Impact of Entropy Monitoring on Volatile Anesthetic Uptake

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ABSTRACT

Background: Electroencephalogram-derived monitoring to assess anesthetic depth may allow more accurate hypnotic drug administration, resulting in decreased anesthetic drug consumption. The authors hypothesized that the use of M-Entropy monitoring (Datex-Ohmeda, Helsinki, Finland) is associated with reduced sevoflurane uptake (primary outcome) in patients undergoing major abdominal surgery.

Methods: A total of 50 patients with an American Society of Anesthesiology score of II–III, scheduled for elective laparoscopic rectosigmoidectomy were randomized into two groups in this randomized controlled trial. In the control group, the target expiratory fraction of sevoflurane was adapted according to standard clinical practice. In the study group, the target expiratory fraction of sevoflurane was adapted to maintain state entropy values between 40 and 60. State entropy values were continuously recorded in both groups but were not available to the anesthesiologist in the control group. In both groups, patients were ventilated using the auto-control mode of the Zeus® (Dräger, Lübeck, Germany) respirator, which allows precise measurements of sevoflurane uptake. Sufentanil was administered using a target-controlled infusion system.

Results: Demographics did not differ between groups. During the anesthesia maintenance phase, state entropy values were lower in the control group than the study group ($P < 0.0001$). Sevoflurane uptake was higher in the control group than the study group (5.2 ± 1.4 ml/h *vs.* 3.8 ± 1.5 ml/h; $P = 0.0012$). Three patients in the control group developed intraoperative hypotension compared with none in the study group ($P = 0.03$).

Conclusions: Monitoring the depth of anesthesia using M-Entropy was associated with a significant reduction in sevoflurane uptake.

What We Already Know about This Topic

- The effect of cerebral monitoring on anesthetic utilization and the benefits of such monitoring to reduce anesthetic administered to patients are controversial

What This Article Tells Us That Is New

- In patients undergoing colectomy and a computer-controlled sufentanil infusion, sevoflurane use was reduced by approximately 30% with the use of M-Entropy
- Extubation time was shorter in the monitored group, but recovery room stay was not different

DEPTH of anesthesia is frequently assessed using electroencephalogram processing systems, such as BIS® (Bispectral Index, Aspect Medical Systems, Natick, MA) and M-Entropy® (Datex-Ohmeda, Helsinki, Finland).[1] The use of these monitors has been claimed to allow more accurate drug administration,[2,3] which has the theoretical benefit of avoiding phases of too light or too profound anesthesia and the associated risks of hemodynamic instability. Outcomes of these studies have indicated that the use of bispectral index monitoring (Aspect Medical Systems) is associated with reduced anesthetic drug consumption and faster recovery,[3] such straightforward evidence is lacking for M-Entropy monitoring. Even though an excellent correlation exists between BIS and state entropy (SE) values,[4] few studies have evaluated the impact of entropy monitoring on anesthetic drug consumption. This is true not only for the intravenous but also for volatile anesthetic agents. Indeed, precise measurements are more difficult for volatile than for intravenous anesthetic agents. The few studies on the subject have used either end-tidal sevoflurane concentration[5] or differences in vaporizer weight,[6] neither of which allows an accurate evaluation of volatile drug uptake. In addition, known interaction between opiates and hypnotics on electroencephalogram-processed variables was not controlled.

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Received from the Department of Anesthesiology, University Hospital Center of Brugmann, Brussels, Belgium. Submitted for publication March 20, 2012. Accepted for publication November 14, 2012. Support was provided solely from institutional and/or departmental sources.

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The current randomized controlled study tested the hypothesis that the use of M-Entropy monitoring (Datex-Ohmeda) in major abdominal surgery is associated with decreased sevoflurane uptake compared with standard clinical practice (primary outcome). We used the Zeus® (Dräger Medical, Lübeck, Germany) ventilator, which allows precise measurement of anesthetic gas uptake.[7] Secondary outcomes included extubation time, occurrence of hemodynamic disturbances, postanesthesia care unit length of stay, and postoperative piritramide consumption.

