Original Article

Effect of Intravenous Tramadol, Acetaminophen in Attenuating Pain on Propofol Injection: Comparison with Lignocaine: A Randomized, Double-blind, Controlled Study

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Abstract

Objectives: Distress and pain due to propofol injection is a very common finding. The aim of our study was to assess the efficacy with lignocaine, tramadol, and acetaminophen pretreatment to alleviate the propofol pain. **Materials and Methods:** Ninety American Society of Anesthesiology (ASA) I and II adults, scheduled for various elective surgical procedures under general anesthesia, were included in the study. They were randomly divided into three groups with 30 patients in each group. Group A received pretreatment with intravenous (IV) lignocaine, group B received IV tramadol, and group C received IV acetaminophen. One-fourth of the total calculated induction dose of propofol was administered over a period of 5 s. The patients were asked about the pain on injection. The intensity of pain was assessed using verbal rating score. A score of 0–3, which corresponded to no, mild, moderate, and severe pain was recorded. Categorical and continuous variables were compared between the groups using Chi-square test and analysis of variance (ANOVA) test, respectively. *Post hoc* analysis was performed using Bonferroni test. Verbal rating scale (VRS), an ordered categorical variable, was compared between the groups using Wilcoxon signed-rank test. A P value of <0.05 was considered significant. **Results:** All the three drugs reduced the incidence and intensity of pain on propofol injection but the order of efficacy in attenuation of pain on the propofol injection was lignocaine > tramadol = acetaminophen. **Conclusion:** Both tramadol and acetaminophen were clinically equivalent to lignocaine in their potency to decrease the incidence of propofol pain.

Key words: Acetaminophen, lignocaine, pain, propofol, tramadol

Introduction

With the decrease in morbid adverse events after surgery, patient satisfaction with perioperative care is assuming more importance. The quality of an anesthetic agent is judged by any recall of discomfort or pain at the time of induction. Propofol is an intravenous (IV) sedative and hypnotic agent commonly used for anesthesia induction. Its rapidity and reliability in causing loss of consciousness and a quick, smooth recovery are favorable features. However, pain on injection when given intravenously is a common problem with propofol and the incidence of this is around 60%.[1] A number of factors have been implicated for the mechanism of pain due to propofol injection but these are not elucidated clearly.

Several strategies to attenuate this pain include the use of antecubital vein,[1] with venous occlusion,[1] lignocaine,[1,2] cooling[3] or warming[4] of the drug, diluting propofol solution,[5] pretreatment with antiemetics,[6,7] metoclopramide,[8] opioids,[8] ketamine,[1,9] and flurbiprofen.[10] Other alternative strategies include various formulations of propofol emulsions such as nano-emulsions.[11]

Lignocaine pretreatment is most commonly used to decrease the injection-related pain and has been shown to be more effective than the modified formulations available.[2,12] The analgesic effect of lignocaine may occur because of a local anesthetic effect or an inhibitory effect on enzymatic cascade, which causes the release of kinins.

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Tramadol is a centrally acting weak μ-receptor agonist and inhibits norepinephrine reuptake as well as promotes serotonin release.[13] The literature has reported a local anesthetic effect of tramadol into an occluded vein when propofol was injected.[14,15] Acetaminophen has analgesic and antipyretic action, and is commonly used for acute pain relief. The literature has reported the use of acetaminophen for prevention of propofol-induced pain during the induction of anesthesia.[16-18] Tramadol and acetaminophen are routinely used as analgesics and are readily available. The aim of our randomized, double blind, controlled study was to compare the efficacy of IV tramadol, acetaminophen, and lignocaine pretreatment in attenuating pain following propofol injection.

Materials and Methods

A prospective, randomized, controlled, double-blind study was undertaken after obtaining the institutional ethics committee's approval. Informed consent was obtained from all the patients included in the study. Ninety patients of either gender in the age group of 18–60 years belonging to the American Society of Anesthesiologists (ASA) grades I and II scheduled for elective surgery requiring general anesthesia were included in the study. Allocation of patients into groups was made according to the random numbers generated by rand (MS-Excel).

