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About the cover: cover shows a magnetic resonance highlighting an epidural abscess with inner cystic organization of multiple air fluid level. Spinal canal is markedly narrowed and spinal cord is compressed, resulting in neurologic symptoms. For more information, see article by Allegri M. et al. beginning on page 392.
Nowadays, regional anesthesia (RA) techniques used for both anesthesia and post-operative analgesia procedures have become increasingly widespread. While the introduction of ultrasonography (USG) for use as a part of these techniques has increased the interest in RA, visualizing anatomic structures during the procedure has also provided a considerable advantage regarding the safety of RA techniques. However, it does not seem possible to advocate that the use of USG can completely eliminate complications.\(^1\),\(^2\) For this reason, it is important to report complications associated with RA in order to safely perform future procedures and to develop novel technologies.

The study entitled “Italian Registry of Complications associated with Regional Anesthesia (RICALOR). An incidence analysis from a prospective clinical survey” by Allegri et al.,\(^3\) published in this issue of Minerva Anestesiologica, is a web-based prospective study comprising 17 centers from Italy. In this study, complications of 117.182 procedures performed for primary anesthesia technique or postoperative analgesia were reported on a volunteer basis. Considering that previous reports about this issue have usually been conducted on a retrospective basis,\(^4\) the study of Allegri et al.\(^3\) is a remarkable work. It is also appreciated that long-term follow-up after RA has been performed and the participants honestly reported their complications. However, since this is a web-based study, missing data entry is an expected limitation. This limitation may cause incomplete reporting of the incidence of some procedures and complications, or incorrect interpretations of the causes and management of a certain complication.

According to our opinion, studies conducted across the country offer advantages for identifying insufficient centers in terms of training and technical facilities. Based on the results of these studies, the centers can be supported and RA-related complications can be reduced.

In the study by Allegri et al.,\(^3\) local anesthetic systemic toxicity (LAST) was observed most frequently in axillary block. The researchers indicated that further investigations are required concerning the use of USG for preventing the development of LAST and post-operative neurologic symptoms (PONS). In cases with complication following USG-guided block, the type of the block used should be reviewed in terms of safety. We suggest that peripheral nerve block techniques with reduced complication rate should be preferred in USG-guided procedures in the future.\(^5\)

Despite the enrollment of patients taking anticoagulant therapy in this study,\(^3\) no hemorrhagic complication was reported. This finding indicates the benefits of the guidelines related to RA and anticoagulant therapy. It is also emphasizes that participants have been increasingly aware of RA-related complications in
such patients. These guidelines should be updated according to the novel anti-thrombotic agents.3, 6

A spinal-epidural abscess was reported as an infectious complication in only one patient.3 This case report was also published in this issue of Minerva Anestesiologica.7 It warns clinicians about compliance of aseptic technique during epidural catheter placement for RA procedures or postoperative analgesia. Furthermore, it also emphasizes the importance of consultation of the febrile patients with local and laboratory signs of infection before the emergence of neurological deficit.

Although the overall incidence of major complications of RA is low, they may cause permanent neurological sequela when these complications occur and are not noticed until too late. Safe and successful applications of RA techniques depend on increased awareness, training, and technical facilities. Detailed reports about techniques, tools, habits, medications, equipment, and complications related to RA techniques will allow performing such procedures more safely in the future. Allegri’s et al.3 nationwide multicenter prospective study investigating RA complications is a pioneering work in this field.

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Pulmonary pathophysiology in obesity: did we miss something?

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Obesity is a complex condition involving an excessive amount of body fat and represents a major risk factor for a number of chronic diseases, including type 2 diabetes, cardiovascular disorder and certain types of cancer.

Due to the high prevalence, obesity is nowadays considered a public health concern in the majority of high-income countries. However, it is spreading globally and becoming an emerging issue also in low- and middle-income countries.1

In the United State, one-third of adults are obese (BMI≥30 kg/m²) and the medical costs for these individuals are about $ 1500 higher than those for normal weight subjects. In Italy, although prevalence is lower than in US (11% of adults are obese), childhood obesity is one of the most serious ongoing challenges for pediatricians.2

Therefore, treating obese subjects is increasingly common both in the operating room and in intensive care units. The care of obesity is often a challenge for the anesthesiologist due to the complex pathophysiology changes occurring in these patients.

In this issue of Minerva Anestesiologica, Rivas et al.3 compare data regarding pulmonary gas exchange in upright and supine position in a cohort of healthy obese female subjects before and after bariatric surgery (BS). They hypothesized that prior to BS, supine position would worsen pulmonary gas exchange abnormalities and that this effect would vanish after the surgery-induced weight loss. Interestingly, they found an unexpected result analyzing the overall population because in obese individuals oxygenation did not deteriorate when supine before BS, in spite of finding of previous series. Conversely, one year after BS in recumbent position oxygenation significantly decreased while alveolar-arterial pO₂ difference increased. Furthermore, the authors intriguingly found a distinctive effect between non-hypoxemic and hypoxemic patients whereas postural oxygenation alterations mainly occurred in the latter. Indeed in this subset, supine one year after BS results in a noteworthy unforeseen pulmonary gas exchange deterioration.

Reason of these findings should be necessarily sought in changes of lungs volume and mechanic, in breathing pattern or in hemodynamic. Unfortunately, the authors failed to show a strong causative physiopathological mechanism, analyzing neither intrapulmonary shunt nor dead space. Measurements of lungs volumes and mechanics might have provided other interpretative hypothesis.

Arguably, hemodynamics seems to be a
conceivable player in determining the study results. Prior BS orthodeoxia would be induced by a decreased cardiac output coupled with an impaired hypoxic pulmonary vasoconstriction. This phenomenon seems to be more critical than the improvement of lung volumes in determining oxygenation when moving from supine to upright position in hypoxemic obese patients.

The observation that after weight loss oxygenation worsens in supine position is quite astonishing. The authors put forth the hypothesis that the abnormal pulmonary vascular adaptation after BS determines this conduct. Alterations observed in MIGET-derived $V_{A}/Q$ descriptors reinforced this assumption.

It should be emphasized that study population consists of obese otherwise healthy female patients and therefore data are not soiled by the possible coexistence of any lungs comorbidities, which are frequent in obese subjects. Hence, a note of caution is required to generalize the findings of this study.

Previous studies have shown that in healthy subjects total respiratory system compliance decreases when shifting from the sitting to supine position.\textsuperscript{4} It has been mainly attributed to the reduction in functional residual capacity resulting from expiratory reserve volume drop.\textsuperscript{5} Indeed, gravitational forces in horizontal position cause a cephalic displacement of diaphragm due to increased abdominal pressure. This phenomenon is well known in anesthesia setting and has been investigated in several physiological studies in non-obese patients.\textsuperscript{6} Instead, limited data\textsuperscript{7-10} are available on partitioned respiratory mechanics and lung volumes of obese patients in the anesthesiaology and intensive care setting.

Hence, ventilation strategy in obese patients is a matter of broad debate. There is some evidence that recruitment maneuver added to PEEP compared with PEEP alone improves intraoperative oxygenation and compliance without adverse effects. Currently, no substantial evidence exists to recommend a specific ventilatory mode.\textsuperscript{11} Intraoperative low tidal volume ventilation should be implemented even in these patients.\textsuperscript{12, 13} Note that tidal volume should be set using predicted body weight and not the actual weight\textsuperscript{14} in order to reduce postoperative pulmonary complication. Again, in these patients low tidal volume ventilation may have a greater protective role in comparison to normal weight patients. Indeed, a supposedly safe tidal volume might be not safe enough and produce a cyclic dynamic overstrain in an obese subject with reduced functional residual capacity.\textsuperscript{15}

Relevant data about mechanical ventilation strategy during surgery in obese patients will come from the ongoing PROBESE trial (NCT02148692). The investigators aim to compare a ventilation strategy using higher levels of PEEP with recruitment maneuvers with one using lower levels of PEEP without recruitment maneuvers in obese patients at an intermediate-to-high risk for postoperative pulmonary complications.

Moreover, another key issue should be mentioned regarding the critically ill obese patients. In fact, in recent year the revival of interest in the transpulmonary pressure measurement\textsuperscript{16} to guide mechanical ventilation\textsuperscript{17} raises a number of questions about safety limits of mechanical ventilation especially in the obese patients. Rib cage fat and increased intra-abdominal pressure usually result in a reduced chest wall compliance and, accordingly, in an early exceeding of the safety plateau pressure threshold (30 cmH$_2$O) defined by the ARDSnet Trial.\textsuperscript{18} This issue was highlighted analyzing data of partitioned respiratory mechanic in a cohort of H1N1 ARDS patients suitable for extracorporeal membrane oxygenation (ECMO) support due to unsafe high plateau pressure.\textsuperscript{19} In this study the authors showed that titrating PEEP neglecting abnormalities of chest wall mechanics may overestimate the incidence of hypoxemia refractory to conventional ventilation and, consequently, lead to inappropriate use of ECMO. Therefore obese patients, often having a stiff chest wall, may benefit of increasing PEEP until a physiologically reasonable transpulmonary plateau pressure limit (supposedly 25 cmH$_2$O) irrespective of total respiratory system plateau pressure. This approach
allowed to improve arterial oxygenation and to avoid an inappropriate use of ECMO.

To conclude, we necessarily must strive to investigate the obese respiratory pathophysiology because this topic is becoming increasingly part of our daily lives and many uncertainties remain.

For instance, Rivas et al. reveals unexpected data. We believed it is just one example of what we currently ignore about the obese lung physiology. The study adds to the field the knowledge that, in obese patients, supine positioning may alter gas exchange in a different manner before and after bariatric surgery. Surprisingly, in the former case arterial oxygenation may improve; in the latter conversely oxygenation may worsen.

In conclusion, findings of this paper add an unexpected piece to the multifaceted puzzle of obese lung pathophysiology. The complexity of this field results in several unanswered issues regarding our daily practice.

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Chronic cervical radicular pain: time to tackle a new horizon

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Cervical radicular pain is a common condition among the multiple presentations of cervicobrachial pain, with an annual incidence of 83 per 100,000 population. 1 It constitutes a major public health problem being one of the main causes of disability, missed workdays, and involves substantial health care costs.

It is described as a pain perceived in the upper extremity caused by the stimulation or dysfunction of the nerve root or dorsal root ganglia. 2 Thus, the pain can be perceived in all structures that are innervated by the affected nerve root such as muscles, joints, ligaments, and the skin without following a dermatomal distribution. 3, 4 The most common causes of cervical radicular pain are cervical spondylosis encroaching on the foramen, disc protrusión, and cervical spinal stenosis. 1

Although the pathophysiology of radicular pain continues to be unclear, 2 the proposed mechanisms include neural compression, inflammation and biochemical mediators, vascular compromise, and intraneural edema. 5, 6 Compression alone is not enough to cause pain, being necessary an inflammatory chemical component. 7 Degeneration of the cervical intervertebral disc plays a major role, since its cells secrete proinflammatory cytokines (IL1α, IL1β, IL6, IL17 and TNF) that induce chemokine and metalloproteinases production, adhesion molecules on endothelial cells, chemoattraction of neutrophils, stimulation of phagocytosis, and production of PGE2 by macrophages amplifying the inflammatory cascade, thus establishing a vicious circle. 8-10 Furthermore, neurogenic factors, generated by both disc and immune cells, sensitize nerve endings and induce expression of nociceptive cation channels in the dorsal root ganglion. 2, 8 Depolarization of these ion channels contributes to the generation of radicular pain.

The diagnosis of CRP must be made with caution in order to direct the treatment with etiologic target. In the absence of a gold standard, the diagnosis is based on a combination of history, clinical examination, and complementary studies that can include medical imaging techniques, being MRI the technique of choice, electrophysiologic tests or diagnostic selective nerve root blocks. 3

The natural history of radicular pain has a favorable prognosis with self-limited symptomatology and it resolves spontaneously even despite treatment. Nevertheless, in a proportion of patients become in a chronic disorder despite an appropriate etiologic therapy.

The treatment of CRP constitutes a challenging problem since most of the recommenda-
tions are based on weak or absent evidence. Pharmacotherapy, rehabilitation and physical therapy, interventional techniques and surgery constitute the different alternatives of treatment.

Pharmacologic therapy is indicated as a first-line treatment, mainly in acute phase of CRP as chronic drug therapy has been shown to be ineffective. Thus, nonsteroidal anti-inflammatory drugs are primarily recommended for short-term treatment in the acute phase. Oral steroids have shown efficacy only on a short-term basis although is not supported by any high-quality study, and its long-term use should be avoided because of side effects. Similarly, there are insufficient evidence to recommend opioids in the treatment of neuropathic pain beyond two months and it is associated with multiple adverse effects. Anti-depressants (tricyclics and selective serotonin reuptake inhibitors) and antiepileptic agents such as gabapentinoids have been considered for chronic CRP, however different trials failed to demonstrate its efficacy in chronic lumbar radicular pain. Other commonly prescribed drugs include benzodiazepines, skeletal muscle relaxants or anti-TNF agents. However, most of them have not been rigorously examined in randomized, placebo-controlled trials.

Physical therapy and rehabilitation are recommended to restoring the range of motion and pain relief due to noninvasiveness, although there is no quality evidence to support this attitude. Moreover, modalities as cervical immobilization or spinal manipulation are not risk-free. When conservative treatment fails, interventional treatment is considered. Fluoroscopically guided cervical epidural injections with steroids and/or local anesthetics are the mainstay of the interventional techniques. Both drugs act decreasing inflammation at the level of the affected nerve root. There is good evidence for the effectiveness of cervical interlaminar epidural injections in managing cervical radicular pain. However, the evidence is poor for cervical transforaminal approach.

Both approaches, fundamentally the last one, are associated with catastrophic neurologic complications and intense debate. It has led the FDA to issue a warning for the use of epidural corticosteroids. Pulsed radiofrequency treatment adjacent to the cervical dorsal root ganglion is another recommended treatment for chronic CRP. In selected patients refractory to other treatment options, spinal cord stimulation may be considered.

A multimodal approach based on the combination of drugs and techniques is applied in clinical setting as it is probably more effective than either monotherapy, although its effectiveness and safety should be formally evaluated in further extension. Nonetheless, one third of patients can have persistent symptoms.

Surgical treatment is considered when radicular pain becomes refractory and long lasting despite of multimodal analgesic therapy. Although some patients may benefit from surgery, there is moderate evidence for the effectiveness of cervical spinal surgery for radicular pain. Thus, most randomized studies evaluating surgery for neuropathic cervical pain have found minimal long-term benefit in most patients. Likewise, surgical interventions can result in post cervical surgery syndrome.

Taking into account all these data, the search for new nonsurgical modalities of treatment takes special relevance. In this issue of Minerva Anestesiologica, Aurini et al. present a new target specific treatment modality, the ultrasound-guided cervical periradicular meloxicam injection, as a promising tool for the control of chronic CRP. This preliminary study indicated that all patients who completed the study reported significant improvements in cervicalbrachial pain and disability, with 94% of the patients showed complete remission during the 90 days of follow-up, having an excellent influence on work status. No side effects were reported. These excellent results could be explained by the suppression of the production of PGE2, proinflammatory mediator that plays an important role to induce radicular pain, due to cyclooxygenase inhibitory effect of meloxicam delivered in the site of pathology. However, it is necessary to consider that the results of the study by Borghi et al. are...
not reproducible as the proposed technique is not compared with good standard neither placebo. Furthermore, periradicular meloxicam injections continue to being off-label at this moment. A prospective, randomized, double-blind study eliminating the possible placebo effect component is mandatory to confirm these promising results.

The debate currently remains over CRP treatment because of the lack of evidence regarding the different management strategies. Future high-quality trials should expand the body of evidence about the effectiveness and safety of this and others interventions. The article of Aurini et al. could represent a new stimulus to look at the horizon to find answers to the multiple unresolved questions raised by the cervical radicular pain.

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Mechanical resuscitation devices under special circumstances in the out of hospital setting

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Cardiopulmonary resuscitation (CPR) especially for longer time is strenuous and exhausting for rescuers because the proper compression depth of 5–6 cm with a frequency of 100–120 compressions per minute is hard muscular effort. Therefore resuscitation guidelines recommend now for years that chest-compression-performing rescuers should change every 2 minutes to provide optimal and to avoid suboptimal chest compression resulting in low cardiac output. The medical device industry also tried to build resuscitation machines to overcome these physical challenges for humans with the final aim to provide continuous chest compression. The ultimate aim of all these exertions is an increased rate of survival after cardiac arrest. Besides some rare developments, 2 devices entered the market. Despite earlier mostly observational reports about improved CPR with the use of these devices, large studies published in the last years could not show superior survival rates for the LUCAS device as well as for the Autopulse device in the in the out of hospital setting.

The 2015 Consensus of Science and Treatment Recommendation (CoSTR) document took that into account in the ALS PICO question number 782. Derived from the CoSTR 2015 both, the North-American and the European recommendations on resuscitation issued in October 2015 do not recommend the general use of these resuscitation devices. Both resuscitation councils consider its use in very special situations, “where sustained high-quality manual chest compressions may not be practical.” Examples described are prolonged CPR in patients with refractory VF or pulseless VT with an onset and offset of return of spontaneous circulation (ROSC) “where provider fatigue may impair high-quality manual compressions (e.g., hypothermic arrest), during interventions in the cardiac catheter lab during coronary angiography, or “CPR in a moving ambulance where provider safety is at risk”.

The valued reader will find in this issue of Minerva Anestesiologica a report by Dr. Rehatschek et al. from the University of Bonn, Germany, about a randomized controlled manikin study during simulated helicopter flight comparing the LUCAS device with manual CPR. They found in this setting that LUCAS delivered significantly better adherence to the guideline-correct compression depth. The 2-mm difference on average might not be of clinical importance but comparing every single compression the LUCAS device was in 36% better than manual compression. That is what we expect from machines and why we apply machines — constant high quality delivery of work.
Unfortunately this application of a mechanical resuscitation device was not translated into better overall CPR performance, even in the simulation setting. The authors do not report a difference in other CPR quality parameters, dosing and application intervals of drugs and defibrillation between both groups. This is in accordance with the mentioned human studies that also could not improve survival after out-of-hospital cardiac arrest.6, 7

Interestingly the authors also looked into the physical activity of the rescue helicopter crew and their cognitive performance after the simulation training with both CPR methods. Nice idea because that is a reason why we install machines in our daily life and also during work, that is to liberate muscle force for better use of our brain resulting in overall better performance. Heart rate of the person performing manual CPR was about 20 beats/min higher than the average 80 beats per min while using LUCAS. Not a big surprise as we know CPR is demanding but on the other hand that increase was not that much. No difference in heart rate was found with all other time points measured. The claimed enhanced cognitive performance was based on a questionnaire about the presence of “relevant medical information” and an “irrelevant word” memory test. Medical information was remembered better in 6.6%, the “irrelevant words” in 11% in the LUCAS group.

The question now is what to do with these results, if the overall performance of the resuscitation during simulated flight was more or less the same. Gässler et al.13 also found that the LUCAS device complied with the ERC-guidelines but the other tested devices worked consistently during their simulated helicopter flight scenarios. The modest increase of heart rate during manual CPR in the current study did not decrease decision making. The fact that in the current simulation study the crew could not remember all information or irrelevant words after the flight also did not affect CPR performance during the flight. The authors claim that LUCAS is more effective and less physically demanding and also enhances cognitive performance compared to manual CPR.

I have my doubts, but that is the advantage of the scientific discussion by publishing research results. The scientific community starts to think about new ways of providing better care.

Important and I would like to stress that out, is the last sentence in the conclusion and also in the key messages: The implementation of such devices needs constant training in a simulation setting to increase the performance of the team. That fact was even recognized in the educational chapter of the 2015 ERC guidelines.14 But before implementing cost-intensive devices we need solid results on improved patient outcome, also in these settings.

What could be the future direction even in such special settings? If we bring in highly educated and equipped resuscitation teams to victims of cardiac arrest, does it really make sense to apply mechanical devices with little proven evidence? On the other hand we see the emergence of extracorporeal life support or e-CPR out of hospital.15, 16 Extracorporeal membrane oxygenation (ECMO) might be an option and is suggested by the ILCOR CoSTR ALS PICO 723.9 Nowadays emergency physicians are trained in the use of ultrasound and fast and safe vascular access. Ultrasound is available for out-of-hospital use. To place proper vascular access for an ECMO device is a training issue but thinkable. Certainly we need to wait for properly designed studies to apply these strategies broadly, but for special patients, logistic and transport circumstances that might be an approach that could really improve survival for prolonged resuscitation effort during cardiac arrest.

References
The heart of the art

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In this issue of Minerva Anestesiologica, Mijderwijk et al. address the use of benzodiazepines (BZD) for premedication for one day surgery patients.1 The well conducted systematic review and meta-analysis includes nineteen studies selected without time interval restriction. The authors focused especially on data regarding time to recovery, psychological phenomena and postoperative somatic symptoms.

The results show that time to recovery is significantly higher in patients premedicated with BZD (particularly the time for eye opening), but the discharge time is not significantly compromised in the BDZ group. Moreover, premedication reduces postoperative headache and nausea, but collected data are inconclusive on psychological phenomena with premedication.

In conclusion, the Authors send three messages: removing BDZ from our clinical practice in day case patients to prevent delayed discharge is not justified; BDZ are linked to a 53% reduction of post-operative side effects; more studies are needed to show any benefits on physiological post-operative sequelae with the use of BDZ.

Certainly we can recognise that the Authors have highlighted an interesting and, recently again, discussed topic.2-5 In this context some questions arise.

Modern anesthesia techniques have led to a reduction in the need of premedication initially developed to contrast the side effects of ether and chloroform that were widely used;6 actually the question has to be about what we want to achieve with the premedication.

Reducing anxiety can be the operator’s main goal, but at least 50% of the patients refuse premedication upon request.7 A positive anxiety can help the patient to better assimilate informations about the peri-operative period, to “share decisions”8 about anaesthesia and surgery. This is important in particular if the drug is prescribed at home, before patient hospitalization, as often in case of day surgery.9 It is important to remember the BZD induced amnesia that can be interpreted as one of their “beneficial effect”, rather than a complication,4 but amnesia can even reduce patient postoperative satisfaction due to the impossibility to remember the attentions given by doctors.5

Another topic can be the choice of a benzodiazepine: Midazolam is the most prescribed, Lorazepam or Alprazolam are better suggested as home prescriptions, as well as, recently, Melatonine.10

The choice of the drug can be guided by the onset and offset time, but also on the timing

Comment on p. 438.
of the scheduled surgery and on the in or outpatient. In fact patients significantly sedated before or after anesthesia may have different problems, needing frequently to be sit on beds or trolleys, requiring a more careful transport and often monitoring;\textsuperscript{11} furthermore we should not forget that BDZ premedication is risk factor for postoperative delirium.\textsuperscript{12, 13}

The effects of BDZ are surely not well predictable in two types of patients increasingly scheduled for day surgery: the elderly and obese, whose absorption distribution and wash out of drugs are very peculiar. This case deserves a tailor-made approach.

At this point, it would be interesting to evaluate which type of anesthesia is planned. Patients scheduled for loco-regional anesthesia rather than for a general anesthesia clearly require a different approach to the periperaoperative sedation. Nevertheless, this population of patients, with some possible residual motor and sensory deficit, would benefit of a fully recovered cognitive status at the discharge time. Pharmacokinetic and administration techniques of modern anesthetics make it possible, whereas the response to the BZD, especially when orally taken, is not so easily predictable.

It is sure that premedication modifies the effect of propofol administered by a Target Controlled Infusion system, by reducing the dose at which the anesthesia is induced, but for example increasing the apnea incidence.\textsuperscript{14} The exact dose-effect relationship between premedication and TCI is not known and thus not calculable.

Having made these comments it appears that patient’s drowsiness is achieved more easily than his/her calmness. Factors influencing a highly apprehensive state needing premedication have to be identified: personality, family environment, disease and type of surgery, care and attitude of the medical and nurse staff during hospital stay.

The paper by Mijderwijk et al. provided interesting but not final conclusions.

We believe that the anesthesiologist presence can deeply understand and influence the patient and that an emotional and supportive relationship instead of a simple informative and skillful preoperative visit may have a positive benefit, improving the anxiety and the confidence. Lawrence DE clearly thought so in 1963 in his paper, a milestone on Humanism in anesthesia.\textsuperscript{16}

Furthermore we strongly think that “medicine is the most scientific of the humanities and the most humanistic of the sciences”, and that the Anesthesiologist is the Internist of the Operating Theatre and certainly the major specialist of sedatives. In the current times of cost saving and high performance pressures, he/she might provide a more humanistic relationship with patients rather than just prescribe a drug. This approach can represent the Heart of the anesthetic Art.\textsuperscript{16}

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How should ethical committees promote research in critically ill patients?

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We read with interest the article by Zamperetti et al., 1 published in this issue of Minerva Anestesiologica, which offers a timely and updated review on the issue of the “informed consent” in emergency situation, providing the opportunity to underline more explicitly some of the points which make this area a recurrent object of both legal and ethical discussion. 2 On one side, this debate is an exemplary case of attention to a very sensitive issue, i.e. the protection of incompetent patients, who become even more fragile when exposed to “experiments”. On the other, the daily clinical reality documents that in acute severe clinical conditions, when patients are obviously incompetent, the last and least concern is their direct or indirect consent.

Very often, patients in emergencies are not in an appropriate status to be adequately informed on a clinical experimentation, since they are either incompetent or under a highly stressed clinical condition. 3 Think about a patient with dyspnea for acute heart failure and pulmonary edema, an aphasic patient after an acute ischemic stroke, or a patient with dyspnea and obnubilation for the development of septic shock. In these cases, most of the time the patient cannot have expressed her/his “informed” consent prior the development of the acute pathological process. Moreover, if the patient was previously competent, there is no legal representative at the time of the manifestation of the pathological condition. Finally, such acute conditions make not feasible to nominate a legal representative, especially when the potential benefit of the intervention tested implies its rapid application. 4 The respect of their human life, dignity, and integrity is assumed to coincide with the capacity of providing the available (though not always accurately evidence-based) responsible care.

While awaiting for the application of the novel European Union regulations, 5 it could be useful to remind some concepts, which are recurrent in the above debate.

First, the leading term is “emergency”. Whenever, in routine care, the incompetence of a patient is associated with a major clinical risk, any due intervention is assured, legitimately and legally, without information or consent. This procedure is a common clinical practice well accepted both on a national and international level, as long as such in-
Intervention is a treatment generally accepted to reverse the health-threatening condition. Second, the key ambiguity of this debate coincides with the misleading concept according to which “experimental clinical research” is a separate domain of care from the usual clinical treatment. In contrast, clinical research coincides with a “mandatory expression of care”, whenever there is a documented uncertainty on one of its component, and there is a plausible, documented, and independently assessed alternative aimed at improving the outcome of patients who do not present any contraindications to the experimental intervention. In fact, how has Medicine generally improved over the years? First, by increasing the knowledge of patient physiology and pathophysiology, and second, by gathering evidence on the potential benefit of novel clinical treatments applied in specific pathological conditions, based on a solid scientific rationale. Both cases imply clinical experimentations, and correspond to the main aims of the Helsinki Declaration, as clearly pointed out by Zamperetti et al.1 Third, the protection of patients’ rights is assured provided that a competent and documented evaluation has verified that nothing of the due care is withdrawn from the patients assigned, in the randomization process, to the treatment arm, where the uncertain and promising, yet unproven, novel therapy is tested. In this framework, a controlled protocol is certainly a better protection of the rights of all patients enrolled, as compared to the routine and uninformed exposure to uncertain interventions. Fourth, the acceptance or the refusal of a protocol by an EC must be based exclusively on the careful evaluation of the methodological coherence of the study protocol with its declared aims.

Despite the evident importance of clinical experimentations, however, in Italy different ECs often apply discrepant criteria on how to deal with incompetent patients, with the excuse of the unclear legislation, and the untold reason of not taking responsibility. Consequently, in doing so, they discriminate de facto critically ill patients from being subjects of clinical research. Is really this action ethical?

The recent and highly significant experience of the Albumin Italian Outcome Sepsis (ALBIOS) Trial (#NCT00707122) has been an important test of the relevance of this question. The trial, funded by the Italian Medicines Agency, has seen the participation of about 100 centers across Italy, with the enrollment of more than 1800 patients admitted to ICU with severe sepsis, and randomized to two arms to test the comparative benefit profile of intravenous albumin replacement as compared to the use of only crystalloids. The prevalent position of the majority of ECs coincided with the recognition that the undefined legislation in relation with the “informed consent” could have been solved by including the suboptimal tool of a “deferred consent”, which is internationally employed and accepted as a compromise.2 A minority of ECs, however, requested (after endless discussions and eventually a denial of approval) the impossible compliance with a formal pre-randomization informed consent. The ALBIOS trial has responded to a critical question, and generated a further and critically important hypothesis to be verified on the most severe patients, i.e. those with septic shock.3, 4 It is clear that only the coincidence and the articulation of a controlled care and a controlled experimentation can be the “ethical”, i.e. responsible and transparent, strategy to respect the patients’ needs.

Confronted with the permanent undefined position of regulatory authorities, it is up to those who care for incompetent patients in emergency conditions the duty to translate as many as possible situations of uncertain care into experimental research projects. Let us hope that also ECs recognize that the safeguard of the important patients’ rights is hierarchically more mandatory than the respect of formal administrative 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.


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ABSTRACT

BACKGROUND: Regional anesthesia (RA) is associated with many advantages, but side effects also occur. Several registries were developed to investigate such complications in many countries, which produced conflicting results. In consideration of the ongoing evolution and improvements in RA, and its widespread diffusion in Italy in the last decade (with increasing experience by anesthesiologists), a reappraisal of the incidence and the characteristics of major complications are useful to improve patient’s safety.

METHODS: A web-based prospective registry was developed in Italy with: 1) quarterly report of total anesthetic acts and RA procedures performed; and 2) voluntary registration of complications on dedicated forms. We evaluated incidence of complications, describing their characteristics and outcomes.

RESULTS: Participants (N=17 hospitals) registered 117,182 procedures, including 63,692 with RA (54.3%, both as primary anesthetic technique and for postoperative analgesia). A total of 34,147 neuraxial blocks (4954 epidurals/CSE, 29,193 subarachnoid blocks) and 29,545 peripheral (single shot and continuous) blocks were registered. Total incidence of complication was 4.6/10,000; incidence was 4.1/10,000 for central blocks and 5.1/10,000 for peripheral blocks, long-term neurologic deficit (at 6 months) was observed after an epidural abscess, while other complications did not lead to any long-term adverse outcomes. No hemorrhagic events or other infections have occurred. Incidence of major complications was 0.07/1000, while minor complications presented in 0.38/1000 cases.

CONCLUSIONS: We confirmed RA as generally safe, but monitoring and diagnosis, together with further research efforts, are needed to improve patients’ care and clarify potential risk factors.


Key words: Anesthesia, local - Complications - Neurologic manifestations - Epidemiology.
Regional anesthesia (RA) is considered safe and beneficial for the patients, but as in all interventional therapies, the possibility of side effects and complications still exists.1-11 A risk-benefit analysis should be carefully evaluated, with the emphasis being placed on complications both related to technique and drugs used during regional procedures;1, 12-17 furthermore, the incidence of side effects associated with RA in patients receiving new anti-thrombotic drugs is still unknown.18 Lack of data and of exhaustive guidelines hinder physicians to have clear protocols for their clinical practice, leading to potential personal/hospital-based approaches, resulting in increased patient risk.19

Even though knowledge about complications’ incidence is essential for the clinical decision-making and consent processes, there are few prospective trials that can support such discussions.20-24 As side effects related to RA are so rare, neither RCT nor meta-analysis offers a useful approach to investigate their real incidence. To overcome this problem, national registries in different countries have been developed to explore RA related complications in recent decades,20-34 focusing both on central and peripheral blocks. Unfortunately, the registries have delivered conflicting results20-36 and have so far provided poor evidence about risk factors for complications. The literature still underlines the importance of new surveys, including a description of each block’s technical features when side effects do occur, in order to better elucidate possible risk factors.37 Important clinical outcomes are often multifactorial by nature, which makes it difficult to distinguish surgical, anesthetic or patient etiology as the underlying reason. New knowledge is always needed to update ongoing changes in clinical practice.

In accordance with this data, we designed a prospective web-based multicenter population-based registry, involving teaching and non-teaching Italian hospitals, to detect RA side effects in different clinical settings and their outcome in a long term (six months) follow-up. For each complication we also registered data about the technique, equipment, medications, and patient.

**Materials and methods**

We performed a prospective observational study, designed according to STROBE guidelines.38 We received IRB approval in the sponsoring center (S. Matteo Hospital - Pavia, Italy) in 2009. The project was registered on Clinicaltrials.gov (registration number NCT02038491, Principal Investigator Massimo Allegri, MD). Advertising of the study was performed in all national anesthesia meetings from 2009 through 2012, as well at the ESRA Italian Chapter Annual Meeting. Any center willing to participate was provided with all the documents needed for local IRB approval, and a “local representative” was nominated to coordinate the project and to be responsible for data collection.

