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Procedural sedation in Belgium : guideline for safe patient care

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Abstract : Guideline produced by the Society for Anesthesia and Resuscitation of Belgium Working Group on Procedural Sedation (SARB-WG-PS).

Keywords : procedural sedation ; patient safety ; guidelines.

Introduction

More and more procedures are performed under superficial or more profound sedation. The number of diagnostic and therapeutic interventions, for which procedural sedation is used is increasing every day (1, 2). This is due to the growth of minimally invasive procedures performed at remote locations (remote from the main Operating Room) and the increasingly frail, older and sick patient population. Also, more novel drugs with a short acting profile and a profile ideally suited for sedation facilitate the growth of procedural sedation in many situations. Additionally, in some areas, a shortage of trained anesthesiologists generates the need for procedural sedation performed by non-anesthesiologists.

However, procedural sedation carries many risks and therefore adequate support, training and monitoring are required to safely execute sedation (1, 2). The current document is produced by the Society for Anesthesia and Resuscitation of Belgium (SARB) Working Group on Procedural Sedation and endorsed by the Belgian College of Emergency Physicians, the Belgian Society of Disaster Medicine, and the Belgian University Professors of Emergency Medicine, and the Interventional Radiology Section of the Belgian Society of Radiology. The goal of the guideline is to enhance the quality and safety of procedural sedation in adults performed by anesthesiologists and non-anesthesiologists. The document translates various recent international guidelines into a guidance document suited for the Belgian situation (1-3). Most importantly, it will not focus on the pediatric population, nor will it address sedation in

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the intensive care unit, the emergency department, and out of hospital emergency interventions. It could serve as a framework for hospitals and anesthesiology departments.

In particular, SARB believes that healthcare professionals delivering procedural sedation must not only be cognizant of the potential complications but must also be able to diagnose the complications, manage them clinically, and provide or request alternative therapies, such as resuscitation and the necessity of general anesthesia to a physiologically unstable patient who may have multiple comorbidities.

For high-risk patient groups or high-risk procedures or more profound levels of sedation, patient safety is best served when sedation is delivered by medically qualified healthcare professionals who are enrolled in or have completed an accredited full training program in anesthesiology.

Definition of procedural sedation

The administration of anxiolytic, sedative, hypnotic, analgesic, and/or dissociative medication(s) to attenuate anxiety, pain, unwanted reflexes and/or motion during a diagnostic or therapeutic procedure. These agents are administered in order to facilitate amnesia, decrease awareness, improve patient comfort and/or safety during a diagnostic or therapeutic procedure (2).

Complications and risks associated with procedural sedation

Practitioners who administer procedural sedation and/or analgesia should be aware that the transition from complete consciousness through the various depths of sedation to general anesthesia is a continuum and not a set of discrete, well-defined stages. The margin of safety of drugs used to achieve sedation and/or analgesia varies widely between patients and loss of consciousness with its attendant risk of loss of protective reflexes may occur rapidly and unexpectedly. Procedural sedation is associated with adverse events (AE's) and mortality, which occur much more frequently with procedural sedation than with general anesthesia or regional anesthesia (2). Too deep sedation, airway obstruction, respiratory or cardiovascular complications may occur insidiously at any time. Therefore, practitioners who administer sedative, analgesic or other drugs that alter the conscious state of a patient, and those who supervise recovery from sedation, must be prepared to identify and manage the potential risks such as :

1. Depression of protective airway reflexes, airway obstruction and loss of airway patency ;
2. Depression of respiration in frequency and depth ;
3. Depression of the cardiovascular system ;
4. Drug interactions or adverse reactions, including anaphylaxis ;
5. Unexpectedly high sensitivity to the drugs used for procedural sedation and/or analgesia which may result in unintentional loss of consciousness, and respiratory or cardiovascular depression ;
6. Individual variations in response to the drugs used, particularly in the extremes of age, and those with pre-existing disease ;
7. The possibility of unintended deeper levels of sedation ; risks inherent in the wide variety of procedures performed under procedural sedation and/or analgesia.

According to Agostino et al. various factors can predict the occurrence of a complication : age, ASA (American Society of Anesthesiologists) score, Mallampati score, emergency and length of the procedure (4). Although various complications can occur, they are rare. Bellolio et al reported on serious complications (5). The most common adverse event is hypoxia, with an incidence of 40.2/1,000 sedations, followed by vomiting with 16.4 to 170/1,000 sedations and hypotension with 15.2/1,000 sedations. Severe adverse events requiring emergent medical intervention were rare, with one case of aspiration in 2,370 sedations (1.2/1,000), one case of laryngospasm in 883 sedations (4.2/1,000), and two intubations in 3,636 sedations (1.6/1,000). Apnea was estimated to occur in 51.4/1,000.

Recently, two tools have been described to record and evaluate in a standardized way the complications and adverse events associated with procedural sedation (6, 7). In 2012, the world SIVA (World Society for Intravenous Anesthesia) international sedation task force described a standardized set of definitions for adverse events occurring during procedural sedation (6). They integrated various international definitions of adverse events into one comprehensive definition of adverse events that is sedation specific : *'Unexpected and undesirable response(s) to medication(s) and medical intervention used to facilitate procedural sedation and analgesia that threaten or cause patient injury or discomfort'*. A tool was then synthetized and published for standardized reporting of adverse events which can be found on the world SIVA website. Minimal, minor and sentinel adverse events were defined as well as the

strategy to manage the adverse events. Outcome is also reported in the tool.

Roback et al. in 2018 reported on the tracking and reporting outcomes of procedural sedation (TROOPS) tool (7). The International Committee for the Advancement of Procedural Sedation (ICAPS, www. ProceduralSedation.org) developed a multidisciplinary, consensus-based, standardized quality-improvement tool intended to be applicable for all types of sedation providers in all locations worldwide. This tool is suitable for inclusion in either a paper or an electronic medical record. It is founded upon the premise that adverse events are best defined by their associated interventions and patient-centered outcomes. An additional, parallel research tool is presented to promote consistency and standardized data collection for procedural sedation investigations.

The SARB Working Group on Procedural Sedation suggests to use a standardized tool such as the SIVA tool or TROOPS tool.

Levels of Sedation

The ASA has defined four levels of sedation where level 4 corresponds to general anesthesia. The four defined levels of sedation are : minimal sedation (anxiolysis), moderate sedation/analgesia, deep sedation/analgesia and general anesthesia. These four levels of sedation can be defined as :

Level 1 : Minimal sedation/anxiolysis : patient has eyes open spontaneously.

Level 2 : Moderate sedation/analgesia : patient responds to verbal commands.

Level 3 : Deep sedation/analgesia : patient reacts only to tactile stimulation.

Level 4 : General anesthesia : patient does not react to stimulation.

This terminology with a subdivision into four clearly defined levels of sedation still stands today as it is incorporated in the latest and recent versions of American (ASA, American Society of Anesthesiology) and European (ESA, European Society of Anaesthesiology) guidelines for procedural sedation (1, 2). In its recommendations on patient safety in anesthesia, the SARB adds a supplementary level (which here would be level 0) defined as “awake and oriented” (8). It must be emphasized that the various levels of sedation are a continuum and evolution to a more profound level of sedation is always possible. Therefore, continuous vigilance, monitoring of the patient and the actual depth of sedation are required.

Governance of procedural sedation

Although sedation is performed by different health care providers worldwide, the Joint Commission on Accreditation of Healthcare Organizations mandates that procedural sedation throughout any accredited institution should be monitored and evaluated by the Department of Anesthesia [2]. In level 1 or 2, anesthesia professionals are not required to be directly responsible for doing sedation, but rather to have an advisory and supportive role and should evaluate safety and quality. In level 1 and 2, the physician performing the procedure for which sedation is requested and administered is responsible for the sedation. The sedation however is performed by another health care provider.

The SARB (Society of Anesthesia and Resuscitation of Belgium) Working Group on Procedural Sedation advises that for level 1 and 2 sedation in ASA 1 and 2 patients, sedation can be performed by or delegated to health care providers that are non-anesthesiologists but that are trained by the Anesthesiology Department. For level 3 sedation or higher and in patients with ASA class 3 or higher, sedation should always be performed by an anesthesiologist. It must be emphasized that the health care professional performing procedural sedation should NOT be involved in the execution of the actual intervention for which procedural sedation is administered. However, in level 1 and 2 sedation, the provider performing sedation can assist the physician doing the procedure. For level 3 or 4, sedation is a task which excludes any other task performed at the same time.

Patient evaluation and preparation

Currently, there is insufficient evidence that pre-procedural evaluation of a patient prior to sedation reduces mortality and morbidity. Observational studies indicate that some adverse outcomes (*e.g.*, unintended deep sedation, hypoxemia or hypotension) may occur in patients with some preexisting medical conditions when procedural sedation is administered. These conditions include : extremes of age, ASA status III or higher, obstructive sleep apnea, respiratory distress syndrome, chronic renal and hepatic impairment, morbid obesity (BMI>40), allergies, psychotropic drug use, history of gastric bypass surgery, pediatric patients who are uncooperative or who have behavior or attention disorders, cardiovascular disorders, and history of long-term benzodiazepine use. Case reports indicate similar adverse outcomes for newborns,

patients with mitochondrial disease, epilepsy with tonic-clonic seizures, and patients with a history of benzodiazepine use (9). The SARB Working Group on Procedural Sedation also warn practitioners on the possibility of more frequent adverse outcomes after procedural sedation in patients with neuromuscular disorders such as amyotrophic lateral sclerosis, and myasthenia. Due to their motor weaknesses, those patients are particularly sensitive to the effects of sedation medications, and are particularly at risk of ventilation problems. Special caution should also be paid to patients with a history, familial or personal, of malignant hyperthermia. Therefore, it is advised that ALL patients undergoing procedural sedation are screened and evaluated prior to sedation. The recommendations are to review previous medical records and interview the patient or family, conduct a focused physical examination of the patient, and review available laboratory test results. The Working Group recommends, if possible, to perform the pre-procedure evaluation well enough in advance (days to weeks). In case of any doubt regarding an eventual increased risk for the patient to undergo level 1 and 2 sedation with regard to his/her past medical history, including neuromuscular disorders and malignant hyperthermia, the advice of an anesthesiologist should be sought at. The pre-procedure evaluation files of patients scheduled to undergo level 3 or higher sedation should be reviewed by an anesthesiologist.

Additionally, pre-procedure preparation is essential. Patients should receive all necessary information on procedural sedation and the alternatives. Information about potential side-effects and the required precautions (such as the need for a third party to assist in the hours after sedation and the prohibition to manage a motorized vehicle) should be made available. Patients should be informed about the correct fasting times (and they should strictly adhere to them). Currently, there is no clear evidence-based fasting protocol for procedural sedation that results in a decreased incidence of adverse effects. Guidelines related to preoperative fasting prior to surgery have become more liberal and allow clear liquids until 2 hours and solid food until 6 hours prior to surgery.

For all patients undergoing procedural sedation it is recommended to have a secure intravenous access, which is open and accessible. However, there might be situations in which an IV access is not absolutely mandatory and actually might induce more problems.

Monitoring and location

Monitoring should be established according to safety first guidelines (8). This should include standard electrocardiographic monitoring (ECG), non-invasive blood pressure monitoring (NIBP), saturation monitoring by pulse oximetry and capnography. Even in spontaneously breathing patients that are not intubated, capnography is essential. Pulse oximetry is not a substitute for ventilation monitoring (1, 2). Parker and co-workers performed a systematic review of the use of capnography during moderate levels of procedural sedation and concluded that capnography reduced the risk of hypoxemia (by 31%), increased the detection of adverse respiratory events, and was not associated with additional harm (10). Capnography will detect respiratory depression at an earlier stage than any other type of monitoring. Each sedated patient in a level 2 state of sedation or higher deserves capnography. Visual evaluation of the patient is necessary at all times and vital signs should be meticulously recorded in a sedation record. A record on regular time points of the actual level of depth of sedation should be performed.

Administration of additional oxygen is debatable since high oxygen concentrations can induce respiratory depression by reducing respiratory drive and can mask respiratory depression. The working group advises to administer supplementary oxygen when oxygen saturation drops below 93% together with other measures. When oxygen saturation is higher than 93% no additional oxygen is absolutely indicated.

Locations in which sedation is performed should have adequate lighting, electrical outlets, oxygen supply, suction equipment, and the rooms should have sufficient size. We refer to the recently published updated Safety First Guidelines in this respect (8). An emergency call system and a clear route for evacuation of a patient on a stretcher in case of emergency should be available.

In each location where procedural sedation is performed, immediate availability to resuscitation equipment must be guaranteed. This includes equipment for advanced airway management in case of difficult airway. Also, equipment for advanced cardiac life support such as a defibrillator must be closely available.

Sedative agents

It is beyond the scope of these recommendations to review in detail the pharmacology of sedative and analgesic drugs commonly used for procedural

sedation. They have been previously described elsewhere in detail (11-13). The attending physician, responsible for sedation, should make a drug selection based on the protocols written by the Anesthesiology Department. To ensure well tolerated, effective and safe drug administration, the health care provider performing sedation should always be aware of the pharmacological properties of each drug and drug combination used. Drug selection should be based on ease of dosing to reach and maintain the desired level of sedation, avoiding adverse events due to excessive dosage, or unexpected reactions to individual drugs or drug combinations. As such, theoretically, the ideal drug for procedural sedation has a rapid onset, short duration of action and time-independent context-sensitive half-time. In addition, it should have an advantageous hemodynamic and respiratory profile. Most of the time, drug combinations are required. Therefore, the clinician should understand the principles of drug interactions to balance between clinical effects and side-effects. The recommended route of administration is the intravenous one, insofar as, in that case, the pharmacokinetics and pharmacodynamics can be better predicted.

Antidotes should be readily available at the location where sedation is performed.

Sedation by non-anesthesiologists can only be performed using standard doses of benzodiazepines in monotherapy and nitrous oxide in monotherapy up to a 50% concentration. Combination therapy or the use of sedative agents such as propofol, ketamine, opioids, or IV dexmedetomidine is reserved to anesthesiologists.

Minimal personnel requirements

Anesthesiologists are adequately trained to perform all levels of procedural sedation. Non-anesthesiology care providers that perform sedation (see above for what is allowed) and the responsible physician should be adequately trained by the Anesthesiology Department to monitor and manage the whole process and associated adverse effects. This includes at least :

– Training to perform pre-sedation assessment as described above.
– Knowledge of fasting guidelines.
– Knowledge of sedative drugs and monitoring devices.
– Knowledge and management of hemodynamic complications.
– Skills of basic airway management.
– Skills on the use of additional oxygen.
– Skills of defibrillation.
– Knowledge of the most common and the most serious complications.

Training of non-anesthesiologists to provide procedural sedation should be controlled and performed by the Anesthesiology Department and by anesthesiologists (1, 2). The treating physician is responsible for the patient and the sedation executed by health care providers when the targeted level of sedation is level 1 or 2. A rescue emergency protocol needs to be available at all times.

Recovery from sedation

All facilities and areas in which procedural sedation is performed should have clear possibilities to monitor patients following sedation. Although there is no clear evidence on who should monitor patients and how long patients should be monitored, from a practical point of view, post-sedation monitoring (with at least NIBP, ECG, capnography and pulse oximetry) is essential to supplement visual observation by a trained nurse. Monitoring for at least 30 minutes after procedural sedation is mandatory and until full patient recovery has occurred.

Discharge criteria should be designed to minimize the risk for cardiorespiratory depression after patients are released from observation by trained personnel. Some discharge scores have been used successfully to assess the patient after sedation. The ALDRETE (14) score is easily feasible and is proposed by the Working Group as a valuable tool. An alternative might be the PADSS score (15). Clear written discharge instructions should be given to the patient and to the patient's caregiver who needs to accompany the patient after discharge. The clinician discharging the patient needs to explain the postoperative plan, the problems that can arise and how to solve them, what is allowed or not allowed during the first 24 hours, including not driving motorized vehicles, and when the patient can return to normal activity. A follow-up should be offered to the patient in case he/she experiences problems after having been discharged home.

Summary of recommendations

1. Procedural sedation is performed with an increasing frequency.
2. Procedural sedation is defined as the use of anxiolytic, sedative, hypnotic, analgesic, and/or dissociative medication(s) to attenuate anxiety, pain, unwanted reflexes and/or motion during

a procedure. These agents are administered in order to facilitate amnesia, decreased awareness, patient comfort and/or safety during a diagnostic or therapeutic procedure.

