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Original Article

Title: **The effect of total intravenous anaesthesia with propofol on postoperative pain after third molar surgery: a double blind randomized controlled trial**

Short title: **Analgesic effect of propofol based anaesthesia**

S.S. Wong[1], M.Y. Leung[2], C.W. Cheung[1]

[1] Laboratory and Clinical Research Institute for Pain, Department of Anaesthesiology, The University of Hong Kong, Hong Kong, China.

[2] Department of Oral and Maxillofacial Surgery, The University of Hong Kong, Hong Kong, China

[1] Laboratory and Clinical Research Institute for Pain, Department of Anaesthesiology, The University of Hong Kong, Hong Kong, China

Correspondence

Dr Stanley Sau Ching Wong

Email: wongstan@hku.hk

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Address: Room 424, Block K

Queen Mary Hospital

102, Pokfulam Road

Hong Kong

Tel: (852) 2255-3327

Fax:(852) 2855-1654

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Conflicts of Interest

None declared

Significance

Choice of general anaesthetic technique can affect postoperative analgesia. The results of this study suggest that propofol TIVA improves postoperative pain and patient satisfaction after third molar surgery compared to inhalational anaesthesia.

Abstract

Background: Total intravenous anaesthesia (TIVA) with propofol may reduce pain after surgery compared with inhalational anaesthetic techniques. Whether propofol provides analgesic benefit may be influenced by the surgical procedure and anaesthetic/analgesic regime. Third molar surgery is a consistent and fairly standard surgical technique that provides a good model for postoperative pain. We investigated whether propofol TIVA or sevoflurane inhalational anaesthesia would produce better quality pain relief after third molar surgery.

Methods: In this double blind, randomized controlled trial, patients scheduled for bilateral third molar surgery received propofol TIVA or sevoflurane inhalational anaesthesia. Postoperative numerical rating pain scores, analgesic consumption, adverse effects, and global pain satisfaction were assessed.

Results: Data from forty-eight patients in each group were analysed. The area under curves for numerical rating scale pain scores were significantly lower in the propofol TIVA group at rest and during mouth opening between 1 to 72 hours after surgery ($p=0.013$ at rest, $p=0.021$ with mouth opening). There was no difference in postoperative analgesic consumption. Propofol TIVA was associated with less postoperative headache ($p=0.041$ in the postoperative anaesthetic care unit, $p=0.036$ in ward). There were no differences in other adverse effects including postoperative nausea and vomiting. Global pain satisfaction and level of postoperative discomfort at 24 hours after surgery was significantly better in the propofol TIVA group ($p=0.008$ and $p=0.009$, respectively).

Conclusion: Propofol based TIVA was associated with reduced postoperative pain after bilateral third molar surgery, but did not reduce postoperative analgesic consumption.

Introduction

Acute postoperative pain is an important clinical problem, with 20-40% of patients suffering from severe pain after surgery (Gerbershagen et al., 2013). Poor acute postoperative pain control is associated with reduced patient satisfaction, delayed recovery, development of chronic post-surgical

pain, and increased morbidity (Beattie, Badner, & Choi, 2003; Kehlet, Jensen, & Woolf, 2006; Rodgers et al., 2000). Strategies to reduce acute postoperative pain are important to improve patient care and perioperative outcomes.

Propofol is a commonly used intravenous anaesthetic drug for both induction and maintenance of general anaesthesia. Total intravenous anaesthesia (TIVA) with propofol has been associated with reduced postoperative pain and opioid consumption compared with inhalational anaesthesia (Chan et al., 2016; Cheng, Yeh, & Flood, 2008; Ji, Wang, Zhang, Liu, & Peng, 2018; Li et al., 2012; Tan, Bhinder, Carey, & Briggs, 2010). However, the overall evidence is not consistent, and other clinical studies have shown no significant analgesic effect (Fassoulaki, Melemeni, Paraskeva, Siafaka, & Sarantopoulos, 2008; Pokkinen, Yli-Hankala, & Kalliomaki, 2014; Wong, Choi, Lee, Irwin, & Cheung, 2018). A meta-analysis of fourteen trials showed that propofol TIVA was associated with a statistically significant, but small reduction in pain scores 24 hours after surgery (Qiu, Choi, Wong, Irwin, & Cheung, 2016). Another meta-analysis showed reduced postoperative pain at 30 min, 1 hour, and 12 hours and reduced opioid consumption in the first 24 hours, but this was not significant when a conservative *P*-value of 0.01 was used to account for substantial heterogeneity (Peng et al., 2016). Whether propofol TIVA reduces postoperative pain may depend on factors such as surgical procedure and the anaesthetic and analgesic technique.

