Combined use of Bispectral Index™ and A-Line™ Autoregressive Index™ to assess anti-nociceptive component of balanced anaesthesia during lumbar arthrodesis

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Background. This study evaluated the A-Line Autoregressive Index (AAI) response to surgical stimulation during lumbar arthrodesis, as an estimate of the anti-nociceptive component of a Bispectral Index (BIS) guided anaesthesia combined with epidural analgesia.

Methods. An epidural catheter was inserted in 23 patients allocated randomly to receive ropivacaine plus clonidine (Group R) or normal saline (Group S) epidurally. General anaesthesia was induced with propofol, cis-atracurium and a remifentanil infusion that was stopped 3 min after tracheal intubation, and maintained using sevoflurane to keep BIS at 50 (range 40–60). Mean arterial pressure, heart rate, end-tidal sevoflurane, BIS and AAI were analysed from 2 min before to 17 min after surgical incision.

Results: While BIS was maintained at 50, AAI significantly increased from a 2 min averaged value of 12 (4) to 21 (7) in Group S within the first 5 min after surgical incision, but did not change in Group R. Maximum AAI values reached during the study period were significantly higher in Group S than in Group R [38 (12) and 27 (10), respectively]. Binary logistic regression analysis allowed the calculation of AAI threshold values above which the probability of predominant nociception over anti-nociception was higher than 95%. At 1 MAC sevoflurane concentration, a 2 min averaged AAI of 35 or an AAI peak value of 62 were associated with such a probability.

Conclusions. During a BIS-guided constant level of hypnosis, AAI response to the onset of surgical stimulation significantly differs according to the analgesic regimen. Further studies are needed to refine the estimation of sensitivity and specificity of this variable in assessing the balance between nociception and anti-nociception during general anaesthesia.

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Anaesthesia is the result of several pharmacodynamic effects of anaesthetic agents including alteration of consciousness, analgesia and autonomic modulation.1 Measuring the depth of anaesthesia requires knowledge of the dose–response relationship between anaesthetic agents and their pharmacodynamic effects. However, clinical evaluation has poor sensitivity and specificity. The Bispectral Index™ (BIS)2 and the A-line™ Autoregressive Index™ (AAI)3-4 have been designed to improve the sensitivity and specificity of depth of anaesthesia assessment. They mainly monitor the alteration of consciousness, which is only one pharmacodynamic aspect of anaesthesia. Few attempts have been made to develop specific monitors of the balance between nociceptive stimulation and anti-nociception during anaesthesia and most of these were based on assessing the modulating effect of pain on the autonomic nervous system5-6 or on the occurrence of movement in response to painful stimulation.7 However, agents used during anaesthesia interfere with autonomic regulation, patients may be receiving non-anaesthetic medications that alter autonomic responses, and neuromuscular blocking agents will attenuate motor responses to noxious stimulation. Therefore, a monitor that could detect other consequences of painful stimulation than movement or responses directly related to the autonomic nervous system would be helpful.

Although AAI and BIS adequately evaluate the hypnotic component of anaesthesia, the effect of a response to painful stimulation is not well established. AAI and BIS differ in terms of their electrophysiological origin. BIS reflects cortical activity8 while AAI corresponds to the transfer of
achieved a steady-state BIS value of 50 (range 40–60) before intubation and sevoflurane concentration was titrated to... 

Materials and methods

Patients and randomization

After the Institutional Ethics Review Board approval and informed consent, 23 ASA I and II patients undergoing routine lumbar arthrodesis in the prone position were recruited to this prospective randomized double-blind study. Exclusion criteria included pregnancy, alcohol or drug abuse, chronic treatment with antihypertensive or cardiovascular medications including β-blockers, and medications acting on the central nervous system such as benzodiazepines, antiepileptic and neuroleptic medications. Patients were allocated randomly to receive either 15 ml of normal saline (Group S, n=13) or a 15 ml fixed volume of ropivacaine 0.2% containing 75 µg of clonidine (Group R, n=10), epidurally, before induction of anaesthesia. A computer generated randomization was provided to the nurse in charge of preparing anaesthetic medications. The anaesthesiologist in charge was blinded to the contents of the syringe and to the AAI recording.