3. Procedural sedation is associated with ad-verse events usually related to obstructive breathing, hypoxemia or cardiovascular instability.
4. Identification of risk factors for complica-tions is essential for health care providers performing sedation.
5. The SARB Working Group on Procedural Sedation suggests to use a standardized tool such as the SIVA tool or TROOPS tool to record complications.
6. The SARB Working Group on Procedural Sedation advises that superficial levels of sedation in ASA 1 and 2 patients can be performed by non-anesthesiologists which are trained by the Anesthesiology Department. Deeper levels of sedation and sedation in ASA class 3 or higher should always be performed by an anesthesiologist. Sedation by non-anesthesiologists can only be performed using standard doses of benzodiazepines in monotherapy and nitrous oxide in monotherapy up to a 50% concentration or by intranasal dexmedetomidine. Combination therapy or the use of sedative agents such as propofol, ketamine, opioids or IV dexmedetomidine is reserved to anesthesiologists.
7. Procedural sedation is an exclusive task. The person in charge of sedation cannot perform the intervention. Only in case of level 1 or 2 sedation, the person performing sedation is allowed to assist the physician.
8. Four levels of sedation as defined by the ASA and SARB should be adopted : Minimal sedation (anxiolysis) ; moderate sedation/ analgesia, deep sedation/analgesia and general anesthesia.
9. All patients should receive in depth pre-procedural and pre-sedation screening, which is performed preferably well in advance of the procedure and sedation.
10. Fasting guidelines should be adhered to, informed consent should be given, and an IV access should be established.
11. Monitoring of sedation should be done according to the SARB Safety First guidelines [8] and should include ECG, NIBP, pulse oximetry and capnography monitoring.
12. Locations should be safe and accessible, and resuscitation equipment should be immediately available.
13. Drugs for procedural sedation should have a rapid onset and short duration of action.
14. Personnel should have knowledge about the sedative drugs used.
15. Non anesthesiology personnel performing sedation should have received adequate training from anesthesiologists.
16. Recovery from sedation is done in a specific area and patients are discharged according to an established discharge score.

Conflicts of interest

MVDV, during the last three years (2018-2019-2020), received honoraria for consultancy, lectures and research from Aguettant, Aspen, CLS Behring, Ever Pharma, Ferrer, Flatmedical, Grunenthal, HeronTx, Janssen Pharmaceuticals, Medtronic, MSD, Nordic Pharma, Sintetica and Viforpharma. MVDV received research grants in the last three years from the Belgian Association of Regional Anesthesia (BARA), European Society of Regional Anesthesia and Pain Therapy (ESRA), Belgian Society of Anesthesia and Resuscitation (BSAR) and the Obstetric Anesthetists Association (OAA).

LB during the last three years (2018-2019-2020), received honoraria for consultancy, lectures and research from Medtronic.

MC during the last three years (2018-2019-2020), received honoraria for consultancy, from Medtronic and a research grant from Teleflex Medical Incorporated.

PF during the last three years (2018-2019-2020), received honoraria for consultancy, lectures and research from Medtronic. PF received no research grants in the last three years.

JJ has no conflicts of interest to disclose.

JM during the last three years (2018-2019-2020), received honoraria for consultancy, lectures and research from Medtronic, Merck, Johnson & Johnson and GE Healthcare. JM received research grants in the last three years from Merck.

BR during the last three years (2018-2019-2020), received honoraria for consultancy, lectures and research from Medtronic.

DvB during the last three years (2018-2019-2020), received honoraria for consultancy, lectures and research from Baxter and Medtronic

VvR during the last three years (2018-2019-2020), received honoraria for consultancy, lectures and research from Medtronic. VvR received no research grants in the last three years.

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(Acta Anaesth. Belg., 2020, 71, 171-174)

Ultrasound transversus abdominis plane (TAP) block versus local infiltration analgesia for acute and chronic postoperative pain control after laparoscopic bilateral hernia repair : a single-center randomized controlled trial

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Abstract : *Background* : we compared the efficacy of transversus abdominis plane (TAP) block versus local infiltration on acute and chronic pain after a first laparoscopic surgical treatment of bilateral inguinal hernia performed in a day hospital.
Methods : In this randomized, prospective, double-blind study, we studied 52 patients scheduled for lapa-roscopic bilateral hernia repair. The patients were randomly allocated to receive local infiltration (group 1) or a TAP block (group 2). The surgeon locally injected the patients in group 1 with a solution of 20 mL of 0.5 levo-bupivacaine. An ultrasound-guided injection of 40 mL 0.25 levobupivacaine was administered to the patients in group 2 by the anesthesiologist. The pain score was assessed using a numeric rating scale at the arrival in the recovery room, one hour after surgery and 6 hours (H+6) after arrival at the recovery room. Subsequently, the pain was assessed 24 hours (H+24), 3 weeks (D21) and 3 months (M3) after surgery.
Results : We observed significant differences in terms of pain at H+6 and at H+24 in favor of the TAP block group. However, there was no significant difference between both groups in postoperative pain after 3 weeks (D21) or after 3 months (M3).
Conclusions : In our study, we observed a significant difference in terms of pain in favor of TAP block versus local infiltration, during the first 24 hours after a first laparoscopic treatment of inguinal hernia. We did not find any significant difference on chronic pain.

Keywords : Pain ; postoperative ; anesthesia ; local ; levobupivacaine.

Introduction

The surgical treatment of inguinal hernia is one of the most common surgical procedures. At least 24 998 cases were treated in Belgium in 2017 (1). Approximately 180-200 inguinal hernia surgeries are performed every year as first treatment in our institution. It is a well-established fact that surgical trauma can lead to chronic pain (2). This pain is mainly caused by nerve lesions in the inguinal canal, due to scar tissue remodeling secondary to the presence of the prosthesis, due to the way the prosthesis is fixed (staples, sutures) or due to recurring of the hernia. The pain can also be visceral, especially in the vas deferens. Chronic pain can affect the patient's daily routine and professional activities, which may have both social and financial impact.

The multimodal approach to postoperative pain treatment, including loco-regional anesthesia, has proven advantages both in terms of pain intensity and sooner recovery (3). The aim of this study is to compare the efficacy of transversus abdominis plane (TAP) block versus local infiltration on acute and chronic pain, after a first laparoscopic surgical treatment of bilateral inguinal hernia performed in a day hospital.

Methods

Study patients

Following approval by the Ethics Committee of the Centre Hospitalier Chrétien (CHC), 58 patients were recruited between November 2017 and October 2018 to participate in this prospective,

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randomized, double-blind study conducted in our institution (Hôpital Saint-Joseph, CHC Liège, Belgium) (see Figure 1). Each patient's consent was obtained before surgery. In order to eliminate the bias coming from the surgeon's influence on postoperative pain, only one surgeon participated in our study. All patients scheduled for surgical treatment of bilateral inguinal hernia were eligible for our study. Patients hospitalized for reasons other than surgery, as well as those with high pain scores at the initial evaluation before surgery, were excluded.

Study design and treatment protocol

Randomization was performed with consecutively numbered, opaque, sealed envelopes opened sequentially to determine the patient's treatment assignment. The patients were divided into two groups. The first group (Group 1) underwent local infiltration, while the second group (Group 2) was treated by TAP block. The local anesthetics were administered in both groups just after induction of anesthesia and before any surgical stimulation. The patients in Group 1 (local infiltration) received an injection of 20 mL of 0.5 levobupivacaine, performed by the surgeon at the site of trocar and camera insertion, with a 21G needle (BD Microlance® 0.8 x 50 mm). Only one surgeon participated in this study. The prosthesis (3D Max® Light Mesh, BARD®) was not fixed. The patients in Group 2 (TAP block) received an ultrasound-guided injection (General Electric Device, LOGIC® P9, linear probe 4-12Hz). The ultrasound probe was oriented transversely to the anterolateral abdominal wall where the three muscle layers (external oblique, internal oblique, and transverse abdominal muscle) were most visible. Then, the probe was moved more posterior and lateral until the emergence of transverse abdominal muscle was clearly visible. The needle (Pajunk® SonoTAP, 21G x 110 mm) was introduced in-plane, and 20 mL of 0.25 levobupivacaine were injected on each side into the plane between the internal oblique and transverse abdominal muscles. The optimal position was confirmed by the hydrodissection of the transverse abdominal muscle plane. Only two anesthetists, with more than 10 years of experience, performed the TAP blocks.

All the patients included received premedication one hour before surgery. This consisted of one tablet of etoricoxib 120 mg and one tablet of alprazolam 0.25 or 0.5 mg. The induction of general anesthesia consisted of one intravenous injection combining propofol (2 mg/kg), sufentanil (0.15 µg/kg) and rocuronium (0.6 mg/kg). All patients received orotracheal intubation. An inhalational anesthetic (sevoflurane) in a 50 oxygen/air mixture was used for maintenance. A drip of one litre NaCl 0.9% was administered peroperatively. All patients received systemic analgesia of 2 g paracetamol and 2 mg/kg tramadol 30 minutes before waking up. The patients were extubated as soon as surgery was complete, and transferred directly to the recovery room, where they were monitored for one hour on average. Postoperative analgesia included administration of paracetamol 1 g four hours after the first injection and every 6 hours afterwards. Etoricoxib 120 mg was given for 5 days starting from the morning after surgery, and tradonal odis 50 mg/8 hours if necessary.

Outcome measures and baseline data collection

Each patient's body mass index (BMI) and classification according to the American Society of Anesthesiology were noted. A Kalkman-score[10] was calculated during the preoperative anesthesia consultation, in order to evaluate the risk for postoperative chronic pain occurrence. We excluded from the study all patients with a Kalkman score of >7/15, patients under anticoagulant therapy or platelet aggregation inhibitors with the exception of acetylsalicylic acid, as well as the patients with a history of allergy to local anesthetics. During the preoperative visit, pain at rest was measured using a visual analogue scale (VAS). Pain score at rest was assessed using a numeric rating scale ranging from 0 (no pain) to 10 (unbearable pain). This was recorded as soon as the patient arrived at the recovery room, then again one hour after the surgery and once more after a 6 hours stay in the recovery ward. When pain scores exceeded 4 on the numeric rating scale, the patients were further treated with titrated doses of piritramide. The pain was also assessed 24 hours after surgery, at the ward, and recorded after a phone call to the day hospital nurse. Finally, the VAS was also measured during the postoperative surgery consultation three weeks and three months after surgery. The nurses and the surgeon performing the pain assessments were unaware of the analgesic technique used in the patient. The difficulty of dissection was evaluated in a subjective way by the surgeon and qualified as easy, normal or difficult. The average duration of surgery, as well as the possible postoperative complications (bleeding, vesical globe, etc.) were also recorded.

Statistical analysis

Quantitative variables were expressed as mean ± standard. Qualitative variables were expressed as frequencies and percentages. Continuous variables were compared using t-test if the variable was normally distributed, or Wilcoxon test if not. The chi-square statistic was used for categorical variables. All statistical testing was two-sided and differences were considered significant when the p value was less than 0.05.

Results

One patient was excluded from the study one hour after waking up, because he developed a hematoma at the surgical site. Five other patients were also excluded, because they underwent inguinal hernia treatment using a different method or with combined surgery such as umbilical hernia or scar revision, see Fig. 1.

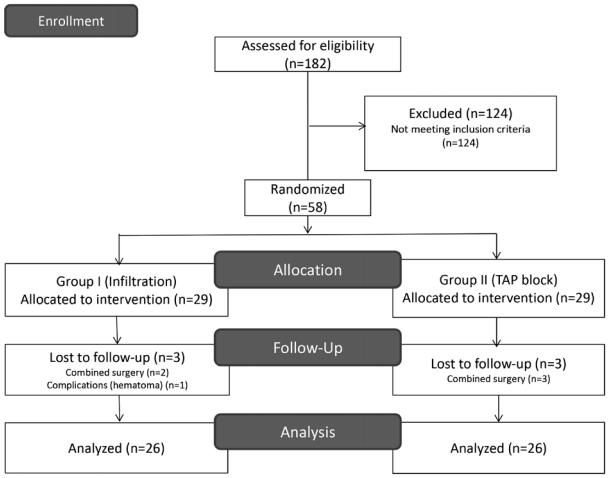

Fig.1. — Randomization flow diagram.

The characteristics of the patients included in the study are shown in Table 1. The average age was 54.1 ± 13.2 years in Group 1 vs. 58.4 ± 14.9 years in Group 2 (p = 0.283). The ratio of male patients was 88.5 in Group 1 vs. 96.2 in Group 2 (p = 0.298). The BMI was 25.1 ± 2.9 kg/m^2 in Group 1 vs. 24.2 ± 2.7 kg/m^2 in Group 2 (p = 0.251). The ratio of ASA I, II and III patients was 57.7, 42.3 and 0 in Group 1 and 38.5, 53.8 and 7.7 in Group 2 respectively (p = 0.186).

Surgery details are given in Table 2. The average duration of surgery from the time of the incision until the last stitch was 37.2 ± 10.7 min. in Group 1 vs. 41.2 ± 9.9 min. in Group 2 (p = 0.114). Surgery was qualified as easy (E), normal (N) or difficult (D) for 76.9 %, 15.5 % and 7.7 % of patients in Group 1 vs. 69.2%, 15.4% and 15.4% of patients in Group 2 respectively (p = 0.680).

Table 1

Characteristics of the two groups after inclusion

	All	Infiltration	TAP block	p
	(n = 52)	(n = 26)	(n = 26)	
Age (years)	56.2 ± 14.1	54.1 ± 13.2	58.4 ± 14.9	0.283
Male (n) (%)	48 (92.3)	23 (88.5)	25 (96.2)	0.298
Average BMI (kg/m^2)	24.6 ± 2.8	25.1 ± 2.9	24.2 ± 2.7	0.251
ASA (n)				0.186
I	25 (48.1)	15 (57.7)	10 (38.5)	
II	25 (48.1)	11 (42.3)	14 (53.8)	
III	2 (3.8)	0 (0)	2 (7.7)	

Table 2

Surgery details

	All	Infiltration	TAP block	p
	(n = 52)	(n = 26)	(n = 26)	
Average duration of surgery (min)	36.2 ± 10.4	37.2 ± 10.7	41.2 ± 9.9	0.114
Dissection (n)(%)				0.680
E	38 (73.1)	20 (76.9)	18 (69.2)	
N	8 (15.4)	4 (15.4)	4 (15.4)	
D	6 (11.5)	2(7.7)	4 (15.4)	

Table 3

Pain scores at rest

	All	Infiltration	TAP block	p
	(n = 52)	(n = 26)	(n = 26)	
Hour +1	1.79 + 1.55	2.15 + 1.57	1.42 + 1.47	0.071
Hour +6	1.85 + 1.46	2.35 + 1.6	1.35 + 1.13	0.031
Hour +24	1.96 + 1.41	2.54 + 1.48	1.38 + 1.10	0.006
Day +21	0.65 + 0.56	0.77 + 0.59	0.5 + 0.51	0.163
Month +3	0.15 + 0.36	0.23 + 0.43	0.08 + 0.27	0.128

In both groups, the same amount of postoperative opioids were used : 4 patients (15.4%) in Group 1 vs. 3 patients (11.5%) in Group 2 received a piritramide injection in the postanesthesia care unit (p = 0.685). The average injected dose was 4 ± 1.63 mg vs. 2.67 ± 1.15 mg (p=0.4). One patient (3.85%) in Group 1 experienced nausea and vomiting in the recovery room. Two patients (7.7%) in Group 2 experienced nausea without vomiting.

No major incident occurred during the surgical procedure in patients of either group. No signs of cardiovascular toxicity or neurotoxicity were observed in the patients. Nor were there allergic reactions, urinary signs or behavioral problems. All patients were able to leave the day hospital on the same day.

The postoperative pain (VAS) scores are shown in Table 3.

Discussion

Chronic pain after inguinal surgery is described as a kind of pain that is present for at least three months after surgery (13). According to studies, its incidence varies from 0.7 to 43.38 (8). The risk of the pain becoming chronic is higher for patients with high scores of early pain in comparison to those having low scores (9 vs. 3, $p < 0.05$), after one week (4). The relevant literature offers contradictory results regarding the superiority of TAP block versus infiltration in terms of acute and chronic pain following this type of surgery. This may be partially due to the different techniques and adjuvant treatments used for analgesia.

Petersen et al. did not observe a decrease in postoperative pain or in the consumption of morphine between TAP block and ilio-inguinal injection in patients treated for inguinal hernia[5]. Other studies have shown identical efficacy with TAP block vs. local infiltration in cases of acute pain. Still, TAP block is more efficient in cases of long-lasting pain for lower abdominal surgery, especially at 24 hours after surgery (6).

Talib et al. showed the superiority of TAP block over local infiltration in terms of nausea and vomiting, as well as of rescue analgesia (7). S. Arora et al. showed that TAP block significantly decreases VAS at rest for more than 24 hours in comparison with local anesthetic infiltration in patients treated for inguinal hernia via laparoscopy (9).

In our study, we observed significant difference in terms of pain at H+6 and H+24, and a non-significant tendency at H+1. However, there was no significant difference in pain on D21 and in M3 postoperatively. In both groups, we injected the same quantity of local anesthetic. The total volume injected was higher in the TAP block group because it is a field block, hence local anesthetic volumes required are high.

There was no difference in the morphine consumption in the recovery room. The fact that the surgeon who performed pain assessment was the surgeon who had performed the procedure could be considered among the limitations of this study. However, this bias may be regarded as one of little importance as, at three weeks and then at three months after the procedure, the surgeon could not truly have remembered the analgesic technique he used on the day of surgery.

