

PAIN

# Sufentanil administration guided by surgical pleth index vs standard practice during sevoflurane anaesthesia: a randomized controlled pilot study<sup>†</sup>

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## Editor's key points

- The surgical pleth index (SPI) has shown some promise in detecting nociceptive responses under total i.v. anaesthesia.
- The utility of SPI under sevoflurane anaesthesia has not been assessed.
- SPI was used to guide administration of sufentanil under sevoflurane anaesthesia.
- There was no difference in adverse events using the SPI to direct sufentanil administration compared with standard care.
- Further research is needed to establish the role of SPI in clinical practice.

**Background.** Evaluation of analgesia and antinociception during anaesthesia is still a challenging issue and routinely based on indirect and non-specific signs such as movement, tachycardia, or lacrimation. Recently, the surgical pleth index (SPI) derived by finger plethysmography was introduced to detect nociceptive stimulation during anaesthesia. While SPI guidance reduced the number of unwanted events during total i.v. anaesthesia (TIVA), the impact of SPI during volatile-based anaesthesia with intermittent opioid administration has not yet been elucidated.

**Methods.** Ninety-four patients were randomized into either SPI-guided analgesia or standard practice (Control). In both groups, anaesthesia was maintained with sevoflurane to keep bispectral index values between 40 and 60. In the SPI group, patients received a sufentanil bolus (10 µg) whenever SPI value increased above 50, whereas in the control group, sufentanil was administered according to standard clinical practice. The number of unwanted somatic events, haemodynamics, sufentanil consumption, and recovery times were recorded.

**Results.** The incidence of intraoperative unwanted somatic events was comparable between the groups ( $P=0.89$ ). No significant differences with respect to hypotensive or hypertensive events were found. The mean (95% confidence interval) sufentanil consumption was non-significantly ( $P=0.07$ ) reduced in the SPI group, 0.64 (0.57–0.71) vs 0.78 (0.64–0.91) µg min<sup>-1</sup>. Recovery times were comparable between the groups.

**Conclusions.** Sufentanil administration guided by SPI during sevoflurane anaesthesia is clinically feasible. In contrast to TIVA, it did not improve anaesthesia conduct with respect to unwanted somatic events, haemodynamic stability, sufentanil consumption, emergence time, or post-anaesthesia care unit care. Therefore, we conclude that anaesthesia regimen has an impact on beneficial effects by SPI guidance.

**Clinical trial registration.** NCT01525537. (Registered at Clinicaltrials.gov.)

**Keywords:** anaesthesia, general; anaesthetics volatile, sevoflurane; analgesia; equipment and monitors

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The measurement of anaesthetic drug effect and individualized titration of anaesthetics may help to avoid under- and overdosage and could therefore provide a safer perioperative treatment of our patients. Whereas underdosage of opioids may be associated with activation of nociceptive pathways and a higher associated risk of haemodynamic responses such as tachycardia and an increased number of complications,<sup>1</sup> a potential overdose may lead to prolonged time

of anaesthesia and an increased number of postoperative complications such as nausea/vomiting, thrombosis, or pneumonia.<sup>2</sup> Processed variables of the electroencephalogram have been suggested to guide administration of hypnotics during anaesthesia.<sup>3,4</sup> However, administration of analgesics is routinely guided by clinical experience and evaluation of somatic or autonomic responses such as movement, sweating, heart rate, or arterial pressure increase. The surgical pleth

<sup>†</sup>Data of the present study were presented in part at Euroanaesthesia 2011 in Amsterdam.

index (SPI, initially named ‘surgical stress index’) is a multivariate index derived from finger-photoplethysmographic signal, including normalized heart beat interval and pulse wave amplitude. SPI was developed in order to reflect the nociceptive–antinociceptive balance during the unconscious state of anaesthesia<sup>5</sup> and has shown to reflect a noxious stimulus better than standard monitoring.<sup>6,7</sup> SPI guidance has shown to provide beneficial effects during anaesthesia using a total i.v. anaesthesia (TIVA) regimen with the two short-acting anaesthetics propofol and remifentanyl, as less consumption of opioids<sup>8</sup> and fewer unwanted events were recorded.<sup>9</sup> However, often anaesthesia is delivered using volatile anaesthetics and opioids like fentanyl or sufentanil.

Therefore, the aim of the present prospective randomized controlled pilot study was to examine SPI-guided sufentanil bolus administration during sevoflurane anaesthesia. Based on a previous publication from our group, we hypothesized that SPI guidance (i) reduces the number of unwanted somatic responses (e.g. coughing, grimacing, movement), (ii) increases haemodynamic stability, and (iii) decreases opioid consumption.

