Original Article

Efficacy of tramadol and butorphanol pretreatment in reducing pain on propofol injection: A placebo-controlled randomized study

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Abstract

Background and Aims: Pain of propofol injection has been recalled by many patients as the most painful part of the induction of anesthesia. Tramadol and butorphanol are commonly used analgesics for perioperative analgesia in anesthesia practice. However, their potential to relieve propofol injection pain still needs to be explored.

Material and Methods: A randomized, double-blind, placebo-controlled study was conducted on 90 American Society of Anesthesiologists I and II adult patients undergoing elective surgery under general anesthesia with propofol as an induction agent. Consecutive sampling technique with random assignment was used to allocate three groups of 30 patients each. Group I patients received an injection of normal saline 3 ml intravenously (placebo) while Group II and Group III patients received injection of tramadol 50 mg and butorphanol 1 mg intravenously, respectively. Before induction of anesthesia patients were asked about the intensity of pain on propofol injection by using visual analog scale (VAS) before the loss of consciousness. Descriptive statistics and analysis of variance with Chi-square test were used to analyze the data. The value of $P < 0.05$ was considered as a significant and $P < 0.0001$ as highly significant.

Results: The incidence of pain in Group I was observed in 80% of the patients, while it was observed in 23.33% and 20% of patients in Group II and III, respectively. Mean VAS scores were 2.27 ± 1.51, 1.14 ± 1.74, and 1.03 ± 1.72 in Group I, II, and Group III patients, respectively. The incidence of pruritus was 10% and 6.7% and erythema in 13.2% and 6.7% in Group II and III, respectively.

Conclusion: Pretreatment with both butorphanol and tramadol significantly reduced pain on propofol injection; however, they exhibited comparable efficacy among each other. Thus, either of these two drugs can be considered for pretreatment to reduce propofol injection pain.

Key words: Butorphanol, pain, propofol, tramadol

Introduction

Propofol is a commonly used drug for induction of anesthesia because of its rapid onset and short duration of action, easy titration, and favorable profile for side effects.[1,2] However, despite these positive attributes, about 28-92% patients experience pain on injection of propofol, with one of three patients reporting severe or excruciating pain.[1,3] The mechanism of propofol injection pain is still unclear; it has been postulated to be due to either a direct irritant effect giving rise to an immediate sensation of pain or an indirect effect via the release of mediators such as bradykinin leading to a delayed onset.[4] As a result, several interventions have been investigated to alleviate the pain associated with propofol

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injection with varying results. Numerous physiological and pharmacological methods have been described in literature so as to decrease the incidence of this pain such as selection of a larger vein,[5] decreasing the speed of injection,[6] or diluting the propofol solution, or pretreatment with lignocaine, ondansetron, metoclopramide, opioids, and thiopentone.[1-10] Tramadol a centrally acting analgesic can also possibly reduce the pain due to propofol injection.[1,5,11] We also hypothesized that intravenous (IV) administration of butorphanol, a synthetic opioid agonist — antagonist can also reduce pain during induction with IV propofol. It is a kappa receptor agonist, as well as a mu-receptor antagonist, resulting in analgesic and sedative properties without profound respiratory depression or euphoria.[12] Studies comparing butorphanol with tramadol in reducing the propofol-induced pain are sparse. Hence, we conducted this randomized, double-blind, placebo-controlled study to compare the efficacy of pretreatment with butorphanol and tramadol for alleviation of pain associated with propofol injection.

Material and Methods

After obtaining approval from the Institutional Ethical Committee and written informed consent of the study subjects, this prospective study was conducted on 90 adult patients belonging to the American Society of Anesthesiologists (ASA) Grade I and II in the age group of 18-60 years scheduled for elective surgery under general anesthesia with propofol as an induction agent. Consecutive sampling technique with random assignment was used to allocate to one of the three groups of 30 patients each and respective drugs were given intravenously in the volume of 3 ml prior to injection of propofol. Patients with a history of chronic pain syndromes, thrombophlebitis, neurological disease, and allergy to the study drugs were excluded from the study. The patients having difficulty in communication were also excluded from the study. The patients were informed of the possibility of a "burning sensation" in the forearm during induction of anesthesia.

The drugs were prepared in identical syringes and in equal volume by the anesthesia technician who was unaware of the study design and were marked with different codes (I, II, III) so that even the anesthesiologists who were recording the observations remained blinded to the drug. A detailed preanesthesia checkup was conducted wherein the patients were educated on the use of visual analog scale (VAS) for assessment of pain during the perioperative period. All patients were advised to be kept nil per oral for 8 h prior to surgery and received uniform premedication in the form of tablet ranitidine 150 mg and tablet alprazolam 0.25 mg night before surgery. In the operating room, an IV line was secured in a peripheral vein on the dorsum of the hand with an 18-gauge IV cannula. The following monitoring was instituted: electrocardiogram for heart rate and rhythm, systolic blood pressure, diastolic blood pressure and mean arterial pressure, respiratory rate, and oxygen saturation. Recording of these parameters was done before induction, during induction, intraoperatively every 2 min up to first 10 min and thereafter every 5 min until the end of the surgical procedure.

