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About the cover: the cover shows the ultrasound transverse approach to measure the depth of the epidural space (AP=Articular Process; TP=Transverse Process; LF=Legamentum Flavum). For more information, see article by Perna P. et al. (pages 41-49).
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EDITORIAL

Pain medicine units: how do they work?

Gennaro SAVOIA

Department of Anesthesia and Resuscitation, AORN A. Cardarelli, Naples, Italy

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Palliative Care and Pain Medicine came out as a new sector of Medicine in the last 40 years. The keystones of development of Pain Medicine were IASP (International Association for the Study of Pain) founded in 1973 by J. Bonica and his friends,1,2 the birth of multidisciplinary Journal Pain in 1975,1 the WHO’s (World Health Organisation) first edition of guidelines on cancer pain in 1986 that includes for the first time the “step analgesic ladder” concept,3 the Montreal declaration of 3 September 2010 stating that “access to pain management is a fundamental human right”.4,5

Chronic pain from moderate to severe intensity occurs in 19% of adult European citizen, with development of a major health problem inadequately treated in nearly half of patients.6 The emerging international challenge to consider chronic pain such as a disease hasn’t closed a clear statement on it. Physiopathological considerations on the way from acute to chronic pain are impressive in favor to consider chronic pain such a disease, but to consider pain alone as a symptom is now prevalent in scientific community.7

Nevertheless, a new classification of chronic pain is proposed in 2015 with the aim to modify ICM-11, thus accepting a variety of chronic pains (primary, cancer, postsurgical and post-traumatic, neuropathic, headache, visceral and musculoskeletal) such as different diseases.8

The development of Pain Center Units, or of Multidisciplinary Pain Units, following “bio-psycho-social model” concept, has emerged as a paradigm for scientific and clinical medical practice improvement. On 2 May 2009 IASP adopted an educational document for organization of “Pain Treatment Services”, distinguishing between “Multidisciplinary Pain Centers” and “Multidisciplinary Pain Clinics”.9 British Pain Society approved on November 2013 a paper named “Guidelines for pain management programmes for adults”, where inclusion of cognitive and behavioural principles into interdisciplinary team for integration of PMP (pain management programmes) seems mandatory in the long-term treatment of chronic pain.10 Now pain medicine units worldwide on multidisciplinary basis are the standard on offering to suffering patients a complete diagnostic-therapeutic pathway with a long term taking care. Which is the effectiveness or the outcome of pain therapy supplied by Pain Medicine Units is a neglected area of clinical research; in other terms, which is the clinical value or how is worth the clinical production (diagnosis and pharmacological and/or interventional therapy) supplied, nowadays the scientific community does not have any answer.

In this issue of Minerva Anestesiologica11 a
Catalane Clinical Group in the name of 12 pain unit that serve near 6 million of residents shows a suggestive prospective observational study. The group recruited 291 patients suffering from chronic pain and compared diagnoses made by referring doctors (orthopedics and family doctor), for evaluating how pain doctors engage patients. The main effects of interventions were evaluated through an interesting series of parameters such as:

- the difference of ante-post diagnostic label (48.5%);
- the variation of pain treatment plan (94.8%) with employment of opioids (46.8%), co-adjuvants (38.2%) and interventional and/or alternative therapies;
- the decrease of the 24-hours worst pain severity by 30.9%;
- the decrease of current pain severity by 27.8%;
- the mean improvement of quality life 0.16 (0.73) following EuroQol 5 Dimension Index;
- improvement of pain visual score by 6.7 (0.31).

The authors presented an epidemiological model for evaluation of pain units. Are these parameters used for evaluation appropriate and exhaustive?

WHO considers national opioids consumption such as a standard for evaluation of cancer pain treatment effectiveness. EuroQol is worldwide considered as a useful and simple method for evaluation of life quality in the setting of chronic diseases.

Italian law n.38/2010 have recently ensured the right of pain treatment suggesting a regional organization structured in 3 level (family doctor, spoke and hub level with a anesthesiologist expert as a coordinator). The 2015 Annual Parliament Report confirms a low but progressive increment in opioids consumption in Italy and in regional network construction of pain therapy units.

We think that an evaluation based only on opioids consumption and on a simple quality life score is limitative. Some chronic pain syndromes have a long way (20-30 years) and epidemiologically they have a variety of acute and remission phases that require a long term charge by pain medicine units with development of diagnostic-therapeutic complex pathways coherent with international validated guidelines. A recent challenge on opioids limitations and doubts on scientific value of interventional indications in chronic non cancer pain indicate the need to revaluate appropriateness of procedures in pain therapy, distinguishing between the effects at brief and long term, balancing benefits, risk and costs. Further more if we compare other desirables needs of a national health service such as regional homogeneous access to interventional care, follow up guarantied at long term, development of interdisciplin ary care comprehensive of physiotherapeutic and psychologic approach, we could identify a long way to get a better outcome in pain medicine.

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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What am I compressing with my supraglottic device?

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In 1988 the Laryngeal Mask Airway Classic (LMAC) (LMA, Teleflex, Wayne, PA, USA) was introduced as a safe and effective device in airway management, both for adult and pediatric patients. During the perioperative period, many factors could be involved in the outcome and safety of the pediatric patient, being the respiratory complications, the most common perioperative critical event, independently if the patient is ventilated through a supraglottic device (SGD) or an endotracheal tube.

A recent meta-analysis 4 suggests that the use of the SGDs compared to the tracheal intubation, decreases the incidence of laryngospasm, desaturation, breath holding and cough during the postoperative period, highlighting the importance of the SGDs as a valuable tool for the pediatric airway management. However, in spite of this good safety profile, the reported complications related to the use of SGDs are not uncommon, such as: potential gastric insufflation, soft tissue abrasion, difficult insertion, spontaneous dislodgement, sore throat, hoarseness and dysphagia.

Since 2003, when the patent for LMAC expired, the SGDs have had some modifications in order to improve their performance and decrease the aspiration risk. These devices are divided into two groups, first and second generation. The main differences between them are that the devices belonging to the second generation has an aspiration canal, bite blockers and a better hypopharyngeal seal, allowing higher airway pressures and a better positive pressure ventilation performance.

In this issue of Minerva Anestesiologica, Aqil et al. 9 compared the spatial relationship of i-gel® and Ambu® AuraOnce on pediatric airway based on three-dimensional magnetic resonance imaging (MRI) measurements. The i-gel® is a SGD of second generation, which has been used in pediatric patients since 2010. It has a soft gel, made of thermoplastic elastomer, with a non-inflatable cuff and has an additional canal for gastric catheter placement (except in size 1). The Ambu® AuraOnce is a SGD of first generation with an inflatable cuff and non-gastric canal, which was introduced to the pediatric anesthesia practice in 2004 and has the unique feature of performed curve shaft. Aqil et al. evaluated the shape of the airway of 60 children with MRI before and after placing both SGDs. The main results were that both devices consistently distorted, in a variable extent and manner, the pediatric airway leading to compression of the tongue, forward...
displacement of the hyoid bone, reduction area of the glottic aperture and the distance between the arytenoids and dilation of the upper esophageal sphincter. In a previous study in adults, both i-gel® and LMA-Supreme® were associated with significant displacement of the tongue, the hyoid bone and reduction of the glottic area.11

The compression of oropharyngeal soft tissues, due to the SGDs, was constantly documented in all subjects of both pediatric 9 and adult 11 studies. The association of mechanical displacement of the upper airway and an excessive inflating pressure of the SGD, which is easily achievable if the cuff is inflated with the maximal recommended volume,12 may result in a decrease of the mucosal perfusion pressure. Both factors may explain some of the common complications associated with the use of the SGDs.

In addition to the difficulty to assess this kind of complication in pediatric population, the reported incidence of complications related to use of the SGDs, may also be underestimated, possibly due to the residual effect of anesthetic drugs and the use of postoperative analgesics.13

The study carried out by Aqil et al. is the first one to evaluate the spatial relationship between two commonly used SGDs and the airway in pediatric patients. It includes an easy and straightforward visual example of why simple things sometimes go wrong. Even if you can ventilate your patient, that does not mean the SGD is properly placed. This paper should be interpreted as a warning in order to increase our attention on the proper insertion technique and the routine use of cuff pressure monitoring,14 independently if the SGD belongs to the 1st or 2nd generation. It also urges the manufacturing companies to develop improved airway devices keeping into account their in-vivo interaction with anatomic structures.

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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Opioids and chronic pain. Data from the “other side of the pond”

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Chronic pain is affecting several million of people all over the world.1, 2 It is a huge clinical and societal problem,3 causing even bigger direct and indirect costs similar to those of cancer, diabetes and heart disease, when considered altogether.2 It is well known that it does not affect only elderly people but a significant percentage of young people having a greater impact on working ability and increasing disability.4 For all these reasons it is mandatory to treat appropriately this syndrome in order both to improve patients’ outcome and reduce societal burden. Obviously, it is necessary a careful diagnosis of the mechanism underlying chronic pain as the pharmacologic therapy has to be mechanism-specific 5 both in nociceptive and in neuropathic pain. The best example is represented by low back pain in which we have always to evaluate not only how the neuropathic component is present,6 but also which is the real pain generator.7

In this setting, opioids continue to represent an important pillar of the therapy if used appropriately. Opioids can modulate chronic pain, but they have always to be considered in a multimodal approach.8 In USA in the last decade we observed an unbelievable increase in opioid use, as the morphine equivalent per capita is almost the double of that used in Germany and 6 times of that used in Italy.9 This marked increase has created a real problematic issue as in 2015 American Academy of Neurology has published a position paper in which they underlined that, according to USA data, there are several risks to prescribe opioids encouraging a more appropriate prescription and limited use.10 This statement is frankly biased by USA data that are completely different of the rest of the world.9 As underlined by a recent article, there are several differences between USA and rest of the world not only in the guidelines, but also in the appropriateness of the opioid use for chronic non-cancer pain.11 As we stated in a previous article,12 it is mandatory to consider also data from “the other side of the pond” (Europe) in a critical way. These data encourages use of appropriate use of opioids, when indicated, in chronic non-cancer pain giving special attention to the chronic follow up and the careful selection of patient who could benefit from this treatment.12

It is needed not only to increase the awareness of the appropriate use of opioids (as of all other drugs) in the treatment of this condition, but also to evaluate more European data also to understand which is the “real European world” in the use of opioids.
Data from Italy are particularly important. On one hand Italy is a Country in which opioid prescription was extremely low; on the other hand it is the first Country in the World that approved a National law (law 38/2010 in 2010), in which it is stated that pain therapy access is a right for each citizen.

In this issue of Minerva Anestesiologica, Miceli et al.\textsuperscript{13} show an important snapshot, performed in 2013, of opioid prescription in Italy, after law 38/2010. They performed a retrospective analysis of opioid consumption by chronic cancer and non-cancer pain outpatients. This study underlined at least two important messages.

The first important data found by the Miceli et al. is that, independently of the application of law 38/2010, in Italy opioids are used less than in other countries: 0.7\% of Italian population is treated chronically (at least 3 opioid prescription consecutively in 3 months) with opioids (a really low percentage considering number of chronic pain patients in Italy). More than 50\% of all opioid prescriptions were constituted by weak opioids (tramadol and codeine). Hence, morphine daily mean dose in chronic non cancer pain patients is greatly lower to that found both in USA\textsuperscript{14} and European\textsuperscript{15} studies. These data are of particular interest also because Marschall et al.,\textsuperscript{15} even though they found that German patients used larger doses of morphine equivalents, clearly demonstrated that they did not find any signal of “opioid epidemic”.

The second important message is regarding the differences between chronic cancer and non-cancer pain patients. Chronic non cancer patients represents the bigger group (94\%) compared to patients with cancer, confirming that chronic pain is mainly a syndrome not related to cancer but with its own entity. Besides that, it was found that patients with cancer use a morphine equivalent mean dose statistically significantly higher than non cancer patients. It is difficult to find a clear reason to explain this impressive difference in opioid dosage, but it is confirmed by other studies.\textsuperscript{14}

In conclusion, in order to really understand the effectiveness and safety of the use of opioids in the treatment of this disease, it is fundamental to analyze also European data that can give a different snapshot. It means that we can not ever forget that chronic pain is a severe disease that has to be correctly treated. When appropriate, opioids represent an important therapeutic option to treat it,\textsuperscript{11, 12} always remembering that these patients need to be routinely followed up in order to adapt the multimodal therapy to the specific needs of the patients in that specific moment.\textsuperscript{5}

Finally, even though opioid epidemic USA data are not confirmed by European data,\textsuperscript{13, 15-17} it is important to evaluate patients that are at risk of side effects in order not to avoid a treatment but to treat them better and more closely.\textsuperscript{18}

\section*{References}


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Development of neurocritical care: enhanced neuromonitoring or better specialists’ cooperation?

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There is little doubt that specialized neurocritical care (NCC) improves outcome of neurological/neurosurgical patients compared to general intensive care units (ICU). Several retrospective studies have demonstrated an association between NCC management and a lower risk of mortality after traumatic brain injury (TBI), intracerebral or subarachnoid hemorrhage (ICH or SAH), or various acute neurological diseases. There are multiple benefits of dedicated NCC units but the long-term limitations of specialization in NCC are often overlooked. For example, a neuro-intensivist who would have specialized in NCC for the last 15 years might have not been trained in echocardiography, losing a major amount of vital information on hemodynamic management at the bedside. This may be one reason why the frequency of myocardial damage and heart failure has been underestimated in NCC patients until recently. Thus, it is important to understand why NCC management is beneficial for patients to implement strategies that improve neurological outcome without staying behind advances in general ICU care. Moreover, there are relatively few NCC units in Europe, needing to translate the experience of the specialized units to general ICUs.

One obvious reason for improved outcome is higher caseloads of patients with neurological injuries in NCC. Case volume has been associated with outcome after ischemic stroke, SAH, ICH, and TBI. Another reason may be a larger use of neuromonitoring techniques. In fact, there has been a huge development of these techniques over recent years. Intracranial pressure (ICP) and cerebral perfusion pressure monitoring have been used routinely since Lundberg published his research on ICP fluctuations after TBI. Yet, recent studies reported a large variation in ICP monitoring across hospitals and some studies reported an association between the use of ICP monitors and mortality. More recently, monitoring of cerebral blood flow or metabolism has been made possible through several techniques including for example transcranial Doppler ultrasonography, thermal diffusion flowmetry, NIRS, jugular venous saturation in oxygen, brain tissue oxygen tension, and cerebral microdialysis. However, monitoring by itself has no effect on outcome. This is the reason why it is very difficult to demonstrate a benefit of neuromonitoring in prospective trials. The recent negative trial of ICP monitoring after TBI is a good example of the problem. Although it may be disappointing to lack evidence-based data for clinical practice, one can understand that physician experience and knowledge, with or without monitoring, is more important than a protocol based on a single number. The article by
Mazzeo et al. in this issue of Minerva Anestesiologica highlights how cooperation between neurologists and anesthesiologists is beneficial for patients. This cooperation has many facets. The expertise of neurologists helps improving anesthesiologists’ knowledge and reliability of neurological assessment. Multiple case reports demonstrate the importance of clinical examination in NCC for detecting complications. Cooperation between neurologists and anesthesiologists also facilitates implementation of new monitoring techniques. An example is electrophysiology (EEG) monitoring. Textbooks and guidelines recommend EEG monitoring in the ICU. Despite these recommendations, very few teams use EEG monitoring routinely. One reason is that the interpretation of EEG signals seems too complicated for many anesthesiologists. However, none of them would consider echocardiography too difficult to use in cardiac patients. As we have learned from cardiologists how to perform basic echocardiography, we can learn from neurologists how to interpret EEG recordings. Of course, neurologists’ expertise will be still required from time to time but cooperation between both specialties makes implementation of the technique much easier. In the near future, the development of techniques at the frontier between intensive care and neurology will still require enhanced cooperation between neurology and anesthesiology. An example is the development of quantitative MRI for the assessment of prognosis in severe brain injured patients. Although MRI is far from being an area of expertise in our specialty, MRI analysis for prognostication of NCC patients is an important area of research in anesthesia and critical care.

This will open up opportunities for discussing the objectives of medium- and long-term rehabilitation with neurologist.

Finally, the article by Mazzeo et al. reminds us that clinical concepts and shared expertise between specialists are more important than monitoring techniques. New tools in the ICU give us information that we have to interpret in a specific clinical context in order to take the right decision at the bedside. We hope this understanding will move our specialties far from too simple preconceived ideas and self-fulfilling prophecies.

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Characteristics and outcomes of chronic pain patients referred to hospital pain clinics: a prospective observational study

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ABSTRACT

BACKGROUND: Understanding the patient referral patterns and medical profiles of patients attending hospital pain clinics, and the therapies offered to them, can provide a useful starting point for evaluating their effectiveness and identifying areas for improvement.

METHODS: A prospective observational study was carried out. Sociodemographic and clinical data were gathered at twelve centres. The diagnoses and pain treatments provided by the referring doctors were compared with the ones provided by pain clinicians. Pain severity and patients’ quality of life were measured prospectively. Descriptive statistics were compared.

RESULTS: Two-hundred sixty-nine patients referred to 12 outpatient hospital pain clinics in Catalonia were followed for 3 months. Most were referred by orthopaedists (50.0%) or primary care physicians (20.2%). The mean age and time since pain onset were 59.4 and 4.1 years, respectively. Pain clinicians changed the diagnostic labels of 48.5% of the patients. Nearly all patients (89.2%) were receiving pain medications prior to referral. Treatment was modified in 94.8%. Pain clinicians used more interventional and/or alternative therapies (65.1% of patients), opioids (46.8%) and co-adjuvants (38.2%). Three months after referral, the 24-h worst and current pain severity had decreased by 30.9% and 27.8% on average, respectively. The mean (effect size) improvements in a quality of life (the EuroQol 5 Dimensions index) and pain (visual analogue scale) scores were, respectively, 0.16 (0.73) and 6.7 (0.31).

CONCLUSIONS: Pain clinicians refined the diagnoses and treatments of patients referred to hospital pain clinics and improved outcomes. Relatively few patients are referred from primary care considering the prevalence of chronic pain in this setting.


Key words: Observational study - Outcome assessment (Health Care) - Pain - Pain clinics - Pharmacoepidemiology - Prevalence - Referral and consultation.

The current status of research, diagnosis and treatment in pain medicine is characterized by the paradox that important, recent advances are hindered and hard to translate into tangible clinical benefits because of the existence of considerable barriers to effective pain care. Understanding pain pathophysiology entails knowledge of the causal and contribu-
tory interactions of physical, psychological, and social factors as well as the inherent plasticity of the nervous system in chronic pain states and diseases in which pain develops and propagates even with scarce or no evidence of a noxious stimulus. Given the complex nature of pain, treatment should be mechanism-based and multimodal. Therefore, an integrated, multidisciplinary approach to management is advocated to optimize treatment outcomes.

Pain clinics have been created over the past four decades with the purpose of providing interdisciplinary assessment and care for pain patients through a team of diverse medical specialists, chiefly from the fields of anaesthesiology, neurology, psychiatry, occupational, physical and rehabilitation medicine. Outcome data on the effectiveness of this multidisciplinary care is in general positive, yet scarce. Epidemiological data is an essential part of any chronic pain research strategy. To the knowledge of the authors, no study has simultaneously examined the characteristics of patients attending pain clinics, referral patterns, therapies prescribed, and outcomes to describe the state of current practice, so improvements can be planned and assessed. Previous studies in recent years have either focused on specific conditions or pain types or have been performed at single centres (to name a few studies performed in our environment, see Perez, Rodriguez, Stern), and they have seldom provided prospective data.

This report concerns a prospective observational study of hospital pain clinics in Catalonia. This region has a population of about 7 million. Epidemiological studies have revealed that pain represents a major medical problem in this region, comparable to those reported in other Western countries. The objectives of the study, which was an initiative of the Catalan Pain Society, were descriptive. Among the goals of this Society are to inform and assist stakeholders involved in pain care in their decision-making processes. To accomplish it, the state of the current practice is evaluated periodically in descriptive studies like the one reported here. Its primary aim was to evaluate the characteristics of the patients referred for care to pain clinics. Secondary aims were to assess the adequacy of diagnostic labels and treatments for pain provided by the referring physicians, the management strategies employed at pain clinics, and their effectiveness.

Materials and methods

Study design, setting and patients

The present research consisted in a prospective evaluation of a series of patients. All hospital pain clinics active in Catalonia in 2008 were invited to participate. One pain clinic specialist at each site (hereinafter referred to as pain clinicians) acted as coordinating investigator collecting information from all eligible patients referred for care at their premises. To enhance sample representativeness, recruitment was carried out strictly in accordance with the chronological order of patients’ attendance. A recruitment target was set at 20 patients per clinic.

The study was performed in accordance with the Declaration of Helsinki. The ethics committees of the participating hospitals approved the study protocol prior to commencing recruitment. All patients provided written informed consent before enrolment.

Eligible participants were outpatients aged 18 years or older who attended the pain clinic for an initial call after referral by another physician. Only patients whose planned follow-up at the pain clinic was 3 months or longer were included. Patients were excluded if they were unable to provide reliable data or understand the study requirements.

Data sources and measurement

Sociodemographic and administrative data, including age, gender, marital status, living arrangement, level of education and work status were collected. The specialty of the referring physician, the diagnostic label assigned to the painful condition when the patient was referred to the pain clinic, and previous pain treatments were recorded too. The investiga-
tors were asked to indicate whether or not in their opinion these previous treatments for pain were appropriate. A complete medical history was taken, either by questioning the patients or by reviewing their medical records. Pain features gathered included topography, duration, maximum severity in the previous 24 hours and current severity scores on 10 cm visual analogue scales (VAS), temporal pattern, presence of breakthrough episodes, and pathophysiological type (nociceptive somatic, nociceptive visceral, neuropathic, or somatoform/ dysfunctional).

At the initial visit, pain clinicians also had to independently provide diagnostic labels for the pain conditions of the patients. The correspondence between the referral diagnosis and the pain clinician’s diagnosis was evaluated. Pain treatments prescribed at the pain clinic were recorded as well. Lastly, patients were asked to complete the generic EuroQol 5 Dimensions instrument (EQ-5D) validated for Spain, to obtain measures of health-related quality of life (HR-QoL). The EQ-5D provides two measures: a preference-based utility measure (herein termed the EQ-5D Index Score), and a holistic measure of wellbeing on a VAS (herein termed the EQ-5D VAS Score).

Follow-up visits took place one and three months after the initial visit. Patients and investigators appraised the evolution of the patients’ pain symptoms and functional status using a Likert-type Scale (much better, better, no change, worse, much worse). Changes in pain features since the previous visit were also recorded. The pain clinicians had to record every change in diagnostic labels or pain treatments since the previous visit. They also recorded adverse reactions related to pain treatments (if any). Patients were asked to complete again the EQ-5D at both follow-up visits.

Data analysis

Observed data were used in all analyses. Missing data were not imputed. Descriptive statistics were used to summarize and analyse the data. Cross-tabulated or stratified descriptions were produced to evaluate the relationships between features of interest (for example, treatments vs. diagnostic labels). For some descriptions, patients were grouped according to the treatment prescribed at the pain clinic: opioids (when the therapy included one or more systemic opioid agents), non-opioids (when the therapy included any systemic drug, but no opioid agents) and interventional/alternative therapies (rehabilitative, physical, or psychological therapies, regional anaesthetic blocks or interventions without systemic pain medications). The English version 13.3 of the Medical Dictionary for Regulatory Activities (MedDRA) was used to code the medical history, diagnostic labels, and adverse reactions. The agreement between the diagnostic labels given by the referring physicians and the pain clinicians was quantified by calculating quadratically weighted kappa indices between the terms of the MedDRA hierarchical structure that led to the two codes assigned to each patient. Quadratic weighting can be used to evaluate the agreement between two ordinal measures because it provides penalties proportional to the magnitude of the discrepancies (for example, one discrepancy at the level of system organ classes reduced the value of weighted kappa much more than one discrepancy at the level of preferred terms). Pharmacological treatments were coded with the 2013 version of the WHO’s Anatomic Therapeutic Chemical Classification System.

As the objectives of the study were descriptive, no formal calculation of the sample size was made. Nevertheless, a recruitment target was initially set at 340 patients with a view to acquiring a precision of at least ±5% to estimate proportions of the source population.

Results

Disposition of patients

Between September 2011 and January 2014, 291 patients were recruited at 12 of the 20 hospital pain clinics that were invited to participate. Although it took 3 months on average to recruit the assigned quota of 20 patients at each pain clinic, the study period was
long because administrative issues delayed the incorporation of some sites. Twenty-two patients were not analysed for the reasons provided in Figure 1. Of the 269 patients remaining, 34 (12.6%) did not complete the study. The flow chart provided on Figure 1 presents the reasons for premature withdrawals and the number of patients who attended each of the study visits.

**Characteristics of patients referred to pain clinics**

Table I provides a summary of patients’ characteristics at baseline. Most patients (134 out of 268, 50.0%) were referred by orthopaedists, followed by primary care physicians (54, 20.1%), neurosurgeons (18, 6.7%), neurologists (11, 4.1%) and rheumatologists (10, 3.7%). Other specialists referred less than 3% of patients each. The time since pain onset was shorter than 6 months in 82 out of 259 patients (31.7%); the positive asymmetry of the distribution is indicated by the considerably lower value of medians compared to means (Table I). Nearly one-half had pure nociceptive pain, and one-fifth had pure neuropathic pain. Pain location was reported for 265 patients. More than two thirds (182 out 265, 68.7%) had only one pain location. Seventy-one (26.8%) had two locations. The most common location was the lower back (127 out of 265 patients, 47.9%), followed by lower limbs (46 patients, 17.4%) and the cervical spine (19 patients, 7.2%). The pain clinicians identified an underlying disease to which pain symptoms could be attributed in 179 out of 269 (66.5%) patients, and nearly all patients (246 out of 269 patients, 91.5%) had comorbid medical conditions. Only 20 patients (7.4%) had cancer. A number of patients suffered mobility issues (157 out of 269 patients, 58.4%), anxiety (114...
patients, 42.4%), or sleep disturbances (111 patients, 41.3%). Depression was less frequent (78 patients, 29.0%). The mean (SD) EQ-5D index and VAS scores were, respectively, 0.47 (0.22) and 53.4 (21.6).

**Adequacy of diagnostic labels for pain conditions**

Figure 2 compares the diagnostic labels assigned by referring physicians and pain clinic-

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**Table I.---Patients' socio-demographic and clinical features by treatments prescribed at pain clinics.**

<table>
<thead>
<tr>
<th></th>
<th>All patients (N.=269)</th>
<th>Treatment prescribed at the pain clinic&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Opioids (N.=126)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Non-opioids (N.=95)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Altern. therap. (N.=44)&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender [N. (%)]</td>
<td>161 (62.9)</td>
<td>72 (57.1)</td>
<td>59 (62.1)</td>
<td>27 (64.3)</td>
<td></td>
</tr>
<tr>
<td>Age, years (mean [SD])</td>
<td>59.4 (15.4)</td>
<td>59.2 (15.7)</td>
<td>59.5 (15.2)</td>
<td>59.8 (15.7)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m² (mean [SD])</td>
<td>27.7 (5.0)</td>
<td>27.5 (4.6)</td>
<td>27.6 (4.6)</td>
<td>28.3 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Patients living alone [N. (%)]</td>
<td>60 (24.8)</td>
<td>27 (24.1)</td>
<td>23 (25.8)</td>
<td>9 (24.3)</td>
<td></td>
</tr>
<tr>
<td>Marital status (N. [%])</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/partnered</td>
<td>180 (67.2)</td>
<td>83 (65.9)</td>
<td>67 (71.2)</td>
<td>27 (61.4)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>37 (13.8)</td>
<td>20 (15.9)</td>
<td>12 (12.8)</td>
<td>5 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>30 (11.1)</td>
<td>13 (10.3)</td>
<td>10 (10.6)</td>
<td>7 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Divorced/separated</td>
<td>21 (7.8)</td>
<td>10 (7.9)</td>
<td>5 (5.3)</td>
<td>5 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Educational status [N. [%]]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>36 (13.7)</td>
<td>14 (11.5)</td>
<td>14 (15.1)</td>
<td>7 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>148 (56.5)</td>
<td>70 (57.4)</td>
<td>51 (54.8)</td>
<td>25 (56.8)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>54 (20.6)</td>
<td>28 (23.0)</td>
<td>19 (20.7)</td>
<td>7 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Superior</td>
<td>24 (9.2)</td>
<td>10 (8.2)</td>
<td>9 (9.7)</td>
<td>5 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Working status [N. (%)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>79 (33.3)</td>
<td>40 (36.0)</td>
<td>27 (31.4)</td>
<td>12 (32.4)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>30 (12.7)</td>
<td>12 (10.8)</td>
<td>10 (11.6)</td>
<td>7 (18.9)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>94 (39.7)</td>
<td>45 (40.5)</td>
<td>31 (36.0)</td>
<td>17 (46.0)</td>
<td></td>
</tr>
<tr>
<td>Housewife/husband</td>
<td>32 (13.5)</td>
<td>13 (11.7)</td>
<td>17 (19.8)</td>
<td>1 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Receiving disability benefits</td>
<td>2 (0.8)</td>
<td>1 (0.9)</td>
<td>1 (1.2)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Time since pain onset, years:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>4.1 (7.2)</td>
<td>4.0 (6.7)</td>
<td>4.5 (8.2)</td>
<td>3.6 (6.7)</td>
<td></td>
</tr>
<tr>
<td>median (inter-quartile range)</td>
<td>1.4 (3.8)</td>
<td>1.1 (4.7)</td>
<td>1.5 (4.0)</td>
<td>1.6 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Worst pain severity last 24 h, cm [mean (SD)]</td>
<td>6.7 (2.3)</td>
<td>6.9 (2.2)</td>
<td>6.6 (2.5)</td>
<td>6.1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Current pain severity, cm [mean (SD)]</td>
<td>5.3 (2.6)</td>
<td>5.3 (2.5)</td>
<td>5.2 (2.7)</td>
<td>5.4 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Pain background diseases [N. [%]]&lt;sup&gt;e,f&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervertebral disc protrusion</td>
<td>32 (11.9)</td>
<td>18 (14.3)</td>
<td>11 (11.6)</td>
<td>3 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Spinal osteoarthritis</td>
<td>26 (9.7)</td>
<td>13 (10.3)</td>
<td>8 (8.4)</td>
<td>5 (11.4)</td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>22 (8.2)</td>
<td>17 (13.5)</td>
<td>2 (2.1)</td>
<td>3 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Spinal column stenosis</td>
<td>20 (7.4)</td>
<td>9 (7.1)</td>
<td>7 (7.4)</td>
<td>4 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Intervertebral disc disorder</td>
<td>11 (4.1)</td>
<td>5 (4.0)</td>
<td>3 (3.2)</td>
<td>3 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Pain pathophysiological type [N. [%]]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure nociceptive</td>
<td>122 (47.5)</td>
<td>62 (51.7)</td>
<td>37 (39.8)</td>
<td>23 (54.8)</td>
<td></td>
</tr>
<tr>
<td>Pure neuropathic</td>
<td>51 (19.8)</td>
<td>18 (15.0)</td>
<td>25 (26.9)</td>
<td>7 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Mixed (nociceptive + neuropathic)</td>
<td>79 (30.7)</td>
<td>37 (30.8)</td>
<td>29 (31.2)</td>
<td>12 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Somatoform/dysfunctional</td>
<td>5 (1.9)</td>
<td>3 (2.5)</td>
<td>2 (2.2)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Pain temporal pattern [N. [%]]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous, constant</td>
<td>103 (39.5)</td>
<td>54 (44.3)</td>
<td>30 (31.9)</td>
<td>17 (41.5)</td>
<td></td>
</tr>
<tr>
<td>Continuous, variable</td>
<td>133 (51.0)</td>
<td>62 (50.8)</td>
<td>50 (53.2)</td>
<td>20 (48.8)</td>
<td></td>
</tr>
<tr>
<td>Intermittent/paroxysmal</td>
<td>20 (7.7)</td>
<td>5 (4.1)</td>
<td>10 (10.6)</td>
<td>4 (9.8)</td>
<td></td>
</tr>
<tr>
<td>Evoked/abnormal sensations</td>
<td>2 (0.8)</td>
<td>0 (0.0)</td>
<td>2 (2.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Evoked + continuous or intermittent</td>
<td>3 (1.1)</td>
<td>1 (0.8)</td>
<td>2 (2.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Treatment was unknown in 4 patients; <sup>b</sup> patients treated with any regimen that contained opioid drugs (might include non-opioid drugs or interventional/alternative therapies as well); <sup>c</sup> patients treated with any regimen that contained non-opioid drugs (might include interventional/alternative therapies as well); <sup>d</sup> patients treated only with interventional/alternative therapies (rehabilitative/physical/psychological therapy or regional anaesthetic interventions); <sup>e</sup> reported are conditions present in at least 5% of patients; <sup>f</sup> background diseases to which pain specialists attributed the pain symptoms. Some percentages used a lower denominator than the subgroup size because of missing data. BMI: Body Mass Index; COPD: chronic obstructive pulmonary disease; SD: standard deviation.
out of 204 patients (48.5%). The divergence reached even the level of system organ classes in 43 patients (20.1%). The kappa statistic (0.40) suggests poor-to-moderate agreement between the referring physicians and pain clinicians. Pain clinicians provided more labels (84 patients received more than one, compared to 35 before referral). Most labels related to spinal or neuraxial conditions (Figure 2). The labels from both groups of physicians differed in 99

Figure 2.—Frequencies of diagnostic labels for pain conditions provided by the referring doctors (left panel) and pain clinicians (right panel). Included in the list are labels assigned to at least 5 patients by physicians in either group. The box to the right shows the mean reduction in pain severity between baseline (initial visit) and the 3-month follow-up visit within some subgroups of patients.