## Methods

After obtaining approval of the institutional review board of the University Hospital Schleswig-Holstein, Campus Kiel, and written informed consent, 94 patients ASA physical status I or II, age between 18 and 65 yr undergoing elective surgery (gynaecological and orthopaedic procedures) were enrolled. Patients were not studied if they had a history of significant cardiovascular (e.g. arrhythmia), renal, hepatic, endocrinologic, neuromuscular, or neurological disease, abuse of alcohol or illicit drugs, were on medication or drugs that may affect autonomous regulation (e.g.  $\beta$ -blocker, clonidine), or pregnant. The trial was registered at [clinicaltrials.gov](https://clinicaltrials.gov) (identifier: NCT01525537).

Patients received 7.5 mg midazolam orally for premedication 1 h before surgery. After arrival in the operating theatre, standard monitoring (non-invasive arterial pressure, ECG, pulse oximetry) and venous access via a forearm vein were established. SPI clip (GE-Healthcare, Helsinki, Finland) for finger plethysmography was placed on the index finger of the opposite arm from arterial pressure measurement and connected to the anaesthesia monitor, visualizing and recording SPI continuously. A detailed description of the SPI, including the algorithm for normalization, can be found elsewhere.<sup>5</sup> The numerical index ranges between 0 (low stress response) and 100 (high stress response). A value of 50 represents a mean stress level during anaesthesia, and a range between 20 and 50 has been used previously to guide analgesics.<sup>9</sup> The skin of the forehead was subsequently prepared and the disposable BIS-XP Sensor (Aspect Medical Systems, Newton, MA, USA) was positioned according to the manufacturer’s recommendations. The BIS Sensor was connected with the M-BIS module of the S/5™ Anaesthesia Monitor (GE-Healthcare). The EEG was recorded continuously (smoothing rate of 15 s) from before induction until end of anaesthesia.

All anaesthetic procedures were carried out by one experienced staff anaesthetist (S.W.). After 5 min of preoxygenation with 100% oxygen, sufentanil ( $0.2 \mu\text{g kg}^{-1}$ ) and propofol ( $2 \text{ mg kg}^{-1}$ ) were administered for anaesthesia induction. After loss of consciousness and adequate facemask ventilation, patients received  $0.6 \text{ mg kg}^{-1}$  rocuronium and the trachea was intubated. Ventilation was adjusted to an end-tidal carbon dioxide concentration between 35 and 38 mm Hg. Sevoflurane was started and adjusted to maintain a bispectral index (BIS) level between 40 and 60 in all patients.

After induction of anaesthesia, randomization into two study groups was performed, using envelopes and computer-generated randomization numbers:

- SPI-guided analgesia group (SPI group)
- Standard practice analgesia group (control group).

In the SPI group, a sufentanil bolus ( $10 \mu\text{g}$ ) was given whenever the SPI value remained above 50 for more than 20 s. In the control group, an additional sufentanil bolus ( $10 \mu\text{g}$ ) was given when mean arterial pressure (MAP) was  $>100 \text{ mm Hg}$  or heart rate (HR) was  $>90 \text{ beats min}^{-1}$ . In both groups, an additional sufentanil bolus of  $10 \mu\text{g}$  was given when somatic response occurred. Movements of extremities or head were defined as major somatic response, while coughing, chewing, grimacing, and efforts to breathe while mechanically ventilated were considered as minor somatic response. SPI values in the control group were not visible to the anaesthetist but electronically recorded and stored.

Inadequate haemodynamics were defined in both groups as: hypotension (MAP  $<60 \text{ mm Hg}$ ), hypertension (MAP  $>100 \text{ mm Hg}$ ), bradycardia (HR  $<45 \text{ beats min}^{-1}$ ), or tachycardia (HR  $>90 \text{ beats min}^{-1}$ ). Besides sufentanil administration, as described above, treatment of inadequate haemodynamics included infusion of crystalloid solution ( $5 \text{ ml kg}^{-1}$  Sterofundin®, B Braun AG, Melsungen, Germany), administration of Akri-nor® (1 ml contains 100 mg cafedrine and 5 mg theodrenaline, Teva GmbH, Ulm, Germany), 10 mg urapidil [if hypertension was still persistent after three sufentanil bolus doses ( $30 \mu\text{g}$ ) within 15 min], and atropine respectively.

