

Aus der Klinik für Anästhesiologie und Operative Intensivmedizin

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im Universitätsklinikum Schleswig-Holstein, Campus Kiel,

an der Christian-Albrechts-Universität zu Kiel

**Comparison of Surgical Stress Index (SSI)
Guided-analgesia and Standard Clinical
Practice during Routine General
Anaesthesia: a Pilot Study**

Inauguraldissertation

zur

Erlangung der Doktorwürde

der Medizinischen Fakultät

der Christian-Albrechts-Universität zu Kiel

vorgelegt von

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Kiel 2009

- | | |
|-------------------------------|-------------------------|
| 1. Berichterstatter: | Priv. –Doz. Dr. Bein |
| 2. Berichterstatter: | Prof. Dr. med. Ambrosch |
| Tag der muendlichen Pruefung: | 6. Oktober 2009 |
| Zum Druck genhmt, Kiel, den | 6. Oktober 2009 |

Gez.: Prof. Dr. Heller

(Vorsitzender der Pruefungskommission)

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List of abbreviations

ACTH	Adrenocorticotrophic Hormone
BIS	Bispectral Index
EEG	Electroencephalography
HR	Heart Rate
LOC	Loss of Consciousness
NIBP	Non-invasive Blood Pressure
NRS	Numerical Rating Scale
OE	Opening Eyes
HBI	Heart Beat Interval
PEC _{prop}	Predicted Effect-site Concentration of Propofol
PEC _{remi}	Predicted Effect-site Concentration of Remifentanyl
P _k	Prediction Probability
PPGA	Pulse Plethysmographic Wave Amplitude
RE	Response Entropy
SE	State Entropy
RE-SE	Difference between Response Entropy and State Entropy
SpO ₂	Peripheral Oxygen Saturation (Pulse Oximetry)
SSI	Surgical Stress Index
TCI	Target Controlled Infusion
TOF	Train – of – Four

1. Introduction

1.1 Background

Both inadequate and excessive depth of anaesthesia due to inappropriate anaesthetic drugs delivery during general anaesthesia may compromise patients' outcome (Bruhn et al., 2006; Buhre and Rossaint, 2003; Monk et al., 2005). Hence, individualizing anaesthesia to minimize both over- and underdosage of anaesthetic drugs administration during general anaesthesia is the pursuit of modern anaesthetic practice.

To reach an appropriate anaesthetic drug delivery, the most important issue is to use indicator(s) that can monitor accurately depth of anaesthesia to guide titrating anaesthetics during general anaesthesia. In routine clinical practice, the dosage of anaesthetic drugs is usually adjusted according to the patient's cardiovascular and vegetative response to surgical stimuli, such as blood pressure, heart rate, sweating, tear production (Buhre and Rossaint, 2003) and movement. However, the vegetative response to surgery is affected by many confounding factors such as α or β agonists or blockers used during surgery and is extremely changeable in the individual patient (Struys et al., 2002). Patient movement in response to noxious stimulation remains an important sign of inadequate depth of anaesthesia, but is also unreliable and is suppressed by muscle relaxants (Sandin et al., 2000). Therefore, continuing efforts have been taken by anesthesiologists to try to develop more reliable methods for monitoring depth of anaesthesia. So far some methods have been proposed and tested for assessing the depth of anaesthesia, which include mainly electroencephalogram(EEG)-derived variables such as spectral edge frequency 95 (SEF95), median power frequency, approximate entropy and bispectral index (BIS), auditory-evoked potential (AEP), and heart-rate variability (HRV).

It is well known that general anaesthesia is a state of unconsciousness induced by

anaesthetic agents and includes three components, hypnosis (loss of consciousness), analgesia (pain relief) and immobilization. It is difficult or impossible to measure all the three components with one variable. A variety of variables have been proposed to monitor depth of hypnosis. Most of them are EEG-derived variables, such as BIS (Bispectral Index Monitor, Aspect Medical Inc., Newton, MA, USA), the Narcotrend index (Narcotrend Monitor, Schiller AG, Baar, Switzerland), State and Response Entropy (GE Healthcare Finland, Helsinki, Finland) and AEP (A-line AEP monitor, Danmeter, Odense, Denmark), which are the most established monitors and have been proved to offer mainly information about the hypnotic state, but have limited efficacy in measuring adequacy of analgesia of the patient during general anaesthesia (Bruhn et al., 2003); (Glass et al., 1997; Struys et al., 2002). Some recent studies have suggested that use of these monitors for guidance of anaesthetics delivery could allow exact dosage of anaesthetic drugs (hypnotics), improve early recovery from anaesthesia, and decrease the frequency of unwanted events during general anaesthesia (Aime et al., 2006; Bruhn et al., 2005; Gruenewald et al., 2007; Vakkuri et al., 2005).

Analgesia is defined as the relief of pain, in other words, as absence of pain in response to stimulation that would normally be painful (Guignard, 2006). However this definition is subjective because the pain itself is a subjective sensation and is a descriptor of a conscious, emotional, private experience induced by a wide variety of events such as surgical damage. During general anaesthesia, the conscious experience of pain disappears. Therefore, in an anesthetized patient it is not appropriate to call the physiological reaction to tissue injury by surgery as “pain”. Some authors (Rantanen et al., 2006; Struys et al., 2007) used an alternative term of “nociception” to substitute the term of “pain” during general anaesthesia in their papers. The term “nociception” covers all activity caused by tissue damage from the peripheral sensory afferent to the brainstem level, where nociception may become apparent as cardiovascular or hormonal responses (Desborough, 2000; Yaksh, 1998).

It is well accepted that excessive intraoperative stress (nociception) results in various physiological changes such as immunological and haemodynamic changes or endocrine 'stress response', which thereby may influence patients' outcome, length of hospital stay, and overall costs of hospital care (Myles et al., 2002; Parker et al., 1995; Roizen et al., 1981). On the other hand, 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 (Urban, 2002). Therefore, to achieve an appropriate balance of nociception – anti-nociception during general anaesthesia is an important issue.

Similar to the depth of anaesthesia, achieving an appropriate depth of analgesia (anti-nociception) depends on accurate assessing of the balance of nociception – anti-nociception which then could be used for guiding analgesic delivery during general anaesthesia.

Numerous of methods have been proposed for assessing the balance of nociception – anti –nociception during general anaesthesia. More commonly used methods are based on isolated, unspecific autonomic reactions, such as the presence or absence of hypertension, tachycardia, or sweating and tearing, which have been proved to be unreliable with a low specificity (Bruhn et al., 2006; Heier and Steen, 1996; Rantanen et al., 2006). Some surrogate measures derived from the spontaneous EEG such as the state and response entropy (SE and RE) have been validated as measures of the hypnotic component of anaesthesia, but have limited accuracy for assessing of nociception - anti-nociception (Huang et al., 2006; Struys et al., 2002; Struys et al., 2003; Vanluchene et al., 2004). One alternative experimental method to estimate only the anti – nociception side of the balance is to determine directly or to model plasma concentration of opioids (Bouillon et al., 2004). Several other methods, including suppression of photoplethysmographic pulse wave amplitude (Rantanen et al., 2006; Seitsonen et al., 2005), activation of facial muscles (Hynynen et al., 1985; Takamatsu

et al., 2006), changes in skin conductivity (Storm et al., 2002), skin vasomotor reflexes (Shimoda et al., 1997) and pupillometry (Ibrahim et al., 2003; Taylor et al., 2003), have also been proposed to assess the nociception - anti-nociception balance. Unfortunately, all measures of nociception – anti-nociception balance mentioned above are subject to inter-individual variability, non-specific, lack sensitivity to actual nociception and are generally without real prediction (Luginbuhl et al., 2006; Luginbuhl et al., 2007; Mathews et al., 2007). More recently, Bonhomme et al. (Bonhomme et al., 2006) tried to use combination of BIS and A-Line Autoregressive Index (AAI) monitor to assess nociception – anti-nociception balance during propofol – remifentanil anaesthesia and found that during a BIS-guided constant level of hypnosis, AAI response to the onset of surgical stimulation significantly differed according to the analgesia regimen. However, the sensitivity and specificity of AAI in assessing the balance of nociception – anti –nociception should be further refined. Therefore, a validated numeric dimension of nociception – anti – nociception balance during general anaesthesia is currently not available (Wennervirta et al., 2008).