Anaesthesia

Alprazolam 0.5 mg and atropine 0.5 mg were given orally 1 h before the induction of anaesthesia. On arrival in the operating room, standard monitoring including ECG, non-invasive blood pressure and peripheral saturation in oxygen \( P_{SaO_2} \) (S/5® Datex monitor, Helsinki, Finland) was started. In all patients, an epidural catheter was then inserted two levels above the planned level of surgery. The BIS electrodes (BIS-Sensor®, A2000 BIS® monitor, version 3.4; Aspect Medical Systems, Inc.) and AAI electrodes (A-Line® AEP electrodes, A-Line® monitor; Danmeter A/S) were placed on the left-hand side of the forehead in all patients and checked for adequate auditory stimuli in both ears. The epidural mixture was given 5 min before the induction of anaesthesia. General anaesthesia was then induced i.v. using remifentanil (0.5 µg kg\(^{-1}\) min\(^{-1}\)) and propofol (2 mg kg\(^{-1}\)). Tracheal intubation was facilitated using \textit{cis}-atracurium (0.2 mg kg\(^{-1}\)) administered immediately after the loss of eyelash reflex. After tracheal intubation, anaesthesia was maintained using sevoflurane in 50% oxygen/air. The remifentanil infusion was stopped 3 min after tracheal intubation and sevoflurane concentration was titrated to achieve a steady-state BIS value of 50 (range 40–60) before surgical incision. In each patient, the steady-state BIS value obtained before incision was kept constant during the study period through gradual adjustments of sevoflurane end-tidal concentration. End-tidal carbon dioxide concentration was maintained between 4 and 4.8 kPa.

Other monitoring included a urinary catheter, temperature probe, warming blanket and muscle relaxation monitoring (TOF-Watch®; Organon, Roseland, NJ, USA) on the left adductor pollicis. \textit{Cis}-atracurium (1–2 mg) was administered intermittently to maintain two or less responses to TOF stimulation throughout the procedure. Mean arterial pressures (MAP) >120 mm Hg were treated with nicardipine (0.5–1 mg) i.v. and those <50 mm Hg with ephedrine (5–10 mg) i.v. Bradycardia (<50 beats min\(^{-1}\)) was treated with atropine (0.5 mg). Before incision, the skin was infiltrated with 20 ml of 0.5% bupivacaine containing 1/200 000 epinephrine. At the time of muscle closure, morphine 3 mg in 10 ml normal saline was administered through the epidural catheter for postoperative analgesia. Absence of motor blockade and sensitivity to cold (ether) were tested in the legs after recovery from anaesthesia.

Data acquisition

The following variables were recorded: heart rate (HR), MAP, end-tidal sevoflurane concentration (E\(_{sevo}\)), BIS and AAI. Data were transferred on a laptop computer from Datex S/5®, Aspect A2000® and Alaris A-Line® monitors, using the RugloopII® monitor-only software (Demed, Temse, Belgium). The sampling rate was 1 per second for electrophysiological variables and 1 per 10 s for other variables. Events were inserted online in files by pressing on the event button on the Alaris A-Line® monitor.

Statistical analysis

Data were expressed as mean (SD) unless otherwise indicated. Normality of distribution was checked when necessary and a \( P \)-value <0.05 was considered statistically significant. Age, height, weight, \textit{cis}-atracurium consumption, length of surgery, mean E\(_{sevo}\) concentration during the period after surgical incision (E\(_{sevo17}\)), duration of diathermy after surgical incision, time from intubation to incision and from induction of anaesthesia to incision were compared using two-tailed unpaired \( t \)-tests. Gender, and need for nicardipine, ephedrine or atropine boluses proportions were compared using \( \chi^2 \)-tests.