Fifteen minutes before the expected end of the surgical procedure, sevoflurane was adjusted to a BIS of 50–60 and no more sufentanil was given regardless of SPI values in order to facilitate emergence. All patients received i.v. 1000 mg metamizol or 1000 mg acetaminophen (in the case of contraindications for metamizol) for postoperative analgesia. Neuromuscular monitoring was used for exclusion of postoperative residual curarization by using the ‘Train-of-four’ (TOF) technique and aiming at a TOF ratio of 0.9. At the end of surgery (final suture), sevoflurane was discontinued and fresh gas flow increased to  $10 \text{ litre min}^{-1}$  for sevoflurane wash-out. Patients were loudly asked to open their eyes every 15 s in order to enable a standardized determination of emergence.

All patients were transferred to the post-anaesthesia care unit (PACU) for standard institutional postoperative care. Physicians and nurses in the PACU were blinded for group assignment. The total time of PACU care, numerical rating scale for pain (1–10) at admission and discharge from PACU, cumulative

administration of the opioid piritramid, and the Aldrete score at discharge from PACU were recorded.<sup>10</sup>

### Statistical analysis and endpoints

The study was conducted as a single-centre, randomized, controlled pilot trial. Only the anaesthesia team but not the patient nor the postoperative care team was aware of group assignment. The primary outcome of the study was to detect whether SPI-guided analgesia leads to a reduction in unwanted somatic events. Therefore, the total number of somatic events (minor, major movement response) were compared. The secondary outcome was an improvement of haemodynamic stability measured as time-fractions within predefined criteria of inadequate haemodynamics, as percentage of total anaesthesia time. Further endpoints were total sufentanil consumption, time of emergence (final suture vs extubation time), postoperative pain, and consumption of analgesics.

**Table 1** Patient characteristic data and their physical status according to the ASA, pre-induction haemodynamics at arrival in the anaesthesia induction room, and anaesthesia times. Data are mean (95% CI) or absolute numbers

	SPI group (n=42)	Control group (n=40)
Gender (f/m)	27/15	27/13
Age (yr)	37 (33–40)	41 (37–45)
Height (cm)	174 (171–177)	172 (169–175)
Weight (kg)	76 (71–81)	77 (71–82)
ASA (I/II)	15/27	11/29
Heart rate (beats min <sup>-1</sup> )	74 (71–77)	74 (70–78)
MAP (mm Hg)	99 (95–103)	99 (95–103)
SPI value	68 (64–72)	66 (62–70)
Total anaesthesia time (min)	153 (135–172)	146 (125–167)
Intubation–incision time (min)	35 (32–37)	36 (32–40)
Incision–suture time (min)	111 (93–128)	102 (83–120)

Statistics were performed using commercially available statistics software (GraphPad Prism 5, Graphpad Software Inc., San Diego, CA, USA). Values of variables over time between the groups were compared by two-way analysis of variance (ANOVA) factoring for time and group assignment. For numerical data, statistical analysis was performed with two-tailed Student's *t*-test (normally distributed data) and the Mann–Whitney *U*-test (not normally distributed data), followed by the Bonferroni correction for multiple comparisons. Nominal data were compared by the  $\chi^2$  test. Emergence times between the groups were compared using the Kaplan–Meier log-rank survival analysis. A *P*-value of <0.05 was considered statistically significant.

Sample size of 82 patients was calculated based on a previous study from our group that showed a reduction from 0.37 to 0.08 per patient with regard to unwanted event of movement in favour of SPI-guided analgesia during TIVA, and taking an  $\alpha$ -error of 0.05 and 90% power into account.<sup>9</sup> Expecting a drop-out rate of 20%, we recruited a total number of 94 patients.