Blanco et al. showed that quadratus lumborum (QL) block has a more prolonged effect than TAP block in reducing morphine consumption and demands after Cesarean section (11). In our series, the effect of TAP block lasted at least 24 hours and this may be due to the very posterior approach of our puncture that can be apparented to a QL block which is probably a better option than TAP block in terms of quality and duration of analgesia with a potential visceral effect (12).

Conclusion

In our study, we observed that there is only a significant difference in terms of postoperative pain in favor of a TAP block versus local infiltration, during the first 24 hours following a first laparoscopic treatment of inguinal hernia. We did not find any difference on chronic pain.

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KLINISCHE GEGEVENS 4.1 Therapeutische indicaties** Opheffing van de door rocuronium of vecuronium geïnduceerde neuromusculaire blokkade bij volwassenen. *Voor pediatrische patiënten:* bij kinderen en adolescenten van 2 t/m 17 jaar wordt het gebruik van sugammadex alleen aanbevolen bij standaardopheffing van een door rocuronium geïnduceerde neuromusculaire blokkade. **4.2 Dosering en wijze van toediening** Dosering Sugammadex mag alleen worden toegediend door of onder supervisie van een anesthesist. Het gebruik van een geschikte neuromusculaire monitortechniek wordt aanbevolen om het herstel van de neuromusculaire blokkade te bewaken (zie rubriek 4.4). De aanbevolen dosis sugammadex is afhankelijk van het niveau van de op te heffen neuromusculaire blokkade. De aanbevolen dosis is niet afhankelijk van de toegediende anesthesie. Sugammadex kan worden gebruikt voor opheffing van verschillende niveaus van door rocuronium of vecuronium geïnduceerde neuromusculaire blokkade: ***Volwassenen*** *Standaardopheffing:* Er wordt een dosis van 4 mg/kg sugammadex aanbevolen indien het herstel ten minste 1-2 posttetanische tellingen (PTC) heeft bereikt na een door rocuronium of vecuronium geïnduceerde blokkade. De mediane hersteltijd van de T4/T1-ratio tot 0,9 is ongeveer 3 minuten (zie rubriek 5.1). Een dosis van 2 mg/kg sugammadex wordt aanbevolen als spontaan herstel is opgetreden tot minimaal het terugkeren van T2 na een door rocuronium of vecuronium geïnduceerde blokkade. De mediane hersteltijd van de T4/T1-ratio tot 0,9 is ongeveer 2 minuten (zie rubriek 5.1). Het gebruik van de aanbevolen doses voor standaardopheffing na rocuronium zal ten opzichte van een door vecuronium geïnduceerde neuromusculaire blokkade leiden tot een iets snellere mediane hersteltijd van de T4/T1-ratio tot 0,9 (zie rubriek 5.1). *Onmiddellijke opheffing van een door rocuronium geïnduceerde blokkade:* Als er een klinische noodzaak bestaat voor onmiddellijke opheffing na toediening van rocuronium, wordt een dosis van 16 mg/kg sugammadex aanbevolen. Als 16 mg/kg sugammadex 3 minuten na een bolusdosis van 1,2 mg/kg rocuroniumbromide wordt toegediend, kan een mediane hersteltijd van de T4/T1-ratio tot 0,9 van ongeveer 1,5 minuten worden verwacht (zie rubriek 5.1). Er zijn geen gegevens beschikbaar die het gebruik van sugammadex aanbevelen voor onmiddellijke opheffing na een door vecuronium geïnduceerde blokkade. *Hernieuwde toediening van sugammadex*: In de uitzonderlijke situatie dat zich postoperatief, na een initiële dosis van 2 mg/kg of 4 mg/kg sugammadex, opnieuw een neuromusculaire blokkade voordoet (zie rubriek 4.4), wordt een herhalingsdosis van 4 mg/kg sugammadex aanbevolen. Na een tweede dosis sugammadex moet de patiënt zorgvuldig gecontroleerd worden om er zeker van te zijn dat de neuromusculaire functie terugkeert. *Hernieuwde toediening van rocuronium of vecuronium na sugammadex:* Voor wachttijden voor hernieuwde toediening van rocuronium of vecuronium na opheffing met sugammadex, zie rubriek 4.4. **Aanvullende informatie met betrekking tot speciale patiëntengroepen** ***Nierfunctiestoornis:*** Het gebruik van sugammadex bij patiënten met een ernstige nierfunctiestoornis (waaronder dialysepatiënten (creatinineklaring < 30 ml/min)) wordt niet aanbevolen (zie rubriek 4.4). Studies bij patiënten met een ernstige nierfunctiestoornis hebben onvoldoende veiligheidsgegevens gegenereerd om het gebruik van sugammadex bij deze patiënten te ondersteunen (zie ook rubriek 5.1). Bij lichte en matige nierfunctiestoornis (creatinineklaring ≥ 30 en < 80 ml/min): de dosisaanbevelingen zijn dezelfde als voor volwassenen zonder nierfunctiestoornis. ***Ouderen:*** Na toediening van sugammadex bij terugkeer van T2 na een door rocuronium geïnduceerde blokkade was de mediane hersteltijd van de T4/T1-ratio tot 0,9 bij volwassenen (18-64 jaar) 2,2 minuten, bij ouderen (65-74 jaar) 2,6 minuten en bij zeer oude patiënten (75 jaar of ouder) 3,6 minuten. Hoewel bij ouderen het herstel vaak trager optreedt, dient dezelfde dosisaanbeveling als voor volwassenen te worden aangehouden (zie rubriek 4.4). ***Patiënten met obesitas:*** Bij patiënten met obesitas, waaronder patiënten met morbide obesitas (body mass index ≥ 40 kg/m2), dient de dosering van sugammadex te worden gebaseerd op het feitelijke lichaamsgewicht. Dezelfde dosisaanbevelingen als voor volwassenen dienen te worden aangehouden. ***Leverfunctiestoornis:*** Er zijn geen studies gedaan bij patiënten met een leverfunctiestoornis. Voorzichtigheid moet worden betracht wanneer gebruik van sugammadex overwogen wordt bij patiënten met een ernstige leverfunctiestoornis of wanneer de patiënt naast de leverfunctiestoornis ook coagulopathie heeft (zie rubriek 4.4). Bij lichte tot matige leverfunctiestoornis: aangezien sugammadex voornamelijk renaal wordt uitgescheiden, zijn er geen dosisaanpassingen vereist. ***Pediatrische patiënten*** De gegevens betreffende pediatrische patiënten zijn beperkt (slechts één studie gericht op opheffing van een door rocuronium geïnduceerde neuromusculaire blokkade, bij terugkeer van T2). *Kinderen en adolescenten:* Bij kinderen en adolescenten (2 t/m 17 jaar) wordt voor standaardopheffing bij terugkeer van T2 na een door rocuronium geïnduceerde blokkade 2 mg/kg sugammadex aanbevolen. Bridion 100 mg/ml kan worden verdund tot 10 mg/ml ten behoeve van een betere nauwkeurigheid van de dosering bij pediatrische patiënten (zie rubriek 6.6). Andere situaties van standaardopheffing zijn niet onderzocht en worden daarom niet aanbevolen totdat nadere gegevens beschikbaar komen. Onmiddellijke opheffing is bij kinderen en adolescenten niet onderzocht en wordt daarom niet aanbevolen totdat nadere gegevens beschikbaar komen. *Voldragen pasgeborenen en zuigelingen:* De ervaring met het gebruik van sugammadex bij zuigelingen (30 dagen tot 2 jaar) is beperkt en voldragen pasgeborenen (jonger dan 30 dagen) zijn niet onderzocht. Het gebruik van sugammadex bij voldragen pasgeborenen en zuigelingen wordt daarom niet aanbevolen totdat nadere gegevens beschikbaar komen. **Wijze van toediening** Sugammadex dient intraveneus te worden toegediend als eenmalige bolusinjectie. De bolusinjectie moet snel worden gegeven, binnen 10 seconden, in een bestaande intraveneuze lijn (zie rubriek 6.6). Sugammadex is in klinische onderzoeken uitsluitend als eenmalige bolusinjectie toegediend. **4.3 Contra-indicaties** Overgevoeligheid voor de werkzame stof of voor een van de in rubriek 6.1 vermelde hulpstof(fen). **4.8 Bijwerkingen** ***Samenvatting van het veiligheidsprofiel*** Bridion wordt gelijktijdig toegediend met neuromusculair blokkerende stoffen en anesthetica bij operatiepatiënten. De causaliteit van bijwerkingen is daarom moeilijk te bepalen. De meest gerapporteerde bijwerkingen bij patiënten die een chirurgische ingreep ondergingen waren hoest, luchtwegcomplicatie van anesthesie, complicaties bij anesthesie, hypotensie ten gevolge van een verrichting en verrichtingscomplicatie (Vaak (≥ 1/100, < 1/10)). ***Tabel 2: Tabel met bijwerkingen*** De veiligheid van sugammadex is beoordeeld bij 3519 unieke patiënten in een gepoolde fase I-III veiligheidsdatabase. De volgende bijwerkingen zijn gemeld in placebogecontroleerde onderzoeken waarbij patiënten anesthesie en/of neuromusculair blokkerende stoffen kregen (1078 patiënten kregen sugammadex vs. 544 patiënten placebo): [Zeer vaak (≥ 1/10), vaak (≥ 1/100, < 1/10), soms (≥ 1/1000, < 1/100), zelden (≥ 1/10.000, < 1/1000), zeer zelden (< 1/10.000)]. Systeem/orgaanklasse/Frequenties/Bijwerkingen (voorkeursterm): Immuunsysteemaandoeningen Soms: Geneesmiddelenovergevoeligheidsreacties (zie rubriek 4.4). Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen Vaak: Hoest. Letsels, intoxicaties en verrichtingscomplicaties Vaak: Luchtwegcomplicatie van anesthesie, Complicatie bij anesthesie (zie rubriek 4.4), Hypotensie ten gevolge van een verrichting, Verrichtingscomplicatie. ***Beschrijving van een aantal specifieke bijwerkingen*** Geneesmiddelenovergevoeligheid: Overgevoeligheidsreacties, waaronder anafylaxie, zijn waargenomen bij sommige patiënten en vrijwilligers (voor informatie over vrijwilligers, zie Informatie over gezonde vrijwilligers hieronder). In klinische onderzoeken bij patiënten die een chirurgische ingreep ondergingen zijn deze reacties soms gemeld; de postmarketingfrequentie waarin zij optreden is niet bekend. Deze reacties, die varieerden van geïsoleerde gevallen van huidreacties tot ernstige systemische reacties (d.w.z. anafylaxie, anafylactische shock), zijn ook voorgekomen bij patiënten die niet eerder blootgesteld waren aan sugammadex. Symptomen die geassocieerd kunnen zijn met deze reacties zijn: overmatig blozen, urticaria, erythemateuze huiduitslag, (ernstige) hypotensie, tachycardie, zwelling van de tong en keelholte, bronchospasme en obstructieve longaandoeningen. Ernstige overgevoeligheidsreacties kunnen fataal zijn. Luchtwegcomplicatie bij anesthesie: Luchtwegcomplicaties van anesthesie omvatten schokbewegingen tegen de beademingsbuis, hoest, lichte schokbeweging, arousal tijdens de operatie, hoesten tijdens de anesthesieprocedure of tijdens de operatie, of aan de anesthesieprocedure gerelateerde spontane ademhaling van de patiënt. Complicatie bij anesthesie: Complicaties bij anesthesie, indicatief voor herstel van de neuromusculaire functie, zijn beweging van een ledemaat of het lichaam of hoesten gedurende de anesthesieprocedure of gedurende de operatie, grimassen of zuigen op de beademingstube. Zie rubriek 4.4 lichte anesthesie. Verrichtingscomplicatie: Verrichtingscomplicaties omvatten hoest, tachycardie, bradycardie, bewegen, en versnelling van de hartslag. Ernstige bradycardie: Na het op de markt komen zijn binnen enkele minuten na toediening van sugammadex (zie rubriek 4.4) geïsoleerde gevallen van ernstige bradycardie en bradycardie met hartstilstand waargenomen. Hernieuwd optreden van een neuromusculaire blokkade: In klinische onderzoeken met patiënten die werden behandeld met rocuronium of vecuronium en bij wie een dosis sugammadex werd toegediend geschikt voor de diepte van de neuromusculaire blokkade (N=2022), werd een incidentie van 0,20 % waargenomen van hernieuwd optreden van de neuromusculaire blokkade gebaseerd op neuromusculaire monitoring of klinisch bewijs (zie rubriek 4.4). Informatie over gezonde vrijwilligers: Een gerandomiseerd, dubbelblind onderzoek heeft de incidentie van geneesmiddelgerelateerde overgevoeligheidsreacties onderzocht bij gezonde vrijwilligers die tot drie doses placebo (N=76), sugammadex 4 mg/kg (N=151) of sugammadex 16 mg/kg (N=148) kregen. Meldingen van vermoede overgevoeligheid werden beoordeeld door een geblindeerde (adjudicatie)commissie. De incidentie van beoordeelde overgevoeligheid was respectievelijk 1,3 %, 6,6 % en 9,5 % in de placebo-, de sugammadex 4 mg/kg- en de sugammadex 16 mg/kg-groep. Er waren geen meldingen van anafylaxie na placebo of sugammadex 4 mg/kg. Er was één enkel geval van beoordeelde anafylaxie na de eerste dosis sugammadex 16 mg/kg (incidentie 0,7 %). Er was geen bewijs van een verhoogde frequentie of ernst van overgevoeligheid met herhaalde doses sugammadex. In een eerder onderzoek met een zelfde opzet, waren er drie toegewezen gevallen van anafylaxie, alle na sugammadex 16 mg/kg (incidentie 2,0 %). In de gepoolde fase I-database zijn bijwerkingen die beschouwd worden als vaak (≥ 1/100, < 1/10) of zeer vaak (≥ 1/10) en frequenter bij proefpersonen behandeld met sugammadex dan in de placebogroep onder andere: dysgeusie (10,1 %), hoofdpijn (6,7 %), misselijkheid (5,6 %), urticaria (1,7 %), pruritus (1,7 %), duizeligheid (1,6 %), braken (1,2 %) en buikpijn (1,0 %). ***Aanvullende informatie met betrekking tot speciale patiëntengroepen*** **Longpatiënten:** In post-marketinggegevens en in één specifiek klinisch onderzoek bij patiënten met een voorgeschiedenis van longcomplicaties, werd bronchospasme gemeld als mogelijke bijwerking. Net als bij alle patiënten met een voorgeschiedenis van longcomplicaties, dient de arts zich bewust te zijn van het mogelijke optreden van bronchospasmen. **Pediatrische patiënten** Uit een beperkte database blijkt dat het veiligheidsprofiel van sugammadex (tot maximaal 4 mg/kg) bij pediatrische patiënten gelijk is aan dat bij volwassenen. **Patiënten met morbide obesitas** In één klinische studie gericht op patiënten met morbide obesitas was het bijwerkingenprofiel over het algemeen vergelijkbaar met het profiel bij volwassen patiënten in gepoolde fase 1 tot– 3-studies (zie tabel 2). ***Melding van vermoedelijke bijwerkingen*** Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **voor België**: Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten - Afdeling Vigilantie, Postbus 97, B-1000 Brussel Madou. Website: www.fagg.be, e-mail: adversedrugreactions@fagg-afmps.be. (Website: http://www.fagg-afmps.be, E-Mail: adversedrugreactions@fagg-afmps.be). **7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN** Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, Nederland. **8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN** EU/1/08/466/001, EU/1/08/466/002. **9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING** Datum van eerste verlening van de vergunning: 25 juli 2008, Datum van laatste verlenging: 21 juni 2013. **10. DATUM VAN HERZIENING VAN DE TEKST** 04/2020**. Legale status van aflevering:** ziekenhuisgebruik. Gedetailleerde informatie over dit geneesmiddel is beschikbaar op de website van het Europees Geneesmiddelenbureau (http://www.ema.europa.eu).

