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About the cover: the cover shows the diaphragmatic thickening at end-inspiration (TEI) at T0 (before propofol infusion) and at T1 (1 min after reaching level 1 on the OAAS scale before gastric probe insertion). The study confirms that US was a suitable and well-tolerated technique for measuring diaphragmatic activity during a routine clinical procedure. For more information, see article by Rocco M. et al. (pages 266-73).
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Editorial

Is life worth living?
It all depends on the liver

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The use of extracorporeal membrane oxygenation (ECMO) seems to be an important issue for clinicians: a literature search with ECMO as a key word in the title including papers published from January 2014 until October 2016 yielded 359 articles, 17 reviews, and 16 editorials. Such a figure depicts the constant evolution through the years showed by ECMO from technical and clinical points of view. Accordingly, despite the fact that this technique is resource-intensive and requires significant institutional commitment and well-trained staff, the use of ECMO has been rapidly increasing in high-income countries with a rising evidence that it ensures clear benefits in patients with different acute illnesses including cardiac arrest and cardiogenic shock.¹

Nevertheless, although in-hospital complications and mortality of patients receiving ECMO decreased over time, they still remain an important issue.¹, ² Among the different organ dysfunctions possibly affecting patients undergoing ECMO, liver failure can represent a severe, life-threatening event. This is mainly due to three factors: 1) the liver plays a pivotal role in almost any body metabolic and immune pathway; 2) there is no specific treatment/therapy for the diseased liver; 3) the liver cannot be routinely monitored with the same precision and intensity that is nowadays possible for other organs and functions, namely the lungs and the cardiovascular system.

In this issue of Minerva Anestesiologica, Blandino Ortiz et al. aimed at studying the liver dysfunction that may affect patients undergoing venous-arterial ECMO in terms of occurrence, time-course and impact on survival.³ The key points of their study are: 1) although an elevation of liver enzymes can occur in the majority (65%) of the patients not all of them show the signs of hypoxic hepatitis; 2) elevated liver enzymes can normalize quickly (within five days since ECMO initiation); 3) there is a lack of association between alteration of liver enzymes and poor outcome.

As noticed by the authors, only few other studies are available about liver dysfunction in ECMO patients with, unfortunately, conflicting findings due to methodological, study populations and definitions heterogeneity. Therefore, the conclusion they drew — i.e. further studies are needed in order to better investigate the association between ECMO and liver outcomes — was inevitable. Still, Blandino Ortiz et al. are to be commended for bringing to our attention the key topic of how liver function...
can be assessed, monitored and possibly preserved in critically-ill patients, with or without ECMO as a treatment.

Preserving liver function is of great importance in patients on ECMO, as in some cases the liver dysfunction can be secondary to specific technical aspects. For instance, in patients supported by ECMO placement of cannulas at the level of suprahepatic veins might determine liver dysfunction, due to inadequate venous drainage. Thus, correct positioning of the cannula tip in the inferior vena cava must be confirmed to avoid cannulation of one of the hepatic veins. Echocardiography plays a key role in avoiding such an issue, as it has the ability to determine the exact position of the cannula. In addition, serial echocardiograms might serve to monitor cardiac chamber size to ensure adequate emptying of the ventricles, thus facilitating unloading of the heart. In this view, central venous pressure (CVP) provides additional information on venous stasis in patients on ECMO, as high CVP values could indicate impairment either in the portal blood drainage or right ventricular failure. Also, a rise in CVP in the setting of stable settings may be indicative of a mechanical obstructive process, which can affect liver function as well.

Studying the liver with its pleiotropic functions is not easy and rapid and repeated assessments of surrogates for global liver function in the critically ill are difficult to achieve. Real-time monitoring of liver function in critically-ill patients is currently not available. In general, the results of different tests may vary considerably, since they assess different hepatic partial functions, which makes comparison difficult. On the one hand, conventional static parameters, such as bilirubin and transaminases, are generally too slow to fit real-time monitoring. On the other hand, the so-called “dynamic tests” that rely on clearance, elimination or metabolite formation can respond more rapidly to changes associated to critical illness than conventional tests, but they are characterized by inherent diagnostic fuzziness regarding discrimination of perfusion to function abnormalities. Moreover, no validated biomarkers are currently available to monitor non-parenchymal functions of the liver, which are considered to be of outstanding significance in deterioration of liver function in the critically-ill.

Finally, there is a very specific feature of the liver that frustrates our efforts in shedding more light on how to better assess liver function in critically-ill patients. The liver participates in host defense and tissue repair through hepatic cell cross-talk, which controls most of the coagulation and inflammation processes. When this control system becomes inadequate or ineffective, as is the case of the possible ECMO-related hypoperfusion/hyperinflammation, a secondary hepatic dysfunction may occur and may sometimes lead to bacterial product spill-over, enhanced procoagulant and inflammatory processes, and, in turn, be responsible for multiple organ failure and death. The liver suffers the consequences of shock- or hyperinflammation-inducing circumstances, which alter hepatic circulation parameters, oxygen supply and inflammatory responses at the cellular level. Moreover, the liver is an orchestrator of metabolic arrangements, which promote the clearance and production of inflammatory mediators, the scavenging of bacteria, and the synthesis of acute-phase proteins. Therefore, the liver can both promote and become a target for remote organ dysfunction. Accordingly, with the currently-available technology and laboratory tests, it is nearly impossible to discriminate whether an altered liver function is “primary” or “secondary”.

Given the above premises, we agree with William James, the “father of American psychology,” who stated: “Is life worth living? It all depends on the liver.” More efforts need to be made in the future to better understand how such a pivotal organ works and fails.

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EDITORIAL

TAP block in neonates:
need to think beyond effectiveness

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The transversus abdominis plane (TAP) block has become a widely used regional anesthesia technique for perioperative pain management in a variety of abdominal surgeries and patients, from neonates to adults. Nearly twenty years after the first description by Rafi 1 and in spite of an important increase in its use and indications, surprisingly a number of unknowns are still unresolved. In the current issue of Minerva Anestesiologica, Kendigelen et al. described the use of ultrasound (US) to perform TAP blocks in neonates and reported its benefits in this high-risk population.2 Nonetheless, this technique could provide a safe and effective perioperative pain management only if we consider its challenging technical and pharmacological aspects in the neonatal population.

One of the greatest concerns in regional anesthesia in neonates is how to be effective with the lowest dose of local anesthetic (LA) in order to avoid local anesthetic systemic toxicity (LAST). A recent analysis of TAP blocks included in the Pediatric Regional Anesthesia Network (PRAN) database, highlighted the potential risk of LAST in children. Nearly 135 of 1994 children included in the regist-

try, received doses potentially associated with LAST.3 Several case reports of LAST have been published after performing TAP blocks in adults.4-6 Pharmacokinetic studies have confirmed that a single dose of 2.5 to 3 mg/kg of levobupivacaine or ropivacaine can easily reach plasmatic concentration associated with neurological toxicity.7-9 A recent pharmacokinetic study, confirmed the rapid and early rise of LA plasma concentration following TAP block in neonates.10 Moreover, due to an immature hepatic metabolism, low plasma concentration of the LA binding proteins and the lack of fully developed nerve fibers, neonates are at greatest risk of LA toxicity.11 Therefore, a reduction of the concentration and the total dose of the LA are essential in this specific population.

Currently, the use of US has become the gold standard for regional anesthesia procedures in pediatric patients, including TAP blocks.12 The key of the block’s success relies on the accurate placement of the LA solution in the fascial layer that separates the internal oblique and the transverse abdominal muscles.13 As demonstrated by Kendigelen et al., the distance from the skin to the TAP is often a few millimeters in neonates. The peritoneum, liver,
spleen or even the kidney, are never very far away from the target plane. Therefore, the use of an appropriate needle’s size (24 or 25 G), an extremely careful skin puncture and real-time needle advancement visualization, done by a pediatric anesthesiologist with experience in sonoanatomy, will increase the safety of the procedure.

The choice of the regional anesthesia technique should include the surgical site, the severity of the surgical insult, the clinical characteristics of the patient and the benefit risk ratio. A multimodal analgesia program including TAP block provide an effective analgesia and could be considered as the first option for minor abdominal surgery in small children. It could also be considered as a safe alternative to major abdominal surgery when an epidural technique is not feasible or contraindicated.

The study by Kendigelen et al. highlight the place of peripheral regional analgesia in neonates as an effective tool for improving perioperative pain control and reduce analgesics requirement after surgery. TAP blocks in neonates could be recommended when is performed with the appropriate expertise, using proper equipment and taking special attention to the dose of LA.

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It is good practice to provide adequate sedation in the critically ill in the Intensive Care Unit (ICU). Nevertheless, over the last few years, sedation in the ICU has passed from a concept of deep irresponsive state, or induced coma, to the need for the patient to reach a state of adequate analgosedation. Together with this latter idea, the concept of comfort in the ICU was born. The Bispectral Index (BIS) is a well-known tool utilized by anesthesiologists to monitor the depth of anesthesia and titrate general anesthetics in the operating theatre. In this issue of Minerva Anestesiologica, Bilgili et al. reviewed the literature on BIS utility in order to provide proper sedation to critically-ill patients. The overall evidence of this review is quite inconclusive. The BIS technique indeed, although beneficial in the avoidance of inadequate anesthesia levels in paralyzed patients is poorly applicable in the ICU setting in which patients are complex and with several comorbidities.

Recently, an interesting concept developed across the intensivists: it was called eCASH, which stands for “early Comfort using Analgesia, minimal Sedatives and maximal Humane care”. According to this idea the concept of deep sedation in the ICU is completely overcome. Sedation should be secondary to pain relief and should aim to the restoration of sleep and wake alternation. On the other hand, adequate analgesia can contribute to early weaning from mechanical ventilation, mobilization, improvement in communication with the family or the care givers and proper rehabilitation.

In our opinion, especially in a period of reduced resources in the health care environment in general and in particular in the acute care setting, specific attention should be addressed to reduce the human and economic costs of a prolonged ICU stay, and proper analgosedation is indeed one of the major determinants. What emerges from the present study is that the current understanding of BIS and its interaction with sedative or general anesthetics, is not helping the quest to conquer adequate sedation in the ICU, probably because sedation itself is inadequate in most of the situations.

Since we are moving to a condition where comfort is considered the best care for our patients, we cannot rely on a single device or a technique to monitor it. Instead, we should focus on finding other means to proper detect the lack of comfort in our critically ill patient, in order to assure improved quality of care.
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Injury-induced immunosuppression: are we finally on the right track?

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In critically ill patients multiple stress events such as infection, trauma, surgery and burn may lead to dysregulation of the immune response with an excessive pro-inflammatory phase and/or a prolonged and profound dysfunction in immune response. This latter, called immune-paralysis, predisposes patient to secondary life-threatening infections and seems to be crucial for long-term outcomes in patients surviving to first hit. Moreover, due to impairment in the innate and adaptive immunity, antibiotic therapy alone may result ineffective in immunosuppressed patients. Therefore, early detection of immune dysfunction and its support by specific strategies may be the key for improving survival.

In the last years the awareness of the pivotal role of immunity in acute illnesses has led to significant advances in the identification of biomarkers useful for the assessment of the immune system competence in critically ill patients. In the current issue of Minerva Anestesiologica, Rouget et al. provided a detailed and exhaustive review of these biomarkers. The authors focused on immature granulocytes, quantitative and qualitative alterations in dendritic cells, monocytes human leucocytes antigen DR, anti-inflammatory interleukins and the recent concept of leucocyte reprogramming.

The role of the possible markers of immunosuppression expressed by B and/or T lymphocytes has been also reviewed in detail, along with a novel transcriptomic view that would allow the identification of genes that are up or down-regulated during a stressing insult.

In addition to molecules and cells described by Rouget et al., further bio-markers may be helpful for identifying an hypo-reactive state of the immune system. A low plasma concentration of the different isotypes of endogenous immunoglobulins at the onset and throughout the course of sepsis has been associated to an increased risk of mortality in septic patients. Due to the pleiotropic effects of immunoglobulins in the inflammatory-immune response, the reasons and the true meaning of this association are still debated. However, several mechanisms by which immunoglobulins may exert anti-apoptotic effects of different immune cells populations have been identified in preclinical models. Therefore, a decreased immunoglobulin plasma levels could facilitate a boost of apoptosis that has been recognized as an important cause of major immune dysfunction during late phases of sepsis. Remaining on apoptosis, caspase 1 is a key component of inflammasomes that trigger a potent proinflammatory response, ultimately inducing a type of cell death defined “pyroptosis”. In addition to its role as marker of an excessive pro-inflammatory condition,
persisting high level of caspase 1 could be also considered an early indicator of immune system hypo-reactivity. A further potential marker of immune dysfunction might be mucosal-associated invariant T (MAIT) cells, a population of T lymphocytes that express a semi-invariant T cell receptor. An important role of MAIT cells in the early stages of bacterial infections has been postulated and a recent study showed that critically ill patients with persistent MAIT cells depletion display a high susceptibility to develop hospital acquired infections.

A proper evaluation of hyper or under-activation of the host immune system may provide a better comprehension of the pathobiology changes occurring in sepsis as well as in other conditions such as trauma, burn and surgery, and may finally guide to a tailored therapeutic approach. For instance, the traditional strategy aimed to suppress the immune system by inhibition of inflammatory mediators could be helpful in patients with an overwhelming pro-inflammatory state, but may be harmful in patients with a suppressed immune response.

The review by Rouget et al. provides a straightforward analysis on the rationale for use and the feasibility of measuring immune-competence at the bedside. Unfortunately, most of the biomarkers described requires sophisticated techniques such as flow cytometry, immunohistochemistry, cytokine ELISA arrays or RNA analysis for gene expression. Despite many of these procedures are complex and have a high cost, we believe that the evaluation of the immune response is today mandatory for a proper management of septic patients. To this aim, official guidelines or consensus conferences are urgently needed to provide clinicians with a sort of “immunoscope” to monitor critically-ill patients and treat them. The future in which specific therapies will be tailored on a sound evaluation of patient pathobiology could be around the corner.

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The effect of routine availability of sugammadex on postoperative respiratory complications: a historical cohort study

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ABSTRACT

BACKGROUND: Postoperative residual curarization is a preventable cause of postoperative morbidity. Although sugammadex has been shown to reduce the risk of residual curarization, it has not yet been shown if this directly translates to a reduction in morbidity. We aimed to demonstrate whether the introduction of unrestricted sugammadex for routine reversal changed the incidence of postoperative respiratory diagnoses and the rate of airway and respiratory complications in the postoperative care unit.

METHODS: A historical cohort study of 1257 patients who underwent general surgical or ear, nose and throat procedures before and after the introduction of unrestricted availability of sugammadex. Patient records were used to identify the incidence of postoperative in-hospital respiratory diagnoses and of airway complications in post-anesthesia care unit, the pattern of muscle relaxant use and the relative costs associated with the routine availability of sugammadex.

RESULTS: Unrestricted sugammadex availability was associated with a significant reduction in the rate of a postoperative in-hospital respiratory diagnosis (odds ratio [OR] 0.20; 95% CI: 0.05-0.72, P=0.01). Furthermore, the use of sugammadex itself was also associated with a reduction in in-hospital respiratory diagnoses (OR=0.26; 95% CI: 0.08-0.94, P=0.04). Unrestricted sugammadex was also associated with a decrease in the need for manual airway support in the recovery room (3.2% vs. 1.1%, P=0.02) and a decrease in patients being transferred intubated to ICU (5.5% vs. 1.3%, P<0.001).

CONCLUSIONS: Unrestricted sugammadex availability is associated with a reduction in postoperative respiratory complications. A well-designed, prospective randomized trial is needed to provide further validation of the data.

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Key words: Cohort studies - Delayed emergence from anesthesia - Humans - Postoperative care - Gamma-cyclodextrins.

Residual postoperative curarization (RPOC) after anesthesia is a common and preventable problem. The incidence in the published literature ranges from 13-89%.1-14 with a meta-analysis showing an overall incidence of RPOC (as defined by train-of-four [TOF] <0.9) of 41.3%.15 Despite this, anesthetists underestimate the incidence of RPOC, with most feeling that the rate of clinically significant residual paralysis is less than 1%.16

RPOC has been linked to postoperative morbidity. The majority is respiratory in nature, reflecting the impairment of laryngeal reflexes and swallowing function17,18 and the impairment of hypoxic respiratory drive at TOF ratio (TOFR) <0.9.19 Postoperative pulmonary complications
are postulated to arise from either increased atelectasis and/or micro-aspiration following inadequate reversal. RPOC has been directly associated with increased critical and hypoxic events in the PACU, and with longer term increased risk of pulmonary complications and radiographic chest X-ray changes.

Most studies into the effects of RPOC have investigated anticholinesterase drugs as reversal agents. Sugammadex differs as it produces rapid termination of neuromuscular blockade via formation of one-to-one complexes with aminosteroid neuromuscular blocking drugs (NMBDs). Published studies investigating the effect of sugammadex have consistently shown a reduction in RPOC incidence. Despite this, evidence that links sugammadex use to a reduction in clinically relevant morbidity is limited and of low quality.

We performed a retrospective analysis of two cohorts of general surgical and ear, nose and throat (ENT) patients, prior to and after the introduction of unrestricted sugammadex at our institution. The primary outcome measured was any in-hospital respiratory diagnosis. Our hypothesis was that the introduction of routine sugammadex would lead to a reduction in respiratory diagnoses. Additionally, we sought to identify differences in the incidence of airway and respiratory events in the postoperative care unit (PACU), changes in the pattern of muscle relaxant use, the incidence of unplanned ICU admissions and in the use of intraoperative monitoring of neuromuscular function. Finally, we aimed to perform a simple cost analysis based on the changed patterns of drug use.

**Materials and methods**

Following local ethics approval (Northern Sydney Local Health District Human Research Ethics Committee, Ref. 1210-377M, approved 10/08/2013), electronic operating theatre databases were accessed to extract all general surgical and ENT patients undergoing surgery over two corresponding three month periods before and after the introduction of unrestricted sugammadex (February 2011). The three-month study period was chosen to offer a reasonable representation of the volume of cases at our institution, and the cohorts were limited to general and ENT cases to select groups with a high incidence of muscle relaxant use. In addition, the same three-month period (August to October) was chosen in both years to minimize interfering factors such as seasonal variation of diseases and to allow for six months of “familiarization” after the introduction of routine sugammadex.

Paper patient medical records were retrieved and accessed to record patient data, and to look for in-hospital respiratory diagnoses, as defined from the medical coding sheet (ICD-9 codes; 465-66, 480-88, 518). Additionally, recovery room notes were reviewed to record the need for airway support (manual, oropharyngeal or endotracheal airways), any documented saturation <90%, the need for reintubation and the need for unplanned intensive care unit (ICU) admission. The anesthetic chart was analyzed to record the use and dose of muscle relaxant and the type of anesthetic given (volatile based anesthesia vs. total intravenous anesthesia, TIVA) and the use of intraoperative neuromuscular twitch (NMT) monitoring.

A simple cost analysis was performed by multiplying the percentage of patients receiving each NMBD or reversal agent by the cost of an individual ampoule of drug (or multiplied by two where glycopyrrolate was used, to represent the standard dose of two ampoules). This approximated a total cost per 100 patients. The drug cost was provided by hospital pharmacy as at February 2014.

**Statistical analysis**

Data was entered into an Excel spreadsheet and analyzed using Excel for Mac 2008 and SPSS v.22. Significance of effect for continuous data was determined using two-tailed Student’s t-test. Categorical data was analyzed for significance using χ² tests (or Fisher’s exact tests when any group N.<5). Binomial logistic regression was used to determine the effects of age, ASA, the use of suxamethonium, the use of NMT monitoring, the type of relaxant and type of reversal used on the dependent
variable of in-hospital respiratory diagnosis. To ensure the assumption of independence of measurement in the variables was met, regression analysis was performed after removing patients with more than one operation during the analysis period (patients only had their first anesthetic during the three-month period included in the analysis).

Results

There were 1281 cases eligible for inclusion in the study. 24 patient files were unable to be obtained despite repeated requests for access (12 in each cohort), resulting in 1257 cases available for review. Of these 1257 cases, a total of 922 received a NMBD as part of their anesthetic and were included in further analysis. Table I shows the numbers in each cohort and the patient demographic data.

The rate of in hospital respiratory diagnosis was non-significantly reduced after the introduction of unrestricted sugammadex (3.3% vs. 1.6%, P=0.13).

After correcting for potential confounders, the cohort with unrestricted sugammadex availability was significantly associated with a reduction in the rate of in-hospital respiratory diagnosis (odds ratio [OR] 0.20; 95% CI: 0.05-0.72; P=0.01), giving a relative risk of 0.21 (0.05-0.73).\textsuperscript{32} Regression analysis also showed the use of sugammadex itself was associated with a reduction of in-hospital respiratory diagnoses (OR=0.26; 95% CI: 0.08-0.94; P=0.04). Increasing age (OR=1.05; 1.02-1.08; P<0.01) and the use of more than one non-depolarizing muscle relaxant (OR=21.2; 2.78-161.2; P<0.01) were both associated with an increase in the likelihood of a respiratory diagnosis.

The binomial logistic regression model fit well with the data using the Hosmer-Lemeshow goodness of fit test ($\chi^2=6.74$, df=8; P=0.57). The model explained 19.7% ($\text{Nagelkerke } R^2$) of the variance in respiratory diagnoses and correctly classified 97.6% of cases.

Figure 1 shows the use of muscle relaxants in the two cohorts. Where it was used, the mean dose of rocuronium was unchanged from 54.6±22.9 mg to 54.7±24.3 mg per case (P=0.22), while vecuronium use per case was 8.0±3.3 mg in the 2010 cohort and 8.9±5.5 mg in the 2011 cohort (P=0.06). There was no difference in the use of NMT monitoring between the two groups (12.7% vs. 12.7%, P=0.98).

Figure 2 shows the use of reversal agents in the two cohorts.

There was a significant difference in the type of anesthetic between the two cohorts, with the percentage of patients receiving volatile based general anesthesia increasing from 69.9% to 77.5% (P=0.01), while TIV A decreased from 27.9 to 21.8% (P=0.03). Combined TIV A/volatile anesthesia was unchanged (2.2 vs. 0.7%, P=0.07).

Table I.—Number of cases and demographic data of cases analyzed.

<table>
<thead>
<tr>
<th></th>
<th>2010 (pre-sugammadex)</th>
<th>2011 (post-sugammadex)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unable to get files</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Cases with relaxant used</td>
<td>362 (70.4%)</td>
<td>560 (73.0%)</td>
<td>0.31</td>
</tr>
<tr>
<td>N. patients</td>
<td>350</td>
<td>526</td>
<td></td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>50.5±20.3</td>
<td>50.2±20.0</td>
<td>0.78</td>
</tr>
<tr>
<td>Male</td>
<td>51.1%</td>
<td>51.4%</td>
<td>0.92</td>
</tr>
<tr>
<td>ASA Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA 1</td>
<td>102 (28.2%)</td>
<td>184 (32.9%)</td>
<td>0.13</td>
</tr>
<tr>
<td>ASA 2</td>
<td>163 (45.0%)</td>
<td>251 (44.8%)</td>
<td>0.95</td>
</tr>
<tr>
<td>ASA 3</td>
<td>90 (24.9%)</td>
<td>114 (20.4%)</td>
<td>0.11</td>
</tr>
<tr>
<td>ASA 4</td>
<td>7 (1.9%)</td>
<td>11 (2.0%)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

All values are presented as number (percentage of cases), where no otherwise specified.

Figure 1.—Difference between two cohorts in percentage use of different neuromuscular blocking agents before and after the routine introduction of sugammadex.

*Significant difference between the two cohorts (P<0.05).
Fewer patients were transferred intubated to the ICU; 7/560 (1.3%) in the 2011 cohort, compared with 20/362 (5.5%) cases in 2010 (P<0.001).

The incidence of respiratory complications in those patients who went to the PACU unit is shown in Table II. Of note, the unrestricted use of sugammadex was associated with a significant decrease in the need for manual airway support in the PACU unit.

The total cost of each NMBD and reversal agent per 100 patients is presented in Table III. There was an overall cost difference of AU$ 1390.86 per 100 patients between the two cohorts, with the increased cost predominantly due to the increased use of sugammadex in the 2011 cohort.

**Discussion**

The use of sugammadex has been associated with a reduced incidence of RPOC, and RPOC has been associated with postoperative morbidity, but there is little evidence directly linking sugammadex use to a reduction in postoperative morbidity.

We found that the unrestricted availability of sugammadex for neuromuscular blockade reversal was associated with a reduction in the risk of an in-hospital respiratory diagnosis by 79%. In addition, the use of sugammadex itself was associated with a 74% reduction in the odds of in-hospital respiratory diagnosis.

The incidence of postoperative respiratory complications in our study was based on documentation on the medical coding sheet, which would not be expected to capture “mild” cases of respiratory impairment. This would explain why our rate of respiratory diagnoses of 3.3% to 1.6% sits on the lower end of with rates reported in the literature of 2-40%.

Several other positive postoperative outcomes were realized. The first of these was a significant reduction in the need for manual airway support in PACU in the 2011 cohort compared to the 2010 cohort (1.08% versus 3.22%). We hypothesize that this is due to less RPOC, leading to improved muscle tone and maintenance of a patent airway by patients. Of note, the reduction in documented manu-

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**Table II: PACU events in the cohort prior to (2010) and following (2011) the introduction of routine sugammadex use.**

<table>
<thead>
<tr>
<th>Event</th>
<th>2010</th>
<th>2011</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any documented airway complication in PACU</td>
<td>1 (0.29%)</td>
<td>8 (1.45%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Unplanned ICU admission</td>
<td>1 (0.29%)</td>
<td>5 (0.90%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Arrival in PACU with ETT</td>
<td>3 (0.88%)</td>
<td>1 (0.18%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Need for reintubation in PACU</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Need for manual airway support</td>
<td>11 (3.22%)</td>
<td>6 (1.08%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Need for oropharyngeal airway</td>
<td>3 (0.88%)</td>
<td>1 (0.18%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Documented SpO₂&lt;90%</td>
<td>3 (0.88%)</td>
<td>4 (0.72%)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Values are presented as number (percentage of cases). Significance testing into differences between the two group (χ² contingency tables, or using Fisher’s exact test where any N.<5).

**Table III: Total cost of relaxant and reversal agents per 100 patients in the period prior to (2010) and following (2011) the introduction of routine availability of sugammadex.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>2010 Cohort</th>
<th>2011 Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rocuronium</td>
<td>AU$ 96.26</td>
<td>AU$ 262.45</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>AU$ 1331.81</td>
<td>AU$ 572.13</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>AU$ 111.28</td>
<td>AU$ 27.02</td>
</tr>
<tr>
<td>Neo/Glyco/Atropine</td>
<td>AU$ 601.09</td>
<td>AU$ 59.68</td>
</tr>
<tr>
<td>Sugammadex</td>
<td>AU$ 36.00</td>
<td>AU$ 2646</td>
</tr>
<tr>
<td>Total cost</td>
<td>AU$ 2176.43</td>
<td>AU$ 3567.29</td>
</tr>
</tbody>
</table>

*Significant difference between the two cohorts (P<0.05).
al airway support in the PACU from 2010 to 2011 coincided with the changing of hospital PACU data entry from a paper to a computer based system. Potentially, the change in data entry systems may have led to a reduced rate of documentation of the use of manual airway support (but not of any of the other measured PACU events), accounting for the fewer reported cases. On the other hand, it could also have lead to an increased rate of documentation and the true reduction in the need for airway support may be greater than shown.

Another somewhat unexpected finding was a significant decrease in the number of patients transferred directly to the ICU intubated in the 2011 cohort compared with the 2010 cohort (1.3% versus 5.5%). This may reflect a more aggressive extubation strategy in 2011, i.e., sicker patients who would normally be left intubated are given a “trial of extubation” with increased physician confidence in the reversal technique. There were no patients in either cohort requiring re-intubation in the PACU or in unplanned ICU admission between the two groups.

With the introduction of unrestricted availability of sugammadex, where changes in the clinical practice of the anesthetists and the type of anesthetic administered. The first is the change in the use of NMBDs. There was a large increase (44.2%) in the use of rocuronium, with a decrease in the use of vecuronium (32%) and cisatracurium (11.1%). The most likely reason for this likely the high affinity of sugammadex for reversal of rocuronium-induced neuromuscular blockade.35 There was no change in the use of suxamethonium as an initial NMBD (7.2% versus 9.1%, P=0.3), suggesting that despite having a fast onset and a rapid and effective reversal agent, rocuronium was not viewed at this institution as an acceptable substitution for suxamethonium in the performance of a rapid sequence induction.

In conjunction with the change in NMBD choice over the studied time period, was a significant move toward the use of sugammadex for NMBD reversal in place of a more traditional combination of neostigmine/atropine or neostigmine/glycopyrrolate. The use of sugammadex increased from 0.8% in 2010 to 58.8% in 2011. In both cohorts, there was an absence of documented reversal in almost 40% of cases.

Along with this change in choice of NMBDs and reversal agents, there was a significant difference in the type of anesthesia administered. Between the cohorts, the use of volatile anesthesia increased from 69.9% to 77.5%, while there was a decrease in TIVA from 27.9% to 21.8%. The rate of combined TIVA/volatile anesthesia did not change. The reason for this is unclear. It has been shown that anesthesia with sevoflurane, when compared with a TIVA anesthetic, results in significantly greater impairment in bronchociliary clearance, which could have implications for postoperative respiratory complications.36 We showed a reduction in respiratory diagnoses despite the reduction in TIVA anesthesia, and regression analysis did not show an association between the type of anesthesia given and the occurrence of a respiratory diagnosis.

We did not find any change in the use of formal NMT monitoring (12.7% versus 12.7%, P=0.98) between the two cohorts. In keeping with previous studies, the overall use of NMB monitoring was low.37 Suggestions have been made that the lack of routine monitoring of neuromuscular function is the single most important contributing factor contributing to RPOC.38, 39 However, a meta-analysis in failed to show any reduction in ROPC with NMT monitoring.15 We also did not show any association between the use of NMT monitoring and postoperative respiratory diagnosis.