### Results

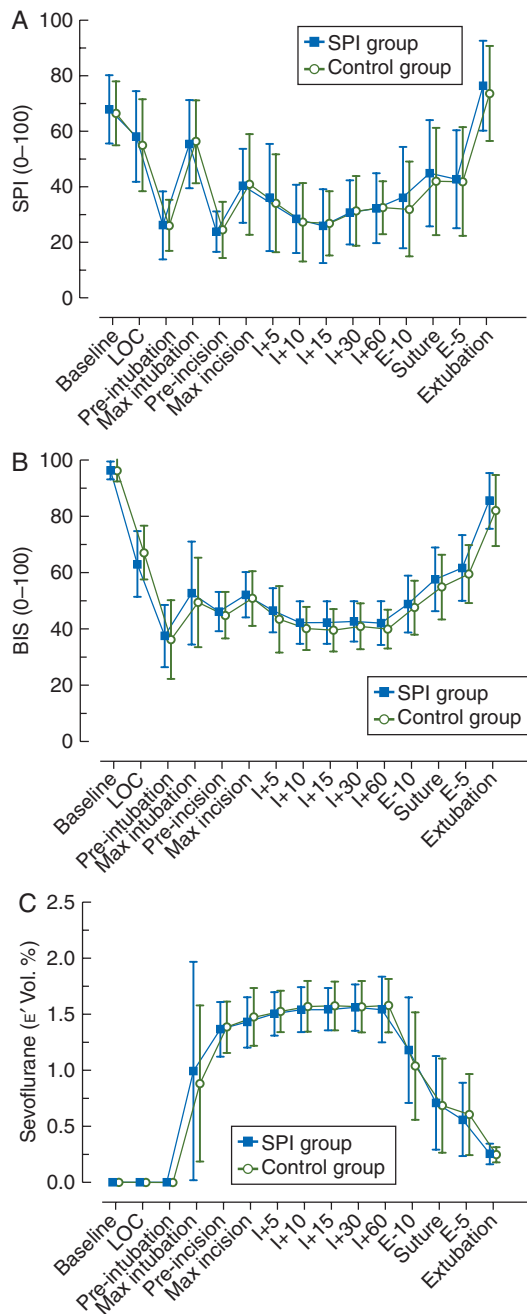
Ninety-four patients were enrolled in the present study. Twelve patients could not be included into final analysis because of withdrawal of study consent on the day of surgery ( $n=1_{\text{SPI}}$ ;  $1_{\text{Control}}$ ), scheduling issues ( $n=2_{\text{SPI}}$ ;  $4_{\text{Control}}$ ), and change of surgical procedure ( $n=2_{\text{SPI}}$ ;  $2_{\text{Control}}$ ). Therefore, data of 82 patients were included into final analysis ( $n=42_{\text{SPI}}$ ;  $40_{\text{Control}}$ ). No differences were found with regard to patient characteristic data, pre-induction haemodynamic values, or duration of anaesthesia or surgical procedure (Table 1).

We did not detect a reduction in incidences classified as unwanted somatic response. The cumulative time spent at haemodynamic values defined as hypotension or hypertension and bradycardia or tachycardia were comparable between the groups (Table 2).

SPI guidance led to a slight reduction in sufentanil consumption in comparison with the control group, with the

**Table 2** Somatic response and haemodynamic instability. Time period within inadequate anaesthesia in terms of total number of minor and major somatic responses; mean events per patient (sd) and inadequate haemodynamics presented as mean percentage of total anaesthesia time within haemodynamic instability (95% CI) in the respective SPI-guided group and standard practice—control group

	SPI group (n=42)	Control group (n=40)	<i>P</i> -value
Somatic responses			
Major	22; 0.52 (0.97)	26; 0.65 (1.09)	0.79
Minor	8; 0.19 (0.55)	5; 0.13 (0.33)	0.64
Total	30; 0.71 (1.07)	31; 0.88 (1.35)	0.81
Inadequate haemodynamics			
Mean arterial pressure			
% of time <60 mm Hg	2.6 (1.3–3.9)	1.0 (0.3–1.7)	0.06
% of time >100 mm Hg	12.9 (7.5–18.3)	8.1 (5.0–11.2)	0.12
Heart rate			
% of time <50 beats min <sup>-1</sup>	10.5 (5.3–15.8)	14.3 (6.0–22.5)	0.44
% of time >90 beats min <sup>-1</sup>	3.1 (0.7–6.4)	2.2 (1.2–3.2)	0.62



**Fig 1** Characteristics for SPI (A), BIS (B), and end-tidal sevoflurane concentration (C) representing major time points during anaesthesia in the SPI (blue) and control (green) groups. Values are mean (SD). Baseline, before induction of anaesthesia; LOC, loss of consciousness; pre-intubation, before intubation; max intubation, maximum value during/after intubation; pre-incision, before start of surgery by incision; max incision, maximum value during/after incision (I); suture, final suture; E, extubation.  $\pm$  values are in minutes.

mean [95% confidence interval (CI)] 0.64 (0.57–0.71)  $\mu\text{g min}^{-1}$  in the SPI group and 0.78 (0.64–0.91)  $\mu\text{g min}^{-1}$  in the control group patients ( $P=0.07$ ).