Third molar surgery is a commonly performed surgical procedure, and is associated with moderate postoperative pain (Au, Choi, Cheung, & Leung, 2015; Cheung, Ng, Choi, et al., 2011). Dental surgery produces an inflammatory pain model (Cheung, Ng, Choi, et al., 2011). Tissue injury from surgery induces an inflammatory response with increased levels of pro-inflammatory cytokines (Alazawi, Pirmadjid, Lahiri, & Bhattacharya, 2016). Pro-inflammatory cytokines such as TNF-α and IL-1β have pro-nociceptive effects and inhibition has been associated with reduced pain responses (Cunha et al., 2005; Watkins, Maier, & Goehler, 1995). In addition, pain with mouth opening after

third molar surgery represents mechanical hyperalgesia (Cheung, Ng, Choi, et al., 2011), which is enhanced by inflammatory stimuli (Lis, Grygorowicz, Cudna, Szymkowski, & Balkowiec-Iskra, 2017). Propofol has anti-inflammatory effects and reduces levels of pro-inflammatory cytokines both in animal and clinical studies (Chen et al., 2005; Corcoran et al., 2004; Corcoran et al., 2006; Ma et al., 2013). In coronary artery bypass surgery, propofol TIVA was associated with reduced levels of pro-inflammatory cytokines at 4 hours after reperfusion (Corcoran et al., 2004; Corcoran et al., 2006). Therefore, we believe that propofol may effectively reduce pain both at rest and with mouth opening after bilateral third molar surgery. Furthermore, propofol inhibits N-methyl-D-aspartate (NMDA) receptors and hyperpolarization-activated cyclic nucleotide-regulated 1 (HCN1) channels, and has free radical scavenging properties (Kingston et al., 2006; Qiu et al., 2017; Thiry et al., 2004; Tibbs et al., 2013; Vasileiou et al., 2009). Propofol has been shown to reduce inflammatory pain in rats by modulating the NMDA receptor (Qiu et al., 2017). These are other mechanisms through which propofol may reduce postoperative pain.

General anaesthesia is used for patients undergoing bilateral third molar extraction and/or deep third molar position in our centre. This represents 30-40% of our total third molar cases. The aim of this study was to investigate the effect of propofol TIVA on postoperative pain in patients undergoing bilateral third molar surgery. Our hypothesis was that propofol TIVA would reduce postoperative pain compared to inhalational anaesthesia with sevoflurane.

Methods

This study was conducted from December 2016 to March 2018 in Queen Mary hospital, which is a tertiary university hospital in Hong Kong, China. The study was approved by the local university's Institutional Review Board (UW 16554, 7TH December 2016). The clinical trial was registered at ClinicalTrials.gov (NCT03058341). Written consent was obtained from all patients participating in the trial. Patients who had an American Society of Anaesthesiologists (ASA) status of I to III, aged 18

to 80 years old, and scheduled for elective extraction of impacted bilateral lower third molar teeth under general anaesthesia were eligible for recruitment. Exclusion criteria was as follows: known drug allergy to propofol, opioids, non-steroidal anti-inflammatory drugs (NSAIDs) including COX-2 inhibitors, paracetamol; alcohol or drug abuse; impaired renal function (defined as preoperative serum creatinine level over 120μmol/L), liver dysfunction (plasma bilirubin over 34 μmol/L, INR ≥ 1.7, ALT and AST over 100U/L), impaired mental state, body mass index over 35kg/m^2, pregnancy, local infection, known psychiatric illness; patients with chronic pain; chronic opioid users; and patient refusal.

This was a prospective, double blind, randomized controlled trial. The patients were randomized into one of two groups. They were allocated to receive either inhalational anaesthesia with sevoflurane (SEVO) or total intravenous anaesthesia with propofol (TIVA). Patients were stratified in randomization using a computer generated random sequence. The sequence was prepared by a statistician unaware of the nature of the clinical study. The sequence was concealed in opaque envelopes and opened at the time of intervention by the attending anaesthetist. Patients were not informed about the type of anaesthesia they would receive. A separate investigator who was blinded from patient allocation collected the data from the patients. The anaesthetist providing general anaesthesia was not involved in data collection.

Patients were not premedicated. On arrival to the operation theatre, a 20 or 22-gauge intravenous cannula was inserted. Standard monitoring with pulse oximeter, non-invasive blood pressure, and three lead electrocardiogram was applied prior to induction. Non-invasive blood pressure was checked at least every 5 minutes throughout the operation.

