Randomized controlled trial of the effect of depth of anaesthesia on postoperative pain


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Background. Our hypothesis was that deep anaesthesia, as estimated by a low target bispectral index (BIS) of 30–40, would result in less postoperative pain than that achieved at a conventional depth of anaesthesia.

Methods. We undertook a randomized double-blind controlled study at two tertiary teaching hospitals in New Zealand (2010–1) recruiting 135 adult patients ASA I–II presenting for non-emergent surgery under general anaesthesia requiring tracheal intubation. Anaesthesia was maintained with desflurane and a multimodal analgesia regimen comprising fentanyl infusion, i.v. paracetamol, and parecoxib. Patients were randomly assigned to either a low BIS (30–40) group or a high BIS (45–60) group. Desflurane concentrations were titrated to achieve these targets. Postoperative pain was assessed by: the pain on awakening (0–10, verbal rating scale, VRSawake) in the post-anaesthetic care unit; pain on activity at 20–24 h after operation (VRSd1A); and the rate of morphine patient-controlled analgesia (PCA) usage over the first 24 h.

Results. There was no statistically significant difference between the two groups for any of the pain scores. The median [inter-quartile range (IQR)] VRSawake was 4.0 (0–8) for the low and 4.0 (0–8) for the high BIS groups (P=0.56). The median (IQR) VRSd1A was 3.0 (1–5) for the low and 3.0 (1.5–4.5) for the high BIS groups (P=0.83). The median PCA morphine consumption in the low BIS group was 0.61 mg h⁻¹ (0.04–1.5) vs 0.43 mg h⁻¹ (0–1.59) in the high BIS group (P=0.98).

Conclusions. We conclude that there is no clinically useful analgesic effect of a deep anaesthesia regimen.

Keywords: depth of anaesthesia; postoperative pain

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of any clinicians who actually used deep anaesthesia to try and reduce postoperative pain, we undertook a randomized blinded trial to investigate the association between high and low levels of general anaesthesia, as measured by the BIS, and post-surgical pain in a broad spectrum of patients undergoing surgery which was anticipated to cause moderate-to-severe pain.

Methods

Ethics

Ethical approval for this study (NTX/09/06/047) was obtained from the Northern X Regional Ethics Committee, Ministry of Health, Auckland, New Zealand (Administrator Pat Chainey) on September 24, 2009. This study was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) number ACTRN12609000350224.

Study subjects and protocol

A total of 135 patients (ASA physical status I or II) undergoing elective surgery were enrolled in the study. Patients were recruited from two major teaching hospitals—Waikato Hospital, Hamilton, and North Shore Hospital, Auckland. We recruited ASA level I–II patients aged between 18 and 65 yr old undergoing elective surgery, where the expected duration of surgery was <180 min, and a general anaesthetic involving tracheal intubation was planned. A healthy population group was chosen to avoid the question of adverse long-term morbidity and mortality associated with deep anaesthesia. Patients were required to be competent to consent to participation, and able to comprehend the verbal response scale (VRS) pain rating. Patients with a preoperative diagnosis of malignancy, epilepsy, neuromuscular disease, psychiatric disease, pregnancy, severe asthma, weight >120 kg or BMI >35 kg m⁻², and chronic opioid use were excluded. No regional anaesthesia, neuraxial block, or total i.v. anaesthesia was permitted for the study.

After informed written consent, the patient was randomized, by the method of concealed envelopes, to one of the two target BIS groups—Low-BIS (target BIS 30–40) and High-BIS (target BIS 45–60). Pain scores were collected by investigators blinded to the group allocation.

