Original Article

Prevention of propofol injection pain: Comparison between lidocaine and ramosetron

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Abstract

Background: Propofol causes a high incidence of pain during intravenous (IV) injection. The aim of this randomized, placebo-controlled, double-blinded study was to determine whether pre-treatment with IV ramosetron, used for prophylaxis of postoperative nausea and vomiting (PONV), would reduce propofol-induced pain as an equivalent to lidocaine.

Materials and Methods: Hundred and twenty American Society of Anesthesiologists grade (ASA) I and II patients were randomly assigned into three groups (40 in each). Group N received 2 ml of 0.9% saline, Group L received 2 ml of lidocaine, and Group R received 2 ml of ramosetron. Mid forearm was occluded manually before injection and released after 1 min and then propofol was injected over 5 s. Patients were observed and questioned 15 s later if they had pain in the arm and pain was scored on a four-point scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. Unpaired Student's *t*-test and chi-square test/Fisher' exact test were used to analyze results.

Results: The incidence of pain in groups N, L, and R were 65, 35, and 30%, respectively. Pain was reduced significantly in the groups L and R ($P < 0.05$). Two patients each in Groups L and R (5% each) had moderate and severe pain. This difference in pain was statistically insignificant, but when compared to Group N (25 and 30%, respectively) it was statistically significant.

Conclusion: Pretreatment with ramosetron 0.3 mg and lidocaine 40 mg are equally effective in preventing pain from propofol injection.

Key words: Injection, lidocaine, pain, propofol, ramosetron

Introduction

Propofol is a common intravenous (IV) anesthetic drug used for induction and maintenance during general anesthesia with rapid onset and short duration of action.[1] However, the incidence of pain following propofol injection varies between 28 and 90% in adults if a vein on dorsum of hand is used.[2,3] The quality of pain was described as extremely sharp, aching, or burning. It has been arranged as the seventh most important problem in current practice of clinical anesthesia by American anesthesiologists.[4]

Strategies to reduce the incidence of pain on injection include adding lidocaine to propofol, cooling or warming propofol, diluting the propofol solution, injection of propofol into a large vein, and pretreatment with IV injection of lidocaine, ondansetron, metoclopramide, an opioid, magnesium, or thiopental with or without tourniquet; all have been tried with variable results.[5-7] It has been demonstrated that ondansetron, a specific 5-hydroxytryptamine ($5HT_3$) receptor antagonist, provided numbness when injected under the skin and is 15 times more potent than lidocaine.[8] It has been further demonstrated that ondansetron successfully relieved pain following propofol injection without any adverse effects in a significant number of patients.[9] In our practice, ramosetron is routinely administered as premedication to prevent postoperative nausea and vomiting (PONV) in patients scheduled for general anesthesia.

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Ramosetron is a serotonin $5HT_3$ receptor antagonist and demonstrates superior efficacy and longer duration to granisetron.[10] We used ramosetron pretreatment to determine its efficacy to decrease the pain of propofol injection as equivalent to lidocaine.

Materials and Methods

Institutional ethical committee approval was obtained and informed written consent was taken from all patients. Hundred and twenty adult patients belonging to American Society of Anesthesiologists (ASA) I and II class, scheduled for elective surgery under general anesthesia were randomly allocated to either of the four groups using computer generated random numbers (40 in each group), for this prospectively randomized, placebo-controlled, double-blinded study. Patients having problems in communication and history of allergic response to either propofol or $5HT_3$ antagonists were excluded from this study.

All patients were kept fasting for 6 h for solid food and were premedicated with tab alprazolam 0.5 mg and tab ranitidine 150 mg night before surgery and 2 h prior to induction. On arrival to the operation theatre, a 20 G cannula was inserted into a vein on the dorsum of the patient's nondominant hand and lactated Ringer's solution was infused. The pretreatment solutions consisted of 2 ml of 0.9% saline (Group N, $n = 40$) as placebo, 2 ml (40 mg, Group L, $n = 40$) of lidocaine (Loxicard 2%, Neon laboratories ltd, Mumbai, India), and 2 ml (0.3 mg, Group R, $n = 40$) of ramosetron (Nozia, Cadila Healthcare Ltd, Goa, India). Pretreatment drug was injected after venous drainage was occluded manually at the mid-forearm for 1 min. Patient's then received one-fourth of the total calculated dose of propofol-LCT (long chain triglycerides) over 5s and 15 s later the patient was assessed for pain during injection of propofol.

The level of pain was assessed by a second anesthetist who was unaware of the group to which the patient had been allocated. Assessment included standard questions asked to the patients about the comfort of the injection, verbal response, and behavioral signs (such as facial grimacing, arm withdrawal, or tears). Pain was graded using a four-point scale: 0 = no pain, 1= mild pain (pain reported only in response to questioning without any behavioral signs), 2 = moderate pain (pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning), and 3 = severe pain (i.e., strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears).[11]

Later anesthesia was induced with intravenous propofol-LCT 2.5 mg/kg. All study drugs were kept at room temperature and used within 30 min of preparation. Tracheal intubation was facilitated with vecuronium and anesthesia was maintained with sevoflurane and fentanyl.

Statistical analysis

Based on the literature, the incidence of pain on injecting propofol is assumed as 80%, and 50% reduction in pain was considered clinically significant. Forty patients were calculated as the minimum size for each group assuming a-value of 0.05 and a power value of 80%. All measured values are presented as mean ± standard deviation and numbers (%). The results were analyzed statistically using unpaired Student's *t*-test and chi-square test/Fisher's exact test. Results were considered statistically significant when *P*-value of <0.05 was obtained. Statistical Packages for the Social Sciences (SPSS; Windows ver. 15.0, SPSS Inc., Chicago, IL) was used for statistical analysis.