Centers that received IRB approval collected data from May 2009 to March 2013; both University and non-University Hospitals within national territory enrolled patients undergoing different types of procedures including adult major and minor surgery, pediatric surgery, obstetric anesthesia, and chronic pain management. Data were collected on a prospective fashion on a universal form used by all centers, which was sent every three months to the coordinating center. Non-anesthesiology physicians often perform regional anesthesia by themselves, and occasionally the published literature contains case reports of
various kinds of difficulties and complications. Therefore, this survey includes only local anesthetic blocks performed by anesthesiologists.

Each patient who eventually developed a potentially related complication (as defined below) after RA was recorded as a “case” for this study, which required additional data to be recorded on a separate form. Parents or guardians were asked for consent in case of underage or legally impaired patients. The report of a complication was voluntary; each representative, once aware of a complication in his/her institution, was in charge of reporting to the sponsoring center/data manager.

**Specific data — report for complications**

All investigators participating to the study were provided by a list of signs to be registered, trying to assure a uniform definition of “complication” between all institutions. Events registered as “complications” were:
- death;
- cardiac failure/arrest;
- respiratory failure/arrest;
- major cardiac arrhythmias;
- central nervous system complications (convulsions; coma);
- signs of Local Anesthetic Systemic Toxicity (LAST) - *i.e.* circumoral and/or tongue numbness, metallic taste, lightheadedness, dizziness, visual and auditory disturbances like difficult focusing and tinnitus, disorientation, drowsiness);
- PostOperative Neurologic Symptoms (PONS) - *i.e.* paresthesia after block placement, anesthesia, motor impairment;
- signs of infections;
- bleeding;
- Post Dural Puncture Headache (PDPH).

Data collected in “case” forms included: age, ASA physical status class, height and weight, and information on surgical technique (type of surgery, open/video-laparoscopic/robotic approach, scheduled/emergency surgery), and on thromboprophylaxis (drugs, timing of suspension before/after blockade).

Another section of the report form addressed the performed technique: equipment (needle: “pencil point” or other needles for spinal, soft-tip or sharp needles for PNBs, ultrasound vs nerve stimulation), drug doses (type and dosage of local anesthetics, as well as type and dosage of adjuvants), performers’ experience in RA and number of attempts to successfully place the block, presence/absence of tourniquet Finally, all applicable adverse effects (as defined above) were registered. Follow-up was planned at 3 and 6 months for patients with neurological complications, and electromyography and electroneurography were performed only on patients with persisting neurologic symptoms at 3 or 6 months.

**Statistical analysis**

Our primary endpoint was to assess cumulative incidence of adverse effects; incidence of such events was also calculated according to different types of blocks.

The study population was estimated based on previous studies of major complications after CNBs, which indicated an incidence of major adverse effects in 4.2 of every 100,000 patients. A sample size of 25,000 produced a two-sided 95% confidence interval with a width from $1 \times 10^{-6}$ to $2.2 \times 10^{-4}$.

**Quality assessment**

A common concern about all registries is that one cannot be totally certain that all data (especially complications) are accurately captured and recorded. We sought to improve adherence through ongoing data checks, frequent contacts with local representatives and updates on the status of the study during meetings.

Monthly data integrity checks were made (equivalence between total number of procedures and the sum of all NAB, PNB and CPNB), together with a check of complications’ reports (to ensure that no duplication of data, incomplete data, or any issue potentially accounting for a reduction in the validity of data occurred). Any issue was immediately addressed through contacts with local representatives, in order to ensure completeness and reliability of data.
Every time a complication report was sent, we asked for a double check by the local representative, to make sure that all data about the complications were recorded, to remember about follow-up (in patients with LAST or at risk for negative outcome), according to the study criteria. We also asked local representatives for a check on their institution’s activity, to ensure accuracy on the number of recorded procedures.

Results

General data

Seventeen teaching and non-teaching hospitals, located in Northern (12), Central (2) and Southern Italy (3) participated to the study. We received 88.2% of expected reports from participants, with 100% of them being returned fully completed.

We registered a total of 117,182 procedures; 63,692 regional anesthesia techniques (54.3%) were performed. A total of 34,147 CNBs were registered: 4,954 epidurals/CSEs blocks and 29,193 subarachnoid blocks; a total of 29,545 PNBs/CPNBs were collected: 10,080 US-guided, 18,506 ENS-guided and 959 landmark-based blocks. Indications included different types of surgery (visceral major surgery, minor surgery, orthopedics, pediatric surgery, obstetric anesthesia, chronic pain management).

We registered 8562 procedures on pediatric patients, with 3474 RA techniques (40.6%).

We collected 5 cases of major complications (death, hemodynamic/respiratory failures, hemorrhagic or infectious complications, permanent neurologic deficits), with an incidence of 0.07/1000. Minor complications (PDPH, LAST, transient neurologic symptoms, minor hemodynamic involvement) were registered in 24 cases (0.38/1000).

Epidural blocks/CSE

A total of 2 complications were registered, with a cumulative incidence of 0.4/1000; 100% of the forms were fully completed. One (0.2/1000) of these side effects, an epidural ab-

![Figure 1.—Magnetic resonance showing the epidural abscess reported in our survey. Spinal canal is markedly narrowed and spinal cord is compressed, resulting in neurologic symptoms. Multiple airfluid levels with cystic organization are evident inside the abscess. Vb: vertebral body; SpC: spinal canal; EA: epidural abscess.](image-url)
Among them, two patients (0.07/1000) presented major side effects: in one patient hemodynamic signs were associated with loss of consciousness (without any long-term damage once treated with fluids, oxygen and ephedrine), in one case a high thoracic (T3-T4 dermatomes) sensitive-motor block was registered, with respiratory failure, severe hypotension and bradycardia (Table I). Three cases of lower limb dysesthesia/paresthesia were registered (0.1/1000); none of them resulted in a permanent neurologic deficit at 6 months. Seven cases of PDPH (0.2/1000) were reported; one was in pediatric patient, but none of them resulted in chronic symptomatic dysfunctions worthy of treatment by neurosurgical approach or epidural blood patches.

**Spinal blocks**

A total of 15 complications related to peripheral nerve blocks (both single injection or continuous) were registered in 14 patients (one patient had multiple complications, Table

**Peripheral nerve blocks**

A total of 15 adverse events, related to peripheral nerve blocks (both single injection or continuous) were registered in 14 patients (one patient had multiple complications, Table

**Table I.**—Description of complications associated to subarachnoid blocks.

<table>
<thead>
<tr>
<th>#</th>
<th>Surgery</th>
<th>Type</th>
<th>Local anesthetic</th>
<th>%</th>
<th>Volume (mL)</th>
<th>Tourniquet</th>
<th>Experience of anesthesiologist</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Inguinal hernia repair</td>
<td>S</td>
<td>HB Bupi</td>
<td>0.5</td>
<td>2.5</td>
<td>N/A</td>
<td>-</td>
<td>PONS</td>
</tr>
<tr>
<td>#2</td>
<td>Femoral synthesis</td>
<td>S</td>
<td>HB Bupi</td>
<td>0.5</td>
<td>2</td>
<td>yes</td>
<td>10-30</td>
<td>PDPH</td>
</tr>
<tr>
<td>#3</td>
<td>Proctologic surgery</td>
<td>S</td>
<td>HB Bupi</td>
<td>0.5</td>
<td>2</td>
<td>N/A</td>
<td>&lt; 10</td>
<td>PDPH</td>
</tr>
<tr>
<td>#4</td>
<td>Proctologic surgery</td>
<td>S</td>
<td>HB Bupi</td>
<td>0.5</td>
<td>2.2</td>
<td>N/A</td>
<td>10-30</td>
<td>PDPH</td>
</tr>
<tr>
<td>#5</td>
<td>Cesarean Section</td>
<td>E</td>
<td>HB Bupi</td>
<td>0.5</td>
<td>2.3</td>
<td>N/A</td>
<td>10-30</td>
<td>PONS</td>
</tr>
<tr>
<td>#6</td>
<td>Proctologic surgery</td>
<td>S</td>
<td>HB Bupi</td>
<td>0.5</td>
<td>2.2</td>
<td>N/A</td>
<td>10-30</td>
<td>PDPH</td>
</tr>
<tr>
<td>#7</td>
<td>Proctologic surgery</td>
<td>S</td>
<td>HB Bupi</td>
<td>0.5</td>
<td>2.2</td>
<td>N/A</td>
<td>&lt;10</td>
<td>Severe hypotension/bradycardia-respiratory failure</td>
</tr>
<tr>
<td>#8</td>
<td>Ankle surgery</td>
<td>E</td>
<td>HB Bupi</td>
<td>0.5</td>
<td>1.1</td>
<td>Yes</td>
<td>10-30</td>
<td>PDPH</td>
</tr>
<tr>
<td>#9</td>
<td>Cesarean section</td>
<td>E</td>
<td>HB Bupi</td>
<td>0.5</td>
<td>2</td>
<td>N/A</td>
<td>10-30</td>
<td>PONS</td>
</tr>
<tr>
<td>#10</td>
<td>Inguinal hernia repair</td>
<td>S</td>
<td>HB Bupi</td>
<td>0.5</td>
<td>2.2</td>
<td>N/A</td>
<td>&lt; 10</td>
<td>PDPH</td>
</tr>
<tr>
<td>#11</td>
<td>Proctologic surgery</td>
<td>S</td>
<td>HB Bupi</td>
<td>0.5</td>
<td>2.2</td>
<td>N/A</td>
<td>&lt;10</td>
<td>PDPH</td>
</tr>
<tr>
<td>#12</td>
<td>Open Prostatic adenoma</td>
<td>S</td>
<td>HB Bupi</td>
<td>0.5</td>
<td>2.2</td>
<td>N/A</td>
<td>&lt;10</td>
<td>Arrhythmia-loss of consciousness</td>
</tr>
</tbody>
</table>

*S: scheduled; E: emergency; HB Bupi: hyperbaric bupivacaine.
RICALOR: AN INCIDENCE ANALYSIS FROM A PROSPECTIVE CLINICAL SURVEY

Table II.—Description of complications associated to PNB/CPNB.

<table>
<thead>
<tr>
<th>Block</th>
<th>Local anesthetic</th>
<th>%</th>
<th>Volume (mL)</th>
<th>Guidance</th>
<th>Tourniquet (yes/no)</th>
<th>Experience of anesthesiologist (years)</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1 Axillary</td>
<td>Mepivacaine</td>
<td>1</td>
<td>30</td>
<td>US</td>
<td>Yes</td>
<td>10-30</td>
<td>LAST (seizures, arrhythmia)</td>
</tr>
<tr>
<td>#2 Axillary</td>
<td>Mepivacaine</td>
<td>2</td>
<td>20</td>
<td>US</td>
<td>-</td>
<td>10-30</td>
<td>LAST (seizures, arrhythmia)</td>
</tr>
<tr>
<td>#3 Axillary</td>
<td>Mepivacaine</td>
<td>2</td>
<td>20</td>
<td>US</td>
<td>Yes</td>
<td>&lt;10</td>
<td>LAST (arrhythmia, respiratory failure)</td>
</tr>
<tr>
<td>#4 Interscalene</td>
<td>Bupivacaine</td>
<td>0.75</td>
<td>75</td>
<td>ENS</td>
<td>No</td>
<td>&gt;30</td>
<td>Phrenic nerve palsy (respiratory failure)</td>
</tr>
<tr>
<td>#5 Axillary</td>
<td>Mepivacaine +</td>
<td>-</td>
<td>10</td>
<td>ENS</td>
<td>No</td>
<td>&gt;30</td>
<td>LAST (minor symptoms)</td>
</tr>
<tr>
<td>#6 Interscalene</td>
<td>Ropivacaine</td>
<td>0.75</td>
<td>25</td>
<td>ENS</td>
<td>No</td>
<td>10-30</td>
<td>LAST (arrhythmia, respiratory failure)</td>
</tr>
<tr>
<td>#7 Femoral</td>
<td>Ropivacaine</td>
<td>0.75</td>
<td>20</td>
<td>ENS</td>
<td>Yes</td>
<td>&gt;30</td>
<td>PONS</td>
</tr>
<tr>
<td>#8 Axillary</td>
<td>Levobupivacaine</td>
<td>0.5</td>
<td>25</td>
<td>ENS</td>
<td>Yes</td>
<td>&gt;30</td>
<td>PONS + LAST (minor symptoms)</td>
</tr>
<tr>
<td>#9 Sciatic</td>
<td>Ropivacaine +</td>
<td>0.5</td>
<td>25</td>
<td>ENS</td>
<td>Yes</td>
<td>&gt;30</td>
<td>PONS</td>
</tr>
<tr>
<td>#10 Femoral + sciatic</td>
<td>Mepivacaine</td>
<td>2</td>
<td>-</td>
<td>ENS</td>
<td>Yes</td>
<td>&lt;10</td>
<td>LAST (minor symptoms)</td>
</tr>
<tr>
<td>#11 Interscalene</td>
<td>Ropivacaine</td>
<td>0.75</td>
<td>-</td>
<td>ENS</td>
<td>No</td>
<td>&lt;10</td>
<td>LAST (seizures)</td>
</tr>
<tr>
<td>#12 Lumbar plexus</td>
<td>Ropivacaine</td>
<td>1</td>
<td>20</td>
<td>ENS</td>
<td>No</td>
<td>&lt;10</td>
<td>LAST (third grade AV block)</td>
</tr>
<tr>
<td>#13 Lumbar plexus</td>
<td>Ropivacaine</td>
<td>1</td>
<td>20</td>
<td>US</td>
<td>No</td>
<td>10-30</td>
<td>Epidural spread - Respiratory failure</td>
</tr>
<tr>
<td>#14 Axillary</td>
<td>Ropivacaine</td>
<td>0.75</td>
<td>30</td>
<td>US</td>
<td>No</td>
<td>&lt;10</td>
<td>LAST (seizures)</td>
</tr>
</tbody>
</table>

II), with a cumulative incidence of 0.5/1000. 100% of the reports were fully completed.

Among the 10 registered cases of LAST (0.3/1000), three presented minor symptoms (metallic taste, tingling and mouth numbness), while seven patients presented major signs of cardiovascular and neurologic toxicity (Table II).

Among the major symptoms, 4 seizures occurred, and 2 patients presented severe bradycardia and cyanosis followed by respiratory arrest and loss of consciousness. The last case was an isolated arrhythmia (AV block) without any other symptoms; the patient had already been examined by a cardiologist in the preoperative setting, establishing that no pacemaker stimulation was required during surgery. After surgery, the patient was admitted to the ICU and treated with external pace-making and close monitoring, without any further consequence. None of these 7 patients presented any residual deficit at 6 months.

Two cases of major hemodynamic and respiratory events were observed (0.07/1000): in one case epidural/spinal block spread occurred, leading to neurologic symptoms and loss of consciousness, bradycardia and respiratory failure. The patient was intubated and then monitored in the post anesthesia care unit until discharge to surgical ward, with no other symptoms or long-term deficits. In one patient a combined involvement of the recurrent laryngeal nerve, phrenic nerve and sympathetic cervical chain with Claude-Bernard-Horner Syndrome was registered during an interscalene brachial plexus block, leading to respiratory failure and need for general anesthesia, but no long-term damage was observed.

Three cases were registered as PONS or prolonged sensory-motor block (0.1/1000): in one case a quadriiceps muscle motor dysfunction was observed after a femoral nerve block for anterior cruciate ligament repair, persisting for 20 days with a further complete resolution; in another patient a sensory dysfunction was observed after an upper limb block for hand surgery, without motor involvement. Finally, one patient presented with a prolonged duration of sensory-motor block (sciatic nerve block - 26 hours) after a combined femoral and sciatic nerve block for total knee replacement, and all symptoms had complete resolution, without any identifiable deficit at 6 months. Unfortu-
nately, basing on our data, we cannot rule out whether these cases were related to RA (intraneural or intrafascicular injection, nerve injury) or not (surgical tourniquet, patient positioning).

Discussion

Through this prospective study involving 17 different Italian hospitals, we recorded a total of 63,692 RA procedures (54.3% of the total surgical procedures performed) in different clinical settings. The incidence of adverse effects after RA technique was 4.6/10,000 patients, supporting the perception of global safety with regional anesthesia.20-40

The incidence of severe complications in epidural blocks matched what was previously found in other studies.20, 25, 30-33 No epidural hematomas were recorded: a previous survey 25 reported a higher incidence, but was retrospective, and covered a 10 year period which saw a substantial increase in epidural procedures along with simultaneous improvement in guidelines accuracy (about the management of thrombo-profilaxis, aseptic technique, pre-existing neurologic deficits). The majority of spinal hematomas were registered in the earlier years and steadily decreased with time, suggesting that an evolution in technique and awareness of risk factors was instrumental in minimizing this complication. The negative long-term outcome after the one case of epidural abscess reminds practitioners that strict vigilance on asepsis 41 is imperative, and that observation should be maintained even after removal of catheters. We cannot provide an explanation for the lower incidence of severe events during subarachnoid anesthesia, as compared to previous studies.20-26 but a decade has passed since the publication of the paper by Auroy et al.,20 and we could argue that improved awareness, as well as better protocols for proper management, may have contributed to this improvement.

The cumulative incidence of complications during PNB and CPNB is similar to what has been reported in previous literature.20, 21 Considering infections, previous paper 21 reported catheter contamination rates of 29%, with 3% of patients demonstrating clinical signs of infection. We did not perform microbiological surveillance, but no patients presented signs of infection in our study. We therefore confirm that PNBs’ associated symptomatic infections are uncommon, but strict attention towards asepsis can potentially further reduce or erase the risk.

PONSs’ incidence in our study has been the lowest reported to date;20, 23, 24 although the incidence of permanent injury is very rare, other researchers 36 have noted that mild transient neurological deficits can be quite high (almost 3%). This evidence argues for methodological discrepancies as a causal factor for the high PONSs’ incidence variability that has been reported in the literature. In a large meta-analysis, the incidence of 3%, was mainly based on studies conducted in the last years of the nineties (1997-1999): new equipment (soft tip needles, nerve stimulation, ultrasound) have developed, and together with increased experience these may account for a reduction in nerve injury. Further, in those studies PONS definition included also cauda equine syndrome, which is now to be considered as anecdotal (and thus reducing the incidence of neurologic deficits). Otherwise, our incidence is the lowest even considering more recent works.23 Theoretically, some cases of PONS may not be identified (once patients are discharged and lost to follow-up). The current policy in Italy is still to keep the patient in the hospital until the block wares off, and none of the institutions involved in the study do discharge patients at home with indwelling catheters. Thus, in the case of our study, the risk of under-reporting of in-hospital PONS should be considered as negligible. Otherwise, we underline that we registered those cases of PONS which were already evident during hospital stay, and we did not pursue any systematic post-discharge follow-up (like in the study by Barrington et al.) 23 to identify those patients who develop symptoms of PONS once at home. Future studies should address this issue during study design, since it may justify a lower reported rate of PONS.

As other investigators have suggested,22 we deliberately did not attempt to distinguish between a primary surgical-, positional-, or nerve block - related etiology because it is often im-
possible to determine or to rule out multiple causes. We wanted to provide a conservative estimate for associated risks of RA in the context of surgery, which we consider, beyond the medico-legal implications, more useful in a patient’s outcome perspective.

Additionally, the incidence of LAST is the lowest reported to date,20-23, 29, 35, 36 We decided to consider also minor symptoms, which could be associated with lower amounts of absorbed LA. Small amounts can be harmful in patients with preexisting cardiac conduction defects,43 and from a clinical, decision-making perspective, we pursued an inclusive approach taking into account the global incidence of LAST.

Respiratory failure was infrequent in our study (0.005/1000), and was associated with specific higher risk procedures such as subarachnoid block, lumbar plexus block and interscalene block. As previously reported,20 these results warn physicians to manage LPB with the same attention of a neuraxial block5 to always take into account the dangers of performing proximal brachial plexus blocks in patients with pre-existing respiratory comorbidities, because of high reported incidence phrenic nerve involvement (PNP).44, 45 Despite this, the clinical impact of PNP can widely vary, and as we documented in this study, life-threatening events should be probably supposed to occur less frequently than expected.

Cumulative incidence of complications following the use of US is not different comparing to ENS guidance (Table III); four cases of LAST occurred despite ultrasound use (as previously reported in other papers)47, 48 and, incidentally, all cases of PONS occurred after ENS-guided procedures (without any statistically significant correlation) and, interestingly, no nerve injury was observed with US. Despite the potential for improved safety using US guidance,49 evidence about reduced incidence of unintentional intravascular needle placement and neural damage is not yet available,43 as the effectiveness of US guidance in improving block safety is inherently limited by its own dependence on operator skill. Finally, data on sedation and LAST are not significant because of the small number of cases, but future surveys on the role of benzodiazepine dosages in masking initial symptoms of LAST could be interesting.

The prospective nature of our survey implies that we have a precise assessment of the total number of performed RA techniques (not based on calculations or approximations). All complications were immediately registered and a follow-up was pursued. Noteworthy, the complications were reported voluntarily; thus, the reported incidence may not reflect the actual incidence of complications, and the risk of underreporting of complications is still present: despite this, we believe that the present design promoted good quality reporting; participants often expressed spontaneous interest in improving the quality of data reg-

Table III.—List of events considered as “complications” and incidence according to the type of block. Data are expressed as number and incidence of events every 1000 procedures, with their 95% confidence interval (in square brackets).

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Epidural/CSE (N=4,954)</th>
<th>Spinal (N=29,193)</th>
<th>PNB/cPNB (N=29,545)</th>
<th>ENS-guided (N=18,506)</th>
<th>US-guided (N=10,080)</th>
<th>Blind (N=9,959)</th>
<th>Total (N=63,692)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death n/(‰)</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Major hemodynamic/respiratory</strong></td>
<td>0 (0)</td>
<td>2 (0.07)</td>
<td>2 (0.07)</td>
<td>1 (0.05)</td>
<td>1 (0.1)</td>
<td>0 (0)</td>
<td>4 (0.06)</td>
</tr>
<tr>
<td>side effects* n/(‰)</td>
<td>[0.02-0.26]</td>
<td>[0.02-0.26]</td>
<td>[0.01-0.36]</td>
<td>[0.02-0.64]</td>
<td>[0.02-0.16]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hemorragic complications n/(‰)</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Infectious complications n/(‰)</strong></td>
<td>1 (0.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.02)</td>
</tr>
<tr>
<td><strong>LAST n/(‰)</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>10 (0.34)</td>
<td>6 (0.32)</td>
<td>4 (0.4)</td>
<td>0 (0)</td>
<td>10 (0.16)</td>
</tr>
<tr>
<td><strong>PONS/sensory-motor alterations n/(‰)</strong></td>
<td>0 (0)</td>
<td>3 (0.1)</td>
<td>8 (0.3)</td>
<td>3 (0.16)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6 (0.09)</td>
</tr>
<tr>
<td><strong>PDPH n/(‰)</strong></td>
<td>1 (0.2)</td>
<td>7 (0.24)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>8 (0.13)</td>
<td></td>
</tr>
<tr>
<td><strong>Total n/(‰)</strong></td>
<td>2 (0.40)</td>
<td>12 (0.41)</td>
<td>15 (0.51)</td>
<td>10 (0.54)</td>
<td>5 (0.49)</td>
<td>0 (0)</td>
<td>29 (0.46)</td>
</tr>
</tbody>
</table>
istration (frequent contacts were made asking questions or requesting missing registration forms), and data about total RA procedures is similar to what has been previously reported in retrospective surveys by the same group of investigators. Additionally, a selection bias may be present: centers more inclined to practice RA could be preferentially interested in participating in this type of registry, and have greater operator skills and experience. However, we observed that centers performing more RA procedures have a higher incidence of complications, suggesting that the greater level of experience does not account for a reduction in complications and possibly could be ruled out as a confounder; otherwise, the higher rate of complications in centers that performed more RA may also be due to better patient evaluation for potential complications and patient follow-up.

Finally, a detail is to be considered when rating the risk associated with different approaches to the same plexus. The higher rate of complications associated with interscalene and axillary brachial plexus block is also dependent on whether or not the other techniques were used in the same rate (or underused). Unfortunately, we did not differentiate between approaches to each plexus, but we guess that their increased risk is also related to the overuse of these two approaches in the clinical practice in our country.

Conclusions

We present data from a large prospective clinical registry with immediate registration of RA-associated complications. The major contributions are, however, the report of the absence of hemorrhagic complications both in central and peripheral blocks (despite the increased use of anti-thrombotic agents and the introduction of new anticoagulants drugs during last years), the lack of infections during peripheral techniques, and the absence of persistent dysfunctions following peripheral nerve blocks. No cases of cauda equina syndrome, transient neurologic symptoms, or cardiac arrest (despite severe hemodynamic compromise in some patients) were reported. Although the risk of underreporting is always present, we believe that the practice of regional anesthesia has undergone significant improvement in terms of safety and operator’s awareness of complications in these 20 years. Unfortunately, catastrophic complications are still reported, but long-term patient injuries may be declining in prevalence. Future, regular surveys will be useful to keep pace with the ongoing significant changes occurring in current clinical practice.

Key messages

— The use of regional anesthesia resulted in a low incidence of major complications, despite such complications can easily lead to persistent disability when not properly diagnosed (and treated).

— Monitoring is mandatory for patient’s safety; anesthesiologists, as well as all the personnel involved in patients’ care (nurses, surgeons) should always investigate early signs of complications to promptly adopt effective interventions, without any delay. Long-term follow up (even after patient’s education to report negative signs) is worth, since complications can be delayed after hospital discharge.

— Pace should be kept with new anti-thrombotic drugs; no hemorrhagic complications were observed in our survey, but new specific guidelines for drug timing according to regional anesthesia are needed to maintain high standard of safety.

— More studies are needed to define the role of ultrasound in avoiding LAST and PONS. Despite the low incidence of LAST, such event is still possible despite US-guidance, and need to be promptly recognized and treated to avoid negative outcomes. Since ruling out the cause for PONS is not always easy, anesthesiologist should put in place all strategies to avoid intra-fascicular injection or nerve damage: despite not significant, a slight favorable effect of US-guidance emerged in our survey.
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Postural effects on pulmonary gas exchange abnormalities in severe obesity before and after bariatric surgery

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ABSTRACT

BACKGROUND: We hypothesized that in morbid obesity, pulmonary gas exchange abnormalities will worsen when supine and that bariatric surgery (BS) will mitigate this effect.

METHODS: Gas exchange was investigated in 19 morbidly obese and 8 non-obese, age-matched control females, spontaneously breathing ambient air, both upright and supine, before and one year after BS.

RESULTS: In control non-obese individuals, no postural changes in arterial blood gases (ABGs) were observed. While obese subjects had more altered PaO2, SaO2, and AaPO2 values than controls (P<0.05 each) when upright, the values unexpectedly remained unchanged when supine. This was also the case in the subset of 6 normoxemic obese but the remaining 13 hypoxemic individuals actually improved ABGs when supine: PaO2 (by +2.7±1.3 mmHg, P=0.06), SaO2 (by +1.5±0.6%), pH (by +0.01±0.01) and AaPO2 (by -3.4±1.4 mmHg); and cardiac output increased (by +0.4±0.2 L·min⁻¹) (P<0.05 each). After BS, PaO2 (from 75.5±2.4 to 89.4±2.4 mmHg), AaPO2 (from 27.0±2.0 to 15.4±2.1 mmHg) (P<0.05 each), and pulmonary gas exchange were improved compared to before BS when upright, but ABGs worsened when supine (PaO2, by -4.6±1.7 mmHg; AaPO2, by +4.2±1.6 mmHg) (P<0.05 each).

CONCLUSIONS: Before BS, ABGs are not altered in normoxemic obese subjects moving from upright to supine, even improving in those with hypoxemia when supine. After successful BS, pulmonary gas exchange improved when upright in all subjects but ABGs deteriorated when supine. However, the important clinical observation is the lack of gas exchange deterioration when supine, which may have implications for critical care and anesthesia settings.

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Key words: Gases, blood - Obesity - Pulmonary gas exchange - Bariatric surgery.

Current clinical guidelines recommend that critically ill obese patients remain upright during perioperative and intensive care conditions to avoid and/or minimize supine-induced gas exchange worsening due to excessive intra-abdominal pressure on dependent lung regions. 1, 2 We have recently shown that prior to bariatric surgery (BS), compared to healthy
subjects, morbidly obese individuals increased intrapulmonary shunt and ventilation-perfusion (\(V_{A}/Q\)) imbalance inducing low arterial PO\(_2\) (PaO\(_2\)) and increased alveolar-arterial PO\(_2\) difference (AaPO\(_2\)) when upright, whereas after BS overall gas exchange disturbances were substantially improved in relation to their own pre-operative data. Here, we hypothesized that prior to BS recumbency would aggravate these pulmonary gas exchange abnormalities due to increased intrapulmonary shunt and further ventilation-perfusion (\(V_{A}/Q\)) imbalance other factors being equal and that BS would improve them.

We tested this hypothesis in the same non-obese and obese individuals reported previously, but separately, given the complexity of the study design. This prompted us to focus exclusively on the postural effects of pulmonary gas exchange before and after BS.

**Materials and methods**

**Study population, study design and ethics**

The principal characteristics and inclusion criteria of 8 control and 19 obese participants, all females, without major multi-morbidities, such as severe-to-moderate sleep apnea syndrome, have been previously reported elsewhere. Control subjects were normal weight, age-matched females who required thoracic computerized tomography (CT) scans for screening and follow-up of in situ cutaneous melanoma; otherwise, these subjects were completely healthy. We herein report the effects of posture on gas exchange. All measurements in both control and obese subjects were always performed when upright with the legs down and when supine using a TotalCare® bed (Hillrom, Pluvigner, France) for 30 min each, in random order. All subjects refrained from any medication during the prior 24 h, before and after BS (median, 51 weeks). All participants signed informed consent. The study was approved by the Ethics Committee of the Hospital Clinic (Protocol 2008/4015).

**Measurements**

**Physiologic blood gases**

Arterial and mixed venous blood samples gases were analyzed for pH, PO\(_2\) and PCO\(_2\) (CIBA Corning 800. Medfield, MA, USA), and the alveolar-arterial PO\(_2\) gradient (AaPO\(_2\)) was calculated using the measured exchange respiratory ratio as reported previously. Oxygen uptake (\(VO_2\)) was calculated using standard formulae.

**Ventilatory and hemodynamic measurements**

Minute ventilation was measured using a Wright spirometer (Respirometer MK8, BOC-Healthcare. Essex, UK). The electrocardiogram, heart rate, mean arterial pressures and oxygen saturation through a pulseoximeter were continuously monitored (HP M 1001A-1006A &B, 1012A, 1020A, 1046A, 1166A; Hewlett-Packard, Waltham, MA, USA) to ensure safety conditions. An 18-gauge plastic cannula was inserted into the radial artery for monitoring systemic arterial pressure and for arterial blood gas sampling. In obese subjects with PaO\(_2\)<80 mmHg (range, 55-79 mmHg; n, 13), a 7-French triple-lumen thermodilution balloon-tipped pulmonary artery catheter (Edwards; Baxter Healthcare Corporation, Irvine, CA, USA) was inserted under echography guidance to exclude the presence of pulmonary arterial hypertension. Pulmonary artery, capillary wedge and right atrial pressures were monitored and pulmonary (PVr) and systemic vascular resistances (SVr) were calculated using standard formulae. Accordingly, in hypoxemic obese individuals, \(V_{A}/Q\) distributions were calculated using arterial, mixed venous and mixed expired inert gases concentrations and cardiac output (\(Q_T\)) was determined by thermodilution. In obese individuals without arterial hypoxemia (PaO\(_2\)≥80 mmHg; range, 82-97 mmHg; n, 6), \(V_{A}/Q\) distributions were estimated without mixed venous sampling and cardiac output was measured by bioimpedance (PhysioFlow®, Manatec Biomed-
cal. Paris, France). Paired inert gas studies were completed in all obese participants.

\( \dot{V}_A/\dot{Q} \) RATIO DISTRIBUTIONS

Measurements of \( \dot{V}_A/\dot{Q} \) distributions were estimated by the multiple inert gas elimination technique (MIGET) in the customary manner. Arterial and mixed venous blood samples and mixed expired inert gases were collected through a metallic heated box by duplicate. The dispersion of pulmonary distribution blood flow and that of alveolar ventilation distribution on a logarithmic scale (Log SDQ and Log SDV; upper normal limits, 0.60 and 0.65, respectively) were calculated. Shunt and dead space were defined, respectively, as the fraction of blood flow perfusing units with \( \dot{V}_A/\dot{Q} \) ratios <0.005 and the fraction of alveolar ventilation distribution with \( \dot{V}_A/\dot{Q} \) ratios >100. All measurements were determined under steady-state conditions, defined by stability (±5%) of both ventilatory and hemodynamic variables, and by the close agreement (±5%) between duplicate measurements of mixed expired and arterial oxygen and carbon dioxide.

Statistical analysis

Results are presented as mean±SEM. We used the unpaired Student t-test to compare control and obese subjects before BS. A generalized linear mixed model was applied to all obese participants such that all their data were analyzed considering three interventions (BS, inspired oxygen fraction, and posture). In this model each individual was considered as a random factor to assess the effects induced by each intervention and their potential interactions. Given the presence of significant consistent interactions among them, we then focus the analysis on the postural effects while breathing ambient air, before and after BS, using paired Student t-test. Corrections were made for multiple comparisons of interventions in obese individuals. A P<0.05 value was considered significant at all instances.

