated with scar pain which often involves a neuropathic component generally of mild intensity. Cesarean delivery is also associated to a lower risk of chronic pain, specifically chronic pelvic pain, than vaginal delivery.
- Chronic pain after vaginal delivery include chronic pelvic pain and/or perineal pain. When present, pain is often severe and affects woman’s mood and quality of life.
- Individual-related factors, more than degree of tissue trauma, are involved in the development of chronic postpartum pain: pre-delivery history of pain and higher pain intensity particularly on movement within 24 h post-delivery stand as important risk factors.
- Peripartum pain control is important to prevent chronic pain after delivery. Effective postoperative regional analgesic techniques (intra-wound infiltration, parietal block) might reduce chronic pain after cesarean section.
- It is worth noting that women are still reluctant to report pain in the context of childbirth and this underlines a need for more education of both women and health care providers.

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Acute coronary ostial stenosis resulting from the left main trunk stenting deformity during the aortic valve replacement

Coronary ostial stenosis, which occurs in up to 3.4% of cases, represents within the first six months following the aortic valve replacement, but that of acute onset during the operation has been infrequent. Also, the causal relationship between the iatrogenic factor including the surgical procedure and the diseased state has not been reported clearly. We document here a case of acute coronary ostial stenosis resulting from the left main trunk stenting deformity caused by the antegrade administration of cardioplegic solution upon the aortic valve replacement.

A 79-year-old woman had the coronary arterial stenting at the left ascending coronary artery (LAD) including the main trunk (#5-7, three drug-eluting stents), as well as, the right coronary artery (#1-2, two bare metal and two drug-eluting stents) under the assistance of the intra-aortic balloon pumping due to her severe coronary disease involving three vessels. She subsequently underwent the aortic valve replacement under a cardiopulmonary bypass (CPB) because of her progressive heart failure (the left ventricular ejection fraction 39.7%) resulting from her severe aortic stenosis (the aortic valve area 0.42 cm² with the stenosis pressure gradient 35 mmHg). We have obtained the consent for this case report from the patient. Her general anesthesia was induced with midazolam 0.1 mg/kg iv in combination with fentanyl 10 µg/kg iv and maintained using a target-controlled infusion of propofol 1 µg/ml, as well as, remifentanil 0.2-0.4 µg/kg/min div. Upon the start of the CPB, the surgeon initially tried the retrograde administration of the cardioplegic solution, but he subsequently changed it in the antegrade fashion since the retrograde approach did not achieve a cardiac arrest. After completion of aortic valve replacement, the surgeon accomplished the aortic cross declamping, and the spontaneous heartbeat resumed immediately. The attending anesthesiologist commenced the inotropic agents’ div including dopamine 5 µg/kg/min and noradrenaline 0.1 µg/kg/min whereas he noticed the impaired left ventricular contracture especially at the area perfused by LAD upon the real-time transesophageal echocardiography. Our cardiac surgical team promptly decided to add coronary artery bypass grafting between the left internal mammary artery and LAD distal to the coronary stents. After completion of the surgical procedure, the intraoperative course including her weaning from CPB was uneventful. Cardiologists performed the coronary angiography to confirm the arterial status three weeks after the surgery and found the severe coronary ostial stenosis (90%) resulting from the left main trunk stenting deformity (Figure 1).

This case is the first to demonstrate the acute coronary ostial stenosis caused by the iatrogenic fashion
during the aortic valve replacement. The most likely mechanism of the left main trunk stenting deformity is surgical procedures related to the antegrade perfusion cannula itself or cardioplegia solution which produces high pressure from the cannula tip. Anesthetic personnel have to be cautious regarding the possible deformity of the main trunk coronary stent by the antegrade cardioplegia, resulting in impaired left ventricular contracture.