The introduction of routine sugammadex was associated with an extra cost of AU$ 1390.86 per 100 patients. However, with the average increased hospital costs (reported in 2006) of postoperative complications ranging from US$ 4868 for ventral incisional hernia repair to US$ 20,486 for colonic resection procedures,40 the prevention of respiratory complications in one patient would potentially offset the extra cost in over one hundred patients.

There are several potential limitations to our study. Firstly, the results may not be generaliz-
able to all surgical patients, as this study only included general surgical and ENT cases. Secondly, despite correcting for known confounders, there is always the possibility that other unmeasured differences between the groups exist that help explain the difference between groups. Thirdly, and most importantly, the retrospective nature of this study means we can only postulate an association between the routine use of sugammadex and the decrease in postoperative respiratory complications rather establish a causative effect.

Conclusions

This paper provides evidence that unrestricted sugammadex use is associated with a reduction in postoperative respiratory morbidity. This unrestricted use is associated with an increased drug cost, but this would likely be offset by potential savings in the treatment of postoperative respiratory complications. The data presented is retrospective in nature and relies on medical record documentation and needs to be validated by a well-designed, prospective randomized trial.

Key messages

- Residual paralysis following intermediate duration muscle relaxants is a common problem.
- Residual paralysis has been linked with postoperative morbidity.
- Sugammadex has been shown to reduce the rate of residual paralysis when compared with neostigmine.
- This paper provides evidence that sugammadex use is associated with reduced postoperative morbidity when compared with neostigmine or no reversal.

References


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

Acknowledgments.—Dr Blake Kesby and Dr Simon Collins were involved in data collection.


Authors' contributions.—Benjamin L. Olesnicky was involved in the design of the study, data collection, collation and analysis and preparation of the manuscript. Catherine Traill was involved in data collection, collation and preparation of the manuscript. Frank B. Marroquin-Harris was involved in data collation, analysis and preparation of the manuscript.

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Altered liver function in patients undergoing veno-arterial extracorporeal membrane oxygenation therapy

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ABSTRACT

BACKGROUND: Multiple organ dysfunction can occur in patients undergoing veno-arterial extracorporeal membrane oxygenation (VA-ECMO); however, liver function has not been well studied in this setting.

METHODS: In a review of our institutional ECMO database (N.=162), we collected aspartate (AST) and alanine (ALT) transaminases, total bilirubin and international normalized ratio (INR) at time of ECMO initiation (baseline) and once daily during therapy in patients who survived for at least 24 hours. Elevated liver enzymes (ELE) were defined if AST and/or ALT were >200 U/L, and acute liver failure (ALF) as the presence of an INR ≥1.5, new onset encephalopathy and an elevated total bilirubin concentrations.

RESULTS: On a total of 80 patients undergoing VA-ECMO, 69 patients met the inclusion criteria (cardiogenic shock, N.=52; refractory cardiac arrest, N.=15; cardiac failure following severe ARDS, N.=2). Of them, 45 (65%) had early ELE after ECMO initiation (median highest AST and ALT were 528 [251-2606] U/L and 513 [130-1031] U/L, respectively). Two thirds of patients with ELE (N.=30) had a progressive reduction in AST and ALT, but the levels were normalized only after 5 (5-6) days. Among patients with ELE, 21/45 (47%) had AST and/or ALT levels above >1000 U/L. A total of 14/69 (20%) patients developed ALF. However, mortality rate was not significantly higher in patients with ELE or ALF when compared to others.

CONCLUSIONS: A substantial proportion of patients needing VA-ECMO have early ELE, which usually improves over days. The prognostic implications are not evident.


Key words: Extracorporeal membrane oxygenation - Liver failure - Enzymes - Treatment outcome.

Since the first successful use of an artificial heart/lung apparatus by John Gibbon in 1953, the extracorporeal circulation technique has been optimized and its applicability expanded to multiple clinical settings. More recently, extracorporeal membrane oxygenation (ECMO) has become increasingly used in patients of severe cardio-pulmonary failure not responsive to conventional therapy. The improvement in equipment and increased experience in several specialized high-volume centers has allowed the extension of its indication...
to other conditions. According to the Extracorporeal Life Support Organization registry, ECMO has been used in over 73,000 cases since 1990; 25% of them were adult critically ill patients, 70% were eventually weaned and 58% were discharged or transferred to a rehabilitation center after the ICU stay.8

Patients receiving ECMO often have other organ dysfunctions, which may be, at least in part, due to the low cardiac output state and severe hypoxemia before ECMO initiation.9 Moreover, prolonged ECMO therapy is often complicated by a systemic inflammatory reaction with persistent vasoplenia and coagulopathy, which can contribute to the development of multiple organ failure.10 As an example, neurological complications related to the ECMO implantation (e.g., seizures, cerebral infarctions or hemorrhage) can be observed in 5-8% of adult patients11 and are associated with lower survival rates. Acute kidney injury (AKI) may develop in more than 30% of patients receiving ECMO9 and has been also associated with a worse outcome.

Few data are available on the impact of altered liver function in patients with ECMO. In a retrospective analysis of 69 consecutive adult patients treated with veno-arterial ECMO (VA-ECMO), Heilmann et al. reported that hepatic failure (defined as increased transaminases and bilirubin), even when occurring concomitantly with increased inflammatory state and altered acid–base balance, was not associated with poor outcome.13 In a more recent single-center retrospective cohort study including a total of 132 patients (N.=54 on VA-ECMO, N.=64 on veno-venous ECMO, N.=14 with sequential therapy), Mazzzeffi et al. reported that approximately 10% developed acute liver failure (defined as increased bilirubin and INR with acute encephalopathy) and had a high mortality.14 Chen et al. showed that in patients suffering from acute myocardial infarction complicated with refractory shock necessitating VA-ECMO, the combination of renal, hepatic (e.g. bilirubin ≥6.0 mg/dL) and neurological dysfunction was more common in non-survivors than in survivors.15

Considering the limited and conflicting findings in this setting and the large heterogeneity in the definition of liver dysfunction, the aim of this study was to evaluate the occurrence and time-course of ischemic liver dysfunction in adult patients undergoing VA-ECMO as well as its impact on survival.

Materials and methods

Study population

This study was performed in the 35-bed Department of Medico-Surgical Intensive Care of the Erasme University Hospital in Brussels, Belgium. In this institution, the ECMO program was initiated in November 2008 and substantially increased (>35 cases/year) since 2010. We reviewed our database of adult (>18 years) patients who were treated with VA-ECMO from November 2008 until December 2013. We excluded from the analysis patients who survived less than 24 hours to analyze the time-course of liver function and to avoid other factors (e.g., massive bleeding, decision of life-sustaining therapies in case of brain death) than liver dysfunction to influence patients’ outcome. The study was approved by the Ethics Committee of Erasme Hospital, which waived the need for informed consent.

ECMO management

Indications for ECMO were recorded in the database. VA-ECMO was mainly implanted with a percutaneous procedure using heparin-coated cannulas (18-22 Fr arterial cannula and 22-25 Fr venous cannula, Medtronic, Minneapolis MN, USA). However, in patients who could not be weaned from cardio-pulmonary bypass (CPB), a central cannulation was performed directly by cardiac surgeons. A centrifugal blood pump (Revolution blood pump, Sorin, Milan, Italy) was initially set at a blood flow of 3.5-5.0 L/min (based on the body surface area). ECMO priming consisted of 700 mL of Plasmalyte solution (Baxter Healthcare Corporation, Deerfield, IL, USA). In patients showing clinical signs of limb hypoperfusion, the leg was perfused with an anterograde sin-
gle lumen 8-Fr catheter (Arrow Inc., Reading, PA, USA) at the end of ECMO implantation. A heat exchanger (HICO Variotherm 550; Hiertz, Cologne, Germany) was used on the ECMO circuit to maintain body temperature at 37 °C (or at 33 °C for 24 hours in patients after cardiac arrest). Monitoring of cardiac function, and in particular the impact of ECMO on left ventricular afterload, was performed in all patients using repeated echocardiography and/or a pulmonary artery catheter. Systemic anticoagulation was achieved by intravenous administration of unfractionated heparin; however, anticoagulation was not given to patients resuscitated from cardiac arrest during the first 24 hours after ECMO implantation or in those patients having bleeding and needing red blood cell transfusions. Mean arterial pressure (MAP) was maintained >70 mmHg by adjusting ECMO blood flow (up to a maximum of 5 L/min) and/or by giving norepinephrine. Patients with major bleeding were treated with fluids and blood products (to keep the hemoglobin level >7 g/dL and the ratio between RBC and fresh frozen plasma close to 1 after the fourth unit).

Data collection

We collected demographic characteristics, presence of pre-existing chronic diseases (on hospital or ICU admission, whichever came first) and admission diagnosis for all patients. Severity of illness was assessed on the day 1 of ECMO using the Acute Physiology and Chronic Health Evaluation (APACHE) II Score and the Sequential Organ Failure Assessment (SOFA) scores. We recorded the need for mechanical ventilation (MV), vasoactive drugs, blood transfusions and the occurrence of systemic complications [massive bleeding, infections (site and pathogens), hemolysis, disseminated intravascular coagulation (DIC)], length of intensive care unit (ICU) stay and overall ICU mortality. ECMO data were also recorded, including blood flow, gas and oxygen flow, multiple runs and duration of ECMO support. To assess liver function, we collected aspartate (AST) and alanine (ALT) transaminases, lactate dehydrogenase (LDH, normal values < 200 UI/L), prothrombin time (PT, normal values >70%), the international normalized ratio (INR, normal values ≤1.2), total bilirubin (normal values ≤1.2 mg/dL) and fibrinogen (normal values >150 mg/dL) at time of ECMO initiation (baseline) and then once daily during the following days during ECMO therapy. We also collected admission and maximal concentrations of total creatine phosphokinase (CK) and troponin T (TnT), as markers of concomitant muscular and myocardial injury.

Definitions

Considering that the main mechanisms of liver damage in VA-ECMO patients is severe hypoperfusion or shock state, we used liver transaminase enzymes to characterize the ischemic injury. Elevated liver enzymes (ELE) were arbitrarily defined by the elevation of AST and/or ALT were >200 UI/L. This cut-off was selected to identify “mild” ischemic liver injury in this setting. Among patients with ELE and according to recommended cut-offs, we defined “hypoxic hepatitis” (HH) as an increase in AST and/or ALT above 20 times the upper normal ranges (≤50 UI/L), e.g., >1000 UI/L. We also reported the time to the highest AST and/or ALT values since ECMO implementation. We considered as “normalized” liver enzymes as AST/ALT value <100 UI/L, as most of these patients may present with hemolysis and persistent transaminase above 50 UI/L, independently from liver hypoxia. The time to normalized liver enzymes was also recorded. Finally, as AST/ALT assessment is not accurate to provide significant information on liver function, we defined ALF using previously published criteria, which included an INR ≥1.5, new onset encephalopathy (defined as a patient not obeying to orders) and an elevated total bilirubin in absence of chronic liver disease.

Massive bleeding was defined as transfusion of >10 RBC units in 24 hours or >4 RBC units in 1 hour. DIC was defined according to standard criteria. Acute kidney injury
(AKI) was defined according to AKIN criteria. Hemolysis was defined as an LDH ≥600 IU/L and total bilirubin >1.2 mg/dL, without considering the reticulocyte count as erythropoiesis may be impaired during critical illness. Potential hepatotoxic drugs/interventions included paracetamol, β-lactams or quinolones, trimetoprim-sulfametoxazol (TMP-SMZ), isoniazid, azoles, metronidazole, amiodarone, some chemotherapy, parenteral nutrition and anti-epileptic drugs.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 21 for Windows. Descriptive statistics were computed for all study variables. A Kolmogorov-Smirnov Test was used, and histograms and normal-quartile plots were examined to verify the normality of distribution of continuous variables. Data are presented as count (percentage), mean±SD or median (25th-75th percentiles). Differences between groups were assessed using a Fisher’s Exact Test for categorical variables and Student t-test or a Mann-Whitney for continuous variables, if normally or not normally distributed, respectively. Data from repeated measures were analyzed using a two-way analysis of variance (ANOVA), with correction for missing values, followed by a Bonferroni post-hoc analysis to evaluate differences between groups for each time point (parametric tests). A Friedman Test for repeated measurements in non-parametric variables was used, followed by a post-hoc Dunn’s Test to analyze differences at each time point. A P<0.05 was considered as statistically significant.

Results

On a total of N.=162 included in our database, 82 patients underwent veno-venous ECMO and were then excluded. Among the 80 patients treated with VA-ECMO, 11 were excluded because of early death (10 after ECPR) and 69 patients were eventually analyzed (Table I); 52 patients had cardiogenic shock, 15 refractory cardiac arrest and 2 severe ARDS associated with myocardial depression. VA ECMO included peripheral cannulation (femoro-femoral) except in 3 patients after cardiac surgery (central ECMO). The median duration of ECMO was 6 (3-9) days and the ICU length of stay was 12 (7-21) days. In 13 patients (19%) treated for refractory cardiac arrest, 24-hour hypothermia (body temperature 32-34 °C) was used during ECMO. The median of APACHE II Score was 23; only two patients had pre-existing liver cirrhosis (both Child-Pugh A). Overall ICU mortality was 54% (N.=37). At ECMO implantation, all patients were on mechanical ventilation, while 66 (96%) and 58 (84%) were on vasopressor and inotropic therapy, respectively. Median lactate levels were 5.0 (2.9-9.4) meq/L. The median initial ECMO blood flow, gas flow and FiO2 were 4.0 (3.0-4.0) l/mim, 3.0 (2.0-4.5) l/min and 1.0 (0.8-1.0), respectively. A total of 45 (65%) patients had ELE; median AST and ALT at ECMO initiation were 92 (48-503) UI/L and 81 (33-283) UI/L, respectively while the highest AST and ALT values during ECMO were 528 (251-2606) UI/L and 513 (130-1031) UI/L, respectively. The median time to ELE development was 2 (0-2) days and the time to the highest AST/ALT values was 2 (1-3) days. Figure 1 shows the time-course over the first 3 days of AST, ALT, bilirubin and INR of patients with and without ELE; no significant difference in INR and bilirubin between groups was observed. Also, fibrinogen levels were similar between ELE and no-ELE patients (on admission: 215 (177-322) mg/dL vs. 236 (176-307) mg/dL; lowest value: 139 (89-195) mg/dL vs. 145 (100-223) mg/dL, respectively). Of all the patients with ELE, 30 (67%) showed a progressive reduction in AST and ALT; however the median time to normalized AST/ALT levels was 5 (4-6) days. Patients with ELE had similar clinical and ECMO characteristics than those without ELE (Tables I, II). Overall mortality rate was higher, although not statistically significant, in ELE patients than others (27/45, 60% vs. 10/24, 42%, P=0.21, Figure 2).

Among the 45 patients with ELE, 25 (56%) had the criteria for HH. APACHE II score — 23 (16-28) vs. 25 (22-28) — on ECMO inser-
Table I.—Characteristics of the study population. Data are reported as count (percentage) or median (IQRs).

<table>
<thead>
<tr>
<th></th>
<th>All patients (N.=69)</th>
<th>ELE (N.=45)</th>
<th>No-ELE (N.=24)</th>
<th>ALF (N.=14)</th>
<th>No-ALF (N.=55)</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>53 (40-60)</td>
<td>52 (39-62)</td>
<td>54 (42-58)</td>
<td>53 (38-61)</td>
<td>53 (41-59)</td>
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<td>Body weight, kg</td>
<td>75 (70-80)</td>
<td>75 (70-82)</td>
<td>70 (67-85)</td>
<td>73 (67-82)</td>
<td>75 (70-80)</td>
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<td>Male, N. (%)</td>
<td>48 (70)</td>
<td>31 (69)</td>
<td>17 (71)</td>
<td>9 (64)</td>
<td>39 (71)</td>
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<td>Medical admission, N. (%)</td>
<td>61 (88)</td>
<td>40 (89)</td>
<td>21 (88)</td>
<td>12 (86)</td>
<td>49 (89)</td>
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<td>Comorbid diseases</td>
<td></td>
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<td>Heart disease, N. (%)</td>
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<td>5 (11)</td>
<td>3 (13)</td>
<td>2 (14)</td>
<td>6 (11)</td>
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<tr>
<td>Diabetes, N. (%)</td>
<td>6 (9)</td>
<td>4 (9)</td>
<td>2 (8)</td>
<td>1 (7)</td>
<td>5 (9)</td>
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<tr>
<td>COPD/asthma, N. (%)</td>
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<td>2 (4)</td>
<td>1 (4)</td>
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<td>3 (5)</td>
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<tr>
<td>Chronic renal disease, N. (%)</td>
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<td>1 (2)</td>
<td>1 (4)</td>
<td>-</td>
<td>2 (4)</td>
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<tr>
<td>Liver cirrhosis, N. (%)</td>
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<td>1 (2)</td>
<td>1 (4)</td>
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<td>1 (2)</td>
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<td>Cancer, N. (%)</td>
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<td>3 (7)</td>
<td>4 (17)</td>
<td>1 (7)</td>
<td>6 (11)</td>
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<tr>
<td>Immunosuppressive agents, N. (%)</td>
<td>9 (13)</td>
<td>4 (9)</td>
<td>5 (21)</td>
<td>2 (14)</td>
<td>7 (12)</td>
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<tr>
<td>On ECMO insertion</td>
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<tr>
<td>APACHE II Score</td>
<td>24 (18-28)</td>
<td>24 (18-28)</td>
<td>23 (19-26)</td>
<td>25 (17-28)</td>
<td>23 (19-29)</td>
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<td>Lactate, meq/L</td>
<td>5.0 (2.9-9.4)</td>
<td>5.0 (2.9-9.4)</td>
<td>6.8 (3.1-9.1)</td>
<td>3.2 (2.4-8.9)</td>
<td>6.1 (3.0-9.4)</td>
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<td>ECPR, N. (%)</td>
<td>15 (22)</td>
<td>10 (22)</td>
<td>6 (25)</td>
<td>1 (7)</td>
<td>14 (25)</td>
</tr>
<tr>
<td>CK, U/L</td>
<td>813 (487-1765)</td>
<td>813 (567-1077)</td>
<td>762 (436-1796)</td>
<td>837 (713-1887)</td>
<td>813 (452-1061)</td>
</tr>
<tr>
<td>TrT, ng/L</td>
<td>215 (115-431)</td>
<td>217 (105-415)</td>
<td>212 (167-474)</td>
<td>177 (120-403)</td>
<td>217 (124-438)</td>
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<tr>
<td>During ECMO therapy</td>
<td></td>
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<tr>
<td>Infections, N. (%)</td>
<td>51 (74)</td>
<td>32 (71)</td>
<td>20 (83)</td>
<td>12 (86)</td>
<td>39 (71)</td>
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<td>Severe bleeding, N. (%)</td>
<td>30 (43)</td>
<td>18 (40)</td>
<td>12 (50)</td>
<td>4 (29)</td>
<td>26 (47)</td>
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<tr>
<td>DIC, N. (%)</td>
<td>11 (16)</td>
<td>8 (18)</td>
<td>3 (13)</td>
<td>1 (7)</td>
<td>10 (18)</td>
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<tr>
<td>Hemolysis, N. (%)</td>
<td>3 (4)</td>
<td>2 (4)</td>
<td>1 (4)</td>
<td>1 (7)</td>
<td>2 (4)</td>
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<tr>
<td>Total RBC transfused, N.</td>
<td>6 (3-9)</td>
<td>5 (3-10)</td>
<td>6 (4-9)</td>
<td>5 (3-8)</td>
<td>6 (4-10)</td>
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<tr>
<td>Total FFP transfused, N.</td>
<td>7 (4-11)</td>
<td>7 (4-10)</td>
<td>7 (3-11)</td>
<td>6 (3-11)</td>
<td>7 (3-11)</td>
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<tr>
<td>Norepinephrine therapy, N. (%)</td>
<td>66 (96)</td>
<td>42 (93)</td>
<td>24 (100)</td>
<td>14 (100)</td>
<td>52 (95)</td>
</tr>
<tr>
<td>Maximum NE dose, mcg/min</td>
<td>70 (25-137)</td>
<td>83 (30-128)</td>
<td>45 (19-180)</td>
<td>26 (24-106)</td>
<td>78 (25-141)</td>
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<td>Dobutamine therapy, N. (%)</td>
<td>58 (84)</td>
<td>39 (87)</td>
<td>19 (79)</td>
<td>12 (86)</td>
<td>46 (84)</td>
</tr>
<tr>
<td>Maximum DB therapy, mcg/kg/min</td>
<td>15 (10-20)</td>
<td>18 (10-20)</td>
<td>14 (5-20)</td>
<td>20 (12-20)</td>
<td>15 (10-20)</td>
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<tr>
<td>MV, N. (%)</td>
<td>69 (100)</td>
<td>45 (100)</td>
<td>24 (100)</td>
<td>14 (100)</td>
<td>55 (100)</td>
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<tr>
<td>Hypothermia, N. (%)</td>
<td>13 (19)</td>
<td>7 (16)</td>
<td>7 (29)</td>
<td>2 (14)</td>
<td>11 (20)</td>
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<tr>
<td>AKI, N. (%)</td>
<td>39 (57)</td>
<td>26 (58)</td>
<td>12 (50)</td>
<td>7 (50)</td>
<td>32 (58)</td>
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<tr>
<td>CRRT, N. (%)</td>
<td>32 (46)</td>
<td>21 (47)</td>
<td>10 (42)</td>
<td>5 (36)</td>
<td>27 (49)</td>
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<tr>
<td>Duration of ECMO, days</td>
<td>6 (3-9)</td>
<td>6 (3-9)</td>
<td>5 (3-8)</td>
<td>7 (4-10)</td>
<td>5 (3-9)</td>
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<tr>
<td>Multiple ECMO, N. (%)</td>
<td>15 (22)</td>
<td>10 (22)</td>
<td>4 (16)</td>
<td>2 (14)</td>
<td>13 (24)</td>
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<tr>
<td>Peak TrT, ng/L</td>
<td>389 (215-678)</td>
<td>355 (210-678)</td>
<td>413 (264-695)</td>
<td>380 (221-750)</td>
<td>389 (216-675)</td>
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<tr>
<td>At least one hepatotoxic drug, N. (%)</td>
<td>69 (100)</td>
<td>45 (100)</td>
<td>24 (100)</td>
<td>14 (100)</td>
<td>55 (100)</td>
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<tr>
<td>Paracetamol, N. (%)</td>
<td>30 (44)</td>
<td>19 (42)</td>
<td>12 (50)</td>
<td>4 (29)</td>
<td>26 (47)</td>
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<tr>
<td>β-lactams/quinolones, N. (%)</td>
<td>66 (96)</td>
<td>42 (93)</td>
<td>24 (100)</td>
<td>13 (93)</td>
<td>53 (96)</td>
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<td>SMT/TMT, N. (%)</td>
<td>1 (1)</td>
<td>-</td>
<td>1 (4)</td>
<td>-</td>
<td>1 (2)</td>
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<tr>
<td>Isoniazid, N. (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Azoles, N. (%)</td>
<td>9 (13)</td>
<td>6 (13)</td>
<td>3 (13)</td>
<td>-</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Metronidazole, N. (%)</td>
<td>4 (6)</td>
<td>1 (2)</td>
<td>3 (13)</td>
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<td>4 (7)</td>
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<tr>
<td>Amiodarone, N. (%)</td>
<td>43 (62)</td>
<td>27 (60)</td>
<td>15 (63)</td>
<td>12 (86)</td>
<td>31 (56)</td>
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<tr>
<td>Chemotherapy, N. (%)</td>
<td>7 (10)</td>
<td>3 (7)</td>
<td>4 (17)</td>
<td>1 (7)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>PN, N. (%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AEDs, N. (%)</td>
<td>6 (9)</td>
<td>4 (9)</td>
<td>3 (13)</td>
<td>2 (14)</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>

Outcomes:

- ELE, N. (%) 45 (65)
- No-ELE, N. (%) 45 (100)
- ALF, N. (%) 14 (20)
- No-ALF, N. (%) 11 (24)
- HH, N. (%) 25 (39)
- ICU length of stay, days 12 (7-21)
- ICU mortality, N. (%) 37 (54)

COFP: chronic obstructive pulmonary disease; SMT/TMT: sulfamethoxazole/trimethoprim; APACHE: acute physiology and chronic health evaluation; ECPR: extracorporeal cardiopulmonary resuscitation; DIC: disseminated intravascular coagulation; MV: mechanical ventilation; AKI: acute kidney injury; CRRT: continuous renal replacement therapy; ELE: elevated liver enzymes; HH: hypoxic hepatitis; ALF: acute liver failure; ICU: Intensive Care Unit; PN: parenteral nutrition; AEDs: antiepileptic drugs; RBC: red blood cells; FFP: fresh frozen plasma; NE: norepinephrine; DB: dobutamine; CK: creatine kinase; TrT: Troponin T.

*Over the first 3 days of ECMO. P<0.05 (ELE vs. no-ELE/ALF vs. no-ALF).
tion as well as the occurrence of ECPR (6/25 vs. 4/20), bleeding (12/25 vs. 6/20), DIC (5/25 vs. 3/20) or the use of vasopressors (22/25 vs. 20/20) and inotropic agents (21/25 vs. 18/20) were similar between ELE patients with and without HH. All other demographics and co-morbidities were also similar between groups (data not shown). Bilirubin (on admission: 1.3 [0.8-2.0] mg/dL vs. 0.6 [0.4-1.2] mg/dL, P=0.002; highest value: 4.2 [2.4-9.9] mg/dL vs. 1.5 [0.9-2.4] mg/dL, P<0.001) and INR levels (on admission: 2.0 [1.5-2.8] vs. 1.5 [1.1-1.8], P=0.001; highest value: 3.6 [2.7-6.1] vs. 1.9 [1.6-2.8], P<0.001) were higher in patients with ELE and HH when compared to those with ELE without HH, while fibrinogen levels were similar. The proportion of patients showing normalized liver enzymes was lower, although not statistically different, in ELE patients with HH when compared to ELE without HH (14/25 vs. 16/20; P=0.11), while the time to normalized liver enzymes was similar: 5 (4-6) vs. 5 (4-5) days, respectively. Mortality rate was higher, although not statistically significant, in ELE patients with HH when compared to those with ELE without HH (18/25, 72% vs. 9/20, 45%, P=0.12).

A total of 14 (20%) patients had ALF; patients with ALF had similar characteristics than those without ALF (Tables I, II). However, initial AST (591 [47-2026] UI/L vs. 80 [44-312] UI/L; P=0.001) and ALT (377 [43-1983] vs. 65 [26-162] UI/L; P=0.002) values were higher in ALF patients than others, while total bilirubin and INR were similar. The median time to ALF development was 2 (1-2) days. Among those 14 patients, 12 (86%) had the criteria for HH. Mortality rate was similar between patients with and without ALF (7/14, 50% vs. 30/55, 55%, P=0.77).

Discussion
In our experience, ELE occurs in about two thirds of patients undergoing VA-ECMO, and 56% of them also have the criteria for HH. Also, ALF occurred in 20% of patients, mostly in patients with HH. Similar demographics, clinical, hemodynamic and ECMO character-
significant reduction in the portal vein flow, which will contribute to diminished hepatic oxygen supply and cause centro-lobular damage.\textsuperscript{25} The biological hallmark of hypoxic liver cell necrosis is a massive increase in serum ast/alt levels, which exceeds >10 times the upper limit of normal values in half of patients.\textsuperscript{23} Overall, the survival to hospital discharge of patients suffering from HH is estimated around 50%.\textsuperscript{23} Moreover, HH is also a known and treatable cause of ALF; however, the diagnosis of ALF remains challenging as some of its typical biological alterations, such as spontaneous hypoglycemia, high levels of serum ammonia, lactic acidosis and coagulation disorders, are not always present or distinguishable from liver abnormalities due to the underlying critical illness.\textsuperscript{26} In our study, elevation of ast and alt was frequent and in more than half of cases these abnormalities met the criteria for HH.

## Table II

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>ANOVA *</th>
</tr>
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<tbody>
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<td>MAP, mmHg</td>
<td>ELE</td>
<td>76 (71-86)</td>
<td>74 (70-85)</td>
<td>81 (73-86)</td>
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<tr>
<td></td>
<td>No-ELE</td>
<td>80 (74-88)</td>
<td>73 (69-81)</td>
<td>79 (72-89)</td>
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<td></td>
<td>ALF</td>
<td>83 (75-86)</td>
<td>73 (67-77)</td>
<td>80 (67-84)</td>
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<td>74 (70-85)</td>
<td>80 (72-88)</td>
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<tr>
<td>HR, bpm</td>
<td>ELE</td>
<td>90 (77-108)</td>
<td>88 (76-109)</td>
<td>85 (72-103)</td>
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<td>85 (78-109)</td>
<td>99 (79-113)</td>
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<td>84 (68-119)</td>
<td>91 (78-115)</td>
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<td>88 (77-105)</td>
<td>85 (71-105)</td>
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<td>CVP, mmHg</td>
<td>ELE</td>
<td>12 (9-14)</td>
<td>12 (10-17)</td>
<td>12 (9-15)</td>
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<td>12 (10-17)</td>
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<td>Lactate, mEq/L</td>
<td>ELE</td>
<td>5.0 (2.9-9.4)</td>
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<td>9.0 (8.4-9.6)</td>
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<td>ELE</td>
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<td>4.1 (3.4-4.2)</td>
<td>4.0 (3.4-4.3)</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>No-ALF</td>
<td>3.6 (3.1-4.1)</td>
<td>4.0 (3.2-4.1)</td>
<td>4.0 (3.1-4.1)</td>
<td></td>
</tr>
<tr>
<td>ECMO FiO2</td>
<td>ELE</td>
<td>1.0 (0.5-1.0)</td>
<td>1.0 (0.6-1.0)</td>
<td>1.0 (0.6-1.0)</td>
<td>0.74</td>
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<tr>
<td></td>
<td>No-ELE</td>
<td>0.7 (0.5-1.0)</td>
<td>0.7 (0.6-0.8)</td>
<td>0.7 (0.6-0.8)</td>
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<tr>
<td></td>
<td>ALF</td>
<td>1.0 (0.6-0.8)</td>
<td>1.0 (0.6-0.7)</td>
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<td>No-ALF</td>
<td>1.0 (0.5-1.0)</td>
<td>1.0 (0.6-0.9)</td>
<td>1.0 (0.6-1.0)</td>
<td></td>
</tr>
</tbody>
</table>

MAP: mean arterial pressure; CVP: central venous pressure; HR: heart rate; ELE: elevated liver enzymes; ALF: acute liver failure.