We enrolled 19 morbidly obese women (age, 51±[SE]2 years; Body Mass Index [BMI], 45±1 kg/m²), all but one never-smokers and 8 non-obese (BMI, 25±2 kg/m²), sex- and age-matched (50±3 years) never-smokers.

Findings before BS

Arterial blood gases (ABGs), pH, oxygen saturation (SaO₂), inert gases and hemodynamic values in the upright and supine postures are set out in Tables I, II, respectively. Note that clinical and lung function tests, including ABGs, pulmonary and systemic hemodynamics and inert gas exchange measurements for all obese individuals when upright have been previously reported but herein reproduced for convenience in both tables for comparison with those measured when supine. ABGs in non-obese participants were within normal limits (Pao₂, 86.5±1.4 mmHg; Paco₂, 37.1±1.2 mmHg; AaPO₂, 18.4±1.4 mmHg; pH, 7.42±0.01; SaO₂, 99±1%) when upright with- out significant changes (PaO₂, -0.2±2.7 mmHg; Paco₂, +1.4±0.8 mmHg; AaPO₂, -1.0±2.6 mmHg; pH, +0.01±0.01; SaO₂, +0.5±0.5%) when supine. Similarly, in all obese individuals considered together, Pao₂ (+0.6±1.6 mmHg), AaPO₂ (-1.1±1.6 mmHg) and SaO₂ (+0.6±0.5%) did not deteriorate when supine. Except for PCWP and SVR, systemic and pulmonary hemodynamic values and \( \dot{V}_A/\dot{Q} \) descriptors were not different from upright to supine (table II). However, there were different postural ABGs effects in obese participants according to the presence or absence of arterial hypoxemia at enrollment (Figure 1). While no postural changes were observed in the 6 normoxemic obese subjects, the 13 hypoxemic individuals (Table I, Figures 1, 2) improved ABGs from seated to supine. Arterial pH (by +0.01±0.01), and SaO₂ (by +1.5±0.6%) increased and AaPO₂ decreased (by -3.4±1.4 mmHg) (P<0.05 each) when supine, without significant changes in PaO₂ (by +2.7±1.3 mmHg; P=0.06) and PaCO₂. Except for a small increase in Q̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̈
### Table I. — Gas exchange findings at upright and supine in obese individuals before and after bariatric surgery.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before surgery</th>
<th>After surgery</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upright</td>
<td>Supine</td>
<td></td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>75.5±2.4 †</td>
<td>76.1±2.6</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>39.0±1.0</td>
<td>39.7±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>AaPO₂, mmHg</td>
<td>27.0±2.0 †</td>
<td>25.9±2.0</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>7.41±0.01</td>
<td>7.41±0.01</td>
<td>NS</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>96±1 †</td>
<td>96±1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>All obese individuals (N.=19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Upright</td>
<td>Supine</td>
<td>P†</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>84.4±2.4 †</td>
<td>84.8±3.1</td>
<td>0.02</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>39.8±1.2</td>
<td>39.7±1.3</td>
<td>NS</td>
</tr>
<tr>
<td>AaPO₂, mmHg</td>
<td>15.4±2.1 †</td>
<td>19.6±2.1</td>
<td>0.02</td>
</tr>
<tr>
<td>pH</td>
<td>7.41±0.01</td>
<td>7.42±0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>99±1 †</td>
<td>99±1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Normoxic obese individuals (N.=6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Upright</td>
<td>Supine</td>
<td>P‡</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>88.4±2.7 †</td>
<td>84.3±5.7</td>
<td>NS</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>35.8±1.7</td>
<td>35.9±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>AaPO₂, mmHg</td>
<td>17.9±2.2 †</td>
<td>22.1±4.3</td>
<td>NS</td>
</tr>
<tr>
<td>pH</td>
<td>7.45±0.01</td>
<td>7.43±0.01</td>
<td>NS</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>99±1</td>
<td>98±1</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Hypoxic obese individuals (N.=13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Upright</td>
<td>Supine</td>
<td>P†</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>69.5±1.9 †</td>
<td>72.3±2.3</td>
<td>0.06</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>40.5±1.1</td>
<td>41.5±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>AaPO₂, mmHg</td>
<td>31.2±1.9 †</td>
<td>27.8±2.0</td>
<td>0.03</td>
</tr>
<tr>
<td>pH</td>
<td>7.39±0.01</td>
<td>7.42±0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>94±1 †</td>
<td>96±1</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM. AaPo₂: alveolar to arterial Po₂ difference; † denotes P-values for comparisons between upright and supine before surgery; ‡ denotes P<0.05 for comparisons at upright between pre- and postoperative conditions; † denotes P-values for comparisons between upright and supine after surgery.

### Table II. — Pulmonary gas exchange, ventilatory, hemodynamic and metabolic findings at upright and supine in all obese (N.=19) individuals before and after bariatric surgery.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before surgery</th>
<th>After surgery</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Upright</td>
<td>Supine</td>
<td></td>
</tr>
<tr>
<td>PVo₂, mmHg</td>
<td>38±1</td>
<td>39±1</td>
<td>NS</td>
</tr>
<tr>
<td>Shunt, %Qr</td>
<td>4.3±1.1 †</td>
<td>3.8±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Log SDQ</td>
<td>0.83±0.06</td>
<td>0.82±0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Log SDV</td>
<td>0.69±0.04 †</td>
<td>0.73±0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Dead space, %V̄a</td>
<td>23.8±3.5</td>
<td>24.1±2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Qr, L·min⁻¹</td>
<td>6.7±0.6 †</td>
<td>6.5±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Q̇v, L·min⁻¹·m²</td>
<td>6.6±0.3 †</td>
<td>6.9±0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Ci, L·min⁻¹·m²</td>
<td>2.6±0.1 †</td>
<td>2.7±0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Psa, mmHg</td>
<td>100±2 †</td>
<td>98±3</td>
<td>NS</td>
</tr>
<tr>
<td>PAP, mmHg</td>
<td>19±1 †</td>
<td>22±2</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP, mmHg</td>
<td>8±1 †</td>
<td>11±1</td>
<td>0.04</td>
</tr>
<tr>
<td>SVR, dyn·cm⁻⁵</td>
<td>1197±78</td>
<td>1079±71</td>
<td>0.01</td>
</tr>
<tr>
<td>PVR, dyn·cm⁻⁵</td>
<td>132±16 †</td>
<td>122±14</td>
<td>NS</td>
</tr>
<tr>
<td>VO₂, mL·min⁻¹</td>
<td>251±14 †</td>
<td>254±17</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM; PVo₂: mixed venous Po₂; Shunt: unventilated units (V̄a/Qr) ratios >0.05, expressed as % of Qr; Log SDQ: dispersion of blood flow distribution and Log SDV, dispersion of ventilation distribution (both dimensionless); Dead space: alveolar units with V̄a/Qr >100, expressed as % of alveolar volume (V̄a); V̄e: minute ventilation; Q̇r: cardiac output; CI: Cardiac Index; Psa: mean systemic arterial pressure; PAP: main pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; SVR: systemic vascular resistance; PVR: pulmonary vascular resistance; VO₂: oxygen consumption; * denotes P values for comparisons between upright and supine before surgery; † denotes P<0.05 for comparisons at upright between pre- and postoperative conditions; ‡ denotes P-values for comparisons between upright and supine after surgery.
increased PaO₂ and decreased AaPO₂ (P<0.05 each) post-BS in the upright posture\(^3\) (Table I, Figure 1). Likewise, all abnormal V\(_A/Q\) descriptors but the alveolar ventilation dispersion (Log SDV) improved and all hemodynamic outcomes (systemic arterial pressure, Q\(_T\), PAP, PCWP, and PVR) and VO\(_2\) decreased (P<0.05 each) after BS as previously reported (Table II).\(^3\) However, ABGs worsened in the supine position: PaO₂ decreased (by -4.6±1.7 mmHg), and AaPO₂ (by 4.2±1.6 mmHg) and pH (by +0.01±0.01) increased (P<0.05 each) without changes in PaCO₂ and SaO₂. While no postural effects were observed in normoxemic obese subjects, hypoxemic obese individuals decreased PaO₂ (by -5.3±1.7 mmHg; P=0.01) and increased pH (by +0.02±0.01; P=0.01) when supine without changes in AaPO₂ (by 4.2±2.1 mmHg; P=0.07), PaCO₂ and SaO₂. Moreover, except for a decrease in Log SDV (improvement), intrinsically related to increases in both PAP and PCWP (by +4±1 mmHg each) (P<0.05 each), no other changes in V\(_A/Q\) descriptors (Figure 2) and systemic and pulmonary hemodynamics were observed.

Discussion

This study shows that, in a selected population of morbidly obese female candidates for BS without major multi-morbidities, pulmonary gas exchange abnormalities including ABGs remain essentially unchanged when moved from upright to supine postures as was also observed in control subjects. Unexpectedly, hypoxemic obese individuals actually improved arterial oxygenation in the supine position. After BS, all obese participants considered together considerably improved pulmonary gas exchange when upright (compared to pre-BS), but then ABGs deteriorated alone when supine. All pre- and post-operative ABG findings were small and associated with few hemodynamic and V\(_A/Q\) changes.

Previous studies

Our findings in normoxemic obese individuals are at variance with those shown by Fare-
participants would worsen in parallel to the expected deterioration of shunt and pulmonary vascular disturbances from upright to supine postures before BS, pulmonary gas exchange abnormalities in our obese subset considered as a single group remained unchanged as well as in obese subjects with normal PaO₂ from upright to supine. By contrast, in hypoxemic obese individuals, arterial oxygenation improved when supine so that it worsened when upright, a phenomenon characteristically seen, although of slightly more magnitude, in patients with hepatopulmonary syndrome (HPS). Nevertheless, the underlying mechanisms differ. In HPS, upright-induced arterial deoxygenation or orthodeoxia is caused by further VA/Q imbalance without changes in non-pulmonary (i.e., minute ventilation,
cardiac output and/or oxygen uptake) determinants of gas exchange, likely produced by an abnormal pulmonary vasculature with more heterogeneous gravitational blood flow redistribution to dependent lung areas. By contrast, in hypoxic morbidly obese subjects, orthodeoxia is induced by decreased cardiac output without ensuing gravitational negative changes in shunt and $V_{A}/Q$ mismatching, likely aggravated by the coexistence of a pulmonary vasculature absent of hypoxic pulmonary vasoconstriction. Should increased cardiac output in the hypoxic morbidly obese when supine be accompanied by higher increases in intrapulmonary shunt, it is most likely that the net effect would have offset the observed improvement in arterial oxygenation.

Alternatively, the absence of ABG changes in all obese subjects when supine can be related to the combination of small postural-induced lung volume changes along with the absence of noticeable $Q_t$ effects. In a recent study in morbidly obese individuals, lung volumes were more restricted than in healthy individuals along with important reductions in expiratory reserve volume and in end-tidal $Q_t$ effects. In a recent study in morbidly obese subjects, total lung capacity (TLC) and its subdivisions, it was shown that despite the increased extra-pulmonary mass load in obese subjects, further falls in TLC and FRC were negligible when supine. Likely, this was not the case in the subset of hypoxic obese subjects in whom the increase in $Q_t$ played a positive influential effect on $P_{aO_2}$ through mixed venous $PO_2$. It remains unknown though what can be the duration of this supine-induced $P_{aO_2}$ improvement in the clinical setting of the real-world of morbidly obese individuals. It may be plausible that after a few hours at supine, the increase in $Q_t$ is limited so that the presence of upright-induced arterial deoxygenation is not patent any more.
clinical relevance. However, the finding that a short period of time (up to 30 min) when supine does not induce arterial deoxygenation prior to surgery can be of interest to anesthesiologists for their daily clinical practice. Obese individuals are usually placed on supine to induce anesthesia, intubation and instrumentation before any surgical intervention.

Key messages

— Prior to bariatric surgery, arterial oxygenation in a cohort of obese females without serious multi-morbidities is not altered but in hypoxemic individuals improved when supine.

— Preoperative supine-induced arterial oxygenation improvement is associated to an increase in cardiac output without ensuing changes in shunt and ventilation-perfusion mismatching.

— After successful bariatric surgery, arterial oxygenation significantly increased in all obese and in pre-operative hypoxemic individuals when upright but worsen when supine.

References


Authors’ contributions.—Eva Rivas, Ebymar Arismendi, Concepción Gistau and Roberto Rodriguez-Roisin conducted the experimental work and were involved in the acquisition and analysis of the data. Roberto Rodriguez-Roisin, Peter D. Wagner, Alvar Agustí and Eva Rivas contributed to the conception, design, and data interpretation of the study. Eva Rivas, Ebymar Arismendi, Concepción Gistau and Roberto Rodriguez-Roisin were involved in the planning and coordination of the study. Eva Rivas, Alvar Agustí, Peter D. Wagner and Roberto Rodriguez-Roisin contributed to the writing of the article and/or had substantial involvement in its critical revision before submission.

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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.

Treatment of chronic cervicobrachial pain with periradicular injection of meloxicam

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ABSTRACT

BACKGROUND: Cervicobrachial pain (CBP) is often resistant to conventional oral analgesics. We hypothesized that the periradicular injection of meloxicam would produce a significant reduction in their intractable CBP. The secondary objective was to assess the impact of the treatment on functional recovery.

METHODS: 48 patients with persistent CBP (>3 months of duration) despite multimodal analgesic therapy received 1-3 periradicular injections of meloxicam, 5-20 mg, at the dermatomal level(s) corresponding to their pain symptoms. Pain level (0=none to 10=severe), rescue analgesics, and functional activity were recorded at baseline and for 90d after the last injection. The injection was repeated if the pain score remained >3 or paresthesia persisted.

RESULTS: The mean pain score was reduced from a baseline of 8.9 (±1) to 1.7 (±2.2) at 90 days after the last meloxicam injection. Following meloxicam treatment(s), only 13% of the patients required oral analgesic rescue medication. All patients increased their functional activity level.

CONCLUSIONS: Cervical periradicular injection of meloxicam reduced CBP by 81% at 90-day follow-up and also improved functional recovery.


Key words: Meloxicam - Spinal injections - Ultrasonography - Brachial plexus neuritis - Chronic pain.

Neck and shoulder pain (i.e., cervicobrachial pain, [CBP]) is a surprisingly common spine disorder. In a general adult population involving 8356 subjects, Swedish investigators reported that 43% suffered from neck pain.1 A recent review by Cohen from the Mayo Clinic in the USA reported an annual prevalence rate of CBP exceeding 30%.2 Persistent CBP has been reported in almost 50% of individuals suffering from neck pain,3-5 and 14% of CBP patients report severe pain with physical dis- abilities despite receiving multimodal analgesic therapy.6

According to Bogduk,7 neck and cervical radicular pain are distinct entities. The IASP defines radicular pain as “pain arising in a limb or caused by ectopic activation of nociceptive afferent fibers in a spinal nerve or its roots or other neuropathic mechanisms. Structural lesions can directly compromise the dorsal root ganglion, or indirectly compromise the spinal nerve and its roots by causing ischemia or inflammation of the axons”. The pain is typically described as knife-like in quality and radi-
ates in a dermatomal distribution that is not necessarily the same as neuropathic pain. A study from the Mayo Clinic found an annual incidence of cervical radicular pain of 83 per 100,000, with C7 involvement in 45-60% of cases. Numerous analgesic modalities have been recommended for managing CBP; however, rigorous scientific evidence supporting their efficacy is often lacking.

We recently reported complete pain relief and daily-life activities (including work and sports) resuming in patients with chronic low back pain following periradicular injection of meloxicam who had failed to respond to conventional multimodal analgesic therapy. Therefore, we conducted a similar case study in CBP patients who failed to respond to multimodal analgesic therapy. We hypothesized that periradicular injections of meloxicam would reduce CBP scores by >30% from their baseline pain level and lead to improved function activity levels.

Materials and methods

After obtaining institutional review board approval for periradicular injection of meloxicam and informed consent from the patients, 48 patients (age: 60±13.6 years) with CBP symptoms (mean duration of 4±6.5 months and a range of 3 months to 30 years) were enrolled between 2011 and 2014 in Bologna, Italy. Inclusion criteria included age >18 years, CBP symptoms for more than 3 months despite receiving multimodal oral analgesic drug therapy, a baseline Numeric Rating Scale (NRS) pain score >3 on an 11-point NRS with 0=none to 10=severe [worse pain imaginable], and no contraindication to receiving a non-steroidal anti-inflammatory drug (NSAID). Exclusion criteria included known allergy to meloxicam, unstable cardiorespiratory or neurologic disorders, or a cutaneous infection at the needle insertion site.

All CBP patients in this case series had been receiving multimodal oral analgesic therapies (e.g., NSAIDs, steroids, paracetamol, oral opioids and gabapentinoids), epidural or perifacet injections and regular physical therapy without any significant improvement in their CBP symptoms. Thirteen patients (27%) had a herniated cervical disc diagnosed by magnetic resonance imaging (MRI) while in the remaining 35 (73%) no structural cause for the CBP symptoms (negative MRI). All patients were initially evaluated to determine their baseline NRS pain score and presence of any paresthesias or other neurological symptoms. A careful physical examination was performed by pain specialist to detect any neurologic impairment. Using a binary (yes/no) questionnaire, the patient’s physical activity was assessed (e.g., ability to work, perform sporting activity, requirements for assistance in activities of daily living, and quality of sleep [insomnia]). Patients did not receive any other analgesic treatments during the 90-day study period except for rescue analgesic medications.

After the dermatomal level(s) involved in the CBP symptoms was identified (C5-C7), periradicular meloxicam was administered with the patient lying in the lateral position. An ultrasound (US) transducer was applied transversely to obtain a short-axis view (Figure 1). A 22-gauge blunt-tip needle was introduced under real-time US guidance from posterior to anterior with in-plane technique externally to the foraminal opening. When injecting the nerve roots, it was important not to inject near the origin as the dura coats the nerve root at its origin and the injection can inadvertently traverse into the intrathecal space. The periradicular approach is not the same as transforaminal injections as the needle point is ~1.5 cm away from the foramina. This injection approach is more similar to an IM injection in close proximity to the inflamed nerve root.

If only one cervical level was involved, the patient received meloxicam 10 mg (1 mL). However, if the pain involved >1 dermatomal level; the patient received 5 mg (0.5mL) at each level to a maximum total dose of 20 mg (2 mL) per treatment session. After performing the periradicular meloxicam injection(s), the NRS scores were reassessed at 1, 5, 10, 20, 40, 60 min and subsequently at 1, 5, 7, 15, 30 and 90 days via telephone follow-up by a research as-
were summarized as mean ± SD and categorical variables as frequencies and percentages. Data for patients receiving 1, 2, or 3 injections were compared using one-way ANOVA, followed by a Bonferroni correction, and for categorical variables were assessed using χ² test. Repeated-measures general linear models were used to analyze the changes in the levels of pain over time. Analyses were performed using IBM SPSS Statistics v.20.

Results

The demographic characteristics and data regarding pain symptoms for the study population are summarized in Table I. The baseline pain score was 9±1 (mean±SD) and the mean duration of CBP symptoms was 4±6.5 years (range: 3 months to 30 years). Data regarding the treatment and the physical disability responses are summarized in Table II. The different subgroups were based on the changes in their functional status after receiving periradicular injection of meloxicam.

Twenty-one patients (44%) required only one meloxicam injection, 18 patients (37%) required two injections, and 9 patients (19%)
were reported in 45 of the 48 patients (94%). The meloxicam injections failed to provide significant pain relief in 4 patients (8%) and 2 patients withdrew from the study prior to completing the 90-day follow-up. No patient experienced side effects from the NSAID medication or complications related to the periradicular injections.

Prior to the meloxicam treatment(s), 90% of the patients were receiving non-steroidal anti-inflammatory drugs (NSAIDs), 94% glucocorticoids, 85% paracetamol 56% oral opioids, 17% gabapentanoids, 25% received epidural steroids and/or local anesthetics (LA), 15% received peri-facet injections, and 65% were administered physical therapy. After receiving the meloxicam injection(s), 42 patients (87%) required no chronic analgesics and the remaining 6 patients (13%) required only occasional NSAIDs. All patients who completed the study reported significant improvements with respect to their level of physical and functional activity at the 90d follow-up assessment (Table II).

The CBP patients population consisted of 15 retired/non-workers and 33 actively employed, and 19 were previously involved in sports-related activities. Due to their CBP, all patients were no longer able to carry out their normal daily activities and suffered from sleep impairment (i.e., chronic insomnia). Three patients also needed assistance with the activities of daily living. After receiving the meloxicam treatment(s), all ‘working-age’ patients were able to resume their work-related activities and/or sports-related activities without experiencing any ‘rebound’ pain symptoms during the 90-day follow-up period.

**Discussion**

Chronic CBP is an important cause of disability and contributes to loss of functional status. Many different pharmacologic and non-pharmacologic therapies have been tried with limited success. Currently, there are no evidence-based treatments for chronic radicular pain. Interestingly, the FDA recently issued a statement that they no longer support

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**Table I.—Demographic characteristics, specific dermatomes levels involved, and duration of CBP symptoms for the 48 CBP patients receiving periradicular injections of meloxicam.**

<table>
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<th>Study sample (%)</th>
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<td><strong>Age (years)</strong></td>
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<tr>
<td>Mean±SD</td>
<td>60±13.6</td>
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<tr>
<td>Range</td>
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<tr>
<td><strong>BMI (kg/m²)</strong></td>
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<tr>
<td>Mean±SD</td>
<td>26.7±4.4</td>
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<td>Range</td>
<td>19-39</td>
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<tr>
<td><strong>Gender (male)</strong></td>
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<tr>
<td>14 (29%)</td>
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<td><strong>N. of involved levels (C₃-C₇)</strong></td>
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<tr>
<td>1 (23.48%)</td>
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<td>2 (19.40%)</td>
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<tr>
<td>3 (4.8%)</td>
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<td>4 (1.2%)</td>
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<tr>
<td>5 (1.2%)</td>
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<tr>
<td><strong>Duration of CBP (years)</strong></td>
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<tr>
<td>Mean±SD</td>
<td>4±6.5</td>
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<td>Range</td>
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<tr>
<td><strong>Baseline pain score (0-10)</strong></td>
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<td>8.9±1.0</td>
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<tr>
<td><strong>Patients who had to discontinue working activity</strong></td>
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<td>33 (69%)</td>
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<tr>
<td><strong>Patients with impaired sport activity</strong></td>
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<td>19 (40%)</td>
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<td><strong>Patients who needed daily assistance</strong></td>
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<td>3 (6%)</td>
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</table>

CBP: cervicobrachial pain; BMI: Body Mass Index.
Table II.—Pain characteristics, meloxicam dosage, number of treatments required, and the early and late (90-day) outcomes following for each of the 48 patient enrolled in this preliminary study.

<table>
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<tr>
<th>Patients (N.)</th>
<th>Age (years)</th>
<th>Duration of pain (years)</th>
<th>Weight (kg)</th>
<th>Dermatomal level(s) treated</th>
<th>Baseline NRS (0-10)</th>
<th>Meloxicam dose (mg)</th>
<th>N. treatments</th>
<th>NRS at 90 days post-treatment</th>
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NRS: Numeric Rating Scale for cervicobrachial pain (CBP).
The common practice of injecting epidural steroids and/or LAs for treating cervical neck pain.\textsuperscript{17}

The first-line analgesic drugs for cervical pain of uncertain origin include NSAIDs and paracetamol. Patients who do not respond to these commonly prescribed non-opioid analgesics are often administered oral opioids and/or centrally-active myo-relaxants. However, Peloso \textit{et al}.\textsuperscript{18} found limited, if any, scientific evidence supporting the use of myo-relaxants and NSAIDs. Some authors have reported on the use of IM injection of LA for chronic mechanical neck disorders and the IV injection of methylprednisolone for acute whiplash,\textsuperscript{19} as well as acupuncture,\textsuperscript{20} in the management of CBP. Even IM botulinum toxin A has been tried for CBP but in a placebo-controlled study was no better than saline in improving cervical pain-related disability.\textsuperscript{15} A review of 359 invasive and non-invasive interventions for neck pain concluded that manual and exercise interventions, laser therapy and acupuncture were more effective than no treatment; however, none of these non-pharmacologic therapies were clearly superior to any other with respect to either short- or long-term outcomes.\textsuperscript{21}

Despite the FDA warning, both epidural\textsuperscript{22} and periradicular injection of steroids combined with LA are still commonly used for treating cervical neck pain. Karppinen \textit{et al}.\textsuperscript{23} observed that periradicular injection of

**Figure 2.**—Mean values and 95% confidence intervals of NRS pain scores. In patients receiving 1 injection (21 patients, 43.8%, black line) pain declined significantly over time (overall within-subject effect \(F=76.5, P<0.001\)) and decreased significantly up to 5 days and stabilized afterwards. In patients receiving 2 injections (18 patients, 37.5%, discontinuous line) pain declined significantly over time up to 40 minutes and then increased until the second inject when pain declined linearly (overall within-subject effect \(F=41.7, P<0.001\)) significantly up to 7 days after. In patients receiving 3 injections of meloxicam (9 patients, 18.8%, grey line) pain declined significantly over time up to 20 minutes and then gradually increased. A decline was subsequently observed from the second injection (overall within-subject effect \(F=31.98, P<0.001\)). All values were significantly different from the pre-treatment baseline values (\(P<0.05\)).

**Figure 3.**—The time-course of pain reduction differed significantly by gender. The onset of pain relief was significantly faster in males compared with females after adjusting for age and BMI (\(P<0.05\)). A significant gap between males and females was already observed at 1 minute.

**Figure 4.**—In the overall sample the NRS score decreased from 9 (at baseline) to 2.4 at 7 days after the last effective treatment (73%) and to 1.7 at 90 days (81%). The NRS change from baseline to 90 days in patients treated with either 1, 2, or 3 injections of meloxicam was 78%, 89% and 72%, respectively. “End of tx” indicates 7 days after the last effective treatment.
steroids for sciatica produced a transient improvement in pain symptoms, but, at 3 and 6 months follow-up; however, patients often experienced a return of their pain symptoms. The addition of morphine to a steroid-LA combination,24 provide no significant benefit but did increase opioid-related side effects. Despite questionable evidence supporting the clinical use of cervical epidural steroid-LA injections25 and the potential for serious complications,9 they are still widely used throughout the world.15

In patients with a herniated thoracic disc, Stetkarova et al.26 reported that periradicular injection of a steroid-LA combination provided significant pain relief. Narozny et al.27 concluded that LA nerve root blocks were effective in ‘minor’ mono-radiculopathy. More recently, Borghi et al.10 demonstrated that periradicular injection of meloxicam produced a sustained decrease in chronic LBP and was associated with a significant improvement in quality of life even in patients who had been previously been treated with periradicular steroids. The periradicular injection technique we employed is not the same as a trans-foraminal injection because the use of US guidance allows the operator to inject near the nerve after it has passed through the foramina.

Meloxicam (Mobic®, Boehringer Ingelheim) produces a marked anti-inflammatory and analgesic effect.28-30 As a result of its preferential COX-2 inhibition, meloxicam is better tolerated with respect to gastrointestinal and anti-platelet side effects than the classical NSAIDs.31 The use of NSAIDs like meloxicam are an important component of all multimodal analgesic regimen.32 However, these data suggest that periradicular injection of meloxicam offers significant advantages over standard oral and parenteral administration of this NSAID.

Although these preliminary findings with periradicular injection of meloxicam are impressive, the lack of a placebo (control) group and the failure to ‘blind’ the patients are obvious deficiencies in the study design. Nevertheless, the enrolled patients had all been previously (and unsuccessfully) treated CBP using standard multimodal analgesic therapies. Importantly, over 90% of the patients in this preliminary study achieved significant relief from their CBP symptoms and also improvement in their functional activity. These preliminary results strongly support the usefulness of this technique in patients suffering from chronic CBP which fail to respond to standard multimodal analgesic therapy. However, larger-scale multi-center, double-blinded, placebo-controlled clinical trials are clearly needed in patients with neck and upper extremity radicular pain to confirm the safety and efficacy of periradicular infiltration with meloxicam on short and long-term clinical outcomes.

Conclusions

We conclude that periradicular injection of meloxicam appears to be a novel and highly beneficial therapy for patients with intractable CBP who failed to respond to standard multimodal analgesic drug regimens. These results suggest that this approach could be used also as early treatment.

Key messages

— These preliminary data demonstrated that ultrasound-guided cervical periradicular meloxicam injections are highly effective in treating chronic CBP in patients who failed to respond to standard multimodal analgesic drug regimens and also early treatment.

— The periradicular injection technique described in this report can be safely performed in the ambulatory setting when ultrasound guidance is used.

— Larger-scale prospective, randomized, double-blind, placebo (or active comparator)-controlled trials are clearly needed to confirm the short and long-term benefits of periradicular meloxicam injections in patients suffering from intractable CBP.
References


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nary edema (PE) is among the most common causes of weaning failure and, more specifically, of failure to successfully complete a spontaneous breathing trial (SBT). The well-documented underlying pathophysiology indicates a high likelihood of reversibility with appropriate treatment. The diagnosis of PE, however, can be challenging. The reference standard diagnostic tool is right heart catheterization, which may affect the outcomes of patients in the intensive care unit (ICU). The weaning process may contribute 40% to 50% of the total MV duration. Many factors can result in weaning failure, which occurs in about 30% of patients.\textsuperscript{1,3}

Left ventricle (LV) dysfunction with pulmonary edema (PE) is among the most common causes of weaning failure and, more specifically, of failure to successfully complete a spontaneous breathing trial (SBT). The well-documented underlying pathophysiology indicates a high likelihood of reversibility with appropriate treatment. The diagnosis of PE, however, can be challenging. The reference standard diagnostic tool is right heart catheterization,
although the findings may prove difficult to interpret during marked inspiratory efforts with large intrathoracic pressure fluctuations or in patients with dyspnea. Studies evaluating noninvasive diagnostic investigations showed that transthoracic echocardiography (TTE) was accurate for detecting LV filling pressure elevation, a sign of LV dysfunction with PE.6 Furthermore, laboratory findings such as serum brain natriuretic peptide (BNP) elevation 4, 7 and plasma protein elevation as a marker for hemoconcentration 8 performed well versus right heart catheterization.

Acute cardiogenic PE is related to an increase in LV filling pressure and, consequently, in pulmonary capillary hydrostatic pressure, leading to the extravasation of hypo-oncotic fluid from the pulmonary capillaries to the lung interstitium and alveoli. This fluid is characterized by a low protein level, usually lower than half the protein level in the plasma. In acute cardiogenic PE, the semipermeable capillary membrane is intact. When the amount of extravasated fluid exceeds 3 L, hydrostatic PE may result in hemoconcentration that manifests as increases in the plasma protein and hemoglobin concentrations.9-11

The aim of this study was to evaluate the diagnostic accuracy of hemoconcentration during an SBT for detecting PE as the cause of SBT failure. Our reference standard was echocardiographic evidence of LV filling pressure elevation during the SBT.

Materials and methods

From August 2010 to March 2012, we included consecutive patients having failed a 2-hour SBT on a T-tube after at least 48 hours of MV. Exclusion criteria were preexisting neuromuscular disease, tracheostomy, mitral valve disease, and chronic or acute (onset during the weaning trial) atrial fibrillation. Both mitral valve disease and atrial fibrillation hinder the interpretation of echocardiography findings.6 Weaning was attempted when patients met previously published criteria.12

The appropriate ethics committee (CPP Nord-Ouest III) classified the research project as a study of standard care, approved the protocol (A10-D13-VOL.10), and waived the requirement for informed consent. Each patient or next of kin was given a study information sheet at study inclusion.

Study protocol

The patients were included at initiation of a second SBT. Before performing the second SBT, we recorded the following: heart rate (HR); mean arterial blood pressure (MAP); respiratory rate (RR); plasma protein, hemoglobin, and BNP; arterial blood gas levels in a blood sample drawn from an arterial catheter; an electrocardiogram; and TTE findings. The LV ejection fraction (LVEF) was assessed using the biplane Simpson’s method. Pulsed-wave Doppler was performed to record transmitral flow for measurement of the early E and late A mitral inflows, and the E/A ratio was computed. Tissue Doppler imaging of the lateral mitral annulus on the apical four-chamber view allowed peak velocity measurement (Ea) and determination of the E/Ea ratio.

A second set of measurements was performed at the end of the SBT, i.e., just before extubation in patients who successfully completed the 2-hour trial and just before reconnecting to the ventilator in the other patients. TTE (Sonos 7500, Philips Medical Systems, Andover, MA, USA; then CX 50 from the same manufacturer starting in December 2011) was carried out by physicians having over two years of experience with Doppler echocardiography in the ICU. All measurements were reviewed by a single person, who was blinded to patient data. Plasma protein was assayed using the Synchron System (Beckman Coulter, Villepinte, France) and hemoglobin using Sysmex XE-2100 (Sysmex Corporation, Kobe, Japan).

