Anesthesiology 2010; 112:1175–83

Comparison of Surgical Stress Index-guided Analgesia with Standard Clinical Practice during Routine General Anesthesia

A Pilot Study

Xinzhong Chen, M.D.,* Carsten Thee, M.D.,† Matthias Gruenewald, M.D.,† Jan Wnent, M.D.,† Christoph Illies, M.D.,† Jan Hoecker, M.D.,‡ Robert Hanss, M.D.,§ Markus Steinfath, M.D.,‖ Berthold Bein, M.D., D.E.A.A.§

ABSTRACT

Background: Surgical stress index (SSI), a novel multivariate index, has recently been proven to react well to surgical nociceptive stimuli and analgesic drug concentration changes during general anesthesia. We investigated the feasibility of application of SSI for guidance of remifentanil administration during propofol–remifentanil anesthesia.

Methods: Eighty patients scheduled for elective ear–nose–throat surgery were randomized into two groups, SSI-guided analgesia group (SSI group) and standard practice analgesia group (control group). In both groups, anesthesia was maintained with a propofol target-controlled infusion and adjusted stepwise by 0.5 μg/ml to keep bispectral index values between 40 and 60. In the SSI group, the predicted effect-site concentration of remifentanil was adjusted stepwise by 1 ng/ml to keep SSI values between 20 and 50, whereas in the control group, predicted effect-site concentration of remifentanil was adjusted according to traditional inadequate analgesia criteria. Anesthetics consumption, recovery times, and incidence of unwanted events were recorded.

Results: Remifentanil consumption (average normalized infusion rate) was lower in the SSI group than in the control group (mean ± SD, 9.5 ± 3.8 $\mu g \cdot kg^{-1} \cdot h^{-1}$ *vs.* 12.3 ± 5.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$; $P < 0.05$). The number of unwanted events was less in the SSI group (84) than in the control group (556; $P < 0.01$). Recovery times were comparable between groups. No patient reported intraoperative recall.

Conclusions: SSI-guided anesthesia resulted in lower remifentanil consumption, more stable hemodynamics, and a lower incidence of unwanted events.

What We Already Know about This Topic

- Surgical stress index (SSI), a measure obtained by photoplethysmography, reacts to the degree of surgical stimulation and to analgesic drug administration
- Whether SSI could guide analgesic drug infusion has not been tested

What This Article Tells Us That Is New

- In 80 patients for elective surgery, titration of remifentanil to SSI resulted in less remifentanil administered compared with standard titration as well as less hemodynamic instability and movement during surgery

BOTH inadequate and excessive depth of anesthesia due to inappropriate anesthetic drug delivery during general anesthesia may compromise patients' outcome.[1,2] Hence, individualizing anesthesia to minimize both over- and underdosage of anesthetic drugs during general anesthesia is a pursuit of modern anesthesiologists.

It is well known that general anesthesia mainly includes two components, hypnosis and analgesia; therefore, anesthesia is usually based on an anesthetic technique consisting of an opioid and a hypnotic (*e.g.*, remifentanil and propofol).[3,4]

A huge body of evidence[5–8] has suggested that titrating anesthetics to values derived from monitors based on processed electroencephalographic variables, such as bispectral index (BIS) and spectral entropy (M-ENTROPY; GE Healthcare Helsinki, Finland, an application of spectral entropy based on acquisition and processing of raw electroencephalogram and facial electromyogram signals by using the published entropy algorithm), may help to reduce drug consumption and shorten recovery times when compared with standard practice protocol. However, few articles[9,10] about

* Associate Professor, Department of Anaesthesiology and Intensive Care Medicine, University Hospital Schleswig-Holstein, Campus Kiel, Germany. Current position: Associate Professor, Department of Anesthesia, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, People's Republic of China. † Resident, ‡ Staff Member, § Associate Professor, ‖ Professor and Chair, Department of Anaesthesiology and Intensive Care Medicine, University Hospital Schleswig-Holstein.

Received from Department of Anaesthesiology and Intensive Care Medicine, University Hospital Schleswig-Holstein, Campus Kiel, Germany. Submitted for publication June 16, 2009. Accepted for publication December 29, 2009. GE Healthcare, Helsinki, Finland, provided the surgical stress index module. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Bein: Department of Anaesthesiology and Intensive Care Medicine, University Hospital Schleswig-Holstein, Campus Kiel, Schwanenweg 21, 24105 Kiel, Germany. bein@anaesthesie.uni-kiel.de.

titrating analgesic drugs during general anesthesia according to a specific variable are available so far.

It has been reported that excessive stress due to inadequate intraoperative analgesia results in various physiologic changes such as hemodynamic responses and endocrine "stress response," which thereby may influence patients' outcome, length of hospital stay, and overall costs of hospital care.[11–13] Analgesics such as opioids may blunt the stress response during surgery by reducing the transmission of peripheral nociceptive stimuli to the central nervous system, preventing spinal reflexes and disrupting the complex pathways in the autonomic nervous system.[14] To achieve an appropriate level of analgesia during general anesthesia, a number of attempts[10,15,16] have been made to develop certain variables assessing the "depth of analgesia" or, perhaps more accurately, the "balance of nociception–antinociception." Several surrogate measures, such as heart rate (HR) variability, the difference between response (RE) and state entropy (SE), and the amplitude of the photoplethysmography have been studied for monitoring the depth of analgesia or balance of nociception–antinociception,[4,10,17] but the results have been disappointing.

Surgical stress index (SSI), a novel multivariate index based on the sum of the normalized pulse beat interval (PBI) and the photoplethysmography, has been shown to react well to surgical nociceptive stimuli and analgesic drug concentration changes during propofol–remifentanil anesthesia,[15] suggesting that the SSI may be used for guiding the administration of analgesics during general anesthesia. Struys *et al.*[18] proved that SSI seemed to be a better measure of the nociception–antinociception balance than SE, RE, HR, or photoplethysmography. However, no study about using the SSI to guide analgesic administration during general anesthesia has been reported so far.