The negative sign denotes that pain severity increased from baseline; the change from baseline was significant (the 95% confidence interval did not include zero); the change from baseline was non-significant (the 95% confidence interval included zero).
Pain clinicians considered that treatments were appropriate in only 39.7% of patients. Treatment was modified in 94.8% of patients at the pain clinics. As a result, 221 out of 269 (82.2%) continued on drugs, and 175 (65.1%) started or continued on interventional or alternative therapies. Most patients received more than one treatment (67.0% more than one drug and 17.7% more than one interventional/alternative therapy). The most common changes were from backache to either intervertebral disc protrusion (9 patients), facet joint syndrome (7 patients), spinal osteoarthritis (5 patients), sciatica (4 patients) or lumbar spinal stenosis (3 patients). Other common changes were from sciatica to either intervertebral disc protrusion (3 patients) or facet joint syndrome (3 patients). Other changes occurred in two or fewer patients.

**Treatments for pain at pain clinics**

Consumption of drugs had already begun when patients were referred to pain clinics in 240 out of 269 (89.2%); interventional and/or alternative therapies had been started in 69 (25.7%). Pain clinicians considered that treatments were appropriate in only 39.7% of patients. Treatment was modified in 94.8% of patients at the pain clinics. As a result, 221 out of 269 (82.2%) continued on drugs, and 175 (65.1%) started or continued on interventional or alternative therapies. Most patients received more than one treatment (67.0% more than one drug and 17.7% more than one interventional/alternative therapy). Figure 3 compares treatments prescribed by referring physicians and pain clinicians. Pain clinicians prescribed more opioids and co-adjuvants (anticonvulsants, antidepressants) and extended the use of interventional/alternative therapies; but
also calculated for the subgroups of patients who shared a diagnostic label that represented at least 3% of the sample (Figure 2). Patients with myofascial pain syndrome, spinal stenosis, facet joint syndrome, and osteoarthritis experienced smaller pain reductions than those with sciatica, procedural pain or backache. The temporal pattern of pain changed in 23 out of 254 (9.1%) patients during the first month and in 13 patients out of 235 (5.5%) during months 2 and 3. In most cases, the pain was still continuous, yet had shifted from constant to variable in severity or from variable to constant. Thirteen patients went from continuous to intermittent pain. Pain clinicians changed the diagnostic label for 10 out of 254 patients (3.9%) and for 11 out of 235 patients (4.7%) during the first month and during months 2 and 3, respectively. Treatments were modified in 73 out of 254 patients (28.7%) during the first month and in 65 out of 235 patients (28.7%) during months 2 and 3. Most of these changes concerned the group treated with opioids.

The measures of HR-QoL also improved. The mean (95% CI, effect size) changes (improvements) from baseline of the EQ-5D index and VAS scores were, respectively, 0.16 (0.13 to 0.19, 0.73) and 6.7 (2.8 to 10.6, 0.31).

A total of 8 serious adverse reactions related to pain medications occurred in 7 patients during the study. Six of these reactions were related to opioids. They led to either treatment discontinuation (4 cases) or dose reduction (2 cases).

Follow-up: effectiveness and safety of treatments for pain

At the end of the study, 146 (62.1%) and 141 (60.0%) patients considered that their pain symptoms and functional status were better or much better. The investigators’ similarly appraised that pain outcomes were positive in 158 patients (67.5%) and functional status improved in 142 (60.7%).

The 24-hour worst and current pain severity decreased on average 2.1 cm (30.9% decrease, 95% confidence interval, CI: 1.7 to 2.5 cm) and 1.5 cm (27.8% decrease, 95% CI: 1.1 to 1.9 cm), respectively. The 24-hour worst pain severity decreased more in patients treated with drugs than in those treated only with interventional/alternative therapies. The opposite was true for the current pain severity. These differences did not reach statistical significance. Patients treated with opioids attained on average slightly lower reductions in the 24-hour worst pain severity (2.1 cm, 95% CI: 1.5 to 2.7 cm) than patients treated with non-opioids (2.3 cm, 95% CI: 1.7 to 2.9 cm). Pain severity reductions were prescribed less plain analgesics (metamizole, paracetamol) and nonsteroidal antiinflammatory drugs (NSAIDs). Prescribing varied from one family of diagnoses to another (Figure 4). Also, pain clinicians made a more balanced use of opioids across pain conditions than the referring physicians did (Figure 2).

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A total of 8 serious adverse reactions related to pain medications occurred in 7 patients during the study. Six of these reactions were related to opioids. They led to either treatment discontinuation (4 cases) or dose reduction (2 cases).
Discussion

The refinement of diagnoses and diversification of treatments by hospital pain clinicians in Catalonia resulted in a net improvement in pain features, particularly severity, and of HR-QoL. Such improvements are consistent with systematic reviews of the reported effectiveness of multidisciplinary pain therapy measured in terms of lower pain severity and improved HR-QoL and functioning.\textsuperscript{19, 20}

The profile of patients described in prior population studies of chronic pain in Spain and other European countries,\textsuperscript{21, 22} resembled partially the aged population with low academic degrees and mostly composed of women living in urban areas that was observed in this study. Notwithstanding, there were noteworthy differences. The women-to-men ratio, the mean age and the proportion of patients on pain medications on referral were higher in this study, whilst the level of employment and the proportion of patients treated and referred by primary care physicians were lower and the time since pain onset shorter than in the cited studies. The higher proportion of patients on pain medications and the shorter time since pain onset despite the older ages in this series suggest that the pain conditions were more severe or challenging than in the total of patients with chronic pain. Short referral times might relate to the perceived need for advice on pain management of referring physicians facing challenging patients. The fact that most patients were referred by orthopaedists instead of primary care physicians, who deal with most patients with chronic pain in Spain,\textsuperscript{23} may be because the orthopaedists see patients with more serious conditions than primary care physicians. However, it may also be a consequence of the difficulties primary care physicians have in prioritizing treatment options in patients with multiple chronic conditions and in deciding when to refer them to pain clinics.\textsuperscript{24} Thus, our data support the rationale behind the promotion of greater collaboration between hospital pain clinicians and primary care physicians, including the adoption of appropriate referral practices.\textsuperscript{6} It is worth noting that similar patterns, including the low referral rate from primary care, were observed in other series of patients recruited from Spanish pain clinics.\textsuperscript{8, 10, 25, 26}

The agreement between referring doctors and pain clinicians’ diagnoses was moderate at best. An accurate diagnosis is important for achieving good pain control, and the fact that the pain clinicians were able to provide more specific diagnostic labels than referring doctors supports the usefulness of the hospital pain clinics. In consonance with diagnoses, pain clinicians also varied patients’ treatments. The use of antidepressants, antiepileptic agents, opioids and interventional/alternative therapies increased at the expense of plain analgesics and NSAIDs. The former medicines are more specific or potent, but also more likely to produce side effects and other complications. Their tailored use by pain clinicians is expected from their expertise. Prescription varied according to diagnoses, but was also influenced by other factors. For example, the prescription of opioids augmented with patients’ education level. Pain clinicians may have felt more confident in assessing the risks associated with prescribing opioids to patients with higher levels of education. The substantial use of opioids in this series supports the notion that the concerns about their use in non-cancer patients that have arisen in US may not be fully exportable to Europe.\textsuperscript{27}

The improvements attained during the 3-month follow-up were considerable. The mean decrease in pain severity of about 30% corresponds to a moderately significant improvement according to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.\textsuperscript{28} Patients’ baseline EQ-5D index scores were well below the normative data for Spain\textsuperscript{29} and other countries.\textsuperscript{30} At the end of the study, they continued to be under normative data, although the improvements observed (0.16 points, or 16% of the full breadth of the scale) are twice the minimum important difference for a HR-QoL measure and correspond to a moderate-to-large effect size (0.73) that was mapped to a moderate improvement in an anchor-based method for interpreting HR-QoL changes.\textsuperscript{31}
Limitations of the study

A limitation of this research is the absence of information about patients who were not referred to pain clinics, as knowing more about such patients would possibly have revealed differences between those who are and are not referred. The time since pain onset was shorter than six months in almost one third of the sample. The findings might not be fully applicable to chronic pain patients. In particular, changes from baseline might have been up-biased as the conditions underlying acute pain could have improved or even resolved within the three-month time frame of this study. Administrative delays prevented the simultaneous participation of all sites. Biases might have come up from variations of environmental and other factors throughout the study period.

Conclusions

In conclusion, the current model of care provided at hospital pain clinics in Catalonia effectively improves outcomes of challenging cases referred by various medical specialists. The refinement of diagnoses and the diversification and tailoring of therapies are factors that contribute to this accomplishment. The quota of patients referred from primary care is low compared with the prevalence of chronic pain in this setting. It seems appropriate to foster communication, referral and collaboration between primary care physicians and pain clinicians to make these gains accessible to more patients.

Key messages

— There is little empirical data on the utilization of pain clinics and the outcomes attained. This study evaluated the referral of patients with chronic pain to hospital pain clinics and their outcomes.

— Patients referred to pain clinics appear to have more severe or challenging clinical conditions that the total of patients with chronic pain.

— Pain clinicians provided more specific diagnostic labels than referring physicians. In consonance with diagnoses, pain clinicians also made substantial changes in patients’ treatments.

— Many patients improved after referral. Referral was not homogeneous across medical specialties. Fostering referral from primary care might serve to improve outcomes in numerous patients.

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Spatial relationship of i-gel® and Ambu® AuraOnce™ on pediatric airway: a randomized comparison based on three dimensional magnetic resonance imaging

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ABSTRACT

BACKGROUND: Gross morphological differences exist among different brands of pediatric supraglottic devices (SGDs). The aim of this study is to compare the spatial relationship of i-gel® and Ambu® AuraOnce (AO)™ on pediatric airway based on three dimensional (3-D) magnetic resonance imaging (MRI) measurements.

METHODS: Sixty patients up to 12 years of age were enrolled and assigned in two groups, i-gel® or Ambu® AO™. After confirmation of proper placement of these SGDs, 3-D MRI scans of head and neck were performed. Another native scan was also obtained after removal of the SGD for comparison.

RESULTS: i-gel® produced significant degree of compression of the tongue (P<0.001) while Ambu® AO™ significantly reduced the axial diameter of glottis (P=0.033) compared to their native values. Both i-gel® and Ambu® AO™ significantly reduced the area of the glottic opening (P<0.001 and P=0.007 respectively); and increased the distance between the hyoid bone and cervical spine (P<0.001 and P=0.001 respectively) in comparison to their corresponding native values. Bowl of i-gel® produced greater dilation of the upper esophageal sphincter at all levels of measurement- upper (P<0.001), middle (P=0.001) and lower (P=0.015) in comparison to Ambu® AO™.

CONCLUSION: Based on 3-D MRI measurements done on living patients, both SGDs distorted the anatomy of pediatric airway compared to their respective native values to variable extent. The relevance of these effects needs further studies on larger patient group in order to reduce morbidity on pediatric airway.

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Key words: Laryngeal masks - Magnetic resonance imaging - Airway management.

Laryngeal mask airways (LMAs) are supraglottic devices (SGDs) and used extensively for maintenance of airway under general anesthesia (GA) in fasting adult and pediatric patients. 1 Although the manufacturers of some of these devices claim that the shape of their SGD has been designed to fit the glottic area based on human cadaveric studies, 2, 3 there ex-
ist gross differences in shape, size of the bowl, tip design, and the curvature of the ventilating tube among these SGD.

Based on structural dissimilarities, we hypothesized that these SGD may have different impact on the delicate pediatric upper airway. On search of literature we found studies focused mainly on clinical performance of these SGD or assessment of position of SGD by fiberoptic evaluation. There is scant literature on the magnetic resonance imaging (MRI) based anatomical relationship (in situ) of these SGD on pediatric airway and we could not find any study in which spatial effect of these devices was studied by using three dimensional (3-D) MRI. We selected i-gel® and Ambu® AO™ based on their MRI compatibility and designed this prospective randomized clinical study to quantify and compare their spatial relationship on the pediatric airway under GA using 3-D MRI measurements.

Materials and methods

After getting approval from Institutional Review Board (IRB) of King Saud University, Riyadh, Saudi Arabia and written informed consent from parents, 60 pediatric patients were enrolled in the study and were randomly divided in two groups by an online software (www.randomizer.org).

Clinical trial registration

ClinicalTrials.gov, NCT02494765.

Inclusion criteria

The patients included in the study were ASA physical status I and II and age up to 12 years, including infants weighing >5 kg. They were scheduled to undergo elective MRI of head and neck area under GA for some medical or surgical disease not involving oral cavity, larynx, pharynx and neck and not likely to require use of muscle relaxants.

Exclusion criteria

Cooperative patients who accepted to undergo the procedure under sedation or without GA, patients with upper respiratory tract infection, fever, known to be suffering from deformity of the face, larynx, pharynx or neck, potentially difficult intubation, full stomach patient, contraindication to SGD placement or GA, history of previous failed SGD insertion or requiring emergency endotracheal intubation during the procedure and the patients whose trachea were already intubated were excluded from the study.

Anesthesia technique

All patients were fasting for 6-8 hours before MRI and no premedication was given to any patient. After placement of standard non-invasive monitors (ECG, SpO2, NIBP), all of them received induction of GA with either 2-3 mg/kg intravenous propofol or inhalational with 8% sevoflurane in 100% O2. Selection of appropriate size of SGD was done on the basis of body weight and according to the recommendations of the manufacturer and was inserted following their guidelines. Before insertion of the Ambu® AO™, its cuff was deflated completely to remove air and filled with a mixture of 0.025 mmol/mL gadolinium (MRI contrast material) in normal saline and then evacuated again to give a wedged shape to the deflated cuff. After insertion, its cuff was filled with the same mixture of normal saline containing the same contrast material. The cuff was filled to an intra-cuff pressure of 44 mmHg measured with a pressure transducer (Argon DTX Plus TM). It was considered a successful SGD placement if at least 7 ml/kg expired tidal volume was achieved using 10 mL/kg inspired tidal volume. Until return of adequate spontaneous ventilation, gentle manual intermittent positive pressure ventilation was used (expiratory valve was adjusted at a pressure of 20-25 cmH2O) and the anesthetic depth was maintained with 2.5-3% inspiratory sevoflurane in 50% O2 air mixture to keep end expiratory sevoflurane concentration between
1.3-1.5 minimum alveolar concentration. Leak pressure was determined on circle system of the machine for all the patients including those with weight <20 kg. For this, the expiratory valve was adjusted at a pressure of 30 cmH2O with a fresh gas flow of 3L/min O2 until an audible leak was heard and then released completely.8

After confirmation of proper SGD placement and anesthetic data collection, the patients were shifted to MRI table for imaging. No muscle relaxant or narcotic analgesic was used in this study and all the patients in both the groups were spontaneously breathing during the scanning process. After the first scan, another scan of the neck and airway was obtained after removal of SGD in deep plane of GA and was labelled as “native scan”. Before removal of the SGD the inspired sevoflurane concentration was increased to 6% to increase the depth of GA. After removal of the SGD, a soft suction catheter (ChannelMED®) was inserted orally and fixed to the angle of mouth by a soft paper tape and connected to 4-6 L/min O2 flow containing 4-6% sevoflurane. The objective was to keep the patients anesthetized during the imaging (native scan) and prevent any movement. An additional fine suction catheter, size 10 Fr, was also inserted orally to reach mid esophagus. The objective of this second suction catheter insertion was to provide little space behind the base of the tongue for breathing to avoid complete airway obstruction under deep plane of GA. A second sequence of images for native scan was taken in this setting and the process lasted approximately 3-4 min in duration.

**Outcome measures**

The primary end point of this study was the degree of the compression of tongue by these SGDs. Secondary endpoint of the study was the depth of insertion of the tip of these SGDs into upper esophageal sphincter (UES). Additional endpoints were their effects on the area of the glottis, distance between arytenoids and spatial effects on other anatomical structures.

**MRI scans measurements**

Scanning was performed in supine position with a 3T whole-body scanner (MAGNETOM, Verio, Siemens Healthcare, Erlangen, Germany) using the customary head and neck coils. The standard scanning protocol comprised of sagittal 3D T1 magnetization-prepared rapid gradient-echo (MP-RAGE) sequence before and after removal of SGD. Image resolution was selected to have a pixel size of (0.9x0.9x0.9) mm³, TE/TI/TR was 3/900/1700 ms and flip angle: 9 degree. Image reconstruction and measurements based on a commercial work station (TeraRecon, INC., Aquarius, iNtuition™ Edition, Ver. 4.4.11.49.4356, San Mateo, CA, USA).

All of the MRI images were assessed and measured by an unblinded senior radiologist. Descriptions/ definitions of various MRI measurements are shown below.

**IMPACT OF THE SGD ON ADJACENT SOFT TISSUES**

*Thickness of the tongue.*—T1 sagittal midline image was used to determine the greatest distance from the upper tongue surface to lower edge of geniohyoid muscle (Figure 1A, B).

*Position of the hyoid bone relative to the cervical spine.*—Hyoid bone location relative to cervical spine was determined by computing the minimum distance from the dorsal margin of hyoid bone to the ventral border of the opposing vertebra (Figure 1C, D).

**DEPTH OF INSERTION OF SGD AND IMPACT ON THE UES**

*Relative to the glottis.*—It was defined as a perpendicular measurement on sagittal images between two parallel lines; one of which passes horizontally through lower margin of glottic opening and the other touching the tip of the SGD (Figure 1A, B).

*Relative to the spine.*—It was defined as a perpendicular measurement on sagittal images between two parallel lines; one of which
passes horizontally at the level of the inferior border of fifth cervical vertebra and the other touching the tip of the SGD.

**Area of UES occupied by the SGD**

On Axial T1, three levels of cross-sectional areas of UES were measured (a) upper margin (b) middle (c) lower margin of the craniocaudal extension of cricoid lamina (Figure 2).

**Impact of the SGD on the Glottis**

*Glottic area and dimensions.—* This was measured at the narrowest glottic part after re-orientation of the respective axial T1 slices to

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Figure 1.—Sagittal T1 MRI of two patients: A) correspond to patient with Ambu® AO™ and B) patient with i-gel®, image C and D correspond to the same patients respectively with the supraglottic airway devices removed. The double arrowhead dashed lines are used to show the distance between the upper tongue surface and the lower edge of geniohyoid muscle. The double arrowhead solid lines are used to show the distance between the dorsal margin of hyoid bone (HB) and the ventral border of the opposing vertebra. The double open arrowhead solid lines are used to show the depth of insertion caudal to glottis inlet (GI).
be parallel to the vocal cords and the encircled area of the glottis.

**Distance between arytenoid cartilages.**—It was defined as the distance between the most medial parts of the vocal process of the arytenoid cartilages on axial T1 slices re-oriented as above.

**Statistical analysis**

The data was analyzed with SPSS version 22 Statistics™ (IBM SPSS Inc., Chicago, IL, USA). Distribution of data was determined by Shapiro-Wilk test which showed that the data was normally distributed. Independent-samples T test was used to evaluate the difference between the effects of the individual SGD. Paired Samples t-Test was used to assess any difference between the variables with and without the SGD device. Wilcoxon Mann Whitney U Test was used to evaluate difference between the ranked data. Pearson’s Chi Square test was used to determine the difference between the categorical data. A P value <0.05 was considered significant. The sample size was calculated on the basis of primary end point of the study for which we used data from
our pilot study and considered that mean difference of 75% tongue compression would be clinically important. In our pilot study, mean tongue compression produced by i-gel® and Ambu® AO™ were 0.41±0.5 and 0.00±0.60 cm respectively. Based on these figures and using 2-sided 5% significance level and a power of 80%, priori power analysis estimated that at least 30 patients would be required in each group.

Results

Sixty patients met the inclusion criteria and were primarily enrolled in the study (Figure 3 Consolidated Standards of Reporting Trials

![Flowchart](image-url)
[CONSORT]). Fifty nine patients completed the study (30 in Ambu® AO™ and 29 in i-gel® group). One patient in i-gel® group had spontaneous movement while second part of the scanning was in process (without SGD) and the imaging cycle could not be completed and was excluded from the study. There was no difference between the groups in age, gender, weight, ASA physical status of the patients and the size of SGDs used and the leak pressure in both the groups (Table I).

Table II shows the impact of the SGDs on tongue. Both of them reduced the distance from surface to floor of the tongue compared to their respective native values. However, the degree of reduction of the distance was statistically significant in i-gel® group (P<0.001) while was insignificant in Ambu® AO™ group. As shown in Table II, both SGDs reduced axial diameter of glottis, however it was statistically significant in Ambu® AO™ group only (P=0.033). Both SGDs significantly reduced the area of the glottic opening (P<0.001), reduced the distance between the arytenoids (i-gel® P<0.001, Ambu® AO™ P=0.007) and increased the distance between the hyoid bone and cervical spine (i-gel® P<0.001, Ambu® AO™ P=0.001) in comparison to their respective native values.

Table III shows the comparison of the depth of insertion of both SGDs and their effects on the UES. The depth of insertion of both the SGDs relative to glottis and relative to cervical spine was similar in both the groups. However,

<table>
<thead>
<tr>
<th>Table I.—Demographic data of the patients, size of supraglottic device used and the leak pressure.</th>
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</thead>
<tbody>
<tr>
<td>i-gel®</td>
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<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>ASA status I/II</td>
</tr>
<tr>
<td>Sex M/F</td>
</tr>
<tr>
<td>Size of supraglottic device 1.5/2/2.5/3</td>
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<tr>
<td>Leak pressure (mm Hg)</td>
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</table>

Values expressed as mean±SD = Standard deviation.

<table>
<thead>
<tr>
<th>Table II.—Effects of the supraglottic device on the laryngeal area and adjacent soft tissues.</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-gel®</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Distance from surface to floor of tongue (cm)</td>
</tr>
<tr>
<td>Axial diameter of glottis (cm)</td>
</tr>
<tr>
<td>Glottic area (cm²)</td>
</tr>
<tr>
<td>Distance between arytenoids (cm)</td>
</tr>
<tr>
<td>Distance between hyoid bone and CS (cm)</td>
</tr>
</tbody>
</table>

CS: cervical spine; Native: values under deep general anesthesia after removal of supraglottic device. Values expressed as (mean±standard deviation).

<table>
<thead>
<tr>
<th>Table III.—Depth of insertion and effect of the supraglottic device on the upper esophageal sphincter.</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-gel®</td>
</tr>
<tr>
<td>Glottis to tip distance (cm)</td>
</tr>
<tr>
<td>CS to tip distance (cm)</td>
</tr>
<tr>
<td>Area dorsal to CC upper margin (cm²)</td>
</tr>
<tr>
<td>Area dorsal to CC mid-level (cm²)</td>
</tr>
<tr>
<td>Area dorsal to CC lower margin (cm²)</td>
</tr>
</tbody>
</table>

C: cervical vertebra; CC: cricoid cartilage. Values expressed as (mean±standard deviation).
i-gel® caused greater degree of dilation of UES at all the three levels of measurement—upper, middle and lower (P<0.001, P=0.001, P=0.015 respectively).

Discussion

Three dimensional MRI is a non-invasive and robust method for studying soft tissues’ anatomic relationships. Our research is unique in that we used 3-D MRI for these measurements. Our main results show that: 1) i-gel® shaft produced greater degree of compression of the tongue compared to Ambu® AO™; 2) both i-gel® and Ambu® AO™ increased the distance between the hyoid bone and cervical spine; 3) both the SGDs reduced glottic area and distance between the arytenoids; 4) i-gel® produced greater dilation of the UES compared to Ambu® AO™.

Compression of oropharyngeal soft tissues by SGDs can have harmful effects and is likely to result in vascular compromise and pressure neuropraxia of multiple cranial nerves. The results of our current study show that in patients where i-gel® was used, there was a significant compression of the tongue and reduction of distance from surface to its floor compared to the native scan. As the curve of the shaft of i-gel® is comparatively less than that of Ambu® AO™, in our opinion, a compression force was exerted by the shaft of the i-gel® (from surface to floor of the tongue) which decreased the distance of the tongue between the surface to its base. In a similar study in adult volunteers, Russo et al. also found greater degree of tongue compression caused by the shaft of the i-gel® in comparison to LMA supreme™, whose curved shaft produced little effect. As tongue is a soft structure and this compression would be translated in the caudal and lateral directions, thus it can be speculated that such compression by i-gel® would push the tongue against the mandible which can compress the lingual or alveolar nerves. Though this compression did not affect any of our patients in this study, it is likely to adversely affect the delicate airway of pediatric patients especially in prolonged surgeries. Lingual nerve paralysis secondary to the use of i-gel® has already been reported.

In this study we found that the glottic area and distance between arytenoids was reduced by both of the SGDs compared to their corresponding native values. The cause of the reduction in the area of glottic opening by SGD is not clear. As cuff of the SGD lies lateral to arytenoid cartilages and its inflation tends to bring arytenoids together and reduce the transverse diameter of the glottis, it can be a likely factor in patients where Ambu® AO™ was positioned. Contrarily, i-gel® has no cuff to be inflated, therefore, we may have to explore other odds in this respect. Moreover, general anesthetics reduce the area of the glottic opening, however, in our current study, the native values were also obtained while the patients were anesthetized.

Our results show that both SGDs significantly increased the distance between the cervical spine and hyoid bone and produced ventral displacement of hyoid bone compared to their native values. The hypoglossal nerve lies above the greater horn of the hyoid bone at the angle of the mandible (before turning forwards and medially towards the tongue) and is vulnerable to neuropraxia due to an overinflated or mal-positioned cuff at this level. However, to the best of our knowledge, the implications of a properly placed SGD with normal cuff pressure on the neurovascular tissues in this region has not been investigated so far.

The tip of the SGDs sits at the level of UES and leads to its dilation and distention which is related to its size and design. In adult patients, Roux et al. found greater incidence of gastroesophageal reflux (GER) with SGD compared with face mask and they related this effect to the physiological relaxation of the lower esophageal sphincter (LES) provoked by the distension of UES produced by SGD. They also noted that the relaxation of LES was not related to degree or pressure inside the cuff; only the stimulation of pharyngeal structures by the presence of cuff provoked this response. Barker and colleagues found 25% incidence of GER in adult patients in whom SGD was placed. If we assume that the effect of SGD...
on pediatric UES is similar to that of adults’ UES then both i-gel® and Ambu® AO™ should probably affect pediatric LES in a comparable manner resulting in its reflex relaxation. Nonetheless, it is not fair to generalize the results of the above mentioned study done on adults to pediatric patients (Supplementary Figures 1, 2, online content only).

**Limitation of the study**

In this study native scans were taken under deep plane of anesthesia at the conclusion of the procedure. Although these native scans were taken without the presence of SGDs, the patients were still under the effect of sevoflurane which is likely to affect the tone and resting position of soft tissues in pediatric airway and these scans may be different from a patient who is not under GA. However, it was not possible to get native scans without GA. Secondly, under deep GA, the tongue can fall back and obstruct the airway; to counteract this, we inserted a soft suction catheter orally into the esophagus to create a small space behind the base of the tongue for breathing. We deliberately avoided insertion of oral airway for this purpose as this rigid device was likely to affect the shape and contours of the soft tissues in this region. The presence of a soft oral suction catheter might have affected the shape of UES. However, it was placed in all patients and is likely to affect both the groups in a similar way. Thirdly, we filled Ambu® AO™ cuff with saline gadolinium mixture instead of air. Although, filling of cuff with fluids may lead to difference in their performance or spatial effects on the surrounding tissues, measurements could not have been accurate without using this contrast. Fourthly, in this study we compared only two types of SGDs, (one from first generation and the other from second generation). Our selection was based on their MRI compatibility and their availability in our institution and these results cannot be extrapolated on other types of SGDs. Additionally, we did not perform fiberoptic evaluation of the correct placement of SGDs because literature shows that there is no correlation between clinically patent airway and the fiberoptic view, therefore, in this study we relied on our clinical assessment. Moreover, all of our patients were spontaneously breathing. As use of neuromuscular blocking agents affect tone and resting position of airway muscles, hence, our results may not be generalized in cases where muscle relaxants are used.

**Conclusions**

Based on 3-D MRI calculations done on living patients, both i-gel® and Ambu® AO™ distort the anatomy of airway compared to their respective native values to variable extent. These SGDs also have contrasting spatial relationship in some measurements, therefore, may differ in morbidity to delicate pediatric airway. As the contours of current SGDs are based on cadaveric studies, the results of our research (done on living patients) and future studies done on larger patient group may help to improve their design in order to reduce morbidity on pediatric airway.