The patients were divided into two groups, with and without PE by echocardiographic criteria (PE+ and PE- groups). In keeping with previous data,6 we defined LV dysfunction as E/A>0.95 and E/Ea>8.5, and we took LV dysfunction to indicate PE.
**Data collection**

We collected the following baseline patient characteristics: age, sex, Body Mass Index (BMI), comorbidities such as heart disease or respiratory failure, reason for ICU admission, and illness severity at admission assessed using the Simplified Acute Physiology Score (SAPS II) \(^\text{13}\) (Table I). We also collected the following data on endotracheal MV: MV duration before inclusion, total MV duration, duration of sedation, duration of weaning from MV (time from the first SBT to extubation), and duration of the second SBT. Changes from ICU admission to study inclusion were recorded for body weight and plasma protein and albumin concentrations. We collected the daily urinary output, body temperature, and use of renal replacement therapy at inclusion; LVEF at ICU admission or weaning initiation, and at inclusion; outcome of the second SBT; and use of the following drugs: antibiotics, cardiovascular drugs (angiotensin-converting enzyme inhibitors, beta-blockers, and calcium-channel inhibitors), and diuretics (Table II).

**Statistical analysis**

Quantitative data were described as mean±standard deviation; their distribution was non-normal and they were therefore compared using the nonparametric Mann-Whitney U Test. Qualitative data were described as n (%) and compared using Fisher’s Exact Test. The two groups were compared using Student’s t-test for independent samples. The plasma protein difference between patients with and without PE was 5 g/L (+7 g/L and +2 g/L, respectively) in the seminal work by Anguel et al. \(^8\) To have 80% power to detect a standardized plasma protein difference of 5 g/L with alpha set at 5%, 16 patients were required in each group.

P values <0.05 were considered significant. Receiver-operating characteristics (ROC) curves were plotted for differences between the PE+ and PE- groups regarding changes in plasma protein and hemoglobin concentrations from SBT initiation to completion. Statistical analyses were performed using Sigmastat 3.5 and SigmaPlot 10.0 (Systat Software Inc., Chicago, IL, USA), and SAS 9.4 software (SAS Institute, Cary, NC, USA).

**Results**

**Study patients**

Figure 1 is the flow chart of weaning outcomes. During the study period (August 2010-March 2012), 834 patients in our medi-

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**Table I.—Baseline characteristics of the patients with and without pulmonary edema.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PE+ (n=21)</th>
<th>PE- (n=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61±14</td>
<td>60±11</td>
<td>0.72</td>
</tr>
<tr>
<td>Male gender</td>
<td>19 (91%)</td>
<td>13 (65%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>9 (43%)</td>
<td>6 (30%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>8 (38%)</td>
<td>6 (30%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Reason for ICU admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>8 (38%)</td>
<td>10 (50%)</td>
<td>NA</td>
</tr>
<tr>
<td>Shock</td>
<td>4 (19%)</td>
<td>7 (35%)</td>
<td>NA</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>5 (24%)</td>
<td>1 (5%)</td>
<td>NA</td>
</tr>
<tr>
<td>Coma</td>
<td>3 (14%)</td>
<td>2 (10%)</td>
<td>NA</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>1 (5%)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>BMI</td>
<td>28±9</td>
<td>30±7</td>
<td>0.14</td>
</tr>
<tr>
<td>SAPS II</td>
<td>49±16</td>
<td>50±15</td>
<td>0.89</td>
</tr>
<tr>
<td>Death</td>
<td>4 (19%)</td>
<td>1 (5%)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Quantitative data are mean±standard deviation and categorical data are n (%). PE: pulmonary edema; ICU: intensive care unit; BMI: Body Mass Index; SAPS II: Simplified Acute Physiology Score version II; \(^\text{13}\) NA: not applicable.
4 patients had either ventilator-associated pneumonia (N.=2) or critical-illness neuromuscular abnormalities (N.=2) and were finally extubated after a mean of 1±3 additional days.

Comparison of patients with and without PE: failure of the second spontaneous breathing trial

The two groups showed no statistically significant differences at baseline (Table I). Table II displays the clinical characteristics during the ICU stay and compares the two groups regarding variables collected during the second SBT. SBT failure was significantly more common in the PE+ group (57% vs. 20%, P=0.03), which had a longer total weaning process and longer time from the second SBT to extubation. Moreover, patients with PE during the second SBT had a larger change in body weight from ICU admission to study inclusion (4±6 vs. -2±8, P=0.01) and a shorter duration of the second SBT (79±42 minutes vs. 111±17 minutes, P=0.02) compared to those without PE diagnosed based on TTE criteria.

Weaning outcomes

Of the 41 patients, 21 (51%) had PE as assessed using TTE during the second SBT (PE+ group) and 20 did not (PE- group). Of the 21 PE+ patients, 9 were extubated after successfully completing the second SBT and survived. The other 12 PE+ patients (12/41, 29%) failed the second SBT and were finally extubated after a mean of 2±4 additional days. In these 12 patients, investigations showed no cause of weaning failure other than PE. Of the 12 patients, 4 died in the ICU, at least 48 hours after extubation.

Of the 20 PE- patients, 16 (80%) were extubated after successfully completing the second SBT and survived. The remaining 4 patients had either ventilator-associated pneumonia (N.=2) or critical-illness neuromuscular abnormalities (N.=2) and were finally extubated after a mean of 1±3 additional days.

Table II.—Clinical characteristics in patients with and without pulmonary edema.

<table>
<thead>
<tr>
<th></th>
<th>PE+ (n=21)</th>
<th>PE- (n=20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF at ICU admission (%)</td>
<td>44±15</td>
<td>48±11</td>
<td>0.61</td>
</tr>
<tr>
<td>MV duration before inclusion (days)</td>
<td>10±5</td>
<td>10±7</td>
<td>0.57</td>
</tr>
<tr>
<td>Total MV duration (days)</td>
<td>13±7</td>
<td>11±8</td>
<td>0.34</td>
</tr>
<tr>
<td>Duration of sedation (days)</td>
<td>5±5</td>
<td>5±4</td>
<td>0.90</td>
</tr>
<tr>
<td>Duration of weaning from MV (days)*</td>
<td>6±5</td>
<td>5±4</td>
<td>0.21</td>
</tr>
<tr>
<td>Weight change, ICU admission to inclusion (Kg)</td>
<td>4±6</td>
<td>-2±9</td>
<td>0.01</td>
</tr>
<tr>
<td>Plasma protein level change, ICU admission to inclusion (g/L)</td>
<td>-1±8</td>
<td>3±12</td>
<td>0.44</td>
</tr>
<tr>
<td>Plasma albumin level change, ICU admission to inclusion (g/L)</td>
<td>-5±6</td>
<td>-2±8</td>
<td>0.22</td>
</tr>
<tr>
<td>LVEF at inclusion (%)</td>
<td>51±14</td>
<td>56±13</td>
<td>0.60</td>
</tr>
<tr>
<td>Urine output at inclusion (L/day)</td>
<td>2.3±1.6</td>
<td>2.3±1.3</td>
<td>0.66</td>
</tr>
<tr>
<td>Body temperature at inclusion (°C)</td>
<td>37.4±0.7</td>
<td>37.5±0.5</td>
<td>0.76</td>
</tr>
<tr>
<td>Antibiotic therapy at inclusion</td>
<td>13 (62%)</td>
<td>12 (60%)</td>
<td>1</td>
</tr>
<tr>
<td>Diuretic therapy at inclusion</td>
<td>7 (33%)</td>
<td>5 (25%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Cardiovascular drug therapy at inclusion</td>
<td>16 (76%)</td>
<td>12 (60%)</td>
<td>0.33</td>
</tr>
<tr>
<td>RRT at inclusion</td>
<td>2 (10%)</td>
<td>0</td>
<td>0.49</td>
</tr>
<tr>
<td>Duration of second SBT (min)</td>
<td>79±42</td>
<td>111±17</td>
<td>0.02</td>
</tr>
<tr>
<td>Failure of second SBT</td>
<td>12 (57%)</td>
<td>4 (20%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Days from second SBT failure to extubation</td>
<td>2±4</td>
<td>1±3</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Quantitative data are mean±standard deviation and categorical data are n (%).

*Time from the first spontaneous breathing trial to extubation.

PE: pulmonary edema; LVEF: left ventricular ejection fraction; ICU: intensive care unit; MV: mechanical ventilation; RRT: renal replacement therapy; SBT: spontaneous breathing trial.
Figure 1.—Flow chart of patients and weaning outcomes.
Table III.—Clinical, laboratory, and echocardiographic changes induced by the second spontaneous breathing trial in predefined groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PE+ (N.=21)</th>
<th>Change</th>
<th>PE- (N.=20)</th>
<th>Change</th>
<th>*P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>E/A ratio</td>
<td>1.2±0.3</td>
<td>1.2±0.3</td>
<td>0.1±0.2</td>
<td>0.9±0.3</td>
<td>0.1±0.2</td>
</tr>
<tr>
<td>E/Ea ratio</td>
<td>9.4±2.5</td>
<td>11.7±2.4</td>
<td>2.3±2.2</td>
<td>7.5±2.7</td>
<td>7.5±2.6</td>
</tr>
<tr>
<td>Plasma protein level (g/L)</td>
<td>52±7</td>
<td>54±6</td>
<td>2±3</td>
<td>53±9</td>
<td>56±9</td>
</tr>
<tr>
<td>Hemoglobin level (g/dL)</td>
<td>9.5±1.4</td>
<td>9.8±1.3</td>
<td>0.3±0.5</td>
<td>10.4±2.3</td>
<td>10.6±2.3</td>
</tr>
<tr>
<td>pH</td>
<td>7.45±0.03</td>
<td>7.44±0.06</td>
<td>-0.01±0.04</td>
<td>7.47±0.03</td>
<td>7.46±0.03</td>
</tr>
<tr>
<td>PaO2 (kPa)</td>
<td>11±2</td>
<td>10±3</td>
<td>-2±2</td>
<td>12±3</td>
<td>10±4</td>
</tr>
<tr>
<td>PaCO2 (kPa)</td>
<td>5±1</td>
<td>5±1</td>
<td>0.3±0.6</td>
<td>5±1</td>
<td>5±1</td>
</tr>
<tr>
<td>BNP (pg/mL)</td>
<td>1062±1582</td>
<td>1182±1788</td>
<td>120±233</td>
<td>565±759</td>
<td>589±803</td>
</tr>
<tr>
<td>HR</td>
<td>87±16</td>
<td>96±18</td>
<td>9±9</td>
<td>100±15</td>
<td>105±17</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>88±8</td>
<td>95±9</td>
<td>8±9</td>
<td>89±13</td>
<td>90±14</td>
</tr>
<tr>
<td>RR</td>
<td>22±6</td>
<td>28±7</td>
<td>6±5</td>
<td>21±7</td>
<td>27±8</td>
</tr>
</tbody>
</table>

Quantitative data are mean±standard.
PE: pulmonary edema; SBT: spontaneous breathing trial; LVEF: left ventricular ejection fraction; BNP: brain natriuretic peptide; HR: heart rate; MAP: mean arterial blood pressure; RR: respiratory rate.*Student’s t-test for independent samples comparing mean change during SBT in the PE+ and PE- groups.

Figure 2.—Changes in plasma protein and brain natriuretic peptide concentrations, E/Ea ratio, and mean arterial pressure during the second spontaneous breathing trial in the groups with and without pulmonary edema.

Table III reports the changes in clinical, laboratory, and Doppler echocardiography variables during the second SBT in the PE+ and PE- groups. The changes in plasma protein and hemoglobin were not significantly different. Only the MAP increase at SBT completion was significantly greater in the PE+ group (Figure 2).

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**ROC curve analysis of diagnostic accuracy**

The area under the ROC curves for changes in plasma protein and hemoglobin concentrations from SBT initiation to completion as predictors of PE were 0.47±0.09 and 0.51±0.09, respectively. Thus, neither variable showed any usefulness for diagnosing PE as the cause of SBT failure.

**Discussion**

Our main finding is that failure of a second SBT due to PE, diagnosed based on TTE evidence of LV filling pressure elevation, was not associated with hemoconcentration, defined as increases in plasma protein and hemoglobin levels.

We are aware of a single previous study evaluating changes in plasma protein concentration during an SBT. Of 46 patients who had failed two previous SBTs, 24 experienced PE defined as a pulmonary artery occlusion pressure (PAOP) increase to more than 18 mmHg as determined by right heart catheterization before and after a third SBT. In this subgroup of 24 patients, the plasma protein concentration increased by 11% (range, 3%-25%), and a greater than 6% increase had 87% sensitivity and 95% specificity for PE. However, this study did not assess the value of a plasma protein increase in indicating SBT failure: although all patients with PAOP>18 mmHg at SBT completion failed the trial, 47% of those with lower PAOP values also failed the trial. The authors suggested that the change in plasma protein concentration between starting and ending the SBT might serve as an alternative to right heart catheterization for assessing weaning-induced PE. The discrepancies between our findings and theirs may be related to several factors. PAOP is extremely difficult to interpret in patients undergoing SBTs, most notably those with dyspnea and large pleural and intrathoracic pressure swings during inspiratory efforts. We therefore used TTE, which proved accurate versus pulmonary artery catheter pressure measurements in a single-center study. However, TTE is operator-dependent and exhibits limited interobserver and intraobserver reproducibility in ICU patients. Finally, the previous study required two failed SBTs, instead of one in our study, and the two studies may have differences in terms of weaning criteria, SBT timing, and case-mix.

The same team confirmed their results by showing a correlation between blood volume contraction and an increase in extravascular lung water. All patients were also assessed by right heart catheterization. Nevertheless, in another study, none of the tested diagnosis tools, including plasma protein and hemoglobin concentrations, helped to predict the outcome of the SBT.

Four findings from our study deserve special attention. First, positive fluid balance, defined as weight gain from ICU admission to inclusion (initiation of the second SBT), was significantly different between the groups with and without PE. A study of E/A and E/Ea to diagnose increased PAOP as a cause of weaning failure showed a similar difference between the groups with and without PE, although the time from SBT initiation to reconnection was longer than the 30 minutes recommended at an international consensus conference held in April 2005 and was significantly different between the groups with and without PE. A study of E/A and E/Ea to diagnose increased PAOP as a cause of weaning failure showed a similar difference between the groups with and without PE (35±22 min vs. 50±10 min, respectively), although the time from SBT initiation to reconnection was far shorter than in our study (about half the time in the PE group). Thus, although weaning failure due to LV dysfunction occurs early during the SBT, a 30-minute test time may be too short to detect weaning failure of cardiac origin. In addition to SBT duration, parameters such as fluid balance should be taken into account before deciding to extubate, and the appropriateness of treatments such as diuretics, vasodilators, and postextubation noninvasive ventilation must
be discussed. Third, the MAP increase at SBT completion seemed associated with weaning failure of cardiac origin, as in previous studies. There is no clear evidence in the literature to support this possibility, which, however, is consistent with the well-described pathophysiology of weaning failure due to cardiac causes, as well as with the effects of controlled MV on the cardiovascular system and the impact of physiological changes on spontaneous breathing. Controlled MV produces a positive intrathoracic pressure, thereby decreasing cardiac flow by diminishing the systemic venous return and also decreasing cardiac work by reducing the LV afterload. In contrast, switching from positive-pressure ventilation to spontaneous ventilation is associated with an increase in venous return and a negative intrathoracic pressure, which increase the LV afterload and myocardial oxygen consumption. Consequently, SBT increases cardiac work and may induce cardiogenic PE via PAOP elevation. LV afterload is mainly represented by MAP. Thus, an MAP increase during SBT suggests weaning failure of cardiac origin. Fourth, although baseline BNP was elevated in the group that developed PE, the discriminating power of this sign was low (0.66±0.09). Baseline BNP elevation probably correlates with weight gain and, therefore, with higher filling pressures before any SBT. Indeed, there is evidence that many factors such as advanced age, sepsis, fluid management, mechanical ventilation, female gender, diuretics, angiotensin-converting enzyme inhibitors, beta-blockers, renal dysfunction, and pulmonary arterial hypertension are confounders that can interfere with BNP homeostasis, in the absence of cardiac dysfunction. In addition, published data on BNP are conflicting. Mekontso-Dessap et al. reported that the baseline plasma BNP level before the first weaning attempt independently predicted weaning failure and correlated with weaning duration. Grasso et al. found that plasma NT-proBNP levels showed significantly greater increases in patients with weaning failure due to cardiac causes. The main limitation of our study is the relatively small number of highly selected patients (i.e., with COPD). Thus, our findings may not apply to other populations. Zapata et al. reported that BNP elevation during SBT predicted weaning failure due to heart failure, whereas Ouanes-Besbes et al. found that NT-proBNP was of no help in predicting the SBT outcome. Our results further indicate that BNP and NT-proBNP fail to predict weaning failure due to cardiac causes. Given our findings and the conflicting data in the literature, caution is in order when using these biomarkers.

Several limitations of our study must be addressed. This is a single-center study with a very low frequency of failure of the first SBT. Therefore, the general applicability of our results may be limited. Second, we detected PE using TTE instead of the reference standard, i.e., right heart catheterization. Echocardiography can be used to estimate the end-diastolic LV pressure as a means of diagnosing weaning failure due to cardiac causes. We used a combination of two echocardiography variables, E/A>0.95 and E/EA>8.5, obtained at the end of the weaning trial. This choice deserves discussion. Both variables are easily assessed on a single echocardiography window. However, their assessment is operator-dependent and their variability can make their interpretation challenging. Assuming that E/EA<8 indicates normal LV filling pressures and E/EA>15 high LV filling pressures then there is a gray zone in the 8-15 range that requires the use of other variables to detect a filling pressure increase, such as the E-wave deceleration time (EDT) measured by transmitral Doppler. These variables were first widely validated in cardiology patients who were breathing spontaneously (i.e., were not receiving endotracheal ventilation) and only subsequently suggested as relevant for the echocardiographic diagnosis of PE. Thus, the TTE variables used in our study, although validated in previous work, may be highly sensitive but less specific for PE, as some patients may have elevated LV filling pressures with no hydrostatic pressure increase within the pulmonary arteries. These
considerations invite questions about the validity of echocardiography for diagnosing PE in the ICU, where examination conditions are far from optimal. Finally, our choices regarding the timing of the SBT and of the second measurements during the SBT may explain a number of discrepancies with other studies. Moreover, we did not evaluate the multiple confounding factors that may have affected the development of SBT failure. In particular, the impact of weight gain in our study may have been overestimated.

Conclusions

Our study does not support the diagnostic usefulness of plasma protein or hemoglobin concentration monitoring during SBTs to detect PE, diagnosed based on validated echocardiographic criteria, as the cause of SBT failure. Other studies are needed to identify the best echocardiographic criteria for heart failure in patients receiving MV and to assess their interobserver and intraobserver variability in a range of TTE conditions. However, our data suggest that close attention to fluid balance control during the weaning process might improve the frequency of successful SBTs. Finally, an MAP increase during SBT suggests weaning failure of cardiac origin.

Key messages

— Neither plasma protein nor hemoglobin levels help to detect pulmonary edema, diagnosed based on validated echocardiographic criteria, as the reason for failing a second spontaneous breathing trial.

— The only factor predicting failure of spontaneous breathing trial failure due to pulmonary edema was a positive fluid balance from intensive care unit admission to initiation of the second spontaneous breathing trial.

— A larger increase in mean arterial pressure during the second spontaneous breathing trial suggested weaning failure due to pulmonary edema.

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failure in patients following a successful spontaneous breathing trial. Chest 2006;130:1664-71.

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Mechanical LUCAS resuscitation is effective, reduces physical workload and improves mental performance of helicopter teams

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ABSTRACT

BACKGROUND: Physical and mental workload during cardiopulmonary resuscitation (CPR) is challenging under extreme working conditions. We hypothesized that the mechanical chest-compression device Lund University Cardiac Assist System (LUCAS) increases the effectiveness of CPR, decreases the physical workload and improves the mental performance of the emergency medical service (EMS) staff during simulated emergency helicopter flights.

METHODS: During simulated helicopter flights, 12 EMS teams performed manual or LUCAS-CPR on a manikin at random order. Compression depth, rate, overall time of compressions, application of drugs and defibrillation were recorded to test the quality of CPR. Heart rate monitoring of EMS members was used as a surrogate of physical workload. Cognitive performance was evaluated shortly after each flight by a questionnaire and a memory test about medical and extraneous items presented to the teams during the flights.

RESULTS: Overall times of chest-compressions were similar, compression rate (101.7±9.6/min) was lower and compressions were deeper (3.9±0.2cm) with LUCAS as compared to manual CPR (113.3±19.3/min and 3.7±0.4cm) (P<0.01, respectively). Heart rates of the EMS staff were increased after manual as compared to mechanical CPR (100.1±21.0 vs. 80.4±11.3, P<0.01). Results of the questionnaire (93.6±6.9% vs. 87.0±7.3% correct answers, P<0.01) and memory test (22.4±15.4% vs. 11.3±7.5%, P<0.02) were significantly better after LUCAS resuscitation. Dosing of drugs, application intervals and rate of correct handling of drugs and defibrillation were not different between LUCAS or manual CPR.

CONCLUSIONS: During simulated helicopter flights LUCAS-CPR improved the efficacy of chest-compressions, was physically less demanding and provided enhanced cognitive performance of the EMS team as compared to manual CPR.

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Key words: Cardiopulmonary resuscitation - Chest wall oscillation - Air ambulances - Workload - Task performance and analysis.

High quality chest-compressions and reduced hands-off intervals are important determinants for survival with good neurological outcome after cardiac arrest. However, cardiopulmonary resuscitation (CPR) during transport is challenging as recent manikin and human studies have demonstrated that the quality of manual chest-compression deteriorates during transport and prolonged CPR attempts amongst others due to increasing fatigue of the emer-
emergency medical service (EMS) staff. Moreover, performing manual chest-compressions on a patient in a moving vehicle may be dangerous for the EMS staff itself. In contrast, mechanical chest-compression devices have been shown to be applicable in ground based ambulances as well as in helicopters and may maintain good quality CPR during patient transport and increase the safety of the staff. However, little is known about potentially different physical and mental demands by performing CPR with manual or mechanical chest-compression. Especially under extreme working conditions, such as transports with ongoing CPR, physically demanding work that is performed concurrently with important cognitive demands may impact mental workload of EMS members by impairing mental processing or decreasing performance resulting in incorrect handling of drugs, ventilation and defibrillation.

We hypothesized that in an emergency helicopter mechanical CPR would be more effective than manual CPR, and reduce physical demands and mental workload resulting in a lower heart rate and better cognitive performance of the EMS team. To test this hypothesis EMS teams performed two different CPR scenarios on a manikin during simulated helicopter flights with and without the Lund University Cardiac Assist System LUCAS (Jolife Inc., Lund, Sweden) which is a battery-driven device providing mechanical active compression-decompression CPR. To determine the effectiveness and quality of CPR the chest-compression rate and depth, the ratio of correct compressions and overall compression times as well as dosing and application intervals of drugs and defibrillation were measured. Heart rates of the medical crew were recorded continuously and mental workload and performance were estimated via cognitive tasks after the simulated flight episodes.

Materials and methods

Design and participants

Approval of this prospective, randomized, cross-over manikin study was waived by the ethics committee of the Medical Association of North Rhine, Duesseldorf, Germany. Twelve advanced life support-certified EMS teams consisting of an emergency physician and a paramedic underwent two simulated helicopter flights of 20 minutes duration, respectively. During each flight the teams had to manage two cardiac arrest scenarios using either manual CPR or LUCAS. The sequence of the flights with manual or mechanical CPR was randomly assigned by the sealed envelopes technique immediately before the first flight of each team.

Materials and measurements

The emergency helicopter simulator Christoph Sim® (helicopter emergency medical service academy, Allgemeiner Deutscher Automobil Club, St. Augustin, Germany) which is a replica in proportion to the actual dimensions of an Eurocopter EC 135 was used. An intubated manikin (AmbuMan megacode®, Ambu GmbH, Bad Nauheim, Germany) was placed on a stretcher locked in the front position of the helicopter during the whole study (Figure 1).

Figure 1.—Fully instrumented manikin with attached LUCAS within helicopter simulator.
The manikin was mechanically ventilated (Oxylog3000, Draeger Medical GmbH, Luebeck, Germany) and connected to an integrated defibrillator/monitoring device (Corpuls3, G. Stemple GmbH, Kaufering, Germany) with defibrillation patches attached to the thorax. During simulated flights with LUCAS the backboard of the device was already placed under the manikin from the beginning of the scenario while the device itself was not allowed to be attached to the patient until recognition of cardiac arrest. Compression depth, compression rate on a beat to beat basis, the time between recognition of cardiac arrest and the first compression, and the overall time without chest-compression were recorded. Since the compression depth of LUCAS was set according to the 2005 AHA guidelines, both manual and mechanical compressions with a depth of at least 40 mm were judged as correct.

All team members were equipped with an ambulatory digital Holter electrocardiography monitor (custoflash 510, custom med, Ottobrunn, Germany) for continuous heart rate recording. Overall performance of CPR, dosing, application times and intervals of drugs and external defibrillations were analysed by video recording. All data were stored on an attached laptop-computer and extracted to Excel XP (Microsoft, USA) and SPSS (IBM SPSS Statistics 19) for further analysis.

Protocol

All participants were blinded to the scenarios and measurements. Since no participant had worked with LUCAS before, each team was allowed to exercise with the device without a time limit outside the helicopter. All participants were told that they would perceive medical relevant and irrelevant information during the flight and that a questionnaire had to be answered and a memory test to be performed after each flight. The interval between the two flights was 60 minutes to allow the teams to recover from the first flight.

In both scenarios, transfers to a tertiary hospital for coronary revascularization were simulated with good flight conditions at calm weather without turbulences. The medical crew heard the typical propeller and engine noises of a helicopter flight and were given different relevant information about the patient, the target hospital and the flight, and further usual communication pattern through headphones (Supplementary Table I, online content only). In addition, five packages each consisting of five extraneous words such as everyday items were presented at irregular intervals (Supplementary Table II, online content only). Three minutes after take-off the first cardiac arrest due to ventricular fibrillation occurred. In order to simulate real-life decision making, it remained at the discretion of the physician and paramedic who started with chest-compressions and who administered drugs and shocks, and whether and how often they rotated. During LUCAS-CPR it also remained at the discretion of the EMS team to begin with manual chest compressions immediately after recognition of cardiac arrest or to delay chest-compressions until LUCAS was attached. Return of spontaneous circulation was simulated both ten minutes after the first cardiac arrest and again another four minutes after the second cardiac arrest was simulated. After a total time of 14 minutes of cardiac arrest and a total flight time of 20 minutes the test was stopped.

Questionnaire and Memory Test

Ten minutes after each flight the physician and paramedic had to answer a questionnaire about the medical items (Supplementary Table III, online content only) and to perform a memory test for the added extraneous non-medical items which were presented during the flight.

Statistical analysis

Results are expressed as mean±standard deviation (SD). The data was assumed to be normal distributed due to the Central Limit Theorem. Student’s paired t-test was used to compare parametric and Fisher’s exact Test to compare categorical data of the two resuscita-
tion scenarios. Randomness of the sequence of the CPR-order of the twelve teams was tested and verified by the runs-test (Supplementary Table IV, online content only). Differences were considered to be statistically significant if P<0.05.

Results

All teams fully completed the simulated helicopter flights and used LUCAS correctly as judged by video analysis. The time intervals from recognition of cardiac arrests to first compression as well as overall compression times, and the ratio of compression time to total time of cardiac arrest were similar with manual and LUCAS-CPR (Table I). With LUCAS the compression rate was significantly lower (101.7±9.6/min), and compressions were significantly deeper (3.9±0.2cm) as compared to manual CPR (113.3±19.3/min and 3.7±0.4cm, P<0.01, respectively). Analysis of every single chest-compression showed that the recommended depth was achieved in 92.4±19.4% of all LUCAS compressions and in 56.0±40.4% of all manual compressions (P<0.01). The ratio of recorded to recommended compression depths rapidly improved during ongoing LUCAS-CPR but was significantly lower and did not improve over time during manual CPR (Figure 2).

Heart rates of the EMS teams were significantly increased immediately after manual as compared to mechanical chest compression (P<0.01) (Table II).

Results of the questionnaire about the presented relevant medical information shortly after the flight simulation phase were better after LUCAS-CPR (93.6±6.9% correct answers) compared with manual CPR (87.0±7.3% correct answers, P<0.01) (Figure 3). With the more challenging free irrelevant word test, differences were also significant: after LUCAS-CPR, participants remembered 22.4±15.4% of the items compared to 11.3±7.5 % after manual CPR (P<0.02) (Figure 3). This tendency of both tests was similar for each participant.

Total doses of adrenaline (epinephrine) and amiodarone, the time of first application of adrenaline, amiodarone and defibrillation were not different during CPR with manual or mechanical chest compression (Table III).

Table I.—Data of cardiopulmonary resuscitation (CPR) with manual and LUCAS-CPR performed by 12 emergency medical service teams.

<table>
<thead>
<tr>
<th></th>
<th>Manual CPR*</th>
<th>LUCAS CPR*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression rate (b/min)</td>
<td>113.3±19.9</td>
<td>101.7±9.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Compression depth (cm)</td>
<td>3.7±0.4</td>
<td>3.9±0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Rate of correct compression depth (%)</td>
<td>56.0±40.4</td>
<td>92.4±19.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time interval from recognition of first cardiac arrest to first compression (s)</td>
<td>73.1±33.8</td>
<td>85.6±40.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>Time interval from recognition of second cardiac arrest to first following compression (s)</td>
<td>91.5±56.6</td>
<td>92.2±48.7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Total compression time during cardiac arrest (s)</td>
<td>659.1±78.8</td>
<td>710.1±56.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ratio of compression time to total time of cardiac arrest (%)</td>
<td>68.7±8.2</td>
<td>74.0±5.9</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Values are mean±standard deviation.
* Tested on a randomized basis, student’s t-test for dependent samples.
compared with manual CPR during simulated helicopter flights. We found that LUCAS-CPR was more effective, physically less demanding and provided enhanced cognitive performance as compared to manual CPR. However, application of drugs and defibrillation were not affected by the method of chest-compression.

In patients with out-of-hospital cardiac arrest two large randomized trials, LINC\textsuperscript{15} and PARAMEDIC\textsuperscript{16} recently have failed to demonstrate an improved outcome after LUCAS-CPR as compared to manual CPR. In these trials patients with the whole spectrum of cardiac arrests except a few causes such as traumatic cardiac arrests were included. However, problems of ongoing CPR during transports, especially helicopter transport, were not specifically addressed. Therefore, the authors of the PARAMEDIC Trial emphasized the accepted role mechanical compression devices will continue to have when...
manual CPR is impracticable or involves an increased risk (e.g., in a moving ambulance). In fact, manual CPR during patient transport is challenging and the quality of prolonged CPR has been shown to deteriorate during any transport mainly due to the extreme working conditions. In previous manikin and human studies mechanical chest-compression devices have been shown to be applicable in ground based ambulance systems and in emergency helicopters with acceptable results. Similarly, we also could demonstrate that LUCAS-CPR was applicable and more effective than manual CPR in an emergency helicopter and did not deteriorate but even improved over the entire time of resuscitation. While in our study the time intervals from recognition of cardiac arrests to the first chest-compressions as well as the overall compression times and the ratio of compression time to total time of cardiac arrest were similar during CPR with and without LUCAS, chest-compressions were actually performed in only 68.7±8.2% and 74.0±5.9% of the demanded time during manual and mechanical chest-compression, respectively. These results are similar to the ratios of failed compression times during simulation courses of in-hospital scenarios on scene or in ambulance vehicles. Analyses of video recordings of our CPR scenarios revealed that pre- and post-shock pauses to reassess cardiac rhythm could have been minimised and resumption of chest-compression could have been achieved faster as recommended by recent guidelines. Moreover, in our study mechanical chest-compression was frequently interrupted for defibrillations by some of the EMS teams even during LUCAS-CPR although continuing mechanical chest-compression during defibrillation is supposed to be an advantage of mechanical over manual compression. Despite in our study all EMS teams were able to attach LUCAS easily and quickly to the backboard of the device which was already placed under the manikin, the rate of correct chest compressions during the first minutes of LUCAS-CPR was quite variable which in some cases may have been caused by an initially not optimal positioning of the device on the sternum. Therefore, we propose to apply not only the backboard of LUCAS but the complete device preventively to high-risk patients and check its’ correct position before the flight. Since a cardiac assist device like LUCAS may only be beneficial when it is used as quickly as possible and as long as necessary our observations clearly emphasize the importance of a device related training program even for experienced EMS teams. Similarly, the authors of the PARAMEDIC Trial found it essential that sufficient resources are made available to support initial and regular refresher training and ongoing quality assurance when implementing mechanical devices into real world EMS systems.

Our study only included transport time within the helicopter, and simulated calm weather. However, in real transport scenarios manual CPR may have to be performed even during loading or unloading of the patient to and off the vehicle which has been shown to be ineffective. During turbulent flight conditions manual CPR may further deteriorate. Therefore, CPR with a mechanical compression device should be even more effective under those actual helicopter rescue simulations as nicely confirmed by Putzer in their manikin study where mechanical chest-compression performed better not only within the helicopter but also during transport of the manikin from the scene to the helicopter and from the helicopter to the emergency room.