This clinical utility study was designed to investigate the effect of using the SSI for guidance of remifentanil administration on recovery times, the incidence of unwanted events such as hypertension, movement, tachycardia, and the remifentanil and propofol consumption during propofol–remifentanil anesthesia during a constant hypnotic level in patients undergoing ear–nose–throat surgery. We hypothesized that first, SSI-guided remifentanil administration results in more stable hemodynamics, less consumption of remifentanil, and shorter recovery times and second, SSI may react well to the intensity of stimuli such as intubation and painful manipulation during surgery.

Materials and Methods

Before Induction of Anesthesia

With the approval of the institutional review board of the University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany and with written informed consent, 80 patients American Society of Anesthesiologists physical status I-II, aged 18–70 yr, scheduled for elective ear–nose–throat surgery expected to last at least 1 h, were randomized into one of the two study groups: SSI-guided analgesia group (SSI group) and standard practice analgesia group (control group). Among the patients enrolled, there were patients undergoing septorhinoplasty (n = 10), septoplasty and sinonasal surgery (n = 12), tympanoplasty (n = 25), parotidectomy (n = 10), neck dissection (n = 14), and finally patients undergoing endoscopic laser resection of laryngeal cancer (n = 9). There were no differences between groups with respect to type and number of procedures enrolled. A computer-generated randomization sheet was used for grouping. Exclusion criteria included history of central nervous system disease (*e.g.*, neurologic disorders, head injury, and seizure disorders), chronic use of psychoactive medication or abuse of alcohol or illicit drugs, and any clinically significant cardiovascular, renal, hepatic, or endocrinologic disorders. Further, patients who showed hemodynamics that would have qualified for being considered as "unwanted event" already at baseline (60 mmHg $<$ mean arterial pressure (MAP) $>$ 100 mmHg or $45 \cdot \text{min}^{-1} > \text{HR} > 90 \cdot \text{min}^{-1}$) were not enrolled. Anesthesia in all patients was supervised by an experienced staff anesthesiologist.

All patients were premedicated with 20–30 mg of dipotassium chlorazepate the evening before and 3.75–7.5 mg of midazolam orally 30 min before the surgery. On arrival in the operating theater, an intravenous catheter was inserted into a larger forearm vein and standard monitoring including noninvasive blood pressure, five-lead electrocardiogram, and pulse oximetery (Spo_2) (S/5® monitor; GE Healthcare) were applied. All patients in both groups were monitored with BIS and SSI. After the skin of the forehead had been degreased with alcohol, BIS® electrodes (BIS® Sensor; Aspect Medical Systems, Natick, MA) were positioned as recommended by the manufacturer and electrode impedance was kept below 7.5 kΩ as required by the manufacturer to ensure optimal contact. SSI monitoring shared the same sensor of pulse oximetry that was clamped on the index finger. The calculation of the SSI was done by 10 s intervals and described elsewhere.[15] Briefly,[18] the PBI from the pulse plethysmography and the plethysmographic photoplethysmography were automatically detected, and the PBI and photoplethysmography time series were extracted. The PBI and photoplethysmography were then normalized, called PBI_{norm} and photoplethysmography$_{\text{norm}}$, using the individual patient's HR and photoplethysmography data history, and the *a priori* PBI and photoplethysmography data distribution was obtained by pooling data from a large adult patient group. This normalization procedure adjusts the individual values so that they are in a scale between 0 and 100 after normalization. As such, the SSI is calculated as

$$\text{SSI} = 100 - (0.33 \cdot \text{PBI}_{\text{norm}} + 0.67 \cdot \text{PPGA}_{\text{norm}})$$

where PBI_{norm} represents the normalized PBI and photoplethysmography$_{\text{norm}}$ represents the normalized plethysmographic photoplethysmography.

A value of 100 represents a high stress level, and a value of 0 represents a low stress level.

Induction of Anesthesia

In all patients, anesthesia was induced with propofol and remifentanil *via* target-controlled infusion pumps (Asena® Alaris; Cardinal Health, Basingstoke, United Kingdom). The pharmacokinetic models introduced by Schnideret *et al.*[19] and Mintoet *et al.*[20] were used for propofol and remifentanil, respectively. The predicted effect-site concentration of propofol (PEC_{prop}) initially started at 4 μg/ml and that of remifentanil (PEC_{remi}) started at 4 ng/ml. After loss of consciousness (LOC), oxygen was given by facemask, and the patients received 0.6 mg/kg of rocuronium. The trachea was then intubated, and the lungs were ventilated to an end-tidal carbon dioxide concentration of 35 mmHg. Immediately after intubation, the PEC_{prop} was adjusted by 0.5 μg/ml step wisely with 4-min intervals to maintain BIS level at 40–60 (the minimum allowed PEC_{prop} was 2 μg/ml), and the PEC_{remi} was not adjusted until the start of the surgical procedure.

Maintenance of Anesthesia and Hemodynamic Control

Continuous monitoring included noninvasive blood pressure, HR, ventilatory parameters, Spo_2, and end-tidal carbon dioxide.

In all patients, irrespective of the individual group assignment, both SSI and BIS values were continuously monitored. In the control group, the SSI monitor was covered with a curtain such that it is invisible to the attending anesthesiologist and the BIS® monitor (Aspect Medical Systems) was not covered, whereas in the SSI group, both SSI and BIS® monitors were uncovered.

The baseline value of noninvasive blood pressure, HR, SSI, and BIS was defined as the average of three consecutive measurements immediately after the patient's arrival in the operating theater. These values were recorded every 2.5 min and at some major time points, such as LOC, tracheal intubation, start of surgery, maximum stimulation during surgery (indicated by the surgeon intraoperatively), end of surgery, eyes opening, and extubation.

During maintenance of anesthesia, all patients were assessed for signs of inadequate anesthesia, hypotension, and bradycardia based on the definitions provided by previous studies (table 1).[6,21–23] Specifically, inadequate anesthesia was defined as the presence of symptoms detailed in table 1 during adequate hypnosis (BIS values ranging between 40 and 60).

Table 1. Criteria for Inadequate Anesthesia and Hypotension, or Bradycardia

Inadequate anesthesia	
Hypertension	Mean blood pressure > 120% of baseline or > 100 mmHg
Tachycardia	Heart rate > 90 beats/min
Somatic arousal	Coughing, chewing, grimacing
Somatic response	Purposeful movement
Hypotension	Mean blood pressure < 80% of baseline or < 60 mmHg
Bradycardia	Heart rate < 80% of baseline or < 45 beats/min

In both groups, PEC_{prop} was adjusted by 0.5 μg/ml step wisely to maintain BIS values in the predefined range.

