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ORIGINAL ARTICLE

Sevoflurane to alleviate pain on propofol injection

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Abstract
Purpose Since the introduction of propofol, several drugs and methods have been used to alleviate the pain on its injection. This study was designed to evaluate the effect of adding sevoflurane 3% during preoxygenation in alleviation of pain on propofol injection.
Methods In this randomized single-blinded study, 100 patients were randomly allocated equally into five groups: sevoflurane–lidocaine–tourniquet (SLT), sevoflurane–lidocaine (SL), lidocaine–tourniquet (LT), lidocaine (L), and sevoflurane (S). Approximately 10 min before the induction of anesthesia, midazolam 1–2 mg was administered intravenously to all patients. All patients received fentanyl 1 μg/kg as pretreatment and a full induction dose of propofol. A blinded anesthesia nurse assessed pain and hand movements throughout the injection of propofol.
Results In the SLT group, all patients (100%) were pain free and had no hand movements. There was no significant difference in pain grade or in hand movements between the L and the S groups, or between the SLT and the SL groups. However, significant differences were observed in pain grade between the SLT and the L groups as well as between the SLT and the S groups. In addition, a significant difference in hand movement was observed only between the SLT and the S groups.
Conclusion The addition of 3% sevoflurane at the time of preoxygenation for 1 min along with routine use of lidocaine–tourniquet completely prevented pain upon propofol injection, whereas sevoflurane by itself provided similar analgesia to premixed lidocaine with propofol.

Keywords Propofol · Pain · Sevoflurane · Lidocaine

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Introduction

Although propofol is a commonly used induction agent for the majority of general anesthesia performed all over the world, pain on injection remains the major disadvantage. The incidence is as high as 70% when no intervention is used [1] to reduce pain, whereas it is 30% when a "mini Bier's block" is used with 40 mg lidocaine for 30–120 s [2, 3]. Various drugs such as ketamine [4, 5], diclofenac [6], ketorolac [7], granisetron [8], dexamethasone [9], tramadol [10], acetaminophen [11], ephedrine [12], remifentanil, alfentanil [13], metoclopramide, and flurbirpofen [14], besides lidocaine, have been used to decrease the incidence of pain.

Several preparations of propofol are available, and the incidence of pain fluctuates widely. Pain at the time of induction of anesthesia remains one of the causes of dissatisfaction among patients at our institute in a survey at the time of discharge. We decided to find the best and the easiest solution to eliminate pain on propofol injection. Sevoflurane in subanesthetic concentration (0.8%) for pain

relief during the first stage of labor was found acceptable and superior to Entonox in one study [15, 16]. Also, sevoflurane has favorable physical qualities for inhaled analgesia and can be administered during preoxygenation without any compromise. Sevoflurane has a low blood–gas partition coefficient of 0.65 that enables rapid uptake into the central nervous system together with fast washout, which results in swift clinical effect [17]. To date, and to the best of our knowledge, no study has been performed to evaluate the role of sevoflurane to alleviate pain on propofol injection. Hence, we designed this study to establish whether sevoflurane alone or in combination with lidocaine is a useful adjunct to alleviate the pain of propofol injection.

Materials and methods

This single-blinded randomized study was approved by the ethics committee of our hospital. After obtaining local research ethical committee approval and patients' or parents' verbal consent, 100 patients were studied between age groups of 13 and 65 years old, of ASA groups I and II, and of either sex, who were scheduled for elective bariatric, general, orthopedic, urological, gynecological, or ear–nose–throat (ENT) surgery. All patients were premedicated with midazolam 1–2 mg intravenously approximately 10 min before induction of anesthesia.

On arrival at the operation theater, infusion of Ringer's solution through a 20 SWG IV cannula (BD VenflonPro; Beckton Dickinson, Helsingborg, Sweden) on the dorsum of the hand was started. All standard monitors were attached. All patients received oxygen 10 l/min during preoxygenation.

We used isotonic propofol containing 10 mg propofol in each milliliter along with excipients soybean oil, glycerol, egg lecithin, and sodium hydroxide, which was used to adjust the pH (Provine 1%; Claris Life Sciences, India). An induction dose of 1.6–2 mg/kg of propofol was given to all patients.