1. DENOMINATION DU MEDICAMENT Bridion® 100 mg/ml, solution injectable **2. COMPOSITION QUALITATIVE ET QUANTITATIVE** 1 ml contient l'équivalent de 100 mg de sugammadex sous forme de sugammadex sodique. Chaque flacon de 2 ml contient l'équivalent de 200 mg de sugammadex sous forme de sugammadex sodique. Chaque flacon de 5 ml contient l'équivalent de 500 mg de sugammadex sous forme de sugammadex sodique. Excipient(s) à effet notoire : Contient jusqu'à 9,7 mg/ml de sodium (voir rubrique 4.4). Pour la liste complète des excipients, voir rubrique 6.1. **3. FORME PHARMACEUTIQUE** Solution injectable (injection). Solution limpide, incolore à légèrement jaune. Le pH est compris entre 7 et 8 et l'osmolalité entre 300 et 500 mOsm/kg. **4. INFORMATIONS CLINIQUES 4.1 Indications thérapeutiques** Décurarisation chez l'adulte après bloc neuromusculaire induit par le rocuronium ou le vécuronium. *Population pédiatrique :* le sugammadex est recommandé uniquement pour la décurarisation en routine après un bloc neuromusculaire induit par le rocuronium chez l'enfant et l'adolescent âgés de 2 à 17 ans. **4.2 Posologie et mode d'administration** **Posologie** Le sugammadex ne doit être administré que par ou sous la surveillance d'un anesthésiste. L'utilisation d'une méthode appropriée de monitorage neuromusculaire est recommandée pour surveiller la récupération du bloc neuromusculaire (voir rubrique 4.4). La dose de sugammadex recommandée dépend du degré du bloc neuromusculaire à décurariser. La dose recommandée est indépendante du protocole anesthésique. Le sugammadex peut être utilisé pour décurariser différents degrés de bloc neuromusculaire induit par le rocuronium ou le vécuronium : ***Adultes*** *Décurarisation en routine :* Une dose de 4 mg/kg de sugammadex est recommandée après réapparition de 1 à 2 réponses minimum au Compte Post Tétanique (PTC) après un bloc neuromusculaire induit par le rocuronium ou le vécuronium. Le délai médian de récupération du rapport T_4/T_1 à 0,9 est alors d'environ 3 minutes (voir rubrique 5.1). Une dose de 2 mg/kg de sugammadex est recommandée après réapparition spontanée de la 2ème réponse au train-de-quatre (T2) après un bloc induit par le rocuronium ou le vécuronium. Le délai médian de récupération du rapport T_4/T_1 à 0,9 est alors d'environ 2 minutes (voir rubrique 5.1). L'utilisation des doses recommandées pour une décurarisation en routine conduit à un délai médian de récupération du rapport T_4/T_1 à 0,9 du bloc neuromusculaire induit par le rocuronium légèrement plus court comparativement au bloc neuromusculaire induit par le vécuronium (voir rubrique 5.1). *Décurarisation immédiate après un bloc induit par le rocuronium :* En cas de nécessité clinique d'une décurarisation immédiate après administration de rocuronium, une dose de 16 mg/kg de sugammadex est recommandée. L'administration de 16 mg/kg de sugammadex 3 minutes après une dose de 1,2 mg/kg de bromure de rocuronium permet une médiane de récupération attendue du rapport T_4/T_1 à 0,9 d'environ 1,5 minutes (voir rubrique 5.1). En l'absence de données, le sugammadex n'est pas recommandé pour une décurarisation immédiate après un bloc neuromusculaire induit par le vécuronium. *Nouvelle administration du sugammadex :* Dans le cas exceptionnel d'une récurrence du bloc neuromusculaire en post-opératoire (voir rubrique 4.4) après une dose initiale de 2 mg/kg ou de 4 mg/kg de sugammadex, il est recommandé d'administrer une dose supplémentaire de 4 mg/kg de sugammadex. Après l'administration de cette seconde dose de sugammadex, le patient devra être étroitement surveillé afin de s'assurer d'une récupération complète et stable de la fonction neuromusculaire. *Nouvelle administration de rocuronium ou de vécuronium après le sugammadex :* Pour les délais nécessaires avant une nouvelle administration de rocuronium ou de vécuronium après décurarisation par le sugammadex, voir rubrique 4.4. **Informations complémentaires concernant des populations particulières** ***Insuffisance rénale :*** L'utilisation du sugammadex chez les patients présentant une insuffisance rénale sévère (avec ou sans dialyse (CLCr < 30 ml/min)) n'est pas recommandée (voir rubrique 4.4). Les études réalisées chez les patients présentant une insuffisance rénale sévère n'ont pas fourni de données de sécurité suffisantes pour permettre l'utilisation du sugammadex chez ces patients (voir également la rubrique 5.1). Insuffisance rénale légère à modérée (clairance de la créatinine ≥ 30 et < 80 ml/min) : les doses recommandées sont les mêmes que celles recommandées chez les adultes sans insuffisance rénale. ***Sujets âgés :*** Après administration du sugammadex à la réapparition de la 2ème réponse au train-de-quatre (T_2) après un bloc neuromusculaire induit par le rocuronium, le délai médian de récupération du rapport T_4/T_1 à 0,9 a été alors de 2,2 minutes chez l'adulte (18-64 ans), 2,6 minutes chez le sujet âgé (65-74 ans) et de 3,6 minutes chez le sujet très âgé (75 ans ou plus). Bien que les délais de récupération chez le sujet âgé soient plus longs que dans la population adulte, aucune adaptation de doses de sugammadex n'est nécessaire dans cette population (voir rubrique 4.4). ***Patients obèses :*** Chez les patients obèses, y compris les patients présentant une obésité morbide (indice de masse corporelle ≥ 40 kg/m2), la dose de sugammadex devrait être calculée sur le poids corporel réel. Chez ces patients les doses de sugammadex recommandées sont les mêmes que pour la population adulte. ***Insuffisance hépatique :*** Aucune étude n'a été réalisée chez les patients insuffisants hépatiques. Chez les patients présentant une insuffisance hépatique sévère ou lorsque l'insuffisance hépatique s'accompagne d'une coagulopathie, des précautions doivent être prises lorsque l'utilisation du sugammadex est envisagée (voir rubrique 4.4). Insuffisance hépatique légère à modérée : le sugammadex étant principalement éliminé par voie rénale, aucune adaptation de dose n'est nécessaire. ***Population pédiatrique*** Les données relatives à la population pédiatrique sont limitées (une seule étude concernant uniquement la décurarisation suite à un bloc induit par le rocuronium, après réapparition de T_2). *Enfants et adolescents :* Pour une décurarisation en routine du bloc neuromusculaire induit par le rocuronium lors de la réapparition de T_2 chez l'enfant et l'adolescent (2-17 ans), la dose de sugammadex recommandée est de 2 mg/kg. Bridion 100 mg/ml peut être dilué à 10 mg/ml pour une plus grande précision de la dose administrée dans la population pédiatrique (voir rubrique 6.6). Les autres situations de décurarisation en routine n'ont pas été étudiées et, par conséquent, le sugammadex n'est pas recommandé dans ces situations en l'absence de données supplémentaires disponibles. La décurarisation immédiate chez l'enfant et l'adolescent n'a pas été étudiée et n'est par conséquent pas recommandée en l'absence de données complémentaires disponibles. *Nouveau-nés à terme et nourrissons :* Les données sur l'utilisation du sugammadex chez le nourrisson (30 jours à 2 ans) sont limitées ; son utilisation chez le nouveau-né à terme (moins de 30 jours) n'a pas été étudiée. L'utilisation du sugammadex chez les nouveau-nés à terme ainsi que chez les nourrissons n'est donc pas recommandée en l'absence de données supplémentaires disponibles. **Mode d'administration** Le sugammadex doit être administré par voie intraveineuse en bolus unique. L'injection en bolus doit être rapide, dans les 10 secondes, dans un cathéter intraveineux déjà mis en place (voir rubrique 6.6). Au cours des études cliniques, le sugammadex n'a été administré que par injection en bolus unique. **4.3 Contre-indications** Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1. **4.8 Effets indésirables** ***Résumé du profil de tolérance*** Bridion est co-administré avec des curares et des anesthésiques chez les patients opérés. Le lien de causalité des événements indésirables est donc difficile à évaluer. Les effets indésirables les plus fréquemment rapportés chez les patients opérés étaient la toux, les complications des voies respiratoires liées à l'anesthésie, les complications anesthésiques, l'hypotension liée aux procédures et les complications liées aux procédures (fréquent (≥ 1/100, < 1/10)). ***Tableau 2 : Tableau de synthèse des effets indésirables*** La tolérance du sugammadex a été évaluée chez 3519 sujets uniques à partir d'une base de données de tolérance regroupant les études de phase I - III. Les effets indésirables suivants ont été rapportés dans les essais contrôlés *versus* placebo, chez les sujets recevant des anesthésiques et/ou des curares (1 078 sujets ayant reçu du sugammadex *versus* 544 ayant reçu du placebo) : [Très fréquent (≥ 1/10), fréquent (≥ 1/100, < 1/10), peu fréquent (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000), très rare (< 1/10 000)]. Classes de systèmes d'organes/Fréquences/Effets indésirables (Termes préférentiels) : Affections du système immunitaire Peu fréquent : Réactions d'hypersensibilité au médicament (voir rubrique 4.4). Affections respiratoires, thoraciques et médiastinales Fréquent : Toux. Lésions, intoxications et complications liées aux procédures Fréquent : Complication des voies respiratoires liée à l'anesthésie, Complication anesthésique (voir rubrique 4.4), Hypotension liée aux procédures, Complication liée aux procédures. ***Description de certains effets indésirables*** Réactions d'hypersensibilité au médicament : Des réactions d'hypersensibilité, incluant l'anaphylaxie, se sont produites chez certains patients et volontaires (pour des informations sur les volontaires, voir le paragraphe ci-dessous «Information sur les volontaires sains»). Au cours des essais cliniques réalisés chez les patients opérés, ces réactions ont été peu fréquemment rapportées et pour les rapports post-commercialisation, la fréquence est inconnue. Ces réactions variaient de réactions cutanées isolées à des réactions systémiques graves (c'est-à-dire anaphylaxie, choc anaphylactique) et se sont produites chez des patients sans exposition préalable au sugammadex. Les symptômes associés à ces réactions peuvent inclure : bouffées de chaleur, urticaire, rash érythémateux, hypotension (sévère), tachycardie, gonflement de la langue, gonflement du pharynx, bronchospasme et événements pulmonaires obstructifs. Les réactions sévères d'hypersensibilité peuvent être fatales. Complication des voies respiratoires liée à l'anesthésie : Les complications des voies respiratoires liées à l'anesthésie incluaient un « bucking » contre la sonde endotrachéale, une toux, un « bucking » modéré, une réaction d'éveil pendant la chirurgie, une toux au cours de la procédure d'anesthésie ou pendant la chirurgie, ou une respiration spontanée du patient liée à la procédure d'anesthésie. Complication anesthésique : Il s'agit d'une restauration de la fonction neuromusculaire, comportant des mouvements d'un membre ou du corps ou une toux pendant l'anesthésie ou la chirurgie, des grimaces ou la succion de la sonde endotrachéale. Voir rubrique 4.4 Anesthésie légère. Complication liée aux procédures : Les complications liées aux procédures incluaient la toux, la tachycardie, la bradycardie, les mouvements, et l'augmentation de la fréquence cardiaque. Bradycardie marquée : Depuis la commercialisation, des cas isolés de bradycardie marquée et de bradycardie avec arrêt cardiaque ont été observés dans les minutes suivant l'administration du sugammadex (voir rubrique 4.4). Récurrence du bloc neuromusculaire : Dans des études cliniques chez des sujets traités par le rocuronium ou le vécuronium, lorsque le sugammadex était administré à la dose recommandée selon la profondeur du bloc neuromusculaire (N = 2 022), une incidence de 0,20 % a été observée pour la récurrence du bloc neuromusculaire, sur la base d'un monitorage neuromusculaire ou de signes cliniques (voir rubrique 4.4). Information sur les volontaires sains : Une étude randomisée en double aveugle a évalué l'incidence des réactions d'hypersensibilité au médicament chez des volontaires sains recevant jusqu'à 3 doses, de placebo (N = 76), de sugammadex 4 mg/kg (N = 151) ou de sugammadex 16 mg/kg (N = 148). Les cas rapportés d'hypersensibilité suspectée ont été jugés en aveugle par un comité. L'incidence de l'hypersensibilité avérée était respectivement de 1,3%, 6,6% et 9,5% dans les groupes placebo, sugammadex 4 mg/kg et sugammadex 16 mg/kg. Il n'y a pas eu de cas d'anaphylaxie après placebo ou sugammadex 4 mg/kg. Il y a eu un seul cas d'anaphylaxie avérée après la première dose de sugammadex 16 mg/kg (incidence 0,7%). L'augmentation de la fréquence ou de la gravité de l'hypersensibilité avec des doses répétées de sugammadex n'a pas été démontrée. Dans une précédente étude avec le même design, il y a eu trois cas d'anaphylaxie avérée, tous avec sugammadex 16 mg/kg (incidence 2,0%). Dans la base de données regroupant les études de Phase I, les effets indésirables considérés comme fréquents (≥ 1/100 à < 1/10) ou très fréquents (≥ 1/10) et plus fréquents chez les sujets traités par sugammadex que ceux du groupe placebo, comprennent dysgueusie (10,1%) , céphalées (6,7%), nausées (5,6%), urticaire (1,7%), prurit (1,7%), vertiges (1,6%), vomissements (1,2%) et douleurs abdominales (1,0%). ***Informations complémentaires concernant des populations particulières*** **Patients ayant une pathologie pulmonaire :** Dans les données recueillies depuis la commercialisation et dans un essai clinique concernant des patients présentant des antécédents de complications pulmonaires, un bronchospasme a été rapporté comme évènement indésirable possiblement lié. Comme avec tous les patients avec des antécédents de complications pulmonaires, le médecin doit être averti de la survenue possible d'un bronchospasme. **Population pédiatrique** Selon une base de données limitée, le profil de tolérance du sugammadex (jusqu'à 4 mg/kg) chez les patients pédiatriques est comparable à celui observé chez l'adulte. **Patients présentant une obésité morbide** Dans un essai clinique spécifiquement mené chez des patients présentant une obésité morbide, le profil de tolérance d'effet indésirable était généralement similaire à celui observé chez l'adulte dans les études poolées de Phase I à III (voir Tableau 2). ***Déclaration des effets indésirables suspectés*** La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration: **en Belgique** : Agence Fédérale des Médicaments et des Produits de Santé - Division Vigilance, Boîte Postale 97, B-1000 Bruxelles Madou. Site internet: www.afmps.be, e-mail: adversedrugreactions@fagg-afmps.be, **au Luxembourg** : Centre Régional de Pharmacovigilance de Nancy - Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) - CHRU de Nancy – Hôpitaux de Brabois, Rue du Morvan 54, 511 VANDOEUVRE LES NANCY CEDEX, Tél : (+33) 3 83 65 60 85 / 87, Fax : (+33) 3 83 65 61 33, E-mail : crpv@chru-nancy.fr ou Direction de la Santé – Division de la Pharmacie et des Médicaments, Allée Marconi - Villa Louvigny. L-2120 Luxembourg, Tél. : (+352) 2478 5592, Fax : (+352) 2479 5615, E-mail : pharmacovigilance@ms.etat.lu. Lien pour le formulaire http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html. **7. TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE** Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, Pays-Bas **8. NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE** EU/1/08/466/001; EU/1/08/466/002. **9. DATE DE PREMIERE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION** Date de première autorisation : 25 juillet 2008. Date du dernier renouvellement : 21 juin 2013. **10. DATE DE MISE A JOUR DU TEXTE** 04/2020. **Statut légal de délivrance**: usage hospitalier. Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne des médicaments http://www.ema.europa.eu.

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Preoperative assessment of expectations, anxiety and preferences for anesthesia in patients undergoing ambulatory knee arthroscopic surgery

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Abstract : *Objective :* In this observational study, we aimed at measuring preoperative anxiety and preferences for anesthesia in patients undergoing knee arthroscopic surgery.
Background : Little is known about preoperative anxieties, expectations and preferences of patients undergoing surgery, for which both spinal or general anesthesia can be provided. Literature shows that spinal anesthesia is associated with lower postoperative co-morbidity and mortality rates as compared to general anesthesia (1-2). Anxiety itself is an important factor influencing patients' outcome (3).
Methods : Every patients >18 years old undergoing an ambulatory arthroscopy of the knee in the surgical day care center of the AZ Nikolaas (in Sint-Niklaas and Beveren), was asked preoperatively to fill in a questionnaire. The questionnaire focused both on the patients' knowledge about and preference of anesthesia, as well as their preoperative anxieties and worries. Patients were asked to score preoperative anxiety on a 5-point anxiety scale for any of 9 aspects/complications of the anesthetic (placement of the IV cannula, spinal puncture, death, awareness, pain, postoperative nausea and vomiting, cognitive impairment, infection, blood loss). During the study period, from January 11/01/ 2019 to 11/06/2019, a total of 806 patients were asked to fill out the questionnaire. 201 of these patients completed the questionnaire and were consequently enrolled in the study. This work has been approved by the Ethics Committee of the AZ Nikolaas on 11/11/2018 and by the Ethics Committee of the University Hospital in Antwerp (UZA) on 19/11/ 2018.
Results : Seventy-five % of patients had a clear preference for their anesthesia technique. Of these, 2/3 opted for general anesthesia. Patients mainly based their preference on a subjective feeling ; a minority had discussed the choice with their surgeon or general practitioner. Rarely, patients indicated the wish to talk to the anesthesiologist about their choice. Fear for a spinal puncture occurred in 40% of patients (median anxiety score 3/5, range 1-5) and was therefore the most prominent anxiety in this patient population.
Conclusions : Patients' greater preference for general over spinal anesthesia was clearly based rather on a subjective than an objective basis. Forty 40% of patients had a substantial fear for spinal puncture. By informing patients about the risks and complications of the different anesthesia techniques, anxiety feelings can probably be alleviated, and a well-judged decision about their anesthesia technique can be made. There is room for improvement in communication and discussion between patients and anesthesiologists about the patients' choice of anesthesia technique.