In the control group, inadequate anesthesia was treated by increasing the PEC_{remi} by 1 ng/ml step wisely until the maximum allowed concentration of 15 ng/ml. If this was judged insufficient, 10 mg of urapidil was given intravenously. Hypotension was treated initially by speeding intravenous infusion, then PEC_{remi} was decreased by 1 ng/ml step wisely until the minimum concentration of 4 ng/ml, and finally, 0.5 ml Akrinor® (an intravenous vasopressor; AWD Pharma, Dresden, Germany; 1 ml contains 100 mg of cafedrine and 5 mg of theodrenaline) was given intravenously. Atropine (0.5 mg) was used for bradycardia.

In the SSI-guided analgesia group, PEC_{remi} was adjusted to keep the SSI values at 20–50 by increasing or decreasing 1 ng/ml step wisely (PEC_{remi} range was also limited between 4 and 15 ng/ml). In the case of $20 < SSI < 50$, inadequate anesthesia was treated as follows: 10 mg of urapidil was administered intravenously for hypertension, 0.5 ml of Akrinor intravenously for hypotension, and 0.5 mg of atropine intravenously for bradycardia. A rescue medication was allowed (propofol bolus of 0.5 mg/kg) if somatic arousal or a somatic response occurred, despite BIS and SSI values within the predefined range.

Recovery Period

To facilitate rapid emergence from anesthesia, 15 min before the expected end of surgery, PEC_{prop} was reduced in all the patients and a BIS value of more than 60 but less than 65 was allowed, whereas the PEC_{remi} remained unchanged until the end of surgery. All patients received 0.1 mg/kg of the opioid piritramide for postoperative analgesia. Both propofol and remifentanil target-controlled infusions were discontinued at the end of surgery. The end of surgery was defined as the final surgical suture. Emergence from anesthesia was assessed by measuring the time to spontaneous opening of eyes and time to extubation.

Postoperative care in the recovery room was supervised by a nurse who was blinded to the study protocol. In the recovery room, the modified Aldrete-Score, postoperative nausea and vomiting, and pain using a 0–100 numerical pain intensity rating scale were recorded. On the first postoperative day, all patients were asked by a blinded investigator if they had any memory or awareness during anesthesia, and the level of satisfaction with the whole procedure was sought using a 0–100 scale (0 means the worst satisfaction and 100 means best satisfaction).

Endpoints and Statistical Analysis

This trial was planned as a pilot study, and no data with respect to the influence of SSI guidance on the conduct of anesthesia were available. The primary endpoint of this study was defined as the number of episodes of inadequate anesthesia. A sample size of 80 was chosen based on a previous

study[6] that found a difference with respect to the incidence of "unwanted events" between an SE-guided propofol administration and a control group. Secondary endpoints were differences in P_k values of SSI, BIS, mean blood pressure, and HR for predicting hypnotic state and the balance of nociception–antinociception: awake *versus* LOC, anesthesia (recorded at the discontinuation of propofol and remifentanil infusion) *versus* opening eyes, LOC *versus* intubation, and normal stimulation (recorded at 5 min before maximum stimulation) *versus* maximum stimulation, respectively.

GraphPad Prism software (Version 4.0; GraphPad Software Inc., San Diego, CA) was used for statistical analysis. For numerical data, statistical analysis was performed with Student *t* test (for normally distributed data) and Mann–Whitney *U* test (for nonnormally distributed data) or one-way ANOVA with Student–Newman–Keuls test (for multiple comparisons); for nominal data, statistical analysis was performed by means of a χ^2 test. Ce_{remi} and Ce_{prop} values as well as SSI and BIS values between groups were analyzed using a two-way ANOVA factoring for time and group assignment followed by Bonferroni correction to account for multiple comparisons.

Prediction probabilities were calculated to compare the performance of SSI, BIS, mean blood pressure, and HR using P_kMACRO and P_kDMACRO spreadsheets as described by Smith *et al.*[24] The jackknife method was used to compute the SE of the estimate. A value of $P_k = 1$ or 0 means a 100% correct prediction of a certain clinical state or other state by a specific monitor, whereas a value of 0.5 means only a 50:50 chance.

By applying Probit analyses, the BIS level at which 95% (ED_{95}) patients reached LOC or emergence from anesthesia and the SSI level at which reached 95% (ED_{95}) patients during extensive stimulation (we analyzed two time points: intubation and maximum stimulation that were defined by the surgeon intraoperatively) were calculated. The emergence time between groups was compared using Kaplan–Meier log-rank survival analysis (calculating the cumulative probability of patients remaining unconscious after discontinuation of the anesthetic drugs).

All tests were two tailed with statistical significance defined as $P < 0.05$.

Table 2. Demographic Data

	SSI Group (n = 40)	Standard Practice (n = 40)
Age, yr	47 ± 17	46 ± 17
Height, cm	173 ± 18	171 ± 93
Weight, kg	78 ± 12	75 ± 17
Gender-M/F (n)	13/27	21/19
ASA I/II (n)	18/22	19/21
Duration of anesthesia, min	152 ± 67	173 ± 84
Duration of surgery, min	109 ± 61	132 ± 81
Intubation to start of surgery, min	24 ± 8	25 ± 10

Values are given as mean ± SD or absolute numbers. No difference between groups.
ASA = American Society of Anesthesiologists; SSI = surgical stress index.

Table 3. Time Fractions of Actual SSI and BIS Values during Anesthesia

	SSI Group (n = 40)	Standard Practice (n = 40)
SSI < 20, %	12 ± 6*	24 ± 8
SSI > 50, %	4 ± 2*	12 ± 5
20 < SSI < 50, %	83 ± 9*	63 ± 8
BIS < 40, %	30 ± 5	24 ± 5
BIS > 60, %	9 ± 4	5 ± 3
40 < BIS < 60, %	73 ± 10	77 ± 10

Data are given as mean ± SD.
* $P < 0.05$, compared with standard analgesia practice group.
BIS = bispectral index; SSI = surgical stress index.