Surgical stress index (SSI), a novel multivariate index based on the sum of the normalized heart beat interval (HBI) and the pulse wave amplitude (PPGA) time series of the photoplethysmography (PPG), has been developed to assess the nociception – anti-nociception balance during general anaesthesia (Huiku et al., 2007). In the study performed by Huiku et al., SSI was showed to have a negative correlation with remifentanil effect-site concentration ($C_{e_{remi}}$) and a positive correlation with the intensity of stimulus during total intravenous anaesthesia with propofol and remifentanil (Huiku et al., 2007). Ahonen et al. also found that SSI reacted well to the level of surgical stress and β -blocker (Esmolol) administration did not influence SSI values during general anaesthesia (Ahonen et al., 2007). Struys et al. and Wennervirta et al. further proved that SSI appeared to have a better performance in detecting nociceptive stimuli during general anaesthesia than state entropy (SE), response entropy (RE), heart rate, or PPGA (Struys et al., 2003; Wennervirta et al., 2008). Though all of the above references suggest that SSI might be used for guidance of

remifentanil delivery during general anaesthesia, unfortunately, no study about using the SSI to guide analgesics titration during general anaesthesia has been reported so far.

We, therefore, designed the present clinical utility study, which includes two groups, SSI-guided analgesia group and standard practice analgesia group, to investigate the feasibility of remifentanil administration guided by SSI monitoring during total intravenous anaesthesia with propofol and remifentanil. We hypothesized that: 1) SSI may react well to the intensity of stimuli at some major time-points such as loss of consciousness (LOC), intubation, maximum stimulation during surgery, extubation, emergence from anaesthesia and so on; 2) SSI-guided remifentanil administration might result in more stable hemodynamic state, less consumption of remifentanil and shorter recovery times.

1.2 Aims and objectives:

- A. To investigate the effects of SSI-guided remifentanil delivery on the consumption of anaesthetics (remifentanil and propofol), the emergence from anaesthesia and the incidence of unwanted events such as hypertension, tachycardia, hypotension, movement, etc., during general anaesthesia.
- B. To further investigate the performance of SSI in assessing the intensity of nociceptive stimuli during general anaesthesia.
- C. To compare the performance of SSI in assessing nociceptive stimuli at major time-points during general anaesthesia with blood pressure (BP), heart rate (HR), state entropy (SE), response entropy (RE), difference between RE and SE (RE-SE), bispectral index (BIS) using prediction probability values (Pk values) as described by Smith et al. (Smith et al., 1996).

2. Materials and methods

This study was approved by the institutional review board of the University Hospital Schleswig-Holstein, Campus Kiel. Written consent was obtained from all patients who were participated in this study.

2.1 Materials

2.1.1. Surgical Stress Index (SSI) monitor

The Surgical Stress Index (SSI) monitor has not been available commercially up to now. GE Healthcare (GE Healthcare Finland, Helsinki, Finland) supplied the monitor to us only for the present study. This monitor is a module of Datex-Ohmeda S/5™ which has many modules like M-entropy module, non-invasive blood pressure (NIBP) module, electrocardiography module, pulse oximetry (SpO₂) module, etc.

Surgical stress index (SSI) is a simple numerical index derived from a photoplethysmography finger sensor which was clamped on the index finger. Calculation of the SSI was done by 10s intervals and is described elsewhere (Huiku et al., 2007) . In brief, the pulse beat interval (HBI) from the pulse plethysmography and the pulse plethysmographic wave amplitude (PPGA) were automatically detected and the HBI and PPGA time series extracted. The HBI and PPGA were then normalized, called HBI_{norm} and PPGA_{norm}, using the individual patient's heart rate and PPGA data history, and the *a priori* HBI and PPGA data distributions obtained by pooling data from a large adult patient group. This normalization procedure adjusts the individual values so that they, after normalization, are in a scale between 0 and 100. As such, the SSI is calculated as:

$$SSI = 100 - (0.33 \times HBI_{norm} + 0.67 \times PPGA_{norm})$$

A value of 100 represents a very high stress level and a value of 0 represents a very

low stress level.

2.1.2 Bispectral Index (BIS) monitor

The BIS[®] XP monitor (Aspect Medical Systems, Newton, MA, USA) was used in the present study. Calculation of BIS values, a electroencephalography (EEG)-derived variable, is based on power spectrum and phase spectrum and quantifies the coupling of phase angles of different frequencies. The BIS integrates several disparate descriptors of the EEG into a single variable. So, the BIS value is a calculated dimensionless variable between 0 and 100. A BIS value of 100 means awake state and a value of 0 means deep coma. The recommended range for adequate depth of anaesthesia (mainly the hypnosis component) is between 40 and 60 (Manyam et al., 2007; Song et al., 1997).

BIS-XP sensor (BIS[®] sensor; Aspect[™] Medical Systems Inc.) which integrates four electrodes was used for obtaining the EEG signal from forehead.

2.1.3 M-entropy module

The Datex-Ohmeda S/5[™] M-entropy module (GE Healthcare Finland, Helsinki, Finland) was used to display the state entropy (SE) and the reponse entropy (RE) values derived also from the EEG signals. The calculation of the M-entropy was described elsewhere (Bein, 2006). M-entropy analyzes the regularity of the spectrum distribution in the range from 0 to 47 Hz in which both EEG and EMG activity are included with using the frontal electrodes. M-entropy generates two distinct numbers, the state entropy and the response entropy. The state entropy is computed over the EEG dominant part of the spectrum (0.8–32 Hz) and the response entropy is computed over a spectrum range from 0.8 to 47 Hz which includes EEG and EMG activity. So, the RE–SE-difference (RE-SE) might then serve as an indicator for EMG activation.

Displayed SE values are presented between 0 and 91, a value of 0 means totally

suppressed EEG activity and a value of 91 means patient awake. And displayed RE values are presented between 0 and 100, a value of 0 means totally suppressed EEG and EMG activity and a value of 100 means no suppression of EEG and EMG activity at all. Recommended range for adequate anaesthesia for both parameters is from 40 to 60.

An integrated 3-electrode sensor was used for obtaining the original EEG and EMG activity signals.

2.1.4 Datex-Ohmeda Multi-functional S/5™ monitor

The Datex-Ohmeda Multi-functional S/5™ monitor (GE Healthcare Finland, Helsinki, Finland) was used to monitor non-invasive arterial blood pressure (NIBP), electrocardiography (ECG), heart rate (HR), pulse oximetry (SpO₂) and train-of-four (TOF) (for neuromuscular transmission monitoring).

2.1.5 Anaesthetics and Drugs used during anaesthesia

Propofol: Propofol-®Lipuro 1% (1 ml of emulsion contains 10 mg of propofol); chemical name: Phenol,2,6-bis(1-methylethyl), 2,6-Diisopropylphenol; molecular formula: C₁₂H₁₈O; molecular weight: 178.27. Manufacturer: B.Braun Melsungen AG, 34209 Melsungen, Germany.

Remifentanil: ULTIVA® (remifentanil hydrochloride); 1mg/amp; chemical name: 3-[4-methoxycarbonyl-4- [(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid methyl ester, hydrochloride salt; molecular formula: C₂₀H₂₈N₂O₅•HCl; molecular weight: 412.91. Manufacturer: GlaxoSmithKline Australia Pty Ltd. 1061 Mountain Highway, Boronia victoria 3155.

Rocuronium: Esmoron® (Rocuronium Bromide), chemical name: 1 - [17(beta)-(acetyloxy)-3(alpha)-hydroxy - 2(beta) - (4-morpholinyl) - 5(alpha) - androstan - 16(beta) - yl] -1- (2-propenyl) pyrrolidinium bromide; Molecular

formula: $C_{32}H_{53}BrN_2O_4$; Molecular weight: 609.70. Manufacturer: N.V. Organon, Kloosterstreet 6, 5340 BH OSS, Netherland.

Piritramide: Dipidolor®, Chemical name: 1 - (3-cyano-3,3-diphenyl-propyl) – 4 - (1-piperidyl) piperidine-4-carboxamide; Molecular formula: $C_{27}H_{34}N_4O$; Molecular weight: 430.58; Manufacturer: JASSEN-CILAG GmbH, 41457 Neuss, Germany.