Before the induction of anaesthesia, the BIS sensor was attached to the patient’s forehead in accordance with the manufacturer’s instructions with the cable to the patients left, and connected to the BIS monitor. Patients received standardized general anaesthesia consisting of an i.v. induction using propofol (1–3 mg kg⁻¹), neuromuscular blocking agent, and maintenance with 0.7–1.4 MAC desflurane. No nitrous oxide was given. The intraoperative i.v. opioid dosing regimen was 2 μg kg⁻¹ fentanyl i.v. bolus on induction, and a 2 μg kg⁻¹ h⁻¹ infusion from the time of surgical preparation to surgical closure. In addition, all patients received 1 g paracetamol, 40 mg parecoxib, 4 mg dexamethasone, and 0.5 mg droperidol via the i.v. route. While no regional anaesthetic techniques were used, local anaesthetic was infiltrated to the wound at skin closure.

After operation, pain relief was obtained in the post-anaesthesia care unit (PACU) with i.v. morphine titrated to achieve a pain score of <4. On the ward, an i.v. morphine patient-controlled analgesia (PCA) pump was provided using a 1.5 mg bolus dose, with a 5 min lockout interval and 8 mg h⁻¹ maximum dose.

Nausea and vomiting was scored on a 0–3 scale, scoring 0 for no nausea or vomiting, 1 for mild, 2 for moderate, and 3 for severe nausea and vomiting on the basis of the nursing notes and number of doses for anti-emetics given.

Drug administration times, cardiovascular, respiratory, BIS, and anaesthetic parameters were recorded using SAFERSleep® OR Software (Safer Sleep LLC, Nashville, TN, USA) electronic recording system.

Fentanyl measurement

Venous blood samples for the measurement of fentanyl levels were obtained at the end of surgery. Measurement of fentanyl using liquid chromatography mass spectrophotometry was carried out by AnQual Laboratories (Auckland, New Zealand).

Intraoperative BIS adjustment and measurement method

Intraoperatively, the concentration of desflurane was titrated according to the target BIS values. End-tidal desflurane concentration was recorded at 1 min intervals. If the clinicians were reluctant to give very low or high concentrations of desflurane because of the risks of awareness or overdose, we suggested that the clinician should titrate the desflurane between 0.7 and 1.4 MAC limits. They could exceed these limits if they were clinically comfortable with the state of the patient. We recorded the median BIS and end-tidal desflurane concentration from the middle half of the operation as the indicators of depth of anaesthesia.

Pain measurements

There were three outcome measurements to quantify postoperative pain: (i) the initial pain score on awakening in the PACU (VRSawake); (ii) on the morning (at 20–24 h) post-surgery during light activity (VRS24h); and (iii) the mean PCA morphine dose rate (mg h⁻¹) for the first day after operation. We used an 11-point integer verbal rating scale (VRS) ranging from 0, ‘no pain at all’, to 10, ‘the worst pain imaginable’.

Statistics

This study was powered using initial VRSawake as the primary outcome measure. From previous studies, we assumed that there would be a difference in pain score of 2, and a standard deviation (sd) of 3.5. We calculated a sample size requirement of 60 in each group to give a power of 0.87. To allow for fall out, we obtained complete data from 135 patients. Data are presented as mean (sd) for normally distributed continuous data, and median (inter-quartile range, IQR) for skewed data; and as numbers for categorical data. We analysed this study on an intention-to-treat basis (according to BIS allocation group). Because it was not always possible to achieve the
target BIS, we also examined any correlation between pain outcomes and actually attained BIS and end-tidal desflurane concentrations. We compared the pain scores between the low and high BIS groups using the Mann–Whitney U-test and assessed correlations using Spearman’s correlation coefficient ($r$). The patients were not stratified in the randomization process, and we found a post hoc significant difference in surgery type between the two BIS allocation groups (as shown in Table 1). We therefore also analysed the data using a two-way Kruskal–Wallis method, with surgery type and BIS allocation group as the explanatory factors.

**Results**

Aside from the end-tidal desflurane concentration and average BIS, the groups were comparable as regards patient characteristic data as shown in Table 1. A total of 23 patients required the use of vasopressors (metaraminol) for hypotension; 14 in the low BIS group and nine in the high BIS group. The difference was not statistically significant ($P=0.21$, $\chi^2$ test).