Results

All 80 patients (40 patients in each group) enrolled in this study were included in the final analysis. There were no differences in patients' demographic data such as age, weight, height, duration of anesthesia, duration of surgery, and duration from intubation to start of surgery between groups (table 2).

Recovery Times and Anesthetics Consumption

There was no difference with respect to time to open eyes between groups (mean ± SD, 8.9 ± 4.3 *vs.* 10.6 ± 4.3 min; $P > 0.05$; table 3). A Kaplan–Meier survival analysis (fig. 1) shows the cumulative percentage of patients who remained unconscious after discontinuation of propofol and remifentanil infusion, indicating that the awakening course of both groups was similar ($P > 0.05$).

Remifentanil consumption (average normalized infusion rate calculated from induction to discontinuation of anes-

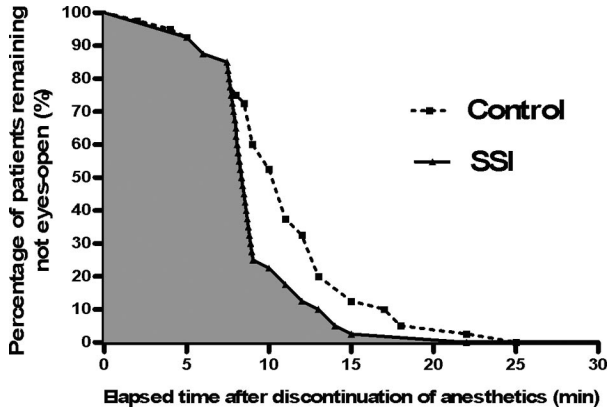

Fig. 1. Cumulative probability of patients remaining unconscious (before opening eyes) after discontinuation of anesthetics (propofol and remifentanil) infusion in the surgical stress index (SSI) group (*filled triangle*; *shaded area*) or the control group (*filled square*; *shaded area*) using Kaplan–Meier survival analysis. Log-rank differences were not statistically significant between groups. $P > 0.05$.

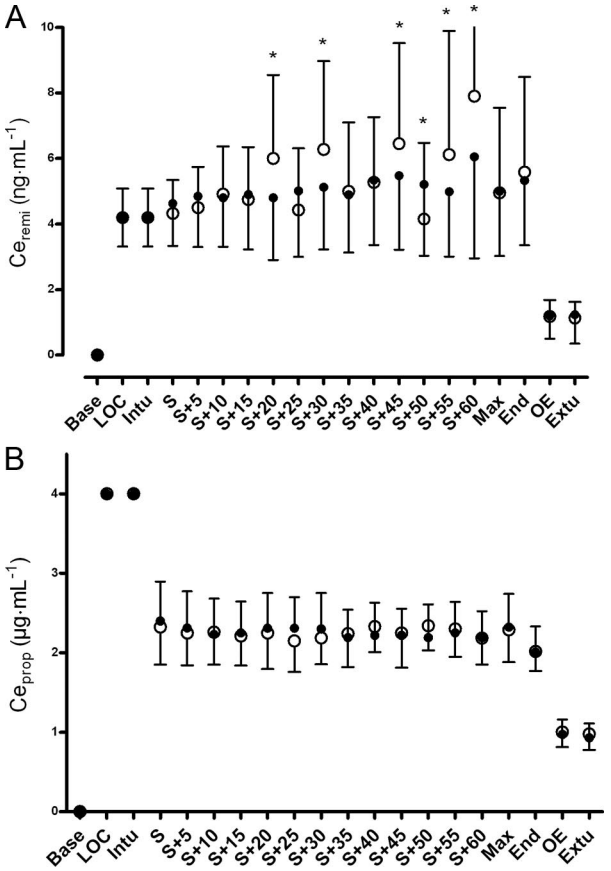

Fig. 2. Changes in predicted effect-site concentrations of remifentanil (*A*) and propofol (*B*) (Ce_{remi} and Ce_{prop}, respectively) in the surgical stress index group (*filled circle*) or the control group (*open circle*) at certain time points during anesthesia: baseline (base), loss of consciousness (LOC), intubation (intu), start of surgery (S), maximum stimulation (max), discontinuation of propofol and remifentanil (end), eyes opening (OE), and extubation (extu). Values are given as mean (SD); * $P < 0.05$ compared with the control group.

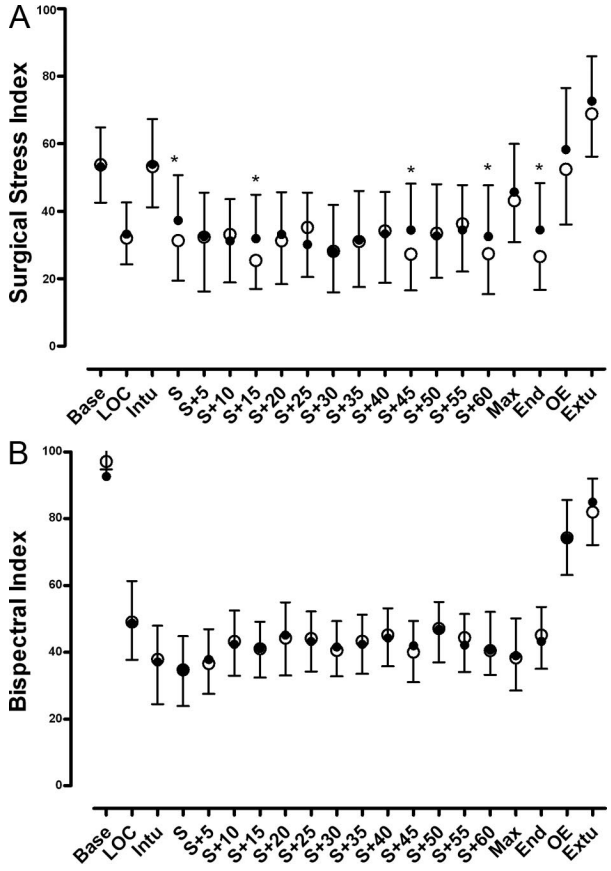

Fig. 3. Changes in surgical stress index (SSI) (*A*) and bispectral index (*B*) values in the SSI group (*filled circle*) or the control group (*open circle*) at certain time points during anesthesia: baseline (base), loss of consciousness (LOC), intubation (intu), start of surgery (S), maximum stimulation (max), discontinuation of propofol and remifentanil (end), eyes opening (OE), and extubation (extu). Values are given as mean (SD); * $P < 0.05$ compared with the control group.

thetics, which refers to total anesthetic dose/duration of anesthesia/weight) was significantly lesser in the SSI group than in the control group (mean ± SD, 9.5 ± 3.8 *vs.* 12.3 ± 5.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$; $P < 0.05$), whereas propofol consumption (average normalized infusion rate) was comparable between groups (mean ± SD, 5.3 ± 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ in the SSI group *vs.* 5.6 ± 1.5 $mg \cdot kg^{-1} \cdot h^{-1}$ in the control group; $P > 0.05$).