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Delirium in the post-anesthesia care unit may be associated with the development of postoperative delirium in a cohort of elderly patients

Postoperative delirium (POD) is an acute and fluctuating disorder characterized by an altered state of consciousness, inattention, and disorganized thinking.1, 2 POD in elderly patients is a frequent complication associated with poor long-term outcomes3, 2 and usually occurs during the first week after surgery.2 However, in the first hours after surgery, including the stay in the Post-Anesthesia Care Unit (PACU), delirium is not routinely evaluated and its incidence and importance has been poorly studied.3, 4 Thus, we carried out a study to determine the incidence of delirium in the PACU using the diagnostic tool confusion assessment method (CAM)5 and the association of PACU delirium with POD in the next days of in-hospital stay.

After approval by the institutional ethics committee, informed consent was obtained from 96 patients older than 65 years scheduled for elective surgery with either general or neuraxial anesthesia in 2015-2016. Patients with a positive preoperative CAM, dementia or those who needed mechanical ventilation immediately after surgery, were excluded. In brief, all patients were anesthetized according to the anesthesiologist’s criteria and after surgery CAM was applied early-on in the PACU when patients reached an Aldrete Score ≥9 to exclude residual effects of anesthesia. Then, all patients were examined with CAM twice every day until the fifth postoperative day or until discharge, whichever occurred first. Three patients were excluded from the study due to a positive preoperative CAM and incomplete data.

Ninety-three patients (36 males and 57 females) aged 73.5±6.9 years were included in the study; the kind of surgeries were orthopedic (18.3%), abdominal (28%), vascular (7.5%), urological (21.5%) and low risk surgery (24.7%); the median duration of surgery was 77 (46-120) min; and the median length of in-hospital stay was four (2 to 6) days. PACU delirium was diagnosed in six patients (6.5%). Of these, three patients developed POD. While, from the 87 patients without PACU delirium, only three patients presented POD. Hence, patients who developed delirium in the PACU had a higher incidence of POD (POD after PACU delirium: 50% versus POD without PACU delirium: 3.4%); RR: 14.3, 95% CI: 3.6 to 49.5; Fisher’s Exact Test, P=0.003 and Log-rank test, P<0.0001). Delirium after surgery at any time (PACU de-
lirium and POD) was diagnosed in nine (9.7%) patients. These patients presented a higher mortality at one month (POD 11% vs. without POD 1%), but not at one year (POD 11% vs. without POD 4%).

In conclusion, this study demonstrates that PACU delirium is associated with POD in patients over 65 years old. The detection of patients with delirium in the PACU is feasible using CAM when patients reach an Aldrete Score ≥9. Early identification of these patients is critical to establish prevention and treatment strategies, which could modify the temporal course, severity, and long-term complications of the POD.

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Authors' contributions.—Rodrigo Gutiérrez designed the study, analyzed results, and wrote the manuscript. Fernando I. Reyes analyzed data and wrote the manuscript. Antonello Penna designed the study, analyzed results, and wrote the manuscript.

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Do residents in anesthesiology feel adequately prepared for handling infections by multiresistant pathogens? Results of a survey in German hospitals

In 2014, MRPs (Multiple Resistant Pathogens) were found in 2,500,000,000 dollars costs, and 2,500,000 hospitalization days.1 As a limited number of antibiotics are in clinical development, strategies for an intelligent use of available antibiotics need to be implemented.2, 3 A Cochrane meta-analysis indicated that a reduction of excessive antibiotic use in the framework of Antibiotic Stewardship (ABS) programs results in lower resistance rates, fewer nosocomial infections, and improved treatment effects.4 In the perioperative domain, anesthesiologists control key interfaces of high antibiotic turnover, i.e., the operating-room and intensive-care units. Surprisingly, no evidence is available concerning their skills in this area. Especially self-assessment and knowledge of anesthesiologic residents (RA) in comparison with board-certified anesthesiologists (BCA) concerning “rational antibiotic use,” “antibiotic report interpretation,” and “MRP treatment” are of strategic interest. From 6-10/2017, a validated survey assessing aspects of antibiotic prescription and resistance (MR2: Multinstitutional Reconnaissance of practice with MultiResistant bacteria)5 was distributed among anesthesiologists in German hospitals to comparatively evaluate knowledge and skills and identify capabilities for improvement, education, and interventions.

