Bispectral index and A-line AAI index as guidance for desflurane-remifentanil anaesthesia compared with a standard practice group: a multicentre study

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Background. This study was designed to investigate the impact of bispectral index (BIS) or A-line AAI index (based on middle-latency auditory evoked potential) monitoring on recovery times and drug consumption when compared with standard anaesthetic practice during desflurane-remifentanil anaesthesia.

Methods. After having obtained approval from the institutional review board and written informed consent, 200 adult patients undergoing minor surgical procedures were randomized to receive a desflurane-remifentanil anaesthetic controlled either solely by clinical parameters or by BIS or AAI to the following target values: during maintenance of anaesthesia to a value of ‘50’ (BIS) or ‘30’ (AAI), 15 min before the end of surgery to ‘60’ (BIS) or ‘45’ (AAI). Recovery times and drug consumption were recorded by a blinded investigator.

Results. Compared with standard practice, patients with BIS or AAI monitoring needed similar desflurane concentrations (standard practice 2.9 [0.5] vol%, BIS 3.3 [0.9] vol%, AAI 2.6 [0.5] vol%), and had similar recovery times (open eyes 5.6 [2.5] min, 5.9 [3.4] min, 5.0 [3.1] min; extubation 6.3 [2.4] min, 6.6 [3.5] min, 5.6 [3.0] min; stating name 7.3 [2.4] min, 7.6 [3.5] min, 7.3 [6.6] min).

Conclusions. Compared with standard anaesthetic practice BIS and AAI guided titration to the used target ranges did not result in a reduction of desflurane consumption or recovery times during minor surgery with use of remifentanil.

Keywords: anaesthetics volatile, desflurane; analgesics opioid, remifentanil; monitoring, bispectral index; monitoring, A-line AAI index

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For bispectral index monitoring (BIS, Aspect Medical Systems, Inc., Newton, USA) a huge body of evidence suggests that it may help to assess the hypnotic component of anaesthesia,1–6 reduce drug consumption,7–13 and shorten recovery times7–13 when compared with a standard practice protocol. Middle-latency auditory evoked potentials (AEP) have alternatively been proposed as measures of anaesthetic depth. AEP have been shown to quantify the action of anaesthetic drugs14 and may be better able to detect the transition from consciousness to unconsciousness than the BIS.15 The A-line AEP monitor (Danmeter, Odense, Denmark) is the first commercially available AEP monitor designed to measure depth of anaesthesia. It generates an index (AAI), which, like the BIS, is a dimensionless number scaled from 100 (awake) to 0. First experiences with the AAI to titrate anaesthesia yielded contradictory results.16 17

In the present multicentre study we investigated the impact of BIS and the A-line AEP monitoring on recovery times and drug consumption when compared with a standard

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anaesthetic practice protocol during desflurane-remifentanil anaesthesia.

Materials and methods
After having obtained institutional review board approval and written informed consent, 200 adult patients at four university anaesthesia departments were randomized to receive a desflurane-remifentanil anaesthetic controlled either by BIS or by AAI or solely by clinical parameters. Men or women, aged 18–80 yr, American Society of Anesthesiologists (ASA) physical status I, II, or III who were to undergo minor surgery expected to last at least 1 h were studied prospectively. Exclusion criteria were a history of any disabling central nervous or cerebrovascular diseases, hypersensitivity to opioids or substance abuse, or a treatment with opioids or any psychoactive medication. After enrolment the patients were randomized by drawing lots from a closed box.

All patients were pre-medicated with midazolam 7.5 mg orally on the morning before surgery. In the operating room an i.v. cannula was inserted into a larger forearm vein and standard monitors were applied. The ECG was continuously recorded using an A-2000 BIS monitor (version XP) and an A-line AEP monitor (version 1.4), simultaneously. After the skin of the forehead had been degreased with 70% isopropanol, both the BIS (BIS XP Sensor, Aspect Medical Systems, Inc.) and the AEP electrodes (Danmeter) were positioned as recommended by the manufacturers. Finally, impedances were measured for each set of electrodes to ensure optimal electrode contact.