The PEC_{remin} at five time points was lower and at one time point was higher in the SSI group compared with that at corresponding time points in the control group ($P < 0.05$; fig. 2A), whereas the PEC_{prop} was comparable at all major time points between groups ($P > 0.05$; fig. 2B). The maximum-reached remifentanil plasma target concentration in both groups was 10 ng/ml.

SSI and BIS Values during Anesthesia

Both SSI and BIS values were collected in all patients, irrespective of the individual group assignment. At certain time points during anesthesia, SSI values were higher in the SSI analgesia group than that at the corresponding time points in the control group ($P < 0.05$; fig. 3A), whereas the BIS values were comparable at all major time points during anesthesia between groups ($P > 0.05$; fig. 3B).

In addition, we analyzed the time fractions of actual SSI or BIS values collected during maintenance of anesthesia: the time fractions of actual SSI value of less than 20 and more than 50 were significantly lower in the SSI group than in the control group (12.4 *vs.* 24.4% and 4.3 *vs.* 12.1%; $P < 0.05$). And the time fractions of SSI value of $20 < SSI < 50$ were significantly higher in the SSI group than that in the control group (83.2 *vs.* 62.8%; $P < 0.01$). In contrast, the time fractions of BIS values of less than 40, more than 60, and $40 < BIS < 60$ were comparable between groups (30.0 *vs.* 23.7%, 8.7 *vs.* 5.2%, and 72.7 *vs.* 76.9%, respectively; $P > 0.05$; table 3).

Performance of SSI, BIS, HR, and Blood Pressure in Predicting Nociception–Antinociception Balance and Depth of Hypnosis

For predicting LOC, only the BIS had a P_k value more than 0.90. The P_k value of the SSI was similar to that of BIS (0.88 *vs.* 0.90; $P > 0.05$), whereas the P_k values of both MAP and

Table 4. Prediction Probabilties (P_k) of Different Variables

	SSI	BIS	MAP	HR
Awake *vs.* LOC				
All patients (n = 80)	0.88 ± 0.03	0.91 ± 0.02	0.78 ± 0.04*†	0.60 ± 0.05*†‡
SSI group (n = 40)	0.92 ± 0.03	0.90 ± 0.03	0.75 ± 0.06	0.57 ± 0.07
Standard practice (n = 40)	0.83 ± 0.05	0.91 ± 0.03	0.82 ± 0.05	0.62 ± 0.06
LOC *vs.* intubation				
All patients (n = 80)	0.87 ± 0.03	0.60 ± 0.05*	0.69 ± 0.04*	0.65 ± 0.04*
SSI group (n = 40)	0.85 ± 0.04	0.61 ± 0.07	0.67 ± 0.06	0.62 ± 0.07
Standard practice (n = 40)	0.91 ± 0.03	0.57 ± 0.06	0.70 ± 0.06	0.68 ± 0.06
Normal *vs.* max stimulation				
All patients (n = 80)	0.85 ± 0.03	0.54 ± 0.05*	0.60 ± 0.05*	0.51 ± 0.05*
SSI group (n = 40)	0.90 ± 0.04	0.54 ± 0.07	0.58 ± 0.07	0.52 ± 0.07
Standard practice (n = 40)	0.82 ± 0.05	0.55 ± 0.07	0.61 ± 0.06	0.50 ± 0.07
Anesthesia *vs.* eye opening				
All patients (n = 80)	0.81 ± 0.04	0.95 ± 0.02*	0.84 ± 0.03†	0.76 ± 0.04†
SSI group (n = 40)	0.83 ± 0.05	0.95 ± 0.02	0.81 ± 0.05	0.82 ± 0.05
Standard practice (n = 40)	0.80 ± 0.05	0.93 ± 0.03	0.88 ± 0.04	0.71 ± 0.06

The comparisons of P_k values between groups were performed only on pooled data of both groups. No differences were found between groups for all parameters.

* $P < 0.01$ compared with surgical stress index (SSI). † $P < 0.01$ compared with bispectral index (BIS). ‡ $P < 0.01$ compared with mean arterial pressure (MAP).

HR = heart rate; LOC = loss of consciousness; Max stimulation = maximum operative stimulation.

HR were significantly lower (0.78, 0.60 *vs.* 0.90, 0.88; $P < 0.01$; table 4).

For indicating the state of intubation, the P_k value of the SSI was the highest among SSI, BIS, MAP, and HR (0.87 *vs.* 0.60, 0.69, 0.65; $P < 0.01$).

For indicating the state of the maximum stimulation during surgery, the P_k value of the SSI was also the highest among SSI, BIS, mean blood pressure, and HR (0.85 *vs.* 0.54, 0.60, 0.51; $P < 0.01$).

For predicting emergence from anesthesia (eyes opening), the P_k value of the BIS was the highest among BIS, SSI, MAP, and HR (0.95 *vs.* 0.81, 0.84, 0.76; $P < 0.01$).

In addition, the BIS value corresponding to the 95% possibility for LOC was 40 (95% CI, 18–48; fig. 4A) and for emergence from anesthesia was 75 (95% CI, 71–81; fig. 4B). The SSI value corresponding to the 95% possibility for the patient to be intubated was 59 (95% CI, 53–70; fig. 5A) and for the maximum stimulation during surgery was 60 (95% CI, 49–91; fig. 5B).