General anaesthesia for patients in the TIVA group was induced and maintained with total intravenous propofol using the Marsh effect site model (Fresenius Kabi). Remifentanil 0.5-1 μg/kg and atracurium 0.5mg/kg was also given during induction. Patients were given oxygen and air. In the SEVO group, patients were induced with intravenous propofol 1.5-3mg/kg, remifentanil 0.5-1 μg/kg, and atracurium 0.5mg/kg. Sevoflurane, air and oxygen were used for maintenance of general anaesthesia for patients in the SEVO group. Sevoflurane was kept between 0.7-1.5 MAC. Bispectral index (BIS) monitoring was applied and depth of anaesthesia was titrated to keep a BIS value of 40-60 in both groups of patients. Apart from the delivery of general anaesthesia, both groups of patients received the same perioperative anaesthetic and analgesic management. Intubation via the nasal route was performed for all patients. FiO_2 was kept between 35-50%. Intravenous remifentanil infusion was given at dose of between 0.1-0.2 $\mu g.kg^{-1}.min^{-1}$ in all patients, and the infusion rate was titrated to keep the mean arterial pressure and heart rate within 20% of baseline values and between 45 to 100 beats per minute, respectively. Mean arterial pressure in the ward was taken as the baseline. If hypertension or tachycardia persisted despite remifentanil infusion of up to 0.2 $\mu g.kg^{-1}.min^{-1}$, antihypertensive agents such as beta-blockers, glyceryl trinitrate, and hydralazine could be given at the discretion of the attending anaesthetist. Local infiltration of 2.7ml of 2% lignocaine with 1 in 80,000 adrenaline was injected around the base of the gum of each third molar tooth by the dental surgeon. Morphine sulphate at a dose of 0.025-0.075 mg/kg was given intravenously before start of surgery and gum incision, and ondansetron 4mg was given intravenously before the end of surgery. The anaesthetic agent (propofol or sevoflurane) and remifentanil infusion was switched off at the end of surgery and reversal of muscle relaxation was obtained with neostigmine 50 μg/kg and atropine 20 μg/kg. Patients were extubated after recovery of consciousness. They were monitored in the post-anaesthetic care unit (PACU) for at least 30 minutes before being discharged back to the ward when vital signs were stable. Resting NRS pain scores (0-10, in which 0 meant no pain and 10 meant the worse possible pain), blood pressure, heart rate, oxygen saturation, respiratory rate and the Ramsay sedation scores were checked every 5 minutes in the PACU. Two milligrams of intravenous morphine sulphate were given every 5 minutes upon patient request when the NRS pain score was over 3/10.

A research assistant unaware of patient allocation collected data in the ward and performed phone follow-up after patient discharge. In the ward, NRS pain scores at rest and mouth opening, and incidence of side effects were recorded every 1 hour for 6 hours, and then once every 4 hours. Oral paracetamol 1g every 6 hours was prescribed regularly, and oral dihydrocodeine 30mg was prescribed as required to a maximum of 4 times daily. Patients were told that they could request dihydrocodeine if their NRS pain score was over 3/10. Patients could choose not to take dihydrocodeine even if their pain score was over 3/10. The dental surgeon determined readiness for final hospital discharge.

Patients were given a diary to record NRS pain scores at rest and with mouth opening, analgesic consumption, and side effects at the 24^{th}, 48^{th} and 72^{nd} hours after operation. Global pain satisfaction using a scale of 0-10 (0 being least satisfied and 10 being most satisfied) was recorded on postoperative day 3. Patients were asked to report their level of discomfort at the 24^{th}, 48^{th}, and 72^{nd} hours after operation. They were asked to choose between: 1) none, 2) mild discomfort, 3) moderate discomfort, or 4) severe discomfort. Oral paracetamol and dihydrocodeine was prescribed as described above for 3 days after operation.

Our primary outcome measurement was postoperative pain relief expressed in average area under curve (AUC) between 1-72 hours after surgery. From our previous work on analgesic efficacy for third molar surgery (Cheung, Ng, Choi, et al., 2011), the estimated NRS treatment outcomes (area under curve 1-72 h) were 198.2 vs 285.2 and the difference was 87 with a pooled standard deviation of 140.1. This corresponded to a pain score reduction of 30.5% compared to the control group. A change of 20-22% has been suggested to correspond to minimum clinically significant decrease in acute pain (Cepeda, Africano, Polo, Alcala, & Carr, 2003; Olsen et al., 2017). In order to detect a difference in pain score reduction of 30.5% compared to the control group, the sample size required to achieve statistical significance of this treatment difference at the 5% level with 0.80 statistical power would be 41 patients per group. To take into account of potential patient dropout (5%) and allowance

for possible extra sample requirements for the secondary outcomes (10%), 48 patients per group were recruited (96 in total).