Keywords : anesthesia ; anxiety ; arthroscopy.

Introduction

Arthroscopy of the knee is a commonly performed procedure in Belgium. It mostly takes place in an ambulatory setting. This procedure can be carried out either under general or spinal anesthesia. Many research papers comparing both anesthesia techniques have focused on clinical outcome parameters, such as time to discharge, time to first bladder voiding, pain scores, nausea scores, etc. in order to optimize the anesthetic technique, be it a general or a spinal anesthesia (4-9). The use of newer and shorter acting local anesthetic agents for spinal use has recently led to a renewed interest in this technique in an ambulatory setting.

Most studies do not take patients' preferences into account. One study may prove the benefit of

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This work has been approved by the ethics committee of AZ Nikolaas on 11/10/2018. Dr. G. De la Meilleure And by the ethics committee of UZA on 19/11/2018. Prof. Dr. G. Ieven
Patients were included between 11/01/2019 and 11/06/2019.

technique A over technique B, but if a patient has a clear preference for technique B, the knowledge gained in the study cannot always be translated into clinical practice. Anxiety is an especially important factor influencing patients' outcome, that should not be underestimated (10-16, 3). Furthermore, patients do not always accept rational arguments ; they often have their own ideas and concerns, that are frequently influenced by their emotions (17-18).

Methods

This work has been approved by the ethics committee of AZ Nikolaas on 11/10/2018 and

by the ethics committee of UZA on 19/11/2018. The reference number was B300201838073 with Prof. Cras as president of the committee. Patients were recruited to this observational study between 11/01/2019 and 11/06/2019. All patients undergoing ambulatory knee arthroscopy in the surgical day care centre of the AZ Nikolaas (Sint-Niklaas and Beveren) were asked to complete a questionnaire preoperatively (see supplementary material) and signed an informed consent form. At the outset, we aimed to enroll 200 patients. During the study period, a total of 806 patients were asked to complete the questionnaire, but due to time constraints in the busy operating theatre schedule, only 201 of these effectively participated.

The questionnaire asked whether patients received preoperative information, and if so, what was the source of preoperative information (surgeon, general practitioner, anesthetist or internet). Subsequently patients were asked about their preference for anesthetic technique, be it general of spinal anesthesia, and on what basis they had decided on their preferred technique. The questionnaire focused not only on the patients' knowledge of anesthesia and their preference of anesthetic technique, but aimed to assess their preoperative anxiety. Preoperative anxiety scores were rated on a 5-point numeric anxiety scale (1 = no fear whatsoever, 5 = maximal imaginable anxiety). This scale was applied to 9 aspects/ complications related to the procedure (IV cannula placement, spinal puncture, death, awareness, pain, PONV, cognitive impairment, infection, blood loss). The patients were also asked to indicate their understanding of the level of training of anesthetists (specially trained nurse, medical specialist, specially trained surgeon or specially trained technician). Finally we asked patients if they already had surgery before, which type of anesthesia they got and if there were any side effects of the anesthesia.

Statistical analysis was performed using excel real statistics. Since the data in our study are ordinal data we used non parametrical tests for statistical analysis. After correction for missing values we applied the wilcoxon signed rank test to prove significance for fear for a spinal puncture over the other fears. P-values were < 0,001 every time, P-value < 0.05 was considered as significant.

Results

Of all patients undergoing ambulatory arthroscopy of the knee during the duration of the study, 201 patients agreed to fill in the questionnaire. Some did it only partially, hence some data were missing. The mean age of the study sample was 51 years (range 18-80 years) and included patients of ASA class between I and III. One hundred and eight (53.7%) patients were males and 153 (76.1%) had previously undergone a surgical procedure. Specifications of our patient sample are described in Table 1.

91 patients (45.3%) said they had received preoperative information about the anesthesia and this was usually from the operating surgeon (49/201, 24.4%). In this sample, patients were rarely advised by their surgeons about the anesthetic technique (23/201, 11.4%).

Of the 201 patients, 151 (75.1%) had a clear preference for a specific type of anesthesia technique : 109 (54.2%) patients preferred general anesthesia, 42 (20.9%) chose to have a spinal. The remaining 50 (24.9%) patients had no clear preference.

As far as preoperative anxiety was concerned, a spinal puncture was clearly very frightening for a substantial number of patients [score 5 : 51/201 (25.4%) ; score 4 : 27/201 (13.4%) ; median anxiety score = 3]. Fear for a spinal puncture was therefore the most prominent anxiety in this patient population (P < 0.001 as compared to all other fears). None of the other aspects of anesthesia in the list was nearly as frightful to patients, no other aspect had a combined score (4/5 + 5/5) of more than 15%.

When asked about the anesthesiologist's training, approximately half of the sample recognized

Table 1
Demographic characteristics of the study sample

N	201
Age [mean (range)]	51 y (18-80 y)
Gender (n, male/female)	108/93
Previous surgery (n, yes/no/missing)	153/44/4
ASA class (n, I/II/III)	145/47/9

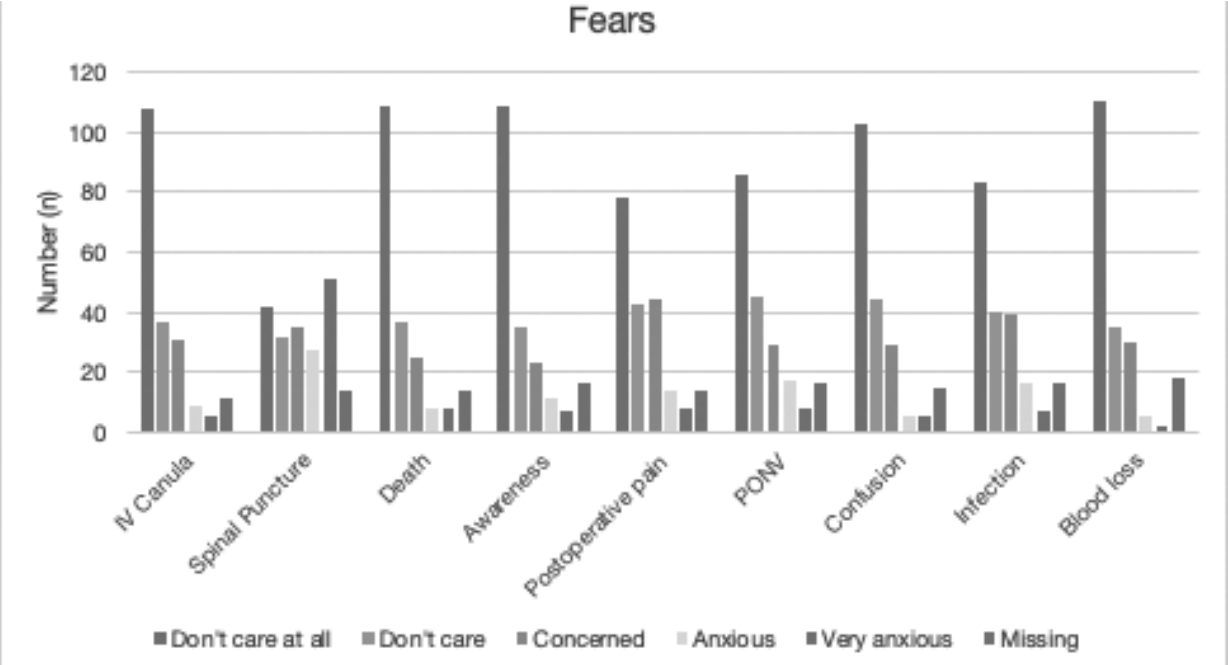

Fig. 1 — Patients' rating of fear regarding IV canula insertion, spinal puncture, death, awareness of surgery, postoperative pain, confusion, and infection. The number of patients for each rating is given.

the anesthesiologist as a medical specialist (109 patients, 54.2%). Interestingly, 23.1% of patients thought that an anesthesiologist was a surgeon.

One hundred and fifty-three (76.1%) patients already had surgery before, of which 37 (24.2%) already had a spinal anesthesia. Of this patient subgroup of 37 patients, 17 (45.9%) chose a spinal anesthesia again, 11 (29.7%) chose general anesthesia, and 9 (24.3%) patients didn't have a preference for a particular anesthesia technique. One hundred (65.4%) patients only had general anesthesia in their history. In this subgroup, only 12 patients (12.0%) preferred spinal anesthesia, 68 (68.0%) patients chose general anesthesia, and for 20 (20.0%) patients, the type of anesthesia did not matter.

Discussion

In spite of limited knowledge about anesthesia techniques, the majority of patients clearly prefer general to spinal anesthesia, even if they have been unable to discuss their choice with a professional in the field. The literature shows that spinal anesthesia is associated with lower morbidity rates, lower major complication rates and, in specific subgroups, lower mortality as compared to general anesthesia (17-19). Fear of the spinal puncture, which is clearly the biggest concern or anxiety in this patient group, can explain the preference for general anesthesia. Preoperative anxiety is associated with worse outcomes and higher postoperative pain scores in many types of surgeries (14, 7-13). Anesthesiologists play an important role in managing patients' anxieties (20). They should be aware of these anxieties and inform the patient through a preoperative consultation, a brochure or information available on the internet about risks and complications of the different anesthesia techniques. This way, anxiety feelings will probably be alleviated and a well-judged decision about their anesthesia technique can be made.

We see no difference in preference for anesthetic technique between patients who got preoperative information and those who did not. A possible explanation for this is the source of information. Seventy-six of the 91 patients (83.5%) who were preoperatively informed received information from a surgeon, the general practitioner or a nurse. Only 15 patients (16.5%) actually spoke to an anesthesiologist, which is the only specialist in this field. If patients are provided with more profound information comprising an elucidation of the advantages and disadvantages of each technique, and provided by the anesthesiologist himself, the distribution of preferences would possibly tend towards a higher preference for spinal anesthesia.

Patients who already had spinal anesthesia before chose a spinal again for this procedure in 45.9% of the cases. Patients who only had general anesthesia in history preferred a spinal in 12.0% of the cases. We can conclude that patients who

already had a spinal puncture before are more likely to choose a spinal puncture again. This indicates the subjective character of the fear for a spinal puncture. A spinal puncture seems not as terrible as many people think before they experienced it themselves.

Recent research in patients undergoing knee or hip arthroplasty surgery shows that a preoperative consultation can significantly influence the choice of the anesthesia technique (20). Unfortunately, patients only recall very little of what they are told during the preoperative anesthesia consultation, despite detailed explanation about the procedure and perioperative care (15-16). Informed consent has evolved as an important aspect in all fields of modern medicine, where patients have been accorded the right to make decisions about their treatment. This should be based on appropriate explanation and advice, and anesthesiologists should therefore aim to inform patients as fully as possible, whilst at the same time respecting their judgement.

Informing patients about the procedures they will undergo is a cornerstone in managing their concerns and fears. Nevertheless, a certain level of anxiety during the procedure itself is often inevitable. There is a wide range of described techniques to reduce anxiety, going from specific communication techniques, to music or virtual reality devices, which can alleviate anxiety and augment the comfort of patients during invasive procedures (such as the placement of an IV cannula or a peripheral nerve block) (21-24).

The results of this study suggest that the general public still has many misunderstandings about anesthesia. Anesthesiologists often have only a short-lasting contact with patients, and only rarely see their patients before the anesthesia itself. Especially in an ambulatory setting, with a healthy patient population, a preoperative anesthesia consultation is not always performed or necessary. Of course, in many hospitals or anesthesia services, patients can have access to information about their anesthesia through websites, information brochures or other channels. These formats, however, do not entirely resolve the problem and do not allow a patient/anesthesiologist relationship to be established. Hardly half of the patients recognize the anesthesiologist as a medical specialist, which shows the ignorance in the patient population about the nature of the anesthesiologists' work.

This study was conducted in a Belgian population. For this reason, our results may not be applicable to other cultures or countries, which can be considered as a limitation. We have to be careful when interpreting the information gathered from the analysis of the subgroup of patients having had previous spinal anesthesia, because of the small sample size.

Conclusion

Most patients have a clear preference for a specific technique, and most of them prefer general over spinal anesthesia for ambulatory arthroscopy of the knee. Fear of a spinal puncture is not to be underestimated, and can help explain this difference. Anesthesiologists should be aware of these anxieties. They should try to inform their patients as completely as possible, and to answer any concerns, as well as provide advice. Patients can therefore make a well-judged decision about anesthetic technique, thus improving their satisfaction with the offered treatment. Despite the growing interest in preoperative assessment and the importance of patient information, however, many misunderstandings about anesthesia still remain.

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Feasibility of sedation with sevoflurane inhalation via AnaConDa for Covid-19 patients under venovenous extracorporeal membrane oxygenation

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Abstract : Critical care centers around the world have faced a shortage of intravenous sedatives caused by the coronavirus pandemic. Many patients infected with SARS-CoV-2 virus develop severe Acute Respiratory Distress syndrome (ARDS) for which some of them are supported by extra corporeal membrane oxygenation. Under these circumstances, the pharmacokinetics of the sedatives is modified. We observed that many of our COVID-19 infected patients receiving Extracorporeal Membrane Oxygenator (ECMO) require high doses of intravenous drugs. Continuous sedation with halogenated gases in the intensive care unit has shown many benefits on systemic inflammation and offers the possibility of a rapid recovery of consciousness. In this article we describe 3 cases that show the feasibility of sedation with sevoflurane via AnaConDa (Sedana Medical AB, Danderyd, Sweden) for Covid-19 patients under ECMO. Halogenated drugs could be considered as an interesting alternative to intravenous sedatives especially in the context of drug shortage.

Keywords : Covid-19 ; SARS-CoV2 ; venovenous ECMO ; extra corporeal membrane oxygenation ; sedation ; AnaConda ; Sevoflurane inhalation ; poly-methyl-pentene membrane.

Introduction

SARS-CoV-2 infection may cause severe ARDS (1). The role of venovenous extracorporeal membrane oxygenation for this condition has shown similar survival rates at 60 days in comparison with previous studies (2). According to the European Life Support Organization registry more than 3200 confirmed or suspected cases have been, or are currently ECMO supported around the world at the moment of this writing (3). The shortage of sedatives and ventilator-associated drugs caused by the pandemic (4) has been a major issue for critical care practitioners, therefore the use of other agents such as inhaled anesthetics is of interest. Our current practice has shown the feasibility of sevoflurane sedation via AnaConDa (Sedana Medical AB, Danderyd, Sweden) for patients under venovenous extracorporeal membrane oxygenation.

Volatile anesthetics

Sevoflurane is the most commonly used volatile inhaled agent in developed countries. Its low blood-gas partition coefficient allows fast recovery of consciousness. It has bronchodilation properties and offers possible advantages of cardiac and lung protection(5, 6). The role of sedation with sevoflurane in the intensive care unit has been investigated many times, and is an alternative solution to intravenous drugs according to the 2015 German guidelines on sedation and delirium management (7).

In patients suffering from ARDS, sedation with sevoflurane compared to midazolam led to better oxygenation and decreased levels of inflammatory markers including a marker of epithelial injury (8). Ferrando et al. demonstrated that sevoflurane reduces the lung inflammatory response and improves oxygenation in acute respiratory distress syndrome to a greater extent than propofol (9). The feasibility of sedation with isoflurane in critically ill patients on ECMO was demonstrated and showed beneficial effects such as fewer opioid requirements and the possibility of spontaneous breathing (10).

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These effects led some authors to conclude that the use of volatile anesthetics in the intensive care unit could increase in the future because of their potential benefits (11).

Halogenated drugs are often used in operating theaters via vaporizers mounted on anesthesia machines with circular circuits. They are eliminated by a scavenging system that vents out the exhaled anesthetic gases in order to maintain a vapor-free environment. Intensive care ventilators use high-flow, non-rebreathing, non-circular circuits. The anesthetic conserving device (AnaConDa) is a system placed between the Y piece and the patient, which allows the administration of volatile anesthetics for these ventilators. It requires a minimum tidal volume, which can be a drawback for non-compliant lungs**.** The device contains a medium that adsorbs exhaled halogenated drugs and releases them during inspiration. This phenomenon is also observed with CO_2 that causes a dead space effect larger than the internal volume of the AnaConDa. For some authors, the impossibility to achieve normocapnia with tidal volumes < 6 ml/kg limit its use with low tidal ventilation strategies (12).

Most of the critical care units are not equipped with a scavenging system for waste gases and the possibility of removing them is achieved by a charcoal filter connected to the ventilator outflow.

ECMO and pharmacokinetics

ECMO affects drug pharmacokinetics (PK) through circuit sequestration, circuit priming, and circuit age (13-15). Some authors described an altered PK profile of intensive care unit drugs under ECMO (16). The distribution of inhaled sevoflurane via AnaConDa for patients under venovenous ECMO is uncertain. A transient loss of volatile anesthetics in PVC tubing has been demonstrated in vitro (17) but should only play a minor role in clinical settings.