**Key message**

— Supraglottic devices differ in shape and contours despite the fact that their manufacturers claim to use cadaveric studies to help their design.

— Based on our distinctive study in which 3-D MRI measurements were used, both i-gel® and Ambu® AO™, distort the anatomy of the airway to variable extent compared to respective native values which may be related to the morbidity of these devices on pediatric airway. For some variables measured in this study, both devices contrasted from each other.

— These devices may differ in their morbidity due to differences in their shape and design. Through this research (done on living patients) we suggest future prospective studies on larger patient group to evaluate spatial relationship in order to improve the design for reduction in their morbidity on pediatric airway.
References


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For supplementary materials, please see the online version of this article.
Outpatient therapeutic chronic opioid consumption in Italy: a one-year survey

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ABSTRACT

BACKGROUND: In Italy since the 38/2010 law concerning Palliative Care and pain therapy has been promulgated, the consumption of opioids started increasing. However, despite the availability of a large amount of data regarding opioid prescription, a database including all patients on chronic opioid therapy does not yet exist.

METHODS: Retrospective analysis of analgesic opioid consumption was performed between January 2013 and December 2013 using the data of national refunded medications for outpatients, collected by Italian Ministry of Health. We considered patients on chronic opioid therapy those patients with at least three opioids prescriptions in three consecutive months and/or six opioid prescriptions in six even not consecutive months in the observation period. We considered cancer patients those with neoplasm exemption code in the scheduled prescription and/or patients with at least one ROOs prescription (rapid onset opioids, approved in Italy for Break Through Cancer Pain-BTCP- only). We also calculated the patient’s morphine daily mean dose (MED) converting all prescribed opioids in equivalent of morphine using specific conversion tables.

RESULTS: This census revealed a total of 422,542 patients in chronic therapy with opioids, of those 369,961 with chronic non-cancer pain and 52,581 with chronic cancer pain. This represents about 4% of the estimated requirement in Italy for both groups based on previous surveys regarding the prevalence of chronic pain.

CONCLUSIONS: Relatively to MED, We found that in Italy chronic cancer pain patients receive doses similar to patients with cancer pain in other Literature reports, whereas patients with chronic non-cancer pain received lower dosages.


Key words: Chronic pain - Neoplasms - Analgesics, opioid.

In Italy since the 38/2010 law regarding Palliative Care and pain therapy has been promulgated, the prescription of opioid drugs was increasing.1 The same trend was documented worldwide.2 Therefore, analysis of national analgesic consumption can provide useful information about pain medication use trends and might enable us to better understand behavior associated with drug prescription.

Analysis of opioid consumption is particularly important, since opioids are key medications for the treatment of moderate to severe pain, and some of them are listed by the World Health Organizations as essential drugs.3

In Italy despite the availability of many data regarding total opioid prescriptions, a database including all patients on chronic opioid therapy still does not exist.

In other words, we can identify the total prescribed opioid amount but we do not know
how many patients are using those drugs, and in which proportion opioids are distributed among them.

We also do not know the mean opioid dose (MED) prescribed to patients on chronic therapy with these drugs.

Identifying appropriateness related to adequacy in terms of amounts and trends of opioid consumption provides precious data for evaluating policy and economic changes.4

The aim of the study was to describe the prescription patterns in patients on chronic opioid therapy in term of number of chronic patients and opioid dosage prescribed. Data, based on register of outpatients refunded prescriptions obtained from Italian Ministry of Health, are registered between January 2013 and December 2013.

Materials and methods

Retrospective analysis of analgesic prescriptions was carried out between January 2013 and December 2013 using data of national refunded medications for outpatients, furnished by Italian Ministry of Health (Office number III, Head Quarter Health Planning). According to the ATC classification (Anatomical, Therapeutic, Chemical) system data was collected from N02A group (central analgesics), with exception of acetaminophen alone. Parenteral formulations and in-hospital prescribed drugs were excluded from the collected data.

Drugs records included the following substances, alone or in combination: morphine (except intravenous formulations), oxycodone, hydromorphone, codeine, tramadol, fentanyl (except intravenous formulations), tapentadol, and buprenorphine except sublingual formulations.

Data from the included prescriptions were: anonymous patient personal identification code, region of residence, ticket exemption code (if present), sex, age, ATC prescribed, date of prescription, dose of the prescribed drug and number of packages prescribed.

Patient’s age was presented divided in multiple groups of five year each (for example 50-54 years, 55-59 years).

We defined “a chronic opioid user” a patients that, within the twelve months of survey, received at least 3 opioids prescriptions in three consecutive months (according to the International Association for the Study of Pain – IASP – definition of chronic pain5 and/or six opioid prescriptions in six months within the twelve months of survey, even in non-consecutive months.

We first divided the patients in three groups: total patients (who received at least one opioid prescription in the 2013), cancer patients and non cancer patients, identifying cancer patients those having the neoplasm Italian ticket exemption code in the single prescription and/or those that received in 2013 year at least one breakthrough cancer pain (BtCp) drug prescription, approved in Italy exclusively for cancer pain (fentanyl citrate, fentanyl buccal tablets, fentanyl sublingual tablets, fentanyl nasal spray).

We also analyzed the monthly chronic patients distribution (from three to twelve months according to chronic opioid user definition described above).

Subsequently all opioid prescribed for each patient were converted using specific conversion tables 6, 7 in MED (morphine equivalent dosage) and them analyzed.8

Statistical analysis

Data are presented as absolute values, percentage or mean±standard deviation (SD); the mean dose of MED are represented as a value and IC 95 (interval of confidence 95%). Sex differences in opioid prescriptions and prescription trends in all patients, cancer and non-cancer ones, were analyzed with two-tailed Student t test for unpaired samples.

Results

A total of 2,520,382 patients had at least one opioid prescription between January 2013 and December 2013 (Table I), 422,542 (prevalence on total Italian population 0.7%) were patients on chronic opioid therapy (16.75% of total opioid prescription-receiving patients
in 2013). We then divided chronic patients in two groups: cancer patients (according to the above mentioned criteria) reaching 52,581 patients (2.08% of total opioid users, prevalence on total Italian population 0.08%) and non-cancer patients 369,961 (representing 14.67% of total patients on opioid therapy, prevalence on total Italian population 0.62%).

A demographic description of sex and age distribution (Figure 1) in chronic patients shows that most of the patients are over 65 years old, mainly females for each age class. Such distribution differs when we analyze those patients dividing them in cancer and non-cancer subgroups: cancer patients have a minor mean age and do not present significant sex difference (Figure 2), non-cancer patients on the other hand are mainly elderly females (Figure 3).

The two tailed t Student test for unpaired samples showed a P<0.05 in sex distribution for all age clusters from 50-54 in overall chronic patients and in non-cancer patients (Figures 1, 3).

Total opioid prescriptions (Table II) during the observation period in Italy has been

<table>
<thead>
<tr>
<th>Months of treatment</th>
<th>N. Chronic patients</th>
<th>Chronic cancer patients</th>
<th>N.</th>
<th>Chronic non cancer patients</th>
<th>N.</th>
</tr>
</thead>
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<td>28,698</td>
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<tr>
<td>Total</td>
<td>2,520,382</td>
<td>422,542</td>
<td>149,861</td>
<td>52,581</td>
<td>2,370,521</td>
</tr>
</tbody>
</table>

Table I.—Chronic pain patients distribution: total (in bold) and monthly of opioid use; data divided also in chronic oncological and chronic non oncological patients.

Figure 1.—Age and sex distribution in chronic opioid users. X axys: age groups (years); Y axys: number of patients.
9,323,790, of those 5,622,172 were for chronic users (60.3%), and the remaining 3,701,618 (39.7%) for non-chronic patients.

The seven most prescribed opioids in general population were the following (in descending order): weak opioids (codeine 35.2% and tramadol 21.5%), oxycodone 18.6%, fentanyl 11.1%, tapentadol 6.1%, morphine 2.4%.

In chronic patients however codeine was less prescribed (27.3%) in favor primarily of oxycodone (21.5%) and fentanyl (15.2%).

The mean number of annual opioid prescription per patient was 3.7±2.5; the non-chronic patients had a mean of 1.8±0.9 annual prescriptions, chronic patients 13.3±8.1 prescription per year, with a mean of 20.6±14.5 prescriptions in chronic cancer patients.

Finally we measured the mean daily opioid
to calculate, because the ROOs (rapid onset opioids) formulation of fentanyl, don’t have a defined conversion value.

We add a flowchart to describe the classification of total opioid patient users in chronic and acute opioid users for presumed cancer and non-cancer pain and the distribution of those prescriptions (Figure 4).

**Discussion**

Presented data show (Table I) that between January 2013 and December 2013 the number of chronic prescriptions of opioids in Italy was 422,542 (prevalence of 0.7%, divided in chronic non cancer pain 0.62% and chronic cancer pain 0.08%) compared to 2,520,382 non-chronic opioid prescription. The chronic use of opioid painkillers in Italy hence is still
an exception rather than a rule, despite various warnings, hidden and explicit campaigns that aim to emphasize elevated chronic use and an abuse potential coming from USA.9 More than 80% of the chronic users suffer non-cancer pain, a fact that might sign of a cultural change in physician behavior, probably promoted by Italian law 38/2010 10 that encourages- at least in initial phase of pain management- and simplifies opioid prescription for moderate to severe pain independently of its origin. This trend emerges despite the widespread opio-phobia that still relegates Italy to the bottom of opioid consumers list in Europe.11

The prevalence of patients with chronic non cancer pain (with moderate to severe intensity) in Italy is approximately 20% namely (12,000,000 residents),12 of those 422,000 during the observation period were receiving prescriptions for their health problem with an appropriate drug (at least until a target oriented care for pain relief was available), representing about 4% of potential candidates, in consideration that Italian population is approximately 60,000,000 citizens (National Institute of Statistics).13

In patients with cancer having a prevalence of about 3.5% (National Institute of Statistics-13), 60% are estimated to face mild to severe pain14 and 53,000 patients are on chronic opioid treatment, being again about 4% only of potential candidates (estimated 1.3 million people).

This means that 96% of chronic pain patients, both of cancer and non-cancer origin, can unlikely have access to appropriate pain therapy at least until the correct diagnosis and specific treatment are performed.

Table II shows that all patients including chronic and the non chronic opioid users were treated in 50% of cases with weak opioids, whereas in chronic opioid users strong opioids predominate on weak opioids; this fact could be due to the pain being more severe when chronic compared to the probably less severe acute pain. The Tables I, II highlight that 17% of the patients taking opioids in 2013 received 60% of the total prescriptions. This data underline the numeric importance of chronic pain patients in terms of use of public resources (a small number of patients-about 422,000 compared to 2,500,000 of total patients-recruit the greatest part of the prescriptions – about 5.600.000 compared to over 9,200,000 total prescriptions).

In patients on chronic opioid therapy among strong opioids oxycodone alone or associated with naloxone is the mostly prescribed drug when non-cancer patients are considered.

Figures 1-3 shows that patients with chronic opioid therapy are elderly, with female predominance, a fact that might be explained by the prevalence of females in italian population and furthermore is in accordance with other literature data.13-15

This fact in our opinion can be also explained by a cultural and socioeconomic phenomena where younger males, often affected by chronic pain, mostly benign, as already explained by Breivik et al.,12 missed the attention of pain therapist.

Table III is fundamental to answer the question about the mean daily dose of opioid therapy: some data in literature 15 showed a mean posology of about 86 morphine equivalent dose (MED) in cancer patients, being similar to data obtained in our study, and about 62 MED in non cancer patients treated with opioids for 6-12 months, being twice the MED revealed by our observation.

In Cepeña’s work 15 collected data from 48.986 patients in a 8 years period (2002-2008) in US, with a mean age of 44.5 years, similar to our results, and a prevalence of female sex, also similar to our findings. Moreover some differences in the age group might be related to the fact that in the US study data were collected from an insurance database in which patients over 65 years, low income patients and people not able to work are often excluded, whereas Italian data include all refunded prescriptions in the 2013 with no restrictions.

Others US studies16, 17 showed lower MED prescriptions respect to Cepeña’s data, at least in particular subset patients (veterans). Edlund16 and Macey17 registered respectively a median MED of 21 mg/die — range 10-997 mg/die — (in the years 2009-2011) and av-
Conclusions

We performed a patient-based (number of users) analysis of the prescribing behavior in Italy during the 2013-year rather than number of opioid packages prescribed in the same period. This has led to a census of more than 422,000 patients on chronic therapy with opioids (about 50,000 cancer patients and 370,000 non cancer patients), representing nevertheless only 4% of the estimated pain therapy applicants.

Relatively to morphine daily dose our data (79.4 MED in cancer patients and 30.1 MED in non cancer patients) showed that in Italy cancer patients received adequate opioid doses, whereas the non cancer patients received minor opioid.

Key messages

— The study used a “number of patients”-centered data base of chronic opioids users instead of “number of drug-pack”-centered data base, already known in literature.
— This database collected all 2013 opioids prescription in Italy (about 9 million of records) provided by Italian Ministry of Health.
— The study analyzed and compared with other countries the mean MED (morphine equivalent dose) of opioids in the scheduled opioids chronic users.

Limitations of the study

The database created is prescription based: We don’t have a clinical confirmation of patient’s pain intensity or a real documentation of the pain condition. We suppose that physicians signed only appropriate opioid prescriptions (namely for moderate to severe pain conditions).

The database does not include opioids prescribed during hospital admission and ward stay.

The definition of “cancer patients” is based and hence limited by the correct and complete compilation of all fields of the prescription as well as by a correct clinical prescriptive indication. This is important, especially for rapid onset opioids (ROOs), approved in Italy for BTP in cancer pain only, with the exclusion of ROOs prescription for Break Through Pain of non-cancer origin (several oral morphine formulations).

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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.

Can pre-procedure neuroaxial ultrasound improve the identification of the potential epidural space when compared with anatomical landmarks? A prospective randomized study

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ABSTRACT

BACKGROUND: Regional epidural analgesia is considered the gold standard for pain treatment in labor. However, epidural catheter placement may be a challenging procedure because of the difficulty in the palpation of anatomical landmarks, particularly in pregnant women. Pre-procedural neuroaxial ultrasound may facilitate the procedure.

METHODS: A prospective randomized controlled study was conducted in a labor ward. Two groups of women undergoing epidural analgesia were randomized: Group A (N.=28), which was subjected to the loss of resistance technique, and Group B (N.=30) which was subjected to an ultrasound (US)-assisted procedure. The real depth of epidural space was calculated in both groups by measuring the needle skin-to-tip distance, while the US depth was measured only in Group B.

RESULTS: The mean number of attempts in group A (3.43±3.8) was significantly higher than in Group B (1.70±0.87, P=0.019). Analysis of data from Group B revealed a strong positive correlation between the epidural real depth and US depth (r=0.88, P<0.0001).

CONCLUSIONS: The US-assisted technique for epidural catheter placement for labor analgesia is safe, effective, easy to perform, and is a valuable aid to improve the identification of the epidural space compared with the palpation of anatomical landmarks and the loss of resistance technique. Pre-puncture ultrasound assessment shows the exact location of the intervertebral space, the optimal point of insertion and the tilt angle of the needle, the depth of the epidural space and any anatomical abnormalities of the spine, thereby increasing the success rate and reducing procedural complications of the blind approach.

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Key words: Epidural analgesia - Epidural anesthesia - Epidural space - Obstetric labor - Ultrasonography.

Regional epidural analgesia is considered the gold standard for pain treatment in labor but the rate of failure ranges from 2% to 20%.¹²³

The placement of the epidural catheter can be considered one of the most difficult manoeuvres in clinical anaesthesia;⁴ this may be due to several factors such as the use of what is currently named the “blind approach”, involving the anatomical identification of the optimal intervertebral space and epidural space

¹ The term “optimal intervertebral space” indicates that in clinical practice, the anesthetist decides to insert the needle through the more palpable and therefore feasible intervertebral space, and this may insertion at one space up or down from L3-L4, which is universally targeted as the most appropriate intervertebral space for labor analgesia.
depth (loss of resistance [LOR] technique).\textsuperscript{5, 6} The anatomical landmarks are not always easy to understand;\textsuperscript{7-9} therefore, the needle direction angle and skin-to-epidural space distance are often difficult to estimate by relying only on the clinical exam of the anatomical landmarks.

Difficulty in palpating and correctly interpreting anatomical landmarks may result in an increased number of puncture attempts, leading to patient discomfort or pain, or outright primary failure of epidural analgesia.\textsuperscript{6}

During pregnancy, the interspinous ligament is more inhomogeneous and soft, and this characteristic may often mimic a LOR similar to that found when the needle is in the epidural space. The epidural space is deeper and narrower, and the “safe zone” between ligamentum flavum and dura mater is reduced.\textsuperscript{2, 10} Furthermore, there is a reduction of the intervertebral space due to the increase in lumbar lordosis and enlargement and rotation of the pelvis that imply an upward shift of Tuffier’s line with a subsequent underestimation of the needle insertion level. The compression of the cava vein and the expansion of the intravascular volume result in the congestion of the epidural veins that increase the risk of vascular cannulation of the epidural catheter.

The epidural technique may not be only “blind” but also “unpredictable”. Aspects like the identification of the desired intervertebral space, the centrality of the vertebral column, the best skin point of insertion for the needle, the optimal angle of insertion, and the depth of the epidural space may be easily predicted with ultrasound (US) imaging.\textsuperscript{11-13}

The aim of our study was to verify if preprocedural neuroaxial US, in comparison with palpation of anatomical landmarks, might improve the identification of the potential epidural space by reducing the number of attempts necessary to place an epidural catheter successfully.

Moreover, we evaluated the accuracy and precision of the transverse echo-graphic approach for the definition of the desired epidural space.

Materials and methods

The research ethics board approved the study with the CEIIAV number 1056-1098/2014, in February 2014. Written informed consent was obtained from all patients in the study.

This was a prospective randomized controlled study conducted in the labor ward of the Operative Unit of Anesthesia of S. Maria delle Croci Hospital, Ravenna. We collected data from February 2014 to June 2014.

All the procedures were conducted by the same anesthetist investigator, who performs more than 150 epidural procedures yearly, which is the minimum standard to work in the labor ward in accordance with local guidelines.

This manuscript adheres to the applicable Equator guidelines.

A sample of patients who underwent epidural analgesia was randomized using a closed-envelope technique in order to have two \textit{ex-ante} similar groups: one group subjected to the LOR technique to find the epidural space, and the other group subjected to an US assessment prior to needle insertion.

Before positioning the epidural catheter, the anesthetist picked at random one envelope from the box and opened it. Figure 1 shows the flow chart of the study.

Group A

The epidural catheter was positioned by palpating anatomical landmarks and LOR technique.

The identification of the desired intervertebral space was performed by assessment of the spine with the patient in the sitting position. The anesthetist performed palpation of anatomical landmarks (iliac crests, lumbar posterior spinous processes, and interspaces) and the most palpable and lower space was chosen (e.g. L3-L4 was preferred to L2-L3 if both were well palpable).

All the procedures were performed in a sterile manner, in accordance with the Hospital Guidelines and the region of desired intervertebral space was anesthetized with 1.5-2 mL of lidocaine 2%. The epidural set used for the an-
identify the desired intervertebral space and the optimal point of insertion.

Spine imaging was performed using the portable SonoSite™ NanoMaxx equipped with a 5-2-MHz C60n Convex probe. The whole procedure of pre-puncture echographic assessment required less than 5 minutes to be performed.

The first approach was the longitudinal paramedian (Figure 2). The probe was positioned vertically, perpendicular to the long axis of the spine, over the sacral area, 3 cm to the left of the midline and slightly rotated towards the center of the spinal canal.

At this level, a continuous hyperechoic line identified the sacrum; the probe was then moved cephalically until it was possible to see a hyperechoic, saw-like image representing the vertebral articular processes and the intervertebral spaces.

When the optimal intervertebral space was identified, it was centered on the screen and the position of the probe was marked on the skin.

The probe was then rotated 90° for the transverse approach (Figure 3A-C). The probe was positioned horizontally, perpendicular to the long axis of the spine. In this position, spinous processes correspond to a hyperechoic signal, immediately under the skin that was in continuity with a triangular hypoechoic acoustic shadow. The probe was then slightly moved caudally or cephalically to define the intervertebral space. Within the interspace, a hyperechoic band was present at the midline; it corresponded to the ligamentum flavum and dorsal dura. A second hyperechoic band, parallel to the first one, represented the anterior dura, the posterior longitudinal ligament, and the vertebral body.

By freezing the image, it was possible to measure the echographic distance between the skin and the first hyperechoic line (distance between the skin and posterior dura, also named ultrasound depth of epidural space [UD]). Keeping the probe still in this position, four points were marked on the skin: the center of the superior aspect and the center of each.

**Group B**

The anesthetist performed a pre-puncture echographic assessment of the spine to identify the desired intervertebral space and the optimal point of insertion.

Spine imaging was performed using the portable SonoSite™ NanoMaxx equipped with a 5-2-MHz C60n Convex probe. The whole procedure of pre-puncture echographic assessment required less than 5 minutes to be performed.

The first approach was the longitudinal paramedian (Figure 2). The probe was positioned vertically, perpendicular to the long axis of the spine, over the sacral area, 3 cm to the left of the midline and slightly rotated towards the center of the spinal canal.

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Thus, 30 patients were allocated to each group (Table I).

For each patient, data on the whole procedure of epidural analgesia were collected. In particular, we collected data on the RD of the epidural space for patients of both groups, and of the two lateral sides of the probe (intervertebral space).

The insertion site was identified by the union of the four markers on the horizontal and vertical planes. The needle inclination was the same as that of the probe in the best acoustic window.

After the identification of the insertion point, the procedure of needle insertion was the same as that in Group A and the same material was used.

In order to compute the sample size necessary to answer our research question, we considered the average number of 2.2±1.1 attempts of Tuohy needle insertion before finding the epidural space with the LOR technique. Based on this, a sample size of 30 patients for treatment was necessary to identify a relevant clinical effect (i.e., reduction of 65% of number of attempts with the US-assisted technique) with a power of 0.80 and a significance level of 0.05.

We examined all parturient women (N.=72) who came to our department for the anesthetic visit in their 34th week of gestation, who requested an epidural analgesia during the study period between February 2014 and June 2014.

Twelve patients were excluded who had at least one of the following exclusion criteria: age <18 years; unable to give consent or denial of consent; impairment of coagulation (International Normalized Ratio [INR] >1.20, platelet count <150,000/μL, activated partial thromboplastin time [aPTT] >1.20); under treatment with an anticoagulant or antiplatelet drug; and skin infection or tattoos in the lumbar region.

![Figure 2.—US longitudinal paramedian approach.](image1)

![Figure 3.—A-C) The US transverse approach; measurement of the depth of the epidural space.](image2)
we collected data on the UD of the epidural space and the US imaging quality of the anatomical structures for Group B only.

The quality of anatomical landmarks was rated as “well palpable”, “sufficiently palpable” and “not palpable”. The visibility of the anatomical structures on US imaging was rated as “good”, “sufficient” and “none”.

The needle redirections (without a new skin puncture) and repositions (with a new skin puncture) were recorded separately. Each ventral advancement of the needle was considered as a “puncture attempt”, even if no additional skin puncture was performed.

The total number of puncture attempts was computed by adding up the Tuohy needle redirections and repositions.

Statistical analysis

All statistical calculations were performed with Microsoft Excel® 2010, SPSS Statistics® v.20 and MedCalc®. Data were analyzed using the $\chi^2$ test and Student’s $t$-test. We performed a nonparametric K-sample test on the equality of medians.

The Bland-Altman analysis was used to compare two different measurements and Pearson’s correlation coefficient was used to estimate the precision.

Results

Data show that the two groups were similar in age, Body Mass Index, weight before pregnancy, weight at delivery time, gestational age and ASA classification (Table I).

Table I.—Characteristics of patients.

<table>
<thead>
<tr>
<th></th>
<th>Group A (N=30)</th>
<th>Group B (N=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31±5</td>
<td>30±4</td>
<td>0.371</td>
</tr>
<tr>
<td>Weight before pregnancy (kg)</td>
<td>62±14</td>
<td>62±7</td>
<td>0.804</td>
</tr>
<tr>
<td>Weight at labor (kg)</td>
<td>74±15</td>
<td>74±7</td>
<td>0.897</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>27±4</td>
<td>27±2</td>
<td>0.769</td>
</tr>
<tr>
<td>Gestational age (days)</td>
<td>278±8</td>
<td>280±8</td>
<td>0.484</td>
</tr>
<tr>
<td>ASA class</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>0.299</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or medians (range). Group A: procedure performed without US; Group B: US-assisted procedure. BMI: Body Mass Index; ASA class: American Society of Anesthesiologist Physical Status Classification.
epidural space was reported (no patient reported unilateral analgesia). Neither complications such as accidental dural puncture nor traumatic catheter placement were noted in both groups. Furthermore, all epidurals were successful in both groups, with patients expressing their satisfaction regarding labor analgesia.

The total number of Tuohy needle redirections and repositions and the total number of puncture attempts (derived as the sum of these two categories) were analyzed and there was a statistically significant difference between the two groups (Table III).

In Group A the mean number of attempts was 3.43±3.8, which was significantly higher than 1.70±0.87 attempts in Group B (P=0.019).

By analyzing the number of redirections, the number of repositions and the total number of attempts, separately for the two groups, it was possible to observe further differences.

In 100% of the cases the number of repositions in Group B was ≤1. In Group A, the percentage of cases that required ≤1 reposition was only 76.7%; the average number of repositions was significantly different between the two groups (P=0.031).

Considering the number of redirections, the needle was readdressed less than 2 times in 80% of the cases in Group A, while the same scenario happened in 100% of the cases in Group B. The average number of redirections was significantly different between the two groups (P=0.031).

In regards to the total number of puncture attempts, it was ≤3 in 76.7% of the cases in Group A and in 96.7% of the cases in Group B. The average number of attempts was again significantly different between the two groups (P=0.057).

In Group B, the US visibility of the anatomical structures of the anterior unit (anterior dura, posterior surface of vertebral body and longitudinal posterior ligament) was described as “good” in 84% of the patients and “sufficient” in 16%; the dural sac visibility was described as “good” in 94% of the patients and “sufficient” in 6%; the posterior unit (ligamentum flavum, epidural space and posterior dura) visibility was described as “good” in 64% of the patients and “sufficient” in 36%.

By considering data from Group B only, we can compare the epidural RD and UD (skin-posterior complex). A strong positive correlation was seen (r=0.88, P<0.0001) (Figure 4).

The average RD of the epidural space in Group B was 5.08±0.62 cm and UD was 4.94±0.60 cm.

The Bland-Altman analysis comparing the RD and UD measures shows a 95% precision of 5.90 mm, with the range between -7.4 and 4.4 mm (Figure 5).

Discussion

In this study, we show that the placement of the epidural catheter with US-assisted technique reduced the number of attempts compared with “blind” access, both in terms of redirections of the needle and in terms of new punctures of the skin, with a consequent reduction in the discomfort of patients.

The evaluation of the efficacy of the US-assisted technique for epidural catheter placement consider either the time spent to correctly execute the manoeuvre or the number of attempts necessary for the correct insertion of the needle; however, the latter may be considered the most important tool and a better

<table>
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<th>Table II. — Measured variables.</th>
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<tr>
<td></td>
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<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Epidural real depth (cm)</td>
</tr>
<tr>
<td>Catheter insertion (cm to skin)</td>
</tr>
<tr>
<td>NRS, pre procedure</td>
</tr>
<tr>
<td>NRS, 20 min after first analgesic bolus administration</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or medians (range). Group A: procedure performed without US; Group B: US-assisted procedure. NRS: Numeric Rating Scale.

*Instead of 30 due to technical difficulties in catheter placement in two patients.
NEUROAXIAL ULTRASOUND FOR EPIDURAL SPACE IDENTIFICATION

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Yeagle observed that the level described clinically is usually lower than the US level while Locks et al. observed the opposite trend. One explanation for this result may be given by the study of Pysyk, which showed that Tuffier’s line (passing between the two iliac crests), corresponding to the anatomical landmark of L4-L5, crosses the intervertebral space L3-L4 in most subjects. Grau et al. conducted a study similar to ours but they observed a population of parturients with abnormal anatomical conditions who were scheduled for epidural anesthesia and they found that the quality of epidural anesthesia was enhanced with US measurement of the epidural space depth.

In this study, there was no significant difference in terms of procedure failure expressed as analgesic efficacy and catheter placement failure, unlike the findings from other studies in the literature; this is most likely due to the small size of the sample. Our study showed a strong correlation between the distance skin-posterior complex and the RD of the epidural space, and is consistent with the data present in the literature.

Table III.—Number of attempts.

<table>
<thead>
<tr>
<th></th>
<th>Group A (N.=30)</th>
<th>Group B (N.=30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. of repositions</td>
<td></td>
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<td>0.024</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.73±2.57</td>
<td>0.6±0.72</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>0 (0-7)</td>
<td>0 (0-2)</td>
<td></td>
</tr>
<tr>
<td>N. of repositions</td>
<td></td>
<td></td>
<td>0.018</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.7±1.31</td>
<td>0.1±0.3</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>0 (0-4)</td>
<td>0 (0-1)</td>
<td></td>
</tr>
<tr>
<td>Total N. of attempts</td>
<td></td>
<td></td>
<td>0.019</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.43±3.82</td>
<td>1.7±0.87</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>0 (0-10)</td>
<td>0 (0-3)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD. Group A: procedure performed without US; Group B: US-assisted procedure.

Accurate knowledge of the intervertebral level desired is only possible with the help of US. In fact, once the lumbosacral joint (interbody space L5-S1) has been identified, you can move cranially to determine the exact level of the intervertebral spaces above (counting up) and identify the intervertebral space desired.

Several studies showed that the correlation between the identification of the intervertebral level by means of anatomical landmarks and the intervertebral level desired varies from 36% to 55%. Whitty and Schlotterbeck observed that the level described clinically is usually lower than the US level while Locks et al. observed the opposite trend. One explanation for this result may be given by the study of Pysyk, which showed that Tuffier’s line (passing between the two iliac crests), corresponding to the anatomical landmark of L4-L5, crosses the intervertebral space L3-L4 in most subjects.

Grau et al. conducted a study similar to ours but they observed a population of parturients with abnormal anatomical conditions who were scheduled for epidural anesthesia and they found that the quality of epidural anesthesia was enhanced with US measurement of the epidural space depth.

In this study, there was no significant difference in terms of procedure failure expressed as analgesic efficacy and catheter placement failure, unlike the findings from other studies in the literature; this is most likely due to the small size of the sample.

Our study showed a strong correlation between the skin-posterior complex and the RD of the epidural space, and is consistent with the data present in the literature.

In our study, it was observed that the US measurement tends to underestimate the actual depth of the epidural space, confirming the findings in the literature. Possible predictor of complications, such as the accidental puncture of the dura, vascular puncture, or the appearance of paresthesias.