Patient demographic data were analysed using Student's t-test and Chi-square test. Intraoperative data including duration of surgery and anaesthesia, remifentanil infusion rate, and morphine consumption were analysed by Student's t-test or Mann-Whitney U-test. Postoperative analgesic drug consumption was analysed using Mann-Whitney U-test, and postoperative adverse effects were analysed by Chi-square test or Fisher's Exact test as appropriate. Integrated values of postoperative NRS pain scores were expressed as weighted average areas under curve (AUC) over 1-12 hours, 12-72 hours and 1-72 hours after surgery using trapezoid rule. The Shapiro–Wilk test was used to assess normality. The AUC NRS pain scores were found to be not normally distributed, and were therefore tested by Mann-Whitney U-test. The statistical tests were considered significant when *P* was less than 0.05. All analyses were performed using the IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp. USA).

Results

Ninety-six patients were recruited (48 in each group). All recruited patients completed the study and results were used for analysis (Fig 1). Recruitment began on 22nd December 2016 and last follow up date was 27th March 2018. There was no difference between groups in patient demographics, duration of operation, duration of anaesthesia, and intraoperative morphine consumption (Table 1). Intraoperative remifentanil infusion rate was higher in the TIVA group (0.15 [0.12-0.2] vs 0.15 [0.1-0.15], *P*=0.003, Table 1). The mean effect site propofol concentration for patients in the TIVA group was 3.1μg/ml (SD+/-0.56).

The time when general anaesthesia was completed was defined as postoperative time 0. Median NRS pain scores at rest and with mouth opening from postoperative time 0 to 72 hours after surgery were recorded (Fig 2). Postoperative AUC NRS pain scores in the TIVA group were significantly lower both at rest and during mouth opening between 1-72 hours (P=0.013 at rest, P=0.021 with mouth opening), 1-12 hours (P=0.036 at rest, P=0.028 with mouth opening), and 12-72 hours (P=0.01 at rest, P=0.024 with mouth opening) (Table 2). There were no differences in the use of intravenous morphine in the PACU, and postoperative use of dihydrocodeine between the two groups (Table 3). Paracetamol was prescribed regularly to patients in both groups and there was no difference in the use of postoperative paracetamol (data not shown). There was no difference in the time to first rescue analgesic use and number of patients requiring rescue analgesics in the PACU (Table 3).

No serious adverse events were reported in this study. Patients in the TIVA group had a significantly lower incidence of headache both in the PACU (P=0.041) and in the ward (P=0.036) (Table 4). Significantly more patients in the TIVA group had no adverse effects in the ward (P=0.022). There were no differences in the incidences of other adverse effects including nausea and vomiting (Table 4). Ramsay sedation scores in the PACU were similar between the two groups (data not shown). Patient reported level of discomfort 24 hours after surgery was significantly better in the TIVA group (P=0.09), but not at 48 and 72 hours after surgery (Table 5). Global pain satisfaction was significantly higher in the TIVA group 72 hours after surgery (8 [7-10] vs 7 [5-8], P=0.008).

Discussion

In this study, we found that propofol TIVA was associated with reduced postoperative pain after bilateral third molar surgery. There was no difference in postoperative analgesic consumption. Propofol TIVA was associated with less headache, but the incidence of other adverse effects was similar between the two groups. Global pain satisfaction scores were significantly higher in the TIVA group.

Postoperative dental pain usually is greatest at around 12 hours, but the duration of pain, reduced mouth opening, and swelling can last for 3 days (Seymour & Walton, 1984; Troullos, Hargreaves, Butler, & Dionne, 1990). To assess the effect of propofol TIVA at different time periods after surgery, we looked at the AUC for NRS pain scores at 1-12 hours, 12-72 hours, and 1-72 hours. Propofol TIVA reduced pain scores during all these time periods, suggesting that it had an analgesic effect during both the early and later acute postoperative period. This is beyond its pharmacokinetic duration of action, suggesting some preventive effects. Third molar surgery is a commonly used model for acute pain clinical trials. The pain stimulus amongst patients after dental surgery is relatively homogenous, pain severity is moderate, and they can be easily categorized (Cooper, 1983). Therefore, it is a pain model that is sensitive for showing the efficacy of analgesic drugs (Au et al., 2015). Postoperative dental pain produces an inflammatory pain model (Cheung, Ng, Choi, et al., 2011). Therefore, our results suggest that propofol is useful in reducing postsurgical inflammatory pain.