* comparing ELE vs. no-ELE and ALF vs. no-ALF (group and time interaction).
The high prevalence of HH among patients with ELE could be explained by the severity of the circulatory failure, which required ECMO after failure of medical therapy. Nevertheless, we did not directly assess liver blood flow neither quantify hepatic hypoxia. As an example, the use of indocyanine green plasma disappearance rate (ICG-PDR) can or the measurement of supra-hepatic vein saturation or transcatheterous hepatic near-infrared spectroscopy may provide more information on liver function and perfusion. Nevertheless, these tools are not easily available and the diagnosis of HH is still largely based on the measurement of AST/ALT levels.

We did not find any particular differences in demographics, clinical or ECMO characteristics between patients with and without ELE or with and without ALF. In particular, although it is recommended to keep central venous pressure (CVP) as low as possible to preserve portal circulation in the case of liver hypoperfusion, similar CVP values were observed between groups in this study. Also, ECMO flow, which is obviously a determinant of splanchnic perfusion, was similar among groups. We could not assess global flow as measurement of cardiac output during VA-ECMO is extremely biased by several confounders. Interestingly, normalization of liver enzymes alterations occurred in most patients, although it required several days. The mechanisms undergoing reduction of liver enzymes are largely unrecognized in this setting, and are probably related to the improvement in liver perfusion and oxygenation due to the optimization of systemic hemodynamics using VA-ECMO. It is possible that a reduction in inflammation and immune dysregulation, as shown in acute on chronic liver failure, or the activation of adult liver stem/progenitor cells could also contribute to hepatic recovery. Importantly, as some of these patients underwent ECPR and may suffer from persistent and extended post-anoxic brain injury, clinicians should recognize that VA-ECMO can adequately support liver function for several days so that some of these patients may become potential liver donors after complete functional recovery.

Mazzefi et al. used a similar definition for ALF than ours but reported a lower incidence (8%); the hospital mortality rate was higher in ALF patients when compared to others (81% vs. 46%, P=0.001). Nevertheless, cardiogenic shock, with subsequent “hypoxic liver injury”, occurs more frequently among VA-ECMO patients while Mazzeffi et al. included also VV-ECMO patients, who are at lower risk of liver hypoperfusion. Interestingly, the mortality rate was similar in their study (49%) and in ours (54%), even though we included only VA-ECMO patients, who are expected to have a higher mortality than VV-ECMO. Moreover, in the absence of other demographic, clinical and hemodynamic data, it is difficult to understand the reasons for a higher mortality rate in the ALF group in the Mazzeffi’s Study, as well as whether ALF was an independent determinant of mortality or represented just a marker of severity (e.g. multiple organ failure occurring after cardiogenic shock). In a second study by Heilmann et al., liver dysfunction, and not ALF, was evaluated by the assessment of increased AST, ALT or total bilirubin. The occurrence of these abnormalities was around 40% but it included also mild alterations of liver enzymes without significant clinical relevance and might explain the lack of correlation with mortality in this cohort. In another study, Chen et al. analyzed the occurrence of ALF using the specific hepatic SOFA sub-score; 15/36 patients eventually developed ALF during their ICU stay and their mortality was higher than in patients without ALF. Nevertheless, only ECPR patients treated with VA-ECMO were included in this study; in the setting of prolonged resuscitation after cardiac arrest, hypoxic liver injury is not a rare complication and is triggered by the duration of resuscitation attempts and is also associated with increased ICU mortality. Thus, it is difficult to extrapolate these findings to a more heterogeneous population of VA-ECMO patients, including post-cardiotomy heart failure and acute myocardial infarction. Finally, in a single-center study (N.=240), Roth et al. reported that alkaline phosphatase and to-
Function and liver failure during ECMO therapy for respiratory support in adults have been examined in several studies. However, the impact of ECMO on liver function remains a topic of debate. Some studies suggest that coagulation disorders could be due to ECMO implementation; however, other studies indicate that ECMO therapy, at least when initiated for respiratory support, did not influence coagulation parameters. Furthermore, differences in ALF definition and heterogeneity with other cohorts may explain the conflicting data with previous studies, where ALF was significantly associated with poor outcome.

Limitations of the study

This study has several limitations. First, we did not assess serum ammonium levels and the occurrence of encephalopathy could be due to other reasons (e.g., post-anoxic injury, sepsis) than ALF. Similarly, most of these patients received sedative agents that may confound the assessment of encephalopathy. Other potential pre-existing diseases (e.g., microvascular disease, aging) might also interfere with the diagnosis of liver encephalopathy, also because we could not collect specific data on minimal alterations of consciousness or delirium. Despite all these limitations, the same definition of ALF has also been previously used in critically ill patients undergoing VA or VV-ECMO. Second, some increase in bilirubin levels could be due to hemolysis, and we did not routinely measure free hemoglobin or haptoglobin in all patients. These limitations may also explain why we observed three patients with the ALF criteria but without ELE. Third, the accuracy of ALF diagnosis could be altered by concomitant acute myocardial or muscular injuries, which may also induce elevation of AST/ALT or bilirubin. However, no significant difference in CK and TnT concentrations were observed between patients with ALF or ELE and others. Moreover, although significant increase of ALT/AST without elevation of bilirubin may suggest a “non-hepatic” involvement, the definition of hypoxic hepatic injury still relies on transaminase assessment while jaundice is generally rare and transient and occurs only in case of severe loss of liver function. Similarly, one may argue that coagulation disorders could be due to ECMO implementation; however, in a recent study, ECMO therapy, at least when initiated for respiratory support in adults, did not influence coagulation parameters. Forth, we did not routinely perform morphologic exams of the liver (e.g., ultrasound); however, hepatic echography may be of interest to exclude other causes of ischemic liver injury (vascular clotting) and to identify signs of chronic liver disease and have a limited diagnostic/prognostic role in the setting of HH. Finally, our study cohort included only 69 patients; we excluded patients who died early and who may have presented with a multiple organ failure since the admission. Nevertheless, early mortality is usually related to the severity of the initial injury rather than to organ failures. Moreover, as no previous study had used the same definition of ELE, we could not perform a sample size calculation to assess the validity of our analysis, which might be then underpowered. Finally, the generalizability of our results might be limited, as the study population was quite heterogeneous and findings reflect the experience at a single center.

Conclusions

Liver dysfunction during ECMO should be further evaluated in prospective large studies to better investigate its association with outcome.

Key messages

— In this study, elevation of liver enzymes occurred in 65% of patients.
— Among patients with elevation of liver enzymes, 21/45 (47%) had the criteria of hypoxic hepatitis.
— Two thirds of patients with elevated liver enzymes had a normalization of this alteration within 5 days since ECMO initiation.
— Alteration of liver enzymes was not associated with poor outcome.
References


Authors' contributions.—Aaron Blandino Ortiz and Irene Lamanna equally contributed as first author.

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 diaphragm is a dome-shaped fibromuscular partition between the thoracic and abdominal cavities. It is undeniable the most important respiratory muscle in humans and the linear relationship between inspired volume and hemi-diaphragmatic movement in both supine and sitting positions \(^1\) observed in normal subjects has led some investigators to examine diaphragmatic contractility during different settings.\(^{2-7}\)

A few studies have evaluated the effect of sedative drugs on diaphragmatic activity \(^{8-10}\) using diaphragmatic electrical activity (EAdi) in different clinical situations. However, there...
are no data available on diaphragmatic activity during sedation for non-invasive procedures in spontaneous breathing patients.

Sedation outside the operating room for invasive and non-invasive procedures is a growing reality involving both anesthesiology and other specialties. This in turn has led to concern due to potential life-threatening complications related to some commonly used sedative drugs.11

Ultrasound (US) provides a simple, non-invasive method of assessing the strength and movement of the diaphragm,12, 13 thus, simplifying the study of this muscle, which is otherwise carried out using invasive methods rarely used in clinical practice. The US diagnostic method was proposed in 198514 for the study of diaphragmatic motion (DM) and in the 1990's for the assessment of its contractility (diaphragmatic thickness, DT).15 Cohen et al. demonstrated that DT could be assessed over a wide range of lung volumes, from residual volume to total lung capacity.16

Thickening fraction (TF) was reported to be a good indicator of diaphragmatic strength.15 This latter diaphragmatic measurement can be obtained in M-mode and has been reported to be useful in evaluating muscle function and its contribution to the respiratory workload.13

The aim of this prospective observational study was to use US to assess the effect of deep propofol sedation on diaphragmatic contractility in spontaneously breathing patients undergoing elective endoscopic procedures and its consequences on the respiratory system.

Materials and methods

The study was approved by the appropriate Institutional Review Board (IRB) of Sapienza University of Rome (no 208012015) and written informed consent was obtained from all subjects. A total of 36 consecutive patients (19 women and 17 men, aged 53±12 years, with a Body Mass Index [BMI] of 23.8±3.6) were enrolled between August and September 2015; all patients underwent elective diagnostic esophagogastroduodenoscopy (EGDS) with CO₂ insufflation under deep propofol sedation. Inclusive criteria were: American Society of Anesthesiologists (ASA) grade 1; age >18 years; normal cardiac, pulmonary, hepatic, and renal function; and absence of neurological and muscular diseases. Exclusion criteria were: lack of informed consent or patients receiving premedication or anticholinergic drugs were excluded from the study.

Sedation was provided by an anesthesiologist using a target controlled infusion (TCI) (Marsh pharmacokinetic model) of intravenous (IV) propofol at an effect site concentration of 3 μg/mL.17 (Alaris Asena PK pump, Alaris Medical UK Ltd, Basingstoke, UK). The infusion was continued throughout the endoscopic procedure, and the infusion rate was adjusted to obtain level 1 according to the Observer’s Assessment of Alertness/Sedation (OAAS) scale.18 Patients requiring >4 or <2 μg/mL or endotracheal intubation for any cause were withdrawn from the study.

Oxygen was administered at a rate of 4 L/min via nasal cannula. Oxygen saturation (SpO₂), end tidal CO₂ (EtCO₂) and respiratory rate (RR) were recorded. Hypoventilation was considered when SpO₂ fell below 95% and/or EtCO₂ rose above 43 mmHg. All hypoventilation episodes were recorded. Ultrasonography was performed by a specialist well trained in diaphragmatic US, using a Mylab 30 Gold Ultrasound (Esaote, Genoa, Italy). All diaphragmatic measurements were obtained in millimeters, and patients were scanned in the left lateral decubitus position.

Some authors19 recommend measuring the thickness of the right rather than the left hemidiaphragm as the latter is often challenging to visualize and measure.

Diaphragmatic thickening was studied in B-mode in the zone of apposition (ZOA) to the rib cage from the 8th to the 9th right intercostal space.20, 21 Using a linear 10 MHz probe, the diaphragmatic muscle was observed as an anechogenic central layer between two echogenic layers consisting of the diaphragmatic pleurae and peritoneum. Many studies19, 20, 22, 23 have shown that measurements of diaphragm thickness in the ZOA are reliable and reproducible, as assessed by either intra-observer or inter-observer reproducibility.20, 24
Measurements of diaphragmatic thickening were obtained at end-inspiration (TEI) and end-expiration (TEE). The diaphragmatic thickening fraction (DTF), which represents the index of diaphragmatic efficiency, was calculated as:

$$ DTF = \frac{(TEI - TEE)}{TEE}. $$

Measurements were performed at three different time points: T0, before propofol infusion; T1, 1 minute after reaching level 1 on the OAAS scale before gastric probe insertion; and T2, 5 minutes after reaching level 5 on the OAAS scale post-endoscopic procedure. All measurements assessed before and after sedation (T0 and T2) were obtained during normal quiet breathing.

The primary endpoint was the change in diaphragmatic contractility in spontaneously breathing patients sedated with propofol. The secondary endpoint was the incidence of hypventilation episodes.

**Statistical analysis**

Based on preliminary results, we determined that a sample size of 36 patients would have 100% power to detect a minimum 15% TF difference, and a maximum within group SD difference of 0.08% considering an alpha error <0.05. Shapiro-Wilk’s test was used to assess normal data distribution. A one-way analysis of variance (ANOVA) was used to test differences in the repeated measurements in normally distributed variables and Bonferroni’s *post-hoc* test was used to compare the data at each time point. For non-normally distributed data we used Wilcoxon’s test. Data are expressed as mean±SD and P values less than 0.05 were considered statistically significant. Data were analyzed using MedCalc software for Windows v. 12.0 (MedCalc, Mariakerke, Belgium).

**Results**

None of the patient dropped out of the study. Changes in all variables during propofol infusion are shown in Table I, and in Figures 1 and 2. DTF decreased by 56.7% during propofol target delivery (T0 versus T1) (P<0.001), whereas, after awakening (T1 versus T2), DTF increased by 76.9% (P<0.001). After awakening, recovery did not reach baseline value, with a 23.4% difference (T0 versus T2) (P<0.001).

In addition, following propofol administration (T0 versus T1), TEI decreased by 26.7%.

| Table I.—Changes in all variables at different study times. |
|-------------|--------|--------|--------|--------|
| Variables   | T0     | T1     | T2     | P value |
| TEI (mm)    | 3.0±0.5| 2.2±0.5| 2.7±0.5| T0 vs. T1: P<0.001 |
|             |        |        |        | T0 vs. T2: P=0.002 |
|             |        |        |        | T1 vs. T2: P<0.001 |
| TEE (mm)    | 2.3±0.4| 1.9±0.4| 2.2±0.4| T0 vs. T1: P<0.001 |
|             |        |        |        | T0 vs. T2: P=0.06 |
|             |        |        |        | T1 vs. T2: P<0.001 |
| DTF         | 0.3±0.07| 0.13±0.06| 0.23±0.07| T0 vs. T1: P<0.001 |
|             |        |        |        | T0 vs. T2: P<0.001 |
|             |        |        |        | T1 vs. T2: P=0.002 |
| Saturation (%)| 99.4±0.6| 96.9±0.8| 99.3±0.7| T0 vs. T1: P<0.001 |
|             |        |        |        | T0 vs. T2: P=1 |
|             |        |        |        | T1 vs. T2: P<0.0001 |
| EtCO₂ (mmHg)| 37.6±0.9| 41.8±1.0| 38.2±0.7| T0 vs. T1: P<0.001 |
|             |        |        |        | T0 vs. T2: P<0.001 |
|             |        |        |        | T1 vs. T2: P<0.001 |
| RR (bpm)    | 12.6±1| 20.9±1.5| 12.8±0.9| T0 vs. T1: P<0.001 |
|             |        |        |        | T0 vs. T2: P=1 |
|             |        |        |        | T1 vs. T2: P<0.001 |

Data presented as mean±SD.

T0: before propofol infusion; T1: 1 minute after reaching level 1 on the OAAS scale before gastric probe insertion; T2: 5 minutes after reaching level 5 on the OAAS scale post-endoscopic procedure; TEI: thickening end-inspiration; TEE: thickening end-expiration; DTF: diaphragmatic thickening fraction; EtCO₂: end tidal CO₂; RR: respiratory rate.
15.8% of TEE. At the end of the procedure (T0 versus T2), TEI maintained a statistically significant reduction (10%, $P<0.001$), whereas TEE completely recovered ($P=0.06$).

In 15 of 36 patients TEI measurements were repeated 5 minutes after T2 and 100% recovery was observed.

Mean $\text{SpO}_2$ level was consistently above 96%, $\text{EtCO}_2$ was below 43 mmHg and no desaturation episodes were noted in the studied patients. Respiratory rate increased from 12.6 to 20.9 breaths/min after propofol administration (T1) returning to 12.8 breaths/min at awakening (T2).

**Discussion**

The main findings in the present study were the following:

— a significant change in diaphragmatic contractility was noted during propofol infusion with a site concentration of 3.0±1 μg/mL;

— a decrease in $\text{DtF}$ of 56.7% at T1 was observed and a 23.4% difference at T2 was maintained;

— a significant increase in respiratory rate at T1 was noted, which returned to normal values at T2, suggesting that propofol infusion induced an alteration in neuro-ventilatory coupling due to a transient, albeit significant, reduction in diaphragmatic contractility;

— only a small decrease in $\text{SpO}_2$ and a small increase in $\text{EtCO}_2$ were observed which were not clinically significant.
Several animal \cite{25-27} and human studies \cite{15} have underlined the effect of propofol on diaphragmatic contractility. Sedation for diagnostic and interventional procedures is now current practice in many settings, and in some instances, gastroenterologists or nurses routinely administer sedation for upper and lower endoscopy.\cite{28} As respiratory depression is the most prominent adverse effect of sedation/anesthesia with propofol, minimum monitoring guidelines \cite{29-32} ensure patient safety outside the operating room.

Recent guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) recommend the administration of propofol by a non-anesthesiologist through perfusion systems as target controlled infusion (TCI) to increase safety.\cite{31} TCI systems are designed to facilitate the delivery of IV anesthetics efficiently and safely, utilizing the effect site concentration. We chose TCI methods using the Marsh pharmacokinetic model to reduce the well-known transient central depressant effect on respiration \cite{33} and the 20-30\% incidence of apnea which is dose- and injection-velocity-dependent.

During the infusion of propofol at a site concentration of 3.0±1 μg/mL, DTF decreased by 56.7\% at T1 with a significant increase in respiratory rate.

Amigoni et al.\cite{10} reported a relevant decrease in diaphragmatic electrical activity after 1 mg/kg of propofol administered as a bolus in 20 children ventilated with neurally-adjusted ventilator assist (NAVA) in a Pediatric Intensive Care Unit 370 seconds after drug infusion due to respiratory depression. In our study, respiratory rate increased significantly at T1 when DTF, TEI and TEE decreased, suggesting compensation of the related tidal volume reduction. EtCO$_2$ showed a small but non-clinically significant increase during T1, suggesting that alveolar ventilation was maintained. SpO$_2$ showed only a small change which was not clinically significant.

In addition, the TCI delivery system would have guaranteed a lower stable and effective propofol concentration leading not only to respiratory depression, but to a transient reduction in diaphragmatic contractility partially counterbalanced by a transient increase in respiratory rate.

DTF did not reach baseline value at T2, maintaining a 23.4\% difference. Aliverti et al.\cite{34} during propofol anesthesia (2-5 mg/kg in 1 minute to achieve central effect/apnea) observed a decrease in end-expiratory chest wall volume, with a more pronounced effect on the diaphragm than on the rib cage muscles. Of note, when breathing was restored after apnea (maintaining doses of 6-9 mg/kg/h continu-
ous infusion) breathing was initiated by the rib cage muscles producing a lower tidal volume but higher respiratory rate.

In addition, inter-subject variability observed in our study during quiet breathing in healthy subjects was consistent with data from other studies which described subjects who either did not use their diaphragm at all or had minimal contraction rather than normal contraction. Harper et al.12 conducted a large patient population survey which showed no significant difference between sides or across age groups, but wide variability in diaphragmatic contractility during quiet breathing was found, thus providing a wide database of healthy controls for future use in the evaluation of diaphragmatic dysfunction. McCool et al.35 analyzed the cause of this variability and confirmed that the dimensions of the diaphragm and thoracic cavity vary with the size of individuals, which is consistent with the principles of elastic similarity, and can predict a wide range in trans-diaphragmatic pressure (Pdi) among normal individuals, which is almost independent of body size.

Limitations of the study

Our study has important limitations.

Firstly, we did not use conventional methods to assess diaphragmatic function, including Pdi measurements, phrenic nerve stimulation or fluoroscopy.36 These methods, in addition to being invasive, are uncomfortable and cumbersome for studying ambulatory procedures such as sedation for endoscopic procedures. We used B-mode ultrasound, which has greater anatomical definition of muscle and its adjacent structures, and a wider panoramic view, compared with M-mode.18, 25, 37 As suggested by Ferrari et al.,38 B-mode diaphragm ultrasound is a simple, rapid, reproducible, and non-invasive test that can be repeated several times, without risk to patients, and provides important information on respiratory function. It was demonstrated 38 that diaphragm ultrasound measurements correlated with lung volumes and maximal inspiratory pressure (PImax).

Secondly, in this study, we did not assess inter-observer reproducibility of diaphragmatic ultrasound in measuring thickness as many other studies have already studied this parameter 23, 24 and placement of the patient in the left decubitus position meant that we were obliged to study the right diaphragm; nevertheless, some studies have shown the right hemidiaphragm to be the easiest side to assess this muscle.19

Thirdly, propofol can have a potential dual effect on respiratory drive and diaphragmatic activity. Although previous studies 11, 13, 39 demonstrated that propofol can reduce P0.1, this variable was not measured in this study. In addition, our results suggest that propofol infusion, at those site concentrations, may induce an alteration in neuro-ventilatory coupling due to a transient, albeit significant, reduction in diaphragmatic contractility without affecting respiratory drive. Our main aim was to assess diaphragmatic thickness changes during deep propofol sedation and whether this reduction in strength would affect muscle activity in healthy patients undergoing a common endoscopic procedure.

Moreover, the EGDS procedures uses insufflation of carbon dioxide (CO2) that, at the end of the procedure, is partially inhaled by fiberoptic tool and partially proceed in the bowel. Carbon dioxide, unlike air, is rapidly cleared from the colon by passive absorption 150 times faster than nitrogen for the higher solubility of CO2 in water 40, 41 and easily expired through the respiratory tract without a significant rise above normal CO2 levels also in an unselected population.42

Different studied have showed no significant residual gas on plain radiograph taken 30 minutes 43 or 1 hour after procedures.44 For all these reasons, we assume that our third measurement was performed in absence of abdominal distension but we cannot exclude that a residual distension could have influenced our third measurement having a confounder influence.

In addition, we studied only ASA1 patients with normal respiratory function and further studies are necessary to evaluate the impact of these complex physiological changes on patients with pre-existing respiratory complications.
Finally, the potential effect of airway obstruction on diaphragmatic motion has also raised concern. Although propofol may cause airway obstruction during deep sedation, we did not observe snoring in any of our patients during the procedure. In addition, spontaneous breathing was always maintained, no desaturation episodes were observed in the studied patients and mean EtCO2 was always below 43 mmHg.45

Conclusions

In conclusion, while diaphragmatic strength decreased during sedation, there were only marginal and non-significant effects on SpO2 and EtCO2 and a transient increase in respiratory rate. Our study also confirmed that US was a suitable and well-tolerated technique for measuring diaphragmatic activity during a routine clinical procedure.

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Key messages

— Propofol decreases diaphragmatic strength during light sedation, but in ASA 1 patients strength variation has only a marginal and non-relevant effect on SpO2 and EtCO2, due to a transient increase in respiratory rate.

— Propofol sedation in spontaneous breathing critically ill patients must be carefully considered as a decrease in diaphragmatic strength could be deleterious. Further studies are required.

— Diaphragmatic ultrasound (DUS) is a non-invasive real-time technique suitable for assessing diaphragmatic strength in several clinical settings. Diaphragmatic dysfunction is often under diagnosed and DUS can be useful for assessing diaphragmatic thickness in mechanically ventilated patients or as a weaning index. Data from the present study may extend the application of DUS to study the effect of sedative drugs on the diaphragm in order to better assess patient safety.

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ProPoFol-related reduced diaphragm activity

Rocco


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

Comparison of two different forms of sevoflurane for anesthesia maintenance and recovery

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ABSTRACT

BACKGROUND: Sevoflurane is a commonly used inhalation agent. There are two forms of sevoflurane in Turkey. The aim of this study was to evaluate the effects of original versus generic sevoflurane products on hemodynamics, time to reach 1 MAC level, inspired and expired sevoflurane levels and postoperative recovery profile.

METHODS: Seventy patients undergoing general anesthesia were divided into two groups as Group Sevo or Group Sojo. After intravenous induction of anesthesia (with the same drugs in both groups), inhalation anesthetic was started. Hemodynamic parameters, Bispectral index (BIS), time to reach 1MAC level, inspired and expired sevoflurane levels, percent vaporizer concentration of sevoflurane, additional remifentanil doses were recorded. In the awakening period, decreasing times of MAC 0.5, 0.4, 0.3, BIS levels, sedation-agitation and Aldrete scores were recorded.

RESULTS: The time to reach 1MAC level was shorter in Group Sevo than in Group Sojo (P=0.01). The fractions of inspired sevoflurane levels were higher at 4, 6, 8, 10, 15, 30, 35, and 45 minutes, the fractions of expired sevoflurane levels were higher at 4, 6, 8, 10, 15, and 20 minutes in Group Sevo (P<0.05). In the awakening period and postoperatively, there were no differences in recorded parameters between the groups.

CONCLUSIONS: Although there are differences in maintenance period of the anesthesia, the two products seem to be comparable routine anesthesia practice. But further studies are needed to enhance our knowledge.

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Key words: Inhalation anesthetics - Sevoflurane - General anesthesia - Consciousness monitors.

Sevoflurane is a commonly used inhalation anesthetic in worldwide anesthesia practice. This product was first synthesized in the USA, then developed in 1990 by Maruishi Pharmaceuticals in Japan. It was first marketed by Abbott Laboratories in 1995, under the trademark Ultane and worldwide as sevoflurane. 1, 2 Forms of sevoflurane with a low water content (Eraldin®, Laboratorios Richmond/Minrad, Buenos Aires, Argentina; Sevoness®, Baxter, Deerfield, IL, USA) or added propylene glycol (Sevocris®, Cristália Produtos Químicos e Farmacêuticos, Rio de Janeiro, Brazil), as a stabilizer, have recently become available in some countries. 1–3 Although generic versions of sevoflurane are considered therapeutically equivalent to the original form, these are different in respect of synthesis methods, formulation characteristics and conditions of storage.

There are two brands of sevoflurane on the Turkish market: Sevoflurane Likid® 100% (Abbott Laboratories, Istanbul, Turkey), which is the original form, and Sojourn® (Adeka İlaç
Sanayi, Samsun, Turkey), which is a generic form. These two products are different in synthesis, storage and water content.\textsuperscript{1, 3} The difference in water content of the two sevoflurane formulations is important. Sevoflurane undergoes chemical degradation which can cause potentially toxic different compounds such as Lewis and hydrofluoric acids. Water functions as a stabilizer, preventing acid degradation of the products.\textsuperscript{1} Although there have been a few \textit{in-vitro} studies in literature investigating the effects and the differences of filling devices of the two forms of sevoflurane, the number of \textit{in-vivo} studies is very limited.\textsuperscript{1, 2, 4+6} It has been speculated that these differences in water content lead to different clinical and anesthetic effects of sevoflurane. In a clinical study of pediatric population, it was pointed out that the water content of sevoflurane affected the fractions of inspired and expired sevoflurane in the awakening period.\textsuperscript{5}

The aim of this study, was to evaluate whether there was any difference between original and generic products of sevoflurane in the time taken to reach 1 MAC level at a fixed vaporizer setting. Secondary endpoints were to determine any effect on inspired and expired fractions (inhalation characteristics) during the maintenance of anesthesia and decreasing times of MAC 0.5 to 0.3 in the awakening period in adults.

**Materials and methods**

Approval for the study was granted by the Ethics Committee of Umraniye Research Hospital (2013-18) and the Turkey Ministry of Health, Clinical Drug Research Center (clinical trial registration no.: 2013-PMS-17). Informed consent was obtained from each patient. This prospective study comprised 70 ASA (American Society of Anesthesiologists) I or II, patients aged 18-65 years, who were scheduled to undergo lower abdominal or urological surgery (herniorrhaphy and ureterolithotripsia) under general anesthesia using classic LMA. Exclusion criteria were patients with neurological, cardiac or mental diseases, Body Mass Index (BMI) >35 kg/m\(^2\), procedures lasting more than two hours or shorter than 45 minutes, the usage of neuroleptics, benzodiazepines, anticonvulsant or other similar medications that might interfere with the inhalation characteristic of sevoflurane. None of the patients received any premedication.

In the operating theatre, venipuncture (18 gauge) was performed and hydration was initiated with 4 mL/kg/h lactate Ringer’s solution. Standard clinical anesthesia monitoring with 3-lead electrocardiography (ECG), noninvasive (systolic, mean, diastolic) blood pressure (NIBP), peripheral oxygen saturation (SpO\(_2\)), temperature and Bispectral Index analysis (BIS) were applied before the induction of anesthesia. Body temperature was maintained within normal limits using a warm blanket.

Anesthesia induction was performed with propofol 3 mg/kg, rocuronium bromide 0.4 mg/kg and remifentanil 1 µg/kg. No inhaled agent was administered during induction. Two minutes after the induction of anesthesia, the LMA was inserted smoothly on the first or second attempt by an experienced anesthetist. If the LMA could not be inserted on the second attempt, the patient was excluded from the study.