**Pain outcomes**

The depth of anaesthesia had no influence on any postoperative pain outcome when analysed on an intention-to-treat basis (Fig. 1). The median (IQR) VRS$_{awake}$ was 4.0 (0–8) for the low and 4.0 (0–8) for the high BIS groups ($P=0.56$). The median (IQR) total amount of morphine administered in PACU was 4.5 mg (0–10) for the low BIS group and 5 mg (0–9.15) for the high BIS group. The median (IQR) value for VRS$_{t1A}$ was 3.0 (1–5) for the low and 3.0 (1.5–4.5) for the high BIS groups ($P=0.83$). The median (IQR) PCA morphine consumption in the low BIS group was 0.61 mg h$^{-1}$ (0.04–1.5) vs 0.43 mg h$^{-1}$ (0–1.59) in the high BIS group ($P=0.45$).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristic data</th>
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<tbody>
<tr>
<td></td>
<td>Low BIS ($n=66$)</td>
</tr>
<tr>
<td>Gender</td>
<td>75% female</td>
</tr>
<tr>
<td>Age</td>
<td>42.1 (17–64)</td>
</tr>
<tr>
<td>Height</td>
<td>1.65 (0.09)</td>
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<tr>
<td>Mean duration (min)</td>
<td>Gynaecological 75</td>
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<td></td>
<td>General surgery 100</td>
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<tr>
<td></td>
<td>Orthopaedic 116</td>
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<td></td>
<td>BMI 27.75 (5.6)</td>
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<tr>
<td></td>
<td>End-tidal desflurane 6.29 (1.29)</td>
</tr>
<tr>
<td>Types of operation</td>
<td>Gynaecological</td>
</tr>
<tr>
<td></td>
<td>Total abdominal hysterectomy 16</td>
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<tr>
<td></td>
<td>Operative laparoscopic surgery 5</td>
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<tr>
<td></td>
<td>Minor surgery (vaginal repair, minor laparoscopic, vaginal hysterectomy) 12</td>
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<tr>
<td></td>
<td>General surgery</td>
</tr>
<tr>
<td></td>
<td>Laparoscopic procedures 19</td>
</tr>
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<td></td>
<td>Open procedures 2</td>
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<td></td>
<td>Orthopaedic</td>
</tr>
<tr>
<td></td>
<td>Open reduction internal fixation of fractures 11</td>
</tr>
<tr>
<td></td>
<td>Joint procedures (joint replacement/reconstruction) 1</td>
</tr>
</tbody>
</table>

**Fig 1** Comparison of postoperative pain scores and PCA use vs BIS target group.
The combined two-way (surgery type and BIS allocation group) Kruskal–Wallis analysis showed that surgery type was significantly associated with $\text{VRS}_{\text{awake}}$ ($P<0.01$), and less so with $\text{VRS}_{\text{d1A}}$ ($P=0.1$); but that the BIS group allocation had no significant association with $\text{VRS}_{\text{awake}}$ ($P=0.45$), or with $\text{VRS}_{\text{d1A}}$ ($P=0.6$). For the overall model, the $P$-values were 0.052 for $\text{VRS}_{\text{awake}}$ and 0.6 for $\text{VRS}_{\text{d1A}}$.

There was a significant separation in the BIS score of about 10 between the two groups. However, the clinicians tended to bias towards a lower BIS anaesthetic with an overall mean BIS of 37.6. In the low BIS group, the mean BIS was 32.6, and was above 40 for 21% of the time. In the high BIS group, the mean BIS was 42.2, and was above 40 for 62% of the time.

**Correlations between end-tidal desflurane, actual BIS, and postoperative pain**

As shown in Figure 2, there was a weak association between end-tidal desflurane and actual BIS, and no association between BIS, end-tidal desflurane, and any of the pain outcomes (Table 2).