In all the patients, anaesthesia was induced with remifentanil infusion at 0.4 μg kg\(^{-1}\) min\(^{-1}\) followed 5 min later by 2 mg kg\(^{-1}\) propofol. After loss of consciousness oxygen was given by facemask ventilation, each patient received 0.1 mg kg\(^{-1}\) of cis-atracurium, and 3 min later the trachea was intubated and the lungs were mechanically controlled ventilated to an end-tidal carbon dioxide concentration of 4.6 kPa. Immediately after intubation, remifentanil was reduced to the rate of 0.2 μg kg\(^{-1}\) min\(^{-1}\) and the desflurane was delivered in the inspired mixture of oxygen and air to obtain an end-tidal concentration of 3 vol%. Thereafter, desflurane was sequentially adjusted according to the predetermined target values of BIS or AAI, or clinical parameters. No more neuromuscular blocking agents were given intraoperatively.

Continuous monitoring included heart rate (HR), systemic arterial pressure, ventilatory frequency, oxygen saturation, and end-tidal concentrations of desflurane and carbon dioxide. The oxygen saturation was measured by pulse oximetry and maintained above 95%. Baseline systolic arterial pressure (SAP) was defined as the lower of the two measurements obtained the day before surgery and immediately before induction of anaesthesia. HR and blood pressure were recorded every 5 min.

During maintenance of anaesthesia, all patients were assessed for signs of inadequate anaesthesia, hypotension, or bradycardia. Inadequate anaesthesia was defined as hypertension, tachycardia or patient movement, eye opening, swallowing, grimacing, lacrimation, or sweating. The definition of adverse haemodynamic responses was adapted from Garrioch and Fitch: responses were classified as ‘hypertension’ (SAP >40 mm Hg from baseline), ‘hypotension’ (SAP <40 mm Hg from baseline), ‘tachycardia’ (HR >100 beats min\(^{-1}\)), and ‘bradycardia’ (HR <45 beats min\(^{-1}\)).

In the standard practice group, if anaesthesia was inadequate the desflurane concentration was increased in steps of 0.5 vol% as necessary. If this was judged insufficient, the infusion rate of remifentanil could be increased in increments of 0.05 μg kg\(^{-1}\) min\(^{-1}\). Hypotension, if any, was initially treated with i.v. fluid replacement; desflurane concentration was then reduced in steps of 0.5 vol%, and finally, an i.v. vasopressor (Akrinor, AWD Pharma, Dresden, Germany, 1 ml contains 100 mg cafedrine and 5 mg theodrenaline) was given at a dose chosen by the investigator.

In the AAI and BIS groups, desflurane during maintenance of anaesthesia was continuously adjusted according to a target value of ‘50’ for BIS or ‘30’ for AAI. In case anaesthesia was judged inadequate despite these BIS or AAI target values, the infusion rate of remifentanil could be increased in increments of 0.05 μg kg\(^{-1}\) min\(^{-1}\). Hypotension was initially treated with i.v. fluid replacement and finally, the i.v. vasopressor was given. In all groups bradycardia was treated with 0.5 mg of atropine.

In all patients, irrespective of the individual group assignment, both BIS values and AAI values were continuously recorded as data pairs in intervals of 5 min by an independent investigator. In the standard practice group both the monitors were covered behind a curtain and invisible to the attending anaesthesiologist, whereas in the BIS or AAI groups either only the BIS monitor or only the AEP monitor was uncovered. All participating anaesthetists were familiar with the use of brain monitors.

Fifteen minutes before the expected end of surgery, desflurane was reduced in all the patients to facilitate rapid emergence from anaesthesia, whereas the remifentanil infusion rate remained unchanged throughout the end of the procedure. In the BIS and AAI groups, desflurane concentration was adjusted to a value of ‘60’ for BIS or ‘45’ for AAI, whereas in the standard protocol group it was reduced as much as was clinically judged possible without allowing for intraoperative awakening. Simultaneously, complete neuromuscular recovery was ensured by neuromuscular monitoring, and all patients received a 100 ml infusion of NaCl 0.9% containing metamizol 25 mg kg\(^{-1}\) for postoperative pain relief.