The present study seems unique in combining both the narrow CPR conditions as well as the physical and mental workload conditions (e.g., intensive movements, high vigilance, safety concerns, and constant decision making) of emergency-trained physicians and paramedics in a relatively long-term fully realistic flight simulation including emergency-related and additional mental task-specific extraneous cockpit-communications and noise parameters related to mental overload and performance. Thus, we tried to adopt a more
complementary or, in psychological terms, a more ecological approach. In fact, in our study not only the flight duration and medical scenario but also the noise and busy communication pattern of emergency helicopter flights have been simulated in order to match the test and the real-life event as much as possible. In particular, the noise level and the ongoing-cockpit communication might affect the mental workload of the EMS team. Such extraneous factors to the mental workload of the EMS team in stress-related situations seem often neglected and not specifically addressed. During our simulated flights heart rates of the EMS staff were markedly increased during manual CPR. In addition to the physically exhausting effects of manual CPR, the combination of an increased physical workload with extreme working conditions within the confined space of a helicopter, rapid movements of the EMS members while performing manual CPR, substantially impaired visual and acustic signals from the patient and monitoring devices in such a noisy environment, and finally potential personal safety concerns due to the unfastened seat-belts may have contributed to the increase in heart rate most likely reflecting an enhanced sympathetic tone of the medical crew.

If physical and extraneous mental load are high, it is clear that performance may be hampered, but having these two forms of load set low does not guarantee that performance and outcome will succeed. On the one hand some technological advancements may have increased the requirement for many health professionals to execute cognitive tasks concurrently with physical activity, on the other hand technological advancements such as the device tested in the present study may lower the physical and probably also the mental workload of emergency teams, and thereby may improve their cognitive performance. In the present study mental performance as tested by memory tests shortly after the simulation phase was significantly better after the physically less demanding mechanical CPR which may provide further evidence to the close relationship between physical load, mental work-
Conclusions

Mechanical chest-compression in an emergency helicopter using LUCAS was more effective, physically less demanding and enhanced cognitive performance of the EMS staff as compared to standard manual CPR. Although we could not demonstrate improved decision making as concerns application of drugs and defibrillation the present findings can be taken as encouragement for the use of mechanical CPR devices in highly volatile rescue situations within helicopters. Before a mechanical compression device is implemented in an emergency helicopter service training of the EMS teams should focus not only on the handling of the device itself but most importantly on the integration of the device into the resuscitation algorithm.

Key messages

— LUCAS-CPR is more effective, physically less demanding and provides enhanced cognitive performance as compared to manual CPR during simulated helicopter emergency flights.

— Despite the cognitive capacity of the EMS members improved with LUCAS-CPR that did not automatically result in a better adherence of the teams to resuscitation guidelines.

— Before implementing LUCAS in emergency helicopters we recommend to establish simulation courses which should focus not only on the technical skills required for the handling of LUCAS but also on the integration of the device into the resuscitation algorithm to be performed.

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For supplementary materials, please see the online version of this article.
Effectiveness of benzodiazepine premedication on recovery in day-case surgery: a systematic review with meta-analysis

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ABSTRACT

INTRODUCTION: Benzodiazepines are frequently used as a premedication. In day-case surgery, anaesthetists are reluctant to administer benzodiazepines preoperatively for reasons of delayed recovery. However, premedication with benzodiazepines might be beneficial regarding postoperative somatic symptoms/complaints (i.e. time to recovery and postoperative side effects) and psychological phenomena.

EVIDENCE ACQUISITION: A systematic review with meta-analysis was performed using all important search engines. Study methodological quality was assessed using risk of bias tables. Mean differences (MD) and odds ratios (OR) were used for continuous data (time to recovery and psychological phenomena) and categorical data (postoperative somatic symptoms) respectively. Random effects modelling was applied. Nineteen studies were included. Overall time to recovery was significantly delayed in patients receiving benzodiazepines (MD 1.75; 95% CI 0.82 to 2.69) although time to discharge was not significantly affected. Postoperative side effects were significantly reduced in patients receiving benzodiazepines (OR 0.47; 95% CI 0.36 to 0.63). Regarding psychological outcome, only anxiety could be statistically analyzed showing no statistical difference (MD 1.47; 95% CI -1.01 to 3.96).

EVIDENCE SYNTHESIS: Although overall time to recovery was significantly prolonged by benzodiazepine premedication, withholding premedication in day-case surgery patients is not justified for such reason, as time to discharge was not negatively affected. Furthermore, benzodiazepines show to have beneficial effects on postoperative side effects.

CONCLUSIONS: For a firm conclusion regarding psychological phenomena, more research is needed. Anaesthetists should take into account this new evidence when they apply their premedication regime in day-case surgery.

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Key words: Benzodiazepines - Meta-analysis as topic - Preoperative care.

Introduction

Benzodiazepines are among the most prescribed drugs used for premedication.1 In a clinical setting, anaesthetists frequently administer benzodiazepines preoperatively as they have unique properties like anxiolysis — one of the main goals of premedication — calming effects and anterograde amnesia as a favourable side effect profile.1 Anaesthetists are reluctant to prescribe premedication (with benzodiazepines) in a day-case setting as patients could be too somnolent postoperatively. Consequently, this may prolong their time to discharge which should be avoided, especially, in day-case surgery. However, a Cochrane Review could not support this hypothesis,2 although they did not focus specifically on benzodiazepine premedication. Furthermore, withholding premedication may not be justified as almost half of the
EFFECTIVENESS OF BENZODIAZEPINE PREMEDICATION

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patients in day-case surgery request something to relieve their stress and anxiety.\(^3\)

In day-case surgery, patient’s somatic symptoms became of minor interest as perioperative morbidity and mortality are extremely low.\(^4\) Therefore, day-case surgery patients place higher priority on psychological phenomena rather than physical recovery in the postoperative period. Along with this, literature shows more attention for psychological aspects of perioperative care.\(^5,6\) Research evaluating benzodiazepine administration in day-case surgery is focusing on psychological phenomena including anxiety, fatigue, aggression and depressive moods.\(^7\)

Preoperative benzodiazepine administration is mostly evaluated preoperatively. However, the reluctance of anaesthetists is based on potential postoperative concerns. Therefore, to determine whether benzodiazepine premedication in day-case surgery is appropriate, thorough research focussing on the postoperative period is needed.

To evaluate the effectiveness of benzodiazepine administration in day-case surgery, we conducted a systematic review with meta-analysis of randomised trials focussing on postoperative somatic symptoms/complaints and psychological phenomena.

This systematic review and meta-analysis tested three related hypotheses:

1. in adult day-case surgery, benzodiazepines as a premedication do elongate time to recovery from general or regional anaesthesia;
2. benzodiazepines as a premedication do beneficially affect postoperative somatic symptoms/complaints;
3. benzodiazepines as a premedication do reduce postoperative psychological sequelae.

Evidence acquisition

The Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines were adhered to.\(^8\)

Literature search

Literature search was performed in Embase, Medline OvidSP, ISI Web of Science, Scopus, Cochrane Central Register of Controlled Trials, PubMed Publisher, and Google Scholar, updated until January 2014. There were no language or publication date restrictions. Main key words for the search queries included day surgery, postoperative psychological aspect, somatic symptoms/complaints, and premedication. The full search is presented in Appendix I.

Study selection

All randomized controlled trials including human adult patients undergoing day-case surgery were included when they really tested premedication. We defined “premedication tested” as any medication given prior to induction of anaesthesia that was continued neither during the surgical procedure nor postoperatively. In addition, the intervention had to be tailored to the premedication itself. We excluded studies where no postoperative outcomes were assessed. Original articles written in English, German or French that included an abstract were maintained in the set in order to reduce language bias. Next, we excluded trials based on clinical anaesthetic and surgical selection criteria. Anesthetic exclusion criteria concerned not undergoing general or regional anaesthesia. Surgical exclusion criteria included not undergoing day-case surgery or undergoing abortion, dental surgery or ophthalmology surgery. Also, trials testing non-benzodiazepines as a premedication were excluded. Finally, non-randomised studies and studies with no placebo control (i.e. methodological criteria) were excluded.

Data extraction and management

Three authors (HM, SVB, RJS) independently analyzed studies for inclusion in the analysis. Two authors (HM, SVB) independently assessed all included studies with respect to their quality. Data was extracted using a preset collection sheet. Authors were not blinded for information regarding the identified studies (e.g. journal, author, institution, date of publication), as it was previously shown that not blinding did not influence the results of meta-
analysis. Disagreement among authors was resolved by consensus.

Included studies were reviewed for data on any of the following outcomes:

1. Somatic symptoms/complaints: time to recovery, time to eye opening, time to first correct response (TCR), time to early recovery (i.e. discharge from the recovery room) and time to discharge; postoperative side effects, including, nausea, vomiting/emesis, dizziness, pain, headache and miscellaneous (coughing and double vision).

2. Psychological outcomes: anxiety, depression, fatigue and aggression.

All outcomes were eligible for assessment when they were measured up to the first postoperative day.

Quality assessment

The Cochrane Handbook of Systematic Reviews of Interventions was used to evaluate the risk of bias of each included study. Selection-, performance-, detection-, attrition-, reporting- and other biases are assessed in this risk of bias tool.

Statistical analysis

Categorical outcome data were evaluated by odds ratios (OR) while continuous outcome data were evaluated using mean differences (MD). Random effects model was used for each outcome. Meta-regression was performed in order to evaluate heterogeneity among studies and included the following covariates: year of publication, quality assessment and the journal’s impact factor. Sensitivity analyses were performed in order to evaluate whether eliminating influential studies affect the results. Studies that exceed Cook’s distance 1/n were found influential. Funnel plots were used to graphically examining small study effects as an asymmetrical funnel shape may indicate publication bias. Inconsistency among studies was evaluated by means of the I²-statistic. An I²-statistic of 25%, 50% and 75% were respectively defined as low, moderate and high inconsistency. We used Review Manager (RevMan) version 5.3 from the Cochrane Collaboration for analysis. Meta-regression was done in SPSS version 20.0 (IBM, NY, Armonk). Statistical significance was fixed at p < 0.05 (two-tailed).

Evidence synthesis

Study selection and characteristics

The search was performed on 31 January 2014. After excluding duplicates (N.=508), 586 studies were screened on the base of title/abstract. Based on the selection criteria, clinical criteria and studies that did use benzodiazepines as a premedication we excluded 497 articles. Fifty full articles were reviewed accordingly. However, three articles could not be retrieved. We excluded 31 studies based on methodological and clinical criteria. Ultimately, 19 Articles were eligible for systematic review/meta-analysis (Figure 1). Table I shows the study characteristics. The risk of bias of the included studies is shown in Appendix II. The risk of bias graph showing each risk of bias as percentages across all included studies is shown in Appendix III. Appendix IV shows the risk of bias scoring of the individual studies.

Somatic symptoms/complaints: time to recovery

Twelve studies were included in meta-analysis with 1445 patients altogether. Applying random effects model resulted into $\text{Tau}^2=2.78$, $\text{Chi}^2=69.73$, df=26, P<0.01, $I^2=63%$. Overall time to recovery was significantly delayed by benzodiazepines with 1.75 minutes (95% CI 0.82-2.69) (Figure 2A).

Time to eye opening was significantly delayed with 1.47 minutes by benzodiazepines (95% CI 0.51-2.42), but we could not find statistical significant differences regarding time to first correct response (P=0.06), time to early recovery (P=0.24) and time to discharge (P=0.39), Figure 2A. Sensitivity analyses did not provide new insights. None of the covariates could explain the heterogeneity among the studies for time to eye opening, early recovery and discharge. However, time to first correct re-
Figure 1.—Flow of information.

response (TCR) increased significantly in studies with a higher methodological quality (Appendix V). All funnel plots of these studies were not considered asymmetrical (Appendix VI).

In addition, Beechey et al., Hargreaves and Raybould et al. could not be subjected to meta-analyses but did report on time to recovery.\textsuperscript{17, 24, 29, 31} Beechey et al. found no difference in the time to awaken from anaesthesia.\textsuperscript{17, 31} Hargreaves found that awakening
**Table I.---Characteristics of included studies.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methods</th>
<th>Participants</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdul-Latif MS et al. (2001)</td>
<td>Randomised placebo controlled double-blind study</td>
<td>50 female patients undergoing day case breast surgery, aged 18-70 years</td>
<td>7.5 mg oral midazolam</td>
<td>Placebo</td>
<td>Somatic symptoms/complaints (time to recovery)</td>
<td>Source of funding not stated</td>
</tr>
<tr>
<td>Ahmed N et al. (1995)</td>
<td>Randomised placebo controlled double-blind study</td>
<td>50 mixed patients undergoing day-case surgery, aged 20-60 years</td>
<td>7.5 mg oral midazolam</td>
<td>Placebo</td>
<td>Somatic symptoms/complaints (time to recovery)</td>
<td>Source of funding not stated</td>
</tr>
<tr>
<td>Bailie R et al. (1989)</td>
<td>Randomised controlled trial</td>
<td>65 female patients undergoing day-case surgery, aged 16-75 years</td>
<td>20 mg oral temazepam</td>
<td>Identical placebo capsule</td>
<td>Somatic symptoms/complaints (time to recovery)</td>
<td>Financially supported by Cognitive Drug Research</td>
</tr>
<tr>
<td>Bauer KP et al. (2004)</td>
<td>Prospective randomised placebo-controlled study</td>
<td>88 mixed patients undergoing day-case surgery, aged 18-65 years</td>
<td>0.04 mg/kg intravenous midazolam</td>
<td>Intravenous saline</td>
<td>Somatic symptoms/complaints (time to recovery; postoperative side effects); Psychological (anxiety)</td>
<td>Source of funding not stated</td>
</tr>
<tr>
<td>Beechey APG et al. (1981)</td>
<td>Randomised placebo controlled double-blind study</td>
<td>60 mixed patients undergoing elective minor surgery as day cases, aged 18-70 years</td>
<td>10 mg oral temazepam</td>
<td>Identical placebo capsule</td>
<td>Somatic symptoms/complaints (time to recovery)</td>
<td>Source of funding not stated</td>
</tr>
<tr>
<td>Berendes E et al. (1996)</td>
<td>Randomised placebo-controlled double-blind study</td>
<td>85 female patients scheduled for breast biopsy</td>
<td>7.5 mg oral midazolam; 20 mg oral clorazepate dipotassium</td>
<td>Placebo</td>
<td>Psychological symptoms (anxiety, depression)</td>
<td>Source of funding not stated</td>
</tr>
<tr>
<td>De Witte JL et al. (2002)</td>
<td>Randomised placebo controlled double blinded study</td>
<td>45 female patients undergoing day-case surgery, aged 18-50 years</td>
<td>0.5 mg oral alprazolam; 7.5 mg oral midazolam</td>
<td>Oral placebo</td>
<td>Somatic symptoms/complaints (time to recovery; postoperative side effects)</td>
<td>Financially supported by NIH Grant GM 58273, the Joseph Drown Foundation, and the Commonwealth of Kentucky Research Challenge Trust Fund</td>
</tr>
<tr>
<td>Duggan M et al. (2002)</td>
<td>Randomised placebo controlled double-blinded study</td>
<td>61 mixed patients undergoing day-case surgery, aged 18-65 years</td>
<td>0.1 mg/kg oral diazepam, 60 min preoperatively; 0.1 mg/kg oral diazepam, 90 min preoperatively</td>
<td>Placebo</td>
<td>Psychological symptoms (anxiety)</td>
<td>Source of funding not stated</td>
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<tr>
<td>Forrest P et al. (1987)</td>
<td>Randomised placebo controlled study</td>
<td>120 mixed patients undergoing day-case surgery; aged 20-60 years</td>
<td>0.25 mg oral triazolam; 15 mg oral midazolam; 10 mg oral diazepam</td>
<td>Oral placebo</td>
<td>Somatic symptoms/complaints (time to recovery)</td>
<td>Sources of funding not stated</td>
</tr>
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<td>Fredman B et al. (1999)</td>
<td>Randomised placebo-controlled double-blinded study</td>
<td>90 patients undergoing brief procedures, aged 65-81 years</td>
<td>0.5 mg intravenous saline</td>
<td>Equal volume intravenous saline</td>
<td>Somatic symptoms/complaints (time to recovery)</td>
<td>Source of funding not stated</td>
</tr>
<tr>
<td>Greenwood BK et al. (1983)</td>
<td>Randomised placebo-controlled double-blinded study</td>
<td>72 mixed patients undergoing day-case surgery, aged 16-65 years</td>
<td>20 mg oral temazepam; 30 mg oral oxazepam</td>
<td>Placebo</td>
<td>Somatic symptoms/complaints (time to recovery)</td>
<td>Source of funding not stated</td>
</tr>
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</table>

*(to be continued)*
Table I.— Characteristics of included studies (continues).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methods</th>
<th>Participants</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Hargreaves J et al. (1988)  
24 | Double-blinded study                  | 90 mixed patients       | 15 mg oral midazolam; 20 mg oral temazepam       | Identical placebo | Somatic symptoms/complaints (time to recovery)   | Roche Products supplied the double-blind randomized premedications |
| Kain ZN et al. (2000)  
25 | Randomised placebo-controlled double-blinded study | 55 mixed patients undergoing day-case surgery, aged 18-60 years | 5 mg intramuscular midazolam                     | Intramuscular saline | Somatic symptoms/complaints (time to recovery; postoperative side effects); Psychological (anxiety) | Financially partly supported by a grant from the National institutes of Helat, Bethesda, Maryland, Roche Pharmaceuticals, Nutly, New Jersey, and the Patrick and Catherine Weldon Donaghue Medical Research Foundation, hartford, CT (Dr. Kain) |
| Loach A et al. (1975)  
26 | Randomised placebo-controlled double-blinded study | 22 female patients undergoing day-case surgery, aged 21-64 years | 1 mg oral lorazepam                             | Placebo          | Somatic symptoms/complaints (postoperative side effects) | Source of funding not stated |
| Mijde Rijk H et al. (2013)  
7 | Randomised placebo-controlled double-blinded study | 398 mixed patients undergoing day-case surgery, aged at least 18 years | 1 to 1.5 mL intravenous lorazepam               | 1 to 1.5 mL intravenous saline | Psychological (anxiety, depression, fatigue, aggression) | Financial support was provided by the Department of Anaesthesiology, Erasmus University Medical Centre |
| Oxorn DC et al. (1997)  
27 | Randomised placebo-controlled double-blinded study | 60 female patients undergoing day-case surgery, aged >19 years | 0.03 mL/kg intravenous saline                   | Somatic symptoms/complaints (time to recovery; Psychological (anxiety, depression, aggression) | Financial support was provided by a grant from Roche Pharmaceuticals and the First International Anesthesia Research Society Frontiers in Anesthesia Award |
| Raeder JC et al. (1987)  
28 | Randomised placebo-controlled double-blinded study | 193 female patients undergoing day-case surgery | 0.1 mg/kg intramuscular midazolam; 0.8 to 1 mL intramuscular Mo-Scop (i.e. morphine 10 mg/mL and scopolamine 0.4 mg/mL) | 0.8 to 1.0 mL intramuscular saline | Somatic symptoms/complaints (postoperative side effects) | Source of funding not stated |
| Raybould D et al. (1987)  
29 | Randomised placebo-controlled double-blinded study | 60 mixed patients undergoing day-case surgery; aged 16-65 years | 7.5 mg oral midazolam; 15 mg oral midazolam     | Placebo          | Somatic symptoms/complaints (time to recovery) | Source of funding not stated |
| Shafer A et al. (1989)  
30 | Randomised placebo-controlled double-blinded study | 150 mixed patients undergoing day-case surgery, aged 15-41 years | 5 mg (1 mL) intramuscular midazolam; 1 mg (2 mL) intravenous oxymorphone; 100 ug (2 mL) | 1 mL intramuscular saline; 2 mL intravenous saline | Somatic symptoms/complaints (time to recovery; postoperative side effects) | Source of funding not stated |

from anaesthesia was significantly longer in the midazolam group compared to placebo and temazepam groups. Raybould et al. showed that the group receiving a benzodiazepine did not show significantly longer recovery times.

Somatic symptoms/complaints: postoperative side effects

Seven studies were included in meta-analysis with 1530 patients altogether.
sults of random effects model yielded $\tau^2=0.00$, $\text{Chi}^2=19.25$, $df=24$, $P=0.74$, $I^2=0\%$. Overall postoperative side effects occurred significantly less in patients treated with benzodiazepines (OR $0.47$, $95\%\ CI$ $0.36-0.63$) (Figure 2B, C).

Nausea (OR $0.34$, $95\%\ CI$ $0.21-0.55$) and headache (OR $0.44$, $95\%\ CI$ $0.25-0.78$) occurred significantly less in the patients treated with benzodiazepines. However, we could not find statistical significant differences regarding vomiting ($P=0.08$), dizziness ($P=0.68$) and the miscellaneous group ($P=0.21$). Categorical data regarding pain showed no statistical significant difference ($P=0.86$) as well as pain scored on a continuous scale ($P=0.55$).

In addition, de Witte et al., Hargreaves and Kain et al. could not be subjected to meta-analyze but did report postoperative side effects.$^{19, 24, 25}$ De Witte et al. found no statistical difference in the incidence of nausea or vomiting and other side effects including dizziness and headache.$^{19}$ Hargreaves found no statistical difference in the incidence of minor side effects.$^{24}$ However, nausea was found in 8 patients receiving temazepam, which was statistically significant when compared to the placebo group. Kain et al. found no significant difference regarding a postoperative pain score (Visual Analogue Scale [VAS] >30) on discharge form the Post Anaesthesia Care Unit (PACU).$^{25}$ Furthermore, undefined adverse effects were not significantly different in PACU.

Sensitivity analysis and meta-regression did not provide new insights (Appendix V). Funnel plot for dizziness was asymmetrical suggesting publication bias; the other funnel plots were considered symmetrical (Appendix VII).

**Psychological outcomes**

A total of 4 studies assessing anxiety were included in meta-analysis with 653 patients.$^{7, 25, 27, 30}$ Random effects model yielded $\tau^2=3.96$, $\text{Chi}^2=15.33$, $df=3$, $P<0.01$, $I^2=80\%$. Anxiety was not significantly affected (mean difference $1.47$, $95\%\ CI$ $1.01-3.96$) (Figure 2D).

Ahmed et al., Bauer et al., Berendes et al., de Witte et al., Duggan et al. and Fredman et al. could not be subjected to meta-analysis but did report on anxiety.$^{14, 16, 18-20, 22}$ Ahmed et al. found no significant difference in patient’s anxiety levels.$^{14}$ Bauer et al. did not found statistical significant difference in patient’s anxiety levels in PACU and at discharge from PACU.$^{16}$ Berendes et al. found that clorazepate dipotassium had significant lower anxiety scores compared to placebo.$^{18}$ No significant difference was found between midazolam and placebo. De Witte et al. found that all patients in the midazolam group reported a sufficient quality of anxiety reduction; 2 patients in the alprazolam group reported insufficient anxiety reduction and 1 patient did not know; 7 patients in the placebo group reported insufficient anxiety reduction and 3 patient did not know, which was statistically significant among groups.$^{19}$ Duggan et al. found no significant difference in anxiety scores (VAS and State part of the State-Trait Anxiety Inventory [STAI-State]) at discharge.$^{20}$ Fredman et al. found that anxiety scores were unaffected during PACU admission.$^{22}$

The studies by Kain et al. and Mijderwijk et al. measured anxiety beyond the first postoperative day.$^{7, 25}$ Kain et al. found a significant greater reduction in anxiety in the benzodiazepine group compared with placebo from 2-30 days after surgery.$^{25}$ Mijderwijk et al., on the seventh day after surgery, found significant greater reduction in anxiety measured by means of the Trait part of the State-Trait Anxiety Inventory (STAI-Trait) and by means of the Hospital Anxiety and Depression Scale (HADS) in the placebo group, although no significant result was found regarding STAI-state.$^{7}$

None of the covariates enabled explaining heterogeneity among the studies (Appendix V). Sensitivity analyses did not provide new insights. The funnel plot was not considered asymmetrical (Appendix VIII).

Only the studies by Mijderwijk et al. and Oxorn et al. have reported about depression, fatigue and aggression.$^{7, 27}$ Oxorn et al. have reported results up to first postoperative day.$^{27}$ They found no significant differences on depression and aggression while Mijderwijk et al. measured these outcomes beyond the first postoperative day.$^{7}$ Although no significant
Discussion

Principal finding

The principal finding of this systematic review with meta-analysis is that overall benzodiazepines did unfavorably affect time to recovery, did reduce the incidence of postoperative side effects but they did not statistically significantly affect psychological outcomes. These findings will be discussed in further detail below.

Time to recovery

The overall test of significance showed that time to recovery is significantly prolonged in patients administered benzodiazepines preoperatively. However, only time to eye opening is significantly prolonged by 1.47 minutes in the benzodiazepine group. Time to early recovery and time to discharge were not affected by benzodiazepines. Although not statistically significant, benzodiazepines tend to prolong TCR. The articles that could not be subjected to meta-analysis are considered to have no influence.

Considering all this, we agree with (some) anesthetists that recovery time is prolonged by benzodiazepines but only at the first stage of recovery. Time to early recovery and time to discharge are clearly not affected by benzodiazepine premedication which is in line with a previous review. Therefore, withholding benzodiazepine premedication for reasons of delayed discharge time seems not justified in day-case surgery.

Postoperative side effects

The overall test of significance showed that premedication with benzodiazepines significantly reduced the incidence of postoperative side effects with 53%. When looking into further detail, benzodiazepine premedication clearly reduce the risk of postoperative headache (56%) and nausea (66%), and show a tendency to reduce the risk of vomiting. The risk of postoperative dizziness, pain and miscellaneous side effects was not statistically significantly affected by benzodiazepines. The articles not meeting the standards for this meta-analysis are considered to have no influence.

Psychological phenomena

We were able to perform meta-analysis for anxiety, showing no statistical significant differences between benzodiazepine or placebo groups. With regards to the other psychological outcomes (i.e. depression, aggression and fatigue), meta-analysis could not be performed at all as they did not meet the eligibility criteria with regards to the time span. Therefore, the effects of premedication with benzodiazepines on psychological phenomena remain inconclusive. Given the shift towards psychological outcome in day-case surgery, we need more research on this topic. This should also be studied beyond the first postoperative day as recommend by others. Furthermore, we need more research on interventions in the preoperative period that could beneficially affect the postoperative period.

Methodological strengths and weaknesses

The rationale for our extensive literature search was to get a solid understanding of the
Figure 2.—A) Forest plot for time to recovery; B, C) Forest plot for postoperative side effects. Regarding Raeder JC et al., postoperative N. was determined proportionally and data regarding “nausea at home” was ignored as this data is likely correlated with “nausea at recovery”; D) Forest plot for psychological phenomena (anxiety).13-30

effects of benzodiazepine premedication in day-case surgery patients regarding somatic symptoms/complaints and psychological phenomena emerging in the postoperative period. By doing so, we minimized the risk of selection bias too. As a consequence, we had to evalu-

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ate many studies for eligibility. Selection bias was also minimized by not excluding studies based on their quality assessment. We tried to minimize language bias by including articles not only written in English but also in German and France, when appropriate. This strategy
seems justified as we included an article written in German. However, potential language bias could not be ruled out. We were able to check the possible influence of the year of publication on the outcomes, as we did not have year of publication restrictions in our literature search. We used a pre-set standardized form for data-extraction and management. Risk of bias tables were used to evaluate the quality of each study, which was done by two authors individually. Discrepancies were resolved by consensus. Meta-regression was performed on each outcome individually. Meta-regression was not always possible as numerical data was not always clearly provided or not provided. To deal with this, we systematically described the results of the outcomes of these studies.

Random effects model was performed for each meta-analysis when heterogeneity was present. For consistency’s sake, we also performed random effects model when heterogeneity was statistically not significant. Another justification for this analysis strategy is that judgements for heterogeneity in meta-analysis can be misleading when the number of included patients is insufficient. Thus we possibly could have under-estimated heterogeneity and therefore we have applied random effects model even when heterogeneity was statistically insignificant.

The fact that heterogeneity is predominantly present in time to recovery and psychological phenomena while heterogeneity is nearly present in postoperative side effects suggests that the assessment sources may be different. With regards to time to recovery, in the majority of the studies it is unclear who actually measured time to recovery. However, in the study by De Witte et al. study nurses observed the patients in the recovery room. Likely, although not specifically stated, they assessed time to early recovery. Accordingly, interjudgement unreliability bias may have emerged and this could be the reason for the wide confidence intervals of this particular study. On the other hand, intrajudgement unreliability may have played a role when, for example, the pre-set definitions for specific time to recovery were not clear. Furthermore, next to these within study variation, in between study heterogeneity is possibly caused by intra- and/or interjudgement bias. Physicians, nurses or investigators may have alternately assessed time to recovery in patients, which is likely to induce bias.

The moderate inconsistency regarding dizziness can be caused by the vague definition of dizziness interpreted by patients. However, it was previously shown that heterogeneity might also be due to publication bias (i.e. small studies with expressive results are likely to be published) and in the case of dizziness publication bias has emerged.

Heterogeneity can also be present due to conceptual concerns, especially in case of psychological outcomes. For example, anxiety itself can be considerably heterogeneous and reasons for heterogeneity can be difficult to clarify. Furthermore, heterogeneity among studies may always be due to change.

In this study, we have focussed on a homogeneous group of drugs used for premedication. As a consequence, we were able to perform meta-analysis and could draw conclusions from our results accordingly. Such a statistical synthesis was previously not feasible due to too many different premedication drugs. A total of eight different benzodiazepines, three different administration routes and different times of administration were nonetheless present in our meta-analysis. Unfortunately, it was methodologically statistically not feasible to evaluate this possible heterogeneity in our meta-regression. However, administration of benzodiazepines is characterized by high efficacy despite differences in route of administration and pharmacological properties.

Conclusions

This systematic review with meta-analysis provides new evidence for beneficial effects of premedication with benzodiazepines in day-case surgery. Benzodiazepine premedication does prolong time to recovery but only at the first stage of postoperative recovery – time to discharge is not affected. Furthermore, ben-
zidazepines seem to reduce the incidence of postoperative side effects with 53%. However, effects on psychological outcomes remain inconclusive. It is recommended that future studies should also focus on other postoperative side effects, and on psychological phenomena.

Key messages

— Witholding benzodiazepine premedication for reasons of delayed discharge time is not justified in day-case surgery.
— Premedication with benzodiazepines reduces postoperative side effects with 53%.
— In day-case surgery, more research on postoperative psychological sequelae is needed.

References

5. Bellani ML. Psychological aspects in day-case surgery.
33. Mattila K, Toivonen J, Janhunen L, Rosenberg PH,

Authors’ contributions.—Herjan Mijderwijk, Robert J. Stolker and Hugo J. Duivenvoorden conception and design; Herjan Mijderwijk, Stefan Van Beek, and Robert J. Stolker: data collection and extraction. Herjan Mijderwijk, Stefan Van Beek, Hugo J. Duivenvoorden and Robert J. Stolker: data analysis. Herjan Mijderwijk, Stefan Van Beek and Robert J. Stolker: interpretation of data; drafting of the manuscript and revising it critically for important intellectual content; final approval of the manuscript submitted.

Funding.—This work was supported by the Department of Anaesthesiology, Erasmus University Medical Centre, Rotterdam, The Netherlands.

Acknowledgements.—We thank Wichor M. Bramer, information specialist at Erasmus MC, for performing the literature search.

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


Appendix I.—Complete literature search, 31 January 2014.