In particular, we demonstrated that the necessary number of punctures of the skin is one in all cases of placement of the epidural catheter with the US-assisted technique while it is on average more than 1 with the blind technique. This advantage is even greater in situations where the anatomical landmarks are hardly appreciable, as in obese patients, in patients with alterations of the spinal column, or in those with a history of spine surgery.

The explanation for the success rate in US-assisted placement compared with the blind technique is the fact that it is possible to establish the exact position of the skin puncture with US: both the exact intervertebral level and the distance skin-epidural space are known. The direction of the needle should be estimated by the degree of tilt and oblique angle of the probe that allows the best target visualization.

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learning curve compared with other anesthetic procedures, but we would like to emphasize the importance of the use of educational *in-vitro* models and the learning or refining of US procedural skills using models (as our anesthetist investigator did in his career) before approaching the clinical scenario. The use of US provides a more secure technique for the patient.

**Conclusions**

Pre-puncture ultrasound assessment clearly shows the exact location of the intervertebral space, the optimal point of insertion and the tilt angle of the needle, the depth of the epidural space and any anatomical abnormalities of the spine, thereby increasing the success rate and reducing the procedure complications of the blind approach.

**Key messages**

— Pre-puncture US assessment shows the exact location of the intervertebral space, the optimal point of insertion and the tilt angle of the needle, the depth of the epidural space and any anatomical abnormality of the spine.

— The US-assisted procedure for epidural catheter placement results in fewer attempts (both in terms of redirection of the needle and of new skin punctures) than the LOR technique, and it may therefore cause less discomfort to the parturient.

— The US approach gives the security of centrality in catheter placement with subsequent symmetry of analgesia.

— The transverse US approach in the study of the column showed a great degree of correlation between US measurements and RD of epidural space.

— The US approach and the US-assisted procedure are relatively easy to perform after a training for specific skills; therefore, its introduction to clinical practice may be appropriate for anesthetists with background US experience.
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.

Postoperative analgesia for elective total knee arthroplasty under subarachnoid anesthesia with opioids: comparison between epidural, femoral block and adductor canal block techniques (with and without perineural adjuvants). A prospective, randomized, clinical trial

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BACKGROUND: Optimal control of acute postoperative pain and prevention of chronic persistent pain in total knee arthroplasty (TKA) remain a challenge. The main hypothesis was that nerve blocks improve postoperative analgesia especially if perineural adjuvants are added.

MÉTHODES: Immediate postoperative pain (24 hours) was evaluated every hour in 639 patients using a verbal rating 11-point scale for patient self-reporting of pain (VRS-11). All patients received subarachnoid anesthesia and were randomly allocated in 8 groups: control group, epidural (EA) and single shots femoral (FNB) or adductor canal blocks (ACB), both with and without adjuvants: dexamethasone (+Dexa) or dexmedetomidine (+Dexm). Patients received intravenous analgesia (metamizole magnesium, dexketoprofen) and rescue analgesia when needed, intravenous (paracetamol and morphine) and/or regional (epidural boluses, femoral and sciatic nerve blocks). Demographics, orthopedic knee scores and adverse effects were also recorded.

RESULTS: A 45.2% of patients had no immediate postoperative pain (P=0.0001). Rescue analgesia was needed in 48.8% of patients (P=0.0001): control group 72.8% of patients, EA 51.9%, FNB 40.0%, FNB+Dexa 33.3%, BNF+Dexm 41.3%, ACB 51.9%, ACB+Dexa 38.3% and ACB+Dexm 61.5% respectively. There were also differences in the total postoperative time without pain (P=0.0001), with mild (P=0.0001) or moderate pain (P=0.001) but not with severe pain (P=0.119). CONCLUSIONS: Peripheral nerve blocks with perineural dexamethasone improve postoperative analgesia for TKA. The addition of dexamethasone to adductor canal block open new possibilities to improve analgesia for TKA, and should be investigated as an alternative to femoral nerve block.


Key words: Anesthesia - Arthroplasty, replacement, knee - Pain - Dexamethasone - Dexmedetomidine.
Total knee arthroplasty (TKA) is a highly distressful major surgery, with a significant potential for complications, not only because of the surgical and anesthetic impact of the procedure, but also because of the demographic and clinical characteristics of the target population. Ideal postoperative analgesia provides sufficient pain relief with minimal opioid consumption and preservation of motor strength to prevent postoperative complications. The application of multimodal techniques including regional anesthesia are broadly used to meet such expectations. Femoral nerve blocks are still the gold standard for an effective analgesia approach in TKA and should be supplemented (if needed) by oral opioids. Nevertheless, the optimal nerve block, combination of blocks and/or combination of catheter and single-shot techniques, is still a matter of debate.

The estimated prevalence of patients who report minor or no improvement of their symptoms and pain after TKA remains high, ranging from 5% to 40%. Optimal control of acute postoperative pain and the prevention of chronic persistent pain remain a challenge because intense acute postoperative pain is per se a risk factor for chronic pain.

In this study, we evaluated eight different regional analgesic techniques in order to find the best one. The main hypothesis was that the addition of perineurial adjuvants to nerve blocks improve postoperative analgesia. The primary outcome, pain, was measured using a verbal rating 11-point scale for patient self-reporting of pain (VRS-11).

Materials and methods

This was a prospective, randomized, clinical trial. Institutional Research Ethics Board approval was obtained at Hospital (Puerta de Hierro Hospital, Madrid, Spain, registry reference number 06.16) and at the Australian New Zealand Clinical Trials Registry (ANZCTR), with allocation ID: ACTRN12616000912482 and trial web address: http://www.ANZCTR.org.au/ACTRN12616000912482.aspx.

A total of 700 patients scheduled for TKA under spinal anesthesia were assessed for eligibility during preoperative anesthesia consultation: 660 were enrolled and 40 excluded (24 declined to participate and 16 not meeting inclusion criteria with coagulation disorders (N.=5), 4 Alzheimer disease (N.=4) and mental disorders (N.=7)).

Written informed consent was obtained from all patients willing to participate in this study. Exclusion criteria included unicompartamental knee arthroplasty, refusal to participate, contraindication to spinal or regional anesthesia and/or allergy to the drugs used.

The patients were examined preoperatively in accordance to an internationally validated orthopedic knee scoring systems for gonarthrosis: “Knee society clinical rating system”, HSS (Hospital for Special Surgery) and KSS (Knee Society score).

Patients were fasted for 8 hours before surgery. Peripheral venous access was secured and routine monitoring with electrocardiography, oxygen saturation, and non-invasive blood pressure were started in the supine position.

All patients received subarachnoid anesthesia. It was performed in the sitting position at L3-4 or L4-5 interspace, with a 25-gauge Whitacre needle. We administered 0.5% hyperbaric bupivacaine (Hyperbaric bupivacaine 0.5%, Braun) according to the following formula: bupivacaine (mg)=height (cm)×0.07, with morphine (Morphine 0.1%, Braun) 0.15 mg and fentanyl (Fentanest®, Kern Pharma) 15 µg. Following injection, patients were immediately kept on lateral decubitus for 6 minutes to improve anesthesia.

There were eight groups: subarachnoid anesthesia only without additional blocks (control group), epidural analgesia (EA) and single-shot femoral nerve block (FNB) and adductor canal block (ACB) both with and without the perineural adjuvants dexamethasone (+Dexa) or dexmedetomidine (+Dexm).

The subarachnoid anesthesia in the epidural group was performed through the epidural needle at L3-4 or L4-5, the catheter advanced 3-4 cm and an infusion of levobupivacaine (Chirocane®, Abbvie) 0.1% + fentanyl 2 µg.mL⁻¹ (rate 6-10 mL.h⁻¹, bolus volume 5 mL, lock in-
Before designing the treatment of this study, we conducted a preliminary analysis of the time course of pain, noting that there were 2 peaks of greater intensity of pain. The first peak (4 to 6 pm) was a low intensity pain that responded to NSAIDs, due to the patient’s perception of discomfort for not being able to move the knee and the tightness induced by bands after the disappearance of the effect of spinal anesthesia. The second peak (8 to 9 the next morning) corresponded with the postural changes to clean the patient and the visit of the rehabilitators, who started the knee movements. So, we established that a dose of 50 mg of dexketoprofen should be administered at 4 pm and 8 am according with the chronologic evolution of pain.

All patients received a standardized postoperative treatment (Figure 1) with cefazolin (Cefazolin 2 g®, Reig Jofre), enoxaparin (Clexane 40 mg®, Sanofi), omeprazole (Omeprazole 40 mg®), and levobupivacaine 0.375% (20 mL in FNB and 30 mL in ACB) and dexamethasone (Fortecortin®, Merck) 4 mg or dexmedetomidine (Dexdor®, Orion-Pharma) 100 µg as nerve blocks adjuvants when used.

Surgeons and anesthesiologists were blinded to the addition of perineural adjuvants (perineural medication was prepared by a nurse adding dexamethasone, dexmedetomidine or 1 ml of saline according to the randomized protocol).

International guidelines concerning recommended delays between enoxaparin administration and neuroaxial techniques including epidural catheter removal were respected.

Nerve blocks were single-shots techniques performed under both ultrasound and nerve stimulation (considered adequate at 0.2-0.5 mA) by experienced anesthesiologists.

Figure 1.—Standardized treatment.
OR: operating room; PACU: postanesthetic care unit; PONV: postoperative nausea and vomiting.
mg®, Normon), metamizole magnesium (No- lotil®, Boehringer Ingelheim), dexketoprofen (Enanyum®, Menarini) and ondansetron (On- dasetron 4 mg®, Normon) or droperidol (Xo- molix®, Kyowa Kirin) when needed.

The rescue analgesia followed this sequential order: paracetamol 1 g IV (Paracetamol 1 g®, Braun), morphine up to 6 mg (Morphine 1%, Braun) and finally rescue nerve blocks if IV drugs were not enough.

The pain was measured every hour (respec- ting the sleep period) using a VRS-11 previously explained to the patients: from 0 (“no pain”) to 10 (“the most horrible pain you can imagine; such as being burned alive”), and they were also advised to notify their nurse if they had pain. Pain was recorded faithfully in accordance with the indicated patient’s VRS-11 scores. According to previous validated studies, pain was considered as mild pain (VRS-11 score 1-3), tolerated without rescue analgesia), moderate (VRS-11 score 4-6, (needs analgesia) and severe pain (VRS-11 score 7-10).

Adverse outcomes were also recorded: nau- sea and vomiting (4-point descriptive verbal scale, 0=no, 1=mild, 2=moderate, 3=severe), hypotension (defined as systolic blood pressure <75% basal value), bradycardia (heart rate <60 bpm), vagal syndromes, arrhythmias and electrocardiographic changes, sedation (Ramsay Score >4), restless- ness (4-point descriptive verbal scale, 0=no, 1=mild, 2=moderate, 3=severe), sweating and bleeding (based on hematocrit and hemoglobin variations in 3 blood test: 1, 8 and 20 hours after surgery).

Statistical analysis

Data were analyzed using IBM SPSS 23 sta- tistical software package (IBM, New York NY, USA), with a significance level (alpha) 0.05 in a two-sided test, power 1.0 and effect size 0.9. The normality of the quantitative parameters was studied with the Kolmogorov-Smirnov test. Comparison of means of independent samples was performed using ANOVA, followed by Dunnett’s Test for post hoc testing, and repeated measures ANOVA was used for paired data. Association between qualitative variables was performed using the chi-square test with Fisher’s Exact Test where appropriate. Trends were studied with the chi-square for linear trend test. A P value <0.05 was considered significant.

Results

A total of 660 patients were enrolled and 639 were analyzed (CONSORT flow diagram, Figure 2): 3 patients did not receive the allocated intervention (1 difficult FNB (FNB), 1 vascular puncture and hematoma (ACB) and 1 difficult spinal puncture (ACB+Dexa), 3 patients lost to follow up (2 ischemic heart disease event (ACB, ea), 1 status epilepticus (FnB+Dexa) and 14 patients had discontinued intervention (3 knee hemorrhages (control, FnB, acB+Dexm), 10 disorientations (3 ea, 2 FnB, 3 ACB, 1 ACB+Dexa, 1 ACB+Dexm) and 1 knee hematoma (ACB+Dexa)).

Patient characteristics are presented in Ta- ble I. The most commonly reported (and of- ten concomitant) diseases, without differences between the groups, were: arterial hypertension, diabetes mellitus, dyslipidemia, severe obesity, atrial fibrillation, ischemic heart disease, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, asthma, hyperuricemia, hypothyroidism, fibromyalgia and alcoholism.

There were no differences in the orthopedic preoperative evaluation of knee osteoarthritis, with the following recorded averages: the HSS scale reveal patients who need support to climb stairs (P=0.447) or move (P=0.720), with ability to walk 5-10 blocks (P=0.650), often helped with a cane (P=0.235) but suffering from moderate to severe pain (P=0.737) that persists even at rest as moderate pain (P=0.686). The KSS scale, ability to walk 5-10 blocks (P=0.390), often in need of a continuous rod (P=0.720) and moderate pain (P=0.514), with great difficulty walking down stairs (P=0.873), needing support (P=0.447), “good and fair” strength of the quadriceps muscle (P=0.434) and “mild to moderate” patellofemoral crepi- tus (P=0.140). The “Knee scale rating” showed: active flexion (113.5±14°, P=0.736),
passive flexion (114.6±13.5°, P=0.740), active extension (6.9±7.5°, P=0.996), passive extension (7.1±7.6°, P=0.997), varus (8.1±4.4°, P=0.126), valgus (1.0±2.8°, P=0.693) and preoperative satisfaction (2.7±1.6, P=0.536) where 0 is dissatisfied and 10 very satisfied.

There were no differences in ischemia (91.0±24.2 min, P=0.898) or surgery times (136.3±33.7 min, P=0.653). There were differences in the percentage of patients with intraoperative events (P=0.001). Arterial hypotension was the most frequent intraoperative event (15.2%), followed by pain (1.4%), vagal syndrome (0.9%), arterial hypertension (0.8%), arrhythmias (0.6%), postoperative nausea and vomiting (PONV) (0.5%), hemorrhage (0.3%) and agitation (0.3%).

The mean stay at PACU was 21.7±1.8 hours (P=0.111). There were differences between the groups in the percentage of patients with postoperative events (P=0.0001). Pain was the most frequent one (20.1%), followed by PONV (3.2%), bleeding (1.8%), arterial hypertension (1.3%), agitation (0.4%), arrhythmias...
(0.3%), vagal syndrome (0.2%) and arterial hypertension (0.1%).

Table II shows the incidence of pain and the need of rescue analgesia. A 54.8% of patients had at least one episode of pain: the 89% of them needed any kind of rescue analgesia while the remaining 11% did not request analgesia.

There were significant differences in the use of intravenous rescue analgesic agents: paracetamol (P=0.001, range of 0-5 g: Control 0.9±0.8 g, EA 0.6±0.9 g, FNB 0.5±0.6 g, FNB+Dexa 0.4±0.6 g, FNB+Dexm 0.7±0.8 g, ACB 0.6±0.7 g, ACB+Dexa 0.4±0.6, ACB+Dexm 0.7±0.8 g), and morphine (P=0.002, range of 0-6 boluses of 2 mg: Control 0.7±1.1, EA 0.4±1.0, FNB 0.2±0.6, FNB+Dexa 0.2±0.8, FNB+Dexm 0.4±1.0, ACB 0.5±1.0, ACB+Dexa 0.2±0.6 and ACB+Dexm 0.5±1.0 boluses of morphine 2 mg respectively).

Concerning the need of rescue analgesic nerve blocks, a 20.2% of patients received one: 17 epidural supplementary boluses, 110 FNB and 2 sciatic nerve blocks (SNB) (P=0.002). A 3.8% needed two (5 epidural, 7 FNB and 12 SNB, P=0.170) and 5 patients (0.6%) needed

**Table II.—Pain and need of rescue analgesia.**

<table>
<thead>
<tr>
<th></th>
<th>Control (N=81)</th>
<th>EA (N=79)</th>
<th>FNB (N=80)</th>
<th>FNB+Dexa (N=81)</th>
<th>FNB+Dexm (N=80)</th>
<th>ACB (N=79)</th>
<th>ACB+Dexa (N=81)</th>
<th>ACB+Dexm (N=78)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22.2</td>
<td>44.3</td>
<td>50.0</td>
<td>64.2</td>
<td>56.3</td>
<td>34.2</td>
<td>55.6</td>
<td>34.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>77.8</td>
<td>55.7</td>
<td>50.0</td>
<td>35.8</td>
<td>43.8</td>
<td>65.8</td>
<td>44.4</td>
<td>65.4</td>
<td></td>
</tr>
<tr>
<td>Rescue analgesia</td>
<td>27.2</td>
<td>48.1</td>
<td>60.0</td>
<td>66.7</td>
<td>58.8</td>
<td>48.1</td>
<td>61.7</td>
<td>38.5</td>
<td>0.0001</td>
</tr>
<tr>
<td>No</td>
<td>72.8</td>
<td>51.9</td>
<td>40.0</td>
<td>33.3</td>
<td>41.3</td>
<td>51.9</td>
<td>38.3</td>
<td>61.5</td>
<td></td>
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<tr>
<td>Yes</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are percentages. Pain (no) is equivalent to completely painless (all VRS-11=0) during the stay in the PACU. Pain (yes) corresponds to presence of at least one episode of pain (VRS-11>0) during the stay in the PACU.

**Table III.—Postoperative pain evolution**

<table>
<thead>
<tr>
<th>Pain</th>
<th>Control (N=81)</th>
<th>EA (N=79)</th>
<th>FNB (N=80)</th>
<th>FNB+Dexa (N=81)</th>
<th>FNB+Dexm (N=80)</th>
<th>ACB (N=79)</th>
<th>ACB+Dexa (N=81)</th>
<th>ACB+Dexm (N=78)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>87.1±13.1</td>
<td>92.1±11.9</td>
<td>94.2±7.9</td>
<td>96.1±6.7</td>
<td>92.6±12.7</td>
<td>91.5±9.0</td>
<td>94.6±8.1</td>
<td>90.1±13.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mild</td>
<td>6.9±10.7</td>
<td>3.0±7.0</td>
<td>2.7±4.6</td>
<td>1.8±4.4</td>
<td>3.7±6.5</td>
<td>3.7±4.7</td>
<td>2.9±5.1</td>
<td>5.5±9.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Moderate</td>
<td>4.2±5.1</td>
<td>3.2±5.4</td>
<td>1.9±4.5</td>
<td>1.6±3.5</td>
<td>2.6±5.5</td>
<td>3.2±5.2</td>
<td>1.6±2.8</td>
<td>3.5±4.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Severe</td>
<td>1.5±3.8</td>
<td>1.5±3.3</td>
<td>0.7±1.9</td>
<td>0.2±1.2</td>
<td>1.0±4.8</td>
<td>0.8±2.3</td>
<td>0.6±2.9</td>
<td>0.7±2.0</td>
<td>0.119</td>
</tr>
</tbody>
</table>

Data are mean±SD of total postoperative time in PACU expressed in percentages. Pain intensity evaluated by the verbal rating scale 0-10 (VRS-11): No pain=0, mild pain=1-3, moderate pain=4-6 and severe pain=7-10.
three rescue blocks (2 epidural and 3 FNB, P=0.022).

Table III exposes the postoperative pain evolution. The patients were free of pain the 92.33% of total time in the PACU and had pain a 7.67% of time (3.82% mild pain, 2.75% moderate pain and 1.1% severe pain).

The chronologic evolution of pain during the postoperative time in the PACU is showed in Figure 3.

We also analyzed the outcomes in pain and need of rescue analgesia between the 3 groups of FNB, the 3 groups of ACB and also comparing the FNB groups vs. ACB groups. We found no differences between FNB groups in pain (P=0.191) or rescue analgesia (P=0.542). Analyzing the adductor canal block groups, we observed that the addition of dexamethasone 4 mg was better in terms of pain (P=0.007) and need of rescue analgesia (P=0.013) than the other two ACB groups, whereas perineural dexmedetomidine had no effect in pain (P=0.078) or rescue analgesia (P=0.079) compared with the ACB group without adjuvants.

Comparing FNB vs. ACB groups, we found differences in pain between FNB+Dexa vs. ACB (P=0.002) and FNB+Dexa vs. ACB+Dexm (P=0.002) and also in rescue analgesia: FNB+Dexa vs. ACB (P=0.005), FNB+Dexa vs. ACB+Dexm (P=0.005) and ACB+Dexa vs. ACB+Dexm (P=0.044) respectively. The best results were obtained with the FNB+Dexa and ACB+Dexa groups, without statistical significance in pain (64.2% of FNB+Dexa patients had all VRS-11=0 vs. 55.6% of ACB+Dexa group, P=0.265), or need of rescue analgesia (33.3% FNB+Dexa vs. 38.3% ACB+Dexa, P=0.515).

Discussion

Our postoperative protocol of TKA is different from other hospitals: includes one day of stay in the PACU and beginning of rehabilitation the day after the surgery. It allows us a more complete postoperative follow-up, including advanced pain management at any time of day or night.

Regarding the demographic data, it is important to remark that the average BMI is 31.6 (obesity grade I), because it has been established a direct correlation between increasing BMI and the occurrence of major cardiovascular complications in TKA.

We would like to note that we did not include a local infiltration analgesia (LIA) group to avoid local anesthetic systemic toxicity, because we use routinely autologous blood reinfusion through a closed system (ConstaVac™ CBCII Blood Conservation System, Stryker, Kalamazoo, MI, USA), and also that we did not used rescue ACB because the lower limb was bandaged.

FNB is considered the gold standard for pain management after TKA. Our results
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are different from Chan et al.\textsuperscript{11} when comparing epidural analgesia and FNB. They could not demonstrate a difference in pain between FNB (any type) and epidural analgesia. However, we find better analgesia and less incidence of rescue analgesia with femoral nerve blocks compared with EA. So, we agree with Bauer et al.,\textsuperscript{1} who affirm that lumbar epidurals have an unfavorable risk/benefit ratio and regional techniques provide comparable pain control.

The ACB has been proposed as alternative technique for pain management after TKA to avoid the disadvantage of FNB motor impairment\textsuperscript{12}, but there are different results and dosages and few randomized clinical trials with enough number of patients to recommend this.\textsuperscript{10,12}

The results of FNB+Dexa and ACB+Dexa groups were quite similar and although they appeared to be slightly favorable for the FNB+Dexa group there were not statistical significance in pain or need for rescue analgesia. So, these minimum differences in pain possibly do not justify the prevalence of FNB as the gold standard, because of the demonstrated quadriceps strength impairment when dexamethasone is added as perineural adjuvant.\textsuperscript{4} In fact, after evaluation of our results, we have changed our daily clinical practice in favor of ACB+Dexa. We have not found other references of ACB with perineural dexamethasone, but these results seem to be a promising starting point for future research.

Sciatic nerve block (SNB) has been recommended sometimes to supplement FNB analgesia in TKA. The latest meta-analysis\textsuperscript{13} suggests that SNB can significantly reduce postoperative opioid consumption and diminish knee pain following TKA compared to no SNB in the setting of FNB. However, major concerns for performing an additional SNB include risk of neuronal injury and increased motor weakness after surgery, so the advantage of SNB when combined with FNB is questioned. We did not practice SNB in this study to avoid bias in the results, but we must say that our clinical practice includes a SNB (5-10 ml of levobupivacaine 0.375% without dexamethasone) in all patients with moderate or severe preoperative pain in the popliteal fossa and/or knee with marked flexion deformity.

In the present study, a total of 158 rescue blocks were needed: 24 epidural supplementary boluses, 120 FN B and only 14 SN B (3 in control group, 4 in FNB, 2 in F NB+Dexa, 1 in F NB+Dexam, and 4 in AC B group respectively). These data could provide support to the need to select previously the patients who could benefit from SNB instead of using it indiscriminately to all patients for TKA. We would like also note that there is no difference between ACB and FNB in the need of rescue SNB.

The results of our multimodal approach for TKA contrasted with those postulated by other groups, such as Jensen’s meta-analysis of 12,000 patients,\textsuperscript{14} who described in patients receiving intravenous analgesia only a 43% with VRS-11 scales of pain >5 at rest, 35%>7 with knee movements and 64% requiring more than 20 mg of morphine daily for treating pain compared with 25%, 20% and 41% respectively in patients receiving treatment active against the pain (femoral nerve block, epidural or infiltration analgesia). We must point out that as a result of an early invasive pain control, the doses of morphine used in our study were very low (average 0.8 mg, maximum 12 mg in 1 patient), and this can help to avoid adverse effects (emesis, sedation and disorientation in the elderly).

Figure 4.—Adductor canal block US anatomy.
Hospital is 6296.88 € (50.71% the prosthesis, 33.44% staff, 15.39% fungible and 0.46% medication). The intravenous rescue analgesia cost from 0.55 to 2.04 €, the nerve block 18.97 to 33.35 € and the epidural 31.65 € respectively, so the cost of rescue analgesia is an insignificant part of the total cost of TKA compared with the clinical benefit obtained.

Conclusions

In conclusion, peripheral nerve blocks with perineural dexamethasone improve postoperative analgesia for TKA. The addition of perineural dexamethasone to adductor canal block open new possibilities to improve analgesia for TKA and we believe that should be investigated more extensively as an alternative to femoral nerve block.

Key messages

— A better pain control in the perioperative period decreases the risk of chronic postoperative pain incidence in patients undergoing total knee arthroplasty (TKA).
— Multimodal and preemptive analgesia are the better approach for pain management in TKA.
— Peripheral nerve block (PNB) is as effective as epidural analgesia for postoperative pain management in patients undergoing TKA. Moreover, it is associated with significantly lower postoperative complications.
— Adjuvants seem to improve the effect of local anesthetics in PNB.
— Adductor canal block appears to be an effective PNB with similar analgesic effect to femoral nerve block after TKA.

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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Goal-directed fluid management in free flap surgery for cancer of the head and neck

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ABSTRACT

BACKGROUND: Goal-directed fluid management using stroke volume variation (SVV) analysis is not well studied in free flap reconstruction surgery in patients with head and neck cancer.

METHODS: Patients operated due to cancer of the head and neck with free flap reconstruction during 2008-2010 and 2012-2014 in Oulu University Hospital were retrospectively evaluated to determine the impact of SVV-guided fluid management on perioperative fluid balance, postoperative complications and hospital length of stay (LOS).

RESULTS: A total of 104 patients were included in the study and in 48 of them SVV was used to guide intraoperative fluid management. The SVV-guided fluid management led to significant reduction in intraoperative fluid load (6070 mL vs. 8185 mL) and hospital length of stay (11.5 vs. 14.0 days). There was no difference in the number of postoperative complications between the groups.

CONCLUSIONS: The SVV-guided fluid management reduces fluid administration in free flap reconstruction surgery with head and neck cancer.

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Key words: Head and neck neoplasms - Surgical procedures, operative - Free tissue flaps - Stroke volume.

Perioperative fluid management has an impact on the outcome of the patients undergoing free flap surgery of the head and neck. Excessive overall fluid administration has been reported to be associated with extended hospital length of stay (LOS) in this patient group. In line with this, fluid management with crystalloids more than 130 mL/kg in 24 hours has been shown to increase postoperative morbidity. Positive fluid balance has also been reported to increase flap failures and postoperative complications in free flap reconstructions of lower extremity and breast.

Stroke volume variation (SVV) analysis based on arterial pressure waveform is a minimally invasive method for monitoring and assessing the patient’s hemodynamic status and to guide intraoperative fluid management. Optimizing hemodynamics with the use of SVV analysis has been found to result in better hemodynamic stability and to reduce serum lactate concentration at the end of operation in major gastrointestinal surgery. In addition, SVV-guided hemodynamic treatment has been associated with a lower rate of postoperative complications and a shortened hospital LOS.
in high-risk surgical patients compared with standard hemodynamic monitoring.\textsuperscript{5, 6} Similar findings have been reported also in high-risk abdominal surgery.\textsuperscript{7}

The beneficial effect of SVV-guided fluid management in free flap surgery of head and neck is unclear. Only a few studies with limited number of patients exist.\textsuperscript{8-10} Accordingly, we determined to retrospectively evaluate the impact of SVV-guided fluid management in free flap surgery of head and neck on perioperative fluid balance, flap failure, other postoperative complications and hospital LOS.

Materials and methods

Setting

This retrospective population based study was conducted in the Oulu University Hospital, which is located in Northern Finland and provides tertiary, university hospital-level care for 750 000 inhabitants. Due to the retrospective study design no statement from the hospital’s ethics committee was obtained. The study was approved by the hospital administration.

Patients and inclusion criteria

All the patients who were operated due to cancer of the head and neck with free flap reconstruction during 2008-2010 and 2012-2014 in the Oulu University Hospital were retrospectively screened. The year 2011 was excluded due to a limited number of operations and a temporary use of alternative surgical technique.

Data extraction

The patients were identified from the operation records of the head and neck surgery unit. Study data were retrieved from the medical records, anesthesia charts, laboratory results, radiological statements and intensive care unit (ICU) database (Centricity Critical Care Clinisoft, GE Healthcare). The data regarding chronic diseases and daily medication were retrieved from medical records. The study data consisted of patients’ demographics, intraoperative variables (predetermined hemodynamic variables, data on fluid balance and the length of operation room [OR] stay), data on postoperative intensive care, including LOS and fluid balance, and postoperative data during the first five postoperative days of hospital stay. Postoperative complications, including flap failure, partial flap failure and the need of reoperations, as well as infectious complications and other major complications were detected from the medical records. Complications that occurred after hospital discharge but within 30 days were included in the analysis; they were recognized from medical records. The hospital LOS was calculated as the time from the day of surgery until discharge. All variables were predetermined a priori based on previous studies\textsuperscript{2, 9, 12} or clinical judgement. The data were collected in structured forms and digitalised.

Free flap surgery procedure and anesthesia

In the Oulu University Hospital the free flap surgery for head and neck is performed by a surgical team that includes an otolaryngologist and a plastic surgeon. During the study period three otolaryngologists made all operations with three plastic surgeons. Tracheostomy is performed when needed under local anesthesia before the induction of general anesthesia.

The routine hemodynamic and respiratory monitoring includes arterial blood pressure, electrocardiograph, pulse oximetry and, if available, central venous pressure. Urine output is recorded hourly. The temperature is monitored by a peripheral probe and a temperature-sensing urinary catheter (core temperature). The neuromuscular blocking (NM) probe and the depth of anesthesia (entropy monitor) are routinely monitored. The general anesthesia and fluid management are performed by the attending anesthesiologists according to the local guidelines using balanced volatile and intravenous anesthesia. Warming blankets, mattresses and intravenous-fluid warmers as well as low flow anesthesia are used to maintain the patient’s normal body temperature. Patients
are routinely admitted to ICU for immediate postoperative care.