Case description 1

The first case is a 55-year-old overweight male patient known for high blood pressure treated by a beta-blocker and a diuretic (bisoprolol and hydrochlorothiazide). He was rapidly transferred from the emergency room to the intensive care unit for acute respiratory failure. Orotracheal intubation and invasive ventilation were initiated in the first hours based on deteriorating gas exchange and altered mental status. In order to prevent droplet transmission, closed circuit endotracheal suctioning was used.

A continuous neuromuscular blockade administration was initiated for 48 hours while the patient was ventilated according to a lung-protective strategy (volume control mode with tidal volumes around 6 ml/kg of predicted body weight with plateau pressures < 30 cm H_2O, a PEEP of 12 cm H_2O, a mean driving pressure of 18 cm H_2O and a fraction of inspired oxygen of 100%. These parameters resulted in an average compliance of 12,2 ml/cm H2O. He received inhaled nitric oxide (10ppm), underwent 16 hours of prone position and was also treated with hydroxychloroquine according to current expert recommendations.

Despite the aforementioned measures, no oxygenation improvements were noticed. A persistent PaO_2/FiO_2 ratio < 80 (on average 68,5 mmHg) during more than 6 hours led to the decision of initiating venovenous ECMO therapy. The implementation was successfully done under stable hemodynamics by femoral and jugular vein cannulation. We used EUROSETS A.L.ONE ECMO oxygenator (Eurosets, Medolla, MO, Italy) at a circuit flow between 4,5 and 5 l/min with an initial fraction of delivered oxygen of 100% and a sweep gas flow adjusted to obtain CO_2 values between 35-45 mmHg.

After ECMO initiation, deep sedation assessed by the Richmond Agitation-Sedation Scale (RASS) of -4 to -5 was hardly achieved by multimodal anesthesia. High doses of sedative drugs were required : propofol 3-3,6 mg/kg/h of total body weight (TBW), clonidine 0,875 µg/kg/h (TBW), ketamine 0,5 mg/kg/h (TBW), dehydrobenzoperidol 2 µg/kg/h (TBW) and midazolam 0,14 mg/kg/h (TBW). Given the potential harmful effect of these high doses and the risk of a delayed recovery we decided to pursue maintenance of sedation with inhaled anesthetics.

Sevoflurane sedation via AnaConDa was started at the rate of 5 ml/h and adjusted in order to obtain end-expiratory concentration (Fet value) around 1 -1,5%. The clinician assessed its administration regularly in order to achieve similar RASS scores. In order to avoid room air pollution with vapors, the charcoal filter FlurAbsorb (Sedana Medical AB, Danderyd, Sweden) was connected to the gas outlet of the ventilator. The introduction of anesthetic vapors allowed to stop the infusion of all the aforementioned drugs in the first hours except clonidine which was reduced to an infusion rate of 0,5 µg/kg/h (TBW).

The sedation with volatile anesthetics lasted 4 days and resulted in spontaneous breathing assisted ventilation. We noted a slight improvement of lung compliance whose average value was 16 ml/cm H_2O during the first 24 hours after the initiation of halogenated gases. This intervention helped maintaining a lung-protective ventilation strategy and the recovery of a diaphragmatic activity without patient-ventilator asynchrony. Finally, the subject was weaned from ECMO 27 days after its initiation. He unfortunately died the day after of a sudden refractory septic shock despite broad-spectrum antibiotics and resuscitation maneuvers including the implementation of a venoarterial ECMO.

Case description 2

The second case is a healthy 54-year-old male without any comorbidity, who was transferred from the Covid-19 ward to the intensive care unit for respiratory failure. He received hydroxychloroquine for five days and was initially treated by non-invasive ventilation. Orotracheal intubation was performed the day after his arrival. He was ventilated in pressure control mode with a maximum plateau of 30 cm H_2O resulting in tidal volumes of 6 ml/kg of predicted body weight, a PEEP of 12 cm H_2O and a fraction of inspired oxygen of 100%. We measured an average lung compliance of 25,7 ml/cm H_2O and a mean driving pressure of 13 cm H_2O during the 24 hours before ECMO therapy. The worsening of gas exchange (PaO_2/FiO_2 ratio of 63,3 before cannulation) despite one session of prone position, inhaled nitric oxide (10ppm) and a continuous neuromuscular blocking agent administration for 24 hours led the clinician to decide for the implementation of venovenous ECMO 5 days after his admission. The ECMO machine delivered a circuit flow of 4,5-5 l/min, a delivered fraction of oxygen of 100% and sweep gas flow adjusted to obtain normal CO_2 values.

Later, because of a moderate pulmonary hypertension, he developed right heart failure for which dobutamine and then milrinone were given. Concomitantly he was treated by ceftazidime during nine days for a ventilator-associated pneumonia (VAP) due to pseudomonas aeruginosa.

In order to achieve a RASS of -4 to -5 the patient needed high doses of sedatives : ketamine 0,75-1 mg/kg/h (TBW), fentanyl 0,625-1,875 mg/kg/h (TBW) 3,75-4,25 mg/kg/h (TBW), clonidine 0,47 µg/kg/h (TBW). The initiation of sevoflurane to reach a Fet value between 1-1.5 % at an average rate of 7 ml/h allowed to stop the infusion of all intravenous sedatives except ketamine which was diminished by half. We also noticed with the same ventilatory settings an improvement of lung compliance whose mean value during the first 24 hours after sevoflurane initiation was 35,3 ml/cm H2O. The patient was kept under inhalational anesthetics for 8 days and experienced no adverse effects from these drugs. Finally, he died of a sudden vasoplegic shock. The autopsy revealed a bilateral organized pneumonia and the infarction of the right middle lobe.

Case description 3

The third patient is a 49-year-old male, known for untreated hypercholesterolemia. After the confirmation of SARS-CoV-2 infection, he received steroids (32mg of methylprednisolone per day) and hydroxychloroquine during five days before his admission in the intensive care unit. At this moment, a deep venous thrombosis of the right leg was treated by therapeutic low molecular weight heparin. Orotracheal intubation and protective lung strategy were initiated five days after his admission.

His gas exchanges continued to deteriorate in spite of one prone position session, protective lung strategy and a continuous infusion of neuromuscular blocking agents for 24 hours. Before the implementation of a venovenous ECMO the patient was ventilated in pressure control mode with a maximum plateau of 30 cm H_2O, a PEEP of 12 cm H_20, a FiO2 of 80% resulting in tidal volumes of 6 ml/kg of predicted body weight and a lung compliance of 26 ml/cm H_2O. The PaO_2/FiO_2 ratio before cannulation was 58. Femoro-jugular venovenous ECMO was successfully implemented at a circuit flow of 4.8 l/min, a delivered fraction of oxygen of 100% and a sweep flow gas of 4.0 l/min. In order to maintain a RASS between -4 and -5, high doses of intravenous sedatives were required : ketamine 0,5 mg/kg/h (TBW), propofol 2,5 mg/kg/h (TBW), clonidine 0,3125 µg/kg/h (TBW) and sufentanil 0,125 µg/kg/h (TBW). A bolus of 5mg of midazolam was required a few minutes before the initiation of the halogenated gases. Sevoflurane was initiated at a rate of 5 ml/h in order to obtain Fet values of 1-1.5% resulting in similar RASS scores. This maneuver allowed stopping all the sedatives except sufentanil. For this case we didn't notice any lung compliance

improvement in the first days following ECMO treatment. However, spontaneous breathing assisted ventilation without patient ventilatory asynchrony was established. The patient was weaned from ECMO after 63 days and resumed his activities 4 months after his admission to the intensive care unit. He suffered from a ventilator-associated pneumonia by staphylococcus aureus treated by oxacilline and later developed a DRESS syndrome supposedly due to hydroxychloroquine.

Discussion

The implementation and management of inhalational anesthetics via AnaConDa was done without any identified issues. The potential aerosolization risk of the virus was considered and we complied with the same airborne and droplet precautions used for SARS-CoV-2 infected patients requiring mechanical ventilation**.** In order to minimize the risk, closed circuit endotracheal suctioning was used. Endo-tracheal tube clamping was realized with ECMO clamps (18) during the installation of the device, which requires disconnection and reconnection from the ventilatory circuit**.** According to Sedana Medical, the virus filtration capacity of AnaConDa is superior to 99.9% for 27 nm particles, which corresponds to less than a quarter of the SARS-CoV-2 virus size (120-160mm) (19). This implies a very low risk of passage through the device to the respiratory circuit. The anesthetic gas analyzer used for all patients (Carescape 8650, GE healthcare, Finland) (20) contains a filter and a D-FEND water trap made from polytetrafluoroethylene with 99.9% virus and bacteria filtration efficiency. Regarding the ECMO membrane, Dres and al. didn't detect SARS-CoV-2 RNA in the membrane oxygenator gas outlet of 25 patients and concluded that the virus does not spread through extracorporeal membrane oxygenation (21).

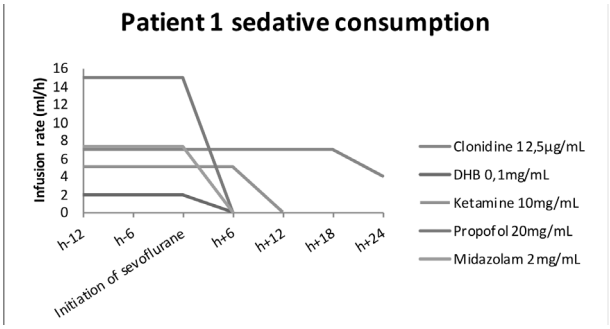
Another concern was the possible elimination of halogenated gas through the ECMO membrane. The A.L.ONE oxygenator is composed of polymethylpentene membranes coated with phosphorylcholine that are supposed to be poorly permeable to volatile anesthetics. Comparing polypropylene and polymethylpentene (PMP) membranes during cardiopulmonary bypass, Prasser showed that blood concentrations of previously applied sevoflurane were better maintained with PMP than with polypropylene membranes (22). Therefore, we first tested the administration of sevoflurane on the extracorporeal circuit by a vaporizer Drager Vapor 2000 (Drager Medical AG, Lubeck, Germany) connected to the gas supply line at a fresh gas flow of 5 l/min with increasing inhaled halogenated concentrations. No sevoflurane was detected in the patient's expired gases by the anesthesia gas monitor connected to the respiratory circuit. Attempts at decreasing sedatives were also unsuccessful. We used in our current practice a PMP membrane coated with acetylcholine and observed that it was not permeable to halogenated gas avoiding any risk of room air pollution. This trial demonstrated that the oxygenator membrane was poorly permeable to the halogenated anesthetic and that its use by inhalation would not result in vapors present in the exhaled gas of the oxygenator.

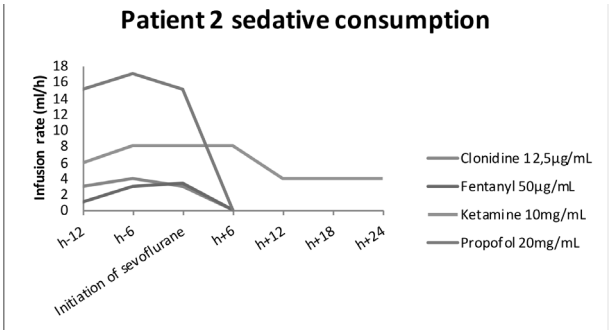
These 3 cases have shown a drastic diminution of intravenous sedatives requirements after the initiation of sevoflurane in order to achieve similar RASS scores (Figures 1, 2 and 3). No adverse effect related to the halogenated anesthetics, and no significant hemodynamic changes were observed during their administration. Several clinical advantages can be emphasized. The quick recovery after sevoflurane temporary withdrawal allowed easy neurological assessment. High doses of intravenous sedative agents increase the risk for delirium and ICU acquired weakness (23). The possibility to decrease their use thanks to halogenated gases might therefore be a beneficial effect. Weaning of intravenous sedatives also led to a reduction of administered fluids (on average 500 ml per day), which is fully in line with a conservative fluid strategy in the settings of ARDS.

Finally, the cost of the kit and vials could be a certain drawback for this practice. This is partly counterbalanced by the total costs of the intravenous sedatives and the ability to avoid paralytics in some cases, thanks to the relaxing properties of volatile anesthetics.

Conclusion

These three cases have demonstrated the feasibility of sedation with sevoflurane inhalation via AnaConDa for Covid-19 patients under venovenous extracorporeal membrane oxygenation. No evidence of implementation or security issues was noticed during the administration of the halogenated gases. In addition to the possibility of easy neurological assessment, inhalational anesthetics contributed to a conservative fluid strategy.





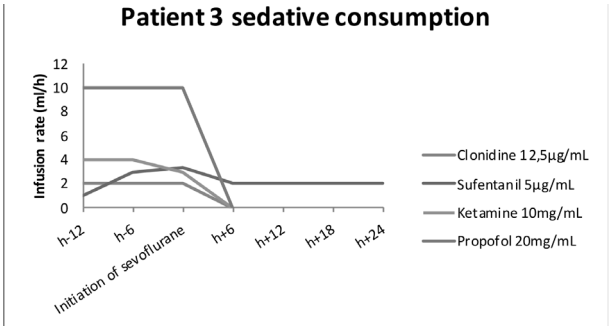


Figure 1, 2 and 3. — These 3 figures represent the sedative consumptions of the 3 patients for a RASS of -4 to -5. For simplicity reasons, the vertical axis of these graphs represents the flow rates (ml/h) of the infusion pumps. The drug concentrations are listed beside the graphs. The horizontal axis is a timeline ranging from 12 hours before the initiation of the halogenated drugs to 24 hours after. Each graduation corresponds to 6 hours. These 3 figures show the decrease of all intravenous sedatives after the initiation of sevoflurane.

Therefore, sevoflurane represents an alternative to intravenous sedatives, especially in case of intravenous drug shortage related to the covid-19 pandemic.

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Case Report : Severe Hypernatremia following treatment for Hyperosmolar Hyperglycaemic State : A pragmatic approach used to manage hypernatremia

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Abstract : The Hyperosmolar Hyperglycaemia State (HHS) is an endocrine emergency with a mortality rate between 10 and 50%. The mainstay for the treatment of this condition is vigorous IV fluid replacement with close monitoring of blood glucose, serum osmolality, and electrolytes. However, after initial resuscitation, patients can develop hypernatremia and raised serum osmolality, which have deleterious consequences. While hypernatremia in HHS can be treated with infusions of 0.45% saline or 5% dextrose, alternate measures such as intravenous (IV) hypotonic fluid infusion [e.g. 0.18% sodium chloride (NaCl) containing 4% dextrose and 0.15% potassium chloride (KCl)], or free water administration through a nasogastric (NG) tube can be used. We report the case of a 70-year-old man, who was initially admitted to a medical high care ward (MHC) with HHS, and was transferred to the ICU 72 hours later with an altered level of consciousness and severe hypernatremia. His treatment consisted in an IV hypotonic 0.18% NaCl infusion containing 4% dextrose and 0.15% KCl. He also received free water through a NG tube at a rate that was calculated to correct natremia at an average rate of 0.55 meq L-1 hr-1 over 72 hours. A multipronged approach was instituted to manage this patient, including, in addition to natremia correction, blood glucose control with insulin, appropriate IV antibiotics to treat infected foot ulcers, adequate analgesic medications, low-molecular-weight-heparin (LMWH) for thromboprophylaxis, proton-pump inhibitors, and continuation of patient's ongoing antidepressant drugs at the time of his Glasgow Coma Score improvement. This case report demonstrates the feasibility and success of IV hypotonic fluid (0.18% NaCl - 4% dextrose - 0.15% KCl), alongside NG free water for correcting sodium levels with lower fluid volumes than would have been otherwise required if corrected with 0.45% saline. This treatment seems to be a reasonable choice for correcting sodium levels and osmolality in HHS patients who present with hypernatremia after an initial resuscitation, insofar as it avoids fluid overload and provides dextrose as an energy substrate, in addition to potassium ions. However, while correcting natremia with hypotonic fluid, other aspects of management should not be ignored.

Keywords : Hyperosmolar Hyperglycaemia State (HHS) ; hypernatremia ; IV hypotonic fluid ; nasogastric (NG) free water.