Number of Unwanted Events

Patients in the standard analgesia group had significantly more episodes of hypertension (84 *vs.* 11, $P < 0.01$), hypotension (67 *vs.* 5, $P < 0.01$), bradycardia (111 *vs.* 23, $P < 0.01$), movement (14 *vs.* 3, $P < 0.01$), and total unwanted events (278 *vs.* 42, $P < 0.01$; table 5). However, we could not find any difference in mean blood pressure and HR at all major time points between groups. Frequency and doses of drugs used for treatment of unwanted events such as atropine (a total of three times and 1.5 mg in the SSI group, and four times and 2 mg in the control group) and Akrinor (two times and 1 ml in the SSI group *vs.* three times and 1.5 ml in the control group) during anesthesia maintenance were not significantly different between groups ($P > 0.05$), and no patient in both groups received urapidil.

Postoperative Period

Postoperative pain, nausea and vomiting, modified Aldrete-Score, and total satisfaction in the recovery room and on the

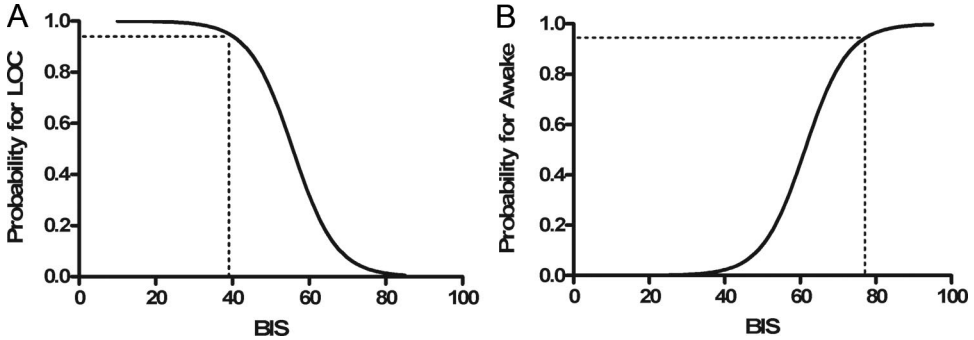

Fig. 4. Logistic regression curves. The probabilities for loss of consciousness (LOC) from awake (*A*) and emergence or awake from anesthesia (*B*) are shown as a function of bispectral index (BIS) values. *Dotted lines* indicate 95% probability.

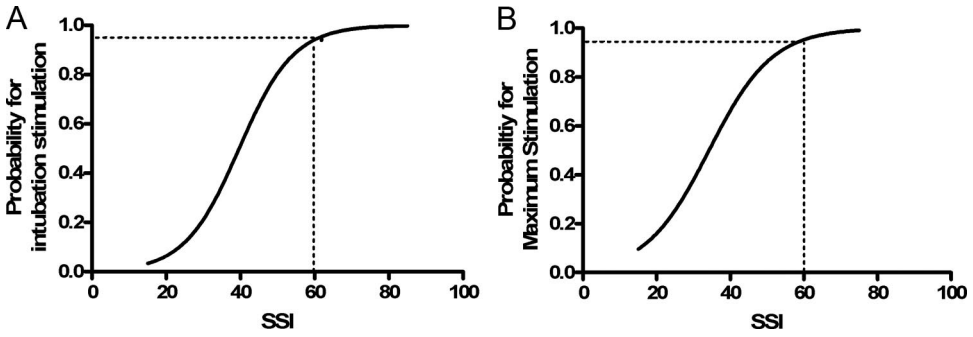

Fig. 5. Logistic regression curves. The probabilities for intubation stimulation (*A*) and maximum stimulation during operation (*B*) are shown as a function of surgical stress index (SSI). *Dotted lines* indicate 95% probability.

first day after operation are given in table 6. There were no significant differences in the intensity of postoperative pain on a visual analog scale, postoperative nausea and vomiting, modified Aldrete score, level of total satisfaction, and physiologic parameters ($P > 0.05$). No patient reported intraoperative recall.

Discussion

The main findings of our prospective, randomized, controlled study are as follows: first, SSI-guided remifentanil titration resulted in a significant reduction of remifentanil consumption and less incidence of unwanted events (hypertension, hypotension, tachycardia, and movement) during surgery when compared with standard practice protocol; second, SSI showed the highest prediction probability for indicating maximum stimulation during surgery.

Till now, many efforts have been made to develop a method to guide analgesic administration during general anesthesia. In a previous study, Mathews *et al.*[10] found that remifentanil titration guided by the difference between RE and SE (RE-SE) during general anesthesia resulted in more stable hemodynamics and a clinically acceptable emergence time. However, the incidence of patient movement was high and they did not investigate remifentanil consumption during anesthesia. Recently, our group[6] evaluated the effect of RE-SE–guided remifentanil titration on remifentanil consumption and found that this titration resulted in lower remifentanil consumption when compared with the standard practice group during propofol–remifentanil anesthesia. However, in that study, propofol infusion was controlled by SE in the SE-RE–guided group, whereas there was no guiding monitor for propofol infusion in the standard practice group. Furthermore, RE-SE difference itself has not been validated to reflect the balance of nociception–antinociception.

BIS is a well-accepted tool to monitor the hypnotic level, and BIS-guided anesthesia has been proved to reduce the risk of awareness during general anesthesia.[25,26] A BIS value of 40–60 has been recommended as an "ideal" range.[26–28] Therefore, in this study, we chose a range of $40 < \text{BIS} < 60$ for guiding propofol titration to keep hypnosis at a constant depth in both the groups.

In our study, the consumption of remifentanil (averaged normalized infusion rate) was significantly lower in the SSI-guided analgesia group when compared with the standard analgesia practice group. This might be explained initially by the higher performance of SSI in assessing the nociception–antinociception balance. It has been shown previously that SSI correlates positively to surgical nociceptive stimuli and negatively to analgesic drug concentration during propofol–remifentanil anesthesia[15] Moreover, the performance of SSI in measuring nociception–antinociception balance was found to be superior to SE, RE, blood pressure, HR, and photoplethysmography.[18,29] In accordance with these find-

Table 5. Number of Unwanted Events during the Intraoperative Period

	SSI Group (n = 40)	Standard Practice (n = 40)
Hypertension	11 (0.28)*	84 (2.1)
Hypotension	5 (0.13)*	67 (1.68)
Tachycardia	0 (0)	2 (0.05)
Bradycardia	23 (0.57)*	111 (2.78)
Movements	3 (0.08)*	14 (0.35)
Total unwanted events	42 (1.05)*	278 (6.95)

Data are numbers of unwanted events during surgery. Data in parentheses are numbers of unwanted events per patient.