The patients were divided randomly (with sealed envelope) into two groups: the Sevo group (N.=35) and the Sojo group (N.=35). Sevoflurane was administered to the patients in Group Sevo and Sojo at vaporizer dial to 1.5% concentration in N\(_2\)/O\(_2\) (50%/50%) mixture. Fresh gas flow was set at 6L/min. Ventilation of the lungs was maintained by an anesthetic machine (Fabius plus-Dräger Medical GmbH, Lübeck, Germany) using volume-controlled ventilation mode with tidal volume 7 mL/kg. The respiratory frequency was adjusted to keep the end-tidal concentrations of carbon dioxide (EtCO\(_2\)) between 30-35 mmHg. No other IV drug was used and the vaporizer dial was not changed until the sevoflurane concentration reached 1 MAC level. Maintenance of anesthesia was adjusted to keep the BIS levels between 40 and 60. If the BIS level exceeded 60 or blood pressure or heart rate increased 20% from baseline; remifentanil bolus dose of
1 µg/kg was injected to maintain appropriate anesthetic level and recorded as an analgesic. Similarly, if the BIS level decreased to 40 or blood pressure or heart rate decreased 20% from baseline, the vaporizer dial of sevoflurane was reduced to 1.2% and recorded.

The heart rate (HR), NIBP, SpO₂, and BIS values were recorded 2 minutes before anesthesia induction, then at 4, 6, 8, and 10 minutes after induction and subsequently every 5 minutes during anesthesia. The time to reach 1 MAC was recorded from opening the vaporizer to the time when end-tidal gas concentration reached 1 MAC level for each product. The EtCO₂, fraction of inspired and expired sevoflurane, percent concentration of vaporizer settings sevoflurane were recorded after induction and during the anesthesia period. The spirometric data were obtained using a Scio Four Oxiplus spirometry device (Dräger Medical GmbH, Lübeck, Germany) and recorded on an anesthesia monitor.

At the end of the operation, the vaporizer was turned off and mechanical ventilation was continued with O₂/Air (50%/50%). In the awakening period, decreasing times of MAC 0.5, 0.4, 0.3 and BIS levels at those times were recorded. No verbal or tactile stimulations were administered in this period. The LMA was removed with the cuff inflated while the patient was breathing spontaneously. The sedation-agitation levels were assessed with the Riker Sedation-Agitation Score (SAS) (Table I) at the time of MAC=0.3 and after the removal of LMA. Patients were then transferred to the recovery room.

Table I.—Riker Sedation Agitation Score.

<table>
<thead>
<tr>
<th>Score</th>
<th>State</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Dangerous agitation</td>
<td>Pulling at ET tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing side-to-side</td>
</tr>
<tr>
<td>6</td>
<td>Very agitated</td>
<td>Requiring restraint and frequent verbal reminding of limits, biting ET tube</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
<td>Anxious or physically agitated, calms to verbal instructions</td>
</tr>
<tr>
<td>4</td>
<td>Calm and cooperative</td>
<td>Calm, easily arousable, follows commands</td>
</tr>
<tr>
<td>3</td>
<td>Sedated</td>
<td>Difficult to arouse but awakens to verbal stimuli or gentle shaking, follows simple commands but drifts off again</td>
</tr>
<tr>
<td>2</td>
<td>Very sedated</td>
<td>Aroused to physical stimuli but does not communicate or follow commands, may move spontaneously</td>
</tr>
<tr>
<td>1</td>
<td>Unarousable</td>
<td>Minimal or no response to noxious stimuli, does not communicate or follow commands</td>
</tr>
</tbody>
</table>

ET: endotracheal.

evaluated immediately after the transfer of the patient to the recovery room and at the 60th minute postoperatively. Adverse events such as respiratory tract irritation (coughing, laryngospasm or breath holding) and nausea/vomiting were recorded.

The vaporizers of the two products used in the study were different but were of the same make (Vapor 2000, Dräger Medical GmbH). All of them had been in use for between 6-12 months and were also calibrated. Each vaporizer was provided by the manufacturer and checked as appropriate to the product. The anesthesiologist was not informed of which form of sevoflurane was used.

Statistical analysis

The NCSS (Number Cruncher Statistical System) 2007 and PASS (Power Analysis and Sample Size) 2008 statistical software programs were used to calculate the power of the study. According to the results of a pilot study of the time to reach 1 MAC level, delta was calculated as 95 seconds with standard deviation (SD): 140, assuming an α level of 0.05 and a power of 0.80, thus a minimum of 35 patients should be enrolled in each group for the study. For the inspired fraction of sevoflurane, at the time points where the difference was statistically significant, the post-hoc power was calculated in the range of 68.4-96.7% and for the expired fraction of sevoflurane, in the range of 65.8-97.8%. When evaluating the study data descriptive statistical methods were used to express the results as mean±SD. For
Both groups comprised 35 ASA I-II patients. No significant differences were determined between the groups in demographic data and duration of anesthesia (P>0.05) (Table II). HR, NIBP, SpO2 and EtCO2 were similar and within the physiological range in both groups at all times (P>0.05).

After induction, the time to reach 1 MAC level was shorter in the Sevo Group (6.3±2.4 minutes) than in the Sojo Group (8.5±5.2 minutes) (P=0.01) (Figure 1). The fractions of inspired and expired sevoflurane were also different between the groups. The fractions of inspired sevoflurane were higher and statistically significant at 4, 6, 8, 10, 15, 30, 35, and 45 minutes during anesthesia in the Sevo Group compared to the Sojo Group (P<0.05) (Figure 2). The fractions of expired sevoflurane were higher at 4, 6, 8, 10, 15 and 20 minutes in the Sevo Group (P<0.05) (Figure 3).

Although the percentage vaporizer concentrations of sevoflurane required to maintain BIS levels between 40 and 60 were recorded at higher levels in the Sojo Group than in the Sevo Group, the differences were not significant (P>0.05). The BIS levels were similar in both groups at all recorded times (P>0.05). Thirteen additional remifentanil boluses were administered (once in 7 patients, twice in 3 patients) in the Sojo Group, and 9 boluses (once in 9 patients) in the Sevo Group. Six patients from the Sevo Group and 5 from the Sojo Group required additional analgesia (twice in 2 patients) while undergoing herniorrhaphy.

**Table II.—Demographic data and duration of surgery (mean±SD) or number (P>0.05).**

<table>
<thead>
<tr>
<th></th>
<th>Sevo Group</th>
<th>Sojo Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43±14</td>
<td>42±12</td>
<td>0.84</td>
</tr>
<tr>
<td>&lt;40 years (N.)</td>
<td>16</td>
<td>18</td>
<td>0.81</td>
</tr>
<tr>
<td>&gt;40 years (N.)</td>
<td>19</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78±15</td>
<td>72±13</td>
<td>0.07</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168±8</td>
<td>148±9</td>
<td>0.72</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>49±25</td>
<td>48±20</td>
<td>0.84</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>24/11</td>
<td>20/15</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Results

Qualitative analysis of data with normal distribution between the groups, the Student’s t-test was used to compare with normal distribution the parameters while Mann Whitney U-test was used for comparison of the parameters not showing normal distribution. Fisher’s exact test and Yates Continuity Correction test were used for comparison of the qualitative data. A P value <0.05 was considered statistically significant.
The number of patients (P=0.78) and the number of additional boluses (P=0.21) were similar between the groups.

During the awakening period, the decreasing times of MAC 0.5, 0.4, 0.3 were recorded as longer in the original form. These differences were not significant (P>0.05) (Table III). SAS were similar at the time of MAC=0.3 (P=0.46) and removal of the LMA (P=0.43). No significant difference was determined compared to nausea (P=1). Modified Aldrete scores were comparable immediately after transfer to the recovery room (P=0.23) and at the 60th minute postoperatively (P=0.79). No signs of respiratory tract irritation such as coughing, laryngospasm or breath holding were observed in either group.

Discussion

The results of this study showed that the time to reach 1 MAC level was shorter and that the fractions of inspired and expired sevoflurane were higher in the original product compared with the generic product.

Sevoflurane is less irritating to the respiratory tract and provides a rapid, smooth induction and recovery from anesthesia than many other agents. Due to its low blood solubility, recovery from anesthesia is rapid. The factors affecting inspirational concentration of sevoflurane are fresh gas flow rate, the volume of the breathing system and any absorption by the machine or breathing circuit. The major factor affecting alveolar concentration is the anesthetic uptake. This is affected by solubility in the blood, alveolar blood flow and the partial pressure difference between alveolar gas and venous blood. The awakening concentration of sevoflurane, which is defined as the end tidal concentration, is independent of gender, duration of anesthesia and type of surgery. Age and temperature are known to influence MAC and MAC-Awake in humans. In order to maintain a BIS level of 40-60 in adults, the required percent end-tidal concentrations of sevoflurane have been reported between 1.04% and 1.81% in several studies. As there was a wide but not extreme age range in the current study, the sevoflurane vaporizer dial was initially set to 1.5% to obtain 1 MAC level. The number of patients younger and older than 40, gender, duration of anesthesia and type of surgery were similar in both groups.

There are two forms of sevoflurane available in Turkey. Even though these two products are rated therapeutically equivalent, there are some differences. Original sevoflurane is manufactured using a single-step process, contains 300-ppm water and is packaged in a plastic polymer bottle. Generic sevoflurane is manufactured using a three-step process, contains an average of <130-ppm water and is packaged in a glass bottle. Both the original and generic products have a high purity of sevoflurane with low variation. The differences in water contents of the two forms of sevoflurane have been the main topic of discussion rather than their purity. Sevoflurane is susceptible to chemical degradation. The degradation products of sevoflurane are Lewis acids and hydrofluoric acid. If these acids are inhaled, they may cause respiratory irritation. Water inhibits such degradation. In-vitro studies have demonstrated that degradation products of the different water content of sevoflurane can influence hydrofluoric acid concentration, pH or compound A production. The clinical implications of these differences are unknown.
There have been a limited number of in-vivo studies evaluating the clinical effects of different sevoflurane forms. In a study by Otsuki et al., equipotent doses of two different forms of sevoflurane on a pig model were determined to have similar effects on hemodynamics. In the current study, the parameters such as HR, blood pressure and EtCO₂ that could alter the pharmacokinetics were similar in both groups.

Tomal et al. evaluated two different forms of sevoflurane (with 300-ppm water or 260-ppm propylene glycol as a stabilizer) on a pediatric population and found that a greater number of children required an additional bolus of sevoflurane to maintain the same anesthesia level in the generic group. At the end of the anesthesia, despite the same concentration in vaporizer dial, the median fractions of inspired and expired sevoflurane were higher and BIS levels were lower in the original sevoflurane group than in the generic sevoflurane group. In the current study, higher inspired and expired sevoflurane fractions were recorded in the original sevoflurane product, whereas percent vaporizer concentrations were similar between the groups at all times. In addition, the recorded time to reach 1 MAC level was shorter in the Sojo Group than in the Sevo Group (6.3 versus 8.5 minutes). Howitz et al. reported the time to reach 1 MAC as 6.2 minutes using fixed vaporizer dial in the original form with 1 L/min fresh gas flow rate.

All these findings are surprising. In the current study, a standardized anesthesia regimen was applied and the depth of anesthesia was controlled by monitoring the BIS. The factors that affect inspirational concentration of sevoflurane, such as fresh gas flow rate and the volume of the breathing system, and hemodynamics and respiratory parameters which affect the pharmacokinetics of sevoflurane were similar between the groups. Furthermore, the vaporizers used in this study were provided and checked by the manufacturer for each product. Tomal et al. reported similar results in pediatric patients with propylene glycol additive sevoflurane on discontinuation of sevoflurane at the end of the anesthesia. Therefore, in the light of the literature results, these differences could be considered to be related to their formulation characteristics especially the water content and solubility. Nevertheless, it is difficult to say exactly what caused the observed differences in the current study design. New technology, and target controlled anesthesia machines allow entry of the desired alveolar partial pressure (Fₐ) of the inhaled agent, and manage fresh gas flow rate and agent administration rates. However, inspired anesthesia concentration is still important with the a conventional delivery system.

During the awakening and recovery period the SAS and Aldrete scores were similar in both groups. No signs of respiratory tract irritation such as coughing, laryngospasm or breath holding were observed in either group. In this study, there was no measurement of the time to eye-opening, or of the fraction of inspired and expired sevoflurane after discontinuation of sevoflurane in both groups. The times to decreasing MAC and BIS levels from 0.5 to 0.3 were recorded. Even though the decreasing times of MAC levels tended to be longer in the original form, the differences were not significant.

Coppens et al. indicated that rapid sequence induction with remifentanil, propofol and rocuronium can be applied without dangerous hemodynamic and arousal responses. In the current study, it was aimed to obtain excellent conditions for the induction period and remifentanil was administered to both groups. However, no other remifentanil bolus was used until the inhalation agent reached 1 MAC level. Previous studies in literature have stated that remifentanil could affect MAC levels of inhalation anesthetics. Despite this knowledge, in the current study, inspired and expired sevoflurane fractions were higher in the Sevo Group when the vaporizer was set to the same dial to obtain BIS levels between 40-60. In addition, the number of patients who received remifentanil and the number of additional bolus doses were no different between the groups. Thus, it was thought that the use of remifentanil did not affect the inhalation characteristics of the two groups in this study.
Limitations of the study

A limitation of this study was that sevoflurane consumption was not measured. In a study by Tomal et al., sevoflurane consumption was evaluated and no difference was found between the two products. However, it was emphasized that the short duration of anesthesia and the calculation method of sevoflurane consumption might have been insufficient to demonstrate significant differences in sevoflurane consumption.

Conclusions

In conclusion, inspired and expired sevoflurane fractions were observed to be higher and the time taken to reach 1 MAC level was shorter in the original form than in the generic form. Therefore, anesthesiologists should pay attention to these features when using different preparations of sevoflurane. Further extensive, evidence-based studies are required to enhance the knowledge of this subject.

Key messages

— At a fixed vaporizer dial, the time to reach 1 MAC level was shorter in the original form than in the generic form.
— The fractions of inspired and expired sevoflurane were recorded at higher levels in the original form during the maintenance of anesthesia.
— No significant difference was observed in the recovery scores and adverse reactions between the two forms of sevoflurane during the awakening and recovery period.

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.

Congresses.—This study was presented as a poster presentation at the 47th National Congress of the Turkish Society of Anesthesiology and Reanimation, which was held in 2013 in Antalya, Turkey.

Transversus abdominis plane block for postoperative analgesia in neonates and young infants: retrospective analysis of a case series

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ABSTRACT

BACKGROUND: The effectiveness of the transversus abdominis plane (TAP) block in children has been well characterized in literature. However, there are only few reports about TAP block in the neonates and low birth weight groups. This is a retrospective observational analysis of ultrasound – assisted TAP blocks in neonates and young infants. The aim of this study was to analyze retrospectively the analgesic effectiveness of TAP block in neonates and infants undergoing abdominal and inguinal surgeries.

METHODS: Thirty-four cases of neonates and infants to (whom) TAP block was applied, were retrospectively analyzed. The TAP block was performed postoperatively in supraumbilical surgeries and preoperatively in infraumbilical surgeries. The TAP block was applied with 0.8 mL/kg⁻¹ of 0.25% bupivacaine in unilateral approach and 1.6 mL/kg⁻¹ of 0.125% bupivacaine in bilateral approach. The CRIES Pain Scale was used for postoperative pain measurement of neonates.

RESULTS: The patient’s age ranged from 2 to 88 day-old with a mean (SD) of 36.2(24.2). Eleven of them were premature babies. The weight ranged from 1.6 to 5.8 with a mean (SD) of 3.7 kg (1.1). Twenty-nine patients were extubated at the end of the surgery and the other patients within 12 hours. 67.7% infants required no additional postoperative analgesic in 24 hours and none of them required narcotic analgesics.

CONCLUSIONS: Our conclusion is that the use of TAP blocks results in low analgesic requirements and a low incidence of postoperative intubation and mechanical ventilation in neonates and infants. It should be considered in this age group of child for postoperative analgesia.


Key words: Nerve block - Infant, newborn - Abdominal wall.

Neonates can start to feel pain at XXIII-XXIV weeks gestation. Untreated painful procedures in neonates can lead to changes in behavior and learning in the long term that can provoke cognitive and neurological impairment.¹, ² The postoperative analgesia in neonates and infants is important for the surgical outcome. The pain management has some challenges, because of the physiological and pharmacological differences of this developmental stage. Inadequate postoperative analgesia in neonates and infants increases the stress response and also increases morbidity and mortality.³ The intravenous
analgesia may have respiratory and metabolic problems with immature organ systems.\textsuperscript{3, 4} Especially, systemic opioids may cause respiratory depression and increases ventilator duration. Regional analgesia could conveniently provide pain relief and a comfortable postoperative period. However, due to the small size of the structure, differences in the resistance of tissues, a variety of indication limitations complicates and needs experience for this procedure in neonates. The regional anesthetic techniques start to performed commonly after the begin of USG guidance, especially in children. Some studies show that TAP block can reduce the pain in some specific surgical procedures in children.\textsuperscript{5} Until now, only few case reports were published about TAP block in neonates and low birth weight groups.\textsuperscript{4, 6, 7} The performing TAP block in neonates are challenging because of their small size and small distances between adjacent critical structures. The Ultrasound (USG) can assist and facilitate the performance of TAP block. The main purpose of this study is to evaluate the postoperative analgesic effectiveness of TAP block in neonates and infants. In addition, the type of surgeries whom TAP block was performed, the approach of TAP block, the analgesic requirement during 24-hour postoperative period and the extubation time were evaluated.

Materials and methods

This study was approved by Ethical Board of our institution (No: 83045809/604.01/02) and all available data between November 2014 and January 2016 was retrospectively collected. Any informed consent from human subjects was obtained as required. The infants younger than 3 months, who underwent any abdominal and inguinal surgeries under general anesthesia and applied TAP block for pain management were included. Data were collected by reviewing patients’ anesthetic, postoperative Neonatal Intensive Care Unit (NICU) and ward records. General anesthesia was induced by sevoflurane (4-5%) and rocuronium (0.6-1 mg/kg) after the application of standard monitors. Anesthesia was maintained with 2% end-tidal concentration of sevoflurane in air/oxygen (FiO\textsubscript{2}=0.4) and remifentanil infusion. Patients were mechanically ventilated using a pressure-controlled mode. The EtCO\textsubscript{2} was maintained between 32 and 38 mm/Hg. The subcostal approach in supraumbilical surgeries (duodenal atresia, pyloric stenosis, biliary atresia and choledoc cyst) and midaxillary or posterior approach in infraumbilical surgeries (inguinal hernia, pyeloplasty, and colostomy) were preferred for TAP block. The TAP block was performed postoperatively in supraumbilical surgeries as surgical incision was at the same location of block and preoperatively in infraumbilical surgeries as location of surgical incision was at different places. The block was performed by using a high frequency linear probe (EsaoteMyLab5-LA523E) and needle of 24G cannula (Vasofix\textsuperscript{®} certo, Braun, Melsungen, Germany) with attached short and thin extension line, after cleaning the skin with chlorhexidine. The needle was advanced at 10-20 degree angle to USG probe with the in-plane approach after internal oblique and transversus abdominis muscle layers were visualized. The target area between these two muscles was confirmed in all cases by injecting 0.5 mL 0.9% NaCl. The 0.8 mL/kg of 0.25% bupivacaine solution for unilateral and 1.6 mL/kg of 0.125% bupivacaine in totally for bilateral TAP block were received.

Patients were transferred to NICU or ward depending on the age and surgery after operation. The CRIES Pain Scale (Crying, Requires increased oxygen administration, Increased vital signs, Expression, and Sleeplessness) was used by trained nurses for pain measurement for postoperative 24 hours. The CRIES Pain Scale for 32 weeks of gestational age to 6 months includes five categories: severity of crying; O\textsubscript{2} requirement; increased vital signs; facial expression; and sleeplessness each with 0 to 2 level and scores range from zero to 10.\textsuperscript{8, 9} Patient have been received paracetamol (10 mg/kg IV) with a CRIES Score>4. The remifentanil infusion for intubated patient and IV tramadol (1-2 mg/kg) for non-intubated patient were administrated with a CRIES Score>7.
Results

We are presenting our experiences in thirty-four cases of neonates and infants whom applied TAP block. All available data was collected between November 2014 and January 2016. Thirty-four patients who underwent ultrasound assisted TAP block for pain management after abdominal and inguinal surgeries were investigated. Patients’ characteristics are presented in Table I.

All patients who underwent infra-umbilical surgeries were extubated in operating room. The patients who underwent supra-umbilical surgeries, especially low birth weight premature babies were extubated in NICU after successful spontaneous breathing trials.

The additional analgesics were administrated in patient with CRIES Score >4 (Figure 1).

Table I.—Patients’ characteristics.

<table>
<thead>
<tr>
<th>Type of surgical procedure</th>
<th>N.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenoduodenostomy</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>Kasai’s technique</td>
<td>5</td>
<td>14.7</td>
</tr>
<tr>
<td>Pyloromyotomy</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Pyloroplasty</td>
<td>4</td>
<td>11.8</td>
</tr>
<tr>
<td>High ligation</td>
<td>12</td>
<td>35.3</td>
</tr>
<tr>
<td>Colostomy</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Roux-en-Y hepaticojejunostomy</td>
<td>2</td>
<td>5.9</td>
</tr>
<tr>
<td>Jejunoojejunostomy</td>
<td>1</td>
<td>2.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TAP block approach</th>
<th>N.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcostal</td>
<td>14</td>
<td>41.2</td>
</tr>
<tr>
<td>Posterior</td>
<td>10</td>
<td>29.4</td>
</tr>
<tr>
<td>Midaxillary</td>
<td>10</td>
<td>29.4</td>
</tr>
<tr>
<td>Unilateral/Bilateral</td>
<td>23</td>
<td>67.7</td>
</tr>
<tr>
<td>Bilateral</td>
<td>11</td>
<td>32.3</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Extubation time</th>
<th>N.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>In operating room</td>
<td>29</td>
<td>85.3</td>
</tr>
<tr>
<td>Postop. 2nd hour</td>
<td>3</td>
<td>8.8</td>
</tr>
<tr>
<td>Postop. 3rd hour</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>Postop. 12th hour</td>
<td>1</td>
<td>2.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postoperative analgesic requirement</th>
<th>N.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcostal approach</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Midaxillary approach</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Posterior approach</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>32.4</td>
</tr>
</tbody>
</table>

Data are reported as number and %, mean (SD), median [IQR].

Discussion

Neonates with congenital anomalies may need surgical repairs in early life period. Pain management of neonatal patient after the surgery is a challenging process. Inadequate treatment of pain has negative outcomes for neonates and infants. Pain experiences in neonatal period have long term effects on the development of pain processing, neuroendocrine and immune systems. Further, this experience have caused emotional, behavioral and learning disabilities.1-3

The systemic opioid usage is limited in neonates, due to the respiratory depression and side effects.4 Continuously using the opioids to provide sufficient analgesia may extend the duration of mechanical ventilation and the extubation time. The patient is already extubated; opioids increase the risk of apnea, which requires close monitoring even minor surgery such as inguinal hernia repairing. In our study, none of patients required opioid analgesics in postoperative period; therefore most patients were extubated at end of surgery or within 12 hours. Paracetamol, is an alternative intravenous drug, may not provide a sufficient analgesia.
The central neuraxial blocks are not the first choice due to technical difficulties and inadequate coagulation factors in neonates. Peripheral nerve blocks can be used when neuraxial block is not desired. According to ADARPEF Study, neuraxial techniques have an incidence of complications that is seven times that of the peripheral regional techniques. Complications of epidural anesthesia are higher in children below 6 months old, being four times that of the over 6 months old. Anatomical relationships and landmarks are different and the distance from skin to epidural space is very small (in infants >6 months is 1 mm/kg). Caudal block is also most common regional anesthesia technique in children. The termination of dura and spinal cord in the spinal canal in infants are lower than adults (dura S4-spinal cord L3 at birth). Therefore the technique for accessing the epidural space should be careful to avoid inadvertent dural puncture or spinal cord damage. It is difficult to place small diameter needles and catheters into subarachnoid space. In addition, small catheters may be kinked, disconnected, dislodged and occluded easily.

The TAP block was primarily performed in children by Fredrickson et al. There are few published reports about TAP block in neonates for postoperative analgesia. Small infants could be technically challenging due to size and closeness of critical structures but blocks were feasible. It is recommended that an experienced anesthesiologist should perform the TAP block, especially in low birth weight neonates.

Fredrickson et al. firstly performed preoperative TAP block in four neonates undergoing hernia repair. They concluded that TAP block is feasible in the neonate and provides effective intraoperative analgesia.

Jacops et al., performed preoperative TAP block in both five neonates and infants undergoing abdominal surgery. They concluded that TAP block can be promising in this age of groups due to reduction in requirement of neuraxial techniques and opioids.

Bielsky et al. also performed bilateral TAP block in two neonates who had an urgent colostomy. They reported that no additional doses of analgesics were received in postoperative 24-hours.

Figure 2.—Distance between surface and TAP was 3 mm and from TAP to peritoneum was less than 1 mm in neonate with 1.6 kg of weight.
We followed the CRIES scores postoperatively for all cases. The most of patients did not need any analgesics in postoperative 24-hours (Figure 1, Table 1). The dermatomal block of the abdominal wall may not cut off this major abdominal surgery pain, but it reduces analgesic requirements and expected extubation time. Most of our patients were extubated at end of the surgery or within 12 hours. The patients with biliary atresia, choledoc cyst and anal atresia needed paracetamol (10 mg/kg one or two doses) in our series. The paracetamol was received to nine of 11 patients whom TAP block were applied with subcostal approach.

We preferred to perform TAP block postoperatively in supraumbilical and preoperatively in infraumbilical incisions. The subcostal approach was applied for supraumbilical incision. We considered that local anesthetic solution might be disintegrated from the transversus abdominis plane due to surgical incision at the same location of block that may be the reason of inadequate block, when it is performed preoperatively. Therefore, we preferred to perform subcostal approach postoperatively. We cannot compare the various approaches due to small numbers and dissimilar surgeries. Although, most block failures were performed by subcostal approach. This can be attributed to any several possibilities: 1) this approach less reliable; 2) surgical incision was higher than TAP block can cover; 3) the surgeries for which we performed a subcostal TAP, were more invasive (e.g. Kasai procedure).

The non-extubated patients in NICU whom regional block (neuraxial or peripheric) is not performed may routinely need sedation and remifentanil infusion. So, it can prolong postoperative extubation period. Even sufficient success of TAP block with subcostal approach is not observed in patients who underwent supraumbilical surgeries, positive affects as reduction in paracetamol administration, no need of opioids, shorten extubation period cannot be underestimated. The mid axillary approach may be added to subcostal approach due to increase success of TAP block in patients who will have major supraumbilical surgeries.

The thickness of abdominal wall is very slim in this age of groups. Those needles have to be inserted parallel to the probe in low angle. We have to be very careful especially during performance of block with subcostal approach due to near adjacency of subcostal abdominal wall to liver and spleen (Figure 2). Besides, the volume of saline which is given to control needle placement has to be much lesser as it can increase the total volume in such low weight patients.

Prospective randomized controlled trial is more preferable, therefore retrospective description, different types of surgeries, varied approaches of performance and variation of time when TAP block performed may constitute the limitations of our study.

We did not experience any complications in our cases. Long et al. reported one blood aspiration and one peritoneal puncture from 1994 patients whom performed TAP block. They notified that the overall complication rate is 0.3% for TAP block in their study. They concluded that safety should not be the major concerns. Despite, Long and et al. reported that so many different dosages of local anesthetic agents were used for TAP block. According to their reports, in one study within 135 cases, the dosage of bupivacaine (>2 mg/kg) that administrated was unsafe. Suresh et al. studies the plasma level of local anaesthetic agent after performance of TAP block with dosage of 1 mL/kg 0.125% bupivacaine in neonates. They reported that the plasma level of bupivacaine was significantly much lower from toxic dosages. However, the analgesic effects of TAP block with that dosage and volume was not investigated.

We reached an adequate analgesia with our dosage and volume within the limits of the maximal dosage. The risk of LAST is also present with boluses of local anesthetic so, continuous infusions may be advantage for more prolonged analgesia. For this reason, it is an important issue to determine reliable therapeutic range of local anesthetics, especially in premature and low weight neonates.
Conclusions

There are only few reports about TAP block in the neonates and low birth weight groups. This study was analyzed the analgesic effectiveness of TAP block in neonates and infants that pain control is challenging process. It would be more precise to say that, TAP block decrease postoperative analgesic requirements in neonates and young infants undergoing abdominal and inguinal surgeries. The minimally invasive and safe analgesic techniques can be solution for postoperative pain management in neonates and young infants. Therefore, TAP block should be considered in this age group for postoperative analgesia.

Key messages

— The transversus abdominis plane (TAP) block has shown analgesic effectiveness in abdominal wall surgery both in adults and children.
— Postoperative pain management of neonates is still not developed enough and becomes a key issue.
— Postoperative pain management of neonates has challenges. The simplest effective and safe technique should be used.
— In this group of ages, TAP block should be performed to minimize the opioid and analgesic requirements in neonates undergoing abdominal surgeries.

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.

Utilizing Bi-Spectral Index (BIS) for the monitoring of sedated adult ICU patients: a systematic review

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ABSTRACT

BACKGROUND: The ideal level of sedation in the ICU is an ongoing source of scrutiny. At higher levels of sedation, the current scoring systems are not ideal. BIS may be able to improve both. We evaluated literature on effectiveness of BIS monitoring in sedated mechanically ventilated (MV) ICU patients compared to clinical sedation scores (CSS).

EVIDENCE ACQUISITION: For this systematic review, full text articles were searched in OVID, MEDLINE, EMBASE, and Cochrane databases from 1986-2014. Additional studies were identified searching bibliographies/abstracts from national/international Critical Care Medicine conferences and references from searched articles retrieved. Search terms were: “Clinical sedation scale”, “Bi-Spectral Index”, “Mechanical ventilation”, “Intensive Care Unit”. Included were prospective, randomized and non-randomized studies comparing BIS monitoring with any CSS in MV adult (>18 year old) ICU patients. Studies were graded for quality of evidence based on bias as established by the GRADE guidelines. Additional sources of bias were examined.

EVIDENCE SYNTHESIS: There were five studies which met inclusion criteria. All five studies were either unclear or at high risk of bias for blinding of participants and blinding of outcome assessment. All papers had at least one source of additional high risk, or unclear/unstated bias.