Other clinical studies have also compared the analgesic effects of propofol TIVA with inhalational anaesthesia when using remifentanil infusion. One randomized controlled trial found that propofol TIVA was associated with reduced early postoperative pain (0.5 and 1 hour) in patients undergoing gynaecological laparoscopies (Li et al., 2012). Another trial found no differences in patients undergoing laparoscopic hysterectomy (Pokkinen et al., 2014). In the current study, we showed that propofol TIVA was associated with significantly better pain scores. The variation in the results can be due to differences in the actual surgical procedure, postoperative analgesic technique, and primary outcome measurement. In the study conducted by Pokkinen et al, the primary outcome was postoperative morphine consumption whereas the primary outcome of the current study was pain relief (Pokkinen et al., 2014). Furthermore, all patients were given patient controlled analgesia with morphine in the study by Pokkinen et al. This may have masked the analgesic effect of propofol, which has generally not been associated with a strong analgesic effect (Qiu et al., 2016).

We did not find a significant difference in consumption of postoperative morphine (in the PACU) and dihydrocodeine. Two other randomized controlled trials also showed no differences in postoperative opioid consumption (Li et al., 2012; Pokkinen et al., 2014). The apparent lack of effect on postoperative analgesic consumption suggests that the actual analgesic effect of propofol is limited. In our study, the difference in median NRS pain scores 24 hours after surgery was 1/10 (1 [IQR 0-2] in TIVA vs 2 [0-3] in SEVO) at rest, and 2/10 (1 [0-3] in TIVA vs 3 [1-4] in SEVO] with mouth opening. It has been reported that a minimum NRS pain score difference of 2/10 is required to be considered clinically important (Farrar, Berlin, & Strom, 2003).

Patients in the TIVA group experienced less headache after surgery. They were also more likely to experience no adverse effects. There were no differences in incidence of other adverse effects. There have been no reports on the effect of propofol TIVA on incidence of headache after surgery, but there is some evidence showing the efficacy of propofol in reducing chronic headache and migraine (Giampetro, Ruiz-Velasco, Pruett, Wicklund, & Knipe, 2018; Mosier, Roper, Hays, & Guisto, 2013). More clinical data is needed to explore possible associations between propofol TIVA and postoperative headache.

Patients in the TIVA group had significantly better global pain satisfaction scores. The higher satisfaction observed in this study was probably due to better pain control and a higher proportion of patients experiencing no adverse effects. Degree of postoperative pain has been shown to be an important factor determining patient satisfaction after surgery (Myles, Williams, Hendrata, Anderson, & Weeks, 2000). Propofol TIVA has also been associated with better quality of recovery, including the recovery dimensions of physical comfort and physical independence (Lee, Kim, Kang, Kim, & Lee, 2015). Patients in the TIVA group in the current study had significantly less self-reported discomfort.

In this study, intraoperative remifentanil infusion rate in the TIVA group was higher than the SEVO group. The difference was minimal between the two groups. High intraoperative remifentanil infusion rates have been associated with acute postoperative tolerance and opioid induced hyperalgesia (Yu, Tran, Lam, & Irwin, 2016). Despite having a higher remifentanil infusion rate, patients in the TIVA group had better pain scores. Propofol has been shown to attenuate remifentanil induced tolerance and hyperalgesia, and it has been proposed that this is because of its inhibitory effect on NMDA receptors (Singler, Troster, Manering, Schuttler, & Koppert, 2007; Yu et al., 2016). Subgroup analysis in a meta-analysis showed that the analgesic effect of propofol TIVA was more pronounced in the presence of remifentanil infusion (Peng et al., 2016). It is possible that propofol TIVA opposed the effect of remifentanil induced tolerance and hyperalgesia in our patients, resulting in less postoperative pain. However, whether this mechanism accounted significantly for reduced pain in the TIVA group patients within this study is uncertain. One clinical study showed that propofol TIVA was associated with significantly less pain and opioid consumption versus sevoflurane when high dose remifentanil was used, but there was no significant difference with low dose remifentanil (Shin et al., 2010). Remifentanil infusion rates of at least 0.2 $\mu g.kg^{-1}.min^{-1}$ and 0.25 $\mu g.kg^{-1}.min^{-1}$ for a sustained period are typically needed for the development of acute opioid tolerance and opioid induced hyperalgesia, respectively (Yu et al., 2016). Since the median intraoperative remifentanil infusion rates for both groups in our study were 0.15 $\mu g.kg^{-1}.min^{-1}$, it was not likely to have resulted in significant hyperalgesia or tolerance. Furthermore, the difference in remifentanil infusion rates between the two groups was small, and unlikely to have significantly affected the results.