Akrinor®: a mixture of intravenous vasopressors, 1ml of Akrinor® contains 100mg cafedrine and 5mg theodrenaline. AWD Pharma, Germany;

Other drugs: Atropine, Urapidil, Metoprolol.

2.2 Methods

2.2.1 Patients and Grouping:

Eighty patients with ASA physical status I or II, aged 18~75 yr, scheduled for elective ear-nose-throat (ENT) surgery expected to last at least 1h were recruited into this study. Exclusion criteria included a history of central nerve systemic (CNS) disease (e.g. neurological disorders, head injury, seizure disorders), chronic use of psychoactive medication or abuse of alcohol or illicit drugs, and any clinical significant cardiovascular, renal, hepatic, or endocrinologic disorders.

We used a computer-generated randomization sheet to assign the 80 patients into two groups: SSI Group (SSI guided analgesia group) and Control Group (standard analgesia practice group), each group included 40 patients.

2.2.2 Anaesthesia and Monitoring

2.2.2.1 Before Induction of Anaesthesia

All patients were premedicated with 20 – 30mg of the benzodiazepine dipotassium chlorazepate the evening before and with 3.75 - 7.5mg of midazolam orally 30min before surgery.

On arrival in the operating theatre, an intravenous catheter was inserted into a larger forearm vein and standard monitoring including non-invasive arterial blood pressure (NIBP), 5-lead electrocardiogram (ECG) and pulse oximetry (SpO₂) (Datex-Ohmeda S/5® monitor, Helsinki, Finland) were applied. All patients in both groups were monitored with Bispectral Index (BIS), M-entropy and Surgical Stress Index (SSI). After the skin of the forehead had been degreased with alcohol and dry, the BIS® XP sensor which integrates four electrodes numbered 1, 2, 3 and 4 respectively was positioned on the forehead as recommended by the manufacturer. The number 1 electrode was at the center of the forehead, approximately 5cm above bridge of nose, number 4 was directly above eyebrow and number 3 on left temple between corner of eye and hairline, Care was taken to keep the impedances of the BIS® XP sensor below 7.5KΩ as required by the manufacturer to ensure optimal contact. M-entropy sensor which integrates three electrodes was also positioned on the forehead as recommended by the manufacturer. The number 1 electrode was attached at the center of the forehead, approximately 3cm above the nose and just adjacent to the lower edge of the BIS® XP sensor, and number 3 on the right temple area between the corner of the eye and hairline. SSI monitoring shared the same sensor of pulse oximetry monitor which was clamped on the index finger. The calculation of the SSI was done by 10s intervals and described above.

2.2.2.2 Induction of Anaesthesia

In all patients, anaesthesia was induced with propofol and remifentanil via target controlled infusion pump (TCI; Asena® Alaris®, Alaris medical UK ltd. UK). For propofol, the pharmacokinetic model of Schnider and colleagues, (Schnider et al., 1998) and for remifentanil, the pharmacokinetic model of Minto and colleagues (Minto et al., 1997) were used. Predicted effect-site concentration of propofol (PEC_{prop}) initially

started at $4\mu\text{g}\cdot\text{ml}^{-1}$ and remifentanyl (PEC_{remi}) at $4\text{ng}\cdot\text{ml}^{-1}$. After loss of consciousness which was defined as the moment the patient dropped a syringe, oxygen was given by facemask ventilation, and patients received $0.6\text{mg}\cdot\text{kg}^{-1}$ rocuronium. The trachea was then intubated 3min later, and the lungs were ventilated to an end-tidal carbon dioxide concentration of 35 mmHg. Immediately after intubation, the predicted effect-site concentration of propofol was adjusted by $0.5\mu\text{g}\cdot\text{ml}^{-1}$ stepwise with 2min intervals to keep BIS values between 40-60, which means that the PEC_{prop} was increased by $0.5\mu\text{g}\cdot\text{ml}^{-1}$ stepwise when BIS values was above 60 and the PEC_{prop} was decreased $0.5\mu\text{g}\cdot\text{ml}^{-1}$ stepwise when BIS value was below 40 with an interval of 2 min. The lower limit of PEC_{prop} set for this study was $2\mu\text{g}\cdot\text{ml}^{-1}$ and no upper limit of PEC_{prop} was pre-set. The predicted effect-site concentration of remifentanyl (PEC_{remi}) was not adjusted until start of surgery.

2.2.2.3 Maintenance of Anaesthesia and Haemodynamic Control

Continuous monitoring included heart rate (HR), ventilatory parameters, oxygen saturation and end-tidal concentration of carbon dioxide (EtCO_2). Systemic non-invasive arterial blood pressure (NIBP) was measured intermittently and the oxygen saturation was measured by pulse oximetry (SpO_2) and maintained above 95%.

In all patients, irrespective of the individual group assignment, SSI, M-entropy and BIS values were monitored continuously and all data from the monitor were captured electronically using the software S/5 Collect (GE Healthcare, Helsinki, Finland), which collects numerical and waveform data information from selected variables. In the Control Group, the SSI monitor was covered with a curtain and invisible to the attending anesthesiologist but visible to the recording physician, whereas in the SSI Group both SSI and BIS monitors were uncovered. In both groups, M-entropy was covered with the same method as the SSI monitor was covered in the Control Group.

The baseline value of NIBP, HR, SSI and BIS was defined as the average of three

measurements immediately after patients' arrival in the operating theatre. NIBP, HR, SSI and BIS were recorded every 2.5min, additionally, at some special time-points, such as loss of consciousness, tracheal intubation, start of surgery, maximum stimulation during surgery, when SSI was >50 or <20, when BIS was >60 or <40, end of surgery, eyes opening and at extubation, all the values were also recorded.

During maintenance of anaesthesia, all patients were assessed for signs of inadequate anaesthesia, hypotension or bradycardia. Criteria of inadequate anaesthesia were modified based on previous studies (Gan et al., 1997; Garrioch and Fitch, 1993; Gruenewald et al., 2007; Kreuer et al., 2003) and are listed in Table 1.

Table 1 Criteria for inadequate anaesthesia and hypotension or bradycardia

Inadequate anaesthesia	
Hypertension	Mean arterial blood pressure > 120% of baseline or >100mmHg
Tachycardia	Heart rate > 90 beats·min ⁻¹
Somatic arousal	Coughing, chewing, grimacing
Somatic response	Purposeful movement
Hypotension	Mean blood pressure <80% of baseline or < 60mmHg
Bradycardia	Heart rate < 80% of baseline or < 45beats·min ⁻¹

In both groups, predicted effect-site concentration of propofol (PEC_{prop}) was adjusted by stepwise increasing or decreasing 0.5µg·ml⁻¹ to keep the BIS value between 40 and 60.

In the Control Group, inadequate anaesthesia was treated by increasing the predicted effect-site concentration of remifentanyl (PEC_{remi}) by 1ng·ml⁻¹ stepwise until the maximum concentration of 15ng·ml⁻¹ was reached. If this was judged insufficient, Urapidil 10mg was given intravenously. Hypotension was treated initially by speeding

intravenous liquid infusion, then PEC_{remi} was decreased stepwise by $1\text{ng}\cdot\text{ml}^{-1}$ until the minimum concentration of $4\text{ng}\cdot\text{ml}^{-1}$, and finally, 0.5ml Akrinor was given intravenously. Atropine 0.5mg was used intravenously for bradycardia.

In the SSI group, PEC_{remi} was adjusted by stepwise increasing or decreasing by $1\text{ng}\cdot\text{ml}^{-1}$ (PEC_{remi} range was limited between $4\text{-}15\text{ng}\cdot\text{ml}^{-1}$) to keep the SSI value between 20 and 50. Under this circumstance ($20 < \text{SSI} < 50$ and PEC_{remi} at $15\text{ng}\cdot\text{ml}^{-1}$), unwanted events during anaesthesia were treated as follows: inhalation of sevoflurane with proper concentration for movement; urapidil 10mg i.v. for hypertension; Akrinor 0.5ml i.v. for hypotension; atropine 0.5mg i.v. for bradycardia and metoprolol 2mg i.v. for tachycardia, repeated if necessary.