Materials and Methods

This prospective controlled randomized single-site study was approved by the ethics committee of the university hospital center of Brugmann, Brussels, Belgium (CE 2005/27). From June 2006 to October 2009, 55 patients with an American Society of Anesthesiologists score of II–III, older than 18 yr who were scheduled for elective laparoscopic rectosigmoidectomy (surgery for more than 2 h) were enrolled in the study. All patients provided written informed consent. Patients with impaired liver (plasma transaminases >2 times normal) or renal (creatinine >2 mg/dl) function or who had history of drug abuse were excluded. Randomization was performed using a system of sealed envelopes. Blocks of 10 envelopes (five assigning to the control group and five assigning to the study group) were prepared for every 10 patients. The responsible anesthetist chose a sealed envelope from the block, assigning the patient to either the control group in which anesthesia depth was maintained based on standard clinical practice or to the study group in which anesthesia depth was maintained based on entropy monitoring. All patients were treated by the same anesthetic and surgical team, who were not involved in the data collection and analysis.

Preoperative medication was maintained up to the day of surgery with the exception of angiotensin-converting enzyme inhibitors, angiotensin II antagonists, oral antidiabetics, and vitamin K antagonists. Premedication consisted of oral alprazolam (0.25, 0.5, or 0.75 mg) 1 h before surgery according to the patient's weight (<50, 50–80, or >80 kg, respectively).

Each patient was continuously monitored by 5-lead electrocardiogram, noninvasive arterial pressure, pulse oximetry, and end-tidal carbon dioxide concentration. In addition to the standard conventional monitors, M-Entropy® (Datex-Ohmeda) electrodes were placed before induction on each patient. The anesthesiologist had access to the entropy data in the study group but was blinded to these data in the control group. Because few differences exist between SE and responsive entropy in curarized patients,[8] we decided to collect only SE data. These data were recorded every 10 s and stored in a computer hard drive.

The induction of anesthesia was the same in both groups and consisted of a target-controlled infusion of sufentanil aiming at a plasma concentration of 0.3 ng/ml before intubation, 2 mg/kg propofol, and 0.2 mg/kg cisatracurium. After tracheal intubation, patients were ventilated with a tidal volume of 8 ml/kg, and the respiratory rate was adapted to obtain an end-tidal carbon dioxide concentration of 30–35 mmHg. During this phase, the target-controlled infusion of sufentanil was decreased to 0.25 ng/ml until the end of bowel anastomosis. Boluses of cisatracurium (1–2 mg) were added if more than one response was observed in a train-of-four stimulation at the orbicular muscle (TOF-WATCH®, MSD, Brussels, Belgium).

All patients were ventilated using the automated closed circuit of the Zeus® respirator (Dräger). Zeus' auto-control mode, with a closed-loop feedback depending on uptake, permits precise quantitative measurement of anesthetic gas consumption (desflurane or sevoflurane).[7–9] Sevoflurane was administered using the auto-control mode, starting with a target expiratory fraction of 1% after intubation and then adapted according to the randomization. Administration of sevoflurane on the Zeus® ventilator is controlled by a knob on which each increment corresponds to a concentration change of 0.1%. In both groups, the sevoflurane concentration was adapted by standardized increments or decrements of 0.3%. For obvious ethical reasons, the alarms for end-tidal sevoflurane concentration were set at 0.7% for the lower limit concentration and at 3% for the higher limit concentration. In the control group, anesthesiologists were blinded to SE values, and the target expiratory fraction of sevoflurane was adapted on the basis of hemodynamic and clinical assessment according to standard clinical practice. This implies the application of incremented or decremented steps of 0.3% target expiratory fraction of sevoflurane to limit mean arterial blood pressure and heart rate changes within 20% of the preinduction values. In the study group, anesthesiologists were blinded to the actual inspiratory and expiratory fractions of sevoflurane; blinding was performed by placing a swab on the screen to hide the values of the actual sevoflurane concentration being administered. Sevoflurane administration was then adjusted through manipulation of the dedicated knob to maintain a target SE value between 40 and 60. In both groups, if hemodynamic variations exceeded 20% of the preinduction values, additional medications (ephedrine, nicardipine, labetalol, and atropine) were used to control it. The precise total sevoflurane uptake was recorded by the Zeus® ventilator (Dräger Medical).

Anesthetic agents were discontinued in a standardized manner in all patients: sufentanil at the end of the distal bowel anastomosis, cisatracurium at the closure of the peritoneum, and sevoflurane at the beginning of skin closure. The anesthetic maintenance phase was defined as the total duration of sevoflurane administration (*i.e.*, from intubation to the beginning of skin closure). Postoperative analgesia consisted of 1 g paracetamol every 6 h and diclofenac (1 mg/kg) every 12 h. In addition, the postanesthesia care unit provided a patient-controlled intravenous analgesia system with intravenous piritramide (bolus: 2 mg, lock-out time: 7 min, maximal allowed dose/4 h: 30 mg). An accurate recording

of piritramide consumption was obtained by analyzing the pump information.