**Table 3** Time fractions of SPI and BIS (% of anaesthesia time) within predefined ranges. Data are mean (95% CI). No significant differences between the groups. SPI, surgical pleth index; BIS, bispectral index

	SPI group (n=42)	Control group (n=40)
SPI <20	23 (19–27)	21 (16–26)
SPI 20–50	66 (62–70)	65 (61–70)
SPI >50	11 (8–14)	14 (10–17)
BIS <40	30 (23–37)	33 (24–41)
BIS 40–60	63 (57–70)	60 (52–67)
BIS >60	7 (5–8)	8 (5–10)

Time response curves for SPI, BIS, and end-tidal sevoflurane concentrations are plotted in Figure 1. ANOVA revealed no significant differences with regard to studied variables. SPI and BIS values were distributed independent of group assignment (Table 3).

The continuously recorded time courses of SPI and HR during the time interval starting 2 min before until 2 min after administration of the first sufentanil bolus after start of surgery (incision) is plotted in Figure 2. Whereas SPI values at the time of sufentanil administration differed significantly ( $P<0.01$ ) between the SPI and control groups with the median [inter-quartile range (IQR)] 54 (50–61) vs 41 (30–55), there was no significant difference with respect to HR 63 (56–76) vs 65 (58–80) between the groups. In the SPI group, the SPI increase was detectable earlier and with a higher amplitude than HR increase.

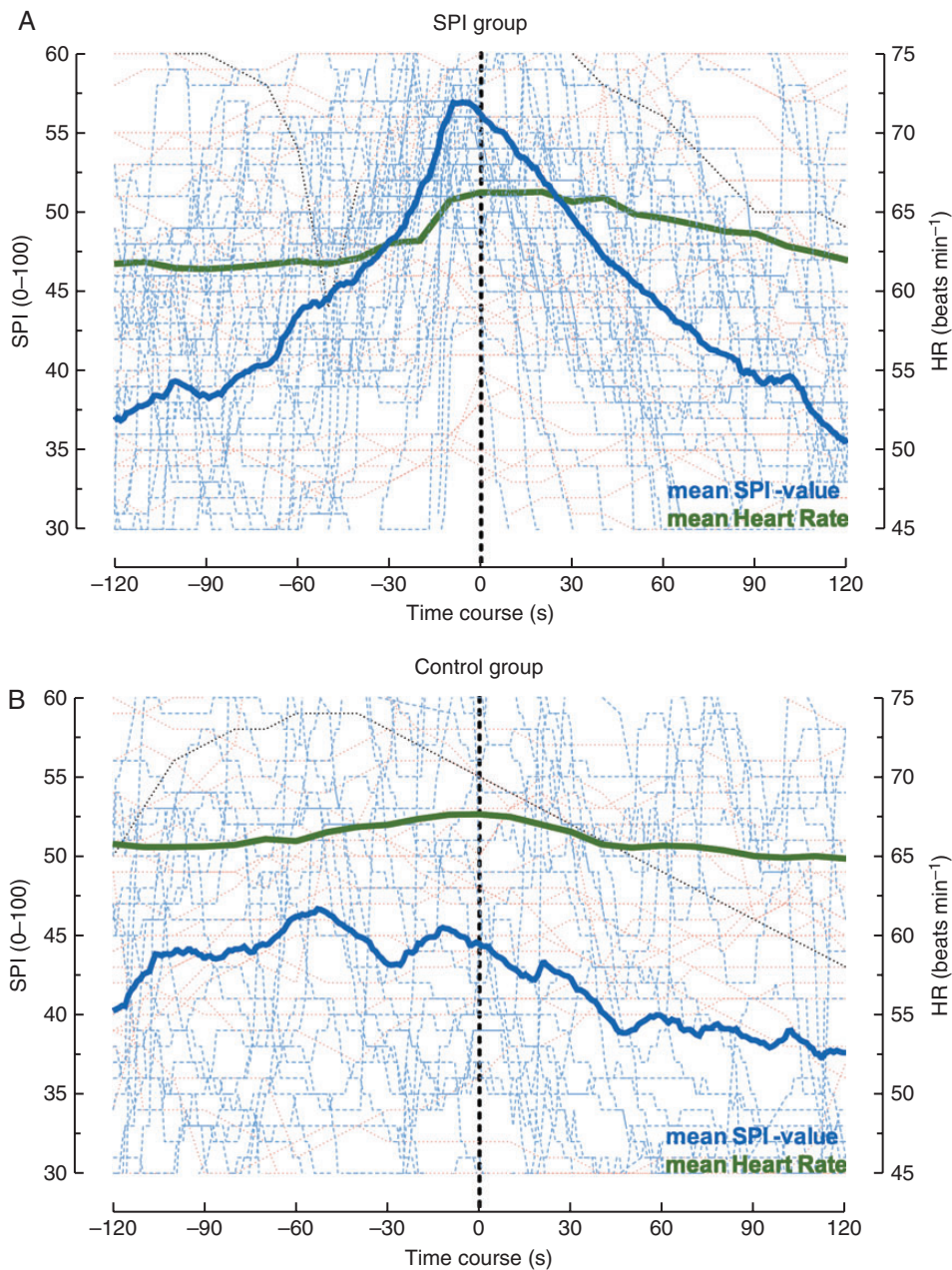
The analysis of maximum change of variables within the time period of 2 min before and after event of somatic response (movement) revealed significant higher  $\delta$  values for SPI in comparison with HR in either group (Fig. 3). Recorded change [median (IQR)] was 26 (13–35) and 23 (14–34) for SPI and 10 (4–22) and 14 (6–22) for HR in the respective SPI and control group patients. This corresponds to a relative change [median (IQR)] of 98 (39–151)% and 62 (37–191)% for SPI and 13 (6–40)% and 25 (9–39)% for HR in the SPI and control group patients, respectively.