Our results show that propofol TIVA improved postoperative pain and patient satisfaction in a clinical inflammatory model of moderate pain. This suggests that the choice of propofol TIVA for general anaesthesia may provide analgesic benefit in surgeries where postoperative pain is moderate in severity and postoperative inflammation is prominent. Since inflammation is usually an important component of acute post-surgical pain, our results may potentially be relevant to other types of surgery. As mentioned earlier, the analgesic effect size of propofol TIVA was small. However, since

acute postoperative pain is often poorly managed, a small analgesic benefit should still be taken into consideration when choosing between anaesthetic techniques. It is important to note that the results of this study cannot be generalized to all types of surgeries, especially in major surgeries and those where postoperative pain is more severe. Meta-analyses have been performed to assess the overall analgesic effect of propofol TIVA in different surgeries. While they suggest a small analgesic benefit associated with propofol TIVA, their results were limited by the presence of substantial heterogeneity (Peng et al., 2016; Qiu et al., 2016). Instead, individual adequately sized randomized controlled trials are probably needed to investigate the analgesic benefit of propofol TIVA in different surgeries. This is in agreement with the concept of procedure specific analgesia, where the development of optimal analgesic regimes for specific surgeries has been advocated (Joshi, Schug, & Kehlet, 2014).

There were limitations in this study. One limitation is that the patients were not prescribed preoperative paracetamol and NSAIDs for postoperative pain control. Pre-emptive NSAIDs have been shown to be effective for reducing pain after dental surgery (Albuquerque et al., 2017; Au et al., 2015). Although regular paracetamol and dihydrocodeine as needed were prescribed, NSAIDs were not. The analgesic regime for the two groups in this study was the same order to evaluate the analgesic effects of propofol TIVA. Nevertheless, our results may not be applicable to patients that are prescribed NSAIDs or preoperative analgesics. Another limitation is that the age of patients recruited was relatively young, with an average age of 26 and 28 years for the TIVA and SEVO group, respectively. This is similar to previous studies on third molar surgery (Cheung, Ng, Choi, et al., 2011; Cheung, Ng, Liu, et al., 2011). Therefore, the results may not be as generalizable to older patients. The study was not powered to specifically detect differences in adverse effects, which is another limitation.

In conclusion, propofol TIVA was associated with better pain control up to 72 hours after bilateral third molar surgery when compared with sevoflurane inhalational anaesthesia. It was associated with less headache. There was no difference in the incidence of other adverse effects and postoperative analgesic consumption. Global pain satisfaction was higher in the TIVA group. Propofol TIVA may be a useful anaesthetic technique for improving pain control after third molar surgery.

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Author contributions

SSW and CWC designed the study. SSW and YYL conducted the study, and acquired data. SSW, YYL and CWC helped analyse and interpret the data. SSW prepared the draft of the manuscript. SSW, YYL and CWC were involved in the revision and final approval of the manuscript. All authors discussed the results and commented on the manuscript. SSW had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure Legends

Figure 1. Flow chart of patients enrolled in the study

Figure 2. Median postoperative (PostOp) numerical rating scale (NRS) pain scores of patients anaesthetized with propofol TIVA (TIVA) and inhalational anaesthesia with sevoflurane (SEVO) at rest (A) and with mouth opening (B) at each recording time point.

Data are expressed as median [IQR]. TIVA (filled circles); SEVO (open circles).

Table 1. Patient characteristics, preoperative data, operative data and length of hospital stay

	TIVA (n=48)	SEVO (n=48)	*P* value
Age (year)	26.0±5.5 (19–49)	28.0±6.0 (20–44)	0.097
Body weight (kg)	63.1±13.2 (42.8–100)	59.4±10.5 (41–91.3)	0.126
Sex (M:F)	21 : 27 (43.8 : 56.2%)	19 : 29 (39.6 : 60.4%)	0.679
ASA (I:II)	41 : 7 (85.4 : 14.6%)	37 : 11 (77.1 : 22.9%)	0.296
Duration of surgery (min)	48.0±19.2 (19–117)	47.7±18.4 (19–106)	0.944
Duration of anaesthesia (min)	78.2±20.9 (47–153)	74.6±16.5 (49–120)	0.357
Intraoperative remifentanil infusion rate ($\mu g.kg^{-1}.min^{-1}$)	0.15 [0.12–0.20] (0.05-0.20)	0.15 [0.10–0.15] (0.08-0.20)	0.003**
Total intraoperative remifentanil used per body weight ($\mu g.kg^{-1}$)	10.6±4.4 (2.7–28.0)	8.1±2.5 (1.0–14.0)	0.001**
Intraoperative morphine used (mg)	2.5 [2–3] (0-4.5)	2.5 [2–3] (0-4.5)	0.266
Hospital stay (days)	1 [1-1] (1-2)	1[1-1] (1-4)	0.229

Data are expressed as mean ± SD (range), number (%), and median [IQR] (range)

ASA indicates American Society of Anaesthesiologists; F, female; kg, kilogram; M, male; Min, minutes; mg, milligram; µg, microgram