Results

There was no significant difference in the demographic characteristics in all the three groups [Table 1]. No patients in any group experienced pain and discomfort during the injection of pretreatment solution. The incidence and severity of pain during IV injection of propofol in various groups is shown in Table 2. The incidence of pain on injection of propofol in the control group was 65% (26/40), as compared to 35% (14/40) in lidocaine group and 30% (12/40) in

Table 1: Demographic data

Patients characteristics	Group N ($n = 40$)	Group L ($n = 40$)	Group R ($n = 40$)
Age (years)	32.6±15.8	32.6±15.2	34.2±15.4
Weight (kg)	56.8±13.4	55.4±14.5	57.6±12.4
ASA I/II	19/21	22/18	21/19
Sex (M/F)	21/19	20/20	22/18

Values are expressed as mean ± standard deviation (SD) or number of patients. There were no significant differences among groups. Group N: Patients who received normal saline, Group L: Patients who received lidocaine 40 mg, and Group R: Patients who received ramosetron 0.3 mg. ASA = American Society of Anesthesiologists, M = Male, F = Female

Table 2: Incidence and severity of pain following propofol injection

	Group N (%)	Group L (%)	Group R (%)	*P*-value
No pain	14 (35)	26 (65)*	28 (70)*	0.003*
Pain	26 (65)	14 (35) *	12 (30) *	0.003*
1 (mild pain)	4 (10)	10 (25)	8 (20)	0.210
2 (moderate pain)	10 (25)	2 (5)*	2 (5)*	0.006*
3 (severe pain)	12 (30)	2 (5)*	2 (5)*	0.001*

*Data is expressed as number of patients (%). Group N: Patients who received normal saline, Group L: Patients who received lidocaine 40 mg, and Group R: Patients who received ramosetron 0.3 mg. *P < 0.05 compared with Group N*

ramosetron group. Ramosetron pretreatment was as effective as lidocaine to attenuate propofol associated pain when compared to saline group ($P < 0.05$).

Two patients each in Groups L and R (5% each) had moderate and severe pain. The difference in pain was statistically not significant with each other, but when compared to Group N (25 and 30%, respectively) it was statistically significant.

Discussion

Considering the extensive use of propofol in clinical practice, the pain frequently reported on induction of anesthesia cannot be neglected. Although it is not a serious complication, efforts are assumed to reduce the severity of the pain or discomfort. Propofol belongs to the group of phenols that can irritate the skin, mucous membranes, and venous intima.[9] Injection pain associated with propofol characteristically occurs immediately or later after the drug injection with a delayed response of 10-20 s.[12] The explanation for the pain includes endothelial irritation, osmolality differences, unphysiological pH, and the activation of pain mediators.[13]

Many methods have been used to reduce the incidence of pain on propofol injection with variable results. Lignocaine added to or given before injection of propofol is widely employed.[6] Gajraj and Nathanson[11] studied the optimal dose of lidocaine for propofol pain and concluded that 30 mg lidocaine is the optimal dose for attenuation of propofol pain. Cooling the propofol to 4°C reduces its injection pain possibly by delaying the activation of enzyme cascade of pain mediators.[14] Injecting into a large forearm vein also reduces the pain, probably by reducing contact between drug and endothelium.[6]

Metoclopramide shares the structural and physiochemical properties with lidocaine and is a weak local anesthetic. It has also shown to be as effective as lidocaine in reducing propofol injection pain.[15] Ye *et al.*,[8] found in rats, that ondansetron is approximately 15 times more potent local anesthetic as lidocaine and this property probably contributes to its antiemetic action. Ondansetron had been shown to relieve pain by its multifaceted actions as a Na channel blocker, a $5HT_3$ receptor antagonist, and mu opioid agonist.[8,16] Ondansetron pretreatment may be used to reduce the incidence of pain on injection of propofol with an added advantage of prevention of PONV.[9,17]

In a study by Ahmed *et al.*,[18] the incidence of propofol injection pain was reduced from 60 to 15% after granisetron pretreatment. Pretreatment with granisetron/lidocaine may be effective not only in attenuating pains during IV injection of propofol, but also in preventing postoperative nausea, vomiting, and shivering.[19,20] In a study by Piper *et al.*,[21] severity but not the incidence of pain on injection was significantly reduced by dolasetron (50 %) compared with placebo and there was no significant difference between dolasetron and lidocaine. Ramosetron is a recently developed $5HT_3$ receptor antagonist. Lee *et al.*,[22] reported the incidence of pain in the groups pretreated with ramosetron 0.3 mg or combination with ramosetron and lidocaine 20 mg were 60 and 38%, respectively. These results show effective reduction in propofol injection pain. Pretreatment with ramosetron alone or with combined pretreatment of ramosetron and lidocaine also prevented pain effectively for moderate to severe pain.

In our study, the incidence of pain was 65% in the placebo group. The incidence of pain pretreated with lidocaine 40 mg and ramosetron 0.3 mg were 35 and 30%, respectively. These results show that there is significant reduction in the pain for propofol injection and both lidocaine and ramosetron are equally effective. Even there is significant decrease in moderate and severe pain (5% in each L and R group) compared with normal saline group (25 and 30%, respectively).

Our study had few limitations. Occlusion at mid forearm was done manually, which will vary from person to person, this could have been overcome by using tourniquet with constant pressure. Also drug could have been injected using syringe pump instead of injecting manually.

We concluded that IV ramosetron when given as pretreatment is as effective as lidocaine on propofol associated pain with an added advantage of preventing PONV.

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