Emergence was not different between both groups. The time to extubation [mean (95% CI)] was 6.6 (5.5–7.9) vs 7.3 (5.5–9.0) min for the SPI and control group patients, respectively. The Kaplan–Meier curves for extubation times (final suture to extubation) are presented in Figure 4.

During PACU, we recorded no difference regarding total time in PACU, pain ratings, cumulative opioid consumption, and Aldrete score between the groups. Detailed data obtained during PACU stay are presented in Table 4.

## Discussion

In the present prospective, randomized, controlled study, we found that guidance of sufentanil administration by SPI monitoring during sevoflurane anaesthesia is feasible and as safe as standard practice. There was no difference with respect to

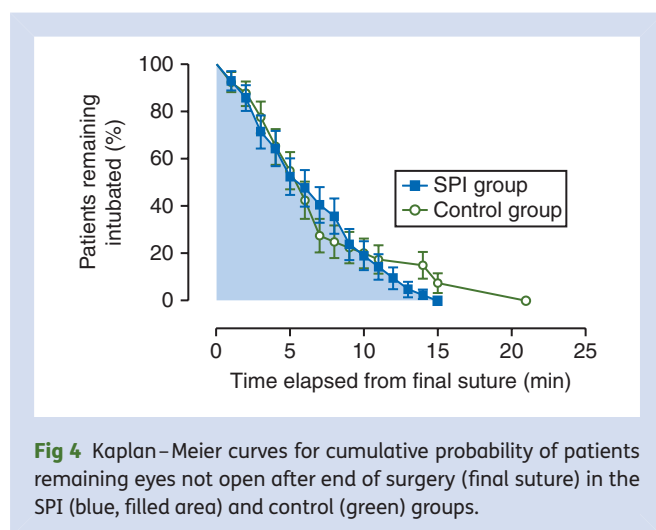
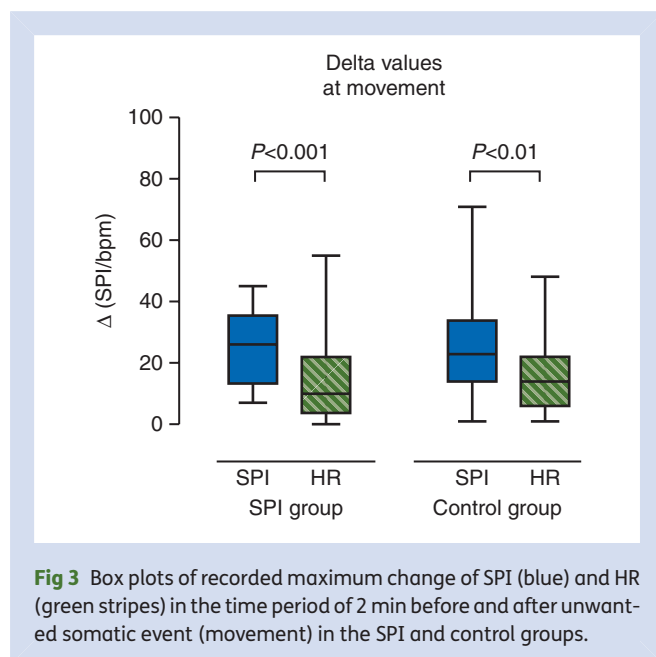


**Fig 2** Time courses of SPI (blue) and HR (green) during time period 120 s before and after sufentanil administration (dashed line) in the SPI (A) and control (B) groups. Values are individual (dotted/thin lines) and mean (solid/bold lines).

unwanted somatic events, haemodynamic stability, sufentanil consumption, emergence time, or PACU care.