The period of interest (referred to as ‘the study period’) for BIS, AAI, HR, MAP and E\(_{sevo}\) variation analysis ran from 2 min before incision to 17 min after incision. This period of interest was further divided into six time points, each of them corresponding to the beginning of a 2 min averaging period of recording. The time points were the following: before incision (PREINC, 2 min before incision), and 1, 3, 5, 10 and 15 min after incision (INC+1, INC+3, INC+5, INC+10 and INC+15). Comparisons between and within groups were performed using two-way mixed-design
ANOVA and Tukey’s HSD tests (DATASIM software, Version 1.1, Drake R. Bradley, Department of Psychology, Bates College, Lewiston, ME, USA). The maximum AAI value reached during those first 17 min after surgical incision (AAIpeak) was recorded for each patient and compared between groups using a two-tailed unpaired t-test.

Binary logistic regression with maximal likelihood estimation was performed to model the relationship between AAI [either the 2 min averaged value at INC+3 (AAIINC+3) or the AAI peak value (AAIpeak)], Esevo17 and the probability for a patient of having received epidural ropivacaine plus clonidine. A detailed description of the method used to perform this analysis and of each calculated variable can be found in the Appendix. For a given Esevo, the obtained equations allowed calculating AAIINC+3 or AAIpeak at which the probability of having not received epidural ropivacaine plus clonidine was 50 or 95%. Using the Matlab® software (version 7.0.1; Mathworks Inc., Natick, USA), the same equations served to plot surface–response curves giving the probability of having received epidural ropivacaine plus clonidine as a function of AAIINC+3 or AAIpeak and Esevo17.

Results

Three patients from Group S were excluded from the analysis because of protocol violation (2 patients) or poor AAI signal (baseline AAI below 40, although electrode impedances were acceptable, 1 patient). Haemodynamic variables were missing in one patient from each group because of technical problems. No significant difference was observed between groups in terms of characteristics or surgical and anaesthetic interventions (Table 1).

Haemodynamics (Fig. 1)

From an equivalent value before incision in both groups, MAP increased significantly and remained significantly higher in Group S after surgical incision [overall mean (SD): 70 (12) and 92 (11) in Groups R and S, respectively]. The maximum AAI value averaged over 2 min significantly increased during the first minutes after surgical incision in Group S (INCl-3 and INCl+3), but not in Group R. The maximum AAI value reached during the 17 min post-incision period (AAIpeak) was significantly higher in Group S than in Group R [38 (12) and 27 (10), respectively, t(18)=2.30, P=0.03]. The peak values did not necessarily occur during the first 3–5 min after surgical incision, when the 2 min averaged AAI was highest in Group S. There was no difference in BIS during the whole study period between groups, but pre-incision values were significantly, although slightly, higher than at INC+15 [52 (7) and 47 (10) vs 47 (11) and 44 (8), in Group R and Group S].

Sevoflurane concentrations (Fig. 2b)

Esevo concentrations were not significantly different between groups, and Esevo was significantly lower at PREINC than at INC+10 in both groups. The overall Esevo concentration after surgical incision (Esevo17) was higher in Group S than in Group R, but not significantly [1.79 (0.56) and 1.59 (0.46), t(18)=0.39].

Binary logistic regression (Fig. 3)

Binary logistic regression analysis allowed modelling of the relationship between AAIINC+3 or AAIpeak and Esevo17, and of the probability of having received epidural ropivacaine plus clonidine. The resultant models fitted the data at an acceptable level, as indicated by Nagelkerke pseudo R2 values of 0.288 and 0.232, and Hosmer and Lemeshow’s χ2-values of 15.445 (P=0.051) and 10.081 (P=0.259), respectively. Predictive accuracy was 75% for the AAIINC+3 model and 60% for AAIpeak. At 2% Esevo, the AAI values associated with 50 and 95% probability of having not received epidural analgesia were 17 and 35 for AAIINC+3 and 29 and 62 for AAIpeak.