2.2.2.4 Recovery Period

To facilitate rapid emergence from anaesthesia, 15min before the expected end of surgery, propofol was reduced in all patients according the experience of the attending anesthesiologist, whereas the remifentanil TCI remained unchanged until end of surgery. In the meantime, all patients received $0.1\text{mg}\cdot\text{kg}^{-1}$ of the opioid piritramide for postoperative analgesia. Both propofol and remifentanil TCI were discontinued at the end of surgery.

The end of surgery was defined as the final surgical suture. Emergence from anaesthesia was assessed by measuring time to spontaneous opening of eyes, and to extubation.

Postoperative care in the recovery room was supervised by a nurse who was blinded to study protocol. In the recovery room, the modified Aldrete-Score (Table 2), postoperative nausea and vomiting, and pain [using a 0-100 numerical pain intensity rating scale (NRS)] were recorded. On the first postoperative day, all patients were asked by a blinded investigator if they had any memory or awareness during anaesthesia, and the level of satisfaction with the whole procedure was investigated

using a 0-100 scale (0 means the worst satisfaction and 100 means best satisfaction).

Table 2. Modified Aldrete-Score

	Modified Aldrete-Score	
Activity	2	Moves all extremities voluntarily or on command
	1	Moves two extremities
	0	Unable to move extremities
Respiration	2	Breathes deeply and coughs freely
	1	Requires assistance, shallow or limited breathing
	0	Apnea
Circulation	2	± 20 mmHg of preanaesthetic level
	1	$\pm 20\sim 50$ mmHg of preanaesthetic level
	0	\pm over 50mmHg of preanaesthetic level
Consciousness	2	Fully awake
	1	Arousable on calling
	0	Not responding
Oxygen saturation	2	SpO ₂ > 92% on room air
	1	SpO ₂ >92% with O ₂ supplementation
	0	SpO ₂ <92% with O ₂ supplementation

2.2.3 Endpoints and Statistical Analysis

2.2.3.1 Endpoints and Sample Size

The primary endpoint of this study was defined as the time to open eyes. A sample size of 40 was based on a previous study (Kreuer et al., 2003), assuming a difference in emergence of 3min at $\alpha= 0.05$ with 90% power. Secondary endpoints were the differences in P_k between SSI, BIS, SE, RE, RE-SE, mean BP, and HR for predicting the nociceptive – anti-nociceptive balance at different event related time points: awake vs loss of consciousness; normal stimulation (recorded at 5min before maximum stimulation) vs maximum stimulation; anaesthesia (recorded at the discontinuation of propofol and remifentanil infusion) vs eyes opening.

2.2.3.2 Software for Statistical Analysis and Data Presentation

SPSS 11.5 for windows statistical package (SPSS inc. Chicargo, IL, U.S.A) was used

for statistical analysis and GraphPad Prism software (Version 4.0, GraphPad Software Inc., San Diego, CA, USA) was used for figures. P_k MACRO and P_k DMACRO (offered by Prof. Smith) spreadsheets were used for P_k value calculation and comparing. All tests were two-tailed with statistical significance defined as $P < 0.05$.

Data were presented as mean \pm SD for numerical data, range or number for nominal data and mean \pm SE for P_k values.

2.2.3.3 Prediction Probability

Comparison of the performance of SSI, BIS, SE, RE, RE-SE, mean BP, and HR for predicting the nociceptive-anti-nociceptive balance (see 2.2.3.1) was performed with prediction probability (P_k) (Smith et al., 1996). P_k was calculated using P_k MACRO as described by Smith et al (Smith et al., 1996). The jackknife method was used to compute the standard error 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. Comparison between the P_k values of different variables was performed with the P_k DMACRO (Smith et al., 1996).

2.2.3.4 Correlations

Correlations between SSI or RE-SE and HR or mean BP, BIS and SE, and so on were evaluated by nonparametric Spearman rank correlation for all data pairs at four major time-points: P1 = baseline before induction of anaesthesia; P2 = immediately after tracheal intubation; P3 = at maximum surgical stimulation; P4 = 15min after maximum surgical stimulation.

2.2.5 Logistic Regression

For SSI and BIS, the logistic regression was calculated for the probability of loss of consciousness, intubation, maximum surgical stimulation and emergence from anaesthesia. The Hill coefficients were calculated to describe the steepness of those relationships.

2.2.3.6 Other Statistical Analysis

For demographic data, consumption of anaesthetic, duration of anaesthesia and surgery, times fraction of SSI and BIS, variables such as SSI, BIS, SE, RE, RE-SE, mean BP, HR and so on at major time-points, independent samples student t test (normally distributed) and Mann-Whitney U test (non-normally distributed) or one-way analysis of variance with Student-Newman-Keuls test (multiple comparisons) were used for numerical data and chi-square test was used for the nominal data.

3. Results

3.1 Demographic Data

All 80 patients (40 patients in each group) enrolled in the present study were included into the final analysis. There were no differences in patients' demographic data such as age, weight, height, and duration of anesthesia, duration of surgery, and duration from intubation to start of surgery between groups (Table 3).

Table 3. Demographic Data

	SSI Group (n =40)	Standard Practice (n =40)
Age (yr)	46.8±16.6	46.0±17.5
Height (cm)	172.9±17.8	170.8±9.4
Weight (Kg)	78.3±11.5	74.6±16.6
Gender-M/F (n)	13/27	21/19
ASA □/□ (n)	18/22	19/21
Duration of anaesthesia (min)	152.0±67.2	173.0±83.8
Duration of surgery (min)	109.0±60.6	131.7±81.4
Intubation to start of surgery (min)	24.1±7.9	24.6±9.6

Values are mean ± SD or numbers of patients. Data are not significantly different between groups. $P > 0.05$.

3.2 Recovery Times and Anaesthetics Consumption

Although the times to open eyes seemed shorter in the SSI group compared to the standard analgesia practice group (8.9 ± 4.3 vs 10.6 ± 4.3 min), difference between groups was not statistically significant ($P > 0.05$; Table 4). A Kaplan-Meier survival analysis is shown in Figure 1. This figure shows the cumulative percentage of patients who remained unconscious (not open eyes) after discontinuation of propofol and remifentanyl infusion, indicating a faster awakening in the SSI-guide analgesia group but with no significance when compared with the standard analgesia practice group ($P > 0.05$).

Table 4. Recovery Times

	SSI Group(n =40)	Standard Practice (n =40)
Eyes-opening (min)	8.8±3.8	10.6±4.3
Extubation (min)	9.8±4.4	11.2±4.6

Values are mean ± SD, no significant difference between groups (independent

samples student *t* test). $P > 0.05$.

Figure. 1

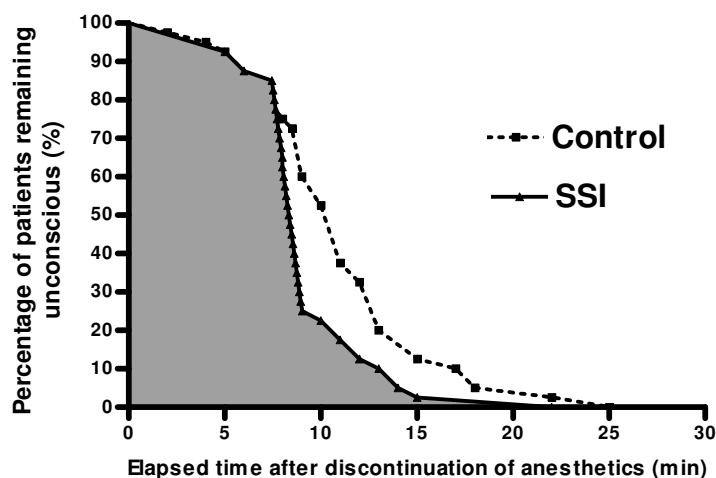


Figure. 1. Cumulative probability of patients’ remaining unconscious (before opening eyes) after discontinuation of anaesthetics (propofol and remifentanyl) infusion in SSI-guided analgesia Group (- ▲ - ; shaded area) or Standard analgesia practice Group (--■--; shaded area) using Kaplan-Meier survival analysis. Log-rank differences were not statistically significant between groups. $P > 0.05$.