Five items on the educational level preceded the sur-
TABLE I.—Raw response rates and multivariable logistic regression models for the evaluation of the independent impact of board certification status (certification for anesthesiology) on selected endpoints.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>BCA (%)</th>
<th>RA (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>P (BC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endpoint 1: at least fair certainty in the correct interpretation of microbiological diagnostics (vs. uncertain to very uncertain) [self-assessment]</td>
<td>81.0%</td>
<td>59.6%</td>
<td>2.66 (1.84-3.85)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endpoint 2: at least fair certainty in the correct choice of a suitable antibiotic substance (vs. uncertain to very uncertain) [self-assessment]</td>
<td>62.2%</td>
<td>27.8%</td>
<td>4.17 (2.95-5.91)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endpoint 3: at least fair certainty in the correct choice of dose, frequency, and duration of antibiotic application (vs. uncertain to very uncertain) [self-assessment]</td>
<td>64.0%</td>
<td>30.9%</td>
<td>3.70 (2.63-5.21)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endpoint 4: at least average knowledge about Antibiotic Stewardship measures (vs. no or minor knowledge) [self-assessment]</td>
<td>49.4%</td>
<td>16.4%</td>
<td>4.57 (3.08-6.78)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endpoint 5: at least average knowledge about pathogen resistance rates in the own hospital (vs. no or minor knowledge) [self-assessment]</td>
<td>43.2%</td>
<td>13.9%</td>
<td>4.45 (2.98-6.77)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endpoint 6: at least average knowledge about hygienic measures and standards in the own hospital [self-assessment]</td>
<td>54.7%</td>
<td>45.3%</td>
<td>2.66 (1.44-4.92)</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Endpoint 7: at least average knowledge about the concrete approach against Clostridium difficile infections (vs. no or minor knowledge) [self-assessment]</td>
<td>83.6%</td>
<td>66.2%</td>
<td>2.44 (1.64-3.63)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endpoint 8: generally, in the field of anesthesiology an adequate and sufficient education concerning guidelines accordant use of antibiotics is performed (vs. no adequate education)</td>
<td>11.9%</td>
<td>4.4%</td>
<td>3.02 (1.56-5.82)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endpoint 9: an obligatory integration of anti-infective therapy in the educational curriculum of the anesthesiology board certification is reasonable (vs. an integration is not reasonable)</td>
<td>85.0%</td>
<td>85.1%</td>
<td>1.01 (0.65-1.58)</td>
<td>0.956</td>
<td>0.959</td>
</tr>
<tr>
<td>Endpoint 10: participation in at least one educational training on the topic of multi-resistant pathogens and antibiotic prescription during the twelve months preceding survey participation (vs. no educational activity)</td>
<td>53.5%</td>
<td>30.4%</td>
<td>2.52 (1.78-3.52)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endpoint 11: correct assignment of the resistance rate of Escherichia coli against Ciprofloxacin in the hospital of each interviewee in the year 2016 (vs. wrong assignment)</td>
<td>25.8%</td>
<td>14.6%</td>
<td>1.82 (1.21-2.72)</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td>Endpoint 12: correct assignment of the MRSA rate in the hospital of each interviewee in the year 2016 (vs. wrong assignment)</td>
<td>62.6%</td>
<td>52.1%</td>
<td>1.51 (1.09-2.08)</td>
<td>0.012</td>
<td>0.015</td>
</tr>
</tbody>
</table>

All multivariable logistic regression models were adjusted for the following criteria: 1) sex of interviewee; 2) occupation of the interviewee at an intensive care unit during the previous twelve months preceding survey conduction; 3) discrete definition of indications and antibiotic prescription by the interviewee during the previous seven days prior to survey conduction; 4) level of care of the corresponding hospital (of each interviewee); 5) availability of department or hospital internal guidelines (for the interviewee) with clear definition of antibiotic use.

BCA: board-certified anesthesiologists; BC: bootstrap corrected; OR: Odds Ratio; 95% CI: 95% Confidence Interval; RA: residents in anesthesiology; MRSA: methicillin resistant Staphylococcus aureus.

