Spectral Entropy Monitoring Is Associated with Reduced Propofol Use and Faster Emergence in Propofol–Nitrous Oxide–Alfentanil Anesthesia

Anne Vakkuri, M.D., Ph.D.,* Arvi Yli-Hankala, M.D., Ph.D.,† Rolf Sandin, M.D., Ph.D.,‡ Seppo Mustola, M.D., Ph.D.,§ Siv Hoymark, M.D., †† Stina Nyblom, M.D., Ph.D.,¶ Pia Talja, M.Sc.,** Timothy Sampson, M.Sc.,†† Mark van Gils, Ph.D., †‡ Hanna Viertio-Oja, Ph.D. §§

Background: This multicenter study evaluated the effect of a new depth of anesthesia–monitoring device based on time-frequency–balanced spectral entropy of electroencephalogram monitoring (GE Healthcare Finland, Helsinki, Finland) on consumption of anesthetic drugs and recovery times after anesthesia.

Methods: The study was a prospective, randomized, single-blind study performed in six hospitals in Finland, Sweden, and Norway. After institutional review board approval and written informed consent from each patient, the patients were randomly allocated to an anesthesia with entropy values either shown (entropy group) or not shown (control group). Anesthesia was maintained with propofol, nitrous oxide, and alfentanil. In the entropy group, propofol was given to keep the state entropy value below 45 and 65, and alfentanil was given to keep the state entropy–response entropy difference below 10 units and heart rate and blood pressure within ±20% of the baseline values. The control group patients were anesthetized to keep heart rate and blood pressure within ±20% of the baseline values. Statistical methods included Mann–Whitney U test and unpaired t tests.

Results: A total of 368 patients were studied. In the entropy group, entropy values were higher during the whole operation and especially during the last 15 min (P < 0.001). Consequently, propofol consumption was smaller in the entropy group during the whole anesthesia period (P < 0.001) and especially during the last 15 min (P < 0.001). This shortened the time delay in the early recovery parameters in the entropy group.

Conclusions: Entropy monitoring assisted titration of propofol, especially during the last part of the procedures, as indicated by higher entropy values, decreased consumption of propofol, and shorter recovery times in the entropy group.

UPON development and marketing of new medical monitoring devices, safety and efficacy are expected. Therefore, a new monitor of hypnotic component of anesthesia should improve the patient care by helping the anesthesia provider in optimizing the drug administration. Such optimization should lead to reduced consumption of anesthetics and adjuvants, fastened emergence, or both, without increasing the incidence of awareness during anesthesia.

Time-frequency–balanced spectral entropy is applied in the Entropy Module of the S/5 Anesthesia Monitor (GE Healthcare Finland [formerly Datex-Ohmeda], Helsinki, Finland). This is a recently released electroencephalographic monitoring method designed to measure the hypnotic component of anesthesia and validated for use during propofol, sevoflurane, desflurane, isoflurane, and thiopental anesthesia.1–4 The Entropy Module collects a one-channel raw biosignal, consisting of both the electroencephalogram and the electromyogram, from the frontotemporal region of the patient’s head. The biosignal is collected with a self-adhesive Entropy Sensor (GE Healthcare Finland) consisting of three electrodes. The signal is amplified, digitized, and processed in the Entropy Module incorporated into the S/5 Anesthesia Monitor. Some further signal processing occurs in the S/5 Anesthesia Monitor by the monitor software. In this process, time-frequency–balanced spectral entropy content of the biosignal is calculated.5 The analysis results in two numbers, state entropy (SE) and response entropy (RE). In the analysis of SE, electrical activity between 0.8 and 32.0 Hz is studied. In an anesthetized patient, the spectral range from 0.8 to 32.0 Hz consists mainly of the electroencephalogram, although a minor amount of electromyographic activity may also be involved.6 In the analysis of RE, entropy content from 0.8 to 47.0 Hz is calculated. The spectral range between 32 and 47 Hz consists mostly of electromyographic activity, although some electroencephalographic activity may also be involved. Therefore, SE is a measure of electroencephalogram activity, whereas RE provides combined information of the electroencephalogram and the frontal electromyogram. Detailed explanation of the calculation of RE and SE has been published separately and is therefore not explained here.5 During anesthesia, electromyographic activity may increase as a result of intensive nociceptive stimulus and during lightening concentrations of anesthesia at the end of surgery, before awakening.7,8 In the monitor display, SE values vary between 0 (suppressed electroencephalogram indicating very