Remifentanyl consumption (averaged normalized infusion rate calculated from induction to discontinuation of anaesthetics) was significantly lower in SSI group when compared to standard practice group ($9.5 \pm 3.8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ vs $12.3 \pm 5.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, $P < 0.05$) (Table 5), whereas there was no difference in propofol consumption (averaged normalized infusion rate) between groups ($5.3 \pm 1.5 \text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in the SSI-guided analgesia group and $5.6 \pm 1.5 \text{mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ in the standard analgesia practice group, respectively, $P > 0.05$) (Table 5).

Table 5. Characteristics of Propofol and Remifentanyl Consumption

	SSI Group (n =40)	Standard Practice (n =40)
For one patient		
Propofol consumption (mg)	1018.5±345.8	1157.7±558.8
Remifentanyl consumption (μg)	2063.5±1579.5	2634.4±1792.1
For one patient normalized [= total anaesthetics dose / duration of anaesthesia (h) / weight (Kg)]		
Propofol consumption (mg·kg ⁻¹ ·h ⁻¹)	5.3±1.5	5.6±1.5
Remifentanyl consumption (μg·kg ⁻¹ ·h ⁻¹)	9.5±3.8 *	12.3±5.2
Reduction when compared to standard	-22.8	NA

practice (%)

Values are mean \pm SD.

* $P < 0.01$, compared to standard practice group. (independent samples student t test between groups).

NA = Not Applicable.

Moreover, the predicted effect-site concentrations of remifentanyl (PEC_{remi}) were lower at the time-point of S+30, S+45, and S+60 (S+30 means 30min after start of surgery, S+45 and S+60 have the same meaning to S+30) in the SSI analgesia group than that at the corresponding time-points in the standard analgesia practice group ($P < 0.05$) (Figure 2A), whereas the predictive effect-site concentrations of propofol (PEC_{prop}) were comparable at all major time-points during maintenance of anaesthesia between groups ($P > 0.05$). (Figure 2B).

Figure 2

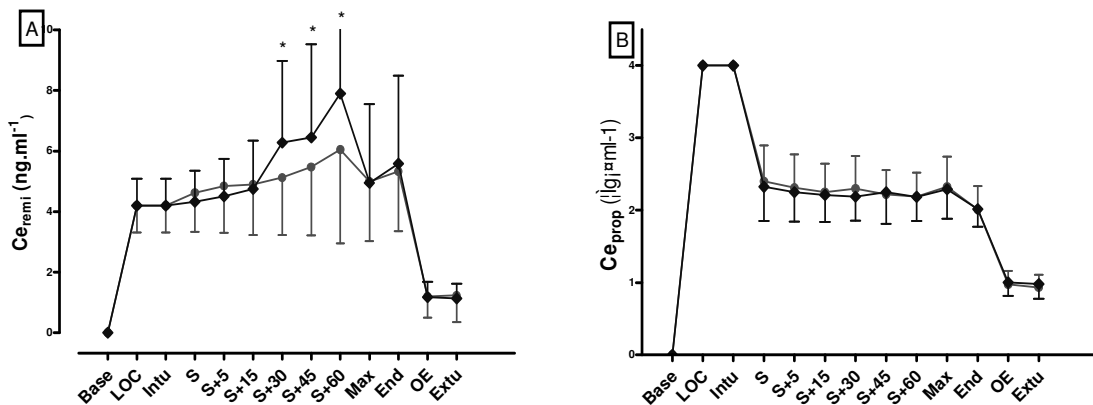


Figure 2. Changes in predicted effect-site concentrations of propofol and remifentanyl in SSI-guided analgesia group (●) or standard analgesia practice group (□) at major time points during anaesthesia: baseline (Base), loss of consciousness (LOC), intubation (Intu), start of surgery (S), Maximum stimulation (Max), end of propofol and remifentanyl (E), eyes opening (OE) and extubation (Extu). Values are mean (SD); * $P < 0.05$ when compared with standard analgesia practice group.

3.3 Surgical Stress Index and Bispectral Index

Both SSI values and BIS values were collected in all patients, irrespective of the

individual group assignment, and are displayed in Figure 3. SSI values were higher at various time-points (start of surgery, 15min after start of surgery, 45min after start of surgery and the end of the surgery) during anaesthesia in SSI group than that at the corresponding time-points in the standard analgesia practice group (Figure 3A) ($P < 0.05$). whereas the BIS values were comparable at all major time-points during anaesthesia between groups (Figure 3B) ($P > 0.05$).

Figure 3.

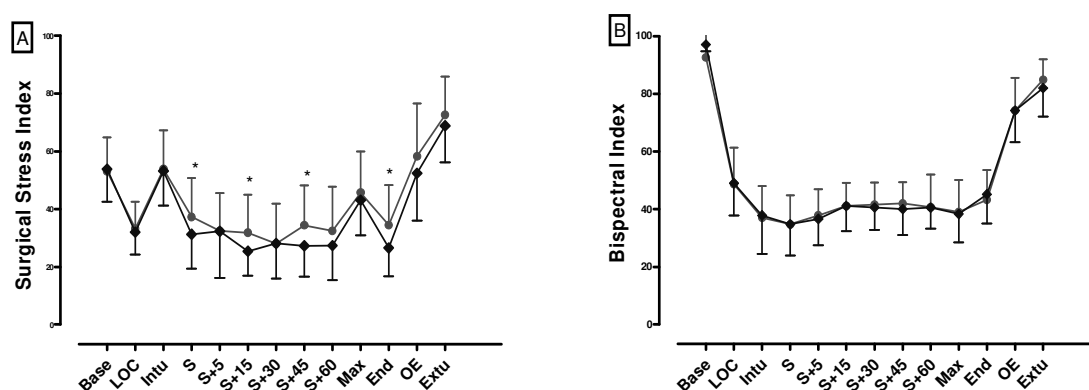


Figure 3. Changes in surgical stress index (SSI) and bispectral index (BIS) values in SSI-guided analgesia group (●) or standard practice group (□) at major time points during anaesthesia: baseline (Base), loss of consciousness (LOC), intubation (Intu), start of surgery (S), Maximum stimulation (Max), end of propofol and remifentanil (E), eyes opening (OE) and extubation (Extu). Values are mean (SD); * $P < 0.05$ when compared with standard practice analgesia group.

Additionally, we analyzed the time fractions of actual SSI or BIS values collected during maintenance of anaesthesia (Table 6): The time fractions of actual SSI value < 20 and SSI value > 50 were significantly lower in the SSI-guided analgesia group than in the standard analgesia practice group (12.4% vs 24.4%; 4.3% vs 12.1%, respectively, $P < 0.05$). Correspondingly time fractions of SSI values between 20 and 50 ($20 < \text{SSI} < 50$) were higher significantly in the SSI-guided analgesia group than in the standard analgesia practice group (83.2% vs 62.8%, respectively, $P < 0.01$). In contrast the time fractions of BIS value < 40 and > 60 , or between 40 to 60 were

comparable between groups (30.0% vs 23.7%, 8.7% vs 5.2%, and 72.7% vs 76.9% in the SSI-guided analgesia group and standard analgesia practice group, respectively. ($P > 0.05$) (Table 6).

Table 6. Time Fractions of Actual SSI and BIS Values during Anaesthesia Maintenance

	SSI Group (n =40)	Standard Practice (n =40)
SSI < 20 (%)	12.4 ± 5.7 *	24.4 ± 7.5
SSI > 50 (%)	4.3 ± 1.5 *	12.1 ± 4.5
20 < SSI < 50 (%)	83.2 ± 9.2 *	62.8 ± 7.9
BIS < 40 (%)	30.0 ± 5.4	23.7 ± 5.0
BIS > 60 (%)	8.7 ± 3.5	5.2 ± 3.0
40 < BIS < 60(%)	72.7 ± 10.0	76.9 ± 10.1

Data are mean ± SD. * $P < 0.05$, compared to standard analgesia practice group. (independent samples student t test between groups).

3.4 Predictive Probabilities (P_k) of anaesthesia depth indicators to Predict the State of Nociception and Hypnosis

We calculated the prediction probabilities of surgical stress index (SSI), bispectral index (BIS), state entropy (SE), response entropy (RE), RE-SE difference, mean arterial blood pressure (MBP), heart rate (HR) to predict certain states: awake vs loss of consciousness (LOC), loss of consciousness (LOC) vs intubation, normal stimulation (1min before maximum stimulation which was defined by surgeon intra-operatively) vs maximum stimulation, anaesthesia (at the end of the anaesthetics administration) vs emergence from anaesthesia (eyes opening) in both groups.