The delivery of anaesthetic was stopped at the end of surgery, which was defined as the final surgical suture. Emergence from anaesthesia was assessed by measuring the times to spontaneous opening of eyes, extubation, stating...
the name, and arrival at the post-anaesthesia care unit. Recovery times were recorded by a blinded investigator. Finally, all patients were visited in the postanaesthesia care unit and on the first and third postoperative day and interviewed about intraoperative recall.

End-points and statistical analysis

The primary end-point of this study was defined as the time taken to spontaneous opening of eyes. Statistical analysis included comparisons of patient characteristics, duration of anaesthesia, end-tidal desflurane concentrations, recovery times, and remifentanil consumption. For nominal data statistical analysis was performed by means of a χ²-test, for numerical data by one way analysis of variance (ANOVA) with Student–Newman–Keuls test for multiple comparisons. All tests were two-tailed with statistical significance defined as P<0.05; data are presented as mean (SD). Statistical calculations were done using SigmaStat 2.03 and SigmaPlot 2000 computer software (both SPSS GmbH, Erkrath, Germany).

Results

At the four university departments a total of 200 patients were enrolled in this investigation with the study groups being similar with respect to age, weight, height, ASA physical status, and duration of anaesthesia and surgery (Table 1). The distribution of the type of surgery and the percentage values of patients reporting intraoperative dreaming and/or postoperative nausea and vomiting during the postoperative interview in each group are given in Table 2. No patient complained of intraoperative recall.

Recovery times (e.g. the time to opening of eyes) in the BIS and AAI groups were comparable with those obtained with standard practice; the mean recovery time was 5.9 (34) min in the BIS group, 5.0 (3.1) min in the AAI group, and 5.6 (2.5) min in the standard practice group (Table 3).

BIS and AAI values were obtained in all three treatment groups irrespective of the individual group assignment and are shown in Figures 1 and 2. While BIS and AAI values were comparable for patients in the standard practice and BIS group, significantly higher BIS and AAI values were observed in the AAI group. In addition, the time fractions of actual (vs targeted) BIS and AAI values obtained during maintenance of anaesthesia were analysed: actual BIS values within a range of 45-55 were observed during 61% of the investigation time. During 23% of the time BIS values were found to be lower, but not below a value of 35 whereas during 16% of the time BIS values were higher than 55. In the AAI group, AAI values between 25 and 35 were reached during 15% of the study time. During 74% of the time AAI values were found to be lower than 25 whereas during 11% of the time AAI values were higher than 35.

Desflurane end-tidal concentrations were lower in the AAI group (2.6 [0.5] vol%) when compared with BIS (3.3 [0.9] vol%) and standard practice groups (2.9 [0.5] vol%) (Fig. 3). At the same time, average normalized remifentanil infusion rates were similar for AAI (0.22 [0.06] µg kg⁻¹ min⁻¹), BIS (0.22 [0.05] µg kg⁻¹ min⁻¹), and standard practice patients (0.23 [0.07] µg kg⁻¹ min⁻¹).

The mean arterial blood pressure values at various time points during anaesthesia were comparable for all treatment groups (Fig. 4). Intervention with a vasopressor was necessary in 49% of the patients with standard practice, in 48% of the patients in the BIS and in 34% of the patients in the AAI group.

Discussion

In the present multicentre study, BIS and AAI monitoring were investigated during a desflurane-remifentanil anaesthetic compared with a standard practice group. Our results
demonstrate that BIS and AAI guidance for the titration of desflurane did not result in a significant reduction of recovery times or desflurane consumption compared with a standard practice protocol.

At first look these findings seem to be surprising and disappointing compared with previous studies, which found more favourable results for EEG-guided anaesthesia.\textsuperscript{7–13} The following issues must be discussed and may explain the differences with the previous studies.

In general, significant differences between the standard practice group and the monitoring groups are easier to find if the EEG/AEP parameter values are lower in the standard.

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**Fig 1** AAI values at various time points of anaesthesia. Data are mean (sd). *P*<0.05 for AAI vs BIS and standard practice group.