The vitality of the flap is postoperatively monitored using Licox®-probe inserted in the operated site, as recommended. It measures the partial pressure of oxygen (pO₂) in body fluids and tissue. The probe is implanted at the end of the operation and it indicates the possible vascular problems in free flaps especially when the flaps are not visible or not suitable for clinical assessments.13

**Stroke volume variation analysis and Vigileo®**

In the Oulu University Hospital the SVV-guided goal-directed fluid management using Vigileo FloTrac®-device was initiated in free flap surgery of head and neck in 2012. Vigileo FloTrac® evaluates a patient’s hemodynamic status based on the arterial pressure signal obtained by a standard peripheral arterial line without external calibration. Using the arterial pressure waveform and individual patient data (age, gender, weight, height) the algorithm produces hemodynamic parameters, including cardiac output (CO), cardiac index (CI), stroke volume (SV), stroke volume index (SVI) and stroke volume variation (SVV).14 The SVV represents a variation of SV during the ventilation cycle and is defined as a difference between the maximum and minimum SVs divided by the mean SV within a given time. The maximum and minimum SV are mean values of the four extreme values of SV during a period of 30 seconds, and the mean SV is the average value for this period. These calculations are made every 20 seconds by Vigileo. The SVV is displayed as a percent value; the normal values in controlled ventilation are less than 10-13%. Greater values can predict fluid responsiveness and are useable tools for optimizing fluid management.15 For a reliable calculation a good quality of arterial pressure signal and regular heartbeat (sinus rhythm and the absence of arrhythmias) is required. The device is validated for patients in mechanical ventilation with closed chest and a tidal volume at least 7 mL/kg.7, 14

**Patient groups**

Patients were divided into two groups based on presence or absence of Vigileo during operation: conventional fluid management (group C) and goal-directed fluid management (group G).

**Conventional fluid management (group C)**

Of the 56 patients in the group C, 36 (64.2%) were treated during 2008-2010. In the group C, the fluid management was guided by the hemodynamic targets, presented as normal values of heart rate, arterial blood pressure, central venous pressure, urine output, and blood gas analysis. Dobutamine was used as a primary vasoactive drug to achieve the blood pressure goals determined by local guidelines (MAP>70 mmHg, SAP>100 mmHg). Norepinephrine was used if sufficient blood pressure was not achieved with dobutamine or if dobutamine caused side effects, including tachycardia and arrhythmias.

**Goal directed fluid management (group G)**

Of the 48 patients in the group G, 47 (97.9%) were treated during 2012-2014. In the group G, the Vigileo FloTrac® device was used for a continuous monitoring of CI and SVV. The fluid management was guided as in the group C and by the measurements from Vigileo. According to local guidelines an additional fluid bolus (usually 250 mL Ringer acetate) was given if SVV was high (>10%) or the baseline was increasing. The fluid challenge was repeated until SVV was <10%. The targeted SAP was >100 mm Hg and/or MAP>70 mm Hg. The target for CI was at minimum the first measured CI in OR or more than 2 L/min/m². Dobutamine was used to maintain the sufficient CI, and norepinephrine was used for the blood pressure if the goals for blood pressure and CI were not achieved with SVV<10%.

**Statistical analysis**

The data were analyzed using SPSS software (SPSS 22, IBM). Categorical variables
are presented as absolute numbers (N) and percentages (%) and compared using Pearson $\chi^2$. Continuous variables are presented as medians with 25th and 75th percentiles (25-75th PCT) and tested using non-parametric Mann-Whitney test. P-value less than 0.05 was considered statistically significant.

Results

During the study period a total of 118 free flap operations were performed. Of these 118 operations, 14 were excluded from the analysis. One involved a patient with a non-malignant tumor, ten were reoperations due to a total or partial flap failure, and in three cases the data were inadequate, leaving a total of 104 cases that were included in the analysis. The ten reoperations were done to nine patients; one patient required three operations within three weeks from the primary operation due to flap failures.

The median age of all patients was 65 years. Of the 104 patients, 59 (56.7%) were males. Group G comprised 48 cases and group C 56 cases. Patients in the group G were older (68 vs. 63 years, P=0.006) and the proportion of non-smokers was higher in this group (75% vs. 52%, P=0.015). Table I presents the demographic data of the patients.

There was no difference in the duration of operation between the groups. Intraoperatively the patients in the group G received significantly less fluids compared to the group C (6070 mL [4710-7135] vs. 8185 mL [6540-10155], P<0.001) resulting in infusion rates of 5.0 mL/kg/h (3.7-7.0) and 6.2 mL/kg/h (5.1-9.0), P=0.007, respectively. The recorded blood loss was lower in the group G (600 mL vs. 800 mL, P=0.022). There were no differences in patients’ temperature or urine output between the groups. In the group G norepinephrine was used as vasoactive drug more often compared with the group C (66.7% vs. 21.4%, P<0.001) (Table III).

Patients in the group G received significantly less fluids from the second to fifth day postoperatively compared with patients in the group C. There was no difference in the postoperative fluid balance between the groups, but the urine output was higher in the group C from the first postoperative day to the fourth postoperative day (Table IV).

Complications were recorded in 69 (66.3%) cases, including 58 (55.8%) medical complications and 52 (50.0%) surgical complications. The rate of medical and surgical complications was comparable between the groups. The hospital LOS and the time tracheostomy was needed were shorter in the group G (11.5 vs. 14.0 days, P=0.024; and 7 vs. 9.5 days, P=0.001, respectively) (Table V).

Because of the high proportion of smokers in the group C we analyzed the effect of smoking on the most common postoperative complications in this study. Delirium was more often recorded in smokers than in non-smokers (33.3% vs. 15.4%, P=0.033), as were the medical complications (43.6% vs. 27.7%, P=0.032), respectively. There was no difference in hospital LOS between smokers and non-smokers (14 days vs. 13 days, P=0.283).

Discussion

The main finding of the present study was that the use of goal-directed fluid management in free flap surgery of the head and neck led to significant reduction in intraoperative fluid load and hospital LOS. However, there were less postoperative wound hematomas among patients with conventional fluid management, but the difference was not statistically significant. We found no difference in the rate of medical and surgical complications between the groups.

There is limited knowledge of the use of the noninvasive methods for measuring cardiac output in free flap surgery of head and neck, even though these methods have been proven to be beneficial in gastrointestinal and other major surgery to optimize fluid management. However, the use of SVV-guided fluid management cannot fully be compared between free flap surgery of head and neck and gastrointestinal surgery because of the major differences in the nature of these surgical operations. In 2011, only 9% to 34.5% of the surgery units in the United Kingdom routinely monitored cardiac output in free flap surgery of head and neck.16, 17
## Table I.—Demographic data of 104 patients.

<table>
<thead>
<tr>
<th></th>
<th>Total N=104</th>
<th>Goal directed fluid management N=48</th>
<th>Conventional fluid management N=56</th>
<th>P value</th>
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<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
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<td>68 (62-76)</td>
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<tr>
<td><strong>Gender, m/f</strong></td>
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<tr>
<td></td>
<td>59/45</td>
<td>25/23</td>
<td>34/22</td>
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</tr>
<tr>
<td><strong>BMI</strong></td>
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</tr>
<tr>
<td></td>
<td>23.1 (20.1-26.1)</td>
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<td>22.8 (19.7-26.1)</td>
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<td><strong>Smoker</strong></td>
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<tr>
<td></td>
<td>39 (37.5)</td>
<td>12 (25.0)</td>
<td>27 (48.2)</td>
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<td><strong>Alcohol abuse</strong></td>
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<td>20 (19.2)</td>
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<tr>
<td></td>
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<td>48 (46.2)</td>
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<td>4</td>
<td>7 (6.7)</td>
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<td><strong>Preoperative laboratory results</strong></td>
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<td><strong>Hemoglobin g/L</strong></td>
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<tr>
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<td>131 (119-141)</td>
<td>131 (120-138)</td>
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<td>0.39 (0.36-0.41)</td>
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<td>280 (212-358)</td>
<td>270 (196-322)</td>
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<td>1.0 (0.95-1.2)</td>
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<tr>
<td>&gt;1 anticoagulant*</td>
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<td>Comorbidity</td>
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<td>MCC</td>
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</tr>
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<td>Diuretic</td>
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<tr>
<td>Oral cavity/tongue</td>
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<tr>
<td>Maxilla</td>
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<tr>
<td>Mandibula</td>
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<tr>
<td>Larynx/pharynx</td>
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</tr>
<tr>
<td>Cutaneous</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Buccal mucosa</td>
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<td></td>
</tr>
<tr>
<td>Palatinal</td>
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<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

BMI: Body Mass Index; APACHE II: Acute Physiology and Chronic Health Evaluation; ASA: American Society of Anaesthesiologists; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; HTA: hypertension arterialis; MCC: coronary artery disease; autoimmune disease=rheumatoid arthritis, vasculitis, connective tissue disease; ACEI= angiotensin-converting-enzyme inhibitor.

*two patients in the conventional fluid management group used ASA and clopidrogel as combination therapy and one patient used ASA and warfarin.

Categorical variables are presented as absolute numbers (N) and percentages (%). Continuous variables are presented as medians with 25th and 75th percentiles (25-75 Pct).
is also a lack of studies on goal-directed fluid management in head and neck free flap operations, and the studies that have been conducted involve a limited number of patients. These few studies have found that goal-directed fluid management based on SVV analysis is a promising method for optimizing hemodynamics in free flap surgery of head and neck.8, 9 Unlike the present study, a recent randomized controlled trial by Hand et al focused on the intraoperative fluid management and ICU LOS.10 Our analysis extended to the total hospital LOS concerning postoperative complications and the fifth postoperative day concerning fluid management.

In the present study the patients treated with the goal-directed fluid management (group G) received significantly less fluids intra- and postoperatively, which is a novel finding in the free flap surgery of the head and neck cancer.9, 10 The recorded blood loss was higher in the group C (800 mL vs. 600 mL, P=0.022). In line with this, the patients in the group C also received significantly more fluids intraoperatively compared with the patients in the group G. How-
ever, more liberal fluid management may have led to greater blood loss and higher tendency to transfusion of red blood cells during operation due to dilution of coagulation factors and decreased blood viscosity. Pulmonary edema and acute lung injury as well as need for respiratory support and prolonged hospital LOS are the potential consequences of aggressive volume resuscitation. Based on the continuous hemodynamic measurements by Vigileo in the group G it was possible to optimise hemodynamics individually. Because the numeric value of CI was available, it guided the attending anesthesiologist to use norepinephrine as the vasoactive drug to achieve the targeted blood pressure instead of reasonably high doses of dobutamine or large amounts of fluids. Despite of the fact that goal-directed fluid management did not improve outcome in our study we believe it is likely to benefit the patients. Tracheostomy was removed earlier from patients treated with goal-directed fluid management, and these patients were more often discharged home from the hospital compared with patients treated with the conventional fluid management. In addition, their hospital loss was shorter. We hypothesize that the difference in the fluid load between the study groups mainly explains these findings. Based on these results the goal-directed fluid management could be a cost effective strategy in free flap surgery of the head and neck; however, the aim of the present study was not to analyze the cost effectiveness of goal-directed fluid management in this setting. It is an issue that needs further study.

The number of recorded complications was high, which was in line with a previous study reporting that 64% of patients had complications after free flap surgery of head and neck. Still, contrary results exist. The present

<table>
<thead>
<tr>
<th>Table IV.—Postoperative variable.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N.=104</td>
</tr>
<tr>
<td>CVP min (mmHg)</td>
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<tr>
<td>Balance d1 (mL)</td>
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<td>Balance d2 (mL)</td>
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<tr>
<td>SOFA admission</td>
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<tr>
<td>SOFA max</td>
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</tr>
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<td>APACHE II</td>
</tr>
<tr>
<td>Furosemide total mg</td>
</tr>
<tr>
<td>Licox minO2</td>
</tr>
<tr>
<td>Sedation (h)</td>
</tr>
<tr>
<td>Respiratory support (h)</td>
</tr>
</tbody>
</table>

D1: first postoperative day; D2: second postoperative day; D3: third postoperative day; D4: fourth postoperative day; D5: fifth postoperative day; SOFA: Sequential Organ Failure Assessment; ICU: intensive care unit; LOS: length of stay; APACHE II: Acute Physiology and Chronic Health Evaluation; Licox minO2: lowest measured value by Licox probe. Categorical variables are presented as absolute numbers (N) and percentages (%). Continuous variables are presented as medians with 25th and 75th percentiles (25th-75th PCT).
Although liberal fluid management has been shown to increase complications, the etiology of late complications is usually multifactorial.

**Limitations of the study**

The limitations of this study include its retrospective design and a small number of patients. Because of the retrospective setting, the intraoperative management was not standardized; however, the surgical technique did not change during the study period. The small study population reduced the power of our data, and it was challenging to show the statistical significance in our series. An increase in the number of patients would have led to a major extension in the study time thus leading to less reliable results.

**Table V.—Postoperative outcome.**

<table>
<thead>
<tr>
<th></th>
<th>Total N.=104</th>
<th>Goal directed fluid management N.=48</th>
<th>Conventional fluid management N.=56</th>
<th>P value</th>
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<tr>
<td>Antibiotic treatment</td>
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<tr>
<td>max 1 day</td>
<td>15 (14.4)</td>
<td>6 (12.5)</td>
<td>7 (12.5)</td>
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</tr>
<tr>
<td>1-5 days</td>
<td>20 (19.2)</td>
<td>11 (22.9)</td>
<td>9 (16.1)</td>
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<tr>
<td>&gt;5 days</td>
<td>69 (66.3)</td>
<td>31 (64.6)</td>
<td>40 (71.4)</td>
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<tr>
<td>Tracheostomy days</td>
<td>8 (5-13)</td>
<td>7 (10-11)</td>
<td>2 (10-11)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospital los</td>
<td>13.0 (9.0-17.0)</td>
<td>11.5 (9-15)</td>
<td>14 (10-21)</td>
<td>0.024</td>
</tr>
<tr>
<td>Discharge disposition</td>
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<tr>
<td>home</td>
<td>62 (59.6)</td>
<td>31 (64.6)</td>
<td>31 (55.4)</td>
<td>0.374</td>
</tr>
<tr>
<td>other</td>
<td>42 (40.4)</td>
<td>17 (35.4)</td>
<td>25 (44.6)</td>
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<td>Medical complications</td>
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<tr>
<td>Stroke</td>
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<td>0 (0)</td>
<td>1 (1.8)</td>
<td>0.352</td>
</tr>
<tr>
<td>AKI</td>
<td>1 (1.0)</td>
<td>1 (2.1)</td>
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<td>0.278</td>
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<tr>
<td>Pneumonia</td>
<td>35 (33.7)</td>
<td>15 (31.3)</td>
<td>20 (35.7)</td>
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<td>AMI</td>
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<td>4 (8.3)</td>
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<td>Delirium</td>
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<td>9 (18.8)</td>
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<td>1 (2.1)</td>
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<td>Pulmonary embolism</td>
<td>1 (1.0)</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
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<tr>
<td>Pulmonary edema</td>
<td>7 (6.7)</td>
<td>5 (10.4)</td>
<td>2 (3.6)</td>
<td>0.165</td>
</tr>
<tr>
<td>Sepsis</td>
<td>7 (6.7)</td>
<td>2 (4.2)</td>
<td>5 (4.2)</td>
<td>0.334</td>
</tr>
<tr>
<td>ICU readmission</td>
<td>7 (6.7)</td>
<td>5 (10.4)</td>
<td>2 (3.6)</td>
<td>0.165</td>
</tr>
<tr>
<td>Medical complications total</td>
<td>58 (55.8)</td>
<td>25 (52.1)</td>
<td>33 (58.9)</td>
<td>0.483</td>
</tr>
<tr>
<td>Surgical complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td>33 (31.7)</td>
<td>12 (25.0)</td>
<td>21 (37.5)</td>
<td>0.172</td>
</tr>
<tr>
<td>Wound haematoma</td>
<td>8 (7.7)</td>
<td>6 (12.5)</td>
<td>2 (3.6)</td>
<td>0.088</td>
</tr>
<tr>
<td>Reoperation</td>
<td>38 (36.5)</td>
<td>17 (35.4)</td>
<td>21 (37.5)</td>
<td>0.826</td>
</tr>
<tr>
<td>Partial flap failure</td>
<td>5 (4.8)</td>
<td>2 (4.2)</td>
<td>3 (5.4)</td>
<td>0.777</td>
</tr>
<tr>
<td>Total flap failure</td>
<td>8 (7.7)</td>
<td>3 (6.3)</td>
<td>5 (8.9)</td>
<td>0.609</td>
</tr>
<tr>
<td>Surgical complications total</td>
<td>52 (50.0)</td>
<td>23 (47.9)</td>
<td>29 (51.8)</td>
<td>0.694</td>
</tr>
<tr>
<td>All complications</td>
<td>69 (66.3)</td>
<td>32 (66.7)</td>
<td>37 (66.1)</td>
<td>0.949</td>
</tr>
</tbody>
</table>

AKI: acute kidney injury; AMI: acute myocardial infarction; DVT: deep venous thrombosis; ICU: intensive care unit; LOS: length of stay. Categorical variables are presented as absolute numbers (N) and percentages (%). Continuous variables are presented as medians with 25th and 75th percentiles (25-75th Pct).
Intraoperative fluid optimization using waveform analysis and arterial waveform analysis in free flap surgery of the head and neck seems to reduce the intra- and postoperative fluid load. Randomised studies with increased number of patients are needed to evaluate its impact on perioperative goal-directed therapy. The reliability of SVV among patients with a high rate of comorbidities is unclear. Hemodynamic monitoring with waveform analysis has been found to be reliable in patients with acute subarachnoid hemorrhage with normal vascular tone.\(^\text{22}\) More than 60% of the patients in the present study had chronic cardiac diseases, which can partly explain the absence of positive impact of the waveform analysis-based hemodynamic monitoring in the present study. In addition, ventilation strategy was not standardized, and this may have influenced the predictive value of SVV.\(^\text{7}\) Furthermore, varying doses of inotropes during operation alter vascular tone and can lead to changing arterial waveform and transiently alter the analysis made by Vigileo.\(^\text{14}\)

Despite the limitations of the present study and possible limitations in the methodology used to guide the fluid management we were able to show the impact of goal-directed fluid management on the intra- and postoperative course in a relatively large number of patients.

Conclusions

In conclusion, the goal-directed fluid management based on arterial waveform analysis in free flap surgery of the head and neck seems to reduce the intra- and postoperative fluid load. Randomised studies with increased number of patients are needed to evaluate its impact on postoperative complications and flap failures.

Key messages

— The SVV-guided fluid management reduces fluid administration and shortens the hospital LOS among patients with free flap surgery of head and neck.

— The noninvasive methods for measuring cardiac output are suitable but not well studied or commonly used in free flap surgery for cancer of the head and neck.

— Both medical and surgical complications are frequent in free flap surgery for cancer of the head and neck.

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.

The link between anesthesiology and neurology: a mindful cooperation to improve brain protection

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A B S T R A C T

Preventing neurological injury is mandatory during the perioperative period of any kind of surgery and in the care of critically ill patients in the intensive care unit. During daily practice, both anesthesiologists and neurologists focus on brain protection as an integral part of systemic homeostasis maintenance. This article highlights the intriguing overlap between anesthesiology and neurology in clinical practice along with its potential implications for outcome. Moreover, it focuses on the importance of the complementary expertise of both specialists in maintaining cerebral homeostasis, with the aim of improving outcome. A review of available evidence on anesthesiology and neurology interplay in clinical practice along with its potential implications for outcome has been conducted. Clinical vigilance and the use of shared monitoring and diagnostic technology could allow early recognition and treatment of cerebral dysfunction occurring in the perioperative period or in the critical care setting, thus reducing morbidity and mortality. In order to improve patient safety and outcome, neurologists and anesthesiologists should more closely and successfully collaborate, using shared monitoring tools and integrating traditional areas of expertise. Daily activity, education, research and training programs in anesthesia and neurology could benefit from a stronger relationship with each other.

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Key words: Neuroprotection - Anesthesiology - Neurology - Intensive care - Education.

M aintaining cerebral homeostasis and avoiding noxious events, which can potentially jeopardize cerebral blood flow, oxygenation, and autoregulation are essential in the clinical practice of both anesthesiologists and neurologists. Optimizing the collaboration of neurologists and anesthesiologists in preserving brain function, by means of exchanging domains of expertise and the use of shared monitoring and diagnostic techniques, has improved patient care and reduced mortality in a wide range of clinical situations, over the last decade. 1-5

Neurologists specialize in diagnosing and treating disorders of the central and peripheral nervous system, and specifically of the brain, spinal cord, nerves, and muscles. Clinical neurobiology, neuropathophysiology, neuropsychology, emergency neurology, neuropathic pain, and neuro-rehabilitation are their recognized fields of interest. Anesthesiology has evolved from the science of administering anesthetics for pain relief to the care of the
patient during the entire perioperative period.\textsuperscript{1} Specific anesthesiological areas are: intensive care, pain medicine, palliative care, emergency medicine, and hyperbaric medicine. In all these fields of competence, the anesthesiologist is dedicated to maintaining brain homeostasis during daily practice, in all decision-making efforts. Some anesthesiologists who are involved with the management of neurologically injured patients are also neurologists and neurologists often specialize in neurocritical care, a common domain for both.

While it is clear that each specialist has a unique distinctive role, this article aims to highlight the concept that a better interplay between neurologists and anesthesiologists in different clinical settings could improve patient outcomes. Furthermore, the role of vigilance to early detect impending cerebral dysfunction in the perioperative period and in the critical care setting is emphasized.

Anesthesia-neurology interplay in the perioperative and intensive care unit settings

The risk of perioperative stroke

Although the brain is the recognized target of anesthetic drugs, no standard monitors for brain function have been established for daily activity in the operating room, while routine monitors mainly focus on respiratory and cardiovascular function evaluation. However, perioperative alterations in cerebral homeostasis may still occur, not only in patients with known neurologic pathologies, but also in patients without any known neurologic impairment, especially in the case of comorbidities or at-risk procedures.\textsuperscript{7, 8}

The incidence of perioperative stroke varies according to type and complexity of surgery and associated comorbidities\textsuperscript{7, 9-12} and the outcome is usually worse than in strokes that occur outside the hospital,\textsuperscript{8, 12} probably because the acute systemic inflammatory response — triggered by the surgery — exacerbates ischemic cerebral injury.\textsuperscript{13-15} The perioperative period has been demonstrated to be an independent risk factor for stroke (odds ratio, 3.9; 95% confidence interval [CI] 2.1-7.4)\textsuperscript{2} and total hip replacement, lung resection and colectomy are at-risk procedures among non-cardiovascular, non-neurological surgeries.\textsuperscript{12} Among risk factors, a cumulative duration of 10 min of intraoperative hypotension has been demonstrated to result in a 1.14-fold increase in the risk of stroke.\textsuperscript{9}

The recognition of the risk of perioperative stroke during non-cardiac, non-neurologic surgery prompted the Society for Neuroscience in Anesthesiology and Critical Care to create a Consensus Statement providing evidence-based recommendations for perioperative care of patients at high risk for this complication.\textsuperscript{3} The importance of a multidisciplinary approach during the preoperative phase (to identify patients at high risk for perioperative stroke, to choose the safest time for elective surgery, and to optimize therapy), in the intraoperative period (to define safe intraoperative strategies) or in the postoperative period (to define organized protocols for emergency neurological evaluation of surgical patients with suspected stroke) is discussed in this article.\textsuperscript{3}

The issue of neurological dysfunction in the ICU

Critically ill patients admitted to the ICU with a non-neurological diagnosis may develop acute brain dysfunction, which can involve structural damage, functional alterations or both. Clinical pictures of the critical illness encephalopathy vary, ranging from altered mental status, coma, seizures, delirium, cognitive dysfunction or new onset focal neurologi-cal deficits.\textsuperscript{18-22} Growing evidence supports the occurrence of systemic inflammation, systemic arterial hypotension, hypercoagulability, new onset atrial fibrillation, and impaired cerebral autoregulation among potential pathomechanisms.\textsuperscript{4-6} A recent study on 146 critically ill patients who had developed an acute onset brain dysfunction while in the ICU revealed that almost 90% of patients had a significant underlying parenchymal brain damage detected by magnetic resonance imaging...
(MRI), and this was independently associated with an unfavorable short-term outcome. The most prevalent abnormalities were white matter hyper-intensities (71%) and acute cerebral infarcts (40%).

The occurrence of neurological sequelae has been increasingly investigated especially in sepsis and acute respiratory distress syndrome (ARDS), which are frequent and potentially life-threatening conditions requiring ICU admission. Delirium and ICU-associated weakness (ICU-AW) are two other pathologies that can have a significant impact on post-ICU recovery.

**Neurological Dysfunction in Sepsis and ARDS**

Sepsis-associated encephalopathy is an acute onset diffuse cerebral dysfunction ranging from agitation, alteration of consciousness to coma. The pathophysiology of this disorder includes inadequate perfusion, endothelial dysfunction, inflammation, cerebral autoregulation impairment and mitochondrial dysfunction. MRI studies demonstrated cerebral infarction in 29%, leukoencephalopathy in 21% and mixed lesions in 8% of septic-shock patients with an acute neurologic change. Sepsis is associated with an increased risk of new onset atrial fibrillation, which is associated with an increased risk for both in-hospital ischemic stroke and mortality. Impaired cerebrovascular autoregulation has been demonstrated in 60% of patients and is proposed as a causative mechanism for sepsis-associated brain dysfunction.

Furthermore, survivors of ARDS often have prolonged and disabling cognitive impairment in addition to impaired physical function. Neurological complications during ARDS, and subsequent functional deficits, are known to significantly affect patient survival and quality of life and should therefore be promptly detected. In particular, in patients undergoing extracorporeal membrane oxygenation (ECMO) support, neurological events such as subarachnoid hemorrhage, ischemic watershed infarctions, hypoxic-ischemic encephalopathy, unexplained coma and brain death are described with a very high incidence (~50% of patients).

**Delirium**

Delirium, defined as a disturbance of consciousness and cognition, which develops within a short period (hours-to-days) and fluctuates over time, appears to be an important neurological complication of intensive care treatment. The underlying mechanisms of delirium are incompletely understood, but are known to include neuro-inflammation, impaired oxidative metabolism and imbalance of neurotransmitters. It has been estimated that delirium occurs in 60–80% of mechanically-ventilated patients and in 20–40% of non-ventilated ICU patients. Delirium is an independent predictor of 6-month mortality and length of hospital stay and is associated with higher disability months–to-years following the discharge.

Recent studies have also hypothesized a connection between delirium duration and both brain structural integrity and cognitive impairment in ICU survivors. The VISIONS Study, a prospective neuroimaging study demonstrated that a longer duration of delirium was associated with smaller superior frontal lobe and hippocampal volumes.

**ICU-Acquired Weakness**

ICU-AW has been identified as a neurological condition directly related to ICU treatment, affecting a high percentage of critical patients. ICU-AW is characterized by two different types of involvement of the peripheral nervous system, one that predominantly affects the nerves, defined as critical illness polyneuropathy (CIP) and one that mostly affects the muscles, known as critical illness myopathy (CIM), although the two conditions often coexist. The effort of diagnosing and preventing ICU-AW can lead to an improved outcome of critically ill patients, reducing the duration of mechanical ventilation, ICU stay and 180-day mortality.
What can anesthesiologists learn from neurologists

Given the risk of perioperative neurological injury, neuro-monitoring is crucial for achieving the goal of neuroprotection and neuroprotective strategies should be pursued for any patient undergoing anesthesia.

The use of neurophysiologic monitoring, traditionally within the domain of neurologists but increasingly becoming widespread in clinical anesthesiology, allows the assessment of the effects of general anesthesia on its main target organ, namely the brain. Moreover, monitoring tools such as intraoperative electroencephalogram (EEG), evoked potentials, or regional cerebral oxygenation monitoring, which allows the detection of otherwise clinically-silent catastrophic perturbations in cerebral homeostasis, could contribute to patient safety. A significantly reduced incidence of major organ morbidity and mortality has been demonstrated in cardiac surgical patients by the utilization of regional cerebral oxygenation monitoring. Near infrared spectroscopy has been used to detect clinically important events of reduced cerebral oxygenation during cardiac and vascular surgery, or during beach chair position surgery.

In the future, more extensive neurophysiologic monitoring could hopefully help in maintaining brain homeostasis, in a similar manner to routine cardiac and respiratory monitoring in maintaining cardiac and pulmonary homeostasis during clinical anesthesiology. To this extent anesthesiologists could benefit from specific neurological expertise, learning essentials of EEG monitoring for anesthesia practice, recently available at www.icetap.org. (International Consortium for Electroencephalography Training of Anesthesia Practitioners).

Implementing the use of neurophysiologic monitoring and modern neuroimaging techniques represents the basis for a more intense collaboration between anesthesiologists and neurologists also in the ICU setting. The pathophysiologic and clinical rationale for the increasing utilization of neuromonitoring in patients with sepsis has been recently reviewed. In a study of patients admitted to a medical ICU, patients with sepsis had a higher rate of electrographic seizures (ESZs) and periodic epileptiform discharges (PEDs) than those without sepsis (32% vs. 9%) and this was associated with death or severe disability at hospital discharge (89% with ESZs or PEDs, vs. 39% if not; OR 19.1, 95% CI: 6.3-74.6). Similar results were achieved in a surgical ICU, where non-convulsive seizures and periodic discharges were frequent (16%) and independently associated with poor outcome (OR: 10.4; 95% CI: 1.0-53.7).

Finally, electroneurographic and electromyographic tests are the main diagnostic procedures used to identify the presence of ICU-AW, and specific simplified electrophysiological examinations used to assess peripheral nerve and muscle function in the ICU setting have been proposed. Muscle biopsy with the electrophoretic determination of myosin has been proposed as a diagnostic tool in patients with suspected CIM. It has also been observed that ICU-AW is often associated with autonomic nervous system dysfunction that can be detected by heart rate variability (HRV) testing. Notably, autonomic dysfunction itself may complicate the clinical course of critically ill patients and HRV is now being increasingly used as a promising diagnostic and prognostic tool for several critical illnesses, as recently reviewed by our group.

What can neurologists learn from anesthesiologists

Management of patients with acute ischemic stroke is a typical example of a common area of research and clinical interest for both specialists, whose collaboration is particularly useful in each phase of ischemic stroke care, i.e. in the emergency evaluation and diagnosis, in the timely delivery of thrombolysis, during general supportive care and in the treatment of acute complications such as malignant edema, hemorrhagic transformation of the infarct, epileptic seizures, acute respiratory distress and venous thromboembolisms.
While on the one side anesthesiologists can be trained to neuroradiological assessment of acute stroke patients to exclude radiological contraindication for thrombolytic therapy, on the other side neurologists can benefit from some traditional anesthesiological areas of expertise. Airway management, the treatment of patients with acute respiratory distress or the early identification of ongoing sepsis, the prophylactic antibiotic use, the management of hemodynamic and respiratory monitoring, the use of vasopressors or the global care of neurocritically ill patients are among the main examples of anesthesiological domains that can help neurologist in the care of these patients.

In particular, the recently published new definitions and recommendations on sepsis help clinicians to early identify patients with or at risk of developing sepsis. Shifting the focus from neurological injury to the possibility of a developing multiple organ dysfunction could help to prompt more timely and appropriate management, thus improving outcome in complicated cases. Furthermore, the anesthesiologist is traditionally concerned with monitoring cross-talk between the brain and other organs, such as the heart and the lungs, during anesthesia and critical care, as recently reviewed.