Group I patients received injection normal saline 3 ml IV (placebo), while Group II and Group III patients received injection tramadol 50 mg and injection butorphanol 1 mg IV, respectively, made up to 3 ml by adding normal saline in a blinded manner.

Patients were preoxygenated with 100% oxygen for 3 min. A tourniquet was applied and inflated to 70 mm Hg in which the IV line was secured. Then the study drugs (tramadol, butorphanol, and placebo) were administered through IV cannula at the rate of 0.5 ml/s. After 2 min of injecting the study drug, tourniquet was deflated and immediately injection propofol 2.5 mg/kg at the rate of 0.5 ml/s was administered for induction of anesthesia. Patients were asked about the intensity of pain on propofol injection by using pain VAS on a range of scores from 0 to 100 before the loss of consciousness.[13] Side effects such as erythema, pruritus, sensation of heat, and allergic reaction were noted postoperatively immediately after the surgery and then 24 h after surgery.

Based on the distribution of pain VAS scores in postsurgical patients who described their postoperative pain intensity as none, mild, moderate, or severe the following cut points on the pain VAS have been recommended for this study: No pain (0-4 mm); mild pain (5-44 mm); moderate pain (45-74 mm); and severe pain (75-100 mm).[14]

Statistical analysis

Based on the results of the previous study and assuming Type-I error (α) at 0.05, Type II error (β) at 0.1, and power of the study at 80% so as to detect a difference of 20% in the incidence of pain between the study and control groups the sample size was calculated as 26 patients in each group. However, we chose 30 patients in each group considering possible dropouts and for better validation of results. The decoding of drugs was done at the end of the study, and the entire data were compiled and analyzed by using analysis of variance and Chi-square test. *Post-hoc* significance test was done to validate the statistical results.

Analysis was performed using statistical software Statistical Product for Social Sciences (SPSS version 11.0 for Windows, Chicago, SPSS Inc.). All the values were expressed as a mean ± standard deviation (SD); range; or percentage. Results were considered statistically significant when P value was <0.05.

Results

The demographic profile was comparable in all the three groups [Table 1]. The incidence of pain in Group I was observed in 80% of the patients [Table 2]. In Group II, 7 patients out of 30 felt pain accounting for an incidence of 23.33%, while in Group III, 6 patients out of 30 felt pain with an incidence of 20%. In Group I, the mean score of pain was (VAS ± SD) 2.27 ± 1.51 while it was 1.14 ± 1.74 and 1.03 ± 1.72 in Group II and Group III patients, respectively [Table 3]. On statistical analysis, VAS in Group I was statistically significant as compared to Group II and III ($P < 0.001$). The other side effects observed besides pain included pruritus and erythema. In Group II and Group III, pruritus was seen in three (10%) and two (6.7%) patients, respectively, while erythema was observed in four (13.2%) and two (6.7%) patients, respectively, in Group II and III. The overall incidence of pruritus and erythema was 23.2% and 13.4% in Group II and III, respectively, which were statistically insignificant [Table 4].

Table 1: Demographic profile

Demographic variable	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	P
Age (years) Mean±SD	39.07±13.39	37.43±13.80	36.23±11.88	0.701^{NS}
Gender, n (%)				
Male	13 (43.33)	10 (33.33)	16 (53.33)	0.295^{NS}
Female	17 (56.67)	20 (66.67)	14 (46.67)	
Weight (kg) Mean±SD	61.87±7.10	58.07±6.41	59.87±4.61	0.061^{NS}
ASA, n (%)				
I	28 (93.33)	27 (90.00)	27 (90.00)	0.872^{NS}
II	02 (6.67)	03 (10.00)	03 (10.00)	
Mean dose of propofol (mg)	143.00±19.68	143.67±19.56	145.67±14.31	0.837^{NS}

Data are mean ± SD. NS = Not significant (P > 0.05), SD = Standard deviation, ASA = American Society of Anesthesiologists

Table 2: Incidence of pain on propofol injection

Group	n (%)
I	24 (80.00)
II	7 (23.33)
III	6 (20.00)

n = Number of patients with propofol injection pain (VAS >0). VAS = Visual analog scale

Discussion

The results of our study imply a significant reduction in pain on propofol administration after pretreatment with tramadol or butorphanol in comparison to the control placebo group. Intergroup comparison revealed that the incidence and severity of pain with propofol injection was less in the study Groups (II and III) when compared to the control group (I), but comparable efficacy was observed among both the study drugs.