The following variables were also recorded: surgical time, time in minutes from the surgical incision to the end of skin closure; sevoflurane uptake (ml/h), amount of sevoflurane in milliliters delivered divided by the duration of administration expressed per hour; sufentanil consumption (ng kg^{-1} h^{-1}), amount of sufentanil administered divided by the duration of administration expressed per hour; sufentanil extubation time, time in minutes from the discontinuation of sufentanil infusion until extubation; and sevoflurane extubation time, time in minutes from the discontinuation of sevoflurane administration until extubation.

The incidence of hypotension, hypertension, bradycardia, and tachycardia (variation of more than 20% from preinduction values of mean arterial blood pressure and heart rate) and the use of additional agents to control it were also recorded and compared between groups. Decisions to discharge from the postanesthesia care unit were based on the modified Aldrete[10] score criteria. This score was obtained every 15 min by a nurse blinded to the patient's group allocation. A minimum score of 9/10 for 30 consecutive minutes was required for discharge. The total amount of piritramide administered during the patient's recovery in the postanesthesia care unit and their duration of stay were also recorded.

Statistical Analysis

The primary objective of this study was to demonstrate that the use of entropy monitoring is associated with a significant reduction in sevoflurane consumption. Preliminary data in the same surgical population showed that routine sevoflurane consumption is 7.4 ± 1.4 ml/h. To detect a 20% reduction in sevoflurane consumption with an α of 0.05 and statistical power of 0.9, 20 patients had to be enrolled in each group. The normal distribution of continuous data was analyzed using the Kolmogorov–Smirnov test. Data with a normal distribution were compared using the Student *t* test and presented as mean with SD. Data with an inhomogeneous distribution were compared using the Mann–Whitney U test and presented as median (25–75 interquartiles). Nominal data were compared using the chi-square test. A *P* value less than 0.05 was considered significant. Mean values of SE recorded every 10 s in the two groups were compared using a two-way ANOVA for repeated measurements. Data analyses were performed using Minitab 15 software (Minitab 15.1.30.0, SARL Paris, France).

Results

Sixty patients scheduled for elective laparoscopic rectosigmoidectomy were screened, with a total of 50 included in the data analysis (fig. 1). No significant difference was found in the preoperative characteristics of the study and control groups (table 1). Surgical time was shorter in the control group than in the study group (135 min [109–157] *vs.* 161 min [134–193], *P* = 0.03). The shorter surgery times in the control group might be a confounding factor with regard to the sevoflurane consumption. Therefore, total sevoflurane uptake data was compared between the two groups using the duration of surgery as a covariant. Unadjusted and adjusted mean differences in total sevoflurane consumption with 95% confidence interval were 3.29 (–1; 7.58) ml and 6.05 (3.02; 9.09) ml, respectively. Sevoflurane uptake per hour was significantly higher in the control group than in the study group (5.2 ± 1.4 ml/h *vs.* 3.8 ± 1.5 ml/h, *P* = 0.0012, fig. 2). The calculated number needed to treat was 4.

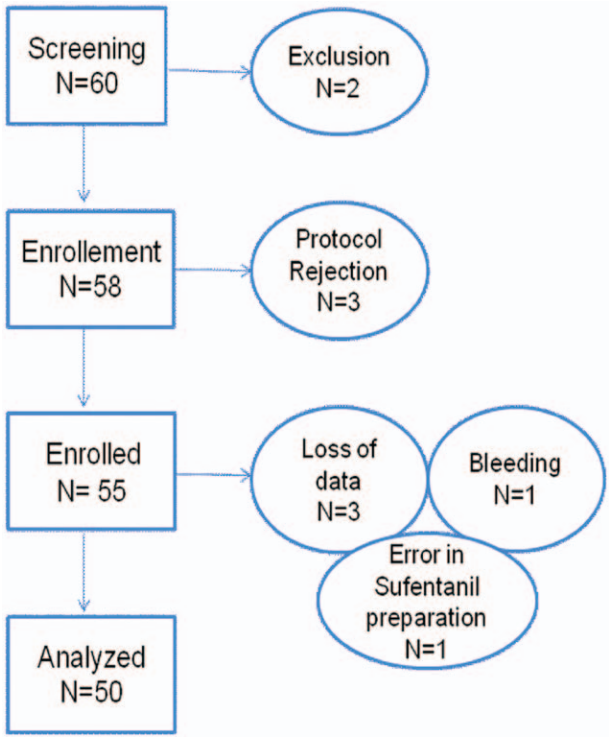

Fig. 1. Flowchart of patient enrollment.