Prevention, early identification and treatment of patients developing ARDS, the most common non-neurologic organ dysfunction occurring in the early phase after severe acute brain injury, is another area in which anesthesiological support could represent an additional value in the care of these patients.

Recent literature also demonstrates the importance of promoting continuous discussion between specialists in a difficult arena such as that of antibiotic prophylaxis in critical illness. A recent multicenter study assessing the effectiveness of antibiotic prophylaxis for reducing pneumonia in patients after acute stroke demonstrated that antibiotic prophylaxis did not reduce post-stroke pneumonia or mortality in patients after acute stroke with dysphagia managed in stroke units and that it might increase the length of hospital stay and poor outcomes.

Preserving neurological outcome is a main concern also in the emergency arena. “Time is brain”, an aphorism typically used for stroke management, should be extended to the entire spectrum of acute brain injury in the emergency setting, particularly during cardiopulmonary resuscitation. Emergency Neurological Life Support (ENLS) emerged from the need to provide physicians with protocols to manage a patient during the first hours of a neurological emergency. Similarly to cardiac arrest for the heart, acute cerebral herniation must be considered as a catastrophic event for the brain, requiring immediate resuscitative measures while underlying mechanisms are explored.

It has been previously observed that the presence of a neuro-intensivist (a specialist that bridges the complimentary expertise of neurologists and anesthesiologists) can help for this purpose, and has been demonstrated to be effective in ICU outcome improvement. The important role, carried out on a daily basis by neuro-intensivists, is one of the strongest indications supporting the interaction between the anesthesia and neurology domains of expertise.

Areas of shared interest that need expertise of both anesthesiologists and neurologists

Pain treatment is a field of common expertise and an area of potential joint research of both anaesthesiologists and neurologists. Chronic pain assessment and neuropathic pain, in particular, represents a major symptom in common neurological disorders such as neuropathy, spinal cord injury, multiple sclerosis, and stroke, and remains a challenge for pain specialists. Traditionally, the diagnostic procedure for neuropathic pain relies in the ability of the clinician to identify painful symptoms, with the help of the clinical history and physical examination, in order to match a neuroanatomical pattern, but it often requires specialized diagnostic techniques to allow the identification of pain components. Specialized diagnostic techniques performed
by the neurologist must have the primary goal of diagnosing the cause of the pain before treating it with a symptomatic approach, thus avoiding misdiagnosis and attendant therapeutic implications. Techniques, like microneurography, laser-evoked potentials and skin biopsy, which were once limited to the research field, are now being introduced into clinical practice.52, 54 Similarly to the diagnostic process, the therapeutic approach to neuropathic pain proceeds in a stepwise-manner, and sometimes requires the expertise of neurologists and anesthesiologists for the management of the different medical resources represented by antidepressants, anticonvulsants, and opioids.55 Recent research in the field of neuropathic pain pathophysiology is opening potential new gates to the pharmacological treatment of pain, investigating the role of proinflammatory cytokines and neurotrophic factors as contributors to pathophysiological mechanisms underlying inflammatory and neuropathic chronic pain states, opioid tolerance, and opioid-induced hyperalgesia. Reducing the release of a wide array of cytokines and neurotrophic factors could represent a potential therapeutic strategy for neuropathic pain, thus suggesting an interesting future field of research for both anesthesiology and neurology.56

In the field of pain management anesthesiologist’s expertise in the provision of regional anesthesia-analgesia, involving the discussion of indications and contraindications of major nerve blocks and the treatment of complications is crucial. Procedures such as blood patch for the treatment of intracranial hypotension resulting from persistent cerebrospinal fluid leakage through the dura mater benefit of anesthesiologist competences and skills.

Outcome prediction after acute brain injury is another typical example of shared interest between specialists in the field of neurocritical illness. The importance of an early outcome prediction is recognized not only to support clinical decision making, but also to provide realistic expectation to the family. Type of lesions, clinical evaluation, patient’s related factors, genetics, the use of scoryng systems, biomarkers, or neuromonitoring tools have all been demonstrated to play a role in outcome prediction,57 but they need to be integrated in a multidimensional picture to be useful in the clinical practice, for which clinical experience and multidisciplinary cooperation remain essential. As an example, electrophysiology testing has become increasingly important as an integrative part of a wider assessment for vital prognostic information that EEG, event-related potentials, and somatosensory-evoked potentials can offer to the clinicians, as in anoxic-ischemic coma, which represents an area of a shared interest for anesthesiologists, neurointensivists, and neurologists.23, 24, 58, 59

In recent decades, electrophysiological monitoring has provided an important contribution not only to clinical anesthesia but also to the understanding of the effects of anesthetics on cerebral function. The clinical and neurophysiological features of general anesthesia and their relationship to sleep and coma have been addressed in a comprehensive review article focusing on the neural mechanisms of unconsciousness induced by anesthetic drugs and underlining distinct EEG patterns in the different states.60, 61 Thus, mechanisms of anesthesia-induced unconsciousness could represent a specific area of common clinical research between neurologists and anesthesiologists, as well as the assessment of cognitive decline potentially occurring after anesthesia, especially in the developing brain.62, 63

Future implications of a closer anesthesiology-neurology interplay

The ability to focus on common objectives and priorities and to share specific competencies is crucial for a multidisciplinary brain injury team. Over the last decade, the need for specialized intensive care of critically ill neurological patients prompted the spread of Neuroscience Intensive Care Units (NSICU) and this has been related to an improved outcome.48-50, 64-66 In line with the increase of NSICU, the discipline of neuro-critical care,61 a specific area of critical medicine and a grow-
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...ing specialty in neurology, should also be further implemented for clinical, educational and research purposes. The already established neuro-critical care fellowship training programs in the USA supports this concept and should be also pursued in the near future in European countries and around the world. Implementation of neuro-critical care programs would particularly benefit young trainees, bridging the fields of neurology, neurosurgery, neuroradiology, neuro-anesthesiology, and critical care medicine, thus providing wide exposure to all these disciplines.

Furthermore, training programs of anesthesiology and neurology, which vary widely around the world, should recognize this priority. From the neurology point of view, adequate formal training in general critical care should be proposed for all neurology residents, as they will be increasingly involved in providing emergency and neuro-critical care. From the point of view of anesthesiology, a stronger neurophysiological and neuropathophysiological basis and a deeper understanding of specific neuromonitoring or neuroimaging tools should be proposed for trainees in anesthesia and intensive care. Specific neuro-critical care training should also be designed for anesthesiologists.

While maintaining the specific domains of expertise in anesthesiology and neurology is essential, a deeper cooperation could result in better education for trainees in both disciplines (Figure 1). To conclude, preventing neurological injury is mandatory in several settings of anesthesiological practice. Anesthesiologists and neurologists should more closely collaborate in clinical, research and educational settings, to be more successful in their neuroprotection mission.

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**Figure 1.**—Distinctive and shared clinical and research fields of anesthesiology-neurology interplay. BLSD: basic life support defibrillation; ENLS: emergency neurological life support.
Key messages

In order to improve patient safety and outcome, neurologists and anesthesiologists should more closely and successfully collaborate, integrating traditional areas of expertise and more extensively using neurophysiological monitoring in anesthesia and intensive care setting.

The presence of a neuro-intensivist (a specialist that bridges the complimentary expertise of neurologists and anesthesiologists) can be effective in outcome improvement.

Training programs of anesthesiology and neurology, which vary widely around the world, should recognize these priorities, for clinical, educational and research purposes.

References


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

**Efficacy of the prophylactic administration of tramadol against postoperative shivering: a meta-analysis of randomized controlled trials**

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**Abstract**

**Introduction:** Postoperative shivering (POS) is a common complication that occurs after regional and general anesthesia. Thus far, numerous studies have reported on the effectiveness of tramadol in preventing or treating POS. Here, we performed a meta-analysis to assess the efficacy of tramadol in the prevention of POS.

**Evidence Acquisition:** We systematically searched PubMed, Embase and the Cochrane Library to identify studies of the efficacy of tramadol in the prevention of POS. The results are expressed as relative ratios (RRs) and the corresponding 95% confidence intervals (CIs).

**Evidence Synthesis:** Seventeen studies with a total of 1438 patients were included. Seven hundred seventy-seven of these patients received tramadol, and 661 received placebo. Compared with placebo, the patients who received tramadol exhibited a significant reduction in the incidence of POS based on subgroup analyses according to anesthesia (RR: 0.27; 95% CI: 0.19-0.37; P<0.00001), different doses of tramadol (RR: 0.26; 95% CI: 0.19-0.35; P<0.00001), the rescue drug used (RR: 0.19; 95% CI: 0.10-0.35; P=0.00001) and the number of patients who experienced severe POS (RR: 0.17; 95% CI: 0.12-0.23; P=0.00001). Moreover, the administration of tramadol did not increase the risks of postoperative nausea and vomiting (PONV), hemodynamic turbulence, respiratory depression or deep sedation.

**Conclusions:** This meta-analysis revealed that prophylactic tramadol effectively prevents POS and reduces rescue medication use without significant adverse effects.

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**Key words:** Tramadol - Shivering - Meta-analysis.
maintain normal body temperatures, are useful but expensive and not practical in all hospitals. In contrast, various pharmacological interventions, including clonidine, pethidine, tramadol, dexmedetomidine, ketamine and ondansetron, are helpful, simple, inexpensive and easy to implement in all settings. The use of these drugs are also restricted by their adverse effects, for example, clonidine may cause bradycardia and hypotension, pethidine may bring about nausea and vomiting, respiratory depression, dexmетодomine may induce sedation, and ketamine may result in hypertension and tachycardia.

Tramadol is a well-tolerated analgesic that is commonly used to control postoperative pain. Many studies have evaluated the efficacy of tramadol in the prevention or treatment of POS. However, no individual meta-analyses have focused on this topic. Therefore, we performed the present meta-analysis to evaluate the efficacy of tramadol in the prevention of POS.

**Evidence acquisition**

**Search strategy**

We conducted a systematic search for studies that compared the effects of tramadol and placebo on POS. The PubMed (1980 to present), Embase (1980 to present) and Cochrane Library (to present) databases were searched with an English-language restriction. Furthermore, the reference lists of the retrieved studies were also searched to identify any potentially relevant articles. We systematically searched for randomized controlled trials (RCTs) using the following keywords: tramadol, shivering, tremor, and shaking.

**Selection criteria**

Two researchers independently reviewed all articles. The inclusion criteria were as follows: RCTs that included comparisons of tramadol and placebo groups and analyses of the incidence of POS in the trials. The exclusion criteria were as the following: a lack of a control group and non-randomized studies.

**Data extraction and quality assessment**

Two independent researchers reviewed each of the included articles and extracted the data to a table (Table 1). The table included the following information: first author, year of publication, Jadad Score, type of surgery, type of anesthesia, randomized groups, sample size, time of the administration the prophylaxis, and outcomes (including the adverse effects). When three or more groups were included, we did not extract the data related to groups that did not involve tramadol or control conditions. For studies that included two or more tramadol groups that received different doses, we extracted the data for all of the groups and we performed subgroup analyses according to the different doses. All discrepancies regarding the research process were resolved by discussion. We used the modified Jadad scale with 7-piont scoring to evaluate the qualities of the included studies.12

**Statistical analysis**

The Review Manager software (RevMan 5.2; the Cochrane Collaboration) was used to analyze the statistical data. The analyses were performed using the relative risks (RRs) for dichotomous data with the 95% confidence intervals (95% CIs). Statistical heterogeneity was evaluated with the I² statistic and P<0.10 and I²>50% indicated significant heterogeneity. The fixed-effects model was used in cases of low-level heterogeneity, otherwise we chose the random-effect model.

**Evidence synthesis**

**Study characteristics**

One hundred eight-two potential studies were identified according to the selected criteria. After screening the abstracts and details, 17 relevant articles that included a total of 1438 patients were ultimately included in this meta-analysis (Figure 1). Seven hundred seventy-seven patients received tramadol and were
Table I.—The characteristics of the included 17 studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Jadad Score</th>
<th>Type of surgery</th>
<th>Type of anesthesia</th>
<th>Randomized group</th>
<th>Sample size</th>
<th>Time of administration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tewari A 2014</td>
<td>6</td>
<td>TURP</td>
<td>Neuraxial anesthesia</td>
<td>Oral clonidine 150 ug, Oral tramadol 50 mg, Oral placebo</td>
<td>40, 40, 40</td>
<td>90 min prior to the surgery</td>
<td>15</td>
</tr>
<tr>
<td>Li X 2014</td>
<td>5</td>
<td>Abdominal surgery</td>
<td>General anesthesia</td>
<td>Parecoxib 40 mg, tramadol 2 mg/kg, Saline</td>
<td>40, 40, 40</td>
<td>30 min before the end of surgery</td>
<td>12345</td>
</tr>
<tr>
<td>Sajedi P 2008</td>
<td>5</td>
<td>Orthopedic surgery</td>
<td>General anesthesia</td>
<td>tramadol 1 mg/kg, Granisetron 40 ug/kg, Meperidine 0.4 mg/kg, Saline</td>
<td>33, 33, 33, 33</td>
<td>At the end of surgery</td>
<td>1245</td>
</tr>
<tr>
<td>Yousuf B 2013</td>
<td>6</td>
<td>Orthopedic, gynecological surgery</td>
<td>General anesthesia</td>
<td>tramadol 2 mg/kg, Saline</td>
<td>62, 62</td>
<td>15 min before wound closure</td>
<td>1234</td>
</tr>
<tr>
<td>Heid F 2008</td>
<td>4</td>
<td>Lumber disc surgery</td>
<td>General anesthesia</td>
<td>tramadol 1 mg/kg, Saline</td>
<td>30, 30</td>
<td>45 min before skin closure</td>
<td>1245</td>
</tr>
<tr>
<td>Bilotta F 2002</td>
<td>5</td>
<td>Lower limb orthopedic surgery</td>
<td>Neuraxial anesthesia</td>
<td>tramadol 0.5 mg/kg, Saline</td>
<td>30, 30, 30</td>
<td>Before anesthesia</td>
<td>15</td>
</tr>
<tr>
<td>Mathews S 2002</td>
<td>6</td>
<td>General/laparoscopic surgical</td>
<td>General anesthesia</td>
<td>tramadol 2 mg/kg, tramadol 1 mg/kg, Saline</td>
<td>50, 50, 50</td>
<td>At wound closure</td>
<td>12345</td>
</tr>
<tr>
<td>Heidari SM 2014</td>
<td>5</td>
<td>Elective surgery</td>
<td>General anesthesia</td>
<td>Or tramadol 50 mg, Oral placebo</td>
<td>40, 40</td>
<td>1h before surgery</td>
<td>123</td>
</tr>
<tr>
<td>Wason R 2012</td>
<td>4</td>
<td>Lower abdominal/limb surgery</td>
<td>Neuraxial anesthesia</td>
<td>Ketamine 0.5 mg/kg, clonidine 75 ug, tramadol 0.5 mg/kg, tramadol 0.5 mg/kg, Saline</td>
<td>50, 50, 50, 50</td>
<td>Before anesthesia</td>
<td>12345</td>
</tr>
<tr>
<td>Tobi K 2012</td>
<td>7</td>
<td>Lower limb orthopedic surgery</td>
<td>Neuraxial anesthesia</td>
<td>tramadol 1 mg/kg, tramadol 1 mg/kg, tramadol 2 mg/kg, tramadol 3 mg/kg, Pethidine 0.5 mg/kg, Saline</td>
<td>43, 43</td>
<td>After anesthesia</td>
<td>123</td>
</tr>
<tr>
<td>Mohta M 2009</td>
<td>5</td>
<td>Abdominal surgery</td>
<td>General anesthesia</td>
<td>tramadol 1 mg/kg, tramadol 2 mg/kg, tramadol 3 mg/kg, Pethidine 0.5 mg/kg, Saline</td>
<td>33, 33, 33, 33</td>
<td>At wound closure</td>
<td>12345</td>
</tr>
<tr>
<td>Bozgeyik S 2014</td>
<td>7</td>
<td>Orthopedic surgery</td>
<td>Neuraxial anesthesia</td>
<td>tramadol 100 mg, Dexmedetomidine 0.5 mg/kg, Saline</td>
<td>30, 30</td>
<td>prior to the surgery</td>
<td>235</td>
</tr>
<tr>
<td>De Witte J 1998</td>
<td>5</td>
<td>Laparoscopic surgery</td>
<td>General anesthesia</td>
<td>tramadol 3 mg/kg, Saline</td>
<td>30, 20</td>
<td>At wound closure near the end of surgery</td>
<td>1345</td>
</tr>
<tr>
<td>Javaherforoosh F 2009</td>
<td>3</td>
<td>Cesarean delivery</td>
<td>Neuraxial anesthesia</td>
<td>tramadol 1 mg/kg, Saline</td>
<td>45, 45</td>
<td>At wound closure</td>
<td>1245</td>
</tr>
<tr>
<td>Angral R 2012</td>
<td>4</td>
<td>Cholecystectomy surgery</td>
<td>General anesthesia</td>
<td>tramadol 1 mg/kg, Saline</td>
<td>40, 40</td>
<td>After anesthesia</td>
<td>125</td>
</tr>
<tr>
<td>Atashkhoyi S 2008</td>
<td>5</td>
<td>Cesarean delivery</td>
<td>Neuraxial anesthesia</td>
<td>tramadol 1 mg/kg, Saline</td>
<td>35, 35</td>
<td>At wound closure</td>
<td>12345</td>
</tr>
<tr>
<td>Saha E 2005</td>
<td>4</td>
<td>Cholecystectomy surgery</td>
<td>General anesthesia</td>
<td>tramadol 1 mg/kg, Saline</td>
<td>30, 30</td>
<td>before wound closure</td>
<td>125</td>
</tr>
</tbody>
</table>

Outcomes: 1 Incidence of POS; 2 Significant shivering (severe shivering); 3 Rescue drug use; 4 PONV; 5 Hemodynamic.

regarded as the intervention group, and 661 patients received placebo and were regarded as the control group. The details of the characteristics of the 17 included studies were described in Table I.13-20 The Jadad scale scores for the RCTs ranged from 3 to 7, and the scores of 12 studies equaled or exceeded 5, which indicated high quality.
The incidence of POS

Sixteen RCTs reported the incidence of POS following prophylactic treatment with tramadol compared with placebo. To examine the influences of confounding factors on the results related to the efficacy of the prevention of POS with tramadol, we performed subgroup analyses according to the type of anesthesia and the different drug doses. Prophylactic tramadol was found to effectively decrease the incidence of POS regardless of the type of anesthesia (RR: 0.27; 95% CI: 0.19-0.37; P<0.00001, I²=61%) or the dose of tramadol (RR: 0.26; 95% CI: 0.19-0.35; P<0.00001, I²=56%). Significant heterogeneity may have been present due to the different types of surgery and the different drugs used for anesthesia. Therefore, we used the random-effects model (Figures 2, 3).13-23, 25-29
Figure 3.—Forest plot of the Meta-analysis of the incidence of POS classified by tramadol dose in tramadol group and control group. The corresponding horizontal line is the 95% CI, the diamond is the pooled RR with the 95% CI, and the random-effects model is used.
POS Scale Score: incidence of severe POS

Fourteen RCTs evaluated the severity of POS; 8 studies used a five-point scale, and 6 studies used a four-point scale. In the majority of the studies, POS scores exceeding 3 (on the five-point scales) or 2 (on the four-point scales) necessitated the use of additional medicine to treat shivering. Therefore, we defined POS scale scores that exceeded 3 or 2 as indicative of severe POS. Prophylactic tramadol was associated with an obvious decrease in the POS scale scores (RR: 0.19; 95% CI: 0.10-0.35; P<0.00001, I²=7%). The fixed-effect model was used because the heterogeneity was acceptable (Figure 4).14-17, 19-24, 26-29

Rescue drug used

Ten RCTs investigated the numbers of patients who were administered the rescue medications. The rescue drugs used to treat POS in these studies were pethidine and tramadol. The RR of 0.17 (95% CI: 0.12-0.23; P<0.00001, I²=56) for rescue drug in the tramadol group was lower than that of the control group. Because the heterogeneity was unacceptable, the random-effects model was applied (Figure 5).14, 16, 19-25, 28

Adverse effects: PONV, sedation and hemodynamic changes

Nine RCTs analyzed postoperative nausea and vomiting (PONV) and no statistically significant difference between the two comparison groups was observed (RR: 1.31; 95% CI: 0.94-1.83; P=0.11, I²=21%; Figure 6).13, 14, 17, 19, 21, 23, 25, 26, 28 We did not perform quantitative analyses of the adverse effects of sedation or hemodynamic changes. Based on the studies, it was apparent that there were no significant differences. Moreover, there were no other severe adverse effects.

Sensitivity analysis

The funnel plots used to analyze the sensitivity were found to be asymmetrical in the incidence of POS (Figure 7) and rescue drug used, only symmetrical in POS Scale Score and PONV, thus publication bias might exist.

Discussion

The major findings of this meta-analysis were that the prophylactic administration of tramadol reduced the incidence of POS, the
severity of POS and the rescue drug used. Additionally, tramadol did not increase the risk of adverse effects. Regarding the optimal dose, 50 mg, and 1, 2 and 3 mg/kg were all found to be effective. We recommend the small dose of 1 mg/kg to avoid adverse effects.

Shivering frequently occurs after regional and general anesthesia. Due to the detrimental effects of shivering, several studies have researched the mechanisms of POS. Generally, shivering is classified into two types: thermoregulatory and non-thermoregulatory.\(^3\) \(^{32-36}\) Thermoregulatory shivering is a response to hypothermia that is related to cutaneous vasoconstriction. In contrast, non-thermoregulatory shivering is associated with vasodilatation.

To the extent of our knowledge, perioperative hypothermia (including hypothermia induced by cold intravenous fluids and cold environments), postoperative pain, the length of anesthesia or surgery, young age and the use of different anesthetics are responsible for POS.\(^2\)

Non-pharmacological methods and pharmacological agents are used to prevent POS. Although pharmacological therapies are the most popular, and various pharmacologic drugs have been examined, there is currently no ideal drug.\(^1\) Pharmacological agents remain contro-

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**Figure 5.**—Forest plot of the Meta-analysis of the rescue drug used in tramadol group and control group, the random-effects model was applied.

**Figure 6.**—Forest plot of the Meta-analysis of PONV in tramadol group and control group, the fixed-effect model was used.
versal in terms of their efficacy and associated adverse effects, which include hemodynamic changes, respiratory depression, nausea and vomiting, and sedation. Due to its low number of adverse effects and greater effectiveness, tramadol has emerged as a potential agent for the control of POS.

Tramadol is an analgesic that is widely used to control moderate to severe acute pain. The function of tramadol is mediated by both opioid and non-opioid systems. Tramadol acts centrally on µ-opioid receptors as an opioid analgesic, and it also inhibits 5-hydroxytryptamine and norepinephrine reuptake, and facilitates 5-hydroxytryptamine release. Currently, the exact mechanism by which tramadol prevents and treats POS is unknown, but it is prone to act on both systems.\(^2\)\(^,\)\(^3\) The most common adverse effect of tramadol is nausea and vomiting, but the incidence of PONV was not found to differ between the tramadol and control groups in the present study. However, antiemetic drugs were used in the majority of the studies, which might have contributed to this lack of difference. Our meta-analysis also revealed that tramadol did not result in hemodynamic changes, sedation or respiratory depression.

Three previous meta-analyses of pharmacological anti-shivering agents have published. Kranke \textit{et al.} reviewed 20 studies and subsequently analyzed 27 trials related to anti-shivering drug.\(^2\)\(^,\)\(^3\) The trials involving tramadol were limited (only 1 and 3 trials respectively) in each of these reviews. Park \textit{et al.} reported on 41 individual and 8 combination anti-shivering treatments. Eight trials were included in the tramadol group to test its efficacy. In contrast, we included 17 articles, adopted a wide range of clinically relevant outcome variables, and we analyzed the severity, the rescue drug used and adverse effects.

\textit{Limitations of the study}

There are some limitations on this meta-analysis. For example, we lacked a valid scale for assessing severity, and studies with four and five point rating scales were included. The use of different scales might have introduced measurement error. Moreover, the funnel plots were found to be asymmetrical in the incidence of POS and rescue drug used, thus publication bias might exist. Last, this study only shown tramadol was better than placebo in the prevention of shivering, but not other anti-shivering agents.

\textit{Conclusions}

In summary, tramadol is an efficacious agent for the prevention of shivering. Prophylactic tramadol effectively prevents POS and reduces rescue medication use without significant adverse effects.

\textbf{Key messages}

— Postoperative shivering (POS) is a common complication that occurs after regional and general anesthesia.
— Though various pharmacological interventions, including clonidine, pethidine, tramadol, dexmedetomidine and ondansetron are studied, till now, no drug is found to be ideal.
— Due to its low number of adverse effects and greater effectiveness, tramadol has emerged as a potential agent for the control of POS.
References


Acute kidney injury in liver transplant candidates: a position paper on behalf of the Liver Intensive Care Group of Europe

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ABSTRACT

INTRODUCTION: Acute kidney injury is associated with high mortality in the perioperative period of liver transplantation. The aim of this position paper was to provide an up-to-date overview with special emphasis on diagnosis, risk factors, and treatment.

EVIDENCE ACQUISITION: The Liver Intensive Care Group of Europe nominated a panel of recognized international experts who reviewed the available literature published from 1990 to January 2016 and produced clinical recommendations. The level of evidence and strength of recommendation were judged according to the Grading of Recommendations Assessment Development and Evaluation system.

EVIDENCE SYNTHESIS: Diagnosis of AKI should be based on the KDIGO criteria. The preoperative risk factors are more related to the patient’s predisposing factors and post-operative risk factors tend to be difficult to control. Therefore, focusing on intra-operative risk factors it would be important to maintain an adequate hemodynamics and to keep inferior vena cava clamping as short as possible. Biomarkers to identify AKI at an early stage are available; however, there is a lack of robust data that indicates their true beneficial effect. Intraoperative renal replacement therapy may be beneficial in some selective cases whereas its postoperative timing is still under debate.

CONCLUSIONS: Perioperative liver transplant risk factors for acute kidney injury are difficult to control. Therefore, the focus should be on intra-operative hemodynamics and nephrotoxic drugs avoidance. Prospective randomized trials are needed to show the beneficial effect of early replacement therapy. In this context, the new biomarkers would be helpful in identifying kidney injury earlier.


Key words: Liver cirrhosis - Liver transplantation - Acute kidney failure - Dialysis.
Introduction

Acute kidney injury (AKI) is associated with significantly increased short- and long-term complications, increased mortality, and high healthcare costs, the reported incidence of this condition after liver transplantation (LT) is as high as 70%. Extensive research on AKI over the last 20 years has significantly advanced our understanding of this condition. In particular, perioperative risk factors associated with the development of AKI in LT candidates have been identified and preventive strategies and treatments have been developed. It is now possible for medical practitioners to recognize and manage AKI earlier. Another important challenge in this field over the last 20 years is establishing the optimum timing to initiate renal replacement therapy (RRT).

The aim of this position paper was to provide an up-to-date overview of AKI in perioperative LT patients with end-stage liver disease (ESLD) with special emphasis on diagnosis using biomarkers, risk factors, and treatment.

Evidence acquisition

In order to provide the clinical community with a straightforward and updated document about a debated and controversial topic, the Liver Intensive Care Group of Europe (LICAGE) nominated a panel of well-recognized international experts who reviewed the available clinical literature and produced practical clinical recommendations. The initial draft was revised by all of the panel members so that the final version resulted from the consensus of the entire working group. A systematic PubMed literature search on kidney failure related to cirrhosis and/or LT published from 1990 to January 2016 was performed, focusing on most relevant studies. The level of evidence and strength of recommendation were judged according to the Grading of Recommendations Assessment Development and Evaluation system. The strength of the evidence was classified into four levels: high (A), moderate (B), low (C), and very low (D) quality evidence, while that of the recommendations was divided into two: strong (1) and weak (2). If no clear evidence existed, the recommendations were based on the consensus advice of the writing committee and the expert opinion(s) reported in the literature.

Evidence synthesis

Pathophysiology of AKI in patients with ESLD

Portal hypertension (PH) is one of the most important pathophysiological mechanisms responsible for the development of AKI in patients with ESLD. PH is associated with significant modulations of splanchnic circulation and triggers systemic vasodilatation with reduced central blood volume. This leads to a drop in mean arterial pressure with subsequent activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, elevated release of vasopressin from the pituitary gland, and increased cardiac output; all of these signs are implicated in producing hyperdynamic circulation that is similar to sepsis-type hemodynamics. These complex hemodynamic changes are responsible for histological myocardial modulation with subsequent systolic and diastolic dysfunction, defined as cirrhotic cardiomyopathy.

Due to reduced renal perfusion, the glomerular filtration rate (GFR) decreases, with subsequent release of aldosterone and renin as well as increased release of vasopressin. All these changes, in combination with low colloid osmotic pressure, result in water retention, ascites, fluid overload, and increased vasostriction of the vas afferent vessels of the kidney. This leads to a further reduction in renal perfusion, which puts the patient at great risk of developing hepatorenal syndrome (HRS).

The systemic inflammatory response also plays a crucial role in the development of AKI in patients with ESLD. These patients appear to be more susceptible to systemic infection than patients without ESLD, and a number of pathophysiologic mechanisms contribute to this effect. Patients with ESLD have increased lipopolysaccharides and tumor...
necrosis factor-α serum levels, which cause splanchnic dilatation. These increased levels, in combination with a decreased local immune response, damage the intestinal mucosa and alter local gut-associated lymphatic tissue function. This leads to increased bacterial translocation. Another mechanism responsible for generalized inflammation is associated with ischemia-reperfusion injury during LT. The affected hepatocytes release nuclear or cytosolic proteins called damage-associated molecular patterns (DAMPs), which can induce inflammation. One DAMP, high-mobility group box-1 (HMGB1), is associated with an inflammatory response and interacts with toll-like receptors, thereby causing renal injury.

It should be noted that a number of other factors can lead to kidney injury in this patient population. These include medications (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]), diuretics, angiotensin-converting enzyme) and factors that can cause hypovolemia, such as gastrointestinal bleeding or paracentesis without volume replacement.

Furthermore, the risk factors for AKI in patients with ESLD are nearly the same as those for developing HRS. It has been demonstrated that even a minor improvement in regard to GFR is associated with a higher patient survival rate.

Diagostic insights of AKI in patients with ESLD

For almost 20 years, acute renal failure in patients with ESLD was defined, according to an ICA criterion, as an increase in serum creatinine (sCr) of 50% from baseline to a final value >1.5 mg/dL (133 μmol/L). Presently, however, ICA experts recommend using the Kidney Disease Improving Global Outcomes (KDIGO) criteria, which are based on changes in sCr, to define AKI (Table I). The definition of AKI in patients with ESLD includes an abrupt reduction in kidney function demonstrated by either an absolute increase in sCr of at least 0.3 mg/dL (≥26.4 μmol/L) in less than 48 hours or a percentage increase in sCr of at least 50% (a minimum increase of 1.5 from baseline) in less than seven days. In addition, a new algorithm based for managing the treatment of AKI in patients with ESLD (Figure 1) has been proposed. This algorithm is related to the stages of AKI and based on several prospective studies.