3.4.1 P_k values of SSI, BIS, MBP and HR (Table 7)

For predicting loss of consciousness (LOC), only the BIS had a P_k value > 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 MBP and HR were significantly lower than that of the BIS and the SSI (0.78 and 0.60 vs 0.91 and 0.88. $P < 0.01$).

For predicting the state of intubation, the P_k value of the SSI was the highest among SI, BIS, MBP and HR (0.87 vs 0.60, 0.69, 0.65, respectively. $P < 0.01$).

For predicting the state of the maximum stimulation during surgery, the P_k value of the SSI was also the highest among SSI, BIS, MBP and HR (0.85 vs 0.54, 0.60, 0.51, respectively. $P < 0.01$).

For predicting the state of emergence from anaesthesia (eyes opening), the P_k value of the BIS was the highest among BIS, SSI, MBP and HR (0.95 vs 0.81, 0.84, 0.76, respectively. $P < 0.01$).

Table 7. Prediction Probabilities (P_k) of Different Variables

		SSI	BIS	MBP	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
Anaesthesia 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

This table shows the prediction probabilities (P_k values) of SSI, BIS, MeanBP and HR for predicting the following states: awake vs loss of consciousness (LOC); loss of consciousness (LOC) vs intubation; normal stimulation (Normal) (1min before maximum surgical stimulation) vs maximum surgical stimulation (Max stimulation) which was defined by surgeon intraoperatively; anaesthesia vs eye-opening in all patients in both group. The comparisons of P_k values between groups were only performed on pooled data of both groups. * $P < 0.01$ compared with SSI; § $P < 0.01$ compared with BIS; # $P < 0.01$ compared with BP. No differences were found between groups for all variables.

Additionally, the BIS value of the 95% possibility for loss of consciousness was 40 (95%CI: 18 - 48) (Figure 4A) and for emergence from anaesthesia (eyes opening) was 75 (95% CI: 71 - 81) (Figure 4B). The SSI value of the 95% possibility for intubation

was 59 (95% CI: 53 -70) (Figure 5A) and for the maximum stimulation during surgery was 60 (95% CI: 49 ~91) (Figure 5B).

Figure 4

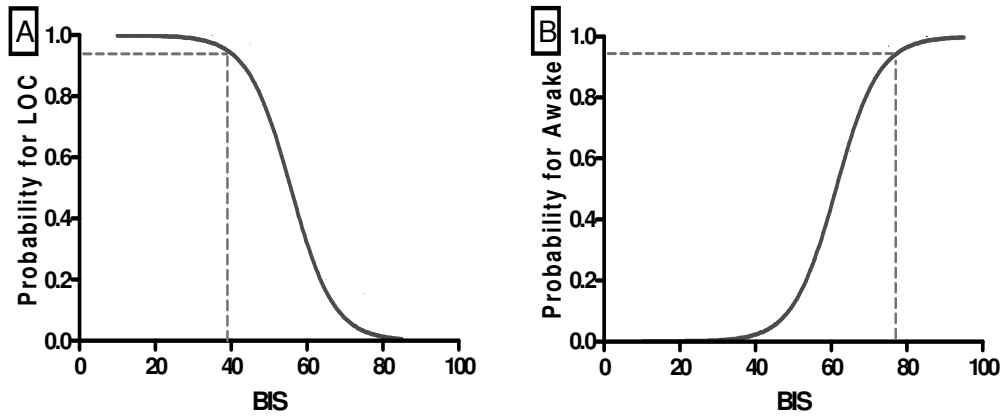


Figure 4. Logistic regression curve shows the probability of BIS to predict two endpoints, loss of consciousness (LOC) from awake (A) and emergence or awake from anaesthesia (B) with all the patients in both groups. Dotted lined indicate the 95% probability.

Figure 5

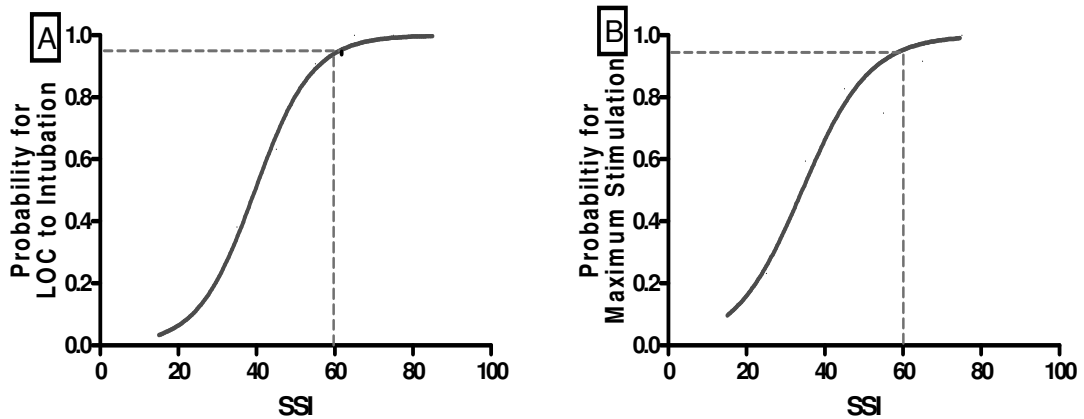


Figure 5. Logistic regression curve shows the probability of SSI to predict two endpoints, intubation (A) and maximum operative stimulation (B) with all patients in both groups. Dotted lined indicate the 95% probability.

3.4.1 Pk values of SSI, SE, RE and RE-SE (Table 8)

For predicting the state of loss of consciousness (LOC), all the four parameters had similar P_k values (0.88, 0.89, 0.88 and 0.95 for SSI, SE, RE and RE-SE difference, respectively, $P > 0.05$).

For predicting the state of intubation, the P_k values of SSI were significantly higher than that of SE, RE and RE-SE difference (0.87 vs 0.59, 0.55, 0.51, respectively. $P < 0.01$).

For predicting the state of the maximum surgical stimulation, the P_k values of SSI were also significantly higher than that of SE, RE (0.85 vs 0.51 and 0.56, $P < 0.01$) and RE-SE difference (0.85 vs 0.79, $P < 0.05$). RE-SE difference had a better prediction probability than SE and RE (0.79 vs 0.51, 0.56, $P < 0.05$).

For prediction of the emergence from anaesthesia (eyes opening), SSI had a worse prediction probability than SE, RE and RE-SE difference (0.80 vs 0.97, 0.98, 0.97, respectively. $P < 0.01$).

Table 8. Prediction Probabilities (P_k) of Different Variables

		SSI	SE	RE	RE-SE
Awake	All patients (n = 80)	0.88±0.03	0.89±0.04	0.88±0.04	0.95±0.03
vs	SSI Group (n= 40)	0.92±0.03	0.91±0.04	0.89±0.04	0.92±0.04
LOC	Standard practice (n= 40)	0.83±0.05	0.90±0.02	0.89±0.03	0.93±0.02
LOC	All patients (n = 80)	0.87±0.03	0.59±0.07*	0.55±0.07*	0.51±0.07*
Vs	SSI Group (n= 40)	0.85±0.04	0.55±0.07	0.60±0.07	0.51±0.07
Intubation	Standard practice (n= 40)	0.91±0.03	0.56±0.05	0.58±0.05	0.51±0.05
Normal	All patients (n = 80)	0.85±0.03	0.51±0.07*#	0.56±0.07*#	0.79±0.05§
vs	SSI Group (n= 40)	0.90±0.04	0.52±0.07	0.63±0.06	0.71±0.06
Max stimulation	Standard practice (n= 40)	0.82±0.05	0.52±0.05	0.59±0.05	0.76±0.04
Anaesthesia	All patients (n = 80)	0.81±0.04	0.98±0.01*	0.98±0.01*	0.97±0.02*
vs	SSI Group (n= 40)	0.83±0.05	0.96±0.02	0.98±0.01	0.92±0.03
Eye-opening	Standard practice (n= 40)	0.80±0.05	0.97±0.01	0.98±0.01	0.94±0.02

This table shows the prediction probabilities (P_k values) of SSI, SE, RE, RE-SE difference for predicting the states: awake vs loss of consciousness (LOC); loss of consciousness (LOC) vs intubation; normal stimulation (Normal) vs maximum surgical stimulation (Max stimulation) which was defined by surgeon intraoperatively; anaesthesia vs eye-opening in all patients in both groups. The comparisons of P_k values between groups were only performed on pooled data of both groups.