The patients were randomly allocated, using sealed envelopes, to one of following five groups of 20 each:

1. Sevoflurane–lidocaine–tourniquet (SLT) group: during preoxygenation, sevoflurane 3% in oxygen was administered for 1 min. While administering sevoflurane, intravenous fentanyl 1 μg/kg was slowly injected over 20 s. A venous tourniquet was applied, and 1% lidocaine 40 mg was injected. The tourniquet was released after 20 s, and propofol was injected in adequate dose over 20 s. Injection of fentanyl, application of venous tourniquet, injection of lidocaine, and the release of the tourniquet all occurred within 1 min. Sevoflurane administration was continued at 3% during propofol injection and then reduced to 2% at the end of the propofol injection.
2. Sevoflurane–lidocaine (SL) group: during preoxygenation, sevoflurane 3% in oxygen was administered for 1 min. While administering sevoflurane, intravenous fentanyl 1 μg/kg was slowly injected over 20 s. At the end of 1 min, propofol premixed with lidocaine (40 mg lidocaine added to 200 mg propofol just before the injection) was injected over 20 s in adequate dose. Sevoflurane administration was continued at 3% during propofol injection and then reduced to 2% at the end of propofol injection.
3. Lidocaine–tourniquet (LT) group: patients were preoxygenated with 100% oxygen for 1 min. During preoxygenation, intravenous fentanyl 1 μg/kg was slowly injected over 20 s. A venous tourniquet was applied, and 1% lidocaine 40 mg was injected. The tourniquet was released after 20 s, and propofol was injected over 20 s in adequate dose.
4. Lidocaine (L) group: patients were preoxygenated with 100% oxygen for 1 min. During preoxygenation, intravenous fentanyl 1 μg/kg was slowly injected over 20 s. At the end of 1 min of preoxygenation, propofol premixed with lidocaine (40 mg lidocaine added to 200 mg propofol just before the injection) was injected over 20 s in adequate dose.
5. Sevoflurane (S) group: during preoxygenation, sevoflurane 3% in oxygen was administered for 1 min. While administering sevoflurane, intravenous fentanyl 1 μg/kg was slowly injected over 20 s. At the end of 1 min, plain propofol was injected over 20 s in adequate dose. Sevoflurane administration was continued at 3% during propofol injection and then reduced to 2% at the end of propofol injection.

In the SLT, the SL, and the S groups, all patients received 3% sevoflurane for 1 full minute before the injection of propofol. Injection of propofol was completed in these groups in 20 s while administering 3% sevoflurane.

The pain on injection of propofol was evaluated throughout the injection, by a blinded anesthesia nurse as follows:

Grade 0: no pain: no complaints, no grimacing, and denial on direct questioning
Grade 1: mild pain: minimal grimacing or complaint on direct questioning, no self-reporting
Grade 2: significant pain: severe grimacing, shouting, or complaining, or self-reporting

Any hand movement was noted and documented by the same blinded anesthesia nurse. Any change in the heart rate or blood pressure from the baseline was also noted.

Table 1 Age, body weight, and sex of patients

	SLT ($n = 20$)	SL ($n = 20$)	LT ($n = 20$)	L ($n = 20$)	S ($n = 20$)	P value
Age in years[a]	31.9 ± 10.9	32 ± 8	30.4 ± 10	29.7 ± 12.7	32.7 ± 12.1	0.892*
Weight (kg)[a]	90 ± 30.5	105 ± 26.8	94.2 ± 10	104 ± 25.4	93 ± 25.9	0.394*
Male/female	3/17	6/14	8/12	3/17	4/16	0.323[#]

SLT sevoflurane–lidocaine–tourniquet, *SL* sevoflurane–lidocaine, *LT* lidocaine tourniquet, *L* lidocaine, *S* sevoflurane

* *P* value using one-way analysis of variance

[#] *P* value using Fisher's exact test

[a] Mean values ± SD

The remaining part of the anesthesia was carried out according to the nature of surgery.

Statistical analysis

A 30% reduction in the incidence of pain with the use of sevoflurane would be considered clinically significant. To provide 80% power to detect such a difference using a two-tailed test at $P \leq 0.05$, a sample size of 20 patients per group was found to be adequate.