**Fentanyl measurement**

Fentanyl was detected at a concentration range between 0 and 4.1 ng ml$^{-1}$ with a median (IQR) for the entire data set of 0.79 (0.25–1.35) ng ml$^{-1}$. There was no difference in the fentanyl levels in the low and high BIS groups (0.79 (0.24–1.45) vs 0.80 (0.27–1.27) ng ml$^{-1}$). Fentanyl levels did not correlate significantly with either $\text{VRS}_{\text{awake}}$ ($r = -0.15$, $P = 0.09$), duration of surgery ($r = 0.01$, $P = 0.95$), or BIS level attained ($r = -0.81$, $P = 0.16$).

There was no significant difference in nausea and vomiting between the two groups.

**Discussion**

The results of this study showed no significant differences between patients subjected to an increased depth of anaesthesia and postoperative pain scores or analgesic requirements. This outcome differs from previous publications, but supports the findings of Baldini and colleagues who found no differences in perioperative cortisol, glucose, or lactate and also pain scores and opioid requirements in patients randomized to low BIS (<25) or high BIS (50) values. Our findings suggest that—at the ranges selected—targeting a deeper anaesthetic depth, as measured by the BIS, would not be a clinically useful strategy for reducing postoperative pain.

The cause for the difference in our results is unclear; however, there were some methodological differences in our study. The previous studies limited their study population to a narrow range of specific procedures with small numbers of patients recruited. We embarked on this double-blinded randomized control study of more than 120 patients including all elective surgical procedures of expected moderate–severe postoperative pain to see whether we could generalize the findings to a typical clinical population. The vagaries of randomization resulted in the low BIS group being allocated more orthopaedic operations (which would likely have high postoperative pain); but this was balanced by the low BIS group also having more minor gynaecological procedures—which would be predicted to have less postoperative pain. When the surgical classification was incorporated into a multivariate analysis, there was still no evidence for a significant difference in pain outcomes between the low and high BIS groups. Thus, we believe that running a deep general anaesthetic is not a clinically useful strategy for reducing postoperative pain.

Unlike the previous studies, we did not use nitrous oxide as part of the anaesthetic regimen. Nitrous oxide appears to have significant modulatory effect on postoperative pain. We

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**Table 2** Correlations between pain scores, BIS, and end-tidal desflurane ($r$, Spearman’s correlation coefficient)

<table>
<thead>
<tr>
<th></th>
<th>$r$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-tidal desflurane vs $\text{VRS}_{\text{awake}}$</td>
<td>$-0.05$</td>
<td>0.62</td>
</tr>
<tr>
<td>End-tidal desflurane vs $\text{VRS}_{\text{d1A}}$</td>
<td>$0.02$</td>
<td>0.81</td>
</tr>
<tr>
<td>End-tidal desflurane vs PCA morphine</td>
<td>$0.06$</td>
<td>0.61</td>
</tr>
<tr>
<td>Actual BIS vs $\text{VRS}_{\text{awake}}$</td>
<td>$0.04$</td>
<td>0.71</td>
</tr>
<tr>
<td>Actual BIS vs $\text{VRS}_{\text{d1A}}$</td>
<td>$-0.17$</td>
<td>0.12</td>
</tr>
<tr>
<td>Actual BIS vs PCA morphine</td>
<td>$-0.14$</td>
<td>0.2</td>
</tr>
<tr>
<td>End-tidal desflurane vs actual BIS</td>
<td>$-0.21$</td>
<td>0.05</td>
</tr>
</tbody>
</table>
postulate that while nitrous oxide on its own is incapable of producing reliable general anaesthesia, the addition of nitrous oxide may result in some benefit for deep general anaesthesia.9–11 It is conceivable that the antihyperalgesic properties of N-methyl-D-aspartate blockers (like nitrous oxide) may interact synergistically with the higher concentrations of volatile anaesthetic drugs to reduce the development of postoperative pain. This interaction has not been systematically studied to our knowledge, although the effects of a comparable, and well studied, N-methyl-D-aspartate blocking drug like ketamine, suggest an appreciable effect might be present. Like Baldini and colleagues, we used desflurane as the maintenance volatile agent because of its rapid recovery characteristics.12 13