Introduction

Acute severe hypernatremia is associated with a severe prognosis. Indeed, sodium levels higher than 160 mmol L^{-1} carry a mortality rate between 42% and 60% (1). Dysnatremias are com-monly encountered during the management of the Hyperosmolar Hyperglycaemia State (HHS), as sodium plasma concentration is usually modified by the therapeutic measures instituted to manage these patients (2). It has been demonstrated that brain cells are partially permeable to glucose, regardless of insulin action, because of a selective expression of transport proteins (3). Therefore, hypertonicity exclusively due to hyperglycemia is physiologically dampened in the central nervous system (CNS) by glucose penetration into the cells. Hypertonicity due to hypernatremia has a greater impact on the CNS. Hence, it has been suggested that natremia is a better predictor of neuro-logical impairment than plasma glucose itself, since severely hyperglycemic patients can be fully asymptomatic in the absence of hypernatremia (4). While hypernatremia in HHS can be treated with infusions of hypotonic saline (5). other alternative measures, such as intravenous (IV) glucose or sterile water, (6, 7). or the delivery of water through a nasogastric (NG) tube are also possible (8). Among hypotonic saline solutions, 0.45% saline is the most commonly used. However, using this solution often requires large volumes, which has the potential for fluid overload, particularly in elderly patients. Recently, a new brand of IV hypotonic fluid is being increasingly used, namely 0.18% sodium chloride containing 4% dextrose

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and 0.15% potassium chloride (KCl). It offers an advantageous correction using lower volumes, and also provides dextrose as an energy substrate, in addition to potassium ions for maintenance. In elderly patient, there is a risk of cerebral edema with the administration of hypotonic solution, whereas under-treatment may be complicated by vascular thrombosis and is associated with a high mortality rate (9). Hence, this hypotonic fluid needs to be administered at a finely calculated rate.

We report here the case of a patient who developed severe hypernatremia after being treated for HHS.

Clinical Case

A 70-year-old male was admitted to our hospital following complaints of vomiting, confusion, abdominal distension, myoclonic jerks, and urinary incontinence. He did not complain of of chest pain and shortness of breath. His past medical history included type-2 diabetes mellitus, chronic elevated blood pressure, and depression. Usual medications included amlodipine 5 mg once-a-day, duloxetine 60mg twice-a-day, gabapentin 300 mg three times a day, gliclazide 160 mg twice-a-day, metformin 500 mg twice-a-day, omeprazole 20 mg once-a-day, trazodone 50 mg twice-a-day, and simvastatin 40 mg once-a-day.

Upon admission, the patient was conscious although confused. His Glasgow Coma Score (GCS) was E4V4M6 (14/15). He was breathing spontaneously room air, and his recorded vital parameters were : pulse rate 82 bpm, blood pressure 154/77 mmHg, respiratory rate 18/min, peripheral saturation in oxygen (SpO_2) 97%, temperature 36.7 °C. Systematic examination was otherwise normal. Laboratory investigations revealed a plasma glucose level of 40.9 mmol L^{-1}, serum osmolality at 339 mOsm Kg^{-1}, plasma ketones at 2 mmol L^{-1}, one cross of urine ketones, a natremia at 134.6 mmol L^{-1}, creatinine at 606 micromol L^{-1}, blood urea (BUN) at 29.3 mmol L^{-1} (see Tables 1, 3, and 6). Arterial blood gases showed a pH at 7.36, a partial pressure in oxygen (PO_2) at 10.25 KPa, a partial pressure in carbon dioxide (PCO_2) of 5.93 KPa, a bicarbonate (HCO_3) concentration of 24.9 mmol L^{-1}, and a saturation in oxygen of 95.5%.

Initial diagnosis of the acute medicine team was HHS, in addition to stage-3 acute kidney injury (AKI-3). A plan was construed to treat HHS in a Medical High Care ward, where the patient remained for 72 hours, as per our internal protocols, which is based on the Joint British Diabetes Societies guidelines on the management of the Hyperosmolar Hyperglycaemia State in adults with diabetes (10), This plan included the infusion of normal saline 1L over 1 hour, and the infusion of insulin at a rate of 0.05 unit Kg^{-1} h^{-1}. A good response was noted to the initial treatment, with an improvement of blood glucose levels. After 60 minutes of treatment, the patient's blood glucose decreased to 36 mmol L^{-1}, and serum osmolality to 336 mOsm Kg^{-1}, while natremia was 136.6 mmol L^{-1} and BUN was 26.3 mmol L^{-1}. Normal saline was instilled at a rate of 0.5 L h^{-1} and the insulin rate was raised from 0.05 unit Kg^{-1} h^{-1} to 0.1 unit Kg^{-1} h^{-1} when the decrease in blood glucose was less than 5 mmol L^{-1} h^{-1}. After 6 hours, the patient's condition further ameliorated with a plasma glucose of 20 mmol L^{-1}, serum osmolality of 324 mOsm Kg^{-1}, natremia of 140 mmol L^{-1}, BUN

Table 1

Upon admission to the Medical High Care

	Admission	After 1 hour	After 6 hours	After 12 hours	After 24 hours	After 48 hours
Blood glucose (mmol L^{-1})	40.9	36	20	15	12.3	12
Serum sodium (meq L^{-1})	134.6	136.6	140	142	144	168
Serum osmolality (mOsm Kg^{-1})	339	336	324	319	318	365
Serum potassium (meq L^{-1})	4.7	4.1	3.8	3.9	4.1	3.6
BUN (mmol L^{-1})	29.3	26.3	24.3	20.0	18	16.8

Table 2

Upon admission to the ICU

	Admission	After 2 hours	After 4 hours	After 12 hours	After 24 hours	After 36 hours	After 48 hours	After 72 hours
Blodd glucose (mmol L^{-1})	11	10.5	11.5	10.6	10	10.2	9.5	8
Serum sodium (meq L^{-1})	180	176	174	171.2	167	160.4	153	141
Serum osmolality (mOsm Kg^{-1})	385	376	373	365	355	341	325	298
Serum potassium (mmol L^{-1})	3.5	3.6	3.8	4.0	4.1	4.2	4.5	4.5
BUN (mmol L^{-1})	14.4	13.8	13.5	12	11	10	9	7.5

Table 3

Bone profile, LFT, and KFT

	Admission to the MHC	24 hours in the MHC	48 hours in the MHC	Admission to the ICU	24 hours in the ICU	48 hours in the ICU	72 hours in the ICU
ALP (U L^{-1})	105	101	90	86	74	70	65
Adj Ca (mmol L^{-1})	2.26	2.22	2.46	2.40	2.32	2.28	2.24
Phosp (mmol L^{-1})	2.11	2.00	1.36	1.08	0.99	1.19	1.42
Total protein (g L^{-1})	77	75	70	65	62	65	67
Albumin (g L^{-1})	42	37	38	36	35	37	39
Globulin (g L^{-1})	33	31	34	30	32	31	33
Total bil (micromol L^{-1})	4	5	4	5	5	4	4
AST (U L^{-1})	8	10	24	63	59	44	34
ALT (U L^{-1})	10	14	16	48	51	37	38
Creat (micromol L^{-1})	606	539	176	150	120	105	99
Magnesium (mmol L^{-1})	0.74	0.83	0.89	0.97	0.95	0.91	0.92
Chloride(mmol L^{-1})	95	101	108	105	102	99	97

Normal values: Adj Ca = 2.2 - 2.6 mmol L^{-1}, Phosp = 0.8 - 1.5 mmol L^{-1}, Total protein = 60 - 80 g L^{-1}, Albumin = 35 - 50 g L^{-1}, Globulin = 21 - 35 g L^{-1}, Total Bil = 3 - 21 micromol L^{-1}, AST = 10 - 45 U L^{-1}, ALT = 5 - 55 U L^{-1}, Creat = 50 - 120 micromol L^{-1}, Chloride = 95 - 108 mmol L^{-1}, eGFR = 60 - 61, Magnesium = 0.7 - 1 mmol L^{-1}.

of 24.3 mmol L^{-1}, and a positive fluid balance of 2 liters. The patient was maintained on IV fluid replacement as per our protocol. After 12 hours, the patient's condition significantly improved with a plasma glucose of 15 mmol L^{-1}, serum osmolality of 319 mOsm Kg^{-1}, natremia of 142 mmol L^{-1}, BUN of 20 mmol L^{-1}, and fluid balance was noted to be positive by 3 liters. The patient was then maintained on IV fluid replacement using normal saline and 5% dextrose, at a rate of 125 mL h^{-1} once blood glucose dropped below 14 mmol L^{-1}.

After 24 hours, the patient was placed on our maintenance protocol, including a variable rate of insulin infusion and a plan to convert insulin administration to a subcutaneous regime once biochemically stable. He appeared to be well responding clinically. Laboratory investigations revealed improving parameters, including a plasma glucose of 12.3 mmol L^{-1}, serum osmolality of 318 mOsm Kg^{-1}, natremia of 144 mmol L^{-1}, BUN of 18 mmol L^{-1} and a positive fluid balance of 4.5 litres. The arterial blood gases revealed a pH at 7.43, a PO_2 of 10.8 KPa, a PCO_2 of 5.14 KPa, a HCO_3 concentration of 25.3 mmol L^{-1}, saturation in oxygen (SO_2) of 95.8%, and a lactate concentration of 1.5 mmol L^{-1}.

Between the 24th and the 48th hour after admission, while being on our maintenance protocol, the patient had improved significantly, except for one vital sign that deserved additional attention, namely a diminished oral intake and an increased urine output. After 48 hours following admission, the patient displayed signs and symptoms of delirium and agitation. He started pulling out his IV lines, exhibited inappropriate speech, and got off the bed. The Sedation Agitation Scale (SAS) Score was recorded at 7. Recorded vital signs were then a pulse rate of 101 bpm, a blood pressure of 108/55 mmHg, a SpO_2 of 98%, and a respiratory rate at 16 min^{-1}. The remaining clinical examination was normal. The recorded input/output volumes were 800 ml/2600 ml. The plasma glucose was 12 mmol L^{-1}, natremia was 168 mmol L^{-1}, serum osmolality was 365 mOsm Kg^{-1}, and BUN was 16.8 mmol L^{-1}. Urine osmolality was noted at 557 mOsm Kg^{-1} thus ruling out diabetes insipidus. A brain CT scan was depicted normal. The inference made by the acute medicine team was a diagnosis of delirium secondary to metabolic encephalopathy, sepsis, and a diuretic phase of recovery from AKI. Lorazepam and haloperidol were administered to control agitation. Blood glucose was controlled by insulin, administered as per a sliding scale. A regimen of antibiotics, namely amoxicillin, as well as antiviral medications was administered for a sepsis of unknown origin. However, correction with half normal saline (0.45% saline) at a rate of 100 mL h^{-1} failed to correct his serum sodium levels, which continued to peak. After 72 hours following admission, the patient continued to be in a state of agitation, and an Intensive Care Unit (ICU) consultation was sought, whereupon patient was transferred to the ICU where he stayed for another 72 hours.

Upon admission to the ICU, the patient had become drowsy, with a GCS dropping to E2V2M5 (9/15). His vital parameters at that time were a pulse rate of 80 bpm, a blood pressure of 105/52 mmHg,

Table 4

Coagulation screen and CRP

	Admission to the MHC	24 hours in MHC	48 hours in MHC	Admission to the ICU	24 hours in the ICU	48 hours in the ICU	72 hours in the ICU
PT (sec)	11	10	9	11	10	12	11
aPTT (sec)	23	24	25	23	22	25	23
Fib (g L^{-1})	3.5	3.4	3.1	3.6	3.5	3.6	3.5
CRP (mg L^{-1})	234	266	141	113	77	25	9

Normal values: CRP = 2 - 10 mg L^{-1}, Fib = 1.8 - 3.6 g L^{-1}, PT = 9 - 12 sec, aPTT = 22 - 28 sec.

Table 5

Full blood count

	Admission to the MHC	24 hours in MHC	48 hours in MHC	Admission to the ICU	24 hours in the ICU	48 hours in the ICU	72 hours in the ICU
RBC ($\times 10^{12}$ L^{-1})	3.86	3.53	3.92	4.09	4.35	3.99	3.90
Hb (g L^{-1})	111	103	112	117	123	112	113
TLC ($\times 10^{9}$ L^{-1})	7.6	6.2	10.9	11.9	14.6	11.7	14.4
Plat ($\times 10^{9}$ L^{-1})	240	217	295	276	250	217	223
Neutro ($\times 10^{9}$ L^{-1})	6.7	5.2	9.1	9.3	7.8	6.4	5.5
Lympho ($\times 10^{9}$ L^{-1})	1.2	1.4	1.5	1.4	2.3	1.9	1.5
Eosino ($\times 10^{9}$ L^{-1})	0	0	0	0	0	0	0
Baso ($\times 10^{9}$ L^{-1})	0	0	0	0	0	0	0

Normal values: RBC = 4.32 - 5.66 × 10^{12} L^{-1}, Hb = 133 - 176 g L^{-1}, TLC = 3.7 - 9.5 × 10^{9} L^{-1}, Plat = 150 - 400 × 10^{9} L^{-1}, Neutro = 1.5 - 6.5 × 10^{9} L^{-1}, Lympho = 1.1 - 5 × 10^{9} L^{-1}, Eosino = 0.1 - 0.7 × 10^{9} L^{-1}, Baso = 0 - 0.1 × 10^{9} L^{-1}.

Table 6

Other tests

Serum protein electrophoresis	No evidence of paraprotein band
ANA	Negative
Serum cortisol level®	361nmol L-1(Normal)
TSH	0.36 mU L^{-1} (0.27 - 4.2 mU L^{-1})
Free T4	2.7 pmol L^{-1} (0.27 - 4.2 pmol L^{-1})
CT Brain	Normal age-related involutional changes. No infarct, hemorrhage, or intracranial lesion noted.
Urine osmolality	557 mOsm Kg^{-1} (after 48 hours in the MHC) 550 mOsm Kg^{-1} (Upon admission to the ICU)

a SPO_2 of 96% in room air. Ulcers were noticed on both feet and swab for culture and sensitivity was taken. Labs revealed a corrected natremia of 180 mmol L^{-1}, a plasma glucose of 11 mmol L^{-1}, BUN at 14.4 mmol L^{-1}, and a serum osmolality at 385 mOsm Kg^{-1}. Urinary osmolality was 550 mOsm Kg^{-1} (see Tables 2 to 6), and an electrolyte-free water excretion was calculated at 600 ml over 24 hours, which suggested that post-AKI polyuria had settled down. Hypernatremia had developed in less than 48 hours, and hence was labelled as acute hypernatremia.

The treatment strategy was devised along following steps :

1. Calculating the free water deficit
2. Determining a suitable serum sodium correction rate
3. Estimating ongoing free water losses (if applicable ~1 L or more)
4. Designing a suitable fluid repletion program that takes into account the estimated free water deficit, the desired serum sodium correction rate, and any ongoing excess of free water losses. Further specific treatment was guided by the presence and severity of signs/symptoms, time of onset, and volume status of the patient.

His airway was patent and not considered to be at risk as his motor function was good. He had strong cough reflexes. Boxing gloves were put on. The arterial blood gases revealed a pH 7.43, a PO_2 at 10.6 KPa, a PCO_2 at 5.04 KPa, a HCO_3 at 25.4 mmol L^{-1}, and a SO_2 at 95.6% (on room air). Hypernatremia was corrected according to the protocol. The replacement fluid was a hypotonic fluid containing 0.18% NaCl, 4% dextrose, and 0.15% KCl, administered intravenously, and free water administered through the NG tube. In order to fully correct sodium within 72 hours at a rate of 0.55 meq $L^{-1}h^{-1}$, the replacement IV fluid had to be given at a rate 99.4 (or 100) mL h^{-1}, and the NG free water at a rate of 50 mL h^{-1}. However, for the first two hours, we allowed the sodium correction to be of 2 meq L^{-1} h^{-1}, followed by a sodium correction rate of 1 meq L^{-1} h^{-1} for the next two hours. Further sodium correction was done at a lower rate of 0.35 meq L^{-1} h^{-1} for the remaining 24 hours, so that the total corrected sodium during the first 24 hours didn't

exceed 13 meq L^{-1} (determined from the original correction rate of 0.55 meq L^{-1} h^{-1}). Thereafter, for the remaining 48 hours, the IV replacement fluid was given at the originally calculated rate of 99.4 (or 100) mL hr^{-1}, allowing full sodium correction within 72 hours. In this context, for the first couple of hours, the replacement IV fluid was given at a rate of 361.45 mL h^{-1} and then at 180.72 mL h^{-1} for the following two hours.

After the first four hours, the replacement fluid was administered at a rate of 63.25 mL h^{-1} for the first 24 hours. Thereafter, during the next 48 hours, the replacement fluid was given at 99.4 (or 100) mL h^{-1}, to allow sodium being corrected steadily at a rate of 0.55 meq L^{-1} h^{-1}. Flucloxacillin was administered on the basis of the identification of a staphylococcus aureus in the swab taken from the toes. Virology revealed negative results, and hence acyclovir was stopped. Adequate analgesia was ensured by the application of lidocaine plasters, the administration of gabapentin 300 mg three times in a day, through the NG tube, and IV paracetamol 1 g twice-a-day. Haloperidol was increased to 1 mg four times a day IV to control agitation.