* Senior Anesthesiologist, Department of Anesthesia and Intensive Care, Surgical Hospital, Helsinki University Hospital, Helsinki, Finland. † Research Professor, Department of Anesthesia, Tampere University Hospital, and University of Tampere, Medical School, Tampere, Finland. ‡ Chief Anesthesiologist, Department of Anesthesia, Kalmar County Hospital, Kalmar, Sweden. § Senior Anesthesiologist, Department of Anesthesia, Central Hospital of South Karelia, Lappeenranta, Finland. †† Senior Anesthesiologist, Department of Anesthesia, Ullevål University Hospital, Oslo, Norway. ** Chief Anesthesiologist, Department of Anesthesia, Saltgrenska University Hospital, Gothenburg, Sweden. *** Research Engineer, †‡ Research Scientist. §§ Chief Scientist, GE Healthcare Finland, Helsinki, Finland. ††† Senior Research Scientist, VTT Information Technology, Tampere, Finland.

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Address reprint requests to Dr. Vakkuri: Surgical Hospital, Helsinki University Hospital, P.O. Box 263, 00029 HUS, Helsinki, Finland. Address electronic mail to: anne.vakkuri@hus.fi. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.
Deep anesthesia) and 91 (indicating an awake state). RE values can vary between 0 and 100. The RE value is always higher or equal to the SE value. When no electromyographic activity is present, SE and RE show the same number. The recommended range for adequate anesthesia for both parameters is from 40 to 60.

The purpose of the different scaling of the two indices is to make electromyographic activation detectable at all levels of anesthesia, because this increases RE above SE. This enables titrating anesthetic agents (hypnotic and analgesic medications). During uncomplicated anesthesia, when SE increases above 60, more hypnotic medication (volatile anesthetic agent, propofol) should be given. When SE is in the recommended range for adequate anesthesia but RE increases 5–10 units above it, this indicates patient responsiveness to surgery and can be interpreted as a sign of uncovered nociception. The first treatment option is to administer more analgesic medication.

The exact level of muscle relaxation where facial frontal muscle activation is no longer possible is not known, but facial frontal muscles are less sensitive to the effects of neuromuscular blocking drugs than are the hand muscles. To gain advantage of the rapid reactions of RE reflecting changing levels of anesthetic adequacy, at least one or two responses should be visible in the train-of-four stimulation.

We designed this prospective multicenter study to evaluate the clinical effectiveness of entropy monitoring. We tested the hypothesis that intraoperative monitoring of entropy would decrease propofol consumption during propofol-nitrous oxide-alfentanil anesthesia, without increasing the incidence of untoward adverse events, and that such monitoring would be associated with faster emergence from general anesthesia.

**Materials and Methods**

Initially, 385 patients scheduled to undergo surgery during general anesthesia were enrolled to this prospective, randomized, multicenter, clinical utility study. Six hospitals participated in the study, three of them in Finland, two in Sweden, and one in Norway. The study was approved by institutional review boards of the participating hospitals, and written informed consent was received from each patient.

Inclusion criteria were as follows: either sex; age between 18 and 80 yr; American Society of Anesthesiologists physical status I, II, or III; ability to read and understand the consent form; and elective surgery procedures estimated to last from 45 to 150 min.

Exclusion criteria were as follows: known psychiatric or neurologic disorders; history of major head injury; substance abuse; medication affecting the central nervous system; acquired scalp or skull abnormalities; uncontrolled hypertension (baseline systolic blood pressure > 160 mmHg or baseline diastolic blood pressure > 105 mmHg); baseline systolic pressure below 90 mmHg; baseline heart rate below 55 beats/min; insulin-dependent diabetes mellitus; renal or hepatic disease; pregnancy; body mass index (weight in kilograms divided by length in square meters) over 33.0 kg/m²; any serious medical condition that would interfere with cardiovascular response assessment; cardiac, vascular, or cranial neurosurgery; intraoperatively activated epidural analgesia; and emergency or other nonelective surgery.