** $P < 0.01$

Table 2. AUC for NRS pain scores at rest and during mouth opening

	TIVA (n=48)	SEVO (n=48)	*P* value
Pain scores at rest			
AUC NRS 1-12h	29.7±21.6	39.8±23.9	0.036*
AUC NRS 12-72h	107.5±92.1	166.3±115.7	0.010*
AUC NRS 1-72h	137.2±109.6	206.4±134.7	0.013*
Pain scores during mouth opening			
AUC NRS 1-12h	34.5±24.0	45.1±24.7	0.028*
AUC NRS 12-72h	159.2±110.7	215.9±126.3	0.024*
AUC NRS 1-72h	193.7±131.5	261.5±145.7	0.021*

Data are expressed as mean ± SD

AUC NRS indicates area under NRS time curve (h); h, hours; NRS, numerical rating scale

*$P < 0.05$

Table 3. Post-operative analgesic drug consumption

	TIVA (n=48)	Sevo (n=48)	*P* values
Rescue analgesic in PACU			
Morphine consumption in PACU (mg)	0.29±0.82 (0-4)	0.25±0.67 (0-2)	0.969
Percentage of patients that required morphine for rescue analgesic	12.5% (6)	12.5% (6)	1.000
Time to first rescue analgesic (min)	39.7±28.8 (22-98) (n=6)	49.8±16.1 (36-78) (n=6)	0.065
Postoperative dihydrocodeine consumption (mg)			
Postoperative 24h	10.0±25.0 (0-120)	9.3±22.0 (0-90)	0.388
Postoperative 48h	12.5±30.2 (0-120)	14.0±33.6 (0-120)	0.832
Postoperative 72h	11.9±36.5 (0-180)	16.7±39.7 (0-180)	0.472
Total dihydrocodeine consumption	36.9±82.2 (0-390)	40.9±89.9 (0-360)	0.919
Percentage of patients that required dihydrocodeine for rescue analgesia	20.8% (10)	22.9% (11)	0.805

Data are expressed as median [IQR] (range), and % (n).

h indicates hours; mg, milligram; min, minutes; PACU, post-anaesthetic care unit;

Table 4. Post-operative adverse effects.

	TIVA (n=48)	SEVO (n=48)	*P* value
In PACU			
Dizziness	4.2% (2)	6.3% (3)	0.646
Nausea	0% (0)	4.2% (2)	0.495
Vomiting	0% (0)	0% (0)	1.000
Sore throat	16.7% (8)	16.7% (8)	1.000
Headache	0% (0)	8.3% (4)	0.117
No adverse effects	77.1% (37)	66.7% (32)	0.256
In ward			
Dizziness	14.6% (7)	18.8% (9)	0.584
Nausea	6.3% (3)	8.3% (4)	1.000
Vomiting	2.1% (1)	0 %(0)	1.000
Sore throat	37.5% (18)	41.7% (20)	0.676
Headache	10.4% (5)	27.1% (13)	0.036*
Swelling	8.3% (4)	14.6% (7)	0.336
Fever	2.1% (1)	10.4% (5)	0.204
Increased sputum	0% (0)	2.1% (1)	1.000
Pruritus	0% (0)	2.1% (1)	1.000
Tiredness	6.3% (3)	8.3% (4)	1.000
No adverse effects	37.5% (18)	16.7% (8)	0.022*

Data are expressed as % (n)

PACU indicates post-anaesthetic care unit

*$P < 0.05$

Table 5. Patient reported level of discomfort.