Sufentanil consumption was not different between the two groups (control group: 0.40 ± 0.12 ng kg^{-1} h^{-1}, study group: 0.34 ± 0.10 ng kg^{-1} h^{-1}, *P* = 0.11). Sevoflurane and sufentanil extubation times were significantly longer in the control group compared with the study group (figs. 3 and 4, respectively).

SE values were adequately recorded in 24 patients in each group. Mean values recorded every 10 s were significantly lower in the control group than in the study group (fig. 5). Hemodynamic disturbances are listed in table 2. One episode of hypotension occurred in three patients in the control group, whereas no episodes of hypotension occurred in the study group (*P* = 0.03). Of these three patients, one was treated with ephedrine 5 mg. One episode of hypertension occurred in seven patients of the control group and in 10 patients of the study group (*P* = 0.55). Of these, one patient in the control group and seven patients in the study group (*P* = 0.05) were treated with nicardipine 0.5–1 mg.

Table 1. Patients' Demographics in the Two Groups

Characteristics and Comorbidities	Control Group (N = 25)	Study Group (N = 25)
Age (yr)	64 ± 16	61 ± 15
Weight (kg)	72 ± 18	80 ± 18
BMI (kg/m^2)	25 ± 5	27 ± 5
Sex (M/F)	17/8	17/8
HTA	10	15
Diabetes	12	20
CAD	5	8
COPD/asthma	2	2
Chronic renal failure	1	2
Atrial fibrillation	2	2
Anemia	1	4
Cancer (+ intestinal cancer)	13	12
GERD/peptic ulcer	9	3
Alcohol consumption	14	16
Tobacco	11	8
Beta blockers	3	1
Calcium antagonists	2	2
Diuretics	1	3
ACEI/Sartans	4	1
Antiplatelet agents	7	3
Statins	4	4
Anti-H1/anti-H2	1	2
PPI	5	3
Oral antidiabetics	3	4

Standardized mean differences for age, weight, and BMI with 95% CI were 2.92 (–5.98; 11.8), –8.2 (–18.34; 1.94), and –2.13 (–4.97; 0.72), respectively.

ACEI = angiotensin-converting enzyme inhibitor; BMI = body mass index; CAD = coronary artery; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; HTA = hypertension; PPI = proton pump inhibitors.

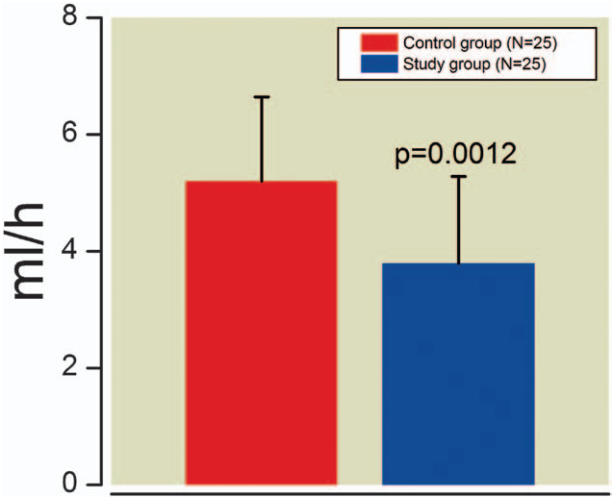

Fig. 2. Intraoperative sevoflurane uptake (ml/h) in the control group (CG) and study group (SG). Data are presented as mean ± SD.