The sample size was estimated based on the study conducted by Wong *et al*., who have shown the incidence of postpropofol injection pain with tramadol to be 30% compared to 27% in the lignocaine group and 83% in the placebo group.[19] The desired sample size for an alpha error of 5% and beta error of 50% using this data would be 30 people for each group. The exclusion criteria included patients with known allergy to the study drugs, allergic disease, patients with Parkinson's disease, vascular insufficiency, moderate to severe cardiac disease, hepatic, renal, pulmonary and neurological diseases (ASA III and IV), patients with obesity, pregnant patients, patients with habituation to analgesics, sedation, or antianxiety drugs, patients on medication with pain modifying drugs, and patients with infection on the dorsum of their left hand.

Study design

The patients were randomly selected using a coded syringe method and divided into three groups of 30 patients each. None of the patients were premedicated before entering the operation room. All the patients were explained about the verbal rating scale (VRS) for assessment of pain on propofol injection. After routine monitoring (electrocardiogram, noninvasive blood pressure, and pulse oximeter), a 20G catheter was inserted into a superficial vein on the dorsum of the hand and Ringer's Lactate (RL) solution was infused at a rate of 100 mL/h. After 5 min, RL infusion was stopped and the arm with IV line was elevated for 15 s for gravity drainage of venous blood. After occluding the venous drainage using a pneumatic tourniquet [pressure inflated to 70 mL of mercury (mmHg)] on the upper arm, the patients were pretreated with one of the study solutions. Group A received 40 mg (5 mL) of lignocaine, Group B received 50 mg (5 mL) of tramadol, and Group C received 50 mg (5 mL) of acetaminophen.

The syringes were prepared by an independent anesthesiologist and all appeared identical. The investigator was blinded to the contents. After 1 min, the tourniquet was released (deflated) and 1/4th of the total calculated dose of propofol (Diprivan®, Fresenius Kabi) was delivered through the IV line over a period of 5 s. No other analgesic or sedation was administered before propofol injection. During the injection, the patients were asked standard questions regarding comfort of the injection. A clinician blinded to the group assignment evaluated propofol-induced pain using a VRS:[10] 0—no pain or no response to questioning; 1—mild pain reported in response to questioning without any behavioural signs; 2—moderate pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning; 3—severe pain, strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears.

Thereafter, induction of anesthesia was continued with IV fentanyl 2–3 μg/kg followed by the remainder of the calculated dose of propofol and rocuronium 0.8 mg/kg to facilitate endotracheal intubation. Anesthesia was maintained with 50% nitrous oxide in oxygen and isoflurane, and the lungs were mechanically ventilated.

Within 24 h after the operation, the injection site was checked for pain, edema, or allergic reaction and postoperative nausea and vomiting by an anesthesiologist who was blinded to the group assignment.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 13 (SPSS Inc. Chicogo, Illinois, USA). Descriptive statistics for continuous variables were expressed as mean with standard deviation (SD) for categorical variables as frequency of occurrence and percentages. Categorical variables were compared between the groups using Chi-square test with Fisher's exact test where applicable. Continuous variables were compared between the groups using analysis of variance (ANOVA). *Post hoc* analysis was performed using Bonferroni test. VRS, a ordered categorical variable, was compared between the groups using Wilcoxon signed-rank test. A P value of <0.05 was considered significant.

Results

No case was excluded from the study after randomization. The demographic data are depicted in Table 1. The data were comparable with regard to age, gender, weight, height, and ASA grading. The data was found to be normally distributed.

Pain assessment

Out of 30 patients in Group A (pretreated with lignocaine), 22 patients (73.3%) had no pain on IV injection of propofol, 5 patients (20.8%) complained of mild pain, and 3 patients (10%) complained of moderate pain. No patient complained of severe pain. Of the 30 patients in Group B (pretreated

with tramadol), 13 patients (43.3%) complained of no pain on IV injection of propofol, 10 patients (41.7%) complained of mild pain, 4 patients (13.3%) complained of moderate pain, and 3 patients (10%) complained of severe pain. Finally, out of the 30 patients in Group C (pretreated with acetaminophen), 13 patients (43.3%) complained of no pain on IV injection of propofol, 9 patients (37.5%) complained of mild pain, 5 patients (16.7%) complained of moderate pain, and 3 patients (10%) complained of severe pain. Statistically, there was no significant difference in the incidence of pain between the three groups (*P* value: 0.1) [Figure 1].