**Fig 2** BIS values at various time points of anaesthesia. Data are mean (sd). **P**<0.05 for AAI vs standard practice group. *P*<0.05 for AAI vs BIS group and standard practice group.
practice group indicating relatively ‘too deep’ anaesthesia. The mean BIS value in our control group was 47 (14) and this was in good accordance with the mean BIS values in the control groups of previous studies using desflurane, that is 40 (11),

Fig 3 End-tidal desflurane concentrations (vol%) at various time points of anaesthesia. Data are mean (sd). P<0.05 for AAI vs standard practice group. *P<0.05 for AAI vs BIS group and standard practice group.

Fig 4 Mean arterial blood pressure (mm Hg) at various time points of anaesthesia. Data are mean (sd). No significant difference between AAI, BIS and standard practice group.
practice patterns associated with the introduction of a new monitor device. Furthermore, results may be influenced by subtle investigator bias leading to an overestimation of the difference between standard practice and the device-monitored groups.

While the mean BIS value in the control group during maintenance of anaesthesia was similar to previous studies, the mean BIS value in the BIS group of the present study was 45 (9) and thereby lower than in previous studies using desflurane. Of note, the mean BIS value is obviously correlated with the amount of reduction of desflurane consumption which was 9% at a mean BIS value of 46, 17% at a mean BIS value of 49, and 30% at a mean BIS value of 60. Considering the low mean BIS value in the BIS group of our study, the missing reduction of the desflurane consumption may well be explained.

The mean BIS values in the AAI group were higher than the mean BIS values in the BIS group. This finding underlines the difficulties that arise when different neurophysiologic parameters with different algorithms are compared. The AAI target values of the present study were chosen as recommended by the manufacturer of the A-line AEP monitor. The published studies have shown similar results to our present finding that a BIS value of 50 is equivalent to an AAI value lower than 30. While titrating propofol to a BIS of 50, Kreuer and colleagues reported a mean AAI of 28 and a median AAI of 26 using the same AAI software version as in the present study. At a mean BIS value of 49 Recart and colleagues found a mean corresponding AAI value of 16; however, the software version in this study was not reported. Thereby, higher mean BIS values in the AAI group resulted in lower end-tidal desflurane concentrations reaching statistical significance at some time points during maintenance of anaesthesia.

Respective considerations can be made for the last 15 min before the end of surgery: we chose target values of 45 for AAI and 60 for BIS for the last 15 min. While titrating propofol to a BIS of 60, Kreuer and colleagues recently reported a mean AAI of 40, which is clearly below the AAI target value of 45 as used in the present study.

With desflurane and remifentanil we used the fastest combination of anaesthetic drugs, which is presently available. Previous studies with desflurane used fentanyl or fentanyl with top-up remifentanil. Consecutively, the recovery in our control group with a time to extubation of 6.3 (2.4) min was faster than in the control group of other desflurane studies with extubation times up to 11 (10) min. Thereby, with desflurane-remifentanil a further reduction of recovery times by means of neurophysiologic parameter monitoring is obviously more difficult to obtain when compared with an anaesthetic technique based on higher doses of the inhaled anaesthetic or propofol.

It is well known that the hypnotic component of anaesthesia is better reflected by the EEG or AEP than the analgesic component of anaesthesia. Therefore, it might be speculated that EEG- or AEP-guided titration of anaesthesia is clinically more useful for a hypnotic-based anaesthetic regimen (low-dose analgesics, e.g. fentanyl, combined with high-dose hypnotics, e.g. 1 MAC volatile anaesthetics) than for a more analgesic-based regimen (high-dose analgesics, e.g. remifentanil, combined with low-dose hypnotics, e.g. 0.5 MAC volatile anaesthetics), which was used in this study.

In conclusion, we evaluated the influence of BIS and AAI guidance on the titration of desflurane-remifentanil anaesthesia in comparison with a standard practice protocol. BIS and AAI-guided titration did not result in a significant reduction of recovery times or desflurane consumption during minor surgery with use of remifentanil.

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