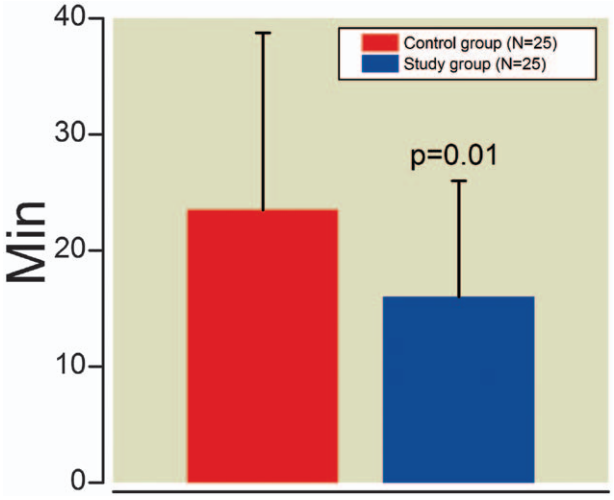

Fig. 3. Sevoflurane extubation time (min): time in minutes from the discontinuation of sevoflurane administration until extubation in the control group (CG) and study group (SG). Data are presented as median (25–75 interquartiles).

Postanesthesia care unit length of stay (control: 90 min [60–155], study group: 105 min [37–157], P = 0.94) and piritramide consumption (control: 11 mg [6–30], study group: 13 mg [8–22], P = 0.29) did not differ between the two groups.

Discussion

We found that M-Entropy (Datex-Ohmeda) monitoring is associated with a significant reduction in sevoflurane uptake and in time to extubation. This reduction was related to a shallower anesthetic depth, as shown by SE values. In addition, the incidence of intraoperative hypotension was lower in patients who were monitored.

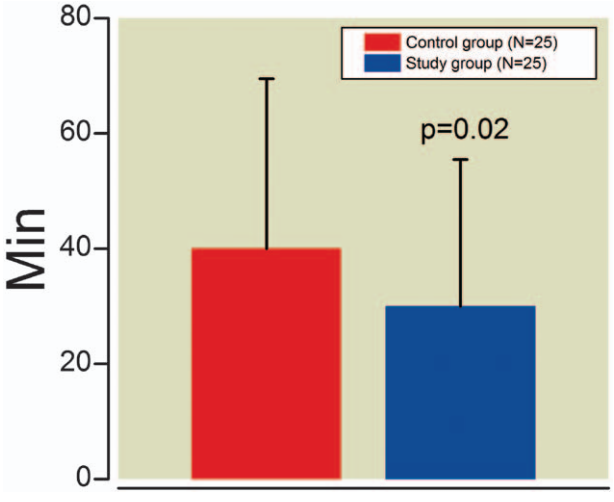

Fig. 4. Sufentanil extubation time (min): time in minutes from the discontinuation of sufentanil infusion until extubation in the control group (CG) and study group (SG). Data are presented as median (25–75 interquartiles).

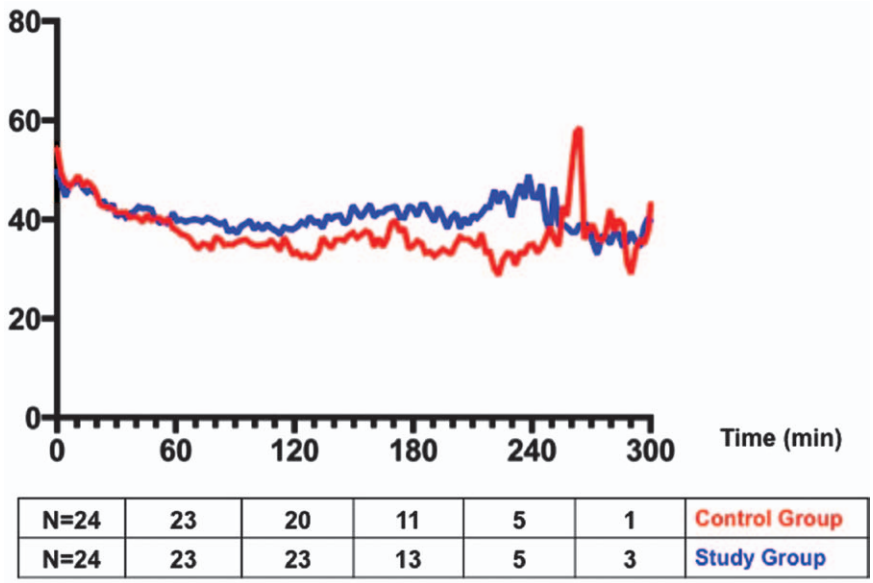

Fig. 5. State entropy (SE) values during anesthesia maintenance phase. Data are presented as the mean values of SE calculated every 10 min in each group. N represents numbers of patients in each group at 0, 1, 2, 3, and 4 h postinduction.