A controversial issue is how to diagnose various types of AKI in patients with ESLD (Table II). It may be possible to exclude both the post-renal and the prerenal types because the former type is relatively infrequent and the latter should be diagnosed and treated by the measures envisaged by the previously mentioned new algorithm. The crux of the problem, therefore, relates to differentiating between (HRS)-AKI and acute tubular necrosis (ATN) or intrinsic AKI. Usually in clinical practice, it is possible to determine whether the patient’s condition is (HRS)-AKI or (ATN)-AKI by applying the diagnostic criteria for HRS, according to the latest ICA consensus.

Prognostic value of AKI in patients with ESLD

Renal dysfunction has been demonstrated as a powerful predictor of morbidity and mortality in patients with ESLD. Indeed, the reported mortality of cirrhotic patients with AKI is as high as 90% in some studies. This high mortality rate correlates with the initial severity of AKI and the extent to which appropriate treatment can reverse it. The cause of renal failure also affects the patient’s prognosis. It has been demonstrated that even a minor improvement in regard to GFR is associated with a higher patient survival rate.

Risk factors for AKI

Preoperative risk factors

Identified in large observational studies, the main pre-operative risk factors for postoperative AKI in LT candidates include age, pre-existing comorbidities (diabetes mellitus
**Table 1.**—Current diagnostic criteria for acute kidney injury (AKI) in the general population and in patients with cirrhosis.

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>RIFLE Criteria</th>
<th>AKIN Criteria</th>
<th>KDIGO Criteria</th>
<th>Conventional criteria for diagnosis of AKI in cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk:</td>
<td>Staging</td>
<td>Risk:</td>
<td>Risk:</td>
<td>Risk:</td>
</tr>
<tr>
<td>sCr increase 1.5-1.9 times baseline; OR</td>
<td>Stage 1: sCr increase ≥0.3 mg/dL; OR</td>
<td>Stage 1: sCr increase ≥0.3 mg/dL; OR</td>
<td>Increase in sCr by ≥0.3 mg/dL within 48 hours; OR</td>
<td>A percentage increase in sCr of 50% or more to a final value of sCr ≥1.5 mg/dL.</td>
</tr>
<tr>
<td>GFR decrease 25-50%; OR</td>
<td>GFR decrease 0.5 mL/kg/h for six hours</td>
<td>GFR decrease 0.5 mL/kg/h for six hours</td>
<td>Increase in sCr by ≥0.3 mg/dL within 48 hours; OR</td>
<td></td>
</tr>
<tr>
<td>Urine output &lt;0.5 mL/kg/h for six hours</td>
<td></td>
<td></td>
<td>Increase in sCr by ≥0.3 mg/dL within 48 hours; OR</td>
<td></td>
</tr>
<tr>
<td>Injury: sCr increase 1.5-1.9 times baseline; OR</td>
<td>Stage 2: sCr increase ≥0.3 mg/dL; OR</td>
<td>Stage 2: sCr increase ≥0.3 mg/dL; OR</td>
<td>Increase in sCr by ≥0.3 mg/dL within 48 hours; OR</td>
<td></td>
</tr>
<tr>
<td>GFR decrease 25-50%; OR</td>
<td>GFR decrease 0.5 mL/kg/h for six hours</td>
<td>GFR decrease 0.5 mL/kg/h for six hours</td>
<td>Increase in sCr by ≥0.3 mg/dL within 48 hours; OR</td>
<td></td>
</tr>
<tr>
<td>Urine output &lt;0.5 mL/kg/h for six hours</td>
<td></td>
<td></td>
<td>Increase in sCr by ≥0.3 mg/dL within 48 hours; OR</td>
<td></td>
</tr>
<tr>
<td>Failure: sCr increase ≥3.0 times baseline; OR</td>
<td>Stage 3: sCr increase ≥3.0 times baseline; OR</td>
<td>Stage 3: sCr increase ≥3.0 times baseline; OR</td>
<td>Increase in sCr by ≥0.3 mg/dL within 48 hours; OR</td>
<td></td>
</tr>
<tr>
<td>GFR decrease 25-50%; OR</td>
<td>GFR decrease ≥0.5 mg/dL with an acute increase of at least 0.5 mg/dL; OR</td>
<td>GFR decrease ≥0.5 mg/dL with an acute increase of at least 0.5 mg/dL; OR</td>
<td>Increase in sCr by ≥0.3 mg/dL within 48 hours; OR</td>
<td></td>
</tr>
<tr>
<td>sCr increase ≥4.0 mg/dL</td>
<td>sCr increase ≥4.0 mg/dL; OR</td>
<td>sCr increase ≥4.0 mg/dL; OR</td>
<td>Increase in sCr by ≥0.3 mg/dL within 48 hours; OR</td>
<td></td>
</tr>
<tr>
<td>for ≥24 hours; OR</td>
<td>for ≥24 hours; OR</td>
<td>for ≥24 hours; OR</td>
<td>Increase in sCr by ≥0.3 mg/dL within 48 hours; OR</td>
<td></td>
</tr>
<tr>
<td>Anuria for ≥12 hours</td>
<td>Anuria for ≥12 hours</td>
<td>Anuria for ≥12 hours</td>
<td>Increase in sCr by ≥0.3 mg/dL within 48 hours; OR</td>
<td></td>
</tr>
</tbody>
</table>

RIFLE: risk, injury, failure, loss, end stage renal disease; AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease Improving Global Outcomes; GFR: glomerular filtration rate; sCr: serum creatinine.

and systemic hypertension), severity of liver disease, and obesity. Pre-existing renal disease has been identified as an independent risk factor in some studies, whereas other studies suggest that HRS may provide some protection against renal dysfunction after LT, if RRT was performed before LT. Severe pretransplant hyponatremia has recently been identified as correlating with a high incidence of postoperative AKI. The pathophysiological mechanisms are still under debate, and it is unclear whether hyponatremia is an independent risk factor for postoperative AKI or a consequence of pre-clinical renal impairment that went undetected prior to LT. **Intraoperative Risk Factors**

Intraoperative blood loss and subsequent blood transfusion (especially packed red blood cells and fresh frozen plasma), hemodynamic variables (mean arterial pressure, pulmonary capillary wedge pressure, systemic vascular resistance), and intraoperative hypovolemia are the main risk factors for AKI identified by most studies. The effect of donor graft remains uncertain, but in some studies, warm ischemic time and donation after cardiac death are identified as the main independent risk factors.
**Table II.**—International Club of Ascites (ICA-AKI) new definitions for the diagnosis and management of acute kidney injury in patients with cirrhosis.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline sCr</td>
<td>A value of sCr obtained in the previous three months, when available, can be used as baseline sCr. In patients with more than one value within the previous three months, the value closest to the admission time to the hospital should be used. In patients without a previous sCr value, sCr on admission should be used as baseline.</td>
</tr>
<tr>
<td>Definition of AKI</td>
<td>- Increase in sCr≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or,</td>
</tr>
<tr>
<td></td>
<td>- A percentage increase sCr≥50% from baseline which is known, or presumed, to have occurred within the prior seven days</td>
</tr>
<tr>
<td>Staging of AKI</td>
<td>- Stage 1: Increase in sCr≥0.3 mg/dL or an increase in sCr≥1.5-fold from baseline;</td>
</tr>
<tr>
<td></td>
<td>- Stage 2: Increase in sCr&gt; two-fold to three-fold from baseline;</td>
</tr>
<tr>
<td></td>
<td>- Stage 3: Increase of sCr &gt; three-fold from baseline or sCr≥4.0 mg/dL with an acute increase ≥0.3 mg/dL or initiation of renal replacement therapy</td>
</tr>
<tr>
<td>Progression of AKI*</td>
<td><strong>Progression</strong></td>
</tr>
<tr>
<td></td>
<td>Progression of AKI to a higher stage and/or need for RRT</td>
</tr>
<tr>
<td></td>
<td>Regression of AKI to a lower stage</td>
</tr>
<tr>
<td>Response to treatment</td>
<td><strong>No response</strong></td>
</tr>
<tr>
<td></td>
<td>No regression of AKI</td>
</tr>
<tr>
<td></td>
<td>Return of sCr to a value within 0.3 mg/dL (26.5 µmol/L) of the baseline value</td>
</tr>
</tbody>
</table>

sCr: serum creatinine; AKI: acute kidney injury; RRT: renal replacement therapy.

Figure 1.—Diagnosis and treatment algorithm for acute kidney injury.

# = AKI at the first fulfilling of AKIN criteria; ° = sCr at the first fulfilling of AKIN criteria.
Postoperative Risk Factors

Literature focusing on risk factors for AKI in the early postoperative period is limited. However, the need for surgical re-intervention, hypoalbuminemia, poor graft function, and immunosuppression therapy seem to be the main risk factors for renal dysfunction after LT.\(^\text{38, 39}\)

**Biomarkers**

In order to be useful, a renal biomarker must detect injury rapidly, must be highly sensitive and specific, and its level should correlate with the extent of injury.\(^\text{40}\) Ideally, a biomarker for AKI is not elevated in chronic kidney disease or with pre-renal azotemia. In addition, there is no consensus regarding whether urinary or plasma markers are more useful. A plasma biomarker can detect renal injury even if the patient is anuric, and its level does not need to be corrected for dilution by, for example, the use of a diuretic. However, urine markers are generally considered more specific for detection of renal injury and less likely to be contaminated by release from other organs than the kidney. Considering these requirements, multiple novel biomarkers have been tested in different scenarios related to renal ischemia-reperfusion injury.\(^\text{41}\)

**Neutrophil Gelatinase-Associated Lipocalin**

Neutrophil gelatinase-associated lipocalin (NGAL) is a 23 kD protein that is rapidly up-regulated and can be detected early after renal ischemia-reperfusion injury. Several authors evaluating urinary NGAL as a marker of renal injury after LT\(^\text{42-44}\) report results similar to those reported for other situations in which AKI occurs, with areas under the receiver-characteristics curve of 0.8\(^\text{42}\) and 0.87\(^\text{44}\) for urinary NGAL and 0.79 for plasma NGAL.\(^\text{43}\) NGAL can be measured using point-of-care devices in the urine (ARCHITECT\(^\text{®}\) analyzer, Abbott Diagnostics) and blood (Alere Triage\(^\text{®}\) NGAL test) and by using routine chemistry analyzers (NGAL Test\(^\text{™}\), BioPorto Diagnostics). These tests are approved for clinical use in Europe. However, FDA approval in the United States is pending.

There is no evidence to date that routine measurement of either urinary or plasma NGAL improves outcomes after LT. However, in combination with more conventional markers, NGAL measurements may help determine the severity of renal injury immediately after surgery.

**Cystatin C**

Cystatin C is a low molecular protein secreted by all nucleated cells and filtrated but not reabsorbed by the kidney. Unlike sCr, its level reflects the GFR independent of muscle mass, although cystatin C increases with age.\(^\text{45}\) Given that it is not a marker of renal injury but of renal function, cystatin C cannot necessarily be compared with the other renal biomarkers. Compared with sCr, cystatin C has been shown to correlate better with GFR after LT.\(^\text{46, 47}\)

**Other Markers**

Two small studies investigated the role of urinary and plasma interleukins such as IL-6, IL-8, and IL-18\(^\text{48}\) and of liver-type fatty acid-binding protein\(^\text{49}\) in LT recipients. The studies demonstrate that these markers predict AKI with a level of accuracy similar to that reported for urinary NGAL. These and other markers, such as Kidney Injury Molecule-1 (KIM-1), have not been evaluated in larger studies of LT patients.

**Renal Biomarker as a Clinical Tool**

In Europe, NGAL and Nephrocheck, both point-of-care urinary tests that each measure two cell-cycle arrest biomarkers (i.e., TIMP-2 and IGFBP7), are approved for clinical use. In the United States, only Nephrocheck is currently approved by the FDA. Approval for the measurement of plasma and urinary NGAL is pending. Nephrocheck has not been evaluated in LT recipients.
**LICAGE expert panel conclusions on biomarkers**

There is currently no evidence that routine measurement of renal biomarkers after LT improves outcomes. However, in specific clinical situations, measuring renal biomarkers may aid in the decision-making process regarding how to initiate calcineurin inhibitors after LT (2B).

Urinary NGAL should be considered first, as it is the most widely analyzed of the approved biomarkers (2C).

Nephrocheck, even though approved in the US and Europe, should not be used in the LT population and requires further validation (1C).

Cystatin C may be a useful tool to assess GFR in addition to or instead of sCr (2B).

**Prevention of AKI**

Patients with ESLD are at high risk of developing AKI, which, in turn is associated with a worse outcome in comparison with patients without renal dysfunction.\(^{50, 51}\) Taking into consideration the risk of developing AKI and the difficulty of early AKI identification, the prevention of AKI should be prioritized in patients with ESLD.

**General principles**

The general principles of AKI prevention have recently been updated for all patients at risk\(^{52}\) and specifically for cirrhotic patients.\(^{19}\) The LICAGE expert panel’s recommendations are as follows:

- discontinuing potentially nephrotoxic agents, including NSAIDs and vasodilators, when possible: (1C);
- decreasing or withdrawing diuretic therapy and reviewing antimicrobial medications, particularly aminoglycosides and amphotericin: (1C);
- monitoring the patient’s urine output and sCr closely: (1C);
- improving the hemodynamics by using volume adjustment in patients with clinically suspected hypovolemia and achieving adequate perfusion pressure using pressers as indicated: (1B);
- recognizing and treating bacterial infections promptly: (1B);
- considering avoiding and/or using alternatives to radiocontrast procedures: (1B).

**Specific measures**

There are a number of specific measures that may help to prevent AKI in ESLD patients.

**TREATMENT OF SPONTANEOUS BACTERIAL PERITONITIS**

The LICAGE panel recommends the timely recognition and treatment of bacterial infections as one of most important therapeutic options for preventing AKI (1B). In patients with ESLD who also have SBP, this treatment includes albumin infusion in addition to antimicrobial medications. It has been demonstrated that this intervention helps to decrease the development of renal failure, thereby improving the survival rate.\(^{53}\)

**ADMINISTERING ALBUMIN AFTER PARACENTESIS**

The LICAGE panel recommends the infusion of albumin at the time of large-volume paracentesis, as it decreases the incidence of postparacentesis circulatory dysfunction and improves the patient’s chances of survival (1B).\(^{54}\)

**CONTRAST-INDUCED AKI**

The LICAGE panel recommends the use of radiocontrast only if absolutely needed and at the lowest appropriate dose. Volume expansion with isotonic solutions (or preferably balanced electrolytes) at the time the contrast agent is administered is recommended. The use of oral N-acetyl cysteine (NAC) can also be considered, although there is no clear evidence that NAC administration is beneficial to this population of patients.\(^{52}\) Contrast-induced nephropathy (CIN) has been challenged recently and extensively discussed in a review.\(^{55}\) The authors con-
cluded that CIN was over-diagnosed and more related to the severity of the patient’s illness (sepsis, septic shock) and to the use of nephrotoxic drugs and some physiologic changes that favored the occurrence of AKI. In a retrospective study, patients were stratified into three risk-groups: low risk (serum creatinine <1.5 mg/dL), middle risk (1.5-2.0 mg/dL), and high risk (>2 mg/dL). A total of 157,140 scans of 53,439 patients were analyzed. After risk adjustment with a propensity score, contrast media was not found to be an independent risk factor for AKI. The AKI was more related to diminished renal function and general poor patients’ condition. Therefore, it seems doubtful that the intravenous use of contrast media causes acute renal failure in critically ill or cirrhotic patients.

Pharmacologic prevention

Many pharmacologic interventions such as a low doses of dopamine, fenoldopam, or atrial natriuretic peptide have been proposed for AKI prevention. To date, however, none of these medications have been confirmed as a useful therapy, and none are recommended for use by the LICAGE panel.

Intraoperative management

No particular surgical technique, including the use of veno-venous bypass, has been proven to protect against the development of AKI. The use of a low central venous pressure (CVP) technique may increase the risk of AKI; however, this concern was not confirmed in a subsequent randomized controlled trial. Also, the use of CVP or stroke volume variation to guide fluid replacement has not been demonstrated to reduce the incidence of AKI.

Immunosuppression

It is well known that calcineurin inhibitors (CNI) can significantly affect renal function. Unfortunately, no protective strategy has been established. Although there are a number of conflicting opinions regarding the potential renal risk mitigations by CNI minimization, none of these are supported by evidence.

Intraoperative renal support during liver transplantation

Intraoperative continuous renal replacement treatment (IO-CRRT) has become available only relatively recently. Thus, there is a paucity of data available on the benefits of IO-CRRT; the literature is mostly case reports and retrospective studies. Impaired kidney function during LT used to be managed using strict fluid restriction, vasopressor support, and continuous metabolic adjustment. However, expanding the indications of LT and changes in organ allocation policy are accompanied by a significantly increased number of patients with pre-existing renal dysfunction. In this setting, the use of IO-CRRT seems to be very helpful for patient management.

To date, three retrospective studies demonstrating that IO-CRRT can be performed safely with significant benefits for the patients have been published.

Decision

The decision to initiate IO-CRRT is made by the transplant team (intensivist, anesthesiologist, surgeon, and nephrologist) and is based on preoperative kidney function, the severity of the condition, anticipated poor tolerance of intraoperative management (transfusion requirements, fluid administration, donor graft reperfusion), and/or anticipated need for postoperative CRRT.

Intraoperative hemodialysis can be administered by either an ICU staff member or a nephrology nurse. Arterial blood gas (ABG) analysis should be performed periodically and the results should be discussed with the anesthesiologist, who is responsible for fluid and electrolyte management intraoperatively.

Dialysate-replacement solutions

The decision whether to add bicarbonate or potassium and in what quantity or a dialysate
or replacement solution should be made on a patient-by-patient basis. Any anticoagulates are not usually used in patients undergoing LT with an acceptable filter circuit lifespan, since there is an increased risk of bleeding associated with heparin and the potential toxicity associated with citrate. In the operating room, dialysis machines run with blood flow rates of 200-300 mL/h and dialysate flow rates of 200-300 mL/h.

**Metabolic acidosis**

Lactic acidosis is a common condition in patients during LT. Lack of lactate metabolism or excessive production of lactate are common causes of this phenomenon. During the anhepatic phase, all hepatic vessels are either partially or completely clamped, which results in significant lactate accumulation. In the neohepatic phase, lactate begins to metabolize at about 60 minutes after graft reperfusion. Lactic acidosis becomes more prominent in the presence of impaired renal function. This concomitant renal impairment makes managing lactic acidosis extremely difficult. In this context, IO-CRRT would be very helpful.

If the patient is under refractory acidosis, further therapeutic options can be instituted by increasing bicarbonate content in the dialysate from 35 mEq/L to 40 mEq/L. In such a case, blood flow should also be increased from 200 mL/h to 300 mL/h or even higher in order to provide a sufficient transfer of bicarbonate molecules through the filter to the patient.

**Hyperkalemia**

Hyperkalemia occurs very frequently during LT. In patients with concomitant kidney injury, hyperkalemia can cause very serious problems during graft reperfusion including hemodynamic derangements such as bradycardia, hypotension, and/or a rhythm disorder such as atrio-ventricular block. The standard concentration of potassium in a dialysate bag is 2 mEq/L. In cases of severe hyperkalemia, however, potassium-free dialysate should be used.

**Effect of intraoperative dialysis on volume management**

ESLD is associated with increased pressure and blood shunting in the splanchnic area, which makes hemodynamic management very difficult — especially in the presence of kidney failure. Patients with ESLD have high vascular compliance combined with increased pooling of blood in the splanchnic circulation. This is associated with a minimal increase in CVP, although the patient appears hypervolemic. Such a characteristic of hemodynamics should be considered during LT when the volume status is usually monitored by CVP.

There is an ongoing discussion regarding whether the patient should be on the “dry” side to avoid graft congestion or on the “wet” side to preserve or improve kidney function. The anhepatic phase, when the inferior vena cava (IVC) is clamped, is considered one of the most challenging parts of LT. After the portal vein and the IVC are clamped, there is a decrease of around 50-60% of the venous return, which is accompanied by a significant drop in systemic blood pressure. At this stage, a volume challenge together with a vasopressor is required to maintain mean arterial pressure at 60-70 mmHg. However, after declamping, sudden volume load may result in right heart decompensation. In such a complicated hemodynamic situation, IO-CRRT can achieve an optimum fluid balance during LT and help ensure hemodynamic stability.

**Recommendation**

The LICAGE panel recommends IO-CRRT as a very helpful tool for managing the treatment of patients with impaired kidney function during LT. All the complications associated with kidney dysfunction such as acidosis, hyperkalemia, and volume overload can be treated very safely (1B).

**Timing of postoperative renal replacement therapy**

The optimal timing for administering renal replacement therapy (RRT) in patients with
AKI postoperatively is not well-defined. It has been demonstrated that early implementation of RRT can help achieve better control of fluid and electrolyte balance in selected patient populations than later implementation of RRT. At the same time, however, early initiation of RRT has been discouraged because of the following potential negative consequences:

1. complications associated with establishing vascular access, including bleeding, pneumothorax; and infection;
2. slower renal recovery after surgery.

In 2012, the KDIGO Working Group defined three emergency indications for the initiation of RRT:

1. life-threatening electrolyte disorders;
2. metabolic acidosis that cannot be controlled with conservative therapy;
3. hypervolemia, particularly when resulting in refractory pulmonary edema.

**General considerations**

The RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria are most frequently used to determine when to initiate RRT. The current literature, however, presents no definitive recommendation concerning the timing of RRT initiation. Several retrospective studies have demonstrated a benefit associated with early RRT initiation. Carl et al. reviewed the survival of septic patients with AKI. The timing of RRT initiation in this study was based on blood urea nitrogen (BUN) level. Early initiation of RRT was associated with a superior 28-day and one-year survival rate. In a prospective trial in a surgical ICU setting, Shiao et al. demonstrated that starting RRT at an advanced RIFLE stage after major abdominal surgery is associated with higher mortality (OR 1.85). However, this finding has not been confirmed by other investigators. In another retrospective study, Shum et al. evaluated patient outcomes in the setting of severe sepsis and septic shock. The timing of RRT initiation was also determined based on RIFLE criteria. Early initiation of RRT (stage R) was not found to be superior in comparison to starting RRT later (stage I or F) in terms of mortality, dialysis requirements, or the Sequential Organ Failure Assessment (SOFA) score. It should be noted that patients in the late RRT group had significantly poorer kidney function compared with that of patients in the early RRT group, which was probably a confounding factor. A recent meta-analysis published by Karvellas et al. indicated that early dialysis has a beneficial effect. The criteria for starting RRT, however, differed across all the studies included in the analysis. Initiation of RRT was either triggered by BUN, serum creatinine, RIFLE stage, or urine output, such that it was not possible to compare the results reported in these studies.

Only a few studies focused on evaluating the use of RRT in the setting of liver failure/LT have been published. Wu et al. examined the use of continuous venous-venous hemofiltration in patients with post-operative liver and kidney failure. They demonstrated that earlier initiation of RRT, based on pre-dialysis BUN level, is associated with improved ICU survival. In a retrospective study, Agopian et al. compared a variety of intra- and postoperative outcomes in patients who had received planned, emergency, or no intra-operative RRT. Patients with planned RRT had significantly fewer intra-operative complications than those who received emergency RRT.

**Recommendations**

Based on the current literature, the LICAGE panel cannot give a general recommendation for beginning RRT at an early stage of AKI (1C). There is evidence, however, that initiating RRT earlier, i.e., at stage F or I (RIFLE criteria), than is usually the case at present, would be beneficial for some patients, particularly if the AKI is progressing rapidly. According to the KDIGO criteria, any decision pertaining to whether or not to begin RRT should be made based on a clinical assessment instead of on the sole basis of laboratory values such as those for serum creatinine or BUN.
RRT must be based on both clinical considerations and laboratory values. As always, an individualized patient-specific approach should be used.

Conclusions

This position paper highlights current knowledge of kidney failure, including efforts to improve kidney function in LT patients. Pre- and postoperative risk factors for AKI are difficult to control; this is why the focus should be on intraoperative hemodynamics and avoiding nephrotoxic drugs (antibiotics and reduced use of CNI). Prospective randomized trials are needed to show the beneficial effect of intraoperative and/or postoperative early RRT. In this context, the new biomarkers would be helpful in identifying AKI earlier and would probably prevent dialysis-dependent kidney failure.

Key messages

— Diagnosis of AKI should be based on the KDIGO criteria.
— Risk factors are already known and were stratified into pre-, intra-, and postoperative risk factors. The preoperative risk factors are more related to the patient’s predisposing factors and postoperative risk factors tend to be difficult to control (immunosuppression, reoperation due to bleeding, bile leak, poor graft function). Therefore, focusing on intraoperative risk factors would be important to maintain an adequate hemodynamics (MAP≥70 mmHg) and to keep inferior vena cava clamping (warm ischemia time for kidneys) as short as possible.
— Biomarkers to identify AKI at an early stage are available; however, there is a lack of robust data that indicates their beneficial effect in terms of avoiding AKI after LT.
— Intraoperative RRT may be beneficial in some selective cases; however, a general recommendation cannot be given.

— Timing of dialysis either pre- or postoperatively is still under debate. There are some promising studies that associate starting dialysis earlier with a better outcome, but it has not been proven with RCTs. The LICAGE panel, however, would prefer early initiation of dialysis.

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Authors’ contribution.—All authors contributed on an equal basis to important tasks such as literature research, drafting the work, writing a section, and/or revising the work for important content; gave their final approval; and agreed that all parts of the manuscript ensure integrity and appropriate investigation at all parts of the manuscript.

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Use of a needle-guided device to facilitate axillary vein cannulation

Dear Editor,

International guidelines strongly recommend ultrasound (US) guidance for central venous catheter (CVC) insertion.1 Compared to anatomical landmark technique, US guidance increases success rate, and reduces procedure-related complications.2-3 US guidance also reduces the number of attempts, and time to successful cannulation of internal jugular (IJ) vein.2 However, adequate studies to prove this benefit for subclavian/axillary vein catheterization are lacking.3 This could be explained by anatomical issues, deepness of axillary vein (the mean distance to skin is 4 cm), and proximity to pleura especially at the axillary subclavian junction (0.5 to 1 cm), but also technical difficulties. In-plane technique allows seeing the whole needle’s course but needs to place the needle in the exact middle of the probe in its long axis. If not achieved, no or only part of the needle is visualized. In the out-of-plane method, only the tip of the needle is visualized, and the course of the needle is not controlled. Needle guidance systems are aimed at improving needle visualization but data supporting their advantage over conventional US guidance are scarce in the setting of axillary vein cannulation.4-5 Site-Rite Prevue+™ (Bard Medical France, Voisins-le-Bretonneux, France) is a portable US device (149×117×52 mm) combining a small 7.5-MHz probe with a needle guidance system. Scales displayed on the screen provide information on size, and depth of the targeted vessel. The venipuncture is performed out-of-plane, i.e. the needle being orientated perpendicularly to the plane of the probe, using a short axis view (the vein is visualized in a transversal view). By making the needle slide into the guide, the operator can observe in real-time needle’s tip perforating vessel wall at the expected depth (Figure 1). We conducted the present study to compare this device to freehand US guidance during IJ, and axillary veins cannulation.

For this purpose, 43 physicians (mean age 33, range 24-60 years; 28 senior physicians — graduated in emergency care [16] or in intensive care medicine [12] — and 15 residents) were included in this randomized controlled study. Thirty-three (77%) declared prior experience in US-guidance for CVC insertion, and none had previously used the tested device. Punctures were performed on an inanimate manikin (Blue Phantom II, CAE Healthcare, Saint Louis, MO, USA), mimicking right internal jugular, and axillary veins, carotid,

Figure 1.—A) Site-Rite Prevue+™ device, needle guidance system; B) needle placed perpendicularly to the plane of the probe (out of plane); C) ultrasound image showing the tip of the needle perforating the targeted vessel wall in a short-axis (transversal) view.
and axillary arteries. A manual pump produced arterial pulse. Aspiration of blue fluid confirms successful venous puncture while aspiration of red fluid means arterial puncture. The M-Turbo® device (Fujifilm SonoSite, Bothell, MA, USA) with a 7.5-MHz linear probe was used for standard US-guidance. The order of punctures, their site (IJ or axillary), and method (standard or tested device) were randomized using a 2-by-2 design in a 1:1:1:1 ratio. The random allocation sequence was generated using a random number table. The number of attempts (needle passes) before success, and times from skin contact to first skin puncture (1), and from first skin puncture to successful venous puncture (2) were recorded. Qualitative and quantitative values were expressed as numbers (percentage), and medians (range), respectively, and were compared using the Mann-Whitney test, and Fisher’s exact test, respectively.

All participants succeeded in performing IJ puncture. One resident failed to puncture axillary vein with both methods. Overall, 86 and 84 approaches were analyzed for IJ and axillary veins, respectively. At the axillary site, the tested device significantly reduced the number of attempts (P<0.01), and the time between first skin puncture, and success (6.9 [2.5-105] versus 15 [3.2-600] seconds, P<0.008). Success rate at first attempt was 81% using needle guidance, whereas it was only 57% with standard method (P=0.03). No significant difference was observed between the two methods for IJ cannulation (Table I).

Consistently with previous findings, these results suggest the interest of needle-guidance devices over freehand method for US-guided axillary CVC insertion.

<table>
<thead>
<tr>
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<th>Internal jugular vein</th>
<th>Axillary vein</th>
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<tbody>
<tr>
<td></td>
<td>Standard US</td>
<td>Site-Rite Prevue+™</td>
</tr>
<tr>
<td>N. of approaches</td>
<td>43</td>
<td>43</td>
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<tr>
<td>Time between skin contact and first puncture</td>
<td>8.6 (1.9-127.2)</td>
<td>12.7 (2.3-109)</td>
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<td>Time between first puncture and success</td>
<td>7 (0.6-101.1)</td>
<td>4.7 (1.0-47)</td>
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<tr>
<td>N. of attempts</td>
<td>1 (1-3)</td>
<td>1 (1-2)</td>
</tr>
<tr>
<td>Success at first attempt</td>
<td>38 (88%)</td>
<td>38 (88%)</td>
</tr>
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</table>

Timed is expressed in seconds. Success was defined as blue liquid return in the syringe. Quantitative and qualitative data are expressed as medians (range), and numbers (percentage), respectively.

*P<0.008 compared to standard US guidance; †P<0.01 compared to standard US guidance; ‡P<0.03 compared standard US guidance.

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Authors’ contributions.—Naïke Bigé and Eric Maury have made substantial contributions in conception, and study design. All authors have made substantial contributions in the acquisition and analysis of data, and in the writing of the manuscript. Naïke Bigé wrote the manuscript. All authors corrected and approved the final version of the manuscript.

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Dear Editor,

Facet joint syndrome (FJS) is a common cause of low back pain. Typically in patients presenting with pain emanating from upper facet joints, this pain tends to extend into the flank, hip, and upper lateral thigh, whereas pain from the lower facet joints is likely to penetrate deeper into the thigh, usually laterally and/or posteriorly. Occasionally FJS causes a neural foramina stenosis which compress the exiting nerves root with clinical features similar to disc herniation such as paresthesia and weakness in the leg pain radiating in the corresponding metamer usually stronger than low back pain. More uncommon areas of pain in FJS are lower abdomen and pelvis.