CONCLUSIONS: BIS monitoring in the mechanically ventilated ICU patient may decrease sedative drug dose, recall, and time to wake-up. The studies suggesting this are severely limited methodologically. BIS, when compared to subjective CSSs, is not, at this time, clearly indicated. An appropriately powered randomized, controlled study is needed to determine if this monitoring modality is of use on the ICU.

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Key words: Consciousness monitors - Deep sedation - Respiration, artificial.

In mechanically ventilated patients, sedative/analgesic agents are often used to minimize discomfort of the endotracheal tube, ventilator, and the underlying pathologic process. Because of related complications and cost, significant care is required to ensure appropriate use of sedative/analgescics in these patients. However, determining the appropriate level of sedation based on clinical sedation scales (CSSs) may be difficult at higher levels of sedation. The use of an objective monitor of sedation, continuous Bispectral (BIS) Index
monitoring, well established in the operating rooms (OR),\textsuperscript{2,5} has not been adequately studied in the intensive care unit (ICU).

While utilization of physiologic parameters — such as variation in blood pressure, heart rate, and respiratory rate — or a change in the sympathetic response resulting in tearing, sweating, and/or restlessness may be used to titrate sedative/analgesic medication, these are suboptimal in ensuring amnesia and analgesia in patients unable to express their discomfort. A more optimal manner to assess the depth of sedation in MV ICU patients is via one of a number of computed clinical sedation scores (CSSs).\textsuperscript{6} Interobserver variability has been a concern with the use of these CSSs, with potential for decreased reliability and validity,\textsuperscript{7} resulting in an over- or under-sedated patient.\textsuperscript{8}

As of the date of this writing, we have found no systematic review or meta-analysis reporting on which sedation assessment modality or tool is best suited for critically ill, MV ICU patients. In 2013 the American College of Critical Care Medicine (ACCM) Pain, Agitation and Delirium (PAD) study performed a limited meta-analysis of the effect of sedative choice on ICU length of stay, but did not evaluate the influence of sedation tools — CSS versus EEG based tools — on ICU-related outcomes.\textsuperscript{9}

Over-sedated patients may have delayed weaning,\textsuperscript{10} an increased incidence of ventilator associated events from prolonged mechanical ventilation\textsuperscript{10} and increased drug use and costs.\textsuperscript{10,11} Conversely, under-sedated patients may suffer anxiety and agitation, and a resultant increased incidence of adverse events such as awareness and recall, post-traumatic stress disorder, and delirium, as well as — potentially — an inappropriate use of neuromuscular blocking agents (NMBAs).\textsuperscript{11,12}

This systematic review of sedation assessment modalities — CSS’s versus BIS monitoring — in MV ICU patients is performed to ascertain whether BIS monitoring, compared with commonly used CSSs, provides significant benefit in clinically measurable outcomes: amount of sedatives/analgesics, ventilator days, ICU and hospital LOS and mortality, and complications such as delirium and recall.

Evidence acquisition

Protocol and registration

We developed a systematic review protocol with pre-specified inclusion and exclusion criteria for study selection, outcome measurements and analysis. The project was registered with PROSPERO (www.crd.york.ac.uk), \# CRD42015017267.

Eligibility criteria

Type of studies

All prospective randomized controlled trials evaluating and comparing the effect of BIS monitoring in sedated, MV ICU patients with any of the CSSs were pre-planned to be included. If there were an inadequate number of prospective randomized studies — less than 5 to 8 — we considered it acceptable to include non-randomized prospective studies. No language, publication status or publication date restrictions were imposed. Correlation studies of BIS and CSSs were excluded since this was not an objective of this review.

Type of participants

Adults (>18 years old) admitted to the ICU requiring sedation/analgesia for MV were included. Non-ventilated patients were excluded.

Type of intervention

The intervention (BIS monitored) group compared any version of BIS monitors to CSSs.

Type of comparator

The control group included any CSS, such as Ramsay Sedation Scale (RSS), Richmond Agitation Sedation Scale (RASS), Sedation Agitation Scale (SAS), and Glasgow Coma Scale (GCS). Some studies used physiologic parameters — blood pressure, heart rate, respiratory rate and anxiety — to titrate sedative/analgesics/anesthetic in the control group.\textsuperscript{4,10,16}
TYPE OF OUTCOME MEASURES

The primary outcome measure was ICU LOS.\textsuperscript{10} Secondary outcome measures included duration of MV, sedative/analgesic dosage/cost, presence or absence of delirium, and infection.\textsuperscript{11-13}

Information sources

The search strategy for studies in this systematic review was both automated and manual. We used electronic databases, reviewing reference from the lists of articles searched to identify trials to be included in the systematic review. For the automated search, the databases used included the digital libraries of PubMed, CCRCT (Cochrane Central Register of Controlled Trials \textit{via} the Cochrane Library), CDSR (Cochrane Database of Systematic Reviews \textit{via} the Cochrane Library), Ovid, Medline and EMBASE. No language limitations were applied. The titles and abstracts of identified references were reviewed, and reference lists of pertinent trials and systematic reviews were used to identify additional studies.


Search

With the guidance of an expert medical librarian, we searched for eligible studies using the following Medical Subject Heading groupings “bi-spectral index AND sedation scale AND intensive care unit AND mechanical ventilation” (Supplementary Tables I, II online content only). For EMBASE, we used the same MESH terms as in OVID MEDLINE. The same search criteria were used across database resources.

Study selection

Eligibility assessment and data abstraction were performed independently in an un-blinded standardized manner by two reviewers, and repeated by a second set of two reviewers. Abstracted data included eligibility criteria, baseline characteristics, interventions, outcomes, and methodological quality. Instances of disagreement between the reviewers were resolved by consensus among the investigators.

Inclusion criteria

Participants: adults (>18 years old) admitted to the ICU requiring sedation and MV.

Intervention: BIS monitoring.

Comparison: Sedation monitoring using a CSS.

Design: Randomized controlled trials; two prospective observational studies\textsuperscript{16, 17} were also included.

Outcome: All outcomes. We pre-planned to accept any acceptable measure of effect, including, but not limited to, risk ratio, odds ratio or risk difference for binary outcomes, difference in means for continuous outcomes, hazard ratio for time-to-event outcomes.

Exclusion criteria

Studies done in the operation room (OR) or post anesthesia care unit (PACU), ICU patients not requiring MV, correlation studies of BIS with CSSs, any study involving Pediatric patients, any study involving non-ICU patients.

Data collection

DATA COLLECTION PROCESS

A data extraction sheet (based on the Cochrane consumers and Communication Review Group’s data extraction template) was developed. One review author extracted the following data (Study characteristics, study environment, study methods and study qual-
ity indicators) from the included studies and a second author checked the extracted data; this process was then repeated by a second group of two authors. Data were independently extracted from all studies fulfilling inclusion criteria.

Data elements

Data extracted from the studies included the study population demographics, age, gender, diagnosis, co-morbidities, length of stay and inclusion/exclusion criteria, study environment (describing the type of hospital and country), and the design and details of randomization procedure (Tables I, II, Supplementary Table III, online content only). Data were also extracted regarding the study quality indicators and statistical analysis tool used as well as details of CSS used, sedatives and narcotics used, dosages and frequency of administration. We extracted details of BIS monitoring equipment, including the type of BIS monitor and software version. The individual study au-

### Table I.—Characteristics of the included studies - method.

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<tr>
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<tbody>
<tr>
<td>To determine if BIS use results in reduction of time spent on MV and reduced ICU length of stay, reduced early and late pneumonia development, reduced sedative dose, and complications?</td>
<td>To determine whether BIS-monitored titration of sedatives in ICU patients on continuous infusions of sedatives and paralytics was cost effective and reduced the incidence of the recall phenomenon.</td>
<td>To compare the value of BIS monitoring and SAS in guiding ICU sedation therapy for the patients undergoing short-term MV.</td>
<td>To assess whether monitoring sedation status using BIS as an adjunct to clinical evaluation was associated with a reduction in the total amount of sedative drug used in a 12 hour period.</td>
<td>To assess the effectiveness of the BIS monitor in supporting clinical sedation management decisions in mechanically ventilated ICU patients.</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Study design</th>
<th>Prospective observational</th>
<th>Prospective observational</th>
<th>Prospective RCT</th>
<th>Prospective RCT</th>
<th>Prospective RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of recruitment</td>
<td>Not clear; appears to use BIS “when available” and based upon opinion of attending physician. All monitored via RASS.</td>
<td>Not clear Control group, Month 1 and 2 Intervention arm</td>
<td>Unclear. Informed consent from Patient’s legal representative.</td>
<td>All eligible patients were recruited within 24 hours.</td>
<td></td>
</tr>
<tr>
<td>Study period</td>
<td>July 2009 to November 2010.</td>
<td>4 consecutive months</td>
<td>March 2008 to Feb 2009</td>
<td>Undefined</td>
<td>Undefined</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Medical-surgical patients admitted in the ICU in a level 2-3 teaching hospital, use of MV for at least 24 hours.</td>
<td>SICU patients</td>
<td>All adult patients aged between 18-60, admitted between Mar. 2008 and Feb. 2009 who received MV for more than 12 hours in ICU.</td>
<td>Adult MV patients admitted to the neurocritical care unit of a tertiary care hospital with a primary neurological or neurosurgical diagnosis and currently on propofol infusion?</td>
<td>All MV, likely to be ventilated for greater than 12 hours and receiving continuous infusion of Morphine and Midazolam.</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Under 18 years old or older than 80, postsurgical patients extubated in less than 3 hours, patients with a neurological condition (ischemic or hemorrhagic or trauma) because of risk of developing intracranial hypertension that can require deeper levels of sedation.</td>
<td>Severe brain injury with GCS &lt;8</td>
<td>Patients with disturbance of consciousness, cardiovascular and cerebrovascular diseases, and liver/kidney diseases which can possibly impair the metabolism of the propofol and midazolam.</td>
<td>Intracranial injury, neurological disorder and facial burns.</td>
<td></td>
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</table>
Table II. — Characteristic of included studies.

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<tbody>
<tr>
<td></td>
<td>Mechanically ventilated</td>
<td>SICU patients</td>
<td>Patients admitted by ICU at</td>
<td>Adult mechanically ventilated</td>
<td>Control: “Standard</td>
</tr>
<tr>
<td></td>
<td>Patients admitted to a Medical-Surgical ICU in a Level 3-4 Teaching Hospital</td>
<td></td>
<td>Beijing Tong Ren Hospital, March 2008 to February 2009,</td>
<td>patients admitted to the NeuroCritical Care Unit with primary neurological/neurosurgical diagnosis &amp; receiving IV propofol.</td>
<td>Care”. BIS: Continuous monitoring until extubation or tracheostomy.</td>
</tr>
<tr>
<td>Number</td>
<td>N.=85 Control-54 BIS – 31</td>
<td>N.=57 Control-31 BIS-26</td>
<td>N.=105 SAS-63 BIS-42</td>
<td>N.=67 35-Ramsay Score</td>
<td>N.=50 25-Control 25-BIS</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;18 and &lt;80 years (no mean given)</td>
<td>Unspecified</td>
<td>SAS: 39.2±10.4 BIS 39.5±7.8</td>
<td>Ramsay: 54.8±15.1 BIS 57.8±19.8</td>
<td>Control: 50±22 BIS 57±21</td>
</tr>
<tr>
<td>Gender</td>
<td>Male Control: 57.4% BIS: 77.4% (P=0.05)</td>
<td>Male Male</td>
<td>Ramsay: 40% BIS: 50%</td>
<td>Male</td>
<td>Male Control: 68% BIS: 64%</td>
</tr>
<tr>
<td>Severity of illness</td>
<td>Comorbidities given Unspecified</td>
<td>APACHE II:</td>
<td>APACHE IV:</td>
<td>APACHE II: median (IQR)</td>
<td>Control: 14 (11, 20) BIS 14 (11, 19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SAS: 4.2±2.3 BIS: 3.6±2.6</td>
<td>Ramsay: 67.4±20.3 BIA: 75.6±21.8</td>
<td>Ramsay: 8.4±2.6 BIS: 7.6±2.7</td>
<td></td>
</tr>
<tr>
<td>Frequency of BIS monitoring</td>
<td>Upon admission and at 24 hours</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>Unspecified</td>
</tr>
<tr>
<td>CONTROL CSS used</td>
<td>RASS</td>
<td>Vital signs changes after stimulation</td>
<td>SAS Ramsay</td>
<td>Hourly subjective clinical assessment – HR, BP, Consciousness Level &amp; Pupillary Size</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Duration CSS monitoring</td>
<td>Unspecified</td>
<td>Unspecified</td>
<td>From the ICU admission to 0600 the next day.</td>
<td>12 hours</td>
<td>Midazolam/propofol</td>
</tr>
<tr>
<td>Sedative used</td>
<td>Midazolam/propofol</td>
<td>Lorazepam, Midazolam, and Propofol</td>
<td>Midazolam/propofol</td>
<td>Propofol</td>
<td>Midazolam</td>
</tr>
<tr>
<td>Narcotic used</td>
<td>Morphine</td>
<td>Cisatracurium</td>
<td>Morphine Yes, unspecified</td>
<td>Fentanyl prn</td>
<td>Morphine</td>
</tr>
<tr>
<td>NMB used</td>
<td>Cisatracurium</td>
<td>BIS of 40-60</td>
<td>Yes, unspecified</td>
<td>Unspecified</td>
<td>Unspecified</td>
</tr>
<tr>
<td>Goals of sedation</td>
<td>Morphine</td>
<td>Vitals after signs after stimulation.</td>
<td>Control: Vital Signs after Stimulation.</td>
<td>Fentanyl prn</td>
<td>Control: Normal</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>BIS: 70-80</td>
<td>BIS: 70-80</td>
<td>Ramsay Score = 4 BIS between 60-70</td>
<td>HR, BP, LOC, &amp; Pupillary Size</td>
</tr>
<tr>
<td>Duration of sedation</td>
<td>Weaning left up to physician judgment</td>
<td>Unspecified</td>
<td>Median (IQR) SAS: 16 hours (13, 18) BIS: 14 (12.9, 17.1)</td>
<td>12 hours</td>
<td>Until extubation or tracheostomy</td>
</tr>
<tr>
<td>Outcome Principal outcome</td>
<td>Length of MV</td>
<td>Cost effectiveness of sedative and paralytic agents</td>
<td>Dosage of midazolam and propofol</td>
<td>Total dose of sedative drug used in 12 hours. Overall sedative use</td>
<td>Total amount of sedative, Amount of sedative administered over time</td>
</tr>
<tr>
<td></td>
<td>ICU stay, incidence of early and late pneumonia, dose of sedatives, costs, complications</td>
<td>Incidence of recall</td>
<td>Mean recovery time. Under sedation event</td>
<td>Length of MV and ICU LOS</td>
<td>Length of MV and ICU LOS</td>
</tr>
</tbody>
</table>

BILGILI UTILIZING BI-SPECTRAL INDEX (BIS) FOR THE MONITORING OF SEDATED ADULT ICU PATIENTS
The assessment of the risk of bias of individual studies included the following: random sequence generation, allocation concealment (a method in which researchers are unable to influence whether the patients end in treated or the control group), blinding of personnel and participants, blinding of outcome assessment, incomplete outcome data, selective reporting (ORBIT classification),\(^\text{15}\) other sources of bias, and \textit{a priori} protocol/analysis plan. Two authors assessed the risk collaboratively (DG and AJL).

### Summary measures

Effect on ICU LOS was the primary measure of BIS utilization when compared to CSSs.

### Planned method of analysis

While meta-analysis was our goal, extreme variability, inconsistency and heterogeneity across the studies made this impossible.

### Evidence synthesis

#### Study selection

Of 385 potential studies, we identified 63 citations 7-14, 16-71 from search of electronic bibliographic databases. Five studies 10, 13, 14, 16, 17 met the inclusion criteria after excluding correlation articles, trials involving pediatric patients and duplicates; because there were only three randomized, controlled trials, we included two prospective observational studies 16, 17 in this systematic review (Figure 1). These five trials were included in qualitative synthesis and systematic review. While there was general agreement amongst all the reviewers, minor differences were resolved with the help of the

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**Figure 1.**—PRISMA Flow Diagram for Study selection.
related to the CSS used. In general, outcome measures were not defined well; there were a limited number of studies for each outcome. While bias varied by study, all studies were either unclear or at high risk of bias with blinding of participants and personnel, and blinding of outcome assessment (Supplementary Table IV, online content online).

Statistical analysis

We could not reliably combine studies in a way that made scientific sense. Studies used different outcome measures, and were silent on, or used different, BIS monitors, which may have included a different algorithm to calculate sedation level. Moreover, the duration of the BIS monitoring was individualized by the study. Thus, we felt combining such overtly different studies could be potentially misleading.

Discussion

BIS CHARACTERISTICS

The BIS was introduced by Aspect Medical Systems in 1994 as a novel way to algorithmically measure the level of consciousness of a patient under general anesthesia by using a limited montage electroencephalogram. This is used in conjunction with other physiologic monitoring, such as electromyography, to estimate the depth of anesthesia and thereby minimize the possibility of intraoperative awareness. The US Food and Drug Administration (FDA) cleared BIS monitoring in 1996 for assessing the hypnotic effects of general anesthetics and sedatives. BIS is a practical, processed EEG parameter that measures the direct effects of sedatives on the brain. It is applied using a frontal montage and provides objective information about an individual patient’s response to sedation/anesthesia.

BIS was initially devised to monitor depth of anesthesia in the OR, as it was intended to replace or supplement Guedel’s classification system for determining anesthetic depth. Use of the BIS monitor is thought to reduce
the incidence of intraoperative awareness during anesthesia. Titrating anesthetic agents to a specific BIS index during general anesthesia in adults allows the anesthesiologist/anesthetist to adjust the amount of anesthetic agent to the needs of the patient, potentially resulting in a more rapid emergence from anesthesia. There are a wide range of BIS modules available currently on the market, including — in the USA — Phillips, GE, Datex-Ohmeda, Dräger Medical, Space labs, Nihon Kohden, Dixtal and Datascopc.

The key application of BIS monitoring is objective assessment of sedation in the patient’s intraoperative and immediate peri-operative phase in the OR and recovery room. The not-so-established, and less frequent, usage of BIS is in the ICU, in postoperative patients who may have received neuromuscular blockade, close monitoring of sedation level in drug induced coma, and for sedation purpose during bedside procedures. It is in these areas that the utility of BIS could be explored.

Summary of evidence

This systematic review on comparison of diagnostic properties and efficacy of BIS monitoring and CSS is the first to summarize available validation studies. We found 5 studies 10, 13, 14, 16, 17 each of which evaluating different outcomes (Table III).

Among the included studies, Olson’s was a prospective study randomizing patients to Ramsay scale or BIS monitoring in addition to Ramsay Scale.13 The study began at 08.00 after consent was obtained. All patients were sedated with propofol. Patients had sedation stopped every 2 hours. Nurses were instructed to dose the propofol infusion to obtain a score of 4 in the control group, or a Ramsay score of 4 and a BIS value between 70 and 80 in the BIS monitoring group. The primary endpoint was the total dose of sedative medication used in 12 hours. There was an approximate 50% reduction in the amount of sedation used: BIS-augmentation 93.5±86.3 mL, Ramsay scale alone 157.8±119.2 mL (P=0.0146). The study’s power analysis suggested 45 patients per group, but randomization was stopped in interim analysis because of the statistical significance achieved.

Zhao et al.14 randomized patients to receive midazolam or propofol sedation. Sedation was suspended hourly and titrated to goals of BIS 50-70, SAS 3-4. The authors showed some differences in BIS-treated versus SAS treated patients. Percent total time under sedation, propofol and midazolam doses were all higher in the BIS group (P<0.05). However, the median time to wake-up was less in the BIS group (0 versus 15 minutes, P<0.05).

Weatherburn’s study 10 was a prospective randomized trial in which patients sedated with morphine and midazolam were randomized to sedation titration based on a BIS score of greater than 70, or subjective clinical assessment which could be augmented based on clinician preference with a sedation scoring tool. The investigators found no differences in the total amount of sedation administered, nor in days of mechanical ventilation, or ICU length of stay. Among secondary outcomes, they did find that the amount of morphine used in BIS patients significantly increased over time (P<0.02 after Bonferoni correction).

There were two abstracts included in this review. Both were considered to be at high risk of bias as the provided information was considered inadequate. In the prospective observational study by Altaba Tena et al.17 of 85 patients, there were not significant differences in duration of ventilation, total dose of sedatives, ventilator-associated pneumonia, or ICU or hospital length of stay. In Kaplan and Bailey’s16 prospective cohort trial, patients with GCS <9 were treated on alternating months either via apparent patient comfort guided by vital sign changes or using a BIS value between 70-80. There were significant differences in amount of sedation used and in the number of patients who recalled a frightening/painful experiences.

A study — which was not part of our original evaluation — of interest is that by Mahmood et al.72 These investigators evaluated 110 traumatized patients, of whom 50% were from motor vehicular crashes, and 88% had...
Table III.—Results.

<table>
<thead>
<tr>
<th>Name of study/outcomes</th>
<th>Intervention N=31</th>
<th>Control N=54</th>
<th>P</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a. ALTABA TENA 17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early VAP N, (%)</td>
<td>4 (1, 10)</td>
<td>4 (2, 10.75)</td>
<td>0.33</td>
<td>NS</td>
</tr>
<tr>
<td>Late VAP</td>
<td>3 (10%)</td>
<td>7 (13.5%)</td>
<td>0.46</td>
<td>NS</td>
</tr>
<tr>
<td>Dosages propofol (mcg)</td>
<td>1996 (800, 4800)</td>
<td>4160 (1860, 6375)</td>
<td>0.15</td>
<td>NS</td>
</tr>
<tr>
<td>Dosages midazolam (mg)</td>
<td>155 (55, 279)</td>
<td>137 (54, 420)</td>
<td>0.87</td>
<td>NS</td>
</tr>
<tr>
<td>Dosages morphine (mg)</td>
<td>77 (33, 240)</td>
<td>96 (44, 214)</td>
<td>0.93</td>
<td>NS</td>
</tr>
<tr>
<td>Dosage cisatracurium (mg)</td>
<td>22.5 (10, 100)</td>
<td>42 (10, 100)</td>
<td>0.73</td>
<td>NS</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>4 (13.3%)</td>
<td>12 (25%)</td>
<td>0.16</td>
<td>NS</td>
</tr>
<tr>
<td>UTI</td>
<td>1 (3.3%)</td>
<td>4 (7.7%)</td>
<td>0.39</td>
<td>NS</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>1 (3.2%)</td>
<td>6 (11.5%)</td>
<td>0.18</td>
<td>NS</td>
</tr>
<tr>
<td>AKI</td>
<td>15 (18%)</td>
<td>19 (22.8%)</td>
<td>0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Failure to extubate</td>
<td>7 (11.1%)</td>
<td>14 (22.2%)</td>
<td>0.5</td>
<td>NS</td>
</tr>
<tr>
<td>LOS ICU days</td>
<td>7.5 (2, 17)</td>
<td>7.5 (4, 19)</td>
<td>0.51</td>
<td>NS</td>
</tr>
<tr>
<td>LOS Hospital days</td>
<td>20 (12, 36)</td>
<td>20 (9, 32)</td>
<td>0.57</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality ICU</td>
<td>12 (14.1%)</td>
<td>16 (18.8%)</td>
<td>0.26</td>
<td>NS</td>
</tr>
<tr>
<td>3b. KAPLAN 16</td>
<td>N=26</td>
<td>N=31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedative cost per patient</td>
<td>$669±1362</td>
<td>$819±2045</td>
<td>&gt;0.05</td>
<td>18% reduction in cost, NS</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>18% reduction in usage</td>
<td>&lt;0.05</td>
<td>Significant Difference</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>18% reduction in usage</td>
<td>&lt;0.05</td>
<td>Significant Difference</td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>47% reduction in usage</td>
<td>&lt;0.05</td>
<td>Significant Difference</td>
<td></td>
</tr>
<tr>
<td>Under sedated</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over sedated</td>
<td>**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recall (frightening/painful events)</td>
<td>4%</td>
<td>18%</td>
<td>&lt;0.05</td>
<td>Significant difference</td>
</tr>
<tr>
<td>3c. ZHAO (14)</td>
<td>N=42</td>
<td>N=63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% total time under sedation</td>
<td>75.2%</td>
<td>52.8</td>
<td>&lt;0.01</td>
<td>Significant difference</td>
</tr>
<tr>
<td>Time period 1 sedated</td>
<td>78.6%</td>
<td>22.2%</td>
<td>&lt;0.01</td>
<td>Significant difference</td>
</tr>
<tr>
<td>Time period 2 sedated</td>
<td>88.1%</td>
<td>20.6%</td>
<td>&lt;0.01</td>
<td>Significant difference</td>
</tr>
<tr>
<td>Time period 3 sedated</td>
<td>81.0%</td>
<td>31.7%</td>
<td>&lt;0.01</td>
<td>Significant difference</td>
</tr>
<tr>
<td>Restlessness after Suction</td>
<td>81%</td>
<td>79.4%</td>
<td>&gt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Increased endotracheal tube resistance</td>
<td>71.4%</td>
<td>74.6%</td>
<td>&gt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Pain free during sedation</td>
<td>92.8%</td>
<td>93.6%</td>
<td>&gt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Delirium after extubation</td>
<td>4.8%</td>
<td>1.6%</td>
<td>&gt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Midazolam (mg/kg/hr)</td>
<td>0.1±0.02</td>
<td>0.09±0.02</td>
<td>&lt;0.05</td>
<td>Significant difference</td>
</tr>
<tr>
<td>Propofol (mg/kg/hr)</td>
<td>0.95±0.23</td>
<td>0.86±0.2</td>
<td>&lt;0.05</td>
<td>Significant difference</td>
</tr>
<tr>
<td>Duration of mechanical ventilation (median, interquartile range), hrs</td>
<td>16.5 (14.5, 19)</td>
<td>17.0 (15, 19)</td>
<td>&gt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Sedation time (median, IQR), hrs</td>
<td>14 (12.9, 17.1)</td>
<td>16 (13, 18)</td>
<td>&gt; 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Time to wake-up (median, IQR), min</td>
<td>0 (0, 20)</td>
<td>15 (0, 47)</td>
<td>&lt;0.05</td>
<td>Significant difference</td>
</tr>
</tbody>
</table>

(To be continued)
suffered head injury; average Glasgow Coma Scale score was 6.9±2.7. While the bias in this study is as remarkable as its results — there was no mention of randomization nor how it was done if it was done, there was no power analysis, and there was, finally, no mention of how the BIS was used nor the BIS value that was aimed for — use of BIS in this study resulted in a decrease in the use of sedation and analgesia, a decrease in agitation, failure to extubate, and tracheostomy, and an approximate 4 day decreased length of stay. While this study has its flaws, it is of great interest.

While BIS monitoring in the mechanically ventilated ICU patient may decrease sedative drug dose,10, 14, 16, 72 recall,16 and time to wake-up,14 given the limitations of the studies and the decided lack of significant differences when using BIS alone or BIS-augmentation of standard clinical care, combined with the potential applicability of this mode of monitoring in the ICU, there is a compelling rationale to use BIS only in ICU patients in a properly powered randomized prospective trial. The clinical experience of one of the authors (AJL), using BIS in the ICU, leads us to think that this modality of monitoring will advantageous in decreasing ventilator days and drug dosages while preventing under-sedation.

**Limitations of the study**

The limitations of this systematic review are significant, as there were few studies meeting the inclusion criteria. Of the studies included, each had significant methodological limitations. Additionally, because of the heterogeneity between the studies regarding the CSS, BIS equipment, ICU setting and statistical analytical tools used, it is not possible to say with any confidence that BIS monitoring improves patient outcomes. More appropriately designed trials are required.

**Table III.** Results (continues).

<table>
<thead>
<tr>
<th>Name of study/outcomes</th>
<th>Intervention</th>
<th>Control</th>
<th>P</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>3d. Olson13</td>
<td>N.=32</td>
<td>N.=35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose of propofol in 12 hr (mL)</td>
<td>93.5±86.3</td>
<td>157.9±119.2</td>
<td>0.0146</td>
<td>BIS augmented group needed half the sedative doses</td>
</tr>
<tr>
<td>Rate of infusion of propofol (mcg/kg/min)</td>
<td>14.6±12.2</td>
<td>27.9±20.5</td>
<td>0.0026</td>
<td></td>
</tr>
<tr>
<td>Risk of propofol infusion exceeding manufacturer’s recommended dosing guide (4 mg/kg/hr) %</td>
<td>0 subjects, 0%</td>
<td>8 subjects, 23%</td>
<td>0.0052</td>
<td>Non BIS group significantly more likely to receive Propofol at rates that exceeded manufacturer’s recommended doses</td>
</tr>
<tr>
<td>Mean recovery time (min)</td>
<td>1.2±2.08</td>
<td>7.5±7.54</td>
<td>&lt;0.0001</td>
<td>BIS augmented group had a rapid emergence from sedation</td>
</tr>
<tr>
<td>Number of under sedation events</td>
<td>0</td>
<td>0</td>
<td>NS</td>
<td>BIS augmented group appeared safe</td>
</tr>
<tr>
<td>Fentanyl used mcg/12 hr</td>
<td>200</td>
<td>350</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Weatherburn10</td>
<td>N.=25</td>
<td>N.=25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedative dosage – midazolam (mean, 95% confidence intervals)</td>
<td>18.4 (10.9 – 30.9)</td>
<td>14.6 (8.8 – 24)</td>
<td>0.85</td>
<td>No significant differences in sedation/analgesia total doses. When doses of midazolam (P=0.03) and morphine (P=0.005) were trended over time in ICU, BIS- patients received more of both drugs</td>
</tr>
<tr>
<td>Analgesic – morphine</td>
<td>22.6 (14.9 – 34.5)</td>
<td>26.6 (17.5 – 40.4)</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation (mean [SD], days)</td>
<td>7.0±0.6</td>
<td>7.0±0.8</td>
<td>0.71</td>
<td>No significant difference</td>
</tr>
<tr>
<td>ICU LOS (Median, [IQR] days)</td>
<td>12 (6, 18)</td>
<td>8 (4, 14)</td>
<td>0.2</td>
<td>No significant difference</td>
</tr>
</tbody>
</table>

Note: Information taken from data / Tables in the original articles and / or after telephonic discussion with authors.
to assess the efficacy of BIS monitoring in different ICU populations and settings.