* $P < 0.01$ compared with SSI; § $P < 0.05$ compared with SSI; # $P < 0.01$ compared with RE-SE difference. No differences were found between groups for all variables.

3.5 Unwanted Events during Anaesthesia

Patients in the standard analgesia group had significantly more hypertension (84 vs 11, $P < 0.01$), hypotension (67 vs 5, $P < 0.01$), bradycardia (111 vs 23, $P < 0.01$) and movement (14 vs 3, $P < 0.01$). Total number of unwanted events was 278 vs 42, $P < 0.01$, (Table 9). However, we could not find any difference in mean blood pressure and heart rate at all the major time-points between groups (Figure 6).

Table 9. Incidence of Unwanted Events Happened during the Intra-operative 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 event during surgery. Data in brackets are numbers of unwanted events per patient. * $P < 0.01$ when compared with Standard Practice Group.

Figure 6

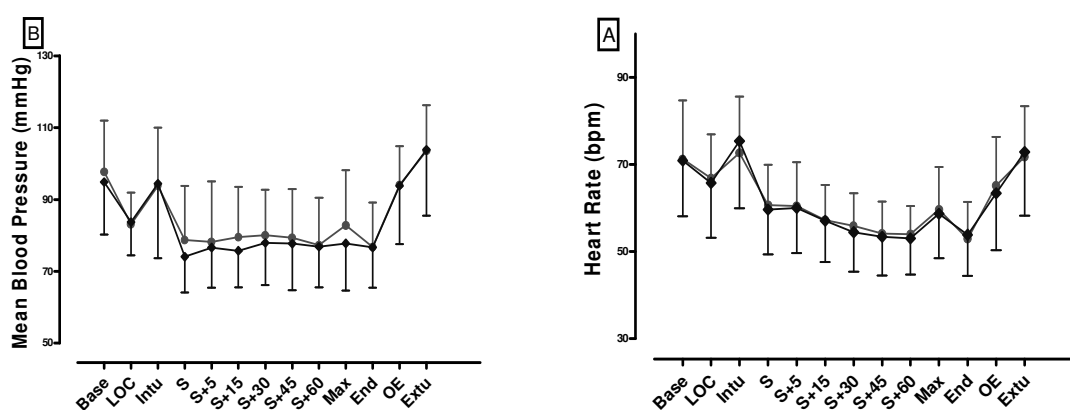


Figure 6. Changes in mean non-invasive arterial blood pressure (NIBP) and heart rate (HR) in SSI-guided analgesia group (●) or standard practice group (□) at major time points during anaesthesia: baseline (Base), loss of consciousness (LOC), intubation (Intu), start of surgery (S), Maximum surgical stimulation (Max), end of propofol and remifentanyl (E), eyes opening (Extu).

(OE) and extubation (Extu). Values are mean (SD); No significant difference between group ($P > 0.05$).

3.6. Postoperative Period

Postoperative pain, nausea and vomiting, modified Aldrete-Score, total satisfaction in the recovery room and on the first day after surgery are shown in Table 10. There were no any significant differences in intensity of postoperative pain (VAS), postoperative nausea and vomiting (PONV), modified Aldrete-score, level of total satisfaction and physiological variables ($P > 0.05$). And no patient reported intraoperative recall.

Table 10. Postoperative Observation (recovery room and on the first day after surgery)

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

Data are median (range) or numbers (proportion). No differences between groups ($P > 0.05$).

Aldrete Score = modified aldrete score, refer to Table 2.

VAS = visual analogue score, scaled from 0 to 10 and 0 means no pain and 10 means the maximum intensity of pain.

PONV = postoperative nausea and vomiting.

4. Discussion

In the present prospective, randomized, controlled clinical study, we investigated the utility of surgical stress index (SSI) for guiding the titration of remifentanyl during a constant hypnotic level controlled by bispectral index (BIS) guided propofol infusion during general anaesthesia with propofol and remifentanyl in patients undergoing ear-nose-throat (ENT) surgery. Our results demonstrate that SSI-guided remifentanyl titration resulted in a significant reduction of remifentanyl consumption, and less incidence of unwanted events (hypertension, hypotension, tachycardia and movement) during surgery when compared with standard practice protocol.

Our results might be of great interest because getting an appropriate analgesic delivery has been a pursuit for all anesthesiologists, which has not been reached so far. In the present study, we used SSI and BIS to guide remifentanyl and propofol infusion, respectively, during general anaesthesia, in other words, we monitored separately the balance of nociception – anti-nociception (stress and analgesic) and hypnosis, which are the main components of general anaesthesia. To our best knowledge, this is the first time that such a study has been performed.

Up to now, many efforts have been made to develop a method to guide analgesic administration during general anaesthesia. In a previous study (Mathews et al., 2007), Mathews et al. concluded that remifentanyl titration during general anaesthesia may be guided by the difference between RE and SE (RE-SE). However, they did not investigate the remifentanyl consumption during anaesthesia. Gruenewald et al. also tried to use the RE-SE difference to guide remifentanyl titration and found that RE-SE difference guided remifentanyl titration resulted in lower remifentanyl consumption when compared the standard practice group during propofol – remifentanyl

anaesthesia (Gruenewald et al., 2007). In their study, however, the propofol infusion was controlled by SE in the RE-SE guided group whereas there was no guiding monitor for propofol infusion in the standard practice group, which is in contrary to the protocol of our present study in which we used BIS for guiding propofol infusion in both group. Furthermore, the RE-SE difference itself has not been validated to be a tool for assessing the balance of nociception – anti-nociception.

It is well known that hypnosis and nociception are partly interrelated: deep hypnosis suppresses nociception (Antognini et al., 2000a; Singh et al., 1999), and significant nociception causes arousal (Antognini et al., 2000a; Antognini et al., 2000b; Guignard et al., 2000; Ropcke et al., 2001). Additionally, hypnotic agents and analgesics have also a synergistic effect with each other. Kern et al. has revealed the tremendous synergy between remifentanil and propofol. BIS is a well-accepted tool to monitor the hypnotic level and BIS-guided anaesthesia has been proved to reduce the risk of awareness during general anaesthesia (2006; Myles et al., 2004). A BIS value of 40 to 60 has been recommended as a ‘ideal’ range (2006; Manyam et al., 2007; Song et al., 1997). Therefore, the facts shown above could explain why we chose a range of $40 < \text{BIS} < 60$ for guiding propofol titration to keep hypnosis at a constant depth in both groups in our present study. We suggest that in such a state, the results of remifentanil consumption resulting from SSI-guidance might be more credible.

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 nociceptive stimulus during general anaesthesia. Huiku et al. proved that SSI correlates positively to surgical nociceptive stimuli and negatively to analgesic drug concentration during propofol-remifentanil anaesthesia (Huiku et al., 2007). Struys et al. and Wennervirta et al. further demonstrated that SSI has a better performance in measuring nociception – anti-nociception balance than SE, RE, BP, heart rate and pulse wave amplitude (PPGA) (Struys et al., 2007; Wennervirta

et al., 2008). In accordance with their findings, the prediction probability (P_k) for SSI to predict the maximum surgical stimulation was 0.85, which was significantly higher than that of SE, RE, RE-SE, HR and BP in the present study. Secondly, the time fractions of actual SSI value > 50 and SSI value < 20 during maintenance of anaesthesia were significantly lower in the SSI-guided analgesia group than in the standard analgesia group, whereas the time fractions of actual SSI value between 20 and 50 were significantly higher in the SSI-guided analgesia group. This indicates that SSI-guided analgesia provided a stable SSI level during maintenance of anaesthesia, in other words, it resulted in a optimal balance of nociception – anti-nociception due to the good correlation between SSI values and nociception – anti –nociception during general anaesthesia. Thirdly, the SSI values at some major time-points during anaesthesia were significantly higher, correspondingly the predicted effect-site concentrations of remifentanyl (PEC_{remi}) at some major time-points during anaesthesia were significantly lower in the SSI-guided analgesia group than in the standard analgesia group. These results may be considered to conclude that the PEC_{remi} s may be overdose at some time-points in the standard analgesia group which in turn resulted in the higher consumption of remifentanyl.