The enrolled patients were randomized to receive propofol-nitrous oxide-alfentanil anesthesia either with entropy values shown (entropy group) or with entropy values not shown (control group).

The patients were premedicated with 0.1–0.15 mg/kg oral diazepam 60 min before anesthetic induction, except in the Norwegian test site, where no premedication was used for administrative reasons. At arrival in the operating room, standard monitors were applied, and a forearm vein was cannulated for infusion of intravenous fluids. After the skin in the forehead was cleansed with 70% isopropyl alcohol, an Entropy Sensor was positioned as recommended by the manufacturer. Recording of the biosignal from the patient’s forehead was started while the patient was awake. The impedance for the Entropy Sensor was checked and noted before induction and was accepted when it was below 7.5 kΩ.

Anesthesia was induced with an alfentanil bolus of 30 μg/kg or less and a propofol bolus of 1.0–2.5 mg/kg and was maintained with continuous infusions of alfentanil (maximum dose 30 μg · kg⁻¹ · h⁻¹) and propofol (maximum dose 9 mg · kg⁻¹ · h⁻¹). If entropy indices suddenly increased, suggesting impending awakening, alfentanil or propofol boluses were allowed. The airway of the patient was secured with an endotracheal tube or laryngeal mask, and the patient was paralyzed with the neuromuscular blocking agent of the anesthesiologist’s choice, when considered appropriate. The lungs were normoventilated with a mixture of oxygen (35–50%) and nitrous oxide (50–65%). The aim in all patients was to provide smooth, hemodynamically stable anesthesia with the shortest possible emergence time and without intraoperative awareness.

The initial eight to nine patients in each study site were assigned to a historical control group (total: 50 patients). The data of these patients were used to establish standard clinical practice of the participating anesthesiologists before they started using entropy monitoring. Entropy indices were collected with S/5 Collect software (GE Healthcare Finland) on a laptop computer but were not displayed. After this work with the historical control patients was completed, entropy monitoring was introduced to the participants, and they were allowed to accustom themselves to the use of entropy monitoring for 3 weeks. Thereafter, the patients were
randomly assigned, according to computer-generated random numbers, into the control group or the entropy group. Each study site was provided with a sufficient number of closed randomization envelopes. With sequential coding, the subjects were treated in blocks of 10 (5 patients in each group). The envelopes were opened in the operating room immediately before the induction of anesthesia.

In the entropy group, the propofol infusion rate was titrated to maintain an SE value between 45 and 65 until the last 15 min of anesthesia. Alfentanil infusion was adjusted so that the RE–SE difference would remain within 10 units. If RE exceeded SE by more than 10 units, the alfentanil infusion rate was increased. Another target was to maintain stable intraoperative hemodynamics, with heart rate and blood pressure within ±20% of the baseline values. Higher than +20% of baseline values induced an increase in the alfentanil infusion rate. Baseline values were those measured during the patient’s preoperative visit. For the last 15 min of surgery, SE values near 65 were recommended; however, they were not to exceed 70. Entropy indices were recorded on a laptop computer with 5-s intervals. Both propofol and alfentanil infusions were closed down, and nitrous oxide was discontinued after skin closure.

In the historical control and control groups, propofol and alfentanil were given to maintain heart rate and blood pressure within ±20% of the baseline value. Propofol and alfentanil infusions were adjusted depending on the signs of unnecessarily deep or inadequate anesthesia. Entropy indices were collected with 5-s intervals on a laptop computer but were not displayed.

The course of anesthesia, surgery, and recovery; the total amount of drugs given; and the occurrence of untoward intraoperative reactions such as movements, coughing, grimacing, eye opening, and episodes of hypertension, hypotension, tachycardia, and bradycardia were recorded. The actual infusion rates of anesthetics were noted manually in the anesthetic record, as were additional doses of anesthetics and any additional drugs given. During emergence, time for disruption of the infusions, recovery of spontaneous breathing and extubation, time to eye opening, time to squeezing of the anesthesiologist’s hand on command, and orientation to time and place were recorded. The time of discharge from the operating room to the postanesthesia care unit (PACU) was recorded.