Strengths

This systematic review was exhaustive, with strict inclusion and exclusion criteria used. Additionally, the senior investigators have extensive experience in neuromonitoring and utilization of perioperative BIS monitoring. Most importantly, this systematic review points out the need for a well-designed, randomized, controlled trial.

Conclusions

We performed a systematic review of randomized trials comparing CSSs with BIS in mechanically ventilated ICU patients. We found numerous issues related to study design, conduct, and quality that, to a great extent, dispute their validity and generalizability in evaluating how, or whether, BIS modality of sedation monitoring has a significant effect on clinical outcomes.

Implications for practice

BIS does not appear to be indicated based on the included studies; a properly powered randomized controlled study is needed. Indeed, the American College of Critical Care Medicine (ACCM), the Society of Critical Care Medicine (SCCM), the American College of Chest Physicians (ACCP), and the American Society of Health System Pharmacists (ASHP), in their clinical practice guideline for the sustained use of sedatives and analgesics in the critically ill patient point out that the routine use of BIS in the ICU is not recommended.73

Future research

The reliability of BIS has been questioned, in part, because its numerical calculation does not rely on an underlying physiological model of how the brain functions, nor on how awareness is generated. Additionally, the BIS value is insensitive to the commonly used anesthetic agent ketamine, which has a mechanism of pharmacological action different than the potent inhaled anesthetic agents. It is possible that different sedatives and analgesics will have a variable effect on the BIS-calculated sedation value, and may require differential validation. Future studies need to focus on the BIS monitoring of patients in different critical care settings, specifically, patients who are in the neuro-critical care unit or who have suffered cerebro-vascular accidents, traumatic brain injuries, and so forth.

Larger studies are required with better control of variables to adequately assess the influence of BIS monitoring on under-sedation, over-sedation, incidence of delirium, and outcomes resulting from prolonged duration of sedation and ICU LOS. In the context of these further studies, we recommend evaluation of infectious complications in BIS-monitored patients as well. It is intuitive — even if potentially incorrect — that if there is a decrease in the sedative dosage in the BIS group, there will be fewer ventilator days, a lesser incidence of ventilator associated events and, potentially, other infectious complications.

Key messages

— BIS monitoring in the mechanically ventilated ICU patient may decrease sedative drug dose, recall, and time to wake-up. The studies suggesting this are severely limited.

— BIS, when compared to subjective CSSs, is not, at this time, clearly indicated.

— An appropriately powered randomized, controlled study is needed to determine if this monitoring modality is of use in the ICU.

— Until this study is performed, we recommend that BIS be used cautiously in the ICU population.

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.

Author’s contributions.—Juan C. Montoya, Leena K. Gupta, H. Lester Kirchner, and A. Joseph Layon conceived of and designed the study. Juan C. Montoya and Leena K. Gupta initially reviewed the literature and provided initial evaluation of included papers; A. Joseph Layon, Beliz Bilgili, and David S. Gloss re-evaluated the literature search and the included and excluded papers; H. Lester Kirchner and Andrea L. Berger were statistical consultants for the study.

All the authors assisted in the writing, reviewing, and editing of the paper; all authors approved the final manuscript. All the authors attest to the integrity of the manuscript.


For supplementary materials, please see the online version of this article.
Biological markers of injury-induced immunosuppression

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ABSTRACT

Severe injuries, such as severe sepsis, burn, trauma and major surgery, lead to an overlapping development of pro- and anti-inflammatory responses. It is now well established that these injuries are associated with the secondary development of immune suppression, which results in significant morbidity and mortality. Recent data suggest that immunostimulatory drugs might prevent these complications. However, intensive care patients are heterogeneous, making patient stratification essential for a targeted treatment. In the present review, we discuss potential biomarkers of injury-induced immunoparalysis, mainly focusing on those that have been associated with poor outcome in various clinical settings. We namely present clinical data on monocyte human leukocyte antigen Dr, lymphopenia, PD-1/PD-L1 and transcriptomic approach.

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Key words: Wounds and injuries - Sepsis - Immunosuppression - Biomarkers - Monitoring, immunologic.

The immune system response to major injuries often leads, after an initial hyperactivation, to an incompetent and hyporeactive immune status (Figure 1). This injury-induced immunosuppression has been described in the past decades in various clinical settings, such as septic shock, severe trauma, severe burns, or major surgery. When persistent or intense, immune paralysis is associated with the development of secondary infections and pejorative outcomes. Despite recent advances in critical care medicine, mortality remains high and often not related to the initial injury, but rather to secondary events — especially infections — that occur during the immunosuppression period. Mechanisms of this immunoparalysis and therapeutic opportunities have been recently published in the particular field of sepsis. In the present review, we will focus on cellular biomarkers of injury-induced immunosuppression resulting from various forms of severe injuries. Unless specified, all studies cited in the present review involved intensive care patients.
BIOLOGICAL MARKERS OF INJURY-INDUCED IMMUNOSUPPRESSION

Need for biomarkers

Even considering the same diagnosis, there is a huge clinical and biological diversity resulting from the complex and highly dynamic interaction between host and injury. The panel of disease severity and patients’ comorbidities increases even more this heterogeneity. This has been suggested to participate in the failure of clinical trials in septic shock. In line, ICU patients’ immune status is heterogeneous but cannot be determined based on clinical signs. Biomarkers of patients’ immune status could help patient stratification such as proposed in the PIRO (predisposition, insult, response, and organ dysfunction) Score.\(^\text{11}\)

Reversing and/or shortening the immunoparalysis phase might be of crucial interest to improve patients’ outcomes.\(^\text{12}\) For instance, one of these promising immunoadjuvant therapies is interferon-gamma (IFNγ). It has been shown to restore the expression of transcripts associated with the development of immunosuppression in an \textit{ex vivo} monocyte endotoxin tolerance model.\(^\text{13}\) IFNγ also partially reversed sepsis-induced immunoparalysis in a human \textit{in vivo} model of Gram negative sepsis.\(^\text{14}\) We can also refer to the work of Meisel et al., who have shown that mHLA-DR guided GM-CSF (granulocyte–macrophage colony-stimulating factor) therapy enables to shorten the time of mechanical ventilation and hospital/intensive care unit stay.\(^\text{15}\)

Because of the aforementioned heterogeneity, critically ill patients may not all benefit from immunostimulatory drugs. Therefore, clinicians need to know the particular immune status of each patient in real time to propose the best personalized care. Finally, markers of patient immune status could be used to monitor treatment efficacy or side effects.

Biomarkers of injury-induced immunosuppression

**Innate immunity**

**NEUTROPHILS AND IMMATURE GRANULOCYTES**

Neutrophils represent the first line of innate immune defense against infection and are the most abundant leukocyte subset. Paradoxically, data about injury-induced neutrophil alterations are scarce. Sepsis leads to the massive recruitment of immature neutrophils. The immature granulocyte fraction can be assessed by a blood cell analyzer, expressing the result in Delta neutrophil index (Dn), which independently correlates with 28-day mortality in patients with sepsis.\(^\text{16}\) Consistently, Mare et al. found a significantly lower immature granulocyte count in the >4-week survival group compared with the patients who died within the first week of sampling.\(^\text{17}\)

We recently studied functional neutrophil alterations during sepsis-induced immunosuppression (day 3-4 and day 6-8), on 43 septic shock patients and 23 healthy volunteers.\(^\text{18}\) A high immature granulocyte count was associated with mortality. In addition, we performed a global evaluation of the neutrophil alterations in septic shock, and highlighted a markedly altered neutrophil chemotaxis (reduced integrin, selectin, and chemokine receptor expression with altered \textit{ex vivo} migration in response to different chemo attractants) and oxidative burst, also associated with mortality. Conversely, and in accordance with the work of Drifte et al.,\(^\text{19}\) phagocytose and activation capacities were
preserved, indicating that neutrophil function is reconfigured rather than globally suppressed.

Impaired neutrophil chemotaxis, altered phagocytosis and bacterial killing were also described in burn \(^{20-23}\) and trauma patients.\(^ {24}\) However, the possible association between neutrophils and mortality/morbidity has only been investigated in sepsis.\(^ {17, 18}\)

**MONOCYTES**

Monocytes are myeloid cells which play a central role in innate immunity. These circulating cells are also able to release pro and anti-inflammatory molecules. After injury, many aspects of monocyte physiology have been studied.

**HLA-DR**

One of the most promising biomarkers of injury-induced immunoparalysis is monocyte human leukocyte antigen DR (mHLA-DR). As developed elsewhere, monocytes from septic patients display an altered antigen presentation, related to lower expression of major histocompatibility (MHC) class II system. This decrease in cell-surface expression of mHLA-DR is a marker of monocyte dysfunction, objectified by lower synthesis of pro-inflammatory cytokines in response to bacterial challenges, lower proliferation rate, and interestingly recovery of monocyte functions after restoration of normal mHLA-DR levels after treatment *ex vivo* and *in vivo*.\(^ {25}\)

Low mHLA-DR expression has been associated to both mortality and secondary infections in various clinical backgrounds: septic shock, severe burn, trauma, pancreatitis, cirrhosis etc. For instance, Gouel-Chéron *et al.* observed that after severe trauma, a ratio of mHLA-DR expression between day 3 and day 2 below 1.2 is an independent predictor of septic complication with an odd ratio of 5 (95% CI [1.6; 19], \(P=0.008\)) after multivariate analysis.\(^ {26}\) Similarly, Venet *et al.* reported an association between mHLA-DR decrease and severity as well as secondary septic shock after severe burn injury.\(^ {6}\)

Overall, mHLA-DR is a robust prognostic marker of mortality and secondary infections in a broad variety of injury contexts. Multi-center clinical trials are still needed to define precise cut-off values, as they may depend on the type of injury.

**IL10 and IL10/TNF ratio**

Interleukin 10 (IL10) is a powerful anti-inflammatory mediator, which namely suppresses dendritic cell and macrophage functions. Many different cell populations may be involved in its synthesis, such as monocytes, and its regulation is complex.\(^ {27}\) In a septic shock population, Monneret *et al.* showed that IL10 correlates with HLA-DR expression and that values were significantly higher among non-survivors.\(^ {28}\) Interestingly, IL10 elevation was already significantly associated to mortality at time of admission and IL10 remained higher during 15 days in the non-survivor group. These results were consistent with previous literature regarding IL10 dosage \(^ {29-31}\) or IL10 mRNA measurement.\(^ {32-34}\) The association between IL10 and septic complication or mortality was also described in burned patients\(^ {35, 36}\) and in trauma patients.\(^ {37}\) IL10 may therefore constitute an early marker of forthcoming immunoparalysis. Some authors also evaluated IL10/TNF ratio, which reflects the pro/anti-inflammatory balance and also correlates with unfavorable outcome.\(^ {28-30}\)

**Other monocyte-related markers**

During sepsis, monocytes show not only impaired antigen presentation, but also decreased pro-inflammatory response, as assessed by the down-regulation of surface markers such as CD10, CD86, CD14, GM CSF receptor, or CX3CR1.\(^ {38-43}\) For all these markers, a reduced expression was associated with mortality. To our knowledge, none of them has been associated with poor prognosis in surgical, burn or trauma context.

Another interesting monocyte surface protein is PD-L1. This marker will be discussed
in a following subsection, together with the protein it binds.

CD163 is a scavenger receptor expressed on monocytes, macrophages, and dendritic cells. It is also known as haptoglobin-hemoglobin receptor, and also exists as a soluble form, sCD163, which is shed into plasma after stimulation by mediators of inflammation. Three clinical studies in septic populations showed that monocyte expression of CD163, or sCD163 level, were higher in non-survivors, even at early time points. Nevertheless, CD163 has not been evaluated in severe burn, surgery or trauma.

Functional testing: endotoxin tolerance

Functional approaches may be interesting, for they give an insight into *in vivo* cell response to an immune challenge. Monocytes from septic patients have been particularly studied; they display a predominantly anti-inflammatory phenotype, this observation leads to the concept of leukocyte reprogramming. Indeed, these cells release less pro-inflammatory mediators (such as TNF, IL6 or IL12) and as much or even slightly more anti-inflammatory molecules (IL10, IL1ra). This reduced responsiveness after LPS stimulation has been described as *Endotoxin Tolerance*. Hence, this method may reveal immune paralysis. Endotoxin tolerance has also been described in severe trauma as well as in major surgery.

Clinical impact of this reprogramming has been recently studied. In a heterogeneous pediatric population with multiple organ failure syndrome, Hall et al. found an association between a reduced *ex vivo* LPS-induced TNF response (in whole blood, on day 7 after admission) and increased nosocomial infection (RR 3.3 [1.8-6.0]) and mortality (RR 5.8 [2.1-16]). Conversely, Van Vught et al. observed an endotoxin tolerant phenotype on septic patient monocytes, but it was not associated with the development of nosocomial infections. As suggested by the authors, this negative result may be related to the early time point that was chosen (day 0). Further multicentric clinical trials are warranted to confirm the prognostic value of this functional approach in different injury contexts, and to determine its optimal timing.

**Dendritic cells**

Dendritic cells (DCs) are professional antigen-presenting cells (APCs), playing a key role in linking innate and adaptive immune systems. DCs capture and process antigens, before migrating to lymph nodes, where they present antigens to lymphocytes. Literature provides strong evidences for both quantitative and qualitative DC alterations after injury. Hotchkiss et al. showed a dramatic reduction in the number of follicular DCs in septic patients compared with controls. MHC class II expression by DCs was also lower in septic patients. This is consistent with the observation that circulating DC count is lower in septic shock patients than in controls as early as day 1, and persistent low circulating myeloid DC count is associated with nosocomial infection. Furthermore, DC loss in septic patients is higher in non-survivor septic patients than in survivors and is inversely correlated with severity scores.

After surgery, DC count increases acutely, and then drops below preoperative levels on days 2-3. Surgery-induced DC depletion is associated with IL12 — a pro-inflammatory cytokine — deficiency. DC functional impairment has also been observed in trauma patients with an *in vitro* reduced differentiation into DCs, a lower IL12 production, and an impaired T cell proliferation. Furthermore, life span and signaling function of DCs may be altered by trauma. Consistently, severe burn patients displayed early low DC count. In addition DCs from burn patients had impaired reactivity, an anti-inflammatory phenotype, and dysfunctional T cell-priming ability.

To sum up, functional and quantitative impairments of DCs have been observed in many
different injury situations, and may be key players of injury-induced immune paralysis. As murine administration of purified DCs and of DC growth factor (Fms-related tyrosine kinase 3 ligand, FLT3-L) reversed mortality and secondary sepsis, monitoring and targeting DCs represent a promising therapeutic strategy.

**Adaptive immunity: T and B cells**

Lymphocytes are central actors in immunity, acting as both effectors and regulators. Not only are they quantitatively altered during injury, but they also display functional anomalies.

**Cell counts**

*Lymphopenia.*—Apoptosis-related loss of immune cells is an important feature of injury-induced immune paralysis. This cell loss affects both T cells (except for Treg cells) and B cells. Lymphopenia is a hallmark of SIRS and septic syndrome, and has also been described in trauma, burn and surgical patients. At day 4 of sepsis, lymphopenia was independently associated with 28-day and 1-year survival and severe lymphopenia was associated with increased development of secondary infections. In this study, lymphopenia at admission was not associated with mortality, contrary to the results presented by Chung et al. Consistently, in emergency general surgical patients, lymphopenia was independently associated with increased in-hospital mortality (OR 3.5 [1.7-7.3]). In trauma as well, failure to normalize lymphopenia in severely injured patients is associated with significantly higher mortality, and with higher rate of nosocomial infections after multivariate analysis (personal data). Moreover, lymphocyte count is cheap and included in routine biology. However, most of the severely injured patients display lymphopenia, which may limit its discriminating power. Effective stratification strategies including lymphopenia are still to be determined.

**Neutrophil-to-lymphocyte ratio.**—Another way to take into consideration lymphopenia is to use the neutrophil-to-lymphocyte ratio (NTL). From a pathophysiological perspective, NTL reflects the complex balance between inflammatory insult and immune suppression. In clinical setting, NTL was first investigated in abdominal surgery. Increased NLR after digestive surgery was associated with an increased risk of complications or death. Moreover, time points and cut-offs were very heterogeneous among these studies, and cancer in itself may interfere with NTL.

Three clinical studies recently assessed NTL in the ICU. In cirrhotic patients with acute complication, high NLR at day 1 was associated with mortality in a multivariate logistic regression. A retrospective study suggested that NTL at admission is associated with 28-day mortality in unselected critically ill patients, however this association was not observed in the septic patient subgroup. Riché et al. refined this result in a septic shock cohort. They highlighted a reversed NTL evolution according to the timing of death: early death was associated with low NTL at admission, whereas late death (≥day 5) was associated with high NTL between day 1 and day 5.

All in all, NTL is an easy and affordable biomarker which may be of interest to detect immune failure, yet the best timing and cut-offs are still to be determined, and, like mHLA-DR, these parameters may depend on the clinical situation.

**Regulatory T cells**

Regulatory T cells (Tregs) are a very specific subset of T cells, crucial for immune tolerance and homeostasis. Indeed, they inhibit the activation and proliferation of most of the other immune cells, by directly killing cytotoxic cells, inhibiting their cytotoxic production, and secreting immunomodulatory cytokines (TGFβ, IL10). As presented recently, the percentage of Tregs increases after the onset of septic shock, burn and trauma. The enhancement of their suppressive functions and the relative and
absolute elevation in their count were associated with mortality in burn.\textsuperscript{81} Chen et al. also described a significant association between Treg count increase at day 7 and mortality in ICU patients with sepsis.\textsuperscript{82} CD39\textsuperscript{+} Treg cells form a specific subset displaying increased suppressive skills. In septic patients, increased expression of CD39\textsuperscript{+} Tregs was associated with mortality and severity of sepsis.\textsuperscript{83}

Conversely, after traumatic brain injury, the level of circulating Tregs was positively associated with neurologic recovery and lower hospital mortality.\textsuperscript{84} Indeed, Treg action is thought to be neuroprotective because, in this context, a down-regulation of inflammation may promote cell survival.

As a conclusion, Tregs may play a role in injury-induced immunosuppression, given their important regulatory properties.

**Increased co-inhibitory receptors**

*CTLA-4, BTLA.*—After antigen recognition, T cell full activation depends on the balance between co-stimulatory and co-inhibitory signals. CTLA4 — cytotoxic T lymphocyte-associated antigen 4 — is expressed in T cells and delivers a negative signal to the primed lymphocyte,\textsuperscript{85} directly antagonizing the co-stimulatory receptor CD28, and participating in T cell tolerance. CTLA-4 expression is increased after burn injury,\textsuperscript{86} after trauma-hemorrhage,\textsuperscript{87, 88} and in sepsis, and inhibits immune cell functions.\textsuperscript{89} Inoue et al. showed a dose-dependent effect of anti-CTLA-4 on survival in a rodent model of sepsis,\textsuperscript{90} with decreased CD8\textsuperscript{+} and CD4\textsuperscript{+} lymphocyte apoptosis. Consistently, blockade of CTLA-4 improved survival in rodent fungal sepsis.\textsuperscript{89} To date, no data is available in human clinical setting regarding its prognostic value.

B and T lymphocyte attenuator (BTLA) is also a lymphocyte inhibitory receptor, expressed in a wide range of cells. BTLA decreases cytokine production and inhibits survival signaling in CD4\textsuperscript{+} lymphocytes.\textsuperscript{91} Consistently with previous literature,\textsuperscript{92} Shao et al. showed that lower percentage of BTLA\textsuperscript{+}/CD4\textsuperscript{+} T cells during the early stage of sepsis was associated with severity and 28-day mortality.\textsuperscript{93}

CTLA-4 and BTLA might constitute interesting biomarkers for injury-induced immune paralysis, but data are still scarce. To address this question, more clinical studies are needed, including the monitoring of nosocomial infections, and exploring a wider range of injuries. Other negative immune regulators have been proposed, such as Lymphocyte-activation gene 3 (LAG-3) or T-cell immunoglobulin and mucin domain 3 (HAVCR2, also known as TIM3), as their expression is increased in septic patients presenting an exhausted T cell phenotype.\textsuperscript{94}

**PD-1/PD-L1.**—Another promising biomarker is PD-1 (for Programmed Death One, official symbol PDCD1). The protein is expressed on the cell membrane of lymphocytes, myeloid and dendritic cells. It binds two ligands: PD-L1 (CD274, also known as B7-H1), PD-L2 (PDCD1LG2, also known as B7-DC or CD273). Both belong to the B7:CD28 family,\textsuperscript{95} and are expressed by epithelial, endothelial and antigen presenting cells. This complex pathway is involved in co-ligation with T cell receptor and leads to lower cytokine production and to an inhibition of cellular proliferation, negatively controlling the immune response.

A murine PD-1 knock-out model exposed to sepsis showed lower mortality and decreased bacterial burden and inflammatory response, in link with a macrophage dysfunction.\textsuperscript{96} In clinical setting, Zhang et al. provided evidence for an up-regulation of PD-1 on T cells and PD-L1 on monocytes of 19 septic shock patients. Interestingly, PD-L1 blockade leads to a decreased apoptosis of T cells after TNF stimulation or T cell receptor ligation.\textsuperscript{97} Guignant et al. found consistent results, and highlighted a correlation between increased PD-1, mortality and nosocomial infections after septic shock.\textsuperscript{98} In this study, trauma patients did not express increased PD1 or PD-L1, contrary to the results presented elsewhere.\textsuperscript{87}
PD-1/PD-L1 expression on immune cells was also increased after surgery, and correlates with the severity of surgical trauma.99 Similarly, T cell apoptosis was partially reversed by anti-PD-1 antibody. Overall, these data indicate that PD-1 might be an attracting biomarker for injury-induced immunosuppression.

**CD127**

Interleukin 7 (IL7) is an essential cytokine involved in survival, development and maturation of T and B cells. It binds to a heterodimeric receptor, consisting of an alpha chain (IL7Rα, also known as CD127) and a gamma chain (CD132), the latter is common to several interleukin receptors. Administration of IL7 restored lymphocyte functions in septic patients.100 IL7 level and CD127 were not associated with mortality in this study. Interestingly, a high level of soluble fraction of CD127 (sCD127) was significantly associated with the development of nosocomial infection. Recently, in a larger cohort of septic shock patients, Demaret et al. found a significant association between increased plasmatic sCD127 (at day 1 and day 3) and mortality.101 However, the function and the regulation of sCD127 and of CD127 are still widely unknown. Soluble CD127 could be an interesting biomarker for identification of a group of patients presenting with higher risk of secondary infections or mortality, but it is unclear whether it is involved in immune paralysis pathophysiology.

**FUNCTIONAL TESTING**

**T cell proliferation.**—Another hallmark of sepsis is the decreased lymphocyte proliferation in response to stimulation. Yet, lymphocyte proliferation is a fundamental part of immune response. Its decrease has been described in sepsis, trauma, severe burn, and after major surgery. It has been associated with nosocomial infections, poor outcome and multiorgan failure syndrome.25 Recent data suggested that reduced lymphocyte proliferation may be driven by an indirect mechanism: in an *ex vivo* human model derived from endotoxin tolerance, Poujol et al. suggested that LPS priming indirectly impairs lymphocyte functions by reducing APCs capacity to activate T cells.102, 103 Nevertheless, such functional approaches are time-consuming, as proliferation requires several days of incubation. This precludes most applications in clinical settings.

**STAT5 phosphorylation.**—STAT5 (Signal Transducer and Activator of Transcription 5) is a key molecule for the response to IL7. Its phosphorylation occurs in response to the recruitment of IL7R and reflects the activated status of the cell. STAT5 phosphorylation (pSTAT5) is enhanced by *ex vivo* rhIL7 (recombinant human IL7) in septic shock patients.100 Low doses of rhIL7 preferentially sustain effector T cells activation, whereas rhIL2 activates regulatory T cells.104 A pilot study from our team suggested that pSTAT5 in septic shock patients was higher in survivors. Non-survivors failed to phosphorylate STAT5 in effector T cells in response to rhIL7.105 Interestingly, pSTAT5 can be assessed by flow cytometry on whole blood samples, making it suitable for daily clinical practice.

**B CELLS**

Regarding B cells, human data are limited. B lymphocytes are a heterogeneous cell population; they can not only differentiate into immunoglobulin secreting plasma cells, but they also produce cytokines and present antigens. However, their role in the pathogenesis of injury-induced immunosuppression has not been firmly established. Sepsis-induced cell depletion also deeply affects B cells, but this has not been specifically associated with mortality.106 Interestingly, patterns in B subset distribution and activation were different between survivors and non survivors. At time of admission, a high percentage of CD23+ (a marker of activation and regulation) B cells appeared to be associated with good outcome, whereas CD80+ (a T cell co-stimulation marker) and CD95+ (a
marker of apoptosis susceptibility) B cell percentages were associated with increased 28-day mortality. The reason of this observation remains to be elucidated. Recently, only B cell and CD16+ monocyte counts were associated with increased mortality. Consequently we may hypothesize that, similarly to other immune cells, B cell functional and quantitative alterations may play a role in injury-induced immune dysfunction. Thus, it might be interesting to shed light on B cell involvement and to develop B cell markers.

Both innate and adaptive immunity: transcriptomic approach

The host response to injury involves numerous intricate pathways (e.g., immune, neurologic and endocrine systems). Given this complexity, rather than focusing on very specific markers, some researchers have recently aimed for a systemic perspective. Genomics, transcriptomics and proteomics have expanded rapidly within the past years. Transcriptomic approach evaluates the transcripts (messenger RNA, also known as mRNA) for many genes. Assuming that certain genes may be over- or under-expressed in reaction to injury, researchers expect to find or confirm diagnostic, prognostic and follow-up markers, and to progress in pathophysiologic understanding. Being able to guide therapeutic strategies disclosing patient immune profile is a seducing concept, however actual scientific knowledge is far from achieving this goal. Still, literature dealing with injury-induced immunoparalysis and transcriptome is abundant (Table I).

General clinical data

As reported by Xiao et al., leukocytes of injured patients (in this study, severe trauma and burns) responded to stress by a global repression of apoptosis susceptibility) B cell percentages were associated with increased 28-day mortality. The reason of this observation remains to be elucidated. Recently, only B cell and CD16+ monocyte counts were associated with increased mortality. Consequently we may hypothesize that, similarly to other immune cells, B cell functional and quantitative alterations may play a role in injury-induced immune dysfunction. Thus, it might be interesting to shed light on B cell involvement and to develop B cell markers.

Table I.—Biomarkers: feasibility and clinical evidence.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Associated clinical outcome</th>
<th>Laboratory technique</th>
<th>Approximate minimal turn-around time</th>
<th>Possible in routine?</th>
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</thead>
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<tr>
<td>Innate immunity</td>
<td>PNN</td>
<td>↑ immature forms</td>
<td>Death</td>
<td>FC, hematological analyzers</td>
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<tr>
<td>Monocytes</td>
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<td>Death, HAI</td>
<td>FC, IHC, PCR</td>
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<tr>
<td>Endotoxin tolerance</td>
<td>↑ PD-L1</td>
<td>Conflicting data</td>
<td>cell culture + ELISA</td>
<td>3 days</td>
</tr>
<tr>
<td>IL10 ad IL10/TNF</td>
<td>↑ DC count</td>
<td>Death, HAI</td>
<td>FC</td>
<td>1h30</td>
</tr>
<tr>
<td>DC</td>
<td>IL-12 synthesis, proliferation</td>
<td>No</td>
<td>cell culture, ELISA</td>
<td>3 days</td>
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<td>Adaptive immunity</td>
<td>All lymphocytes</td>
<td>Lymphopenia</td>
<td>Death</td>
<td>FC, hematological analyzers</td>
</tr>
<tr>
<td>CTLA4, BTLA</td>
<td>↑ CTLA4</td>
<td>Few data</td>
<td>FC, IHC</td>
<td>1h30</td>
</tr>
<tr>
<td>PD-1</td>
<td>↑ PD-1</td>
<td>Death</td>
<td>FC, IHC</td>
<td>1h30</td>
</tr>
<tr>
<td>CD127</td>
<td>↑ CD127</td>
<td>Death, HAI</td>
<td>FC, IHC</td>
<td>1h30</td>
</tr>
<tr>
<td>T cells</td>
<td>Proliferation</td>
<td>Data, HAI, MOF</td>
<td>cell culture + FC</td>
<td>3 days</td>
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<td>Tregs</td>
<td>↑ Treg percentage</td>
<td>Death</td>
<td>FC</td>
<td>1h30</td>
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<td>Both</td>
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<td>CD74, CX3CR1</td>
<td>Few data. Death?</td>
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<tr>
<td></td>
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<td>microarray</td>
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</tbody>
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* if a unitized industrial method were developed.
oritization affecting >80% of the cellular functions and pathways. Authors refer to this phenomenon as “genomic storm”. Researchers observed simultaneous increase in expression of innate immune genes and suppression of adaptive immunity, in both injury situations. This supports the hypothesis of a common behavior, which would not rely on the stress type. This novel paradigm has also been described after severe blunt trauma and in sepsis.

Xiao et al. studied differentially expressed genes in complicated (recovery >14 days, no recovery, or death) versus uncomplicated clinical recovery (recovery in <5 days). Interestingly, authors highlighted an up-regulation of pro-inflammatory pathways in the complicated group, associated with down-regulated antigen presentation and T cell regulation.