The choice of the range of SSI between 20 and 50 ($20 < SSI < 50$) for guiding remifentanyl titration in the present study might be questioned because an optimal range of SSI during anaesthesia has not been recommended yet (Wennervirta et al., 2008). We chose the range of $20 < SSI < 50$ for guidance of remifentanyl titration during maintenance of anaesthesia in the SSI-guide analgesia group according to the initial findings of a previous study (Struys et al., 2007). In this study it was shown that SSI values were around 20 at baseline when there was no stimulation and PEC_{remi} was at a high level, and SSI values were over 50 after stimulation when the PEC_{remi} was at a lower level. In the present study, the feasibility of the range of $20 < SSI < 50$ used for guiding analgesic titration during general anaesthesia might also be justified, at least to some extent, by the fact that the hemodynamic state was more stable (low incidence of hypertension, hypotension and bradycardia) and less movement episodes

in the SSI-guided analgesia group when compared with standard analgesia group. Moreover, we also analyzed the SSI value of the 95% possibility after intubation and after the maximum operative stimulation using binary logistic regression. The results showed the SSI value of the 95% possibility for intubation was 59 and for the maximum surgical stimulation was 60, which may further support retrospectively our choice of the range of $20 < \text{SSI} < 50$ for guidance of analgesic administration during general anaesthesia. However, whether the range of $20 < \text{SSI} < 50$ is “ideal” needs to be further investigated by more clinical studies.

Interestingly, although the recovery times (times to opening eyes) seemed shorter in the SSI-guided analgesia group than in the standard analgesia group, the differences between groups did not reach the level of statistical significance. This is in contrary to previous studies (Gan et al., 1997; Gruenewald et al., 2007) in which BIS or Entropy were used to guide propofol administration or RE-SE difference to guide remifentanil administration, and found BIS-guided or Entropy-guided anaesthesia resulted in faster emergence. In their studies, lower consumption of propofol was in the BIS- or Entropy-guided group, whereas in our study, the consumption of propofol was comparable between groups since both groups were guided by BIS with respect to propofol titration. The comparison of our study and the previous studies with respect to recovery time and anaesthetic consumption indicates that the emergence time may be determined mainly by the propofol consumption but little by the remifentanil consumption during general anaesthesia.

For evaluation of the performance for SSI to assess nociception – anti-nociception balance, we used the well accepted method, prediction probability P_k , developed by Smith et al. (Smith et al., 1996). The results showed that the P_k values for SSI to predict maximum surgical stimulation and intubation were higher than for other variables studied, BIS, SE, RE, RE-SE, BP and HR, which is in accordance with other previous studies (Ahonen et al., 2007; Huiku et al., 2007; Wennervirta et al., 2008). This further proved that the EEG-derived parameters, BIS and Entropy, mainly

monitor the hypnotic state. BP and HR have been traditionally considered to assess the depth of nociception – anti-nociception balance. However, in the present study, the P_k values for BP and HR to predict maximum surgical stimulation and intubation were almost near to 0.5 which means that their predictive power is not better than ???. Given that the stimulation intensity during surgery varies frequently, the intermittent measurement of blood pressure might be a reason of why the performance of BP in detecting the nociceptive stimulus level was not good in the present study. HR was found to be lower with remifentanil anaesthesia by increasing vagal tone (Komatsu et al., 2007). Gurkan et al. concluded that remifentanil causes direct negative chronotropic and positive inotropic effect (Gurkan et al., 2005). Therefore, the HR might be insensitive to surgical stimulation during remifentanil anaesthesia, in other words, the performance of HR in detecting the nociception – anti-nociception might be low. When considering the results, however, it must be kept in mind that exact numeric P_k values are only comparable between identical study condition only (Gurkan et al., 2005; Wennervirta et al., 2008).

The present study has limitations. First, it might be argued that the investigator was biased in the standard analgesia practice group. Of course, ‘learning contamination’ bias (Roizen and Toledano, 1994) 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 (Kreuer et al., 2003). In the present study, however, the protocol of analgesic administration was strictly pre-determined in both groups. More importantly, in the standard analgesia practice group, the adjustment of predicted effect-site concentration of remifentanil (PEC_{remi}) was clearly defined. Almost all the endpoints for adjustment of remifentanil titration were quantified, e.g. increasing PEC_{remi} at mean BP over 100mmHg or HR over 90 or movement, decreasing PEC_{remi} at mean BP below 60 or HR below 45. Therefore, significant investigator bias can obviously be excluded as a confounding factor for the explanation of the present results.

Second, BP was measured intermittently in our study. The BP values we collected may have not responded to every episode happened during anaesthesia because most of the episodes, e.g. movement, maximum surgical stimulation, have a very short duration and last only some seconds. Therefore, if BP had been measured continuously with an arterial line, the BP values probably would have reacted more timely to changes in nociception. Thereby, the continuous invasive BP might be as good as SSI in predicting the nociception –anti –nociception balance (Wennervirta et al., 2008).

Third, as described by Wennervirta (Wennervirta et al., 2008), rocuronium used in our study may have had an influence the heart rate. Moreover, muscle relaxants may also influence BIS values (Bonhomme and Hans, 2007; Pope et al., 2000). Given that we used rocuronium comparable in both groups, it could be thought that the results have not been influenced substantially.

In conclusion, we investigated the effects of SSI guidance on the remifentanyl titration in comparison to a standard analgesia practice group during propofol-remifentanyl anaesthesia. SSI-guided remifentanyl titration resulted in lower remifentanyl consumption, more stable hemodynamic state, lower incidence of unwanted events and comparable recovery times when compared to standard clinical analgesia practice. Furthermore, we also found that SSI had better performance in detecting maximum surgical stimulation and intubation than SE, RE, RE-SE, BIS, BP and HR. More studies are needed to further investigate for the usefulness of SSI in daily clinical practice.

5. Summary

It is well-known that excessive intraoperative stress (nociceptive stimulus) results in various physiological changes, such as immunological, haemodynamic or endocrine 'stress response', which thereby may compromise patients' outcome, influence the length of hospital stay and overall costs of hospital care. To achieve an appropriate balance of nociception – anti-nociception during general anaesthesia is very important and necessary.

Achieving an appropriate balance of nociception – anti-nociception during general anaesthesia depends on an indicator which can assess accurately the balance of nociception – anti-nociception to guide analgesic delivery. Surgical stress index (SSI) has been proven to have a better performance in assessing the balance of nociception – anti-nociception during general anaesthesia compared with more traditional variables like blood pressure and heart rate.

We designed a prospective, randomized, controlled clinical study, which included two groups – SSI-guided analgesia group and standard analgesia practice group, to investigate the effect of SSI-guided analgesia on recovery time, anaesthetics consumption, incidence of unwanted events during general anaesthesia with propofol and remifentanil during a constant hypnotic level.

The results demonstrated that SSI-guided analgesia resulted in a significant reduction of remifentail consumption, less incidence of unwanted events (hypertension, hypotension, tachycardia and movement) and in a similar recovery time during general anaesthesia when compared with the standard analgesia practice protocol.

Our study also further proved that SSI has a better performance in detecting the balance of nociception – anti-nociception than state entropy (SE), response entropy (RE), difference between response entropy and state entropy (RE-SE), blood pressure and heart rate during general anaesthesia.

However, the ‘ideal’ range of SSI for guiding analgesia needs to be further investigated.

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7. Acknowledgements

First of all, I want to express sincerely my gratitude to my supervisor, Prof. Berthold Bein, DEAA for his invitation to Kiel and his great support for my study, for his scientific supervision and careful modification of the dissertation.

Secondly, I give my thanks to Dr. Werner Jeckstroem for his great support during my clinical data collection, to Dr Carsten Thee and Dr. Jan Wnent for their cooperation in performing the study, to Dr. Matthias Gruenewald for his help in statistical analysis, to all the nurses worked in the ENT anaesthesia department for their kind cooperation.

Thirdly, I would also like to thank GE Healthcare Finland for providing the SSI monitor and SSI sensors.

Finally, I thank my wife for supporting my study abroad and for her caring about our son during my stay in Kiel.

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