Among the total 90 patients, 48 patients (53.3%) had no pain on IV injection of propofol, out of which 24.4% belonged to Group A, 14.4% to Group B, and 14.4% to Group C but statistically, this was not significant. Twenty-four patients (26.7%) of the total 90 patients had mild pain on IV injection of propofol, out of which 5.6% were from Group A, 11.1% from Group B, and 10% from Group C. Twelve patients (13.3%) of the total 90 patients complained of moderate pain on IV injection of propofol, out of which 3.3% were from Group A, 4.4% were from Group B, and 5.6% were from Group C. Six patients (6.7%) of the total 90 patients complained of severe pain on IV injection of propofol, out of which 3.3% were from Group B and 3.3% were from Group C. None of the patients from Group A complained of severe pain. Most of the patients had nil to mild pain (80%), whereas only 6.6% of the study population had severe pain, with moderate pain accounting for only 13.3% of the total.

The side effects assessed after 24 h were comparable in all the three groups [Table 2]. None of the 90 patients in all the three groups had any edema or allergy at the site of injection 24 h after IV injection of propofol.

Discussion

Our study compared and evaluated the incidence of propofol pain with the commonly used analgesics intraoperatively, tramadol and acetaminophen with the gold standard lignocaine. Though there was no significant difference between the three study drugs, lignocaine was more effective. There were no patients with severe pain and most of the patients reported having no pain in the lignocaine pretreatment group, though it was statistically not significant.

Propofol is an IV sedative and hypnotic agent commonly used for anesthesia induction. Its rapidity and reliability in causing loss of consciousness associated with quick, smooth recovery makes it the IV anesthetic agent of choice. Pain on injection of propofol has been reported since the initial studies[20] and is still a limitation of this otherwise excellent IV anesthetic agent. Chemically, propofol belongs to the group of sterically hindered phenols.[21] Hence, like the phenols, it irritates the skin, mucous membrane, and venous intima and causes pain on injection.

Though pain on injection is not a serious complication, it is a common problem, with the incidence varying between 40% and 86%.[22] It interferes with patient satisfaction, as the quality of an anesthetic is judged by recall of discomfort or pain at the time of anesthetic induction. The pain on injection of propofol could be due to other factors too, the osmolality of the solvent used for the preparation,[23] the pH

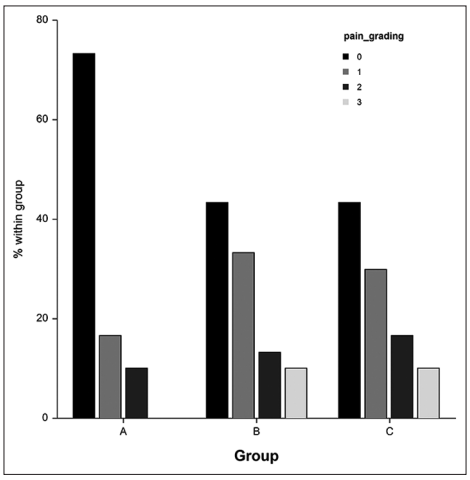

Figure 1: Grading of pain scores as per the verbal rating scale in the three groups (A) Group lignocaine (B) Group tramadol (C) Group acetaminophen

Table 1: Comparison of demographic data between groups

Variable	Group A	Group B	Group C	Probability value
Age	39.2 (9.7)	34.8 (10.07)	37.8 (9.6)	0.4
Height (cm)	162.2 (6.5)	164.7 (6.7)	164.1 (6.7)	0.335
Weight (kg)	60.8 (4.8)	60.8 (4.8)	61.4 (5.1)	0.887
Gender				
Male	19 (63.3%)	20 (66.7%)	25 (83.3%)	0.17
Female	11 (36.7%)	10 (33.3%)	5 (16.7%)	
ASA grade				
1	23 (76.7%)	26 (86.7%)	26 (86.7%)	0.5
2	7 (23.3%)	4 (13.3%)	4 (13.3%)	

cm: Centimeters, kg: Kilograms, SD: Standard deviation, ASA: American Society of Anesthesiologists

Table 2: Assessment of side effects

Variable	Frequency (percentage)			*P*
	Group A	Group B	Group C	
Pain at the injection site after 24 h				
Present	2 (6.7)	7 (23.3)	3 (10)	0.14
Absent	28 (93.3)	23 (76.7)	27 (90)	
Edema at injection site after 24 h				-
Present	0 (0)	0 (0)	0 (0)	
Absent	30 (100)	30 (100)	30 (100)	
Allergy at the injection site after 24 h				-
Present	0 (0)	0 (0)	0 (0)	
Absent	30 (100)	30 (100)	30 (100)	
Postoperative nausea and vomiting				
Present	3 (10)	5 (16.6)	3 (10)	0.64
Absent	27 (90)	25 (83.4)	27 (90)	

h: Hours, P: probability value

of solution,[24] and concentration of propofol in the aqueous phase of emulsion.[25]