* $P < 0.01$ when compared with standard analgesia practice group.

SSI = surgical stress index.

Table 6. Postoperative Data

	SSI Group (n = 40)	Standard Practice (n = 40)
Aldrete Score	6.3 (2–10)	6.2 (2–10)
VAS (pain)	4.2 (1–10)	4.3 (1–10)
PONV	12 (30%)	14 (35%)
Satisfaction	95 (80–100)	93 (75–100)

Satisfaction was graded by a scale from 0 to 100, 0 means worst level and 100 means the highest level. Data are median (range) or numbers (proportion). No differences between groups.

Aldrete Score = modified Aldrete Score; PONV = postoperative nausea and vomiting; SSI = surgical stress index; VAS = Visual Analogue Scale, scaled from 0 to 10 (0 means no pain and 10 means the maximum intensity of pain).

ings, we found that the prediction probability (P_k) for SSI to predict the maximum surgical stimulation was superior to blood pressure and HR. In this study, the time fractions of $20 < SSI < 50$ were significantly higher and of $SSI > 50$ or < 20 were lower in the SSI-guided group than in the standard analgesia group.

Interestingly, although remifentanil consumption was higher and SSI values were generally lower in the standard practice group, suggesting a kind of overdosing, the incidence of hypertension and movement was even higher in the standard group, suggesting underdosing. This sounds counterintuitive at first. However, the incidence of hypotension and bradycardia was also higher in the standard group, which also indicates overdosing. With respect to remifentanil plasma concentration, the PEC_{remi} at certain time points was either significantly higher or lower in the standard practice group compared with the SSI-guided group. Consequently, we suggest that the SSI-guided remifentanil titration resulted in more stable hemodynamics and traditional standard practice resulted in a somehow "roller coaster"-like hemodynamics, where episodes of underdosing resulting in hypertension were responded by overdosing resulting in hypotension.

In this study, the choice of the range of SSI between 20 and 50 ($20 < SSI < 50$) for guiding remifentanil titration might be criticized because an optimal range of SSI during anesthesia has not been recommended yet.[29] However, a previous study[18] showed that SSI values were around 20 at baseline without simulation and PEC_{remi} was at a high level, and SSI values were more than 50 after stimulation when the PEC_{remi} was at a lower level. In this study, the feasibility of the range of $20 < SSI < 50$ used for guiding analgesic titration during general anesthesia might also be justified, at least to some extent, by the fact that hemodynamics were more stable (low incidence of hypertension, hypotension, and bradycardia) and lower movement episodes in the SSI-guided analgesia group when compared with the standard analgesia group. In addition, we analyzed the SSI value obtained with 95% possibility after intubation and after the maximum surgical stimulation using Probit analyses. The results showed that the SSI value corresponding to the 95% possibility for intubation stimulus was 59 and for the maximum surgical stimulation was 60, which may further support retrospectively our choice of the range of $20 < SSI < 50$ for the guidance of analgesic administration during general anesthesia. However, whether the range of $20 < SSI < 50$ is ideal needs to be further investigated by more clinical studies.

Interestingly, SSI seemed to be able to predict LOC (P_k was 0.83) and emergence from anesthesia (P_k was 0.80) in our study. Although no surgical or other nociceptive stimuli existed before anesthesia, patients were under extensive stress state due to mental anxiety. Consequently, the SSI values were higher at baseline than at LOC. Second, after discontinuation of anesthetics, the nociceptive stimuli resulting from endotracheal tube and operative tissue injury still existed whereas the PEC_{remi} was decreased. Thus, the balance of nociception–antinociception was probably changed to the left side, and SSI values increased. However, whether the SSI has ability in measuring hypnotic level during general anesthesia cannot be concluded yet based on the results of our study.

This study has the following limitations. First, it might be argued with the question of investigator bias in the standard analgesia practice group. Of course, "learning contamination" bias[30] must be addressed as a problem of unintended improvement of standard clinical practice patterns happened with the introduction of a new monitor device, thereby reducing the difference of results in a randomized trial.[21] However, in this study, the protocol of analgesia was strictly predetermined in both groups. More importantly, in the standard analgesia practice group, the adjustment of PEC_{remi} was clearly defined. Almost all the endpoints for adjustment of remifentanil titration were quantified, for example, increasing PEC_{remi} at MAP more than 100 mmHg or HR more than 90 or movement, and decreasing PEC_{remi} at MAP less than 60 or HR less than 45. Therefore, significant investigator bias can be obviously excluded as a confounding factor for the explanation of our results.

Second, MAP was measured intermittently in our study. MAP values collected may not reflect every episode of inadequate anesthesia because most of the episodes, for example, movement, maximum surgical stimulation, have a short duration and last only for some seconds. Therefore, if MAP had been measured continuously, the MAP values probably would have reacted more timely to changes in nociception. Unwanted events that served as signs of inadequate analgesia might also have been detected earlier compared with intermittent MAP measurement. Therefore, continuous invasive blood pressure recording combined with clinical signs of inadequate analgesia might be as good as SSI in predicting the nociception–antinociception balance.[29]

In conclusion, SSI-guided analgesia resulted in lower remifentanil consumption, more stable hemodynamics, lower incidence of unwanted events, and comparable recovery times when compared with standard clinical analgesia practice. Furthermore, we also found that SSI had better performance in detecting the nociception–antinociception balance than BIS, MAP, and HR. More studies are warranted to further investigate the utility of SSI in daily clinical practice.

The authors are grateful to GE Healthcare, Helsinki, Finland, for providing the SSI module. The authors are indebted to Werner Jeckstroem, M.D. (Staff Member, Department of Anaesthesiology and Intensive Care Medicine, University Hospital Schleswig-Holstein, Campus Kiel, Germany), for his enthusiastic support.