Pain scores (measured with a visual analog scale) and opioid consumption were recorded in the PACU. The incidence of postoperative nausea and vomiting; the nurse’s estimation of time needed in the PACU, of the patient’s need for care, and of the patient’s general recovery; the patient’s satisfaction with the anesthesia; and the actual time spent in the PACU were all recorded.

We interviewed the patients twice regarding to their opinions of anesthetic care and possible intraoperative memories with a modified Brice interview,9 first in the PACU and again during the first postoperative day. Patient estimation of postoperative nausea and vomiting and pain (visual analog scale score) on the day after anesthesia was studied.

Statistical Analysis

The sample size estimate was based on an a priori analysis of awakening time after propofol anesthesia. Based on the awakening time data after propofol anesthesia in a recent study,10 we calculated a minimum need for 147 patients in each group to detect a 20% difference in time in patients’ responses to a verbal command with a power of 0.8 and α of 0.05. To test the normality of data, the Kolmogorov–Smirnov test with Lilliefors estimation of significance level was used along with visual estimation of histograms. The differences in hemodynamic variables, age, weight, height, and the duration of anesthesia were tested with an unpaired t test. For differences in all other variables, the Mann–Whitney U test was used. Kaplan–Maier analysis was performed to test differences in cumulative recovery as a function of time after anesthesia.

Results

Fifty patients were initially enrolled to determine the preexisting anesthetic practice and patient recovery at each study site. Three hundred thirty-five subsequent patients at the six participating hospitals were randomized to either entropy-controlled anesthesia or standard clinical practice (control group). Each study site collected 35–90 patients. The study patients underwent different types of gynecologic, abdominal, urologic, orthopedic, breast, thyroid, and inguinal hernia operations. Seventeen patients were excluded: 14 because of lack of registered data, 1 because of violation of the inclusion criteria, 1 because of accidental use of a potent inhalational agent, and 1 due to respiratory arrest during the emergence phase. The data from 368 patients (48 historical controls, 160 controls, and 160 entropy patients) were included in final analyses.

We detected only minor differences between the historical control and control groups. In general, there were no statistical differences between these groups, except for the following: blood pressure at 1 min after intubation (P = 0.037), propofol consumption during the last 15 min (P = 0.001), and alfentanil consumption during the last 15 min (P = 0.02), which were all higher in the historical control group than in the control group (data not shown). Otherwise, the groups did not differ, and the historical control data are therefore not presented.

Although several isolated recovery times for the entropy group were different between the different study
sites, the evidence of quicker recovery in the entropy group was a consistent overall outcome. Therefore, results from pooled data from all sites are presented. The entropy and control groups were comparable in their demographic characteristics (table 1). Both of these groups had more women than men because many of the participating centers included mainly gynecologic surgery patients in this study.

In the entropy group, entropy values were higher during the whole operation and especially during the last 15 min ($P < 0.001$; table 2). Therefore, along with the lighter level of hypnosis, propofol consumption was smaller in the entropy group ($P < 0.001$; table 2). This applied during the whole operation and again especially during the last 15 min ($P < 0.001$; table 2). The parameters of early recovery were shorter in the entropy group (table 2). The cumulative percentages of patients not responding to verbal command after anesthesia, those not orientated to time and place as a function of time were significantly smaller in the entropy group ($P < 0.001$; fig. 1). Pain scores and opioid analgesic requirements did not differ between the study groups in the PACU.

Hemodynamic data were similar between groups. Heart rates and blood pressures did not differ between groups until skin closure, where the entropy group had higher heart rate ($65 \pm 11$ vs $60 \pm 10$ beats/min [mean $\pm$ SD]; $P = 0.029$) and blood pressure ($83 \pm 10$ vs $79 \pm 12$ mmHg; $P = 0.008$).

The incidence of untoward intraoperative reactions (movement or increased muscle tension, tearing, coughing, frowning, eye opening, and episodes of hypertension, hypotension, tachycardia, or bradycardia) did not differ between the groups.