Very; further 50 items evaluated the following aspects:

- certainty concerning antibiotic prescription;
- self-assessment of knowledge about MRP and antibiotic prescription;
- classification of MRP-associated issues;
- individual basis for decision-making concerning antibiotic prescription;
- frequency of participation in specific educational activities;
- knowledge about ABS-measures;
- assessment of the curriculum for the anesthesiologic board-certification on the topic of anti-infectives.

Questionnaires returned with ≥94% data completeness (≥52/55 items) were evaluated. The independent impact of the educational status on defined endpoints was analyzed by multivariable logistic regression models adjusted for sex of interviewees, practice at an intensive-care unit during the past year, responsibility for indications and antibiotic administration (past seven workdays), level of care of each hospital, availability of internal guidelines defining anti-infective use. Internal validities were evaluated with the bootstrap-method (1000 samples).

In all 16 participating departments (including seven university departments) 1268 questionnaires were distributed according to the number of physicians employed (median team-size: 45; interquartile range: 32-105). 684 of the returned questionnaires complied with the aforementioned quality-criteria (return-rate: 54%); 676 were evaluable.
The results confirm the frequent prescription and antibiotic administration by anesthesiologists (Table 1). About 75% of anesthesiologists had administered antibiotics during the past seven workdays. Encouragingly, more than 80% affirmed the availability of departmental guidelines. As expected, BCA indicated better knowledge than RA regarding correct antibiotic prescription and local resistance rates of pathogens, more self-confidence in their skills, and enhanced knowledge regarding rational antibiotic use and ABS-measures; furthermore, they participated more frequently in educational trainings. Disappointingly, the majority of interviewees considered the hospital-internal education insufficient. 85% of both BCA and RA advocated an obligatory integration of anti-infective therapy in the curriculum for the anesthesiology board-certification (currently not incorporated).

Obviously, survey studies (including the present) yield relevant limitations, such as expectation-bias as a source of wrong information and non-response bias. Nonetheless, the return-rate of 54% is more than 10% higher than achieved for the previous MR2-surveys approaching urologists, surgeons, gynecologists, and internists.2,3,5 Furthermore, the results of the participating hospitals display homogeneity in separate analyses. As only larger German hospitals were evaluated, the results might not entirely represent the national and international clinical reality.

From the results of this survey one can derive a tremendous need for education of anesthesiologists regardless of their educational level and the necessity to further implement structured ABS-programs in German hospitals. Hospitals as well as anesthesiology as medical specialty are in charge of meeting this challenge. Institutionally available formal guidelines need to be filled with life. Besides restrictive measures (e.g. expert authorization), provisions such as audit, feedback, and educational outreach through reviewing patient cases have shown their potential to improve prescribing behaviours.4 Additionally, the anesthesiologic curriculum would be the obvious tool to implement a certain standard. Frequent and repeated educational activities should be requested from all anesthesiologists, not only those with particular interest in the subject. Since German board-certifications do not require obligatory upgrades, the relevant medical and scientific societies (BDA and DGAI) should contribute to increase visibility of ABS-programs.

To summarize, the present results should prompt a critical evaluation of the status quo regarding knowledge penetration about MRP and ABS-measures — also outside German hospitals. While curricula and the precise role of anesthesiologists in operative medicine may geographically differ, the threat of MRP is global. Finally, anesthesiologists should aim at being the trailblazers and pioneer with commitment to prove their core capability regarding these relevant tasks, rather than wait until rules are imposed on them from outside.