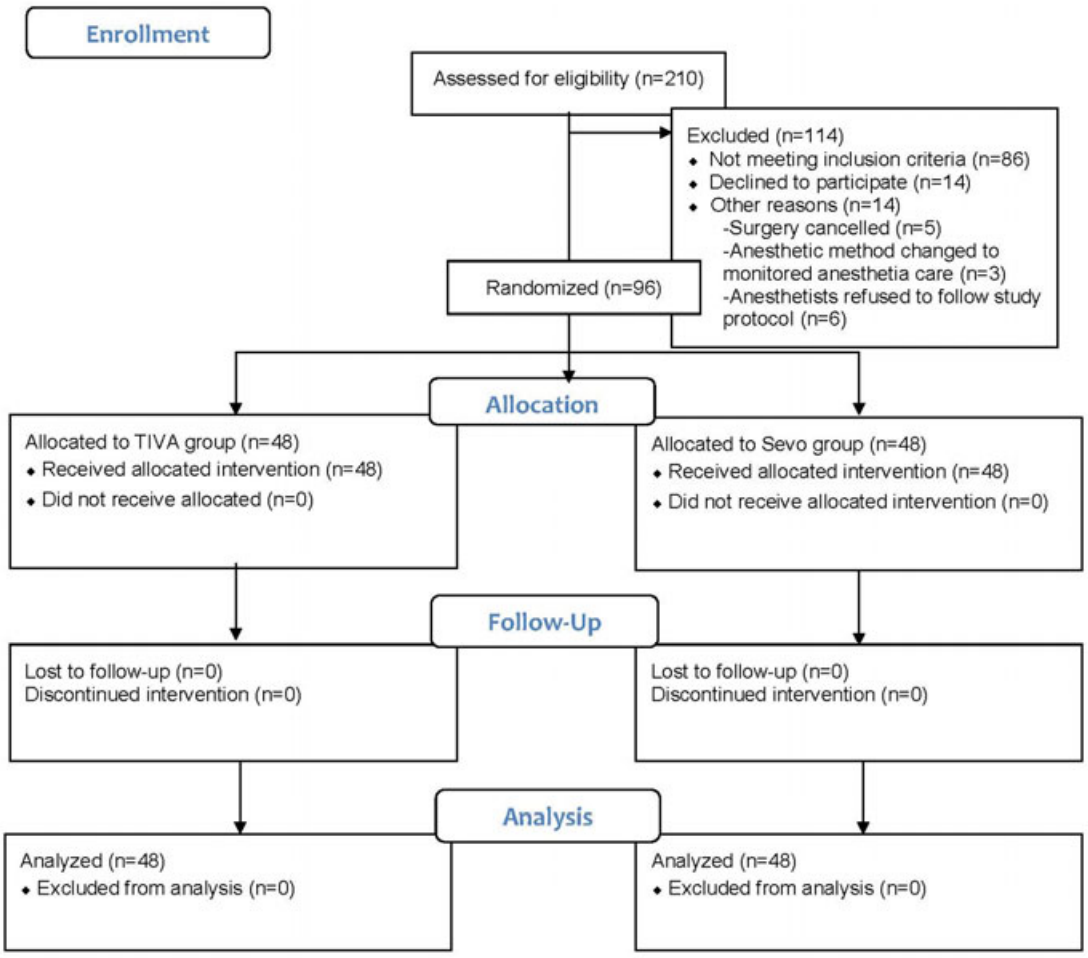
	TIVA (n=48)	SEVO (n=48)	*P* value
Level of discomfort			
Postoperative 24h			
Moderate to Severe	12.5% (6)	35.4% (17)	0.009**
None to Mild	87.5% (42)	64.6% (31)	
Postoperative 48h			
Moderate to Severe	10.4% (5)	22.9% (11)	0.100
None to Mild	89.6% (43)	77.1% (37)	
Postoperative 72h			
Moderate to Severe	10.4% (5)	18.8% (9)	0.247
None to Mild	89.6% (43)	81.3% (39)	

Data are expressed as % (n)

h indicates hours

** $P < 0.01$

Remarks: tested by Chi-square test



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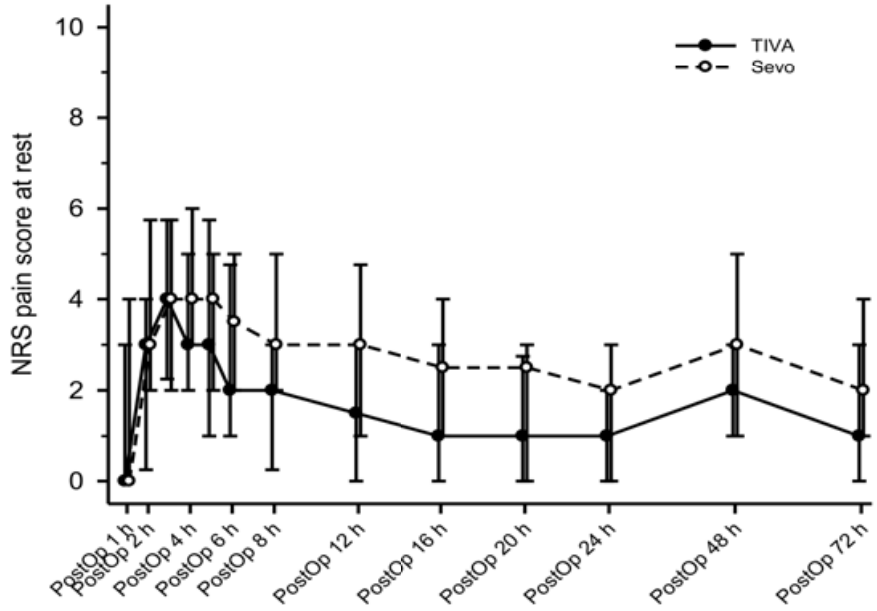

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