Recovery in the PACU was similar between groups. The incidence of postoperative nausea and vomiting, the nurse’s estimation of time needed in the PACU, the nurse’s estimation of the patient’s need for care, the nurse’s estimation of the patient’s general recovery, the patient’s satisfaction with the anesthesia, and the actual time spent in the PACU were similar between the two study groups.

Patient estimation of postoperative nausea and vomiting or pain on the day after anesthesia did not differ between groups.

None of the patients reported any anesthesia- or surgery-related memories in the two postoperative interviews.

**Discussion**

This trial shows that entropy monitoring allows individualized titration of propofol, resulting in reduced propofol consumption and shorter recovery times compared with standard practice. Previous reports have shown that entropy monitoring can discriminate between consciousness and unconsciousness and that it correlates with alterations in anesthetic adequacy, such as movement and blood pressure responses to noxious stimulation. The results of the current study on entropy are also consistent with previous reports showing that various electroencephalogram-derived indices can be useful in optimizing anesthetic care. Patients

### Table 1. Demographic Data, ASA Physical Status, and Duration of Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Entropy (n = 160)</th>
<th>Control (n = 160)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>45 ± 14</td>
<td>47 ± 13</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>168 ± 9</td>
<td>169 ± 9</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>71 ± 12</td>
<td>71 ± 12</td>
<td></td>
</tr>
<tr>
<td>Male/female, n</td>
<td>44/116</td>
<td>39/121</td>
<td></td>
</tr>
<tr>
<td>ASA physical status, I/II/III</td>
<td>113/42/5</td>
<td>101/57/2</td>
<td></td>
</tr>
<tr>
<td>Anesthesia duration, min</td>
<td>106 ± 48</td>
<td>107 ± 49</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean $\pm$ SD. There were no significant differences between groups.

ASA = American Society of Anesthesiologists.

### Table 2. Drug Consumption, Recovery, and Entropy Values

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 160)</th>
<th>Entropy (n = 160)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol, mg $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$</td>
<td>0.11 (0.03, 0.21)</td>
<td>0.10 (0.04, 0.23)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Alfentanil, $\mu$g $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$</td>
<td>0.57 (0.16, 1.6)</td>
<td>0.60 (0.12, 2.2)</td>
<td>0.54</td>
</tr>
<tr>
<td>Spontaneous breathing, min</td>
<td>7.07 (1.00, 28.5)</td>
<td>4.74 (0.00, 18.0)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Exsufflation, min</td>
<td>9.16 (1.67, 32.3)</td>
<td>5.80 (3.00, 27.3)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Eyes open, min</td>
<td>10.8 (2.23, 43.2)</td>
<td>6.08 (0.15, 37.5)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Squeezes hand on command, min</td>
<td>12.7 (2.43, 48.1)</td>
<td>8.60 (1.17, 47.4)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Discharge from OR to PACU, min</td>
<td>13.0 (5.00, 49.8)</td>
<td>10.3 (8.83, 42.4)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Discharge from OR to PACU, min</td>
<td>15.1 (4.08, 113)</td>
<td>10.3 (1.17, 48.7)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Discharge from PACU, min</td>
<td>150 (7.1, 1.020)</td>
<td>134 (50, 1.293)</td>
<td>0.21</td>
</tr>
<tr>
<td>Average SE during anaesthesia</td>
<td>44 (15, 70)</td>
<td>50 (34, 78)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Average RE during anaesthesia</td>
<td>46 (16, 81)</td>
<td>52 (35, 84)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>SE last 15 min</td>
<td>47 (16, 77)</td>
<td>52 (33, 86)</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>RE last 15 min</td>
<td>48 (17, 84)</td>
<td>55 (35, 94)</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

Data are presented as median (range).

OR = operating room; PACU = postanesthesia care unit; RE = response entropy; SE = state entropy.
who underwent entropy monitoring achieved endpoints of early recovery (e.g., spontaneous breathing, eye opening, ability to follow command, orientation to time and place) faster than patients in the control group and were therefore transportable from the operating room to the PACU with a shorter delay.