After two hours, his corrected Na was noted to be 176 meq L^{-1}, serum osmolality to be 376 mOsm Kg^{-1}. After four hours, the corrected Na was 174 meq L^{-1}, and serum osmolality was 373 mOsm Kg^{-1}. At the end of 12 hours, the patient achieved a corrected Na of 171.20 meq L^{-1}, a serum osmolality of 365 mOsm Kg^{-1}, and his GCS had improved to E3V3M6 (12/15). On the 2nd day after ICU admission, i.e. 24 hours after commencing sodium correction in the ICU, the patient's GCS improved further to E3V3M6 (13/15). He was delirious although manageable on haloperidol. Vital signs were a pulse rate of 82 bpm, a blood pressure of 110/56 mmHg, and a SPO_2 of 98% (on room air). Labs revealed a corrected serum Na at 167 mmol L^{-1}, a plasma glucose at 10 mmol L^{-1}, a serum osmolality at 355 mOsm Kg^{-1}, and a BUN at 11 mmol L^{-1}. Arterial blood gases revealed a pH at 7.43, PO_2 at 11.6 KPa, a PCO_2 at 5.44 KPa, a HCO_3 at 26.3 mmol L^{-1}, a SO_2 at 97.4%, and a lactate level at 1.58mmol L^{-1}. Forty-height hours after the commencement of the treatment in the ICU, the patient's GCS improved further to E4V4M6 (14/15). His serum sodium level decreased to 153 meq L^{-1}, serum osmolality to 325 mOsm Kg^{-1}, BUN to 9 mmol L^{-1}, and plasma glucose to 9.5 mmol L^{-1}. He was initiated on a NG low sodium diet at a rate of 30 mL h^{-1}, increased subsequently to 50 ml h^{-1}. Finally, after 72 hours of ICU treatment, the patient's GCS became normal at E4V5M6 (15/15), he was no longer delirious (CAM-ICU score of 0), and his labs revealed a corrected serum sodium at 141 meq L^{-1}, a serum osmolality of 298 mOsm Kg^{-1}, a BUN of 7.5 mmol L^{-1}, and a plasma glucose of 8 mmol L^{-1}. He was transferred from the ICU to the High Dependency Unit (HDU), where he completed his course of antibiotics, tolerated full orals, and was switched on metformin and regular insulin subcutaneously. The patient was subsequently discharged from the hospital.

Discussion

Definition and diagnosis of HHS

The characteristic features of HHS (10) are hypovolemia, marked hyperglycemia(>30 mmol L^{-1}) without significant hyperketonemia (<3 mmol L^{-1}) or acidosis(pH >7.3, HCO_3 >15 mmol L^{-1}), and an osmolality >320 mosmol Kg^{-1} (10).

Hyperglycemia results in an osmotic diuresis, and renal losses in excess of sodium and potassium (11). Fluid losses in HHS are estimated to range between 100-220 ml Kg^{-1}, sodium losses between 5 and 13 mmol Kg^{-1}, chloride between 5 and 15 mmol Kg^{-1} and potassium between 4 and 6 mmol Kg^{-1} (12).

Osmolality is useful both as an indicator of the severity and for monitoring the rate of change with treatment. As frequent measurement of osmolality is not usually available in UK hospitals, osmolality should be calculated as a surrogate, using the formula : 2 sodium concentration + glucose concentration + urea concentration (10).

Changes in mental performance are presorted during HHS (10). Some authors (13) have suggested that changes in mental performance correlates with the severity of hyperosmolality, with confusion being common at an osmolality >330 mosmol kg^{1}. An assessment of cognition should accompany a full history, physical examination, and review of drug therapy upon admission. Of course, tests of cognition must be viewed in comparison to the premorbid state, which in the elderly inpatient is often lacking (10).

Treatment goals in HHS (10)

The treatment goals in HHS are to normalise osmolality, replace fluid and electrolyte losses, normalise blood glucose, prevent arterial or venous thrombosis, prevent other potential complications such as cerebral edema or central pontine myelinolysis, and prevent foot ulcerations. The goal of the initial therapy is the expansion of the intravascular and extravascular volume, and to restore peripheral perfusion. The base fluid that

should be used is 0.9% sodium chloride with added potassium added as required (14). Fluid replacement alone without insulin will lower blood glucose, which will reduce osmolality causing a shift of water into the intracellular space. This inevitably results in a rise in serum sodium (a fall in blood glucose of 5.5 mmol L^{-1} will result in a 2.4 mmol L^{-1} rise in sodium). This is not necessarily an indication to give hypotonic solutions (10). Rapid changes should be avoided (10) – a safe rate of fall in plasma glucose is between 4 and 6 mmol L^{-1}. If the inevitable rise in sodium is much greater than 2.4 mmol L^{-1} for each 5.5 mmol L^{-1} fall in blood glucose (15), it suggests inefficient fluid replacement. Thereafter, the rate of fall of plasma sodium should not exceed 10 mmol L^{-1} in 24 hours (16). The aim of treatment should be to replace approximately 50% of the estimated fluid loss within the first 12 hours and the remainder within the following 12 hours, though this may be in part determined by the initial severity, degree of renal impairment and co-morbidities such as heart failure, which may limit the speed of correction. The aim is to achieve a gradual decline in osmolality, ranging between 3 to 8 mOsm Kg^{-1} h^{-1} (10). Insulin should be started at time zero if ketonemia is present (that is when 3-beta-hydroxybutyrate is >1 mmol L^{-1}). The recommended insulin dose is a fixed rate of IV insulin infusion at 0.05 units Kg^{-1} h^{-1} (10). A target blood glucose between 10 and 15 mmol L^{-1} is a reasonable goal. Complete normalization of electrolytes and osmolality may take up to 72 hours (10). Antibiotics should be given when there are clinical signs of infection or imaging/lab tests. Patients with HHS have an increased risk of arterial and venous thromboembolism (17,18). All patients should receive prophylactic LMWH for the full duration of hospitalization, unless contraindicated (10).

These patients are at increased risk of pressure ulceration. An initial foot assessment should be undertaken, and heel protectors applied in those with neuropathy, peripheral vascular disease, or lower limb deformity. If the patients are too confused or sleepy to cooperate with the assessment of sensation, one should assume that they are at high risk. Feet should be reexamined daily (10).

Management of hypernatremia

The diagnostic criteria (19). of hypernatremia are based on serum sodium concentration. Hypernatremia is defined as a serum sodium concentration >145 mmol L^{-1}. Severe hypernatremia has variously been defined as a serum sodium concentration >152 mmol L^{-1}, >155 mmol L^{-1}, or >160 mmol L^{-1}, no consensus has been reached on the exact level (19-22). Extremely high sodium levels occur in salt poisoning. Time of onset (19). is also important. Patients with hypernatremia that has developed slowly (e.g. over days, weeks, or months) are commonly asymptomatic, while patients with hypernatremia that has developed rapidly (e.g., over a few hours) will be symptomatic. Hypernatremia that develops in <48 hours is usually classified as acute, while hypernatremia that develops over ≥48 hours is chronic (19).

In face of hypernatremia, the useful diagnostic tests (19). include the measurement of a serum electrolyte concentration panel, glucose, urea, and creatinine (10). These tests should be ordered in all patients with suspected or confirmed hypernatremia. They may reveal other electrolyte abnormalities, renal impairment, or uncontrolled diabetes mellitus. Some patients may display associated hypokalemia or, more rarely, hypercalcemia. Patients with hypernatremia often have high serum urea and/or creatinine levels. High urea levels may worsen hypernatremia by causing osmotic diuresis (23, 24).

Urine osmolality (19). should also be ordered in all patients with hypernatremia, as it may help determining the underlying etiology. A low urine osmolality (<150 mmol Kg^{-1}), below or equal to plasma osmolality, suggests diabetes insipidus. When urine osmolality is high (>500 mmol Kg^{-1}), higher or equal to plasma osmolality, it suggests pure volume depletion not due to diabetes insipidus (e.g. gastrointestinal or insensible losses). A urine osmolality not too distant from plasma osmolality (between 200 and 500 mmol Kg^{-1}) suggests a renal concentrating defect, most commonly due to renal failure, osmotic diuresis, and/or use of diuretics.

Unlike hyponatremia, hypernatremia is always associated with serum hyperosmolality (>295 mmol Kg^{-1}) (19).

Urine electrolytes concentration measurement (19), as well as urine flow rate (19) should be ordered in patients with urinary losses to determine electrolyte-free water excretion. The formula $V \times 1-(U_{Na}+U_K/P_{Na})$ can be used, where V = urine flow rate, U_{Na} = urinary sodium concentration, U_K = urinary potassium concentration, and P_{Na} = plasma sodium concentration. The resulting value indicates how much electrolyte-free water is being lost through the urine at any given time (e.g., per hour, per day) (25, 26). However, it does not provide a value for the total amount of free water needed to correct hypernatremia (27). A low value (<0.5 L day^{-1}) suggests an inadequate free water intake, a high

value (≥1 L day^{-1}) suggests large free water losses, and a very high value (>5 L day^{-1}) suggests diabetes insipidus (19).

Other tests can also be considered. A desmopressin challenge test (19). should be ordered in patients with suspected diabetes insipidus. This test helps differentiating between central and nephrogenic diabetes insipidus. It consists in giving a standard dose of desmopressin, and measuring serum osmolality, urine osmolality, and urine volumes hourly over a 4-hour period. Patients with central diabetes insipidus respond to desmopressin with a reduction in urine output and increased serum osmolality. Patients with nephrogenic diabetes insipidus have little or no response. Measuring the serum arginine vasopressin level (19) may also be useful to distinguish central diabetes insipidus from nephrogenic diabetes insipidus, being low in case of central diabetes insipidus. A brain magnetic resonance imaging of CT scan is recommended in all patients with central diabetes insipidus, to find out the underlying cause, such as a pituitary tumor or other abnormalities (19).

Another important point in the management of hypernatremia is the assessment of the extracellular volume of fluids (28). If this volume is low (dehydration signs), it should be restored, if normal, water losses should simply be replaced, and if high (edema), diuresis should be enhanced while replacing lost volumes by hypotonic fluids. If hemodynamic monitoring is available, the intravascular volume status can serve as an estimate of the extravascular volume status, in the absence of hypoproteinemia, which shifts the fluids from the intravascular to the extravascular space (28). The intravascular volume status can be evaluated using the relationship between the cardiac filling pressures and the cardiac output.

The fluid management of HHS is similar to the one described for hypovolemic hypernatremia (28). Volume deficits tend to be more pronounced in HHS than in simple hypovolemic hypernatremia, because of osmotic diuresis that accompanies the glycosuria. Therefore, rapid correction of plasma volume is done by isotonic saline as we did in the reported case. Once the plasma volume is restored, free water deficits are estimated and replaced. Moreover, corrected plasma sodium should be used to guide therapy, insofar as hyperglycemia draws water from the intravascular space (28). The corrected plasma sodium can be calculated as [(current glucose - 100 mg dl^{-1}) / 100) × 1.8)] + measured sodium (28).

The calculation of free water deficit for replacement is based upon the assumption that the product of the Total Body Water (TBW) and plasma sodium concentration (P_{Na}) is always constant, namely current TBW × current P_{Na} = normal TBW × normal P_{Na} (28). Substituting 140 meq L^{-1} for a normal P_{Na} and rearranging terms yields the following relationship : current TBW = normal TBW × (140/Current P_{Na}) (28). The normal TBW in liters is usually 60% of lean body weight in Kg in men, and 50% in females. However, when hypernatremia associated with free water deficits, the normal TBW should be approximately 10% lower than usual (29). Thus, in men, the normal TBW is 0.5 × body weight. Once the current TBW is calculated, the water deficit is taken as the difference between the normal and current TBW : TBW deficit (in L) = normal TBW - current TBW (28). The volume needed to correct the water deficit is determined by the concentration of sodium in the replacement fluid as follows : replacement volume (in L) = TBW deficit × (1/1-x), where 'x' is the ratio of sodium concentration in the resuscitation fluid to the sodium concentration in the isotonic saline (28). The volume deficit should be replaced slowly, so that serum sodium concentration decreases by 0.5 meq L^{-1} each hour, typically requiring 48 to 72 hours to limit the risk of cerebral edema (30). Patients with severe symptoms (i.e., neurological symptoms) require more urgent treatment and more rapid correction of the sodium level during the first 2-3 hours, to prevent long-term neurological complications (e.g., myelinolysis). In that case, the serum sodium concentration should be lowered by 2 mmol L^{-1} h, followed by a correction rate of around 0.5 mmol L^{-1} h^{-1} after 2 to 3 hours (31).

In the patient we report here, we used the IV hypotonic fluid available in our ICU, namely 0.18% sodium chloride containing 4% dextrose and 0.15% KCl, as well as free water instilled through the NG tube. We calculated the total body water deficit as mentioned above, using the Lean Body Mass (LBM) calculated according the James formula for males [eLBM = 1.1 Weight – 128 (Weight/$Height^2$)]. Patient's weight was 96 Kg and height as 182 cm, which leads to a LBW of 70 Kg. In this case, normal TBW is 42 L, current TBW is 42 × 140/180 = 32.6 L, the TBW deficit is 42 - 32.6 = 9.4 L. Considering NG free water replacement at a rate of 50 mL h^{-1}, it equals to 1200 mL over 24 hours and 3600 mL over 72 hours. Thus, for the computation of replacement volume, we deducted 3600 ml from 9.4 L, which equated to 5800 mL. The replacement volume calculated for our IV hypotonic fluid (0.18% sodium chloride containing 4% dextrose and 0.15% KCl) was 5800 × (1/1-x), where 'x' corresponds to the

sodium concentration in the correction fluid divided by the sodium concentration in normal saline, that is 30 / 154 = 0.19. Placing this 'x' value in the above formula reveals that the replacement volume = 5800 × (1/1-0.19) = 7160 mL. In order to fully correct sodium within 72 hours at a rate of 0.55 meq L^{-1}/hr, the replacement fluid had to be administered at 99.4 (approximately 100) mL hr^{-1}. If saline 0.45% had been used instead, our replacement volume would have been 11600 mL, which would have been administered at 161 mL h^{-1}. As a consequence, our replacement fluid provided correction with a lower volume (7160 mL) and a lower rate of administration. During the first two hours, we allowed sodium correction at a 2 meq L^{-1} h^{-1} rate (meaning administering the replacement fluid at 361.45 mL h^{-1}), followed by a sodium correction rate of 1 meq L^{-1} h^{-1} (replacement fluid at 180.72 mL h^{-1}) for the next two hours. After this period, sodium was corrected at a lower rate of 0.35 meq L^{-1} h^{-1} (replacement fluid at 63.25 mL h^{-1}) for the remaining 24 hours, so that the total corrected sodium during the first 24 hours didn't exceed 13 meq L^{-1} (determined from the original correction rate of 0.55 meq L^{-1} h^{-1}). Thereafter, for the remaining 48 hours, the replacement fluid was given at an originally calculated rate of 99.4 (or 100) mL h^{-1}, allowing full sodium correction within 72 hours. After commencing the administration of the replacement fluid, at the end of first 24 hours, the patient's GCS considerably improved to E3V4M6 (13/15), as did his serum osmolality, though he continued to be in a state of manageable delirium. After 48 hours, his GCS further improved to E4V4M6 (14/15), and he was placed on a low sodium NG diet, which was initiated at 30 mLh^{-1} and increased subsequently to 50 mLh^{-1}. Interestingly, this low sodium diet didn't change the sodium correction rate. Sodium continued to decrease as per our calculated anticipated rate. Finally, 72 hours after the beginning of the treatment in the ICU, GCS became normal E4V5M6 (15/15) and his CAM-ICU (delirium) score was 0. He was then transferred from the ICU to the HDU, where he was switched on Metformin and regular subcutaneous insulin, before being discharged from the hospital.

Conclusions

Serum sodium is a better indicator of neurological impairment than blood glucose levels, as demonstrated in our patient who, when brought into the ICU, had attained stable blood sugar levels between 10 and 15 mmol L^{-1}. However, his corrected sodium level was still substantially deranged at 180 meq L^{-1}. Using 0.18% sodium chloride containing 4% dextrose and 0.15% KCl provided correction with lower fluid volumes and rates of infusion than 0.45% saline. In addition, this fluid provided not only dextrose for energy substrate but potassium ions for maintenance. By deducting the free water administered through the NG tube from the replacement volume of the correction fluid, the calculated replacement volume worked as anticipated to lower the serum sodium level. Furthermore, NG feed was added low sodium as the patient's condition improved, and this had no impact on the anticipated sodium correction rate or osmolality. We therefore advocate a multipronged approach for dealing with those patients and regarding sodium correction, using hypotonic IV fluids, NG free water, monitoring of blood glucose levels, and their maintenance within a normal range using regular insulin as per a sliding scale (32). Other important aspects of treatment should also be instituted, namely antibiotics to treat infection (in this case, infected foot ulcers), adequate pain relief (in this case with paracetamol, lidocaine plasters, and analgesic drugs like gabapentin), control of delirium (in this case with haloperidol), prevention of thrombosis using LMWH, and prevention of peptic ulcers using proton pump infibitors (in this case omeprazole). In our opinion, the IV hypotonic fluid we used alongside NG free water appears to be a reasonable choice for correcting the sodium levels and osmolality in HHS patients who present with hypernatremia after initial resuscitation. While correcting sodium with hypotonic fluid, other aspects of management should not be ignored.

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Patient's perspective : Patient was happy that doctors all over the world are going to learn from his case and its discussion will add valuable points to medical literature.

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CONTENTS

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