Discussion

In this study, we observed an increased AAI during the first minutes after surgical incision while maintaining a constant
level of hypnosis through a BIS-guided sevoflurane administration. This is the first study to demonstrate that the use of two different electrophysiological monitors of anaesthetic depth together provides information regarding the anti-nociceptive component of anaesthesia at a constant level of hypnosis. BIS is known to increase in response to nociceptive stimulation during anaesthesia.10 In this study, we used BIS to drive sevoflurane administration, to maintain a value in the range 40–60. This did not mean that BIS did not react to nociceptive stimulation.

AAI is similar to BIS as a monitor of depth of hypnosis and also increases in response to nociceptive stimulation.11 12 When used alone, it is not a better predictor of response to painful stimulation than BIS.13 The mechanism of the increase in AAI in response to nociceptive stimulation during a steady level of hypnosis is not known and deserves further investigation. AAI depends on the amplitude and latency of middle latency auditory evoked potentials (MLAEPs), and thalamic cholinergic neurons of the ascending reticular formation are involved in their generation.14 Intermittent facilitation of MLAEPs by the ascending reticulo-thalamic activating system and spinoreticular or spinothalamic nociceptive inputs may explain the AAI response we observed. The shorter delay for AAI calculation (1.7 s) compared with the 30 s BIS latency could also facilitate the detection of pain-induced changes of MLAEPs.

The 2 min smoothed AAI increase in response to surgical stimulation in Group S occurred within a delay of 3–5 min but was not evident thereafter. Gradual adjustment of the sevoflurane concentration to maintain BIS at its target, combined with short breaks in surgical activity might have flattened the AAI response when averaged among the entire group of patients, while not preventing AAI peak values.

The intensity of surgical stimulation can be considered as having been identical in both groups. Indeed, during lumbar arthodesis, the first 15 min of surgery are fairly reproducible. Therefore, we can assume that nociception was predominant in Group S and anti-nociception in Group R, as a result of the different analgesic regimens. Although we did not test the sensory block, we can reasonably assume that it extended over the surgical site with the dose of ropivacaine plus clonidine received.15 16 Precise evaluation of the sensory block would have required a test immediately before surgical incision. This was not possible as the patients were anaesthetized at that time. Similarly, we did not record the sensory levels at recovery because of the variation in surgical time and morphine had been administered epidurally by then. However, impaired cold perception to ether was confirmed after recovery in Group R. Using higher doses of ropivacaine could have increased the analgesic level difference between groups, but would also have increased the risk of motor blockade. Clonidine was added to the epidural mixture to increase and prolong the effect of ropivacaine, without impairing motor function.17 Skin infiltration was identical in both groups and, on average, the time between stopping remifentanil and incision was 30 min.
During surgery, the concentration of sevoflurane tended to be higher in Group S than in Group R, but the difference did not reach statistical significance and may have lessened the AAI response to nociceptive stimulation. For that reason, we performed the logistic regression analysis. It allowed modelling the influence of sevoflurane on the relationship between the AAI response and the presence or the absence of epidural ropivacaine plus clonidine. In addition to AAI_{peak}, AAI_{INC+3} was chosen as a relevant variable because ANOVA had shown that the increase in smoothed AAI was highest at this time point. Looking at the surface–response curves, the higher the sevoflurane concentration, the lower the AAI value corresponding to 50% probability of having deep level anti-nociceptive component of anaesthesia. This reflects the anti-nociceptive effect of sevoflurane, which seems to be more marked on AAI peak value than on smoothed AAI value (the slope $\beta$ was steeper for the AAI_{peak} than for the AAI_{INC+3} model). The minimal effect of sevoflurane on AAI response is not surprising as it has more potent hypnotic than anti-nociceptive properties.

The logistic regression analysis revealed that the accurate prediction rate of AAI_{INC+3} was better than that of AAI_{peak} (75 and 60%, respectively). Inter-individual differences in sensitivity to painful stimulation, intensity of
surgical stimulation or both may explain not achieving 100%. A larger series of patients and calibrated painful stimulation is required.