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<thead>
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<th>Database</th>
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Embase
(‘ambulatory surgery’/de OR (((ambul* OR day OR daycare OR outpatient* OR office*) NEAR/3 (surg* OR operati*)))/ab,ti) AND (‘psychological aspect’/de OR psychology/exp OR emotion/exp OR depression/exp OR fatigue/de OR exhaustion/de OR stress/exp OR ‘adaptive behavior’/de OR ‘surgical stress’/de OR (psycholog* OR emotion* OR anxiet* OR fatigue OR exhaust* OR depress* OR OR perception* OR (somatic NEAR/3 (symptom* OR complain*)))/ab,ti) AND (mental OR preoperat* OR postoperat* OR perioperat* OR operative* OR surg*) NEXT/1 stress OR (adapt* NEAR/3 behavio*) OR coping)/ab,ti) AND (adult/exp OR ‘middle aged’/de OR aged/exp OR (adult* OR aged)/ab,ti) AND (premedication/de OR benzodiazepine/de OR ‘anesthetic agent’/exp OR ‘antidepressant agent’/exp OR ‘tranquilizer’/exp OR (premedicat* OR pretreatment* OR (pre NEXT/1 (medicat* OR treatment*)) OR preanesthet*/ preanaesthet* OR anaesthetic* OR anesthetic* OR ((anxiert* OR antianxiert* OR ataract*) NEAR/3 (agent* OR drug*))/ab,ti) AND (random* OR factorial* OR crossover* OR (cross NEXT/1 over*) OR placebo*/ OR ((doubl* OR singl*) NEXT/1 blind*) OR assign* OR (allocat* OR (volunteer*)/ab,ti) AND (crossover procedure/de OR ‘double-blind procedure’/de OR ‘randomized controlled trial’/de OR ‘single-blind procedure’/de) NOT ([animals]/lim NOT [humans]/lim)

Medline OvidSP
(‘ambulatory Surgical Procedures’/ OR (((ambul* OR day OR daycare OR outpatient* OR office*) ADJ3 (surg* OR operati*)))/ab,ti) AND (exp psychology/ OR psychology.xs OR exp emotions/ OR depression/ OR exp fatigue/ OR ‘Stress, Psychological’/ OR ‘Adaptation, Psychological’/ OR ‘surgical stress’/ OR ‘psycholog* OR emotion* OR anxiet* OR fatigue OR exhaust* OR depress* OR perception* OR (somatic ADJ3 (symptom* OR complain*)))/ab,ti) AND (mental OR preoperat* OR postoperat* OR perioperat* OR operative* OR surg*) ADJ3 (stress OR (adapt* ADJ3 behavio*) OR coping)/ab,ti) AND (exp adult/ OR (adult* OR aged)/ab,ti) AND (premedication/ OR...
"Preanesthetic Medication"/ OR exp benzodiazepines/ OR exp "anesthetics"/ OR exp "antidepressive agents"/ OR exp "Tranquilizing Agents"/ OR (premedicat* OR pretreatment* OR (pre ADJ (medicat* OR treatment*)) OR preaneste* OR preanaesthesia* OR premedicat* OR pretreatment* OR preanesthet* OR preanaesthetic* OR anesthetic* OR ((anxiet* OR antianxiet* OR ataract*) ADJ3 (agent* OR drug*)) OR benzodiazepine* OR anxiolytic* OR tranquil* OR antidepress*).ab,ti.) AND (Clinical Trial.pt. OR randomized.ab,ti. OR placebo.ab,ti. OR dt.fs. OR randomly.ab,ti. OR trial.ab,ti. OR groups.ab,ti. NOT (Animals/ NOT Humans/))

**Cochrane**

(((ambul* OR day OR day care OR daycare OR day case OR outpatient* OR office*) NEAR/3 (surg* OR operat*))).ab,ti) AND (psycholog* OR emotion* OR anxiet* OR fatigue OR exhaust* OR depress* OR perception* OR (somatic NEAR/3 symptom* OR complai*)) OR (mental OR preoperat* OR postoperat* OR perioperat* OR operative* OR surg*) NEXT/1 stress) OR (adapt* NEAR/3 behavio*) OR coping).ab,ti) AND ((adult* OR aged).ab,ti) AND ((premedicat* OR pretreatment* OR (pre NEXT/1 (medicat* OR treatment*)) OR preanesthet* OR preanesthesia* OR anaesthetic* OR anesthetic* OR ((anxiet* OR antianxiet* OR ataract*) NEAR/3 (agent* OR drug*)) OR benzodiazepine* OR anxiolytic* OR tranquil* OR antidepress*).ab,ti)

**Web-of-science**

TS=(((((ambul* OR day OR day care OR daycare OR day case OR outpatient* OR office*) NEAR/3 (surg* OR operat*))).ab,ti)) AND (psycholog* OR emotion* OR anxiet* OR fatigue OR exhaust* OR depress* OR perception* OR (somatic NEAR/3 symptom* OR complai*)) OR (mental OR preoperat* OR postoperat* OR perioperat* OR operative* OR surg*) NEXT/1 stress) OR (adapt* NEAR/3 behavio*) OR coping).ab,ti) AND ((adult* OR aged).ab,ti) AND ((premedicat* OR pretreatment* OR (pre NEXT/1 (medicat* OR treatment*)) OR preanesthet* OR preanesthesia* OR anaesthetic* OR anesthetic* OR ((anxiet* OR antianxiet* OR ataract*) NEAR/3 (agent* OR drug*)) OR benzodiazepine* OR anxiolytic* OR tranquil* OR antidepress*).ab,ti) AND (random* OR factorial* OR crossover* OR (cross NEAR/1 over*).ab,ti) OR placebo* OR ((doubl* OR singl*) W/1 blind*).ab,ti) OR assign* OR allocat* OR volunteer*))

**Scopus**

TITLE-ABS-KEY(((ambul* OR day OR day care OR daycare OR day case OR outpatient* OR office*) W/3 (surg* OR operat*))).ab,ti)) AND (psycholog* OR emotion* OR anxiet* OR fatigue OR exhaust* OR depress* OR perception* OR (somatic W/3 symptom*) OR complai*) OR (mental OR preoperat* OR postoperat* OR perioperat* OR operative* OR surg*) PRE/1 stress) OR (adapt* W/3 behavio*) OR coping).ab,ti) AND ((adult* OR aged).ab,ti) AND ((premedicat* OR pretreatment* OR (pre PRE/1 (medicat* OR treatment*))) OR preanesthet* OR preanesthesia* OR anaesthetic* OR anesthetic* OR ((anxiet* OR antianxiet* OR ataract*) W/3 (agent* OR drug*).ab,ti)) OR benzodiazepine* OR anxiolytic* OR tranquil* OR antidepress*).ab,ti) AND (random* OR factorial* OR crossover* OR (cross W/1 over*).ab,ti) OR placebo* OR ((doubl* OR singl*) W/1 blind*).ab,ti) OR assign* OR allocat* OR volunteer*)))

**PubMed publisher**


**Google Scholar**

"ambulatory/day/daycare surgery/operation" psychological/psychology/emotions/depression/fatigue/exhaustion/stress/coping/anxiety premedication/benzodiazepine/tranquilizer/anxiolytic/antidepressant random/randomized/randomized/clinical/clinical trial/placebo/group
### Appendix II.—Risk of bias table – authors' judgement

<table>
<thead>
<tr>
<th>Reference</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdul-Latif MS et al.(^{13}) Support for judgement</td>
<td>Unclear risk Comment: not reported whether random sequence generation was performed.</td>
<td>Unclear risk Comment: not reported whether allocation concealment was achieved.</td>
<td>Low risk Comment: Anaesthetists were blinded as well as the patients.</td>
</tr>
<tr>
<td>Ahmed N et al.(^{14}) Support for judgement</td>
<td>Unclear risk Quote: “...patients were randomly allocated to receive either Midazolam 7.5 mg or a placebo...” Comment: insufficient information about the sequence generation process.</td>
<td>Unclear risk Comment: not reported whether allocation concealment was achieved.</td>
<td>Low risk Quote: “The study was done in a double blind manner:”</td>
</tr>
<tr>
<td>Bailie R et al.(^{15}) Support for judgement</td>
<td>High risk Quote: “The hospital pharmacist, who was not involved in the study, had previously allocated them to one of two groups.” However: “Because of a delay in obtaining matched placebo capsules, the first 26 patients of 65 patients were allocated to group 1.”</td>
<td>Low risk Quote: “...was unknown to the researcher undertaking the cognitive assessments and to those conducting initial evaluation of data.”</td>
<td>Low risk Quote: “All testing and initial evaluation of data was conducted double-blind.”</td>
</tr>
<tr>
<td>Bauer KP et al.(^{16}) Support for judgement</td>
<td>Unclear risk Comment: not reported whether random sequence generation was performed.</td>
<td>Low risk Quote: “Study syringes were prepared by the pharmacy. Patients, anesthesiologists, and investigators were blinded to the contents of each syringe until the study was completed.”</td>
<td>Low risk Quote: “Patients, anesthesiologists, and investigators were blinded to the contents of each syringe until the study was completed.”</td>
</tr>
<tr>
<td>Beechey APG et al.(^{17}) Support for judgement</td>
<td>Unclear risk Quote: “The patients, who gave informed consent, were randomly allocated into two groups...” Comment: insufficient information about the sequence generation process.</td>
<td>Unclear risk Comment: not reported how allocation concealment was achieved.</td>
<td>Low risk Quote: “A double-blind trial was therefore undertaken...” “...placebo capsules of identical appearance were used...”</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Incomplete outcome data (attrition bias)</td>
<td>Selective reporting (reporting bias)</td>
<td>Other bias</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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</tr>
<tr>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Comment: not reported whether time to recovery was blindly assessed.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>Quote: “The anaesthetist involved in recording observations was unaware of the patient grouping.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>Comment: 9 patients are excluded from the analyses. Reasons for the exclusions are not given. Furthermore, it is likely that these missings all belong to the placebo group, and, consequently, imbalancedness is likely to emerge.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>Quote: “Six patients in the placebo group were withdrawn. Four patients in the temazepam group were withdrawn. Comment: Imbalancedness emerged: &gt;20% withdrawn from the placebo group versus 10% withdrawn. Furthermore, investigators themselves have withdrawn the patients.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear risk</td>
<td>Low risk</td>
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<tr>
<td>High risk</td>
<td>Quote: “Patients, anesthesiologists, and investigators were blinded to the contents of each syringe until the study was completed.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>Quote: “…a total of 118 patients signed a consent form. Of that number, 13 patient were withdrawn from data analysis for protocol violations, and 17 patients were withdrawn from data analysis because of missing data.”</td>
<td></td>
<td></td>
</tr>
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<td>Unclear risk</td>
<td>Low risk</td>
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<td>Unclear risk</td>
</tr>
<tr>
<td>Comment: not reported whether blinding of outcome assessment was achieved.</td>
<td>Low risk</td>
<td>Comment: no missing outcome data.</td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>Comment: no missing outcome data.</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Comment: unclear if blinding of outcome assessment was achieved.</td>
<td>Low risk</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
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<td>Unclear risk</td>
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</tr>
<tr>
<td>Comment: no other sources of bias identified.</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
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<tr>
<td>Unclear risk</td>
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<td>De Witte JL et al.19</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td></td>
<td>Quote: “...patients were randomly assigned to receive...” Comment: insufficient information about the sequence generation process.</td>
<td>Comment: not reported how allocation concealment was achieved.</td>
<td>Quote: “...outpatients participated in a double-blinded study...” Comment: the commercially available drug tablets were placed in opaque capsules filled with an inactive powder.</td>
</tr>
<tr>
<td>Duggan M et al.20</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td></td>
<td>Quote: “Randomization was performed using a random numbers table.”</td>
<td>Quote: “Randomization was performed using a random numbers table by the research division, pharmacy, Beaumont Hospital.” Comment: central allocation.</td>
<td>Quote: “We conducted a double-blind, randomized study...” Comment: Group III received a placebo.</td>
</tr>
<tr>
<td>Forrest P et al.21</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td></td>
<td>Quote: “…patients were randomly allocated to receive...one of four oral premedicants from coded envelopes...” Comment: insufficient information about the sequence generation process.</td>
<td>Comment: not reported how allocation concealment was achieved.</td>
<td>Quote: “Patients were randomly allocated to receive, in a double-blind manner...”</td>
</tr>
<tr>
<td>Fredman B et al.22</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td></td>
<td>Quote: “computer-generated randomization table.”</td>
<td>Comment: not reported how allocation concealment was achieved.</td>
<td>Quote: “90 geriatric patients were enrolled in to this... double-blinded study.”</td>
</tr>
<tr>
<td>Greenwood BK et al.23</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td></td>
<td>Quote: “…the patients were randomly allocated to one of the three groups...” Comment: insufficient information about the sequence generation process.</td>
<td>Comment: not reported how allocation concealment was achieved.</td>
<td>Quote: “A double-blind between-patient trial was designed...” Comment: “All patients received a similar soft gelatin capsule...”</td>
</tr>
<tr>
<td>Hargreaves J et al.24</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
</tr>
<tr>
<td></td>
<td>Quote: “The author wishes to thank Rocke Products for supplying the double-blind randomized premedication...” Comment: not reported whether random sequence generation was achieved.</td>
<td>Comment: not reported how allocation concealment was achieved.</td>
<td>Quote: “Ninety patients...were allocated to three groups in a double-blind study...” Comment: “This comprised an active and a dummy preparation for the two study groups and a dummy preparation for the placebo group.”</td>
</tr>
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<td>Unclear risk</td>
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<td>Unclear risk</td>
</tr>
<tr>
<td>Comment: not reported</td>
<td>Comment: no missing outcome data.</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
<td></td>
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</tr>
<tr>
<td>Comment: not reported</td>
<td>Quote: “One patient was excluded as she required admission to the hospital overnight.” Comment: this missing data was judged to have no clinical impact.</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
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<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Comment: not reported</td>
<td>Comment: no missing outcome data relative to time to recovery. However, some missing data in other parts of the study; unclear if this leads to risk of bias.</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
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<td>whether blinding of outcome assessment was achieved.</td>
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<tr>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Quote: “...a “blinded” coinvestigator continuously monitored the patient’s.” “PACU staff was unaware of patient enrolment.” Comment: this missing is judged to have no clinical impact.</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
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</thead>
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<td>Kain ZN et al.\textsuperscript{25}</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Support for judgement</strong></td>
<td><strong>Quote:</strong> “Randomization was performed according to a computer-generated list created from a random numbers table.”</td>
<td><strong>Quote:</strong> “Blinding an randomization were handled by Yale-New Haven Hospital’s investigational pharmacy.”</td>
<td><strong>Quote:</strong> “Blinding an randomization were handled by Yale-New Haven Hospital’s investigational pharmacy, an no other individuals (e.g. anesthesiologists, surgeons, investigators) were informed of the particular treatment group of which a particular subject was assigned.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Comment:</strong> central allocation.</td>
<td><strong>Comment:</strong> central allocation.</td>
</tr>
<tr>
<td>Loach A et al.\textsuperscript{26}</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Support for judgement</strong></td>
<td><strong>Quote:</strong> “The allocation was made on the basis of numbers from random tables.”</td>
<td><strong>Quote:</strong> “The allocation was made on the basis of numbers from random tables, and the code held by the Ward Sister.”</td>
<td><strong>Quote:</strong> “A randomised double blind trial was carried out.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Comment:</strong> Although the code was held by the Ward Sister, it is unclear who enrolled the patients in the study. Furthermore, it is likely that no appropriate safeguards are taken.</td>
<td><strong>Comment:</strong> Likely that patients were blinded too.</td>
</tr>
<tr>
<td>Mijderwijk H et al.\textsuperscript{2}</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Support for judgement</strong></td>
<td><strong>Quote:</strong> “Randomisation was done by a computer-generated table.”</td>
<td><strong>Quote:</strong> “Randomisation was done by a computer-generated table, and patients were assigned subsequent numbers upon inclusion. Nurses who were not further involved in the care of these patients prepared the study medication according to the randomisation table.”</td>
<td><strong>Quote:</strong> “The study was double blinded; the researchers, patients and all healthcare professionals involved in patient care were blinded to the treatment allocation.”</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Comment:</strong> central allocation.</td>
<td><strong>Comment:</strong> central allocation.</td>
</tr>
<tr>
<td>Oxorn DC et al.\textsuperscript{27}</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td><strong>Support for judgement</strong></td>
<td><strong>Quote:</strong> “On enrolment, patients were randomly allocated.”</td>
<td><strong>Quote:</strong> “Sixty sealed envelopes were prepared.”</td>
<td><strong>Quote:</strong> “A syringe labelled study drug was prepared on the day of surgery by an anesthesiologist not involved with the conduct of the anesthetic. The anesthesiologist administering anesthesia was blinded to the patients group.”</td>
</tr>
</tbody>
</table>

Comment: insufficient information about the sequence generation process.
<table>
<thead>
<tr>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
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</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Quote: “...no other individuals (e.g. anesthesiologists, surgeons, investigators) were informed of the particular treatment group of which a particular subject was assigned.”</td>
<td>Quote: “Six subjects were excluded from the final sample because of noncompliance of the anesthesia staff to the study protocol. These subjects were excluded on the day of surgery, and no data were obtained regarding their postoperative course.” Comment: unclear to which treatment group these patients belong; unbalancedness likely. Furthermore, no specific reasons for exclusion provided.</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
<td>Comment: no other sources of bias identified.</td>
</tr>
<tr>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Comment: not reported whether blinding outcome assessment was achieved.</td>
<td>Comment: no missing outcome data on the outcome of interest for this review. From two patients, however, blood samples could not be obtained and these patients were missing on some other outcomes.</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
<td>Comment: no other sources of bias identified.</td>
</tr>
<tr>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Comment: as ‘blinding of participants and personnel.’</td>
<td>Quote: “An Intention-to-treat analysis was applied.” “14 patients from the lorazepam group and six patients from the NaCl 0.9% group were lost to follow-up for at least one of the measurement points. This difference was not significant.” Comment: reasons for lost-to-follow up clearly described; no imbalancedness detected.</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
<td>Comment: no other sources of bias identified.</td>
</tr>
<tr>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Quote: “The patient’s responses were assessed by the same nurse who was blind to the patient’s treatment group.”</td>
<td>Comment: no missing outcome data for our outcomes of interest. Furthermore, 4 missing data detected which was balanced over the treatment groups.</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
<td>Comment: no other sources of bias identified.</td>
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<td>Raeder JC et al.28</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Support for judgement</td>
<td>Quote: “The patients were then randomly allocated to one of the three groups” Comment: insufficient information about the sequence generation process.</td>
<td>Quote: not reported how allocation concealment was achieved.</td>
<td>Quote: “The patients did not know which premedicant they received. Mo-Scop or placebo were given double-blind from coded ampoules.”</td>
</tr>
<tr>
<td>Raybould D et al.29</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td></td>
</tr>
<tr>
<td>Support for judgement</td>
<td>Quote: “...they were allocated at random to one of three groups.” Comment: insufficient information about the sequence generation process.</td>
<td>Quote: not reported how allocation concealment was achieved.</td>
<td>Quote: “A double-blind, between-patient trial was designed.” “All patients received a gelatin capsule with up to 20ml of water.”</td>
</tr>
<tr>
<td>Shafer A et al.30</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
</tr>
<tr>
<td>Support for judgement</td>
<td>Quote: “Patients were randomly assigned using a computer-generated random number list.”</td>
<td>Quote: “Only the pharmacist who prepared the study-drug vials knew to which group a patient was assigned.” Comment: central allocation.</td>
<td>Quote: “Only the pharmacist who prepared the study-drug vials knew to which group a patient was assigned.” “...all study drugs were administered in a double-blinded manner.”</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Incomplete outcome data (attrition bias)</td>
<td>Selective reporting (reporting bias)</td>
<td>Other bias</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------------------------------------------</td>
<td>-------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Comment: the outcome relevant for this review was based on patient's self-assessment. However, outcomes reported that were not relevant for this review were assessed by health care professionals. It remains unclear if those were blinded.</td>
<td>Comment: 186 of 193 patients did not complete postoperative questionnaire. Reasons for these missing data are not provided. However, these missings are judged to have no clinical impact.</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
<td>Comment: no other sources of bias identified.</td>
</tr>
<tr>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Quote: “The observer was trained, was the same throughout and was unaware of the medication given.”</td>
<td>Quote: “Several patients had to be withdrawn from the study because of problems in the timing of operation or because more major surgery was indicated.” Comment: 7 patients had to be withdrawn, which was judged to satisfactory balanced over the treatment groups (placebo versus active). This was judged to have no clinical impact.</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
<td>Comment: no other sources of bias identified.</td>
</tr>
<tr>
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<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Quote: “A blinded observer noted the incidence of coughing, and assessed overall difficulties during the induction and maintenance phases of anesthesia.” Comment: outcome relative to this review are assessed by patient’s self-assessment.</td>
<td>Quote: “Overall, an 89% response rate was obtained on the follow-up questionnaires.” Comment: Although no reasons for these missing are provided, these missings are judged to have no clinical impact.</td>
<td>Comment: all outcomes are reported as dictated by the study protocol as written in the Methods section.</td>
<td>Comment: no other sources of bias identified.</td>
</tr>
</tbody>
</table>
Appendix III.—Summary risk of bias graph.

Appendix IV.—Individual risk of bias scores.
Appendix V.—*Meta-regression.*

<table>
<thead>
<tr>
<th>Covariate</th>
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<td>Postoperative side effects</td>
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</table>

B=regression coefficient; CI=confidence interval; TCR=time to first correct response; Na=not applicable.
Appendix VI.—Funnel plots for time to recovery.

- Time to eye opening.
- Time to first correct response.
- Time to early recovery.
- Time to discharge.

Appendix VIII.—Funnel plots for time to recovery.

- Headache.
- Nausea.
EFFECTIVENESS OF BENZODIAZEPINE PREMEDICATION

MIJDERWIJK

Vomiting.

Dizziness.

Pain.

Pain, continuous.

Miscellaneous.
Appendix VIII.—Funnel plot for phenomena.
Suffering and fear of one’s own death. Many ICU procedures are invasive and may cause considerable distress. Furthermore, frightening hallucinations and paranoid delusions are common.\textsuperscript{1, 2} Research suggests that the cumulative stress patients experience in ICU can affect their

**Abstract**

**Introduction:** Patients frequently suffer stress in intensive care units (ICUs) and many develop serious psychological morbidity after discharge. Little is known about the nature and efficacy of interventions to reduce ICU-related distress. There is growing evidence that administering sedative drugs can be harmful. Therefore, we carried out a systematic review of non-pharmacological interventions to reduce ICU-related distress.

**Evidence Acquisition:** A systematic search was conducted using Medline, Embase, Psychinfo, Cinahl, and the Web of Science. Included studies evaluated the effect of non-pharmacological interventions to reduce ICU stress. Study populations were adults in mixed or general ICUs. Outcomes were stress or psychological distress in or after the ICU, using self-report or physiological measures. No meta-analysis was possible due to heterogeneity, therefore studies were arranged according to intervention type, and outcomes examined together with risk of bias criteria.

**Evidence Synthesis:** Twenty-three studies were eligible, including 15 randomized controlled trials. Non-pharmacological interventions included music therapy (11 studies), mind-body practices (5) and psychological interventions (7). Twelve studies showed a beneficial effect. However, only three of the 12 had a low risk of bias, and many studies in the review were under-powered to detect an effect. Only 5 studies measured a medium/long-term psychological outcome such as PTSD or depression at 2-12 months.

**Conclusions:** Evidence indicates that non-pharmacological approaches to reducing ICU distress, in particular psychological interventions, may be beneficial. The evidence base would be strengthened by the implementation of fully-powered studies using robust designs that measure longer-term outcomes.

(Cite this article as: Wade DM, Moon Z, Windgassen SS, Harrison AM, Morris L, Weinman JA. Non-pharmacological interventions to reduce ICU-related psychological distress: a systematic review. Minerva Anestesiologica 2016;82:465-78)

**Key words:** Intensive care units - Psychotherapy - Music therapy.
long-term psychological well-being and recovery.\textsuperscript{3, 4} Systematic reviews show that after ICU, the prevalence of post-traumatic stress disorder (PTSD) ranges from 19-27\%\textsuperscript{5, 6} and the median prevalence of depression is around 28\%.\textsuperscript{7}

Poor psychological outcomes are associated with intrusive memories, delusional memories, stressful experiences and disturbed mood in ICU.\textsuperscript{1, 3, 4} Furthermore, acute stress in the ICU has been found to be a strong risk factor for later adverse psychological outcomes.\textsuperscript{4, 8, 9} High levels of anxiety, trauma and depression are likely to significantly impair an individual’s physical and functional recovery, as well as causing a significant reduction in quality of life and well-being.\textsuperscript{10, 11} Therefore there is considerable clinical interest in identifying interventions that could reduce psychological distress in- or post-ICU and to improve the psychological well-being of survivors.

In practice, stressed ICU patients have been treated with sedative drugs such as diazepam and other benzodiazepines. However the administration of these drugs to ICU patients has increasingly been associated with adverse effects such as delirium and hallucinations in the ICU, and flashbacks following the ICU.\textsuperscript{4, 12} However, little is known about the efficacy of non-pharmacological interventions to reduce distress in ICU and long-term psychological morbidity after ICU, and no systematic reviews have been conducted to assess this. This paper aims to systematically review the evidence from studies published in the last 15 years reporting the effects of non-pharmacological interventions aimed at reducing stress and psychological distress in patients who are expected to survive the ICU. Interventions for patients at the end of life were not included as the aim and content of these interventions would be different from interventions designed to reduce stress in survivors.

Evidence acquisition

Criteria for study selection

Types of studies

Included studies were designed to examine the effect of non-pharmacological interventions to reduce stress and psychological distress carried out during or following an ICU admission. Any non-pharmacological interventions were included, providing that the intervention aim was to reduce stress, anxiety or psychological distress in patients who were expected to survive the ICU. Any study design was accepted if its aim was to evaluate an intervention. End-of-life interventions were excluded.

Types of participants

The study populations were adults who had been admitted to mixed or general ICUs. Studies only including specific diseases were excluded to ensure the results could be extrapolated to a general intensive care population. Studies of fewer than 20 participants were excluded, as they are extremely likely to have bias.

Types of outcome measures

Studies were included if they measured stress or psychological distress in or following an ICU admission using a validated method. Studies could also use a physiological measure of stress such as heart rate or blood pressure. Sleep was also included as sleep problems can be seen as a proxy measure of stress.

Exclusion criteria

Studies were excluded if they were not in the English language, if the full text was not available or if they were published prior to 2000 considering that the nature of intensive care provision has changed significantly over time. Only papers published in peer reviewed journals were included.

Search strategy

A systematic search was conducted in March 2015 using the following databases: Medline, Embase and PsycInfo, Cinhall and the Web of Science. As an example, the search terms for the Medline database search are shown in
Supplementary Table I (online content only). The search terms were adapted slightly for the remaining databases. Results from the search strategy were managed using Endnote and all duplicates were removed. One author (AH) sequentially reviewed the titles and abstracts to determine which studies were eligible for inclusion in the review. Any papers not meeting the eligibility criteria were removed. The full texts of the remaining papers were then read by two authors (AH, ZM or SW) to determine whether they were eligible. The reference lists of the included papers were read to identify any other potentially relevant studies.

Assessment of risk of bias in included studies

Each included study was assessed for the risk of bias. This assessment was conducted using relevant criteria, as advised in the PRISMA guidelines. The criteria were randomization, similarity between groups at baseline, outcome measurement, statistical analysis and sample size. Studies were assigned a score of low risk (2), unclear risk (1) or high risk (0) for each aspect, with a total possible score of 10 (Supplementary Table II, online content only). Studies scoring 0-6 overall were deemed to have a high risk of bias, studies scoring 7-8 had an unclear risk of bias and only studies scoring 9 or 10 had a low risk of bias. Every paper was assessed for risk of bias by two researchers (from SW, ZM, JW or DW). Agreement was reached between researchers on all studies’ risk of bias.

Data extraction

A standardized data extraction table was drawn up and validated by all researchers. Once the final set of papers had been determined, data from each paper were extracted into the standardised data table. Data were extracted on the study’s aim; design; participants recruited, included and followed up; recruitment process; setting; inclusion and exclusion criteria; length of stay in ICU, psychological history, gender, ethnicity, socio-economic status, ICU clinical characteristics, details of control group; intervention details, outcome measures and results. The data extraction of each paper was conducted independently by one of three researchers (SW, ZM, AH).

Evidence synthesis

No meta-analysis could be carried out due to the heterogeneity of interventions, outcomes, length of follow-up and statistical methods used and the lack of consistency in reporting results. Therefore studies were arranged according to intervention type, and outcomes examined together with risk of bias criteria (Tables I-III).

As seen in Figure 1, the original search retrieved 2639 references. After screening of titles, abstracts and full texts, and manually searching reference lists, 23 papers were included in the review. Characteristics of the studies

Summaries of the characteristics of the included studies are shown in tables. These included 11 music interventions (Table I), 5 mind-body interventions (Table II), and seven psychological interventions (Table III). Of these 23 studies, 15 were RCTs (including a pilot RCT) and two were randomised crossover designs. The remaining papers were: one comparative controlled study, one comparative time series, two pre-post-studies (3 periods); one historical control study, and one secondary analysis of a sub-group from an RCT. In total, data from 2,135 patients from 44 ICUs were included in the review. Twelve studies included only ventilated patients. Six of the 23 studies were multi-centre. Of the 23 studies, two were conducted in Iran, two in Turkey, one in Canada, three in the US, two in Taiwan, two in China and the rest in Europe (Netherlands, Sweden, UK, France, Italy, or multi-centre).

Population characteristics

All patients were adults in a mixed or general ICU. The percentage of males in the study ranged from 34% to 79%. The range of aver-
Table I.—Characteristics and results of studies investigating music / nature sound interventions.

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of bias score (10 lowest risk; 0 highest)</th>
<th>Design</th>
<th>N of Ps recruited (N. in statistical analysis)</th>
<th>Inclusion criteria/setting</th>
<th>Exclusion criteria</th>
<th>Patient characteristics</th>
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<tbody>
<tr>
<td>Saadatmand et al. 2012</td>
<td>9</td>
<td>RCT (Intervention vs. control groups)</td>
<td>60 (60)</td>
<td>Mechanically ventilated patients in ICU, Iran.</td>
<td>e.g. Glasgow Coma Score 8 or below; mentally incompetent and unable to communicate, psychiatric, neurological illnesses</td>
<td>34% male Mean age 44 Mean length of stay: 7.6 days</td>
</tr>
<tr>
<td>Beaulieu-Boire et al. 2013</td>
<td>9</td>
<td>Randomized crossover study (Intervention vs. control –groups)</td>
<td>55 (49)</td>
<td>Ventilated patients in mixed ICU, Canada. ventilation &gt; 3d</td>
<td>Deafness, pregnancy</td>
<td>65% male Mean age 62 Mean length of stay: 11.5 days Acute Physiology and Chronic Health Evaluation (APACHE II) 26</td>
</tr>
<tr>
<td>Su et al. 2012</td>
<td>8</td>
<td>RCT (intervention vs. control groups)</td>
<td>28 (28)</td>
<td>All patients in mixed medical ICU, Taiwan, APACHE &lt;25. ICU stay &gt;1 day</td>
<td>Alcoholism, hearing impairment, physical restraint</td>
<td>61% male Mean age 62 APACHE II 19</td>
</tr>
<tr>
<td>Korhan et al. 2011</td>
<td>8</td>
<td>RCT (Intervention vs. control groups)</td>
<td>60 (60)</td>
<td>Patients ventilated in mixed ICU, Turkey. ICU stay= 1 day</td>
<td>e.g. Psychiatric or neurological illnesses, taken neuromuscular blocker or antihypertensive drug, inadequate hearing</td>
<td>53% male Mean age 45 Mean length of stay: 8.3 days</td>
</tr>
<tr>
<td>Wong et al. 2001</td>
<td>8</td>
<td>Randomized Crossover Study (intervention and control groups)</td>
<td>20 (20)</td>
<td>Patients ventilated in mixed ICU, China. ICU stay &gt;1 day</td>
<td>e.g. Not mentally competent, hearing problems, unable to communicate, not undergoing mechanical ventilation</td>
<td>75% male Mean age 59 Mean length of stay: 6.1 days</td>
</tr>
<tr>
<td>Han et al. 2010</td>
<td>8</td>
<td>RCT (Music vs. headphone vs. usual care groups)</td>
<td>137 (137)</td>
<td>Ventilated patients mixed ICU, China ICU stay &gt;1 day</td>
<td>Hearing impairment, skull injury patients on CMV or CPAP</td>
<td>43% male Mean age 46 Mean length of stay: 3.5 days</td>
</tr>
<tr>
<td>Chlan 2013</td>
<td>7</td>
<td>RCT (Music vs. headphone vs. usual care)</td>
<td>373 (373)</td>
<td>Patients ventilated in 12 general ICUs. USA. ICU stay &gt;1 day</td>
<td>Incapacity, unresponsive, delirious, aggressive ventilation</td>
<td>66% male Mean age 59 Mean length of stay: 7 days APACHE III 63.6</td>
</tr>
<tr>
<td>Dijkstra 2010</td>
<td>7</td>
<td>Pilot RCT (Intervention vs. control groups)</td>
<td>20 (20)</td>
<td>3 ICUs in a university teaching hospital, Netherlands</td>
<td>Ramsay score of 1, “too sluggish”, non-responsive to any touch or auditory stimulus</td>
<td>60% male Mean age 52 Mean length of stay: 27.3 days APACHE II 22.8</td>
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<tr>
<td>Lee et al. 2005</td>
<td>7</td>
<td>RCT (Intervention vs. control groups)</td>
<td>64 (64)</td>
<td>Patients ventilated in general ICU. China. ICU stay &gt;not stated</td>
<td>Haemodynamically unstable participants</td>
<td>71% male Mean age 69 Mean length of stay: 2.5 days</td>
</tr>
<tr>
<td>Chlan &amp; Engeland 2013</td>
<td>7</td>
<td>Descriptive design (secondary data analysis of sub-group from an RCT with 3 groups – music vs. headphone vs. usual care)</td>
<td>65 (65)</td>
<td>12 ICUs in five hospitals in USA.</td>
<td>Patients receiving aggressive ventilator support, were unstable hemodynamically, unresponsive, receiving chronic ventilator support prior to hospitalization, or had a documented mental health problem</td>
<td>61% male Mean age 57 Mean length of stay: 7.9 days APACHE III 57.2</td>
</tr>
<tr>
<td>Almerud &amp; Peterson 2003</td>
<td>4</td>
<td>Comparative study (intervention vs. control groups)</td>
<td>20 (20)</td>
<td>Patients ventilated in general ICU. Sweden. ICU stay &gt;1 day</td>
<td>Severe psychiatric condition, severe depression or learning difficulties</td>
<td>40% male Mean age 66 Mean length of stay: 11.5 days</td>
</tr>
<tr>
<td>Intervention</td>
<td>Outcome of interest – anxiety/stress measure</td>
<td>Results (outcome of interest)</td>
<td>Other Outcomes (Measures)</td>
<td>Results (other outcomes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------</td>
<td>------------------------------</td>
<td>---------------------------</td>
<td>-------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 minutes listening to nature sounds in rest period (controls rested in silence)</td>
<td>Anxiety using Faces Anxiety Scale, score range 1-5, every 30 minutes during intervention period and 30 minutes after intervention</td>
<td>Difference between anxiety scores of the two groups (P&lt;0.001). Odds of higher anxiety score 4.5 times more in control group</td>
<td>Agitation measured using Richmond Agitation Sedation scale every 30 minutes during intervention and 30 minutes after intervention</td>
<td>Difference between agitation scores of the two groups (P&lt;0.001). Odds of higher agitation scores 11.24 times more in control group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 minutes slow-tempo music morning and evening</td>
<td>Arterial blood pressure (mmHg) at end of intervention period/60 minutes</td>
<td>No differences in arterial blood pressure</td>
<td>Blood cortisol (nmol/L) at end of intervention period</td>
<td>Unclear if cortisol differed between groups, but it decreased during music intervention (815 vs. 727 nmol/L)</td>
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</tr>
<tr>
<td>45 minutes of “sedating piano music” at bedtime</td>
<td>Sleep quality using VSH Sleep Scale the following morning (score range =0-1500mm based on 15 visual analogue scales)</td>
<td>Sleep scale scores higher in intervention group: 545 vs 497, P&lt;0.05. (Higher scores = better sleep quality)</td>
<td>“Relaxation indices” - Heart rate (HR), respiratory rate (RR) and mean arterial pressure (MAP) measured every five minutes during the intervention</td>
<td>Intervention group had lower HR, RR and MAP at varying time points, suggesting benefit for intervention group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-minute music intervention (not specified when)</td>
<td>Respiratory rate at 30, 60 and 90 minutes (0 minutes = start of intervention period)</td>
<td>Significant difference in RR between groups (P&lt;0.05, RR lower in intervention group)</td>
<td>1. Change in RR over time (90 mins) 2. Change in HR over time (90 mins)</td>
<td>1. Reduction in RR and HR over time in intervention group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-minutes listening to Chinese or Western music, or 30-minute rest (all Ps had both, crossing over)</td>
<td>Reduction in anxiety (State-Trait Anxiety Inventory: STAI, score range 20-80) from baseline to 30 minutes</td>
<td>Greater reduction in anxiety in intervention than control conditions (mean difference: 11, P&lt;0.05)</td>
<td>Differences in RR (number of respirations in 1 minute) from baseline to 30 minutes</td>
<td>No differences found.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One 30-minute session listening to choice of relaxing music (classical or Chinese)</td>
<td>Change in state anxiety (using STAI, scores 20-80) between baseline and 30 minutes</td>
<td>Significant difference in anxiety reduction across 3 groups (P&lt;0.01). Mean reductions: music 10.7, headphone 3.3 and control 0.8</td>
<td>Mean difference between groups for 1. HR 2. RR</td>
<td>Differences in HR (P&lt;0.05) and RR (P&lt;0.01). Intervention group had greater reduction in HR and RR over music period.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-initiated music whenever desired while ventilated (max 30 days). Guided by music therapist</td>
<td>Anxiety assessed daily with the 100mm VAS-A. 0=no anxious at all 100=most anxious ever</td>
<td>Anxiety scores consistently lower during study period, by 19.5mm onVAS-A, in intervention group cf controls (P&lt;0.01)</td>
<td>Sedation exposure, operationalised as: 1. Dally sedative drug intensity score 2. Sedative dose frequency</td>
<td>Greater decrease over time in sedation intensity score and sedation frequency in music group (P&lt;0.05, P&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Three 30 minute music sessions over 2 days (patient or family choice)</td>
<td>Decrease in systolic blood pressure (SBP) between baseline and 30 minutes</td>
<td>No significant difference in decrease of SBP between groups</td>
<td>Difference in decrease of RR and HR between groups</td>
<td>No significant differences identified between groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single 30-minute music intervention (Chinese or Western)</td>
<td>Anxiety (STAI) at 30 minutes</td>
<td>No significant reduction in anxiety</td>
<td>Difference in RR at 30 minutes</td>
<td>No significant difference in RR at 30 minutes between groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients listen to preferred music when desired – while on ventilator (30-day maximum)</td>
<td>Urinary free cortisol – 24 hour urine collections but timing of collections not clear in relation to intervention</td>
<td>Treatment showed no decreases in cortisol over time or when compared to control groups</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 minute music intervention at bedtime</td>
<td>RR at 30 minutes</td>
<td>No differences between groups</td>
<td>HR at 30 minutes</td>
<td>No differences between groups</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table II.—Characteristics and results of studies investigating mind / body interventions.