We report a case of FJS with pelvic pain as the main symptom.

A 59 year-old woman presented to our hospital complaining of a some year history of chronic lower abdominal wall and pelvic pain. Her symptoms had to date been treated in another community hospital mainly by gynecologists. The lady had undergone bladder neck needle suspension and hysterectomy, as she also suffered from urinal incontinence and uterus prolapse. Finally the patient underwent laparoscopy because of the pain.

These surgical procedures did not alleviate her pain.

During the course of her investigations and treatment fibromyalgia was also diagnosed by a rheumatologist and the patient reported central nervous system side effect (“malaise”) with many of the prescribed drugs (i.e. pregabaline, duloxetine and various opiates).

Oral steroids were also prescribed in the past by her general practitioner but the patient reported discomfort caused by cutaneous rash so she stopped their intake. She was taking acetaminophen 500 mg as needed to help reduce her pain, and these were ineffective. The pain affected quality of her sleep but worsened during the day and with physical activity. No paresthesia was reported by the patient.

Lumbar X-rays showed osteoarthritis located in the zygapophysial joints L4 to S1, while a low extremities electromyography performed 2 years ago had not demonstrated nerve disease or injury.

During our initial physical examination, we noted the patient had dull pain at deep palpation of her low mesogastrium and hypogastrium and intense pain palpating lumbar paravertebral area L4-5 and less intense pain at L5-S.

The pain caused when palpping her lumbar area radiated in lower abdominal wall and anterior pelvic area (groin and vagina). No other painful areas were detected whilst palpating her abdominal and pelvic region. It was also noted that her pain increased with spinal rotation. No clinical signs of lumbosacral radiculopathy were detected.

According to clinical examination and imaging we suspected lumbar Facet Joint Syndrome L4-5 so we performed a bilateral ultrasound guided diagnostic block at L3 and L4 medial branch, in particular targeting bony contact with the cranial junction of the transverse process and the base of the superior articulare processes (Figure 1).

We injected lidocaine 20 mg (1 ml) for each block and the pain was markedly reduced after few minutes, a residual pain (20% of the previous pain) was located in the back at the L5-S1 level with no radiation so we also blocked the L5 medial branch with the same technique and drugs used for L3 and L4 blocks and the pain almost disappeared 5 minutes later. The total amount of lidocaine used for this diagnostic procedure was 120 mg.

One week later we performed ultrasound guided intra articular L4-5 and L5-S1 facet joints injections of triamcinolone and levobupivacaine on the patient. We injected 1.5 ml of solution containing normal saline, triamcinolone 10 mg and levobupivacaine 1.25 mg in each facet joint (Figure 2). We repeated the same treatment again twice, 7 and 14 days after the first treatment.

Her Numerical Rating Score (NRS) decreased from 10 at the beginning of the treatment to 2 at the end of...
Dear Editor,

Chest X-ray (CXR), especially if performed at bedside, often underestimates presence and severity of lung contusions (LC). On the other hand, lung ultrasound (LUS), which is a powerful tool allowing to accurately diagnose and monitor traumatic injuries of the chest, can provide useful additional informations.1-4 We report the case of a patient in whom CXR suggested that part of a surgical drain tube was still in the chest after its removal, whereas LUS allowed to interpret the radiological image correctly as a LC due to the pressure of the tube on the visceral pleura.

A 79-years-old Caucasian female patient (height 150 cm; weight 50 Kg; BMI 22.2), who was a former smoker, underwent urgent coronary artery bypass surgery. Before closing the sternum, one drainage tube was positioned in the mediastinum, and one in the left pleural space. At the end of the procedure, the patient was admitted to the cardiac surgery intensive care unit (CICU) and successfully weaned from mechanical ventilation in the first postoperative day (POD 1). CXR after tracheal tube removal showed a minimum bilateral pleural effusions, no signs of pneumothorax.

An unusual chest X-ray showing part of a drain tube still in the thorax after its removal and some suggestive ultrasound findings

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Letters to the Editor

Graphic signs of LC had disappeared in CXR and LUS carried out on POD 7.

LCs are initially characterized by the presence of an interstitial infiltrate, which develops one or two hours after the primary injury (edematous phase). This is followed by the flooding phase, which reaches a maximum 24 to 48 hours later, and in which alveolar spaces are filled with blood, inflammatory cells, and tissue debris. In our patient, a LC originated from the continuous pressure exerted by the pleural drainage on the visceral pleura and, possibly, by the suction through drainage holes. The CXR performed after removing surgical drainages coincided with the maximum of the flooding phase (Figure 1B). In the report, the radiologist, who was unaware of chest tube removal, described the presence of a pleural drainage. Consequently, LUS was performed to rule out the possibility that a piece of the tube was retained in the chest. In correspondence of the basis of the left lung, the exam pointed out a moderately hypoechoic and irregularly delineated pleural-based lung lesion from which B-lines originated (Figure 2A, B). Since these findings have been described to be consistent with the diagnosis of LC, no further action was taken. Respiratory parameters and hemogasanalytic values remained stable. Postoperative course was uneventful. The patient was moved to the surgical ward on POD 3, and discharged from the hospital on POD 8.

Sonographic and graphic signs of LC had disappeared in CXR and LUS carried out on POD 7.

Figure 1.—A) CXR after tracheal tube removal clearly shows the pleural drainage aimed basally to favor fluid drainage (white arrows), drainage holes are also visible; B) CXR after surgical drainage removal: a weaker radiopaque tube-like image is still present in the left hemithorax (black arrows) whereas the holes are no longer visible. C, D) LUS after surgical drainage removal shows a moderately hypoechoic pleural-based image (black arrowheads) from which B-lines originate (white arrowheads); this finding corresponds to an irregularly delineated peripheral lung contusion.

and the presence of a surgical drainage clearly visible in the left pleural space as a radiopaque stripe allowing identification of a number of holes and with the tip aiming basally to favor fluid drainage (Figure 1A). Drain tubes were removed on POD 2 and CXR was repeated: a radiopaque tube-like image was still present in the left pleural space, coinciding with the previous one, but weaker and with no holes detectable (Figure 1B). In the report, the radiologist, who was unaware of chest tube removal, described the presence of a pleural drainage. Consequently, LUS was performed to rule out the possibility that a piece of the tube was retained in the chest. In correspondence of the basis of the left lung, the exam pointed out a moderately hypoechoic and irregularly delineated pleural-based lung lesion from which B-lines originated (Figure 2A, B). Since these findings have been described to be consistent with the diagnosis of LC, no further action was taken. Respiratory parameters and hemogasanalytic values remained stable. Postoperative course was uneventful. The patient was moved to the surgical ward on POD 3, and discharged from the hospital on POD 8. Sonographic and graphic signs of LC had disappeared in CXR and LUS carried out on POD 7.

LCs are initially characterized by the presence of an interstitial infiltrate, which develops one or two hours after the primary injury (edematous phase). This is followed by the flooding phase, which reaches a maximum 24 to 48 hours later, and in which alveolar spaces are filled with blood, inflammatory cells, and tissue debris. In our patient, a LC originated from the continuous pressure exerted by the pleural drainage on the visceral pleura and, possibly, by the suction through drainage holes. The CXR performed after removing surgical drainages coincided with the maximum of the flooding phase (Figure 1B). LC was then visible as an opacity with relatively well-defined borders that suggested the presence of the drainage or part of it (Figure 1B). LUS was then visible as an opacity with relatively well-defined borders that suggested the presence of the drainage or part of it (Figure 1B). LUS was very effective to rule out this suspect, providing additional information. Recently, LUS has been shown to be able also to assess LC extension and severity identifying patients at risk of developing ARDS 72 hours after a severe blunt trauma. Furthermore, clinically-integrated LUS has been shown to be helpful to

[Figure 1 and Figure 2 images are described in the text]
correctly schedule CT scan and other advancing imaging avoiding harmful ionizing radiation if not needed. To conclude, according with a growing body of overwhelming evidence, this case strongly supports the role of LUS as a valuable tool for bedside evaluation and monitoring of critical lung injuries with a greater accuracy than the traditional CXR.

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A year in review in Minerva Anestesiologica 2016. Critical Care. Experimental and clinical studies

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Circulation

Hemodynamic goal-directed therapy (HGDT) utilizes monitoring techniques to optimize oxygen delivery.\(^1\)\(^,\)\(^2\) In a systematic review, meta-analysis, and meta-regression, Giglio et al. evaluated the effectiveness of perioperative HGDT.\(^3\) The Authors found that mortality decreased significantly only in high-risk patients (i.e. those characterized by a mortality rate higher than 10%). This finding confirmed the results of two other systematic reviews recently published.\(^4\)\(^,\)\(^5\) However, when the analysis was restricted to high quality studies, no significant benefit was associated to HGDT. A point of strength of the analysis was that 58 studies and 8,171 patients were included; however, mortality was not defined as a fixed time point and some goal parameters differed among trials. In the corresponding editorial, Uhlig and Spieth commented that five “forgotten factors” often neglected in perioperative RCTs are of paramount importance for outcome. They are: 1) the patient (risk factors, comorbidities); 2) the surgeon (experience, type of surgery); 3) the anesthesiologist (experience); 4) the team and resources (experience, advanced monitoring tools); and 5) the goal (standard definitions, treatment).\(^6\)

In last years, dynamic indices have gained increasing popularity to predict fluid responsiveness.\(^7\) Nevertheless, to interpret their results correctly, some limitations should be considered. They were discussed in an experts’ opinion by Fisher et al., who concluded underlining the value of the “dynamic use” of dynamic indices.\(^8\) Practically, parameters like pulse pressure and stroke volume variation may be more predictive of fluid responsiveness if variations rather than absolute values are taken into account. Furthermore, the com-
To optimize protective ventilation, it is necessary to tailor tidal volumes to the size of the aerated lung. On this purpose, the comprehension and assessment of respiratory mechanics are crucial. Terragni et al. reviewed the literature of the application of dynamic pressure-time curves (Stress Index) to avoid alveolar collapse and overdistension. Available evidence suggested that such analysis is a non-invasive, continuous, reliable, operator-independent method to monitor lung mechanical properties at the patient bedside.

In order to increase the size of the aerated lung, recruitment maneuvers (RMs) are largely utilized, but indications and modalities are still poorly standardized. Chiumello et al. were the authors of a review on clinical evidences on RMs and their potential biological effects. Particular importance was given to the use of RMs during general anesthesia, and a flow chart was produced to guide physicians in clinical practice.

During mechanical ventilation, many patients present asynchronies (ineffective inspiratory efforts during expiration, double-triggering, aborted inspirations, and short and prolonged cycling), independently from the ventilator modes. A correct approach favors the interventions on ventilator settings rather than on sedation/analgesia depth. Harnisch et al. investigated the effects of changing the inspiratory cycling criteria (to vary the time point in which ventilator cycles from inspiration to expiration) on airway flows and pressures in a simulated COPD lung model. By modifying the criteria, the authors could reproduce patient-ventilator asynchronies. In the related editorial, Kacmarek pointed out that nearly all commercially-available ventilators are suitable for closed-loop control algorithms to prevent asynchrony, and it is highly advisable that industry implements the necessary software. Meanwhile, clinicians should monitor patient-ventilator interaction and correct asynchrony whenever it occurs.

Neurally Adjusted Ventilatory Assist (NAVA®) is a technique aimed to improve pa-
tient-ventilator interaction and decrease asynchrony. Since its introduction into the clinical practice, over 15 years ago, NAVA achieved a diffuse favorable opinion among intensivists due to its intrinsic capacity of optimizing patient-ventilator interaction with a sort of ventilator assistance in which inspiratory pressure delivered by the ventilator is proportional to the electric activity of the diaphragm (EAdi). Beck et al. systematically reviewed the literature regarding the use of NAVA in children as a ventilation mode and also as a tool to monitor the electric activity of the diaphragm (Edi). They concluded that NAVA is feasible and safe during invasive and noninvasive ventilation and that, in comparison with conventional ventilation, it improves patient-ventilator interaction, lowers the peak inspiratory pressure, improves children comfort, requires less sedation, and reduces ICU length of stay.

In the next years, critical care practitioners will face the challenge posed by automated algorithms of mechanical ventilation. The rationale for automation is to tailor the ventilator pattern continuously, to match patient needs, and to decrease the caregiver workload. Intellivent®-Adaptive Support Ventilation (I-ASV) mode automatically arranges ventilator setting to minimize the work of breathing by matching an “ideal” combination of respiratory rate and tidal volume. Targets for gas exchange are established based on clinical conditions (presence of ARDS, chronic hypercapnia, brain injury, or normal lungs). Minute volume, PEEP and FiO2 are consequently varied to achieve the desired values of peripheral O2 saturation and end-tidal CO2. In June, MA published the results of an RCT by Bialais et al., in which Intellivent®-Adaptive Support Ventilation (I-ASV) mode was compared with manual adjustment of ventilator setting. That was the first study to test I-ASV over a prolonged time period (48 hours). Results can be summarized as follows: 1) I-ASV was safe in acute respiratory failure; 2) tidal volume fell in the optimal range for more time than during conventional ventilation, but maximal pressure (Pmax) was more often higher than the optimal range; 3) PEEP and RR values were similar in the two ventilation modalities; 4) as expected, the I-ASV significantly reduced caregiver workload in terms of manual ventilator adjustments. Some concerns regard high Pmax values registered during I-ASV mode, and their potential effects on the ventilator induced lung injury (VILI).

Noninvasive ventilation (NIV) is considered a first-line treatment in many conditions, such as chronic obstructive pulmonary disease (COPD) exacerbations and postoperative acute respiratory failure. However, its use is still limited by patient correlated problems, like absence of compliance with NIV interface and asynchrony. Cabrini et al. summarized the large literature that supports NIV utilization, listed some steps to improve patient-ventilator interaction, and concluded with a plea for a larger utilization of that technique.

In last years, oxygen therapy with high-flow nasal cannulas (HFNC) literally exploded in literature and presumptively in clinical practice. In the October issue, an “experts’ opinion” by JD Richard and an accompanying editorial by Terragni and Cossu focused on the prevention of O2 desaturation by HFNC during or immediately following tracheal intubation in critically ill patients. The topic is important since profound desaturation eventually occurs after laryngoscopy in 20-25% of patients and is a risk factor for intubation-related complications. In comparison with standard oxygen therapy and non-invasive ventilation, HFNC advantages rely on efficacy, simplicity of use, lack of contra-indications and most important, capacity to bring oxygen in the lower airways also during apnea.

**ECMO**

A few noticeable contributions on ECMO management were published, dealing with coagulation management, vascular complications, and echocardiographic monitoring.
In ECMO patients, hemorrhagic and thromboembolic problems are a major cause for morbidity and mortality. Adequate monitoring is therefore, a crucial point. Bollinger et al. reviewed the laboratory tests utilized on this purpose. They underlined the importance of Point-of-care (POC) tests, such as rotational thromboelastometry (ROTEM) and thromboelastography (TEG). POC tests may be particularly useful when using new alternative drugs, such as bivaluridin. The relationship between POC tests and conventional coagulation tests (aPTT) was studied by Ranucci et al. in patients who underwent postcardiotomy ECMO. Blood contact with extracorporeal circuits may alter coagulation, for instance by causing an acquired von Willebrand syndrome. The results from a study by Panigada et al. ruled out the risk of coagulation impairment directly caused by blood contact with the extracorporeal circuit during VV-ECMO.

Ischemia of lower limbs is a serious complication of ECMO due to the insertion of large cannulas, which are often occlusive. A single center retrospective analysis pointed out a high incidence of that complication; most ischemic limbs recovered after starting an anterograde perfusion, but others required fasciotomy. On that basis, routine prophylactic use of anterograde perfusion is strongly recommended, as well as restricting ECMO utilization to expert and referenced centers.

Echocardiography plays an important role for the choice between VV- and VA-ECMO, in checking the correct position of cannulas, and in monitoring cardiac function. The presence of a physician trained in echocardiography was indeed recommended in ECMO teams by a recent position paper. Lazzeri et al. reviewed the results of echocardiographic repeated assessments in 75 patients during VV-ECMO. They found that pulmonary hypertension and right ventricle dilatation were common and that the latter was an independent predictor of mortality. Those findings supported the suggestion to perform daily echocardiography examinations focused on right ventricle for the entire duration of ECMO treatment.

Sepsis and infection

Although the frequency of sepsis increased, related mortality has decreased over the past decade. This result was partly due to new and more refined diagnostic tools. Genomics is opening up a whole modern means of diagnosing, prognosticating, and directing treatment in sepsis, which were summarized in a review by Douglas and Russel. In next years, genomics will probably change the approach to sepsis management; meanwhile, the trials to identify and validate sepsis biomarkers should not overlook the genomic approach. For the moment, the search for new ones continues. De La Torre-Prados et al. studied mid-regional pro-adrenomedullin, a promising biomarker of sepsis, which showed a significant prognostic value when measured within 24 hours from the onset of septic shock. Real-time polymerase chain reaction technology provides useful tools for sepsis management. Dinç et al. evaluated the SeptiFast test, which may be useful when added to blood culture in the diagnosis and management of sepsis, provided that the risk of false negative results with PCR will be addressed.

Cardio-circulatory dysfunction is a key aspect of sepsis. Two reviews addressed this issue. Latini et al. revised the etiology, pathophysiology, monitoring, and clinical manifestations of cardiac dysfunction in septic patients. Beloncle et al. examined the physiological rationale and evidence for the choice of a target mean arterial pressure value in septic shock.

Risk factors are important to prevent infections. On this regard, Sbrana et al. conducted an interesting matched case-control study aimed to assess clinical and epidemiological risk factors associated with KPC-Kp VAP development in a cohort of critically ill patients who harbored previous tracheal and rectal colonization. After adjusting for confounding factors, earlier non KPC-Kp infections and the duration of previous antibiotic therapies were significantly associated with VAP occurrence; conversely, short-term inhalation pneumonia prophylaxis was the only independent
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Neurocritical care

In early phases of traumatic brain injury (TBI), poor neurological outcome is mainly related to intracranial hypertension (ICHT). In May, MA published a prospective study on 16 patients affected by severe TBI, in whom blood-brain barrier (BBB) permeability was studied by contrast-enhanced computed tomography. The main finding was tracer extravasation in peri-contusional areas, in particular in the presence of ICHT. Some patients had undergone neurosurgical procedures, but it was not clear whether blood-brain barrier (BBB) disruption was influenced by surgery. Although BBB damage is often associated with ICHT, therapies effective on the latter do not necessarily improve patient outcome. Among the others, recently proposed progesterone administration did not provide any benefit on neurological recovery.

Cossu et al. analyzed 26 studies that evaluated the impact of ICP on the outcome of patients affected by subarachnoid hemorrhage (SAH). They found that severe ICHT was associated with higher mortality, but was not predictive of long-term neurological outcome. In SAH, Doppler ultrasonography had a positive prognostic value of 57% and a negative predictive value of 92% (95% CI: 83-96%) to diagnose vasospasm (17 studies, 2870 patients), but there is no evidence that this may impact on outcome. Other monitoring tools have been tested to guide therapy and improve survival. Continuous EEG monitoring may detect non-convulsive seizures, which occurred in 12% of patients and were associated with unfavorable neurological outcome in a cohort of 402 SAH patients. S100β protein is a biomarker which has gained large interest in neuro critical care. Increased levels of this protein were associated with poor prognosis, with a cut-off >0.13 μg/L, both in SAH and in spontaneous non-aneurysmal intracranial hemorrhage.

Evaluation of hypoxic-anoxic brain injury is difficult in the early postresuscitation phase after cardiac arrest because clinical examination is usually unreliable due to pharmacological sedation and cooling procedures. Outcome prediction requires a multimodal approach. S100β and neuron-specific enolase (NSE) at 24 hours were highly predictive of neurological outcomes 48 hours after a cardiac arrest treated with targeted temperature management (TTM). Absent cortical responses to somatosensory evoked potentials during, and after TTM may have a 100% prognostic value of poor neurologic outcome. The absence of EEG response to painful stimuli and the persistence of status epilepticus may indicate poor functional outcome. In a series of 167 patients affected by cardiac arrest, false prediction of poor neurological outcome by malignant EEG
patterns was 21% 12 hours after cardiac arrest, and 0% at 72 hours.\textsuperscript{89}

In the February issue, Santacruz \textit{et al.} reported the effects of 20% mannitol (M) as compared with hypertonic saline (HS) in a swine model of intracranial hypertension; to mimic a brain mass, a balloon was inserted in the right frontal lobe and inflated.\textsuperscript{90} Differently than other studies focused on the effects of the osmotic therapy on intracranial pressure and cerebral perfusion pressure,\textsuperscript{91} this elegant study focused on brain cellular metabolism. As expected, both M and HS decreased intracranial pressure, but rather surprisingly, they also increased tissue perfusion and cerebral oxygenation, and decreased the lactate/piruvate ratio. As suggested by the authors, these results should prompt further studies to identify osmotic that improve cerebral metabolism.

\textbf{Renal failure}

A systematic review and meta-analysis on the incidence of acute kidney injury in postresuscitation care were published in the September issue.\textsuperscript{92} It provided the reader with a wide and detailed perspective on incidence and severity of kidney injury, which depends on peri- and postarrest factors, and on the current debate on the best timing for renal replacement therapies, which are necessary in almost one-third of survivors.\textsuperscript{93} The related editorial pointed out future directions for clinicians and researchers.\textsuperscript{94}

\textbf{Ethics}

Research on incompetent patients is a common, but very problematic issue in the critical care setting. Zamperetti \textit{et al.} addressed this topic and the complex framework of laws and regulations in force in the European countries.\textsuperscript{95, 96} The Authors discussed the problem of multicenter trials and consequent involvement of multiple Research Ethics Committees (RECs); highlighted the fragility of so-called “delayed consent”; and supported the role of clinicians’ ethical and legal responsibility so that an incompetent subject could be enrolled in an emergency trial simply by applying the criteria of inclusion laid down in the study protocol and approved by RECs. The Authors of the accompanying editorial wished that safeguard of important patients’ rights take precedence over the respect of formal administrative procedures.\textsuperscript{97}

In many countries, donation after circulatory death (DCD) is a valuable option for the procurement of organs for transplantation.\textsuperscript{98-100} Giannini \textit{et al.}, on behalf of the Working Group on DCD of SIAARTI and the Italian Society for Organ Transplantation (SIOT), highlighted the main ethical, clinical, organizational, and legal issues at stake, with a specific focus on Italian legislation.\textsuperscript{101} The authors stressed that quality and appropriate-ness of critical care are ethical prerequisites for organ donation and recommended that: (a) the decision to withdraw disproportionate life support treatments is made independently of the possibility of organ donation; (b) the organ retrieval procedure neither causes nor hastens death; and (c) the dead donor rule is strictly respected. In Italy, the law requires 20 minutes of silent ECG to over-guarantee brain death and the dead donor rule. Giannini \textit{et al.} believe that this time interval should be reconsidered and shortened even if, in their opinion, the issue of mandatory prolonged warm ischemia is mitigated by the intensivist high level of expertise, by the excellent organization of the Italian transplant network, and by the new and innovative techniques for organ protection and reconditioning.

The end-of-life (EOL) decision process still represents one of the most complex issues (in clinical, ethical, deontological, and legal terms) in modern-day medicine and shows great variability worldwide.\textsuperscript{102} The “Courtyard of the Gentiles”, a department of the Vatican’s Pontifical Council for Culture, in collaboration with the SIAARTI produced an interesting and balanced position paper about ethical and legal principles that should characterize the doctor-patient relationship and form the basis of laws for regulating EOL decisions.\textsuperscript{103, 104} This position paper resulted from the cooperation of a wide expert panel of believers and non-believ-
ers, that included doctors, philosophers, ethicists and jurists.

Communication is considered of paramount importance in everyday medical practice. Since family members of critically ill patients believe that communication skills of physicians are as important as clinical skills, and insufficient training in communication is considered a major barrier to improve end-of-life care, ICU staff should be trained in conflict management, meeting facilitation skills, and assessment of family needs, stress, and anxiety levels. Warrillow et al. proposed some stimulating views with practical paths to address this issue. Interestingly, they suggested that communication in ICU is conceptualized as clinical procedures like CVC insertion, with indications, contra-indications, modifications required, complications, and a planned, structured approach for the task itself.

Implementation of Rapid Response Systems (RRS) results in more frequent do-not-resuscitate orders and limitations of therapy, so that Medical Emergency Teams (METs) find themselves very often initiating and/or participating in palliative and end-of-life care. A survey by Cabrini et al. unveiled that Italian intensivists involved in MET activity complain frequent doubts and conflicts (mainly with ward physicians) during in-hospital emergencies, as well as a negative impact on their emotional and moral condition. Unfortunately, most Italian hospitals do not provide ethics training or protocols. The problem is mainly cultural and training should be considered the “key word” in tackling this kind of difficulty. Just as for communications skills, clinical ethics must be fully recognized as a specific area of professional competency that needs to be improved or updated.

Nutrition

In the August issue, MA published an expert’s opinion by Preiser and Taccone, in which the key clinical issues about nutrition were summarized: which patients should be considered, when to start and which route, how many calories, how many proteins, and how to assess the risk-benefit ratio.

In last years, the focus of nutritional management in critically ill patients changed from simple energy and azote supplementation to a more complex approach in which nutrients may influence multiple organ failure. Rosenthal et al. reviewed the rationale of immunonutrition and concluded that specific nutritional strategies may modulate the colonization of the upper gastrointestinal tract, reverse mucosal hypoperfusion, and regulate the immune response driven by the gut in the setting of multiple organ failure. Unfortunately, conclusive evidences are still lacking for most immuno nutrients. Anetta et al. performed a comprehensive review of the effects of glutamine, omega-3-fatty acids, arginine, and mixtures of trace elements and antioxidants (with a special interest in selenium). They concluded that none of these compounds have evidence-proved benefits, and some of them may be even harmful. Is this the end to the era” for farmaconutrition?

Blood and coagulation

Transfusion management is a major challenge in anesthesia and critical care. A recently published survey revealed that only 62% of physicians adopt an algorithm to guide perioperative blood management. In a systematic review and meta-analysis, Ripollés Melchor et al. analyzed six randomized controlled trials (2156 patients) that compared the effects of lower vs. higher hemoglobin thresholds for packed red blood cell transfusion on mortality in critically ill patients. They concluded that restrictive strategy was at least as effective as liberal one, but a non-significant trend toward increased mortality was associated to the formers in the subgroup of patients with acute coronary syndrome. In the accompanying editorial, Vincent and van der Linden recommended individualizing the decision about red blood cell transfusion, especially in the presence of acute coronary syndrome.

Repeated hemodynamic evaluations are essential to avoid hypovolemia in bleeding trau-
ma patients.\textsuperscript{127} On this purpose, Vetorello \textit{et al.} proposed the indexed heart to arm time (iHAT) as a non-invasive tool based on modified pulse transit time indexed to the time interval between R waves in the ECG.\textsuperscript{128} They studied 30 healthy volunteers in whom hypovolemia was simulated by application of negative pressure to the lower body and found that iHAT correctly identified the decrease in stroke volume caused by the reduced cardiac preload.

Viscoelastic hemostatic assays (VHAs), like thrombelastography (TEG) and rotational thromboelastometry (ROTEM), provide point-of-care-diagnostic information on clot formation and dissolution at the patient bedside.\textsuperscript{129} Figueiredo \textit{et al.} reviewed the use of VHAs in trauma patients and concluded that these devices predict massive transfusion and mortality, and provide precious information to target the administration of platelets and coagulants.\textsuperscript{130}

New oral anticoagulants (NOACs) may cause a lower risk of bleeding in comparison with conventional ones. Vargas \textit{et al.} reviewed the strategies to monitor coagulation and reverse anticoagulation in patients treated with NOACs.\textsuperscript{131} In general, only supportive and non-specific reversal strategies are available to control bleeding under NOACs, but specific antagonists have been recently tested (Andexanet alfa for direct factor Xa inhibitors like Apixaban and Rivaroxaban\textsuperscript{132} and Idarucizumab for the direct thrombin inhibitor Dabigatran\textsuperscript{133}).

**Miscellanea**

Organizational and teamwork aspects together with the delivery of critical care outside the ICU walls has proven to improve patient long-term outcome.\textsuperscript{134} Cabrini \textit{et al.} stressed the importance of a patient-centred critical care approach, the key elements of which were the effective communication, the holistic approach to match patients’ needs and wishes, and the presence of rapid-response teams to start critical care outside the ICU.\textsuperscript{135} That approach needs a multidisciplinary team in which the intensivist has the role of team-leader.\textsuperscript{136-8}

Nowadays, biological and clinical research provides healthcare professionals with a massive amount of information. Guidelines translate evidence into practice, have an impact on health care, and play an important role in the elaboration of public health policies. Nonetheless, correct procedures are needed to create reliable guidelines,\textsuperscript{139} because poor quality ones may contribute to inappropriate recommendations and low adherence.\textsuperscript{140-2} Girardis \textit{et al.} assessed the quality of five international guidelines for analgo-sedation in critically ill patients according to the AGREE II score.\textsuperscript{143} They concluded, reassuringly, that the guidelines were robust and supported for use. Page and Casarin commented the role of guidelines in an interesting editorial.\textsuperscript{144}

The prevalence of the post-traumatic stress disorder (PTSD) in adult patients admitted to ICUs ranges from 19\% to 27\%.\textsuperscript{145} High levels of anxiety, trauma and depression are likely to cause a significant reduction in quality of life and well-being after critical care.\textsuperscript{146} Wade \textit{et al.} reviewed 23 RCTs on non-pharmacological interventions aimed to reduce ICU-related distress.\textsuperscript{147} Music therapy, mind-body practices, and psychological interventions had some beneficial effects on short- and long-term stress in critical care patients. However, only a few studies had a low risk of bias and reported a medium/long psychological outcome; hence, a meta-analysis was impossible due to the heterogeneity among the studies examined.

The choice of correct endpoints is a critical issue in a trial design.\textsuperscript{148} Groeneveld carried out a review on different mortality endpoints used in studies on critically ill patients.\textsuperscript{149} He pointed out that data on mortality are highly heterogeneous due to variable intervals of time, and to the existence of two different approaches, i.e. location-dependent vs. duration-dependent mortality.\textsuperscript{150, 151} The Author proposed the use of 28-day mortality as the primary endpoint of all clinical studies, and 90-day mortality as a secondary endpoint. The rationale behind this recommendation was the greater influence of confounding factors on long-term endpoints.

Finally, Ingrassia \textit{et al.} performed a survey to evaluate the degree of preparedness of fif-
teen Italian hospitals to manage potential disasters. Only three hospitals were considered to have an effective level of preparedness; in the remnants, command system, surge capacity, and safety were not sufficiently implemented. The Authors concluded that the draft of national standards, guidelines and procedures is highly desirable.

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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.

### TOP 50 MINERVA ANESTESIOLOGICA REVIEWERS

**Top 50 reviewers June 2016-November 2016**

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