The purpose of the historical control group was to get all of the study sites adjusted to the research protocol rather than to compare practices with and without central nervous system monitoring. This type of study setup is customary in utility studies when introducing a new central nervous system–monitoring method, but because the real learning phase has already occurred with the first electroencephalographic anesthesia-monitoring devices, such as the Bispectral Index® (BIS®, Aspect Medical Systems, Newton, MA), its significance is probably minor.

Utility trials similar to this study have been performed for several commercially launched depth-of-anesthesia monitors, all of which have demonstrated that adding a depth-of-anesthesia monitor to routine equipment has a sparing effect on awakening time, drug consumption, or both. Whether widespread use of these monitors has influenced the standard practice of dosing of anesthetic agents has not been studied. All of the participants in the current study had substantial previous experience with electroencephalogram-based depth-of-anesthesia monitors. This was not the case for the participants in the earliest trials. It is possible that experience from electroencephalogram-monitored cases has impact also on the dosing of anesthetic agents for unmonitored cases, thereby decreasing the average doses in the control groups of these studies.

We detected no cases of intraoperative awareness in this study. The patients were interviewed only twice, which may have affected this result. However, careful attention was paid at the end of anesthesia as not to lighten the anesthesia too much to speed up recovery. The number of the study subjects is small when considering the incidence of awareness during anesthesia, and the study population contained no special risk groups of intraoperative awareness. However, electroencephalographic monitoring during anesthesia has been shown to reduce the incidence of awareness both in high-risk groups and in unselected patient populations. Relatively small changes in the entropy levels reduced the propofol consumption sufficiently to speed up recovery significantly. However, while striving to improve the operating room turnover, this must not be done at the expense of patients’ well-being. Unconsciousness must be ensured throughout the operation.

Hemodynamic profiles were similar in the entropy and control groups. This is to be expected, because hemodynamic responses guided the alfentanil dose in the study protocol in both groups, not only in the control group. Hence, the alfentanil dosage did not differ be-

![Fig. 1. The cumulative percentage of patients not responding to verbal command (top), not yet discharged from operating room (OR) to postanesthesia care unit (PACU) (middle), and not oriented to time and place (bottom) after anesthesia as a function of time was significantly smaller in the entropy group (gray area) compared with the control group (white area) (P < 0.001).](http://pubs.asahq.org/anesthesiology/article-pdf/103/2/274/358572/0000542-200508000-00010.pdf)
between groups, either. Lacking of exact guidelines for the adjustments of alfentanil infusion rate in the entropy group according to RE responsiveness in relation to hemodynamic changes was a shortcoming in our study protocol. Whether RE reveals more or a different kind of information about intraoperative nociception than mere hemodynamic changes warrants further study.

Similarly to some earlier reports,12,15 no difference was detected in the PACU discharge criteria between the study groups. Besides rapid recovery after propofol-alfentanil anesthesia in general, this may be related to differences in the recovery protocols between study sites of this not only multicenter but also multinational study, because the study protocol did not override the hospital policy for discharge criteria from the PACU to the ward. A recent study did not show any improvement in the mean duration of stay in the PACU in inpatients when compared between BIS-monitored and control groups when the anesthetic regimen was not standardized.19 However, also in this study, sevoflurane consumption was smaller in the BIS-monitored group than in the control group, despite the fact that the BIS-monitored group received more anesthetic agent than was recommended in the study protocol (mean BIS value of 47 in the BIS group, when the suggested target level was 50–60). In our study, the actual time spent in the PACU did not differ between groups, either. This time depended on many factors, such as the ward’s capacity to accept new patients from the PACU and the availability of extra time and personnel required to optimize the patient’s perioperative analgesia by applying interscalene plexus blocks after shoulder operations. Hence, the PACU discharge time describes the overall patient logistics in different hospitals rather than the effect of entropy monitoring.

In conclusion, entropy monitoring reduced propofol consumption during propofol-alfentanil-nitrous oxide anesthesia and improved early recovery after anesthesia when compared with anesthesia guided by hemodynamic responses and clinical signs of inadequate anesthesia.

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References