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of bias score (10 lowest risk; 0 highest)</th>
<th>Design</th>
<th>Inclusion criteria/setting</th>
<th>Exclusion criteria</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vahedian-Azimi et al. 2014 25</td>
<td>9</td>
<td>RCT (Intervention vs. control groups)</td>
<td>Patients in general ICU, Tehran, &gt; 10 days hospitalised, GCS 7 - 12</td>
<td>Contraindication for changes of body position or body massage</td>
<td>51% male GCS 8</td>
</tr>
<tr>
<td>Henricson et al. 2008 26</td>
<td>8</td>
<td>RCT (Intervention vs. control groups)</td>
<td>All patients, general ICU, Sweden. ICU stay &gt;24 hours</td>
<td>Acute neurological disease, head injury, psychosis.</td>
<td>64% male Mean age 67 Mean length of stay: 5 days APACHE 21</td>
</tr>
<tr>
<td>Korhan et al. 2014 27</td>
<td>7</td>
<td>RCT (Intervention vs. control groups)</td>
<td>Ventilated patients in ICU, Turkey. GC S&gt;9</td>
<td>Psychiatric/ neurological illness</td>
<td>53% male Mean age 51</td>
</tr>
<tr>
<td>Chen et al. 2012 28</td>
<td>7</td>
<td>RCT (Intervention vs. control groups)</td>
<td>Stable patients in ICU, Taiwan, APS &lt;15</td>
<td>Hand/foot amputees, bilateral paralysis, sedative users, sleeping pills &gt; month</td>
<td>76% male Mean age 71 APS 12.1</td>
</tr>
<tr>
<td>Hayes &amp; Cox 1999 29</td>
<td>4</td>
<td>Comparison of pre-, during and post-intervention</td>
<td>Patients in general ICU, UK</td>
<td>Head trauma, raised intracranial pressure</td>
<td>52% male Mean age 54</td>
</tr>
</tbody>
</table>

Age ages of patients was 44-71. Nine studies included a measure of illness severity such as the APACHE (Acute Physiology and Chronic Health Evaluation) II score. The average length of stay ranged from 2.5-27.3 days.

Interventions

Music and Mind-body Therapies

In most studies (Table I), music was played to patients through headphones while they were mechanically ventilated in the Intensive Care Unit. Control groups mostly used noise-cancelling headphones without music at the same time. Music was played for 30-90 minutes for one or more sessions per day, or at the patient’s discretion. The majority of the interventions used calming, slow-tempo classical or other traditional music, and one study used nature sounds. The mind-body interventions (Table II) included tactile touch,26 valerian acupressure,28 reflexology 27 and massage,25, 28 delivered in the ICU by nurses, family or others.

The psychology interventions (Table III) included one clinical psychology intervention; three ICU patient diary interventions,30, 32, 33 one relaxation and guided imagery intervention delivered by nurses;34 one intervention for nurses to facilitate family participation in psychological care;36 and one post-ICU self-help rehabilitation programme including advice about psychological self-care.31 The clinical psychology study involved a range of interventions, including psycho-education, counselling and stress management, delivered by three clinical psychologists and other trained staff members. The diary studies involved an ICU diary being kept for the duration of the patient’s stay by healthcare professionals or fam-
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome of interest – stress measure</th>
<th>Results (outcome of interest)</th>
<th>Other Outcomes (Measures)</th>
<th>Results (other outcomes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 minute massage delivered by trained family member</td>
<td>SBP at one hour post intervention</td>
<td>SBP significantly lower in intervention (122) than control (128) group.</td>
<td>DBP (diastolic blood pressure) and HR at one hour</td>
<td>No differences between groups in DPB and HR</td>
</tr>
<tr>
<td>Tactile touch (effleurage) with soft background music for one hour per day during rest period for 5 days</td>
<td>Anxiety (Faces Anxiety Scale, score 1-5) on days 1-5 immediately post-intervention</td>
<td>No significant differences in anxiety between groups on day 1, 3, 4, 5. Day 2: post-intervention anxiety was significantly lower in intervention group (P&lt;0.05)</td>
<td>Daily doses of sedatives (midazolam and propofol) observed and reported in mL per day</td>
<td>No significant differences found in sedation requirement between groups on any day</td>
</tr>
<tr>
<td>30 minutes of reflexology twice daily for five days</td>
<td>Change in SBP from 0 to 30 minutes</td>
<td>Significant difference between groups in change in mean SBP from 0 to 30 mins, on all days (SBP decreased in intervention group) (P&lt;0.05)</td>
<td>Change in DBP and HR from 0 to 30 minutes</td>
<td>Significant difference between groups in change in DBP and HR from 0 to 30 mins, on all days (SBP decreased in intervention group)</td>
</tr>
<tr>
<td>Valerian acupressure (applying acupressure to points on wrist and foot with valerian oil) on 2nd night post-enrolment</td>
<td>Sleep hours measured by actigraphy on night after intervention</td>
<td>Intervention group had more hours of sleep (7.8 vs. 7.1, P&lt;0.01)</td>
<td>Minutes spent awake. Sleep quality (Stanford Sleepiness Scale, SSS). Highest level of wakefulness =1 on the SSS. Highest level of sleepiness – 7</td>
<td>Intervention group had fewer minutes awake (14.2 vs. 54.6, P&lt;0.01) and lower SSS scores (2.5 vs. 3.4 P&lt;0.01)</td>
</tr>
<tr>
<td>5 minute foot massage by trained researcher (range: 1-10 sessions per patient)</td>
<td>HR (bpm) during intervention compared to pre- and post-intervention</td>
<td>HR lower during intervention (94.7 bpm) than pre- (97.3, P&lt;0.01) or post- (96.3, P&lt;0.05)</td>
<td>Arterial blood pressure (mmHg) and respirations (breaths per minute) during intervention compared to pre- or post-intervention</td>
<td>Arterial BP lower during intervention than pre- (83.6 vs. 85.5, P&lt;0.01) Respirations lower during intervention (21.3) and post- (21) than pre- (23.1) (P&lt;0.01)</td>
</tr>
</tbody>
</table>

**Figure 1.—** Flow-chart showing identification of records; screening of titles, abstracts and full-text articles; and inclusion of final studies.
Table III.—Characteristics and results of studies investigating psychological interventions.

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of bias score (10 lowest risk; 0 highest)</th>
<th>Design</th>
<th>N of Ps recruited (n in statistical analysis)</th>
<th>Inclusion criteria/setting</th>
<th>Exclusion criteria/setting</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al. 2010 30</td>
<td>10</td>
<td>RCT (Intervention vs. control groups)</td>
<td>352 (333)</td>
<td>Ventilated patients, 6 European mixed ICUs, ICU stay &gt; 72 hours, Ventilation &gt; 24 hours</td>
<td>Pre-existing psychosis or PTSD</td>
<td>64% male Mean age 58 Mean length of stay: 13 days APACHE II 19</td>
</tr>
<tr>
<td>Jones et al. 2003 31</td>
<td>9</td>
<td>RCT Control (routine ICU follow-up) vs. Intervention (routine follow-up plus rehabilitation manual)</td>
<td>126 (102)</td>
<td>Patients who had previously been ventilated in ICU in three hospitals in the UK.</td>
<td>ICU &lt; 48 hours, burn injury, neurological patients, pre-existing psychotic illness.</td>
<td>55% male Mean age 58 Mean length of stay: 14 days APACHE II 17</td>
</tr>
<tr>
<td>Garrouste-Orgeas et al. 2012 32</td>
<td>7</td>
<td>Intervention period between two control periods</td>
<td>143 (52)</td>
<td>All patients in general ICU, France ICU stay &gt; 4 days</td>
<td>Dementia, not fluent in French</td>
<td>58% male Mean age 65 Mean length of stay: 18 days SAPS II 41.7</td>
</tr>
<tr>
<td>Peris et al. 2011 33</td>
<td>7</td>
<td>Historical Control</td>
<td>376 (209)</td>
<td>Ventilated trauma patients, mixed ICU, Italy, ICU stay &gt; 72 hours</td>
<td>Psychotic illnesses, previous critical illness, psychiatric medication, drug use or addiction</td>
<td>79% male Mean age 44 Mean length of stay: 19 days SAPS II 41.8</td>
</tr>
<tr>
<td>Richardson 2003 34</td>
<td>7</td>
<td>RCT (Intervention vs. control groups)</td>
<td>36 (29)</td>
<td>Medical, surgical and coronary patients in 3 mixed ICUs, Utah</td>
<td>E.g. dementia, psychosis, neurological impairment, severe hypotension</td>
<td>47% male Mean age 58</td>
</tr>
<tr>
<td>Knowles &amp; Tarrier 2009 35</td>
<td>6</td>
<td>RCT (Intervention vs. control groups)</td>
<td>36 (36)</td>
<td>Patients in general ICU, UK, ICU stay &gt; 48 hours</td>
<td>Suicide attempt, psychological symptoms, dementia</td>
<td>58% male Mean length of stay: 9 days APACHE II 15</td>
</tr>
<tr>
<td>Black 2010 36</td>
<td>6</td>
<td>Comparative time series</td>
<td>170 (138)</td>
<td>General ICU in an inner city public hospital Northern Ireland</td>
<td>Patients with family members who were physically unable to participate in the intervention due to being unable to visit, patients with no living family, patients with a terminal diagnosis.</td>
<td>Mean length of stay: 13 days</td>
</tr>
</tbody>
</table>

Family members. The diary was given to the patient either at discharge or at one month post-discharge. Three of the psychology interventions were clearly delivered within the ICU, 33, 34, 36 the rehabilitation intervention was delivered post-ICU, 31 while the diary method included both in-ICU and post-ICU components.

Outcome measures

Five music studies used a scale measure of anxiety as their primary outcome and one measured sleep quality using a sleep scale (see Table I for details of measures). The other five music studies used physiological measures...
of stress such as heart rate, respiratory rate, urinary free cortisol\textsuperscript{12,13} or blood pressure. The mind-body interventions (Table II) measured blood pressure, heart rate, hours of sleep and anxiety as primary indicators of ICU stress. Outcomes in music and mind-body studies were generally measured during or immediately after the intervention period, in some cases over a number of days. Five of the seven psychological interventions (diaries, clinical psychology, self-help rehabilitation) measured psychological distress at 2-12 months using validated measures for PTSD, depression or anxiety (Table III). The family participation

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Outcome of interest – anxiety/stress measure</th>
<th>Results (outcome of interest)</th>
<th>Other outcomes (measures)</th>
<th>Results (other outcomes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU diary kept during stay, given to patients one month post-discharge</td>
<td>Prevalence of PTSD at 3 months (using Post traumatic stress Diagnostic Scale, PDS)</td>
<td>PTSD lower in intervention group (5% vs. 13%, P&lt;0.05)</td>
<td>PTSD-related symptoms (PTSS-14 screening tool) at 3 months</td>
<td>No differences in PTSS-14 scores between groups</td>
</tr>
<tr>
<td>In addition to routine follow-up, intervention patients used 6-week self-help rehab manual of psychological, and physical advice</td>
<td>Depression (Hospital Anxiety and Depression Scale, HADS) at 8 weeks</td>
<td>No significant differences between groups in anxiety or depression</td>
<td>PTSD (Impact of Events Scale, IES) at 8 weeks</td>
<td>No difference in PTSD between groups</td>
</tr>
<tr>
<td>ICU diary, started on 4\textsuperscript{th} day of admission, given to patients on discharge from ICU</td>
<td>PTSD related symptoms (IES-Revised) at 12 months</td>
<td>Lower PTSD scores for diary (21) compared to pre-diary (35) and post-diary periods (30, P&lt;0.05)</td>
<td>Anxiety and depression at 3 months postdischarge (HADS)</td>
<td>No differences in anxiety or depression at 3 months</td>
</tr>
<tr>
<td>Clinical psychology intervention delivered for duration of ICU stay</td>
<td>PTSD (IES-R) 12-months postdischarge</td>
<td>Lower rate of PTSD in intervention group (21% vs. 57%, P&lt;0.01)</td>
<td>Anxiety and depression (HADS) at 12 months</td>
<td>No differences in depression or anxiety</td>
</tr>
<tr>
<td>Nurse-delivered relaxation and guided imagery sessions on two consecutive evenings</td>
<td>Sleep quality on mornings following intervention sessions (VSH Sleep Scale – score range 0-800mm based on 8 visual analogue scales)</td>
<td>No significant difference in sleep quality scores between groups</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>ICU diary, given to patients one month postdischarge</td>
<td>Anxiety (HADS) at 2 months postdischarge</td>
<td>Reduction in anxiety scores for intervention group (mean change 1.9, P&lt;0.05). No reduction in control group. But between-group difference unclear</td>
<td>Depression (HADS) at 2 months postdischarge</td>
<td>Reduction in depression scores for intervention group (mean change=2.5, P&lt;0.01). No reduction in control group. But between-group difference unclear</td>
</tr>
<tr>
<td>Nurse-facilitated family participation in psychological care during ICU stay</td>
<td>HR</td>
<td>No differences in HR between groups</td>
<td>BP</td>
<td>No significant differences in BP</td>
</tr>
</tbody>
</table>
study used HR to indicate stress, while the relaxation/guided imagery study measured sleep quality with a sleep scale.\textsuperscript{34}

**Risk of bias assessment**

Overall there were five studies with a low risk of bias (scoring 9 or 10: Supplementary Table III, online content only). Four studies had a high risk of bias (scoring 0-6), while in 14 studies the risk of bias was unclear (scores of 7 or 8). The music grouping included 2 low risk, 8 unclear risk and one high risk studies. The mind-body grouping included one low-risk, 3 unclear risk and one high-risk studies. Finally the psychology grouping included two low-risk, 3 unclear risk and two high-risk studies.

**Effect of interventions**

Twelve of the 23 studies showed a clear effect of the intervention on the outcome of interest. Of these studies showing a benefit, three were low-risk, eight were unclear risk and one was a high-risk study.

**Effect of music interventions**

Six out of 11 studies found that music therapy reduced stress. One of these studies was low-risk, the others were unclear risk. The low-risk study\textsuperscript{14} showed that anxiety and agitation were reduced in ventilated patients listening to nature sounds for 90 minutes, during the intervention and at 30 minutes after it.

**Effect of mind-body interventions**

Improvement was found in four of the five mind-body intervention studies. Of these studies, one was low-risk, three were unclear risk and one was high risk. The low risk study\textsuperscript{25} showed a reduction in systolic blood pressure after one hour, in ICU patients who received a 60-minute massage from a trained family member. Reflexology, valerian acupressure and foot massage were also associated with reduced stress.

**Effect of psychological interventions**

Three of the seven psychological interventions found a significant difference in the primary outcome. Of these one was low risk and two were unclear risk. The low-risk study was an RCT of a patient diary intervention.\textsuperscript{30} There was a reduction in PTSD prevalence at 3 months in the intervention group, who received a diary kept during their ICU stay one month post-discharge. Another diary intervention\textsuperscript{32} and the clinical psychology intervention\textsuperscript{33} were associated with reductions in longer-term psychological distress.

**Discussion**

In this systematic review, 23 studies were identified that evaluated non-pharmacological interventions to reduce distress or psychological distress in ICU patients. Of these, 12 studies showed a clear beneficial effect on primary outcomes including physiological stress indicators or self-report measures of psychological distress.

Music/nature sounds was the most common intervention, with eleven studies. There were also five mind-body studies and seven psychological studies. Both music and mind-body studies were characterised by short-term measures of stress including physiological indicators and anxiety scales, while more of the psychological studies measured longer-term outcomes using validated questionnaires for PTSD, depression or anxiety.

There was mixed evidence for the music therapy group, with six of 11 studies showing an effect on stress. The risk of bias was low in only one of these studies.\textsuperscript{14} A limitation of the music studies was the lack of longer-term follow up. However, focus on short-term outcomes did reflect the aim of such studies, which was to reduce anxiety during uncomfortable medical procedures. Some of these studies had small sample sizes. Another potential limitation was the heavy reliance on physiological measures of stress, as the autonomic stress response has been found to vary across individuals.\textsuperscript{37} The group of five mind-
Body interventions were found to be generally effective in the short term for reducing stress. However only one of these studies (family-delivered massage) was low risk for bias, sample sizes were fairly small and all studies focused on short-term measures.

Three of the group of seven psychological studies proved effective (two diary interventions and a clinical psychology service) in reducing longer-term psychological outcomes, but only one was low-risk. Evidence is strongest for this third group taking into account study designs used, length of follow-up, measurements methods employed and strength of effects (Table III).

What conclusions can be drawn from this systematic review for the future? Caution is needed because the strength of evidence for the effect of non-pharmacological interventions to reduce ICU stress is unclear at present, based on the findings of this review. Nevertheless, elements of these interventions appear promising. Studies suggest that music, nature sounds, various forms of massage and reflexology could all be employed to reduce acute stress among ICU patients, including mechanically ventilated patients. As acute stress is an important precursor of long-term psychological morbidity such as PTSD, these short-term practices could also have an impact on longer-term outcome. They might certainly be popular with patients and families, given a trend to using more complementary or mind-body therapies, with less reliance on drugs. The risk of harm from such therapies is not generally high, but protocols and training for staff are needed as some critically ill patients would not be able to receive certain complementary therapies.

Potentially these elements could be delivered within complex interventions that include psychological techniques to bring about longer-term improvement for patients with stress in the ICU. The strongest evidence for psychological interventions to date is for the use of ICU patient diaries. The idea of diaries is that they could reduce patients’ risk of developing PTSD (a disorder characterised by intrusive memories of a trauma) by filling in memory gaps, which are common among ICU patients. It is thought that diaries could lessen the impact of delusional memories, which are associated with post-ICU PTSD, by strengthening factual memories (thought to be protective against PTSD). However diaries have been critiqued for a lack of sound theoretical basis underlying their proposed mechanism of action. There is also a great deal of variation in the practice of how diaries are compiled and when they are given to patients. Finally their acceptability to patients is not known.

The single study in the review that evaluated the provision of psychotherapeutic support from psychologists in the ICU had an unclear risk of bias. It covered a wide range of activities including stress management, counselling, psycho-education, and coping strategies aimed at anxiety, depression, discomfort, hopelessness and helplessness. Consequently there was no standardised procedure, making interpretation difficult, and constraining scientific replication. However, the study resulted in a very large significant reduction in PTSD at 12 months, suggesting that further exploration of the effectiveness of psychological interventions for critical care patients would be worthwhile. This would require careful consideration of key risk factors for long-term post-ICU distress such as mood disturbance, acute stress, early intrusive memories, hallucinations and delusions, to guide the selection of psychotherapeutic techniques that could have an impact on these specific symptoms.

The present review is limited by a number of factors. First, the variety of outcome measures used meant that performance of a meta-analysis was not possible. In this review, scale measures of anxiety and sleep quality, as well as physiological stress markers were included to reflect ICU stress. However, future reviews may benefit from limiting the outcome measures included, to provide more generalizable findings, aiding interpretation and comparison. The risk of bias assessment could have been improved by using the recently published, validated Cochrane risk of bias assessment tool. However several of its key criteria (e.g. blinding) were not relevant to these studies. These limitations could have resulted in an
over-estimation of the strength of the evidence. However this was avoided by using a stringent cut-off for identifying low-risk studies (risk of bias scores of 9 or 10).

Many questions remain unanswered from this review. It is not possible to say definitively whether there is a clinically important effect of non-pharmacological interventions to reduce ICU-related stress, given the heterogeneity of both methods and results across studies. Furthermore, it remains unclear whether non-pharmacological interventions, if effective, might be of more benefit to certain sub-sets of patients, such as those with high baseline anxiety or a predisposition to psychological morbidity due to family background, previous trauma or prior psychological conditions. Future studies might determine whether non-pharmacological interventions are more effective when patients are screened for acute stress or anxiety.

It is also not known how non-pharmacological interventions compare to “pharmacological” interventions, such as changing sedation practice. Hypothesised associations between drugs, delirium and post-ICU psychological outcomes have not yet been established by robust intervention studies. One small trial 40 found that post-traumatic stress symptoms were reduced in a group of patients who received daily sedation interruption. However, the study (of only 32 patients) found no significant difference in PTSD diagnosis rate. Furthermore, a study 41 of lightly sedated compared to heavily sedated patients found no subsequent difference in PTSD, anxiety or depression in lightly sedated patients.

Conclusions

Evidence from this review indicates that non-pharmacological approaches to reducing ICU-related distress may be beneficial to patients. These could include elements of music therapy, mind-body practices or psychological support. However this review also highlights the need for improved conceptualisation of psychological interventions to be used in ICU. Furthermore the majority of studies investigating non-pharmacological interventions to reduce patient stress in or following an ICU admission have an unclear or high risk of bias, and predominantly centre around short- to medium-term outcomes. The present review highlights the need for larger studies in this area, utilising more robust study designs such as RCTs, and measuring longer-term outcomes with validated measures of psychological distress. Future research could include the evaluation of complex interventions that include elements of music, mind-body work or psychological support, to reduce in-ICU or post-ICU psychological distress.

Key messages

— As critical care patients frequently suffer acute and long-term stress that may be exacerbated by the effects of sedative drugs, a review of non-pharmacological interventions to reduce ICU-related stress is timely.

— This review identified 23 studies, including 15 randomized controlled trials, evaluating three types of non-pharmacological intervention to reduce ICU stress: Music or nature sound therapy; mind/body practices and psychological interventions.

— Of the 23 studies, more than half (12) showed that a non-pharmacological intervention reduced short-term or long-term stress in critical care patients. However the overall pattern of evidence was inconsistent and study designs were weak.

— Given early cautiously promising results, robust studies such as RCTs should evaluate non-pharmacological interventions to reduce stress in ICU, specifically psychological interventions, as the strongest of the three groups of interventions reviewed here.

References


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

For supplementary materials, please see the online version of this article.

How to protect incompetent clinical research subjects involved in critical care or emergency settings

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ABSTRACT

Clinical research is an essential component of medical activity, and this is also true in intensive care. Adequate information and consent are universally considered necessary for the protection of research subjects. However, in emergency situations, the majority of critical patients are unable to consent and a valid legal representative is often unavailable. The situation is even more complex in Italy, where the relevant legislation fails to specify how investigators should manage research in emergency or critical care setting when it involves incompetent patients who do not have an appointed legal representative. While special measures for the protection of incompetent subjects during emergency research are necessary, not allowing such research at all dooms critically ill patients to receive non-evidence-based treatments without the prospect of improvement. The recently-issued EU Regulation n. 536/2014 will probably help shed light on this situation. Indeed, it specifically addresses the issue of “research in emergency situations” and introduces detailed rules aimed at protecting patients while allowing research.

In this article, we argue that obtaining informed consent during emergency research on incompetent subjects in unrealistic, and that in most cases substituted judgment on the part of a proxy carries major flaws. Strict criteria in evaluating the risk-benefit ratio of proposed intervention and a careful evaluation of the trial by a local or national Research Ethics Committee are perhaps the most practicable solution.


Key words: Research - Informed consent - Intensive care units - Emergency medicine.

Emergency research in incompetent patients is a common but problematic issue. Due to the large sample size required, multicenter studies are usually necessary. Such studies have to overcome center and country variability in the approval process. In Italy, the level of this variability is striking and Italian Research Ethics Committee (RECs) often take opposite
decisions based only on the different interpretation of the current law, as we will discuss further on.

This raises important issues in relation to research in critical care or emergency settings, when involving temporarily incompetent patients (e.g., comatose patients), or highly distressed patients that cannot rapidly provide a truly informed consent. The aim of this paper is to present the current legal framework in Italy, compare it with the recent developments in European Union legislation and discuss such developing regulation.

Information and consent in emergency research

Clinical research is an essential component of medical activity, even in emergency situations. Effective therapies mean better outcomes and reduced morbidity and mortality; these goals can be achieved only by means of research. Not allowing such studies stops progress in knowledge, condemning critically ill patients to receive inferior non-evidence based treatments, without any prospect of improvement. Critically ill patients should be protected from such undesirable lack of evidence.

In order to also protect subjects involved in research studies, adequate information and subsequent valid consent are mandatory both in the international context and in the European Union (EU) legal framework (see WMA Declaration of Helsinki, 2013, points 25-26 and Directive 2001/20/EC, articles 2.j and 3.2.b-d). Informed consent may be granted either by the patient or by the legal representative of the incompetent patient (see WMA Declaration of Helsinki, 2013, points 27-29 and EU Directive 2001/20/EC, articles 3, 4 and 5). These measures of protection work in non-critical settings (e.g., research on psychiatric patients or on incompetent patients with degenerative conditions). However, in emergency situations, the vast majority of patients are incompetent and legal representative are absent: they cannot be adequately informed and are consequently unable to consent. In addition, as might be the case in cardiac arrest research, there is no time or opportunity for consent to be given.

The specific issues of clinical research on incompetent patients in emergency settings had not been addressed in the EU legal framework until April 2014, leading to uncertainty on the legal feasibility of such research.

The present situation in Italy

The European Directive 2001/20/EC will still be in force at least until May 2016. In Italy, such directive has been implemented by the Legislative Decree n. 211/2003, whose art. 3 states that only the involved subject can give valid consent for research. According to art. 5, the “legal representative” is the only legal substitute for the incompetent patient; yet, the Decree fails to specify who is to be intended as legal representative in emergencies.

According to Italian law, in case of incompetent adults, the legal representative is a legal guardian specifically appointed by the Court — a process which optimistically takes weeks. How then could be possible to involve incompetent adults in emergency research when a legal guardian is not available, as indeed happens in most cases?

A possible, extreme solution is to consider every form of research on the incompetent adults forbidden. Yet, this construct makes emergency clinical research in adult incompetent persons impossible at all, unless there is a previously appointed legal substitute (as in case of previous mental impairment). This deprives critically ill patients of evidence-based improvements in care and is clearly unethical.

An alternative solution is to consider that the protection measure of legal representation, as it has been developed in the Italian legal order, does not cover emergency situations, in the absence of a previously appointed legal substitute. As a consequence, art. 5, lett. a) of the Legislative Decree n. 200/2007 should not apply to emergency situations. On the contrary, according to art. 4 of the same Decree,
the point 4.8.15 of the Annex I to the Ministerial Decree 15.7.1997, which implemented the GCP CPMP/ICH/135/1995 in Italy, must be considered applicable:

“When prior consent of the subject is not possible, and the subject’s legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject’s legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested”.

This means that currently the destiny of a research protocol in emergencies depends on a case by case evaluation of the local REC. The REC has to assess if the special measures provided in the protocol are adequate for the protection of the rights, safety and well-being of the perspective subjects. The aim can be achieved through:

— measures concerning the “acceptability” of the risk/benefit ratio — involving the study design, limitation of inherent risks, necessity of a second expert opinion, stress on the investigator responsibility, use of more strict inclusion criteria etc., or

— measures concerning the participation of the perspective subjects — involving the information and assent of the person even partially competent, the respect of any previously expressed objection by the patient, a proxy consent, the delayed consent.

In the absence of other applicable regulatory requirements, this evaluation totally relies on the REC’s discretion.

Things are changing: the EU scenario


“This Regulation should provide for clear rules concerning informed consent in emergency situations. (…) For such cases, intervention within an ongoing clinical trial, which has already been approved, may be pertinent. However, in certain emergency situations, it is not possible to obtain informed consent prior to the intervention. This Regulation should therefore set clear rules whereby such patients may be enrolled in the clinical trial under very strict conditions”.

Accordingly, the new regulation provides special protection measures at art. 10 and 35 (Appendix) and it mostly seems in line with art. 30 of the WMA Declaration of Helsinki, 2013, setting four fundamental principles:

1. good clinical research must be promoted, even on incompetent subjects and in emergency situations, in order to meet health needs and priorities of this group of patients;
2. clinical research in this setting requires special protection measures, including: a) a strict relationship between the clinical trial and the medical condition which causes the patient’s incompetence, b) the necessity to conduct the clinical trial in emergency situations; c) the expectations of benefits and of only minimal risks or burdens for the perspective subjects.
3. informed consent from the subject or from a legally designated representative should be sought as soon as possible (delayed consent).
4. the clinical trial should have been previously reviewed by a REC.

Protecting incompetent patients through informed consent?

Two kinds of measures are currently used in order to protect the subjects of clinical research.

The first kind of protective measures relate to the acceptability of the risk/benefit ratio of the study design. They may give answers to the need of reasonably balancing the promotion of scientifically sound and clinically relevant re-
search and the physical protection of incompetent patients involved in clinical research. The second kind of protection measures concern the involvement of the participants and the protection of the identity of the research subjects and their rights to privacy and self-determination.