Based on our model, at sevoflurane 1 MAC (2%), a 2 min averaged AAI value higher than 17 or an AAI peak value higher than 28 during the first minutes after surgical incision is indicative of a 50% probability of predominant nociception. Similarly, averaged or peak AAI values corresponding to 95% probability of such a risk were 35 and 62. These theoretical values could serve as thresholds to guide anti-nociceptive strategies during general anaesthesia. It suggests that maintaining AAI at 20 through adjustments of the anti-nociceptive component of anaesthesia, while maintaining a constant hypnotic through a BIS-guided hypnotic administration, would insure a low risk of nociception. This needs to be confirmed by further studies.

The potential confounding factors of our study are related to the BIS window defining the level of hypnosis, the use of diathermy and the administration of adrenergic medications. One may question whether the observed changes in AAI actually reflect a difference in the balance between nociception and anti-nociception or are the result of natural fluctuation. BIS values of 40–60 have been used by other authors to define a constant level of hypnosis. It corresponds to a well-defined moderate hypnotic state, where synchronized-fast-slow activity of the EEG is the main determinant of BIS calculation. It is unlikely to be natural fluctuation as we observed individual AAI values as high as 58 in Group S, while the highest value observed in Group R was 41.

The use of diathermy may have influenced AAI value more in one group, or affected the adjustments of sevoflurane concentration to maintain BIS. However, intermittent cessation of diathermy allowed reliable BIS recording during the periods of interest and the total length of use was comparable between groups.

Adrenergic medications are known to induce arousal, increase BIS and reduce latencies of MLAEPs in sedated patients. This arousal effect is not observed when anaesthesia is deep enough to maintain BIS between 40 and 60, as in our study. The number of patients receiving ephedrine during the study period was similar in both groups and no change in BIS or AAI was noted after administration of ephedrine.

In our study, the higher MAP in Group S was probably the consequence of the absence of epidural sympathetic
blockade and/or lower level of anti-nociception. It is not possible to determine the relative impact of each of these factors. HR was not different between groups. Therefore, haemodynamic variations were not discriminant in our experimental setting.

We conclude that AAI pattern provides information regarding the anti-nociceptive component of anaesthesia when monitored while keeping a BIS-guided constant level of hypnosis. The AAI response to the onset of painful stimulation is a key factor to consider in that respect. Further studies are needed to refine estimation of sensitivity and specificity of this variable in assessing adequacy of analgesia.

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Appendix

Binary logistic regression with maximal likelihood estimation

This analysis was performed using the SPSS software (SPSS 12.0; SPSS Inc., Chicago, IL). We defined independent variables (covariates), namely AAI_{INC+3} (2 min averaged AAI value at INC+3), AAI_{peak} (maximum AAI value reached during the post-incision period of recording) and E_{sevo17} (mean end-tidal sevoflurane concentration during the same period), and a dependent variable, namely the probability for a patient of having received epidural ropivacaine plus clonidine. The software estimates the coefficients $\alpha$ and $\beta$ and a constant $a$ that best fit the equation $P(x) = \ln \left[ \frac{P}{1-P} \right] = a + \alpha x + \beta y$, where $P$ is the probability of having received epidural ropivacaine plus clonidine, $x$ is AAI_{INC+3} or AAI_{peak}, and $y$ is E_{sevo17}. Alpha, $\beta$ and $a$ are provided with standard errors (SES). Nagelkerke pseudo $R^2$ test is a logistic analogy to the $R^2$ provided by classical least square regression, but it is not equivalent. A Nagelkerke pseudo $R^2$ ranging between 0.2 and 0.4 is considered satisfactory. Hosmer and Lemeshow’s $X^2$-test provides a $X^2$-value and a probability, which is highest when goodness-of-fit is best. It tests the null hypothesis that there is no difference between observed and predicted value of the independent variable. If this probability is $>0.05$, the above-mentioned null hypothesis cannot be rejected, implying that the model fits the data at an acceptable level. Overall percentage of accurate prediction by the model is also given by the software.

References
1 Woodbridge PD. Changing concepts concerning depth of anesthesia. Anesthesiology 1957; 18: 536–50

21 Dahaba AA. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. *Anesth Analg* 2005; 101: 765–73