An individualized titration of anaesthetics is important to avoid potential under- and overdosing, which may lead to adverse events potentially harming the patient.<sup>2</sup> Monitoring the hypnotic drug effect has gained clinical acceptance and has been used to guide propofol or volatile anaesthetics administration.<sup>11–13</sup> Even automated administration of hypnotics using a closed-loop system was attempted and showed to be clinically feasible.<sup>14</sup> However, individual titration of analgesics, or specifically opioids, is still challenging as monitoring

the nociceptive–antinociceptive balance is not yet clinically established. Routinely, administration of analgesics is guided by clinical experience and largely based on somatic or autonomic responses, such as movement, sweating, HR, or arterial pressure increase. During the last decade, more interest was spent on reliable quantification of the nociceptive–antinociceptive balance by analysing simple and complex reflex pathways,<sup>15–16</sup> skin conductance,<sup>17</sup> pupillometry,<sup>18</sup> electroencephalogram,<sup>19</sup> electrocardiogram,<sup>20–21</sup> and pulse plethysmographic signal.<sup>22</sup> Hence, the non-invasive SPI was developed for quantification of the nociception–antinociception



**Table 4** Patients' data obtained in the PACU. Data are median (IQR). NRS, numerical rating scale (0–10) for pain

	SPI group	Control group	P-value
Total PACU time (min)	118 (85–146)	118 (86–149)	0.79
NRS arrival PACU	3 (2–5)	3 (1–5)	0.63
NRS discharge PACU	2 (1.75–3)	2 (1.25–3)	0.79
Aldrete score (0–14)	13 (12–14)	14 (12–14)	0.53
Piritramide (mg)	3.75 (0–8)	3.75 (0–11)	0.88

balance during anaesthesia, taking into account the normalized photo-plethysmographic amplitude and the heart beat interval.<sup>5</sup> To date, beneficial effects have already been described for guidance of analgesics by some of these variables.<sup>23 24</sup>

Using the SPI for guidance of opioids resulted in higher haemodynamic stability, fewer unwanted events, and decreased opioid consumption.<sup>9</sup> In outpatient anaesthesia, reduced anaesthetic consumption and shorter recovery were reported.<sup>8</sup> However, the vast majority of these studies was performed during an anaesthesia regimen using the short-acting anaesthetics propofol and remifentanyl, and data during anaesthesia using volatile anaesthetics and bolus titration of opioids are currently not available.

Anaesthesia regimen using a volatile anaesthetic (e.g. sevoflurane) and bolus titration of the opioid (e.g. sufentanil) is common practice and actually accounts for about one-third of all anaesthesia procedures performed in our department.

Both SPI guidance and standard practice were comparable with regard to values of SPI, BIS, and sevoflurane concentration during major anaesthesia time points. We therefore conclude that SPI guidance may be a feasible and safe method for this anaesthesia regimen.

However, using SPI guidance during sevoflurane/sufentanil anaesthesia did not lead to a difference with respect to the number of unwanted somatic events, haemodynamic stability, sufentanil consumption, emergence time, or characteristics during post-anaesthesia care. This is in contrast to the data during propofol/remifentanyl anaesthesia, where we detected a decreased number of unwanted events and decreased remifentanyl consumption in the SPI-guided group.<sup>9</sup>

This effect can most likely be explained by the different application modus and the difference in pharmacokinetics. Continuous application and rapid adjustment of remifentanyl is a very appropriate method as remifentanyl is relatively context insensitive. In contrast, sufentanil has an approximate duration of action of 30 min, and therefore, bolus administration will cause large fluctuations of the effect-site concentration and titration may be much more challenging. However, guidance of sufentanil by SPI revealed no additional risk for the patient compared with standard practice in this pilot study. Further, it has to be considered that spinal mechanisms of anaesthetic-induced suppression of motor responses differ between sevoflurane and propofol.<sup>16</sup> Current data suggest a direct influence of sevoflurane on spinal motor reflex pathways, whereas induced immobility by propofol may be much more influenced by supraspinal inhibition. Therefore, comparable application of sevoflurane between the groups in the present study led to inhibition of motor responses independent from opioid guidance and thus attenuated the preventing effect for unwanted somatic events due to SPI guidance seen during propofol anaesthesia.<sup>9</sup>