Statistical analysis was carried out using SPSS for Windows software program version 15 (SPSS, Chicago, IL, USA). Data are presented as mean (SD), number, (%) or median. $P < 0.05$ was considered statistically significant. The demographic data of each group were compared using analysis of variance (ANOVA). The sex difference and the number of patients with pain or having hand movement between groups were compared using Fisher's exact test. Pain grades and hand movements were compared using the Kruskal–Wallis test, and the Mann–Whitney test was used for pairwise comparisons between groups for post hoc analysis. Also, P values obtained with Mann–Whitney test were multiplied by 10 for Bonferroni's correction.

Results

There were no significant differences between the groups in age, weight, and sex distribution, although there was a female dominance in each group (Table 1).

The distribution of pain grades is shown in Fig. 1. All patients the SLT group were totally pain free. The L group had the least number of patients who were pain free. Some patients had hand movements in the later stage of injection of propofol; distribution of this is shown in Fig. 2. These hand movements were observed after almost 75% of the required dose was injected.

There were no significant differences in pain grade or hand movement between the SLT and the SL groups nor between the L and the S groups. However, significant

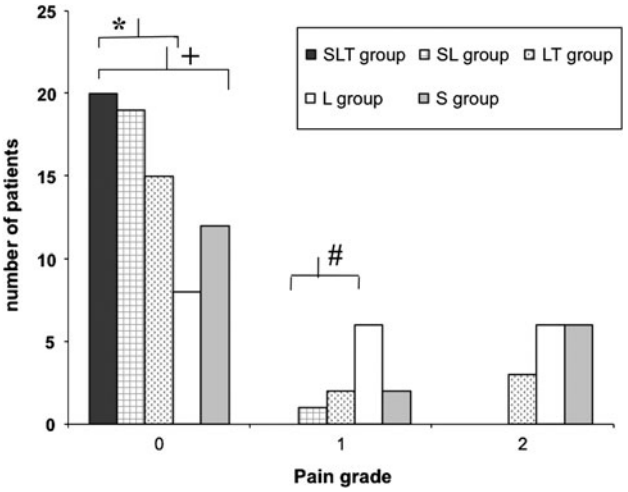

Fig. 1 Distribution of pain grade in the five groups: $^{*}P = 0.001$, SLT group versus L group; $^{+}P = 0.014$, SLT group versus S group; $^{\#}P = 0.002$, SL group versus L group using Mann–Whitney test. *SLT* sevoflurane–lidocaine–tourniquet, *SL* sevoflurane–lidocaine, *LT* lidocaine tourniquet, *L* lidocaine, *S* sevoflurane

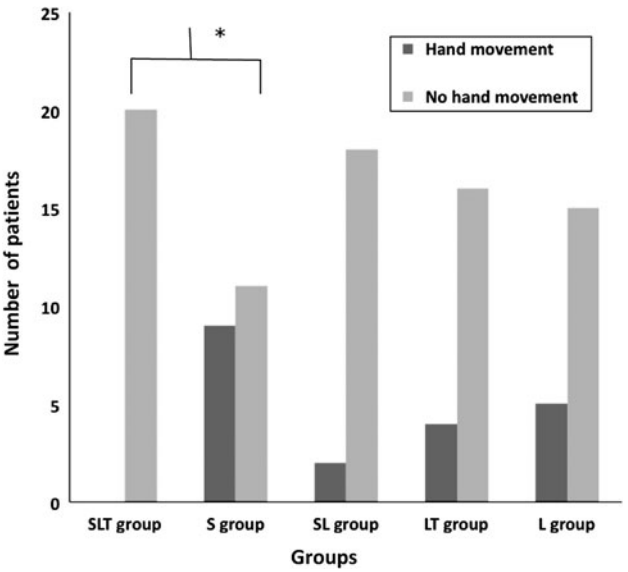

Fig. 2 Distribution of hand movement in the five groups: $^{*}P = 0.014$, SLT group versus S group using Mann–Whitney test. *SLT* sevoflurane–lidocaine–tourniquet, *SL* sevoflurane–lidocaine, *LT* lidocaine tourniquet, *L* lidocaine, *S* sevoflurane

differences were observed in pain grade between the SLT and the L or the S groups (Fig. 1). Also, there was a significant difference in hand movement between the SLT and the S groups (Fig. 2).