To date, the literature gives many other examples of the ability of the transcriptomic approach to analyze the patient’s immune status in a global way. As proposed by Rittirsch et al. in trauma patients, the combination of clinical and transcriptomic markers may represent an even more interesting tool. Further studies are needed to develop predefined set of markers and to evaluate their predictive value regarding the diagnosis and prognosis of immune dysfunction.

**Examples of transcriptomic-discovered markers:** CD74, CX3CR1

Cazalis et al. used transcriptomic approach in a more targeted manner. In a prospective septic shock cohort, they investigated the link between MHC class II-related gene expression (by qRT-PCR) and mortality at day 28. Among these, low CD74 at day 3 after the onset of shock was associated with 28-day mortality after multivariate logistic regression analysis (OR 3.4 [1.2 to 9.8], P=0.026). CD74, also called HLA-DR antigen-associated invariant chain, is a protein involved in MHC II heterodimer synthesis and export towards the cell surface. CD74 still needs validation in a larger multicenter study.

CX3CR1 is a chemokine receptor expressed on monocytes, NK cells, and some lymphocyte subpopulations. It is involved in adhesion and migration of leukocytes and is thought to amplify pro-inflammatory immune response. In a microarray study, we observed an 8-fold increase of CX3CR1 in survivors compared with non survivors, which corresponded to the highest factor of change. We later reported that CX3CR1 (mRNA and protein) was strongly down-regulated in monocytes. Consistently, this down-regulation was associated with mortality.

Although these data are preliminary, both examples suggest that transcriptomic approach may allow to discover and to evaluate new biomarkers of immunoparalysis.

**Conclusions**

In parallel with explosive inflammatory processes, injury causes major immune dysfunctions leading to a significant morbi-mortality. Innate and adaptive immunity may both be severely compromised, in different extents depending on the patient immune profile. Being able to detect and follow immunoparalyzed patients and dysfunction subtypes is an important issue, for a targeted immunostimulating treatment may improve greatly their outcome. To date, available markers have a prognostic value, but researchers now aim to develop diagnostic tools. Such biomarkers could help targeting diagnosis procedures, allowing the clinician to define patients at risk to develop opportunistic infections. The most promising markers — i.e. markers both associated with clinical outcome in several types of injury and performable on routine basis — are decreased mHLA-DR and lymphopenia. In the light of the complexity of injury-induced immune response, combinations of biomarkers may represent an interesting line of investigation.

This review outlines current knowledge on biomarkers of injury-induced immunosuppression. It was not intended to be an in-depth survey of the whole subject and does not represent an exhaustive listing of studies in the field. We sincerely apologize for works not cited in this manuscript.
Key messages

— Injury-induced immunosuppression is a healthcare burden; patients suffering from it may benefit from immunostimulating treatments.

— Biomarkers of injury-induced immunosuppression are needed to specifically identify those patients that may benefit from immunoadjuvant therapies.

— For now, the most promising biomarkers are low mHLA-DR, lymphopenia and increased PD-1/PD-L1 pathway.

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The goal of this perspective report is to present the foundational concepts of perioperative opioid-less (conscious) analgesia.

Opioid-free or opioid-less anesthesia/analgesia: reasons and speculations

The concept of opioid-free anesthesia has recently gained interest among anesthesiologists, surgeons, and other perioperative physicians because of the growing evidence from a large number of clinical studies that have demonstrated the beneficial effects of opioids reduction in the context of surgery. Furthermore, the minimization of the use of opioids during the perioperative period is one of the cornerstones elements of the “enhanced recovery after surgery” programs. However, it is important to
highlight that notion of opioid-free anesthesia should be extended into the immediate and intermediate postoperative period, thus perhaps the concept should be coined as “opioid-free” or “opioid-less perioperative care”.

There are at least 3 important reasons to understand why an opioid-free or opioid-less perioperative care could become a reality and all of them are relevant to patient care issues and healthcare policies (Figure 1). Firstly, there is growing evidence indicating that patients who receive large doses of opioids during their perioperative hospital admission not only experience inadequate pain control but they are also at risk for developing an important number of opioid-related adverse events (ORADEs), an increase in the risk of mortality and an incremented cost of care. Secondly, the so-called “opioid epidemic” in the USA has been linked to the misuse and diversion of opioids prescribed in the perioperative period. And thirdly, there are some concerns regarding the use of opioids in cancer patients since these drugs could be associated with tumor growth and cancer recurrence.

**ORADEs, inadequate analgesia, hyperalgesia and high costs of care**

Opioids are associated with significant adverse events (i.e., ileus, nausea and vomiting, respiratory depression) mostly seen when they are administered in moderate-to-large amounts. However, the administration of opioids in low quantities can cause ORADEs in patients with comorbidities known to affect their metabolism or enhance their affinity to the opioid receptors. For instance, the requirements of intrathecal opioids are lower in obese than non-obese parturient women. As another example, elderly patients have a higher risk of developing ORADEs because of the concomitant use of multiple drugs, drug-drug interactions (psychoactive drugs in particular), diminished renal clearance, and possibly decreased hepatic function.

Despite the large use of opioids for perioperative analgesia, more than 75% of the patients undergoing surgery report inadequate pain relief. In a recent study by Mudumbai et al., the authors found that the median time-to-opioid-cessation after surgery was 15 days in opioid-naïve patients and even longer in those taking opioids preoperatively. These findings confirm that even when postoperative pain is poorly managed, the need for opioids is still long. In addition, patients with inadequately treated postsurgical pain are more likely to receive large doses of opioids and have a higher risk for developing postoperative persistent pain. As a result, these patients will be more likely to be readmitted to the hospital or seek consultation with pain physicians. Both, readmissions and expert consultations are associated with an increase in the costs of care.

The use of potent opioids in the perioperative period appears to be a linked to the development of chronic surgical pain. A recent study has demonstrated that the use of “strong” opioids is associated with a 30% increase in the chances to develop chronic postmastectomy pain. It remains uncertain whether opioids are directly linked with the development of persistent pain but it is well-known that the amount of opioid used perioperatively correlates with inadequately treated pain. Opioids can per se trigger hyperalgesia, this phenomenon is also known as opioid-induced hyperalgesia (OIH). All opioids can cause OIH however, there is evidence to conclude that the administration of remifentanil and fentanyl in high doses is strongly associated with OIH. It is worth noticing that because of the ultra-short anal-
Opioids and cancer outcomes

A body of growing evidence indicates that opioids have significant effects on several steps of carcinogenesis and cancer progression and in some instances can be associated with cancer recurrence.11-13 Opioids receptors, and in particular mu opioid receptors (MOR), have been found in malignant cells including prostate cancer cells, glioblastoma cells, lung adenocarcinoma cells and breast cancer cells. In-vitro studies have shown that activation of MOR induce cleavage of the DNA and stimulate phosphorylation/activation of Src, Gab-1, PI3 kinase, Akt and STAT3 via the interaction with the epidermal growth factor receptor in human lung cancer cells.14-17

MORs are also present in lymphocytes that participate in the active process of eliminating cancer cells. Although the evidence remains controversial, some studies indicate that morphine and fentanyl can facilitate tumor spread by diminishing the killing activity of natural killer cells.18-20 Opioids can also impact the angiogenesis process. While long-term exposure or high-doses of opioids impair angiogenesis, short-term treatment of human umbilical vein cells with physiological concentrations of endomorphin-1 and -2 increase cell proliferation, migration, and adhesion.21

Although the evidence from basic science data points towards a predominant protumoral effect of opioids, the clinical data have shown mixing results. In patients with non-small cell lung cancer, most studies point towards an association between the use of opioids and worse survival outcomes.13, 22-24 In patients who had radical prostatectomy, fentanyl did not have a

In most modern healthcare systems, the increased costs associated with opioids based anesthesia or analgesia is multifactorial. First, patients who develop ORADEs stay longer in the hospital than those without complications, which it can increase the costs of hospitalization. As an example, patients who had ORADEs following total joint arthroplasty were approximately 8 times more likely to have a prolonged hospital course in comparison to those without adverse events. To add complexity to the matter, opioid selection also appears to influence outcomes. A recent study that demonstrated a decrease in the use of morphine but at the expense of an increase in the prescription of hydromorphone, also showed that a higher rate in the use of rescue analgesics, a longer length of stay and a higher rate of readmissions to the hospital. All of these factors have been linked to an increase in the cost of care.

Inadequately treated postoperative pain, acute tolerance, lack of understanding of opioid selection and OIH can explain why some patients are often discharged from the hospital with large counts of opioids pills. As a consequence, the risk of drug misuse and diversion is high. It is worth noticing that oxycodone and hydrocodone (two of the most commonly prescribed opioids in the perioperative period) are the most frequent drugs associated with diversion, abuse, and overdose.

Because of the potential devastating consequences associated with ORADEs such as respiratory depression, the increased costs associated with them, and the recent rise in opioid-related abuse and overdose, several authorities and agencies including the United States Center for Disease Control have called for the creation of quality improvement and patient education programs dedicated to monitor and reduce inadequate opioid prescribing strategies. Perhaps, one the first step towards this goal would be the use of aggressive non-opioid based analgesic techniques specifically designed to provide opioid-free or opioid-less perioperative care.

Gesic effect of remifentanil patients often experience an abrupt cessation in analgesia that can lead to high postoperative pain scores and large opioid consumption in the immediate postoperative period.10 Hence, the ultra-short duration of analgesia of remifentanil should not be confused with its hyperalgesic effects. To complicate matters, the addition of opioids with long-lasting analgesic (i.e., hydromorphone) effects during the infusion of remifentanil does not improve postoperative pain scores or reduce opioid consumption immediately following surgery.10

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evidence to indicate opioid-free anesthesia in patients undergoing oncologic procedures. However, opioids should be used with caution in this population of patients to minimize ORADEs and facilitate postsurgical recovery. Oncological patients who require adjuvant therapy are more likely to initiate their treatment soon after surgery if they experience an uneventful recovery.

Multimodal analgesia: the cornerstone of opioid-free/-less perioperative care

Perioperative multimodal analgesia refers to the use of a variety of pharmacological and non-pharmacological therapies with two majors goals: 1) to improve postoperative analgesia, and 2) reduce ORADEs (Figure 2). 32-35 Most studies indicate that those patients who have undergone surgery in the context of multimodal analgesia and have received none or extremely low doses opioids experience a better surgical recovery, develop fewer ORADEs and are discharged earlier from the hospital.

When indicated, regional anesthesia and analgesia even in combination with general anesthesia should be one the key components of any multimodal opioid-free/-less analgesia technique. 36-40 Neuraxial and peripheral nerve anesthesia techniques as well as newer strategies such as wound infiltration, the transverse abdominis plane block and scalp blocks have demonstrated to reduce opioid consumption. Local anesthetics alone or in combination with systemic adjuvant drugs such ketamine, clonidine/dexmedetomidine, lidocaine, gabapentinoids, acetaminophen or cyclo-oxygenase inhibitors have been successfully used for opioid-free anesthesia/analgesia techniques. For instance, we have demonstrated a reduction of 84% in the intraoperative consumption of morphine equivalents in patients undergoing hyperthermic cytoreductive abdominal surgery by using combined general-epidural anesthesia in conjunction with oral celecoxib, tramadol and pregabalin and the systemic infusion of lidocaine, dexmedetomidine and/or ketamine. 41 Similar results have been found in patients undergoing hepatobiliary surgery and gynecological surgery (Drs. José

**Figure 2.**—How multimodal analgesia can improve care in the perioperative period.
Soliz and Javier Lasala, personal communication and abstract publications).

Although most of the non-opioid analge-sics used during and immediately after surgery have shown opioid-sparing effects, their efficacy is limited to a short period of time that do not last beyond hospital stay, which increases the chance of opioid prescription.42, 43 For instance, ketamine during and after (72 hours) scoliosis surgery has failed to improve chronic pain outcomes and pregabalin does not provide protective effects against postmastectomy or posthoracotomy pain syndromes.44 Therefore, a multimodal analgesia approach to provide adequate pain relief beyond the duration of hospitalization is needed not only to avoid the development of postsurgical persistent pain but also to decrease the exposure of patients to opioids.

In conclusion, opioid-free or opioid-less perioperative care should be implemented to reduce ORDADEs and decrease the costs associated with them. The risks associated with drug diversion are far superior to the fear of inadequate analgesia when appropriate multimodal anesthesia and analgesia techniques are used. Although still controversial, the use of opioids during oncological surgery could be associated with an increase in recurrence in certain tumors.

Key messages

— Opioids are the most commonly prescribed analgesics in the perioperative periods, but the healthcare costs associated with opioids related adverse events are high.

— Opioid-induced hyperalgesia, opioid misuse and diversion are the consequences of ineffective strategies of opioid based postoperative analgesia.

— Large perioperative opioid use might have a negative impact in the survival of patients with cancer.

— Multimodal analgesia modalities are essential to effectively implement opioid-less perioperative strategies.

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Young A, Buvanendran A. Recent advances in multimodal analgesia. Anesthesiol Clin 2012;30:91-100.


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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.

Regional anesthesia and antithrombotic agents: instructions for use

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ABSTRACT

The use of anticoagulant agents represents a serious limitation of regional anesthesia, due to the risk of spinal hematoma. Examining all the principles currently available, it has been possible to notice that published guidelines are very often incomplete or also differ significantly on the rules to be followed relating to a specific drug. A comparison was carried out between the guidelines of major scientific societies in order to take a practical and simple user guide which operators can consult. The more and more frequent occurrence of patients who undergo dual antiplatelet and need to be subjected to surgery was taken into account, considering regional anesthesia as a possible alternative to general anesthesia in conditions of election and not deferrable urgency. We describe the main anticoagulant drugs used in therapy. Regarding the low-molecular-weight heparins, we have reported the most important properties, highlighting the substantial differences of their use detectable by comparison between American and European Guidelines. A similar comparison has been made for the main antiplatelet drugs, including aspirin, and thrombin inhibitors. A particular chapter is dedicated to new oral anticoagulant drugs, especially for the low possibility of allowing regional anesthesia. The comparison between the main guidelines often highlights substantial disparities and weak evidences, so operators must carry out a careful risk-benefit analysis prior to regional anesthesia.

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Key words: Local anesthesia - Spinal epidural hematoma - Fibrinolytic agents.

Performing neuraxial anesthesia in patients receiving antithrombotic drugs is controversial due to the increased risk of spinal epidural hematoma.

The spinal hematoma, defined as a symptomatic bleeding internal to the neuraxis, is a rare and serious complication of the central anesthetic block. The actual incidence of such a complication is unknown. The probable incidence of major bleedings after performing a central block without specific risk factors has been approximately calculated as less than 1:220,000 for the spinal anesthesia and less than 1:150,000 for the epidural anesthesia.1 The highest bleeding risk is connected to positioning and removing an epidural catheter, the lowest to the single-shot spinal, while another variable is connected to the caliber of the needle used.2, 3 About 60-80% of all major bleedings is associated to hemostatic disorders or bleedings from the needle.4

Numerous studies on a high number of patients have shown the relative safety of performing central blocks during an antiplatelet therapy, but the total number of enrolled patients was relatively low.5 Three spinal hematomas during a therapy with ticlopidine or clopidogrel have been described.6-8 NSAI...
widely used in pain treatment protocols, are not anticoagulant drugs, but they, similarly to aspirin, interfere with platelet aggregation mechanisms. The administration of NSAIDs alone does not increase the bleeding risk, but it has been shown that the association with other anticoagulants increases the frequency of spontaneous hemorrhagic complications, bleeding at the injection sites and spinal hematomas.\textsuperscript{2, 9, 10}

Due to its rarity, recommendations regarding neuraxial regional anesthetic procedures with concurrent thromboprophylaxis are not based on prospective randomized studies, but rather on case reports and expert opinions. The latter are based mainly on knowledge of the pharmacokinetics of the individual agents concerned. A rule of thumb adopted by most national societies puts the time interval between cessation of medication and neuraxial blockade at two times the elimination half-life of the drug. This approach has recently been recommended by others.\textsuperscript{11}

We have carried out a broad review of the main anticoagulant drugs used in therapy, describing the most important properties, with particular reference to the mechanisms of action and duration of their activity. Therefore, we have analyzed the guidelines published by major scientific societies, comparing the recommendations provided for the correct use of drugs and the relative levels of evidence.

Here we have considered and compared the main guidelines compiled by the main study groups and scientific associations in several American and European countries. In this moment, these guidelines represent the reference point in the exercise of anesthetic activities in different countries, even if they contain indications often unsupported by clear evidence, but, even more, significantly different indications which confuse the operators and we wanted to emphasize.

Precisely because of the reduced characteristics of systematic reviews held by these guidelines, and considering that no RCTs have been published in the last two years regarding the use of anticoagulants in patients undergoing locoregional anesthesia, we believe that the current method to assign a score according to the PRISMA guidelines does not have the conditions to be applied, with no result except for considering all major guidelines currently in use as “insufficient.”

We have graded the level of recommendations and the level of evidence using the definitions of the Committee for Practice Guidelines of the ESC (Table I).\textsuperscript{12}

### Low-molecular-weight heparins

With the release of low-molecular-weight heparins (LMWH) for general use in the United States in May 1993, labeled indications included thromboprophylaxis at a scheduled dose of 30 mg every 12 hours, with the first dose administered as soon as possible after surgery. An alarming number of spinal epidural hematomas, some with permanent paraplegia, were reported,\textsuperscript{13} triggering a warning from the US Food and Drug Administration (FDA). The marked increase in the frequency

<table>
<thead>
<tr>
<th>Classes of recommendations</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Class I</td>
<td>Evidence and/or general agreement that a given treatment or procedure is beneficial</td>
</tr>
<tr>
<td>Class II</td>
<td>Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the treatment or procedure</td>
</tr>
<tr>
<td>Class IIA</td>
<td>Weight of evidence/opinion in favor of usefulness/efficacy</td>
</tr>
<tr>
<td>Class IIB</td>
<td>Usefulness/efficacy is less well established by evidence/opinion</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence or general agreement that the treatment or procedure is not useful or effective and in some cases may be harmful</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level A</td>
<td>Data derived from multiple randomized clinical trials or meta-analyses</td>
</tr>
<tr>
<td>Level B</td>
<td>Data derived from a single randomized clinical trial or large non-randomized studies</td>
</tr>
<tr>
<td>Level C</td>
<td>Consensus of opinion of the experts and/or small studies, retrospective studies, registries</td>
</tr>
</tbody>
</table>
of spinal hematoma in patients anticoagulated
with LMWH prompted a reevaluation of the
relative risks and benefits of neuraxial block-
ade. Collation of these cases in the USA
allowed the risk of spinal epidural hematoma
during concurrent administration of LMWHs
to be calculated at 1:40,800 for spinal anesthe-
sia, 1:6600 for single-shot epidural anesthesia,
and 1:3100 for epidural catheter anesthesia.
What seems to be a relatively high incidence
of bleeding has been attributed to the twice
daily administration of LMWH, and the lack
of recommendations at that time regarding
time intervals between neuraxial puncture or
catheter removal and thromboprophylaxis.
The response in the USA has been to introduce
recommendations that are stricter than those
in place in Europe, proposing avoidance of
LMWH the entire time epidural catheters are
in place. In particular, the ASRA guidelines
have consistently recommended against the
administration of twice-daily LMWH in a pa-
tient with an indwelling epidural catheter.
Although once-daily LMWH dosing in the
presence of an epidural catheter is safe, it has
been recommended to be cautious if the patient
has received an additional hemostasis-altering
medications, including antiplatelet therapy.

The anesthetic management of the patient
receiving LMWH suggested by the American
Society of Regional Anesthesia and Pain Med-
icine mainly consists in the following points:
— in patients on preoperative LMWH
thromboprophylaxis, needle placement should
occur at least 10 to 12 hours after the LMWH
dose;
— in patients receiving higher (treatment)
doses of LMWH, a delay of at least 24 hours is
recommended to ensure normal hemostasis at
the time of needle insertion;
— in case of postoperative LMWH, pa-
tients with postoperative LMWH thrombopro-
phyaxis may safely undergo single-injection
and continuous catheter techniques;
— in case of twice-daily dosing, the first
dose of LMWH should be administered no ear-
lier than 24 hours postoperatively. Indwelling
catheters should be removed before initiation
of LMWH thromboprophylaxis. If a continu-
ous technique is selected, the epidural catheter
may be left indwelling overnight, but must be
removed before the first dose of LMWH. Ad-
ministration of LMWH should be delayed for
2 hours after catheter removal;
— in case of single-daily dosing, the first
postoperative LMWH dose should be admin-
istered 6 to 8 hours postoperatively. The sec-
ond postoperative dose should occur no sooner
than 24 hours after the first dose. Indwelling
neuraxial catheters may be safely maintained.
However, the catheter should be removed a
minimum of 10 to 12 hours after the last dose
of LMWH. Subsequent LMWH dosing should
occur a minimum of 2 hours after catheter
removal. No additional hemostasis-altering
medications should be administered due to the
additive effects.

In Europe, the widespread adoption of a sin-
gle daily dose of enoxaparin 40 mg produced
a lower incidence of complications. A retro-
spective analysis in Sweden found out that
the risk was 1:156,000 after spinal anesthesia
and 1:18,000 after epidural anesthesia, with
bleeding occurring more rarely in obstetrics
(1:200,000) than in female orthopedic patients
undergoing knee arthroplasty (1:3600). Risk
factors for spinal hematoma after neuraxial
regional anesthesia were identified as lack of
guidelines, administration of antithrombotic
agents, female sex, and difficult punctures.
Subsequent reports from various countries
indicate that spinal epidural hematoma af-
ter neuraxial blockade occurs in 1:2700 to
1:19,505 patients, with one report indicat-
ing that hematoma may be more common after
lumbar (1:1341) compared to thoracic epidural
anesthesia (1:10,199).

According to the European guidelines, to
avoid bleeding complications, there should
be a time interval of at least 12 hours between
subcutaneous administration of LMWH at
prophylactic doses and neuraxial blockade or
removal of an epidural catheter (Class IIa,
level C). If thromboprophylaxis with LMWH
is prescribed in a twice-daily schedule, com-
pared to a once daily regimen, the risk of epi-
dural hematoma may be increased because the
trough levels of anti-Xa activity are higher.
In this situation, one dose of LMWH should be omitted creating a 24-hour time interval before catheter removal and the subsequent dose (Class IIb, level C). Similarly, when therapeutic doses of LMWH are administered once or twice daily, catheter placement or removal should also be delayed for at least 24 hours after the last dose (Class IIa, level B).

A meta-analysis of preoperative versus postoperative studies shows that LMWH given 12 hours preoperatively does not reduce the risk of VTE compared to a postoperative regimen.\textsuperscript{24} As antithrombotic drugs increase the risk of spinal epidural hematoma after neuraxial blockade, a postoperative start may be advantageous, especially in patients who are receiving also aspirin (Class IIIb, level C).

Spinal epidural hematoma is not restricted to LMWH and similar drugs, but can occur with any agent that interferes with hemostasis. New antithrombotic drugs are continually under development. The administration of these medications in combination with neuraxial anesthesia must be carefully considered and we can apply lessons learned from the LMWH experience to develop initial management recommendations \textsuperscript{25} (Table II).

**Fondaparinux**

Fondaparinux, an injectable synthetic pentasaccharide, produces its antithrombotic effect through factor Xa inhibition.\textsuperscript{26} The EXPERT study included a total of 5387 patients, among whom 1428 undergoing regional anesthesia procedures: a single dose of fondaparinux was omitted the evening before catheter removal \textsuperscript{27} and this provided a time interval of 36 hours before catheter removal and 12 hours (6 hours according to the AAS guidelines) \textsuperscript{28} between catheter removal and the next dose of fondaparinux. Neuraxial regional anesthe-

<table>
<thead>
<tr>
<th>Table II.—Recommended time intervals before and after neuraxial puncture or catheter removal.</th>
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</thead>
<tbody>
<tr>
<td><strong>Time before puncture/catheter manipulation or removal</strong></td>
</tr>
<tr>
<td><strong>Unfractionated heparins (for prophylaxis, ≤15,000 IU/day)</strong></td>
</tr>
<tr>
<td><strong>Unfractionated heparins (for treatment)</strong></td>
</tr>
<tr>
<td><strong>Low-molecular-weight heparins (for prophylaxis)</strong></td>
</tr>
<tr>
<td><strong>Low-molecular-weight heparins (for prophylaxis)</strong></td>
</tr>
<tr>
<td><strong>Fondaparinux (for prophylaxis, 2.5 mg per day)</strong></td>
</tr>
<tr>
<td><strong>Rivaroxaban (for prophylaxis, 10 mg/day)</strong></td>
</tr>
<tr>
<td><strong>Apixaban (for prophylaxis, 2.5 mg b.i.d.)</strong></td>
</tr>
<tr>
<td><strong>Dabigatran (for prophylaxis, 150-220 mg)</strong></td>
</tr>
<tr>
<td><strong>Coumarins</strong></td>
</tr>
<tr>
<td><strong>Hirudins (lepirudin, desirudin)</strong></td>
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<tr>
<td><strong>Argatroban</strong></td>
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<tr>
<td><strong>Acetylsalicylic acid</strong></td>
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<tr>
<td><strong>Clopidogrel</strong></td>
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<tr>
<td><strong>Ticlopidine</strong></td>
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<tr>
<td><strong>Prasugrel</strong></td>
</tr>
<tr>
<td><strong>Ticagrelor</strong></td>
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<tr>
<td><strong>Cilostazol</strong></td>
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<tr>
<td><strong>NSAIDs</strong></td>
</tr>
</tbody>
</table>

New oral anticoagulants

The new oral anticoagulants (NOACs) currently include thrombin inhibitor dabigatran and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban).

The ASRA guidelines on regional anesthesia did not make recommendations, probably because of the lack of studies, whereas the European and the Scandinavian guidelines based their recommendations on the half-life of the drugs. The European and Scandinavian guidelines adopted a two-half-life interval between discontinuation of the drugs and neuraxial injection.

Current recommendations for neuraxial blocks with new oral anticoagulants are different when they are used for postoperative thromboprophylaxis after hip or knee replacement or for prevention of thromboembolic disease in patients with nonvalvular atrial fibrillation (AFIB), because in the first case much lower doses are given compared with patients with AFIB.

Dabigatran is an oral reversible monovalent thrombin inhibitor. The oral prodrug dabigatran etexilate is metabolized by plasma esterases into dabigatran. Currently it is licenced to be given once daily 220 mg starting with 110 mg within 1-4 hours after surgery for 10 days after knee replacement surgery and for 28-35 days after hip replacement surgery, while is typically given 2×150 mg daily in AFIB patients.

The long (12-17 hours) half-life of dabigatran in healthy patients suggests a time interval of 34 hours (1-1.5 days) between the last dose of dabigatran and catheter manipulation or withdrawal. However, the manufacturer advises against the use of dabigatran in the presence of neuraxial blockade (Class III, level C). Analyzing licensing studies involving 4212 neuraxial blocks, the first dose of dabigatran was given at least 2h after epidural catheter removal. Other suggestions for next dose range from 2 to 12 hours.

When used in patients with AFIB, if a neuraxial block for surgery is planned, the suggested withdrawal time is 3.5-4 days.

Rivaroxaban is a potent selective and reversible oral activated factor Xa inhibitor. When used for thromboprophylaxis, Rivaroxaban is generally administered once a day, 10 mg within 6-10 hours after surgery for 5 weeks after hip replacement surgery and two weeks after knee replacement surgery.

A minimum of 18 hours between the last dose of rivaroxaban (10 mg) and removal of an indwelling catheter, and a minimum of 6 hours before resumption of the drug has been recommended by the Scandinavian Society guidelines. The European Society guidelines recommend an interval of 22 to 26 hours between the last dose of rivaroxaban and removal of an indwelling catheter (Class IIA, level C), and an interval of 4 to 6 hours between epidural catheter removal and the next dose of rivaroxaban (Class IIB, level C). These two recommendations represent a two-half-life interval between rivaroxaban discontinuation and epidural catheter placement or removal. Extreme caution is recommended when rivaroxaban is used in presence of neuraxial blockade (Class IIb, level C).

Rivaroxaban is given 1×20 mg for deep venous thrombosis treatment or stroke prevention inpatients with nonvalvular AFIB. Experts recommend Rivaroxaban discontinuation for 2-3 days before neuraxial puncture. Experts’ opinions concerning resumption after catheter removal range from 5 to 24 hours.

Apixaban is an oral, reversible, direct factor Xa inhibitor related to rivaroxaban. It is given twice a day 2.5 mg within 12-24 hours after hip or knee replacement surgery for 32-38 days and 10-14 days, respectively. Although the Scandinavian guidelines did not make recommendation on the interval between cessation of apixaban and neuraxial injection because of lack of available data, the European guidelines suggest a time interval of 26-30 hours between the last dose of apixaban (2.5 mg) and catheter withdrawal and that at
least one dose should be omitted (Class IIb, level C). After catheter withdrawal, the next dose of apixaban may be given 4-6 hours later (Class IIb, level C). The Scandinavian guidelines recommend 6 hours after a neuraxial injection or catheter removal before resumption of the drug. Extreme caution is recommended when using neuraxial blockade in the presence of apixaban (Class IIb, level C).

Apixaban is given 2x5 mg daily for the prevention of stroke and systemic embolic disease in adult patients with nonvalvular AFIB. Expert opinions defining the time from Apixaban discontinuation to neuraxial block placement range from 3 to 4 days.32, 34

Edoxaban, a new Xa inhibitor, has currently been approved in the USA and Japan for the reduction in the risk of stroke and systemic embolic disease in patients with nonvalvular AFIB with a dose of 60 mg once a day. Indwelling epidural or intrathecal catheters should not be removed earlier than 12 hours after the last administration of edoxaban and the next dose of edoxaban should not be administered earlier than 2 hours after the removal of the catheter. However, in analogy to expert reasoning with rivaroxaban and apixaban, edoxaban should be stopped 2 days before a neuraxial puncture or epidural catheter manipulation.29

In Table III the timing to be observed for a safe administration of these drugs is summarized.

