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

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Editor's key points

- Recent studies suggest that deeper anaesthesia might be associated with reduced postoperative pain.
- The authors performed a controlled trial in which patients were randomized to light or deep bispectral index-guided desflurane anaesthesia.
- Blinded investigators found no differences in postoperative pain scores and morphine requirements.

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, VRS_{awake}) in the post-anaesthetic care unit; pain on activity at 20–24 h after operation (VRS_{d1A}); 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)] 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) VRS_{d1A} 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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Effective postoperative pain management has been associated with enhanced recovery times, the prevention of long-term post-surgical pain, and a reduction in hospital stay. Acute pain stimulates an endocrine-metabolic response.[1] Recent studies have suggested that deeper anaesthesia could attenuate this response and decrease postoperative pain.[2 3]

Henneberg and colleagues[2] studied 43 patients undergoing elective gynaecological surgery using mid-latency auditory-evoked potentials and found that 30% more morphine was needed for postoperative pain control in those patients with 'lighter' levels of anaesthesia. Using the bispectral index (BIS) as a marker of depth of anaesthesia in patients undergoing major urological surgery, Soumpasis and colleagues[4] found higher pain scores and greater analgesic requirement in the high BIS group. Gurman and colleagues[5] used EEG spectral edge frequency in patients undergoing gastric banding and demonstrated pain scores in the recovery area to be 50% higher in the more lightly anaesthetized group compared with those with 'deeper' levels of anaesthesia. Finally, Sahni and colleagues reported lower pain scores and reduced analgesic requirement in patients undergoing laparoscopic cholecystectomy who were randomized to low BIS scores.[6] All these studies used nitrous oxide and looked at limited types of operations (gastric banding, major urology, abdominal hysterectomy). In contrast, Baldini and colleagues'[3] small study showed no difference in either pain or endocrine response between the high- and low-dose anaesthesia. Because there seemed to be some conflict between the results of these studies, and the fact that we were unaware

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.[7]

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 post-operative pain: (i) the initial pain score on awakening in the PACU (VRS_{awake}); (ii) on the morning (at 20–24 h) post-surgery during light activity (VRS_{d1A}); 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 VRS_{awake} 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