The heart rate and blood pressure of all patients remained within 20% of the base value during the injection of propofol. Agitation and hemodynamic instability were not observed in the groups in which sevoflurane was used, as we were able to communicate with our patients.

Discussion

Despite the use of propofol as the drug of choice for induction of anesthesia in millions of patients every year, about three of five patients experience pain on its injection, with one of these three patients reporting severe or excruciating pain [18].

Although the use of lidocaine either as pretreatment or mixed with propofol has been the established norm for many years, fentanyl [20, 21] also has been used by several investigators in the past with fairly good outcome on alleviating the pain on propofol injection. At our institute, sevoflurane is regularly used for maintenance of anesthesia while most patients receive fentanyl at the time of induction of anesthesia. Hence, the use of these three agents does not require any extra effort or time on a busy schedule.

In our study, use of sevoflurane with fentanyl and lidocaine 40 mg as a 'mini Bier's block' (SLT group) resulted in 100% elimination of pain on propofol injection, and none of the patients had any hand movements. Although the mechanisms of actions of lidocaine and fentanyl have already been suggested by previous investigators [19], we propose a threefold action of sevoflurane in eliminating pain. First, sevoflurane probably acts centrally because of its weak analgesic effect. Second, its sedative action may have had some role in minimizing the reaction to pain. Last, its vasodilatory effect also may have had a role in reducing the pain on propofol injection. It has been reported that sevoflurane causes subjective drowsiness, slow reaction times, and loss of memory function in subanesthetic doses [22, 23]. Manyam et al. [24] have reported synergistic interaction between remifentanil and sevoflurane for sedation and all analgesic endpoints, and hence it may have similar synergistic interaction with fentanyl.

It is assumed that in a steady state, alveolar concentration of inhalation anesthetic is represented by end-tidal concentration. Studies have also shown, however, that there are significant differences in alveolar (i.e., assumed to be end tidal), inspiratory, and arterial concentrations of inhalation anesthetic agents, even when a steady state was achieved [25, 26]. Also, it is impossible to achieve a steady state within 1 min, which was the main reason end-tidal sevoflurane concentration after 1 min was not measured in our study.

Toscano et al. [27] showed that inspired concentrations of sevoflurane over 2% to achieve a target end-tidal concentration of 1–1.5% might alter pain intensity scores in labor. Also, sevoflurane 8% with 75% N_2O in O_2 have been used for vital capacity inhaled induction (VCI) within 1 min [28]. We used 3% concentration in oxygen and we were able to communicate with our patients who received sevoflurane during injection of propofol.

In our study, most of the patients were female (76%). No gender difference in the incidence of propofol injection pain has been reported by some [19], although female patients were more sensitive to pain on the injection of propofol in a recent study [29].

It may be argued that the speed of injection can affect the pain perceived by the patient during the injection. In our study, the speed of injection was not controlled, and the required dose was injected in approximately 20 s in all patients. In a quantitative systematic review of pain on propofol injection in which 56 randomized controlled trials between 1981 and 1999 were analyzed, there was no evidence of any relationship between the size of the catheter and the speed of injection and the likelihood of pain on injection with propofol [1].

In a recent study, use of ketamine 1 mg/kg before the injection of propofol in a very small dose (5 ml) for placement of a double-lumen endotracheal tube in patients undergoing lung surgery eliminated the pain completely, although increased secretions were a distinct disadvantage [30]. Use of sevoflurane with fentanyl and the lidocaine–tourniquet technique in our study also eliminated the pain completely while the full induction dose of propofol was injected, and there was no disadvantage of increased secretions, although operation theater pollution may be considered against its favor. Another limitation of this study is that the induction time in all five groups was not noted and compared between the groups.

To conclude, the addition of sevoflurane 3% at the time of preoxygenation for 1 min is a useful adjunct to the routine use of lidocaine–tourniquet to alleviate pain on propofol injection completely, whereas sevoflurane alone provides analgesia similar to premixed lidocaine with propofol.

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