In this study, the analgesic component of anesthesia was standardized using a target-controlled infusion system that allows a precise target effect of sufentanil dosing in all patients, independent of the amount of sevoflurane administered. Thus, the differences between the two groups cannot be attributed to the effect of opiates on anesthetic depth.[11,12]

Most of the studies that have evaluated the effects of electroencephalogram-derived monitoring on perioperative hypnotic agent consumption have used the BIS® device (Aspect Medical Systems, Inc., Norwood, MA). A meta-analysis of 11 controlled randomized studies with a total of 1380 one-day surgery patients reported that BIS monitoring is associated with a 19% reduction in anesthetic consumption and a 4-min shorter stay in the recovery room.[3] To date, two studies have investigated the effects of entropy monitoring on reduced propofol consumption; Vakkuri *et al.*[2] reported a 10% reduction in propofol consumption, whereas Ellerkman *et al.*[13] failed to show such an effect. Three studies have evaluated the effects of M-Entropy (Datex-Ohmeda) monitoring on sevoflurane consumption,[5,6,14] and all three showed a significant reduction in sevoflurane consumption. However, the methodology used in these studies to assess sevoflurane consumption was rather imprecise and based on the measurement of expired sevoflurane fraction[5] or simply by weighing the vaporizers.[14] In contrast, the current study used an accurate measurement of sevoflurane uptake. The Zeus® ventilator (Dräger) uses an innovative gas administration system that allows not only a marked reduction in anesthetic gas consumption but also a precise measurement of the amount delivered.[7–9] Even if volatile anesthetic consumption is low when using this ventilator, our data showed an additional 27% reduction of sevoflurane consumption with the use of M-Entropy. Moreover, entropy monitoring resulted in faster tracheal extubation. The institutional practice involves extubation in the operating theater. Therefore, a decrease in the median extubation time of 7 min represents a relevant shorter occupation time of the operating room, allowing for more efficient resource utilization. In addition, incidence of hypotensive episodes was significantly reduced in the study group.

Table 2. Adverse Intraoperative Hemodynamic Events

Patients with At Least One Episode of	Control Group (N = 25)	Study Group (N = 25)	*P* Value
Hypertension	7	10	0.37
Hypotension	3	0	0.03
Tachycardia	5	8	0.33
Bradycardia	1	0	—

Depth of anesthesia and incidence of hypotension have been reported to influence postoperative morbidity and mortality. In a prospective observational study including 1064 patients undergoing major noncardiac surgery, Monk *et al.*[15] reported that incidence of hypotension and a deep level of anesthesia (defined as a BIS value <45) were independent risk factors for postoperative 1-yr mortality. Further studies however indicated a more complex interaction between low BIS values, the presence of comorbidities, and hypotension episodes on the one hand and medium and long-term outcome on the other hand.[16–18]

Although the number of patients developing intraoperative hypertension was similar in both groups, more patients in the study group were treated with nicardipine. This difference can be explained by the specificities of the study protocol. In the control group, the anesthesiologist was blinded to the SE values and therefore treated hypertension in the first place by increasing the sevoflurane concentration, assuming

insufficient depth of anesthesia as the causal factor. In the study group, on the contrary, because SE values were available and maintained between 40 and 60, the anesthesiologist excluded inadequate depth of anesthesia as the cause of hypertension, which was therefore treated with nicardipine. It might therefore be hypothesized that monitoring depth of anesthesia may help the anesthesiologist to better define the etiology of intraoperative hemodynamic disturbances and apply the most appropriate treatment.

Entropy monitoring did not change the length of stay or the piritramide consumption in the postanesthesia care unit. However, taking into account the pharmacokinetic profile of sevoflurane, the reduction in perioperative sevoflurane consumption is not expected to influence these two variables.

The results of the current study should be interpreted within the constraints of the specific methodology used. Although targeted SE values and sufentanil effect-side concentrations were within the range of routine clinical practice, other targets may have yielded different results.

In conclusion, under the conditions of our study, monitoring the depth of anesthesia with M-Entropy (Datex-Ohmeda) was associated with a significant reduction in sevoflurane uptake and faster extubation. This monitoring also helped avoid episodes of profound anesthesia and hypotension.

The authors acknowledge Faraoni David, M.D., Staff Anesthesiologist, University Hospital Center of Brugmann, Brussels, Belgium, for his help in the figures presentation.

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