Propofol, by an indirect action on the endothelium activates the plasma kallikrein-kinin system and releases bradykinin, thereby producing venous dilation and hyperpermeability, which increases the contact between the aqueous phase of propofol and free nerve endings, resulting in pain on injection.[26]

From the time of discovery of this induction agent, several drugs have been tried for the attenuation of propofol-induced pain. The most current systematic review and meta-analysis has reported lignocaine pretreatment as the best technique with venous occlusion for attenuation of pain due to propofol injection.[1] But research still continues for identifying other related molecules to mitigate the pain of propofol. The optimal dose of lignocaine for effective pain relief was researched to be around 40 mg. Hence, this dose was taken for pain relief as a control and gold standard. Pain due to propofol is an established variable in our clinical curriculum. A control such as saline was not considered as this is unethical for not using any pretreatment strategy for the attenuation of pain, which is already an established fact. Johnson *et al*., studied the efficacy of lignocaine on the pain produced by IV injection of propofol using lignocaine pretreatment (20 mg and 40 mg) and lignocaine (20 mg and 40 mg) mixed with propofol. They found lignocaine of 20 mg or 40 mg doses reduced the discomfort in comparison with propofol alone. A dose of 40 mg was more effective than 20 mg.[27] However, the literature reports the failure rate between 13% and 32%.[28,29] In our study, lignocaine 40 mg was used and was effective in decreasing the incidence of propofol pain compared to tramadol and acetaminophen, though statistically not significant.

Acetaminophen and tramadol have both shown as effective alternative strategies for attenuation of pain but not to the extent of lignocaine. Levant *et al*. studied rat neonatal glial cells in culture and reported that bradykinin enhanced both basal and lipopolysaccharide-induced prostaglandin E2 (PGE_2).[30] It has been shown that acetaminophen selectively suppresses peripheral PGE_2 and increases COX-2 gene expression in a clinical mode of acute inflammation.[18] A study by Ando *et al*. has shown that propofol characteristically causes vascular pain that occurs in response to prostanoids, particularly PGE_2, which is selectively suppressed by acetaminophen.[31] The intensity of propofol pain can be correlated with the levels of bradykinin and PGE_2. The latest study on acetaminophen in 2010 by Borazanan has established the optimal dose of acetaminophen to be around 1 mg/kg.[16,17] In our study, we have used 50 mg tramadol, which is equivalent to 1 mg/kg for a 50-kg adult as it is easy to constitute the volume required for administration and to evaluate whether this dose is comparable with the other two study drugs.

In the study conducted by Canbay *et al*., the overall incidence of pain during IV administration of propofol in the control group was 64% compared to 22% with IV acetaminophen and 8% with the IV lignocaine group. Our study results correlated with the results of the study by Canbay *et al*.[16] Acetaminophen in a dose of 50 mg is also effective in reducing the pain although not as much as lignocaine. In cases where lignocaine pretreatment fails or is not available, acetaminophen can be supplemented as a sole agent or a premedicant to decrease the incidence of pain with propofol.

Tramadol is a centrally acting weak mu-receptor agonist and inhibits norepinephrine reuptake as well as promotes serotonin release.[13] There are studies postulating that it has a peripheral action on the free nerve endings of blood vessels.[32] Most studies used 1 mg/kg of tramadol, which was found to be an effective alternative.[14,19] We used 50 mg tramadol (equivalent of 1 mg/kg), which is again easy to constitute and compare. Our results are consistent with the findings of other cited studies regarding the effectiveness of tramadol as a pretreatment molecule to attenuate pain. Tramadol 50 mg is a useful premedicant, with the added benefits of pain attenuation to propofol and availability.

Tramadol and acetaminophen are cost-effective pretreatment techniques, and can be used alone or in conjunction with other available and established techniques such as lignocaine and venous occlusion to obtain a pain-free environment at the time of propofol induction.

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Conflicts of interest

There are no conflicts of interest.

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