References

1. Buhre W, Rossaint R: Perioperative management and monitoring in anaesthesia. Lancet 2003; 362:1839–46
2. Monk TG, Saini V, Weldon BC, Sigl JC: Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 2005; 100:4–10
3. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, Shafer SL: Pharmacodynamic interaction be-

tween propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, Bispectral Index, and electroencephalographic approximate entropy. ANESTHESIOLOGY 2004; 100:1353–72
4. Woodbridge PD: Changing concepts concerning depth of anesthesia. ANESTHESIOLOGY 1957; 18:536–50
5. Bruhn J, Kreuer S, Bischoff P, Kessler P, Schmidt GN, Grzesiak A, Wilhelm W: Bispectral index and A-line AAI index as guidance for desflurane-remifentanil anaesthesia compared with a standard practice group: A multicentre study. Br J Anaesth 2005; 94:63–9
6. Gruenewald M, Zhou J, Schloemerkemper N, Meybohm P, Weiler N, Tonner PH, Scholz J, Bein B: M-Entropy guidance *vs.* standard practice during propofol-remifentanil anaesthesia: A randomised controlled trial. Anaesthesia 2007; 62:1224–9
7. Recart A, Gasanova I, White PF, Thomas T, Ogunnaike B, Hamza M, Wang A: The effect of cerebral monitoring on recovery after general anesthesia: A comparison of the auditory evoked potential and bispectral index devices with standard clinical practice. Anesth Analg 2003; 97: 1667–74
8. Kalkman CJ, Drummond JC: Monitors of depth of anesthesia, quo vadis? ANESTHESIOLOGY 2002; 96:784–7
9. Bonhomme V, Llabres V, Dewandre PY, Brichant JF, Hans P: Combined use of Bispectral Index and A-Line Autoregressive Index to assess anti-nociceptive component of balanced anaesthesia during lumbar arthrodesis. Br J Anaesth 2006; 96:353–60
10. Mathews DM, Cirullo PM, Struys MM, De Smet T, Malik RJ, Chang CL, Neuman GG: Feasibility study for the administration of remifentanil based on the difference between RE and state entropy. Br J Anaesth 2007; 98:785–91
11. Myles PS, Hunt JO, Fletcher H, Watts J, Bain D, Silvers A, Buckland MR: Remifentanil, fentanyl, and cardiac surgery: A double-blinded, randomized, controlled trial of costs and outcomes. Anesth Analg 2002; 95:805–12, table of contents
12. Parker SD, Breslow MJ, Frank SM, Rosenfeld BA, Norris EJ, Christopherson R, Rock P, Gottlieb SO, Raff H, Perler BA, Williams GM, Beattie C: Catecholamine and cortisol responses to lower extremity revascularization: Correlation with outcome variables. Perioperative Ischemia Randomized Anesthesia Trial Study Group. Crit Care Med 1995; 23:1954–61
13. Roizen MF, Horrigan RW, Frazer BM: Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision—MAC BAR. ANESTHESIOLOGY 1981; 54:390–8
14. Urban BW: Current assessment of targets and theories of anaesthesia. Br J Anaesth 2002; 89:167–83
15. Ahonen J, Jokela R, Uutela K, Huiku M: Surgical stress index reflects surgical stress in gynaecological laparoscopic day-case surgery. Br J Anaesth 2007; 98:456–61
16. Rantanen M, Yli-Hankala A, van Gils M, Ypparila-Wolters H, Takala P, Huiku M, Kymalainen M, Seitsonen E, Korhonen I: Novel multiparameter approach for measurement of nociception at skin incision during general anaesthesia. Br J Anaesth 2006; 96:367–76
17. Ledowski T, Bein B, Hanss R, Paris A, Fudickar W, Scholz J, Tonner PH: Neuroendocrine stress response and heart rate variability: A comparison of total intravenous *versus* balanced anesthesia. Anesth Analg 2005; 101:1700–5
18. Struys MM, Vanpeteghem C, Huiku M, Uutela K, Blyaert NB, Mortier EP: Changes in a surgical stress index in response to standardized pain stimuli during propofol–remifentanil infusion. Br J Anaesth 2007; 99:359–67
19. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. ANESTHESIOLOGY 1998; 88: 1170–82
20. Minto CF, Schnider TW, Shafer SL: Pharmacokinetics and pharmacodynamics of remifentanil. II. Model application. ANESTHESIOLOGY 1997; 86:24–33
21. Kreuer S, Biedler A, Larsen R, Altmann S, Wilhelm W: Narcotrend monitoring allows faster emergence and a reduction of drug consumption in propofol–remifentanil anesthesia. ANESTHESIOLOGY 2003; 99:34–41
22. Garrioch MA, Fitch W: Anaesthesia for carotid artery surgery. Br J Anaesth 1993; 71:569–79
23. Gan TJ, Glass PS, Windsor A, Payne F, Rosow C, Sebel P, Manberg P: Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. BIS Utility Study Group. ANESTHESIOLOGY 1997; 87:808–15
24. Smith WD, Dutton RC, Smith NT: Measuring the performance of anesthetic depth indicators. ANESTHESIOLOGY 1996; 84:38–51
25. Myles PS, Leslie K, McNeil J, Forbes A, Chan MT: Bispectral Index monitoring to prevent awareness during anaesthesia: The B-Aware randomised controlled trial. Lancet 2004; 363:1757–63
26. Practice advisory for intraoperative awareness and brain function monitoring: A report by the American Society of Anesthesiologists task force on intraoperative awareness. ANESTHESIOLOGY 2006; 104:847–64
27. Song D, Joshi GP, White PF: Titration of volatile anesthetics using Bispectral Index facilitates recovery after ambulatory anesthesia. ANESTHESIOLOGY 1997; 87:842–8
28. Manyam SC, Gupta DK, Johnson KB, White JL, Pace NL, Westenskow DR, Egan TD: When is a bispectral index of 60 too low: Rational processed electroencephalographic targets are dependent on the sedative-opioid ratio. ANESTHESIOLOGY 2007; 106:472–83
29. Wennervirta J, Hynynen M, Koivusalo AM, Uutela K, Huiku M, Vakkuri A: Surgical stress index as a measure of nociception/antinociception balance during general anesthesia. Acta Anaesthesiol Scand 2008; 52:1038–45
30. Roizen MF, Toledano A: Technology assessment and the "learning contamination" bias. Anesth Analg 1994; 79: 410–2