Both these kinds of measures have to be used, in line also with the EU Regulation n. 536/2014.

Yet, in case of emergency research on incompetent subjects, a previously collected informed consent is simply unfeasible (by definition, as the subjects are incompetent).

As for deferred consent, it is evident that consent can protect a patient only if given before an action is performed. Deferred consent can work only for the subsequent treatments and for the use of personal data. On the contrary, in prospective randomized protocols, after a potentially dangerous intervention (a drug has been administered, an operation has been performed), consent can have little space in practice in order to protect the patient. Collecting valid consent from next-of-kin is also problematic. In Italy, though this practice has no full legal value, researchers often inform the relatives and take into account their reporting of the patient’s wishes. This practice is often not feasible in emergencies due to several reasons; first, the time constraints, as a next-of-kin is usually unavailable in the therapeutic window frame-time; second, different family members could give different versions of the patient’s wishes and/or may fail to accurately report them; third, emotional stress can significantly bias the decision of relatives in emergency situations.

Protecting incompetent patients through risk/benefit ratio evaluation: the role of RECs

We believe that measures regarding the acceptability of the risk/benefit ratio of the study design can protect the incompetent subjects of emergency trials much more than information and consent. Regulation EU n. 536/2014 sets suitable rules for this aim. In fact, Article 31 (Clinical trials on incapacitated subjects) and Article 32 (Clinical trials on minors) state that clinical trials may be conducted only where — among other conditions — there are scientific grounds for expecting that participation in the clinical trial (1) will produce a direct benefit for the subject concerned outweighing the risks and burdens involved; or (2) [...] will pose only minimal risk to, and will impose minimal burden on the subject concerned in comparison with the standard treatment of the minor’s condition. On the contrary, in Article 35 (Clinical trials in emergency situations) the two standards of “direct clinically relevant benefit for the subject” and “minimal risk to, and minimal burden on, the subject in comparison with the standard treatment” are both mandatory for the subject’s inclusion. These two strict prerequisites are designed to protect the incompetent subject of emergency research, when he/she cannot decide (he/she is incompetent) and a guardian is not (yet) available. The role of the REC here is crucial as it has the task to verify that the clinical trial design really respects these requirements.

As a matter of fact, an efficient local REC can provide a much better evaluation of the planned intervention, by ensuring effective protection of research subjects and promoting good clinical research in emergency settings. All REC’s members should be experienced professionals who should be able to evaluate all the relevant issues related to protocol safety and have sufficient time for adequate discussion. No other people, and surely not the subject’s relatives pressed in an emergency situation, can make a better evaluation. Yet, such a Committee should work in close contact with the research clinicians.

At present, in Italy, most RECs do good pre-emptive work: they examine the different aspects of the protocol, the information sheets and the insurance issues. But after that, the task of optimal performance and protocol adherence is left to the clinicians.

Our proposal is to trust clinicians: those who perform clinical research have specific legal and moral responsibilities. But, at the same time, we think that the strengthened criteria verified by the RECs in evaluating the design of an emergency trial involving incompetent subjects should be sufficient for the inclusion (Figure 1).
The problem of multicenter trials (and multiple RECs)

But again: what to do in multicenter trials, where many centers (and many RECs) are involved? How can agreement be reached?

In a recent document, the Italian National Committee for Bioethics expressed hopes for a significant legislative change in Italy, which could enable multicenter emergency research on incompetent patients, provided that:

1. the clinical trial has been approved by an Ad-Hoc National REC composed by expert clinicians, lawyers, patients’ representatives, bioethicists;
2. if a patient has not previously refused to be involved in medical research, he/she has to be promptly enrolled;
3. deferred consent is used for subsequent treatments and for permission to use previously gathered data;
4. publication of negative results is recommended.

The proposal of the National Committee for Bioethics is open to challenge. The main problem is to assemble expert members in different disciplines who are able to represent the different working realities (university and big city hospitals, little community hospitals in rural areas). Moreover, to evaluate all multicenter studies regarding emergency and involving temporarily unable patients, this “ad-hoc national REC” should have adequate number of planned meetings: a dire challenge, also from an economic point of view. Another problem is that such a committee could be perceived as too far away and disconnected from researchers.

On the other hand, this solution could ensure a more balanced equilibrium between the local interests (autonomy of local REC) and the community interests (the possibility to perform phase III studies).

We will wait and see how the scenario will evolve, hoping for a clearer set of rules that allow critically ill patients in emergency conditions or in intensive care unit to receive the best treatment, based on the best available research data.

Key messages
— Clinical research is an essential component of medical activity; it has to always be guaranteed, both for individual and social interests, even in emergency conditions.
— Adequate information and consent are unfeasible in critically-ill patients and a legal representative is often not promptly available.
— Special measures for the protection of incompetent patients have to be harmonized with the possibility to conduct research in emergencies, in order to reach evidence based treatments.
— The careful evaluation and approval of the trial by the competent Ethics Committee appears as the best solution, together with surveillance during trial progress and the timely consent collection from patient.
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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.

EU Regulation n. 536/2014 on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC

Article 10 — Specific considerations for vulnerable populations
1. (…)
2. Where the subjects are incapacitated subjects, specific consideration shall be given to the assessment of the application for authorisation of a clinical trial on the basis of expertise in the relevant disease and the patient population concerned or after taking advice on clinical, ethical and psychosocial questions in the field of the relevant disease and the patient population concerned.

Article 35 — Clinical trials in emergency situations
1. By way of derogation from points (b) and (c) of Article 28(1), from points (a) and (b) of Article 31(1) and from points (a) and (b) of Article 32(1), informed consent to participate in a clinical trial may be obtained, and information on the clinical trial may be given, after the decision to include the subject in the clinical trial, provided that this decision is taken at the time of the first intervention on the subject, in accordance with the protocol for that clinical trial” and that all of the following conditions are fulfilled:
   (a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the clinical trial;
   (b) there are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition;
   (c) it is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative;
   (d) the investigator certifies that he or she is not aware of any objections to participate in the clinical trial previously expressed by the subject;
   (e) the clinical trial relates directly to the subject’s medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the clinical trial is of such a nature that it may be conducted exclusively in emergency situations;
   (f) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject’s condition.

3. Following an intervention pursuant to paragraph 1, informed consent in accordance with article 29 shall be sought to continue the participation of the subject in the clinical trial, and information on the clinical trial shall be given, in accordance with the following requirements: (a) regarding incapacitated subjects and minors, the informed consent shall be sought by the investigator from his or her legally designated representative without undue delay and the information referred to in Article 29(2) shall be given as soon as possible to the subject and to his or her legally designated representative; (b) regarding other subjects, the informed consent shall be sought by the investigator without undue delay from the subject or his or her legally designated representative, whichever is sooner and the information referred to in Article 29(2) shall be given as soon as possible to the subject or his or her legally designated representative, whichever is sooner. For the purposes of point (b), where informed consent has been obtained from the legally designated representative, informed consent to continue the participation in the clinical trial shall be obtained from the subject as soon as he or she is capable of giving informed consent.

4. If the subject or, where applicable, his or her legally designated representative does not give consent, he or she shall be informed of the right to object to the use of data obtained from the clinical trial.

Article 99 — Entry into force
This Regulation shall enter into force on the twentyninth day following that of its publication in the Official Journal of the European Union. It shall apply as from six months after the publication of the notice referred to in Article 82(3), but in any event no earlier than 28 May 2016.
Another failed attempt of neuroprotection: progesterone for moderate and severe traumatic brain injury

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ABSTRACT

Two large phase-III prospective, multicenter, controlled, double-blind, randomized clinical trials (the PROTECT III study; the SYNAPSE study) evaluated the effectiveness of an early administration of progesterone in patients with moderate to severe traumatic brain injury (TBI). In the PROTECT III Trial, patients were included if the admission Glasgow Coma Scale (GCS) was within 4-12, whereas the SYNAPSE Trial only included patients with GCS 4-8. The total dose of progesterone was nearly similar in both studies and drug administration was initiated early after injury (within 4 hours for a total of 96 hours in PROTECT; within 8 hours for 120 hours in SYNAPSE). In the PROTECT Trial, primary outcome was 6-month favourable neurological outcome (defined using the Glasgow Outcome Scale), while in the SYNAPSE trial it was the 6-month Glasgow Outcome Scale (GOS). Secondary outcomes, in both studies, included 6-month mortality.

In PROTECT, the proportion of patients with favourable outcome was similar between groups (51% for progesterone vs. 56% for placebo; RR 3.03 [95% CI 1.96-4.66]); in SYNAPSE, no difference in GOS between the progesterone and placebo group was found (OR 0.96 [95% CI 0.77-1.21]). There was no difference in 6-month mortality or any of the other secondary outcomes between groups in the two trials. These studies demonstrated that early progesterone administration did not provide any benefit on the neurological recovery of TBI patients.

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Key words: Brain injuries - Progesterone - Neuroprotection - Treatment outcome.

Traumatic brain injury (TBI) is a leading cause of death and disability among young persons worldwide and the incidence is rising in the elderly population. The rehabilitation of TBI survivors usually takes years and many of them are left with permanent disability. The financial burden of TBI management to the society remains significant.1

The initial therapy of severe TBI patients is mainly aimed at the prevention of secondary brain injuries; the initial insult to the brain (or “primary injury”) is generally considered irreversible. The current therapeutic arsenal in the acute phase include, amongst all, admission to a specialized intensive care unit (ICU), surgical removal of space-occupying lesions, optimization of cerebral oxygenation and perfusion, control of increased intracranial pressure and prevention and treatment of other complications (e.g. hyperthermia, seizures, sodium balance disorders, dysglycemia). Guidelines have been published in order to standardize...
TBI management. As such, the neurological outcome and overall survival of TBI patients have gradually improved in the last decades, especially when aggressive therapy was provided.\(^3\)

Importantly, in the hours, days and weeks after the initial injury, a complex cascade of molecular and cellular events is progressively initiated and intensified, which can eventually lead to additional tissue damage and cell death. None of the available supportive therapeutic interventions is able to specifically attenuate or inhibit these pathological pathways; however, the fact that TBI is not a single event occurring at the time of injury, but a continuous process, offers a window of opportunity for additional targeted therapies. Unfortunately, no pharmacological intervention has been shown to positively affect the neurological recovery of TBI patients;\(^4\) moreover, more than thirty clinical trials using different potential neuroprotective drugs have failed in this setting.\(^5\)

Progesterone is an endogenous steroid hormone that is involved in the menstrual cycle, pregnancy and embryogenesis. However, it is not only synthesized by the ovaries and placenta, but also within the central nervous system, in particular by neurons and oligodendrocytes. Progesterone receptors are expressed in the fetal brain during gestation, where they are involved in normal brain development and myelination, but also in adults, where they have a potential role in neuro-regeneration.\(^6\) The fortuitous observation that pseudo-pregnant female rats had improved functional outcomes and decreased edema after experimental TBI\(^7\) was the first hint towards a possible role for neurosteroids in brain protection. In the following years, several hundreds of animal studies have reported on the neuroprotective effects of progesterone in experimental TBI, stroke and spinal cord injury.\(^8\) Progesterone has been shown to reduce brain edema, possibly by influencing the permeability of the blood-brain-barrier, through the up-regulation of the P-glycoprotein pump (which is an ATP-dependent transport protein responsible for the very poor permeability of endothelial layers to many drugs) and decreasing the expression of aquaporin 4 (which is a water channel playing an important role in cerebral water homeostasis). Progesterone also promotes neuronal survival, by down-regulating several pro-apoptotic factors, while up-regulating anti-apoptotic factors and brain-derived neurotrophic factors. At the same time, progesterone acts on the inflammatory pathway by attenuating the expression of pro-inflammatory cytokines (such as IL-1\(\beta\), TNF-\(\alpha\), NF-\(\kappa\)B, and IL-6), and by a modulatory effect on the complement system. In addition, other beneficial effects have been attributed to progesterone, such as the reduction of oxidative stress and the attenuation of glutamate-mediated excitotoxicity (Figure 1).\(^5\), \(^9\) Two small phase II trials\(^10\), \(^11\) showed that early administration of progesterone after severe TBI was safe. In addition, patients treated with progesterone, had a lower mortality at 30-days\(^10\) or 6-months\(^11\), and modestly improved functional neurological outcomes were observed in both trials.

Guided by the results of these animal and clinical trials, the PROTECT (Progesterone for the Treatment of Traumatic Brain Injury) III\(^12\) and the SYNPSE (Study of the Neuroprotective Activity of Progesterone in Severe Traumatic Brain Injuries)\(^13\) studies have been set up and conducted in parallel to evaluate the
effects of progesterone therapy on neurological outcome of TBI patients.

Discussion on the studies

The PROTECT III Trial was prematurely stopped for futility after two-thirds of all planned patients were included. In the SYNPSE Trial, 1195 patients with severe TBI were finally included. Despite more than 2000 patients enrolled in these two trials, no benefit of progesterone over placebo with regards to neurological recovery or mortality was observed. The results of all five published randomized trials on progesterone therapy for TBI patients are summarized in Table 1.

Unfortunately, the search for a potential neuroprotective drug for TBI has been once again unsuccessful. These two randomized controlled trials have been extremely well conducted and designed, according to all current methodological standards. Moreover, particular attention had been paid to avoid the main errors encountered with other neuroprotectant agents, such as an insufficient statistical power, the use of insensitive outcome measures or the inclusion of heterogeneous patients. All pre-clinical and phase II human data appeared to be very promising, and were used to design both trials. Efforts were made to avoid treatment variability across sites: in the PROTECT III trial, patients were monitored in real time and immediate feedback was provided in case of non-compliance with a standardized management protocol. Robust outcomes were chosen and assessed early as well as after 6 months, in order to detect any possible long-term benefit. In view of the tremendous efforts and financial costs involved in these large trials, this failure is a huge disappointment.

When evaluating these studies, some particular issues may be considered to explain the reasons for their negative findings. First, in both studies, TBI was classified according to the Glasgow Coma Scale (GCS) on admission, a clinical assessment of the initial presentation, effects of progesterone therapy on neurological outcome of TBI patients.

Table I.—Summary of the randomized clinical trials evaluating the effects of progesterone on neurological outcome after traumatic brain injury.

<table>
<thead>
<tr>
<th>Setting</th>
<th>ProTECT 9</th>
<th>Xiao 10</th>
<th>Shakeri 11</th>
<th>PROTECT III 11</th>
<th>SYNPSE 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (PG/placebo)</td>
<td>100 (77/23)</td>
<td>159 (82/77)</td>
<td>76 (38/38)</td>
<td>882 (442/440)</td>
<td>1195 (591/588)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>GOS at 1 month</td>
<td>GOS at 3 months</td>
<td>GOS at 3 months</td>
<td>GOS-E at 6 months</td>
<td>GOS at 6 months</td>
</tr>
<tr>
<td>Median age (yrs)</td>
<td>36</td>
<td>31</td>
<td>34</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Median GCS on admission</td>
<td>NR</td>
<td>6</td>
<td>6</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Favourable Neurological Outcome (PG vs. placebo)</td>
<td>All patients – 25% vs. 16%</td>
<td>3-month: 46% vs. 30%</td>
<td>50% vs. 28% *</td>
<td>All patients – 48% vs. 52%</td>
<td>50% vs. 50%</td>
</tr>
<tr>
<td></td>
<td>Moderate TBI – 21% vs. 27%</td>
<td>6-month: 57% vs. 42%</td>
<td></td>
<td>Moderate TBI – 27% vs. 36%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe TBI – 55% vs. 0%</td>
<td></td>
<td></td>
<td>Moderate to severe TBI – 51% vs. 56%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TBI – 57% vs. 70%</td>
<td></td>
</tr>
<tr>
<td>Mortality (PG vs. placebo)</td>
<td>13% vs. 30% *</td>
<td>3-months: 18% vs. 32%*</td>
<td>31% vs. 45%</td>
<td>19% vs. 16%</td>
<td>22% vs. 22% **</td>
</tr>
</tbody>
</table>

*P<0.05; **mortality was not reported separately in the SYNPSE trial. Percentage refers to the proportion of patients who died OR were severely disabled at 6 months (GOS 4 and 5 combined).

PG: progesterone; TBI: traumatic brain injury; GOS: Glasgow Outcome Scale; GOS-E: Extended Glasgow Outcome Scale; NR: not reported.
in order to estimate the severity of the underlying injury. However, TBI encompasses a wide and heterogeneous range of different types of injury that can all lead to the same non-specific motor or pupillary symptoms, each with different mechanistic causes (e.g. subdural or epidural hematomas, contusions, edema, diffuse axonal injury, ischemia or inflammation). A “one-treatment-fits-all” approach is probably not appropriate for these different types of brain damage. Other parameters, including the presence of edema, of raised intracranial hypertension, of space-occupying lesions, may be considered in the future to further characterize the subgroup of patients who may benefit the most from therapy. Such a more individualized classification of TBI (based on biomarkers or clinical/imaging findings) may reduce the heterogeneity of the studied population, although the price to pay may be a more limited generalizability of the final results. Second, other confounders, such as age and gender, should also be considered in the recruitment process. In the PROTECT study, there was no age limit to include patients (although most of them were around 35 years of age). It is disputable whether neuroprotective strategies are as effective in older TBI victims, because of their reduced capability of neuro-regeneration, or pre-existing decline in cognitive functions. Because female patients are still capable of producing valuable endogenous progesterone, it could have been useful to assess the initial levels of circulating neurosteroids hormones, in order to avoid the administration of supplemental hormones to subjects with adequate levels. Third, the outcome measures that are currently used, although robust and well validated, might not be sensitive enough to detect all potential benefits. Although advanced neurocognitive testing is extremely time and effort consuming, other large trials, for instance in critically ill children, have demonstrated that this is feasible, even at such a large scale, and that more subtle neurological benefits that matter to our patients can be picked up this way. Fourth, the administered therapy may have been associated with significant adverse events. In the PROTECT study, the occurrence of thromboembolic events was significantly increased in patients treated with progesterone when compared to others (17% vs. 6%). A detailed investigation into the 33% of subjects who died from non-neurological causes, could lead to a better understating of unexpected side effects. Fifth, it is possible that the preliminary clinical trials on progesterone might not have been robust enough to justify these large studies. The two phase II trials were small and the observed benefit was only modest, observed at one month and not relevant with regard to functional neurological outcome, which was selected as the primary outcome in both PROTECT III and SYNAPSE trials. This might have led to an over-optimistic estimation of the possible benefits for progesterone, which, in combination with a better than expected outcome in the placebo group, could have contributed to the failure of both phase III trials. Finally, the poor understanding of the pathophysiology of TBI might explain the difficulty to translate laboratory findings to clinical practice. The use of data from large international networks may understand to better describe the mechanisms of secondary brain injury in this setting and to a better standardization of patients’ care.

In clinical practice, progesterone therapy cannot be recommended in moderate to severe TBI patients. However, the role of sex hormones on neuroprotection has not been completely elucidated and several unresolved issues deserve further clarification. There is an incomplete understanding of the inflammatory and neuro-endocrine cascade leading to the increased serum and cerebral progesterone levels that have been associated with poor outcome in patients with severe TBI. Other stress hormone abnormalities, such as increased cortisol concentrations, accompany critical illness; their role in the amplification of additional neurosteroid production should be further investigated. Other factors, such as changes in hormone transport and metabolism, and *de novo* synthesis of neurosteroids within the brain should be taken into account when investigating the role of sex steroids in neuroprotection for acute brain injury. More-
over, some of the most important neuroprotective properties of progesterone seem to be related to one of its metabolites, allopregnanolone.\textsuperscript{18} While progesterone effects are mediated by specific nuclear receptors, allopregnanolone acts as a potent positive modulator of $\gamma$-amino butyric acid type (GABA)-A receptors and of the mitochondrial permeability transition pore,\textsuperscript{19} suggesting that this compound could be a potential neuroprotectant for TBI. Finally, experimental studies in TBI have demonstrated that combining progesterone with magnesium or vitamin D could potentially be more effective than progesterone alone.\textsuperscript{20, 21}

When exploring these potentially promising research paths, it is important to learn from the experiences from PROTECT III and SYNAPSE trials. In the future, a more systematic approach and evaluation of the preclinical data and phase II clinical trials is necessary. Initial studies should focus on identifying appropriate subgroups of patients, classified according to the pathophysiology of the injury, rather than the presentation; on defining relevant outcomes, as well as biomarkers to guide the clinical management; to optimize dosing and timing of potential neuroprotectant drugs. Results from these studies should be pooled, critically evaluated and reported in an open and rigorous way. Findings should be replicated in more than one, and preferably several, phase II trials. This more extensive and strategic early phase research will probably lead to less compounds that will make it to phase II at a final stage. In addition, as small studies are only hypothesis-generating, clinical management of TBI patients should be validated by larger studies or at least meta-analysis including an adequate number of patients, which will significantly reduce the risk of bias.\textsuperscript{22} Finally, innovative adaptive trial design might allow to better identifying those patients in which the drug has a higher probability of benefit. These new approaches will hopefully result in the development of neuroprotectants that are more specific but also more efficient for specific subgroups of TBI patients.

### Key messages

— Early administration of progesterone offers no outcome benefit in moderate or severe TBI.
— An increased risk for thromboembolic events has been observed in patients treated with progesterone when compared to control patients in one study.
— A more coordinated and extensive early phase research might improve future trial design in TBI.

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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.

Spinal epidural abscess: stay focused, stay tuned! A clinical report with negative neurological outcome from the “Italian Registry of Complications associated with Regional Anesthesia - RICALOR”

Dear Editor,

Spinal-epidural abscess (SEA) may occur with thoracic epidural analgesia (TEA). We inserted a 20-gauge epidural catheter at T7-T8 in a 57-years-old patient (Whipple procedure), in aseptic conditions (surgical cap, face mask and sterile gloves; skin disinfection with 10% povidone-iodine and sterile draping). Her past medical history included hypertension (ASA II). A single-use elastomeric pump was prepared under sterile conditions and replaced on postoperative day (POD) II. On POD V, patients presented systemic inflammation characterized by pyrexia and leukocytosis with negative blood cultures, attenuating (but not resolving) up to POD VIII; epidural was removed (documenting an erythematous swelling area at the entry point). On POD VIII mid-abdominal pain and distension with perihepatic fluid collections (negative for any bacterial growth) were reported and empirically treated with teicoplanin (400 mg/daily), with partial resolution of the inflammatory status. On POD XII mid-back pain joined with progressive bilateral sensory loss (lower limbs, up to T4 dermatome) and motor deficit, leading to lower limb paralysis in a few hours; the MRI showed marked narrowing of the spinal canal and abnormal signal from the posterior epidural space (T6-T8). An emergency laminectomy of T6, T7, T8, and a partial laminectomy at T5

Figure 1.—MRI cuts documenting the epidural abscess with enhanced signal; A) sagittal plane; B) sagittal view — particular at thoracic level with abscess; C) transverse view; D) sagittal plane — evidence of cavitations and air-fluid levels within the epidural abscess.
and T9 was performed (Figure 1). Methicillin-sensitive *Staphylococcus Aureus* was isolated, highly sensitive to teicoplanin, which was increased to 600 mg/daily to reach the therapeutic interval, and continued up to POD 30. Sensory deficit recovered within one month; a sphincters’ dysfunction persisted (urinary retention requiring intermittent self-catheterization) up to one year. Motor impairment was persisting at three years (patient unable to walk without crutches).

We are currently running a prospective audit on epidural in our Institution, and this was the only SEA on more than 1800 patients, as well as the only SEA (on 4954 epidurals) documented in the “RICALOR” Study; otherwise, our experience shows that despite SEA is infrequent, long-term negative outcomes are not. Inoculation of bacteria along the needle track seems to be the most likely mechanism for epidural contamination. Strict aseptic technique is a major issue both during catheter’s placement (hat, long sleeves surgical gowns, gloves and face-mask, large sterile drape, skin disinfection with chlorhexidine), and management (sterile infusions, closed delivery systems, minimal bag changes, filters); catheter’s insertion site should frequently be inspected and maintained sterile, and catheter should be removed after 96 hours in any case (prolonged catheterization is also a risk for SEA), when exposed (due to dressing’s dislodgement) or if any sign of local infection occurs (reported in 70% of patients with SEA). Likewise, infection may also originate by bacterial spread from an infectious focus through the blood stream.

As most case reports do, we did not retrieve any obvious cause to epidural infection: since blood cultures and abdominal drainage were all negative, hematic spread from a distant focus is unlikely; we presume that the epidural space was directly contaminated by local bacteria. The strict aseptic procedure was followed during the procedure, but the prolonged catheterization (5 days) and pump’s replacement may account for infection. Otherwise, the main issue was the delayed diagnosis; SEA presentation can be insidious in nature: early signs can be unspecific, and misdiagnosis is common. In our case, delayed back pain, as well as the association of abdominal pain and abdominal fluid collections blamed abdominal complications for creating systemic inflammation. Unfortunately, mild but persisting signs of systemic and skin inflammation did not raise the suspicion of SEA, nor did dressing swabs nor catheter tip were cultured; furthermore, an antibiotic therapy was started but resulted ineffective due to low serum concentrations, arguably allowing the progression of the underlying abscess. This case confirms the importance of strict surveillance on patients developing fever, as well as local and/or laboratory signs of infection, without waiting for neurological deficits to occur. Early diagnosis and proper management are the mainstays for a positive outcome, promoting strict adherence to guidelines (assepsis, surveillance) since SEA remains infrequent, but rapidly evolving and potentially disastrous.

**References**


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**Impact of Axotrack™ for ultrasound-guided central venous catheter insertion: a randomized controlled study conducted on inanimate manikin**

Dear Editor,

Current guidelines recommend ultrasound guidance for central venous catheter insertion (US-guided CVC insertion). However, all physicians do not use this method. An explanation could be the difficulty encountered with an “in-plane” approach to follow needle progression because it has to be accurately placed in the
Twenty two declared previous experience in US-guided CVC insertion. Any participant had previously used the tested device. The manikin (Blue Phantom II, CAE Healthcare St. Louis, MO) mimics right internal jugular and subclavian veins, and carotid and subclavian arteries. A manual pump produces arterial pulse. Aspiration of blue fluid confirms venous puncture, whereas aspiration of red fluid rules in arterial puncture.

We used the M-turbo® device (Sonosite, Bothell, WA, USA) equipped with either a regular 7.5 MHz linear probe (control approach) or a specific probe (experimental approach) designed to adapt the Axotrack™ device (Soma Access Systems, Greenville, SC, USA). In clinical practice, using ultrasound guidance, the infraclavicular approach to central venous catheterization is achieved by puncturing the axillary vein, whereas the supraclavicular approach may be obtained through internal jugular or subclavian vein puncture. In the present study, the order in which punctures were performed on field explored. This can be obtained by positioning the needle in the exact middle of the probe. If not achieved, no or only part of the needle is visualized and complications occurred at a rate similar to what is observed with the landmark approach. Moreover, success rate at first attempt reported in studies is not 100% which is puzzling if one assumes that the procedure is performed under visual control. An observational study suggested usefulness of a device aimed at facilitate needle path visualization: Axotrack™. The device is an ultrasound probe incorporating a needle guidance system that permits a real-time information on both direction and depth of the needle continuously during the whole procedure (Figure 1). We planned the present study to assess the impact of this device for US-guided CVC insertion in an inanimate manikin.

After signing an informed consent form, 37 physicians - median age 37 [28, 45], graduated (29) or being in their graduating process (8), in emergency (15) or intensive care medicine (22) - were included in the study. Twenty two declared previous experience in US-guided CVC insertion. Any participant had previously used the tested device. The manikin (Blue Phantom II, CAE Healthcare St. Louis, MO) mimics right internal jugular and subclavian veins, and carotid and subclavian arteries. A manual pump produces arterial pulse. Aspiration of blue fluid confirms venous puncture, whereas aspiration of red fluid rules in arterial puncture.

We used the M-Turbo® device (Sonosite, Bothell, WA, USA) equipped with either a regular 7.5 MHz linear probe (control approach) or a specific probe (experimental approach) designed to adapt the Axotrack™ device (Soma Access Systems, Greenville, SC, USA). In clinical practice, using ultrasound guidance, the infraclavicular approach to central venous catheterization is achieved by puncturing the axillary vein, whereas the supraclavicular approach may be obtained through internal jugular or subclavian vein puncture. In the present study, the order in which punctures were performed on

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All values are expressed as median (range). Times are given as seconds and needle passes as number of occurrences. *P=0.008 compared to classic approach; **P=0.0001 compared to classic approach; ***P=0.02 compared to classic approach.

Figure 1.—Picture of the Axotrack (A) and its ultrasound images (B).
a simulator - supraclavicular (internal jugular) or infraclavicular site (axillary vein), control or experimental - were randomized (using a table). The number of needle passes required before success and the times (seconds) between 1) skin contact and first needle pass, and 2) first needle pass and success were recorded. Values are expressed as median (range). The U Mann-Whitney test was used to compare quantitative values. Proportions were compared using the χ² test or the Fisher exact test, as appropriate.

Finally, all participants performed their four catheter insertion and 148 approaches were therefore analyzed. AxoTrack™ decreased time required for venous puncture and the number of needle passes only at the infraclavicular site (Table 1). This was observed whatever previous experience in US-guided CVC insertion, suggesting that it also facilitates insertion among the most skilled physicians. This could be due to the greater intrinsic difficulty encountered for CVC insertion at the infraclavicular site (size and depth of axillary vein compared to jugular vein, pleura proximity) which often delays the first skin contact with the larger probe used in the control group. Conversely, at jugular site, the device increased the time between skin contact and first pass. This could be explained by chin proximity making AxoTrack™ sometimes difficult to handle in this area. Most of physicians approving AxoTrack™ use (60%) were naïve in the field of US-guiding CVC insertion (85% vs. 14%, P=0.001). These results suggest the potential interest of such devices for US-guided CVC insertion.

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Tetanus and TakO-Tsubo: is there a relationship?

Dear Editor,

Tako-Tsubo Syndrome (TTS), also defined “Left Ventricular Apical Ballooning Syndrome” because of the typical aspect of the left ventricle (LV) characterized by transient wall motion abnormalities involving the LV apex, is often precipitated by emotional or physical stress. Clinically it mimics an acute coronary syndrome without obstructive coronary disease. Etiopathogenesis of TTS remains unclear but an important hypothesis is the excess of circulating catecholamines. Some reports stated that autonomic dysfunction associated with medical illness, like Tetanus, might conduce to the development of myocardial damage. 2, 3 Autonomic instability with labile blood pressure, myocardial dysfunction and sympathetic overactivity are common in Tetanus. 4 We present a case of Tetanus and TTS in order to reveal a
possible connection between the two conditions, represented by autonomic dysfunction.

A 61 year-old woman was hospitalized because of cervical-chest pain and sweating. After worsening of pain, elevation of myocardial necrosis markers and ECG changes, she received therapy for myocardial ischemia. Symptoms persisted and rigidity involving superior and inferior limbs appeared. We diagnosed generalized Tetanus. She was treated with human tetanus immunoglobulin and antibiotics. During hospitalization she presented severe hemodynamic instability. Laboratory tests showed Troponin levels by 2.82 ng/mL. ECG revealed sinus tachycardia, ST-segment elevation and low voltage in V3-V6 leads. Echocardiography showed total akinesis of the LV mid segments and of the apex with severe systolic function impairment. We considered the diagnosis of TTS. A gradual improvement of the patient’s clinical condition was confirmed by instrumental exams. At the discharge the patient was oriented and collaborative. Echocardiography confirmed the hypokinesis of the apex. A coronary angiography resulted normal.

Management of tetanus is essentially supportive, using mechanical assisted ventilation, control of general spasticity and autonomic events. Our patient had a severe form of Tetanus characterized by generalized spasticity, impairment of respiratory function and autonomic events involving the cardio-vascular system (hypotension alternating with hypertension). These autonomic manifestations could represent a connection between Tetanus and Tako-Tsubo in our patient. Sympathetic overactivity appears to play a very important role in the pathophysiology of TTS. Several studies found high levels of catecholamines in suffering patients. It is unclear why some patients are more susceptible than others, maybe genetic heterogeneity of the adrenergic receptors renders them more or less sensitive to adrenergic stimuli which may explain this variability. The reason why myocardial stunning localizes preferentially at the apex could be that it has a greater density of adrenergic receptors. Our patient met all the Mayo Clinic criteria for diagnosis of TTC and she presented a global and multisegment ventricular dysfunction. The hypothesis of multi-vessel coronary spasm is unlikely. Toxic myocarditis may occur in Tetanus and may lead to hypotension, but the specific nature of myocardial lesions suggest that they may be catecholamine-induced rather than a direct effect on the myocardium of tetanus toxin. So the hypothesis of ventricular dysfunction as the result of a direct effect of the catecholamines on the myocardium is more credible. Therefore we conclude that Tetanus is a stressful event and it could represent a trigger for TTS.

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CORRIGENDUM

In volume 81, issue no. 9 – March, page 1044, in the article entitled “An additional tip to facilitate glidescope intubation”, the correct authors’ names are: Turkstra T.P., Rachinsky M., Batohi P.
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