We used an anaesthetic regimen which included a standardized fentanyl infusion. We measured the fentanyl levels at the end of surgery in order to be sure that any possible observed analgesic effect in the low BIS group could not be accounted for by a diminished fentanyl clearance—secondary to the high concentrations of desflurane. No such effect was seen. The analgesia used in our study was different from the other studies which used a variety of analgesia regimens: anaesthetist-directed fentanyl boluses,27 remifentanil infusion,2 or a combination of morphine and tramadol.17 All our patients received a multimodal analgesia regimen, consisting of an opioid, nonsteroidal anti-inflammatory, and paracetamol. Hence the optimized background analgesia may have obscured any (modest) analgesic effect from differences in anaesthetic depth. One of the reasons for using a continuous fentanyl infusion was to make it easier for the clinicians to run a reasonably light anaesthetic. However, in practice, the consultant anaesthetists were reluctant to titrate towards a BIS of 50–60, and the BIS values in the high BIS group ended up in the lower end of the manufacturer’s recommended range of 40–60. Thus, although we ended up with a separation of 10 BIS units between the groups, we effectively compared standard anaesthesia depth vs deeper anaesthesia. Nevertheless, it was clear that excessively deep anaesthesia showed no benefit for postoperative pain in a representative group of patients. We also analysed the data on the basis of actually achieved anaesthetic depth (as measured by actual BIS and end-tidal desflurane), but again found no trace of a correlation with postoperative pain intensity.

The separation of BIS levels was difficult to achieve in many patients and it may have been that achieving extremely low BIS values would have led to a different result. However, the potential adverse effects of low BIS levels are unknown. Sessler and colleagues24 have suggested the combination of low BIS, low arterial pressure, and low MAC (minimum alveolar concentration) are associated with a significant increase in mortality. While causation is not known, there may be a reluctance to deliberately reduce BIS levels for limited analgesic benefits.14 The poor correlation between desflurane concentrations and BIS is probably the main reason why it is sometimes quite hard to achieve the target BIS range. This is in agreement with the results reported from a much larger study by Whitlock and colleagues25 who found that the relationship between volatile anaesthetic concentrations and BIS was very unreliable. Because nitrous oxide does not cause a decrease in the BIS, it is easier to give a smooth anaesthetic at relatively higher BIS values, than would be the case when nitrous oxide is not part of the anaesthetic regimen. In essence, the use of nitrous oxide enables something like 0.5 MAC of extra anaesthetic to be given to the patient without causing a decrease in BIS.

In conclusion, while previous reports have suggested a potential reduction in pain and opioid requirements in patients subjected to an increased depth of anaesthesia, our study suggests that—when administered in the absence of nitrous oxide and in the presence of a typical multimodal analgesic regimen—the targeting of deep anaesthesia using desflurane does not result in any clinically useful analgesic effect in the postoperative period.

Authors’ contributions
C.J.L.: assisted study design and protocol, Ethics committee approval; recruited all patients at Waikato District Health Board; collated spreadsheet of data points, and interviewed patients; drafted manuscript. G.M.J.: coordinated laboratory aspects of study at University of Waikato, prepared blood samples for fentanyl measurement, and analysed lab reports; assisted with statistical analyses and with drafting manuscript. M.C.: recruited patients from Waitemata District Health Board, assisted with study design. M.K.: initiated project, assisted with study protocol, and assisted with Ethics submission; supported local patient recruitment and involved with manuscript submission. M.S.: prepared Ethics approval; involved with development of consent forms, participant information sheets, and data collection forms. J.W.S.: initiated project and development of study design and protocol; involved with local patient recruitment; carried out statistical analysis, and drafted manuscript.

Declaration of interest
None declared.

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