We chose a control group in this study by administering a placebo so as to gauge the efficacy of tramadol and butorphanol for the amelioration of propofol injection pain, rather than opting for traditionally established gold standard lignocaine pretreatment. Moreover, with the focus shifting to newer drugs in a quest to find a better alternative to alleviate the pain on propofol injection, it seems reasonable to use opioids as a part of standard induction regime.

Opiates were shown to exert peripheral analgesic action in addition to their well-known central effects though a clear-cut discrimination between peripheral and central analgesics is debatable.[9] The analgesia produced by both peripheral and central mechanisms may be additive or even synergistic. Moreover, peripheral opioid receptors have been described and shown to mediate analgesic effect when activated by opioid agonists.[15,16] The analgesic effect observed in our study with both tramadol and can be attributed to the peripheral analgesic effect secondary to their venous retention for 2 min.

The higher incidence of patients (80%) experiencing higher mean VAS scores (2.27 ± 1.48) in Group I (placebo) are comparable with the 74-83% incidence reported by various other studies.[1,17] Tramadol has also been found to be as effective as lignocaine in reducing the incidence and severity

Table 3: Mean score of pain with intergroup comparison

Group	Mean score of pain (VAS)±SD	Post-hoc Tukey for VAS			
		Comparison	Difference	P	Significance
I	2.27±1.51	Group I versus II	1.800	<0.001	Highly significant
II	0.47±0.94	Group I versus III	1.933	<0.001	Highly significant
III	0.33±0.71	Group II versus III	0.133	0.887	Not significant

Data are mean ± SD, P < 0.001; highly significant. SD = Standard deviation, VAS = Visual analog scale

Table 4: Side effects of pretreatment drugs in all groups

Side effect	Group I			Group II			Group III		
	n	*N*	Percentage	*n*	*N*	Percentage	*n*	*N*	Percentage
Pruritus	0	30	0	3	30	10	2	30	6.7
Erythema	0	30	0	4	30	13.2	2	30	6.7
Vasovagal attack	0	30	0	0	30	0	0	30	0
Sensation of heat	0	30	0	0	30	0	0	30	0
Allergic reaction	0	30	0	0	30	0	0	30	0
Urinary retention	0	30	0	0	30	0	0	30	0
Overall Side effects	0	30	0	7	30	23.2	4	30	13.4

Pruritus: $\chi^2 = 1.071$, df = 2, P = 0.585, not significant, Erythema: $\chi^2 = 2.169$, df = 2, P = 0.338, not significant, n = Number of patients having side effects, N = Sample size of group

of propofol-induced pain. Moreover, it also grants an added advantage of intraoperative analgesia.

Tramadol is a centrally acting weak μ-receptor agonist which inhibits noradrenaline re-uptake as well as promotes serotonin release, potentiates the monoaminergic system and can be used to treat moderate and severe pain.[15] In addition to its systemic effect, the local anesthetic effect of tramadol on peripheral nerves has been shown in both clinically and laboratory studies.[15,18,19] Desmeules *et al*. confirmed that the analgesic effect of tramadol is apportioned between the opioid and monoaminergic components.[20] Jou *et al*.[21] suggested that tramadol affects sensory and motor nerve conduction by a similar mechanism to that of lidocaine which acts on the voltage-dependent sodium channel leading to axonal blockage.

Butorphanol is 5-8 times more potent than morphine. After the IV administration, the onset of analgesia occurs within 1 min with a peak effect in about 4-5 min. The site of action of butorphanol in reducing the pain of propofol injection is not clear, but it could be either through opioid receptors (central and or peripheral), local anesthetic action, or both. The incidence of pain on propofol injection in this study after pretreatment with butorphanol was observed to be approximately 20%. This incidence is almost similar to the findings of earlier study by Aggarwal *et al*. who reported an incidence of merely 20% on propofol injection while using butorphanol as pretreatment.[12]

The incidence of pain observed in the tramadol group (23.33%) in the our study was comparable to the results of Wong and Cheong[11] who compared lignocaine with placebo and observed an incidence of 27% and 83%, respectively ($P < 0.001$). Thus, it can be inferred that tramadol is as effective as lignocaine in alleviating propofol injection pain thereby granting the patient a smoother comfortable experience of propofol induction.

Fewer side effects, like pruritus and erythema, were observed with tramadol pretreatment (10% and 13.2%, respectively) while this incidence decreased further with butorphanol pretreatment (6.7%). The findings of our study are nearly similar to the results of Martin *et al*. who reported a similar incidence of pruritus and erythema with tramadol pretreatment.[22]

Conclusion

Thus, we conclude that pretreatment with perioperatively used opioids tramadol 50 mg or butorphanol 1 mg effectively reduced the pain of propofol injection with fewer self-limiting mild side effects such as pruritus and erythema. Though statistical significance could not be achieved among both study drugs, we propose future studies exploring use of both tramadol and butorphanol as a pretreatment in relieving pain on propofol injection in large samples of surgical population.

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Conflicts of interest

There are no conflicts of interest.

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