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Pelvic plexus block: a new sonographic technique for acute pelvic pain

Pelvic surgeries are very common and include obstetric, gynecological and rectal procedures. They usually result in intense postoperative pelvic pain. At present, lumbar epidural is the only available regional technique that can control this pain. Pain from all pelvic viscera (except the ovary and fallopian tube) is transmitted by the pelvic plexus (also known as inferior hypogastric plexus). Pelvic plexus is formed by the superior hypogastric, pelvic and sacral splanchnic nerves. It lies deep to the pelvic parietal fascia which extends as the piriformis fascia lining the piriformis muscle (Figure 1).1,2

A trans-sacral pelvic plexus block has been used for chronic pelvic pain management.3 However, it requires fluoroscopic guidance. To popularize the use of pelvic plexus block in acute pain management, we describe a simple sonographic trans-piriformis technique: the pelvic plexus (PP) block (Figure 1). The patient is placed in either lateral, prone or sitting position (based on preference of the anesthetist). The curved ultrasound probe is placed horizontally, four fingers lateral to gluteal cleft to identify the piriformis. It is then adjusted (slid caudally, rocked medially) to identify the related vessels, sciatic nerve and rectum (a hyperechoic surface) so as to avoid their injury. The needle tip is advanced slightly deep to piriformis; from lateral to medial using in-plane technique. After careful aspiration and electrical stimulation, 30 mL ropivacaine (0.16%) is injected.

Piriformis muscle is a distinct sonographic landmark, as it is the only muscle passing through the greater sciatic foramen.4 Because of its simplicity, PP block can be used for almost all pelvic surgeries. It anesthetizes

Figure 1.—Pelvic plexus (PP) anatomy and PP block technique. A, B) Axial (schematic) and sagittal (cadaveric) pelvic views. The PP is formed by the superior hypogastric, pelvic and sacral splanchnic nerves. It lies between the rectal fascia and the pelvic parietal fascia which extends as the piriformis fascia. This fascia lines the pelvic surface of the piriformis muscle and is related to the pelvic and sacral plexuses as well as the internal iliac branches. C) For PP block: the patient is placed in lateral position. The curved ultrasound probe is placed horizontally lateral to gluteal cleft to identify the piriformis. D) The probe is then adjusted (slid caudally, rocked medially) to identify the related sciatic nerve and rectum (a hyperechoic surface). The needle (blue line in the online version) is inserted lateral to the probe and the tip is advanced (using in-plane technique) slightly deep to piriformis.

GC: gluteal cleft; Gmi: gluteus minimus; Gmx: gluteus maximus; HgN: hypogastric nerve; IIB: internal iliac branches; IS: ischial spine; MR: meso-rectum; OI: obturator internus muscle; OIF: obturator internus fascia; PBI: posterior border of ischium; Pi: piriformis muscle; PiF: piriformis fascia; PP: pelvic parietal fascia; PPx: pelvic plexus; PsF: pelvic splanchnic nerve; PsF: pelvic splanchnic nerve; R: rectum; RF: rectal fascia; S: sacrum; SG: sympathetic ganglion; SN: sciatic nerve; SsN: sacral splanchnic nerve. B) Fresh frozen specimen was obtained from cadaveric lab, in the Department of Anatomy at Ain Shams University, Cairo, Egypt.
almost all pelvic organs and may also spread to the pudendal nerve, thereby anesthetizing the perineum. It can provide long lasting complete analgesia (zero VAS); for pure pelvic surgery as in vaginal hysterectomy and theoretically for vaginal delivery (not yet tested). Unlike epidural anesthesia; PP block does not seem to impair the hemodynamic stability or patient mobility, and top-up doses are not required.

On the other hand, PP block needs to be performed bilaterally. Internal iliac branches (inferior gluteal and internal pudendal) run deep to piriformis. Careful needle advancement and aspiration are of utmost importance. To avoid intra-sacral plexus injection, it is also essential to add a low electrical current stimulation (0.3 mA), and if this elicits lower limb twitches (gluteal, hamstring, leg or foot), the needle should be repositioned. This block anesthetizes the autonomic nerves supplying the bladder and may spread to the sacral plexus causing retention and/or lower limb numbness. Fortunately, the bladder is usually catheterized in pelvic surgery and the local anesthetic concentration is too low to cause motor blockade. Neuro-lytic agent should never be used in this approach. PP block cannot treat back pain associated with lithotomy position. For pelvic surgery with an abdominal incision, an abdominal wall block should be added. PP block is a deep block and requires experience. It is safer to abandon the block if the pelvic surface of piriformis or the vessels beneath are not clearly defined (as in morbid obese).

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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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