### Antiplatelet drugs

Antiplatelet medications, including NSAIDs, thienopyridine derivatives (ticlopidine and clopidogrel), and platelet GP IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban) exert diverse effects on platelet function.

Low-dose aspirin, when used for secondary prophylaxis, has been shown to reduce the risk of stroke and myocardial infarction in the range of 25% to 30%.35-37 Furthermore, the discontinuation of aspirin for secondary prophylaxis is associated with significant risk and a platelet rebound phenomenon may occur, resulting in a prothrombotic state.39 When aspirin is used for primary prophylaxis, its value in preventing cardiovascular events is unclear.40, 41

Non-aspirin NSAIDs bind reversibly and competitively inhibit the active site of the COX enzyme. The degrees of reversible inhibition of COX-1, after single doses of frequently used NSAIDs (diclofenac, ibuprofen, indomethacin, naproxen, and piroxicam), depend on the selected NSAID and measured time frame in the first 24 hours.42

NSAIDs that selectively inhibit the enzyme COX-2 do not alter platelet function.43

ASRA and European guidelines recommend that central neuraxial blocks may be performed in individuals using aspirin or NSAIDs.16, 25 On the basis of the available data, NSAIDS, including aspirin, when given in isolation, do not increase the risk of spinal epidural hematoma and are not a contraindication to neuraxial block (Class IIb, level C). Spinal anesthesia has better a support than the epidural one (Class IIb, level C).

To avoid any negative effect of NSAIDS on platelet function and neuraxial block, it is

### Table III.—Simplified scheme of suggested times when neuraxial blocks are planned during NOACs administration.

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Drug used for postoperative thromboprophylaxis (low doses)</th>
<th>Drug used for AFIB (high doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time before puncture/catheter manipulation or removal</td>
<td>Time after puncture/catheter manipulation or removal</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1-1.5 days</td>
<td>2 to 12 hours</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>22-26 hours &lt;sup&gt;€&lt;/sup&gt;</td>
<td>4-6 hours &lt;sup&gt;€&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>18 hours &lt;sup&gt;s&lt;/sup&gt;</td>
<td>6 hours &lt;sup&gt;s&lt;/sup&gt;</td>
</tr>
<tr>
<td>Apixaban</td>
<td>26-30 hours &lt;sup&gt;€&lt;/sup&gt;</td>
<td>4-6 hours &lt;sup&gt;€&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>No data &lt;sup&gt;s&lt;/sup&gt;</td>
<td>6 hours &lt;sup&gt;s&lt;/sup&gt;</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>12 hours</td>
<td>2 hours</td>
</tr>
</tbody>
</table>

NOAC: new oral anticoagulant; AFIB: nonvalvular atrial fibrillation. <sup>€</sup> European guidelines; <sup>s</sup> Scandinavian guidelines.
sufficient to miss a dose the evening before a planned procedure or catheter removal.

The Scandinavian guidelines for the performance of central neuraxial blocks in individuals using aspirin, based their recommendations on the indication for aspirin use and the daily dose. In individuals who take aspirin for secondary prevention, a shorter discontinuation time of 12 hours was recommended. For individuals who do not use aspirin for secondary prevention, the discontinuation time is 3 days unless the dose is greater than 1 g/day for which the discontinuation time is extended to 1 week.28

For NSAIDs, the Scandinavian guideline recommendations are guided by the specific half-life for each drug.28

Although the administration of aspirin alone does not appear to increase hematoma formation, a higher rate of complications has been observed in both surgical and medical patients when heparins were administered concurrently.3, 44 Because preoperative, versus postoperative, thromboprophylaxis is not proven to be beneficial,45 a cautionary approach in the presence of aspirin would be to start VTE prophylaxis postoperatively (Class I, level B).

In patients who are receiving NSAIDS, we recommend against the performance of neuraxial techniques if the concurrent use of other medications affecting clotting mechanisms, such as oral anticoagulants, UFH, and LMWH, is anticipated in the early postoperative period because of the increased risk of bleeding complications.16

The thienopyridines block the ADP receptor, P2Y12 subtype.

Ticlopidine has a long elimination half-life and causes an irreversible inhibition of platelet function.46 The European guidelines 25 suggest a time interval between discontinuation of this thienopyridine therapy and neuraxial blockade of 10 days, while the American guidelines 14 days.16

Clopidogrel is a prodrug.47 Neuraxial anesthesia should only be performed at least 7 days after the last intake (Class IIa, level C),16, 25 whereas the Scandinavian guidelines noted that a 5-day interruption is probably adequate.28

Prasugrel, a novel thienopyridine, is a prodrug,47, 48 has a rapid onset, 10 times greater than that of clopidogrel,49 and is a particularly potent antiplatelet agent. In view of this properties, neuraxial anesthesia should be strongly discouraged during prasugrel treatment, unless a time interval of 7-10 days can be observed (Class III, level C),25 whereas the Scandinavian guidelines states that a 5-day stoppage may be sufficient.28

Ticagrelor acts directly on the P2Y12 receptor. Like prasugrel, it provides much faster, greater and more consistent P2Y12 inhibition than clopidogrel.49 However, neuraxial anesthesia should be discouraged during treatment with ticagrelor, unless at least 5 days have lapsed since the last dose (Class III, level C).25

For resumption of the antiplatelet drug after a neuraxial procedure or catheter removal, the Scandinavian guidelines recommended that the drug has to be started after catheter removal, whereas the European guidelines recommended 6 hours after catheter removal before prasugrel and ticagrelor can be started.25

Blocking the glycoprotein IIb/IIIa receptor, the final common pathway of platelet aggregation, represents the most potent form of platelet inhibition. It is reversible. After administration, the time to normal platelet aggregation is 24 to 48 hours for abciximab and 4 to 8 hours for eptifibatide and tirofiban.50, 51 As glycoprotein IIb/IIIa inhibitors are used only in acute coronary syndromes, in combination with antiocoagulants and aspirin, and as cardiac surgery procedures are usually conducted as emergencies with continuing anticoagulation, neuraxial blockade is contraindicated (Class III, level C). If a catheter has to be removed after their administration, most guidelines recommend waiting at least 48 hours after abciximab, and 8-10 hours after tirofiban or eptifibatide.52 Neuraxial techniques should be avoided until platelet function has recovered.

Thrombin inhibitors

Direct selective thrombin inhibitors include recombinant hirudin derivatives (desirudin, lepirudin, and bivalirudin), indicated for thromboprophylaxis (desirudin) and VTE...
**Table IV.—Comparison of different guidelines in the management of patients receiving antithrombotic therapy.**

<table>
<thead>
<tr>
<th>Antplatelet medications</th>
<th>Subcutaneous UHF</th>
<th>Intravenous UHF</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DGAI</strong></td>
<td>NSAIDs: no contraindication; hold LMWH, fondaparinux 36-42 h. Thienopyridines and GP IIb/IIIa are contraindicated</td>
<td>Needle placement 4 h after heparin; heparin 1 h after needle placement or catheter removal</td>
<td>Needle placement and/or catheter removal 4 h after discontinuing heparin, heparinize 1 h after neuraxial technique; delay bypass surgery 12 h if traumatic</td>
</tr>
<tr>
<td><strong>BARA</strong></td>
<td>NSAIDs: no contraindication. Discontinue ticlopidine 14 d, clopidogrel 7 d, GP IIb/IIIa inhibitors 8-48 h in advance</td>
<td>Not discussed</td>
<td>Heparinize 1 h after neuraxial technique. Remove catheter during normal aPTT; reheparinize 1 h later</td>
</tr>
<tr>
<td><strong>ASRA</strong></td>
<td>NSAIDs: no contraindication. Discontinue ticlopidine 14 d, clopidogrel 7 d, GP IIb/IIIa inhibitors 8-48 h in advance</td>
<td>No contraindication with twice-daily dosing and total daily dose &lt;10,000 U, consider delay heparin until after block if technical difficulty anticipated. The safety of neuraxial blockade in patients receiving doses &gt;10,000 U of UFH daily, or more than twice daily dosing of UFH has not been established</td>
<td>Heparinize 1 h after neuraxial technique, remove catheter 2-4 h after last heparin dose; no mandatory delay if traumatic</td>
</tr>
<tr>
<td><strong>CHEST</strong></td>
<td>NSAIDs: no contraindication. Discontinue clopidogrel 7 d before neuraxial block</td>
<td>Needle placement 8-12 h after dose; subsequent dose 2 h after block or catheter withdrawal</td>
<td>Needle placement delayed until anticoagulant effect is minimal</td>
</tr>
<tr>
<td><strong>ESA</strong></td>
<td>NSAIDs: no contraindication. Discontinue ticlopidine 10 d, clopidogrel 7 d, GP IIb/IIIa inhibitors 8-48 h in advance</td>
<td>A time interval of 4-6 h between heparin administration and puncture or catheter manipulation and withdrawal. Further administration of low-dose heparin at least 1 h after the block</td>
<td>A time interval of 4-6 h between heparin administration and puncture or catheter manipulation and withdrawal. Further administration of low-dose heparin at least 1 h after the block. Intraoperative heparinization is not a contraindication to neuraxial blockade</td>
</tr>
</tbody>
</table>
Table IV.—Comparison of different guidelines in the management of patients receiving antithrombotic therapy.

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Fondaparinux</th>
<th>Direct thrombin inhibitors</th>
<th>Thrombolytics</th>
<th>Herbal therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR&lt;1.4 for needle/catheter insertion and withdrawal</td>
<td>Needle placement 36-42 h after last dose, wait 6-12 h after catheter removal for subsequent dose</td>
<td>Needle placement 8-10 h after dose; delay subsequent doses 2-4 h after needle placement</td>
<td>Absolute contraindication</td>
<td>No contraindication</td>
</tr>
<tr>
<td>INR&lt;1.4 for needle/catheter insertion and withdrawal</td>
<td>Needle placement 36 h after last dose. Indwelling epidural catheter not recommended</td>
<td>Needle placement 8-10 h after dose; delay subsequent doses 2-4 h after needle placement</td>
<td>Absolute contraindication</td>
<td>Not discussed</td>
</tr>
<tr>
<td>Normal INR (before neuraxial technique); remove catheter when INR≤1.5 (initiation of therapy)</td>
<td>Single injection, atraumatic needle placement or alternate thrombo prophylaxis. Avoid indwelling catheters</td>
<td>Insufficient information. Suggest avoidance of neuraxial techniques</td>
<td>Absolute contraindication</td>
<td>No evidence for mandatory discontinuation before neuraxial technique; be aware of potential drug interactions</td>
</tr>
<tr>
<td>Avoid or limit epidural analgesia to &lt;48 h. Remove catheter when INR&lt;1.5</td>
<td>Single-injection spinal safe. Avoid epidural analgesia</td>
<td>Not addressed</td>
<td>Not addressed</td>
<td>Not addressed</td>
</tr>
<tr>
<td>INR&lt;1.4 for needle/catheter insertion and withdrawal</td>
<td>Needle placement 36 h after last dose, wait 12 h after catheter removal for subsequent dose. Therapeutic doses: contraindication to neuraxial technique</td>
<td>Needle placement 8-10 h after dose; delay subsequent doses 2-4 h after needle placement</td>
<td>Absolute contraindication</td>
<td>No evidence for mandatory discontinuation before neuraxial technique; be aware of potential drug interactions</td>
</tr>
</tbody>
</table>
the first group, it is advisable to wait at least 8-10 hours — and longer if possible — between the administration of these agents and neuraxial puncture, and to avoid combinations with other antithrombotic agents (class i, level c). in case of argatroban, when hepatic function is good, normalization of the aPtt takes only 2-4 hours after the end of infusion, due to the short half-life of 35-45 minutes. For all treatment (lepirudin) in patients with HIT type II, and argatroban, approved for the treatment of HIT type II.33, 54

If neuraxial blockade is considered, a distinction needs to be made between patients with a history of HIT, who require only thromboprophylaxis, usually with low-dose danaparoid, and those with acute HIT type II, in whom therapeutic anticoagulation is required.25 In the first group, it is advisable to wait at least 8-10 hours — and longer if possible — between the administration of these agents and neuraxial puncture, and to avoid combinations with other antithrombotic agents (Class I, level C). In case of argatroban, when hepatic function is good, normalization of the aPTT takes only 2-4 hours after the end of infusion, due to the short half-life of 35-45 minutes. For all

### Table IV.—Comparison of different guidelines in the management of patients receiving antithrombotic therapy (continues).

<table>
<thead>
<tr>
<th>Antplatelet medications</th>
<th>Subcutaneous UHF</th>
<th>Intravenous UHF</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIAARTI</td>
<td>NSAIDs: no contraindication. Discontinue ticlopidine 10-14 d, clopidogrel 7 d, GP IIb/IIIa inhibitors 8-48 h in advance</td>
<td>No contraindication with twice-daily dosing and total daily dose &lt;10,000 U, consider delay heparin until after block. No other drugs</td>
<td>Heparinize 1 h after neuraxial technique; remove catheter 2-4 h after last heparin dose. No mandatory delay if traumatic</td>
</tr>
<tr>
<td>SSAI</td>
<td>ASA for secondary prevention: 12 h before neuraxial technique; ASA for primary prevention: interruption 3 d before neuraxial technique or catheter removal. ASA high doses: discontinue 7 d. NSAIDs discontinuation before neuraxial technique: diclofenac, ibuprofen, ketoprofen 12 h, indomethacin, ketorolac, lornoxicam 24 h, naproxen 48 h, piroxicam, tenoxicam 2 wk, COX-2-specific inhibitors no effect on platelets. Discontinue ticlopidine and clopidogrel 5 d; dipyridamol: no interval required</td>
<td>Not discussed</td>
<td>≤5000 U (70 U/kg)/day. Needle placement and/or catheter removal 4 h after discontinuing heparin, normal aPTT and platelets; heparinize 1 h after neuraxial technique; &gt;5000 U (70-100 U/kg)/day, same indications before, but heparinize 6 h after neuraxial technique; &gt;100 U/kg/day, same recommendations, start epidural evening before surgery</td>
</tr>
</tbody>
</table>

against the performance of neuraxial techniques in patients receiving thrombin inhibitors (grade 2c).16

Discussion

A comparison of various Guidelines reveals similarities (Table IV) in the management of patients who receive thrombolytics, UFH, and
antiplatelet therapy. The ASRA guidelines for LMWH are much more conservative than the corresponding European statements owing to the large number of hematomas in North America. It is notable that an indwelling epidural catheter during single-daily dosing of LMWH is still considered safe in Europe. However, if the patient is receiving antiplatelet therapy, LMWH will not be administered 24 hours before needle placement and/or catheter removal. An additional major difference is the management of the patient who receives fondaparinux. The German guidelines allow maintenance of an indwelling epidural catheter, although this is recommended against in both the Belgian and the ASRA statements. Finally, European guidelines support neuraxial techniques (including continuous epidural analgesia) in the presence of direct thrombin inhibitors. However, this is relatively contraindicated by the ASRA guidelines.

A special case concerns patients undergoing dual antiplatelet therapy: patients with unstable coronary syndromes, previous percutaneous coronary interventions, and stent implantations, benefit from long-term dual platelet aggregation inhibition with aspirin and clopidogrel.

It is now well-established that the duration of dual antiplatelet treatment among patients with PCI and coronary stents is 4-6 weeks after bare metal stents (BMS) implantation, 3 months after sirolimus drug-eluting stents (DES) implantation, 6 months after paclitaxel DES implantation, and 3-6 months for second generation DES implantation. Patients with a drug-eluting stent are at risk for a particularly long period, due to late and incomplete endothelialization.

If this treatment combination is prematurely withdrawn following coronary intervention, the risk of acute stent thrombosis and myocardial infarction is substantially increased, with high mortality. This also appears to be the case even when perioperative bridging is carried out using heparin, and the platelet aggregation inhibitors are only withdrawn very briefly. Consequently, the American Heart Association currently recommends that drug-eluting stents are only used provided no surgery is planned within the following 12 months, and the patients show a high degree of compliance. A cardiologist should be consulted before any interruption of platelet aggregation inhibition, and clopidogrel with aspirin should be administered during the perioperative period (Class I, level C).

The risk of preoperative withdrawal of antiplatelet drugs to perform a regional or neuraxial blockade is not justified, because clopidogrel withdrawal in case of unstable plaques or uncovered stents increases infarction and death rates 5-10 times. Clopidogrel plus aspirin during the week preceding an operation is contraindicated in all forms of regional anesthesia. Spinal hematoma has been described during clopidogrel treatment, but the risk of spinal or epidural hematoma with dual antiplatelet therapy is unknown. Regional anesthesia is commonly employed in patients with CAD because of its protective cardiovascular effects. When compared to the cardiac death rates of general anesthesia, upper thoracic epidural anesthesia is known to decrease cardiac morbidity by 40%. However, in a meta-analysis of 1173 patients, neuraxial blockade at levels below T6, alone or in combination with general anesthesia, do not reduce the cardiac risk, mortality, or infarction rate.

Furthermore, in abdominal vascular surgery, a decrease in cardiac complication rate with combined anesthesia compared to general anesthesia (10% vs. 18%), is clearly evident only in high-risk patients. Since regional anesthesia is contraindicated (risk of spinal hematoma) in all subjects receiving clopidogrel plus aspirin during the week prior to surgery, and since stopping clopidogrel, in the case of unstable plaques or uncovered stents, increases infarction and death rates by 5-10 times, more research work is urgently needed in the area.

Conclusions

The comparison of the Guidelines of the main Societies shows, for the majority of considered anticoagulants, very strong differences, particularly concerning the time intervals to be respected in carrying out regional anesthesia procedure. Furthermore, the evidences for
prescriptions to be taken are weak. Therefore, the decision for or against regional anesthesia always requires a careful risk-benefit analysis, noting any history of bleeding, followed by a physical examination looking for signs of increased bleeding tendency, for example petechiae or hematoma (Class I, level A). Several conditions may be associated with altered coagulation. These include the perioperative use of various anticoagulant drugs, low platelet count, renal and/or hepatic failure, chronic alcoholism, chronic steroid therapy, and perioperative infusion of dextrans. Laboratory tests, if indicated at all, should be appropriate to the individual (Class I, level A).

The perioperative cessation of anticoagulant drugs to improve the safety of neuraxial block needs to be critically evaluated. An alternative anesthetic technique should be used if it is judged that the administration of the anticoagulant must not be interrupted (Class IIa, level C). Therefore, if neuraxial blockade is felt to be beneficial to a given patient, a spinal anesthetic technique may be a valuable alternative as current data from the literature suggest that spinal puncture may be associated with lesser risk of spinal hematoma than epidural anesthesia.

Finally, the guidelines are not intended to bypass clinical judgment. When the anesthesiologist decides not to comply with these guidelines, the reasons should be noted in the patient’s chart.

Key messages
— A strong disparity often exists between the guidelines of the main scientific societies, creating confusion among the operators in the choices of daily clinical practice.
— The evidence for prescriptions to be taken is weak.
— The decision for or against regional anesthesia always requires a careful risk-benefit analysis, especially in doubtful or controversial cases.
— In case of NOACs use, avoid regional anesthesia procedures.

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.

Cervical facet joint syndrome: a possible cause of chronic cervicobrachial pain

Dear Editor,

We have read with keen interest the original article by Aurini et al. about the treatment of chronic cervicobrachial pain (CBP) using ultrasound-guided periradicular injection of meloxicam.1

The paper reports excellent results in treating both patients with a herniated cervical disc (27%) or those with no structural cause for CBP (73%). The injections were performed at levels C5 to C7 which is consistent with the international literature which also demonstrates these roots as the most frequently involved in CBP.2, 3

We are highly appreciative of the comprehensive description of such a useful treatment option for this common disease and therefore we would like to give our contribution to the discussion to further improve the potential benefit of the treatment described.

Our major concern regarding this paper is that it does not highlight cervical facet joint (CFJ) syndrome, nor does it describe its potential role in the genesis of CBP. The authors include peri-facet injections in the long list of treatments received by the patients without discussing it fully.1

According to the studies performed by Fukui et al. the referred pain arising from CFJ C4-C5, C5-C6 and C6-C7 can have clinical features partially similar to the CBP radiated to the upper extremities you have described.3

As 73% of your patients have no structural causes of CBP demonstrated by magnetic resonance imaging (MRI), the possibility of a CFJ syndrome should have been considered and diagnosed with a moderate to strong degree of accuracy using a medial branch block performed at the level of the suspected joint and the one above.4, 5

The ultrasound-guided approach described to perform periradicular injection is a safe approach to prevent intraforaminal injection (1.5 cm away from the foramina), but requires a volume of drug (1 mL if one single nerve root is involved) that can spread and reach the close cervical facet, therefore it could partially explain the therapeutic effect of your treatment in patients with negative MRI as usually the volume used to perform cervical periradicular injection varies between 0.25 and 0.5 mL.6

According to Manchikanti et al., there is no evidence that common degenerative changes on cervical MRI correlate with neck symptoms except with disk herniation and spondylosis (that usually cause radicular pain), thus the only way to exclude a CFJ syndrome in patient without disk herniation should have been a medial branch block.4

This could have detected some cases of CFJ and changed treatment strategy by maybe considering the injection of meloxicam in the CFJ.

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Analysis of cerebral glucose metabolism in patients with post-operative cognitive dysfunction

Dear Editor,

Postoperative cognitive dysfunction (POCD) is a perioperative complication of unknown etiology with an incidence of 25.8% among the elderly following non-cardiac surgery.1 Even though symptoms may be temporary, association with premature retirement, prolonged dependency on social transfer payments and increased mortality have been reported.1,2 Of interest, recent studies have hypothesized a common pathophysiological mechanism of POCD and Alzheimer’s disease.3,4 An answer to the question whether sustained effects on the central nervous system as seen in these diseases are the pathophysiological foundation is essential for effective prevention and treatment. FDG-PET-CT is an established tool in the diagnosis of neurodegenerative diseases, typically revealing hypometabolic regions in the posterior cingulate gyri, precuneus, and parietotemporal association cortices.5 As these changes precede the clinical onset, FDG-PET-CT allows pre-clinical detection of these diseases.5 We here report a prospective pilot study using FDG-PET-CT in patients with POCD to evaluate for pre-clinical neurodegenerative disease.

After approval from the institutional review board, informed written consent was obtained from 93 patients of 70 years and older undergoing orthopedic, urologic or visceral surgery with an expected operating room time >2 h. Patients with medication impairing cognitive functions or history of atrial fibrillation, stroke, cardiac surgery, cerebrovascular disease, deep vein thrombosis or preexisting mental disorders were excluded. Patients were then subjected to a neuropsychological test battery based on previous studies1 prior to the day of surgery and 4 days after. Twenty-three (24.7%) patients were excluded from the study due to cognitive impairment in the pre-test or due to refusal to re-test.

The incidence of POCD was 32.9% (N.=23) and did not differ in age, body mass index, gender, operating room time, frequency of combined anesthesia, social background, ASA and NYHA scores, education level, anxiety, fatigue, pain, depression scores, pre-operative test results, perioperative hemoglobin or CRP. Postoperative scores assessing medium term memory (VLMT7, P=0.006 and VLMT W-F, P=0.003) and concentration (FWT-II P=0.040 and FWT-III, P=0.032) were significantly worse in patients with POCD.

Patients positive for POCD (N.=10, 13 were discharge before scan or refused) were subjected to a FDG-PET-CT scan and revealed impairment of glucose uptake in 5 of 10 cases (Table I). We observed a generalized, global impairment of glucose uptake in 2 cases and patterns consistent with neurodegenerative disease in 3 cases, 2 consistent with Alzheimer and 1 resembling fronto-temporal dementia. However, only 2 reached statistical significance using the Alzheimer-module (PALZ). We found that alterations went in line with differences in a test assessing executive functions postoperatively (RWT S, P=0.005) as well as significantly worse decline in scores assessing mental flexibility (TMT-B, P=0.032).

Taken together, our study shows that clinically

<table>
<thead>
<tr>
<th>Glucose uptake</th>
<th>PMOD T-Sum</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Focal decrease temporo-ocipital left, borderline decrease temporo-polar right</td>
<td>Normal</td>
<td>Report commensurate with age</td>
</tr>
<tr>
<td>2 Decrease temporo-mesial and basal</td>
<td>Normal</td>
<td>Report commensurate with age</td>
</tr>
<tr>
<td>3 Normal</td>
<td>Normal</td>
<td>Report commensurate with age</td>
</tr>
<tr>
<td>4 Discreet decrease fronto-mesial</td>
<td>Normal</td>
<td>Positive</td>
</tr>
<tr>
<td>5 Decrease fronto-mesial, temporal</td>
<td>Normal</td>
<td>Formally consistent with fronto-temporal dementia, visual impression is a rather unspecific decrease of uptake</td>
</tr>
<tr>
<td>6 Decrease frontal and fronto-mesial, temporo-parietal, temporo-basal</td>
<td>Positive</td>
<td>Formally consistent with Alzheimer’s disease or fronto-temporal dementia, global hypometabolism</td>
</tr>
<tr>
<td>7 Focal decrease temporo-lateral right</td>
<td>Normal</td>
<td>Report commensurate with age</td>
</tr>
<tr>
<td>8 Decrease temporo-parietal, cingulum</td>
<td>Normal</td>
<td>Consistent with early onset Alzheimer’s disease</td>
</tr>
<tr>
<td>9 Decrease frontal right and perisylvic, temporo-lateral</td>
<td>Normal</td>
<td>Significant unspecific, global decrease, not consistent with neurodegenerative disease</td>
</tr>
<tr>
<td>10 Decrease frontal, parietal</td>
<td>Normal</td>
<td>Borderline significant unspecific, global decrease, not consistent with neurodegenerative disease</td>
</tr>
</tbody>
</table>
diagnosed POCd may in fact go in line with alterations of brain glucose metabolism, but that a statistically significant number of patients does not reveal any impairment. Therefore a pathophysiology constituting or resembling Alzheimer’s disease can not fully explain the incidence of POCd. Occurrence of the observed alterations, and their respective distribution patterns do not draw a homogenous picture and thus argue that POCd is a collective of heterogeneous etiologies.

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Mucosal injury aspect immediately after a standard TEE use for cardiac surgery and emphasize that shearing forces, associated to an inadequate probe mobilization in a locked position can lead to tearing of esophagus. Non pulsatile flow, prolonged cardio pulmonary bypass, mechanical compression and excessive heat are also factors which can cause ischemic esophageal wall injury. Therefore, safety measure to limit possible TEE injury have been describe in Hilberath’s et al. work which recommends several measures that can be taken to limit the risk for esophageal mucosa damage: 3 keep the probe tip unlocked, use of the minimal acoustic power necessary to obtain adequate images, turn off the probe, and be careful for inadvertent heating of the probe.

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References


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Perioperative management of a patient with cold agglutinin disease undergoing segmental hepatectomy

Dear Editor,

Cold agglutinin disease (CAD) is an autoimmune hemolytic disease caused by the presence of cold-reacting autoantibodies. Activation of cold agglutinins (CAs) occurs when the patient’s body temperature falls below their thermal amplitude during an operation, leading to hemagglutination, hemolysis, and microvascular thrombosis. Specific measures taken to prevent perioperative hypothermia were successfully used in a patient with CAD undergoing segmental hepatectomy.

A 60-year-old male was scheduled for elective segmental hepatectomy. Based on the preoperative clinical and laboratory findings, a diagnosis of CAD was made. On the surgery day, the operating room was prewarmed to 24 °C. Upper and lower body forced-air warming devices were applied during the perioperative period. Posterior skin surfaces were also warmed by a circulating-water mattress. All intravenous fluids and surgical irrigation solutions were prewarmed to 39 °C. A Humid-VentFilter was placed in the airway circuit to humidify the anesthesia gases. Esophageal and skin temperature was maintained above 36 °C. Warming measures were continued postoperatively for 24 hours. The patient made an uneventful recovery without evidence of hemolysis or microvascular thrombosis.

The severity of CAD is dependent on the patient’s plasma titer of CAs and their thermal amplitude (i.e., the highest temperature at which antibodies interact with red blood cells). Patients with a low titer of CAs (≤256) and low thermal amplitude of CAs (<30 °C) can safely undergo major surgery procedures without changes in standard clinical practice. However, patients with clinically-significant CAD (e.g., clinical signs of acrocyanosis of their extremities, a high titer of CAs, and a high thermal amplitude of CAs >30 °C) can present a challenge for anesthesiologist due to their risk of intraoperative agglutination and hemolysis. Screening for the presence of cold agglutinins involves obtaining a history related to acrocyanosis of their extremities when exposed to the cold, positive bedside testing (e.g., the ice cube test and Ehrlich finger test), and high levels of plasma agglutinins. For clinically-relevant CAD, prophylactic treatments including corticosteroids, rituximab and/or fludarabine are necessary prior to surgery.

Inadvertent perioperative hypothermia can occur during major surgical procedures. Strict avoidance of hypothermia during the perioperative period is mandatory for patients with CAD. In this case, a preoperative diagnosis of CAD allowed necessary steps to be taken to avoid perioperative hypothermia and subsequent agglutination and hemolysis. Prewarming of the operating room and application of warming devices before induction of anesthesia decreased the central to peripheral temperature gradient, thereby minimizing core heat loss from thermal redistribution. In addition, the use of packed red blood cell transfusions was limited to avoid the introduction of new antigens and complement factors. Warming measures should be continued postoperatively until normal thermoregulation is restored and the patient is able to manage his/her own temperature control.

In conclusion, patients with clinically-significant CAD require preoperative intervention with corticosteroids, rituximab and fludarabine to suppress production of aberrant IgM protein. Careful temperature monitoring must be undertaken during the perioperative setting in conjunction with a preemptive warming strategy to avoid CA activation. A proactive perioperative management strategy allows patients with CAD to safely undergo major surgical procedures.

References


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## TOP 50 MINERVA ANESTESIOLOGICA REVIEWERS

Top 50 reviewers August 2016-January 2017

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