We analysed time courses of SPI and HR values before and after somatic response (movement) occurred. In both groups, a significant increase in SPI and HR was detected during movement (Fig. 3). However, the increase in SPI was significantly higher than for HR. This suggests that SPI monitoring is more sensitive for detection of nociceptive–antinociceptive misbalance than monitoring HR alone and is in good agreement with previous findings where a higher sensitivity for a changing nociceptive input was reported for SPI compared with HR.<sup>7</sup> These findings raise the question, whether a simple range of

SPI values (as used in this study) or rather an analysis of the change in SPI over time is more suitable for detection of inadequate antinociception and guidance of analgesics. All patients received a single dose of neuromuscular blocking agent and therefore a possible effect in the reduction in unwanted events (movement) by SPI guidance may have been missed.

With regard to sufentanil consumption, we detected a non-significant trend towards a reduced requirement in the SPI group patients. The clinical relevance of this reduction is likely to be small, as no difference with regard to emergence or PACU data was detected. Previously, a lower consumption of remifentanil in the SPI group during propofol/remifentanil anaesthesia was described.<sup>9</sup> In comparison with sufentanil, remifentanil dose adjustment can be done more precisely due to its pharmacokinetic profile classified as ultra-short acting,<sup>25</sup> and the opioid-saving effect may therefore be less pronounced by using sufentanil. In the SPI-guided group, we detected an earlier and more pronounced increase in SPI values in comparison with HR values before the first application of sufentanil during surgery was prompted. That indicates that SPI may provide earlier detection of possible inadequate analgesia than HR. On the other hand, this relationship could not be detected before sufentanil administration in the control group patients, suggesting that sufentanil administration may not always have been appropriate at that time. This can explain the possible sufentanil-sparing effect in the SPI group.

There was no difference with regard to emergence time or PACU care between both groups. Emergence was comparable with previous results during propofol/remifentanil anaesthesia.<sup>9</sup> Even though sufentanil has a longer half-life than remifentanil, the study protocol which allowed higher BIS values during the period at the end of surgery avoided possible prolongation of emergence. Further numerical ratings of pain, use of opioids during PACU, and stay in PACU were comparable, which could be expected when anaesthesia is comparable. Whether SPI monitoring will beneficially influence pain monitoring in the PACU needs further evaluation.<sup>26</sup>

The results of the present study have some limitations. First, monitoring of nociception–antinociception balance during anaesthesia is still a challenging issue and the SPI is a novel variable. Even though it may reflect analgesic drug effect and nociceptive input,<sup>5, 7</sup> there is still uncertainty about the optimal threshold values for the SPI.<sup>27</sup> We used the same range (20–50) as described for propofol/remifentanil anaesthesia,<sup>9</sup> but our current data suggest to further include a change of SPI over time for titration of analgesics. The present study was not designed to record any effect of age on SPI. With increasing age, the incidence of cardiovascular diseases increases and monitoring analgesia by using the autonomic regulation can be altered due to neuropathy or deterioration of the central nervous system.<sup>28</sup> Therefore, the validity of the SPI in older patients needs further evaluation. Besides, a possible investigator bias and ‘learning contamination’ bias must be considered,<sup>29</sup> as a new monitoring device may lead to unintended improvement of standard clinical practice. However, the study was designed to exclude

confounding factors by predefining strict criteria for administration of sufentanil. We detected a substantial fraction of BIS values below the anticipated threshold of 40 (Table 3), indicating deeper hypnosis. However, as there were no differences between the groups, there may be no impact on the results of the study. Arterial pressure was only measured intermittently. A reliable continuous non-invasive arterial pressure measurement may provide faster information in the standard practice group and could therefore lead to faster analgesics adjustment.

In conclusion, guidance of sufentanil bolus administration by monitoring SPI was feasible and safe, but did not differ to standard practice with regard to unwanted somatic events, haemodynamic stability, sufentanil consumption, emergence, and post-anaesthesia care. This study suggests that the anaesthesia regimen has impact on the beneficial effects evoked by SPI guidance of analgesics. Further investigations are needed to gain more understanding into monitoring and guidance of nociception–antinociception balance during anaesthesia and should be performed using the change of SPI value as a trigger variable.

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## Declaration of interest

B.B. has received honoraria as a consultant and lecturer from GE Healthcare, the manufacturer of the SPI module.

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