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Original Article

Does Granisetron Pretreatment Relieve Pain Due to Propofol Injection?

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ABSTRACT

Background: Propofol is the most commonly used induction agent, but causes pain on injection in many patients. Various techniques have been tried and tested for reducing pain due to propofol injection with different results.
Objective: To compare the use of pretreatment with granisetron in comparison with lignocaine in reducing pain on propofol injection.
Patients and Methods: 104 patients (ASA I-II) posted for elective surgeries under general anesthesia were randomized into two groups and managed as follows: Group G: 2ml (1mg/ml) granisetron, and group L; 2ml of 2% lignocaine pretreatment using tourniquet followed by 2ml (20mg) of propofol injection and pain assessment was done by a independent observer and graded as either severe, moderate, mild or no pain according to the response of the patients to the injection.
Results: In lignocaine group the incidence of pain was 21.2% compared to 46.2% in the granisetron group.
Conclusion: Pretreatment with lignocaine is more effective in relieving pain on propofol injection than granisetron.

Keywords: Propofol, Granisetron, Lignocaine, Pretreatment.

INTRODUCTION

With decreasing number of morbid adverse events after surgery, the emphasis has inclined towards patient comfort and perioperative management. Propofol is presently the most frequently used intravenous anesthetic agent, preferred for its smooth onset of action and prompt, pleasant recovery, but pain on its injection is a major concern which varies between 30 to 90%[1]. Pain on propofol injection was rated as the 7th most important problem among the low morbidity outcomes of current clinical anesthesiology[2].

Numerous approaches have been attempted to prevent or reduce pain at the site of propofol administration, which include non pharmacological approach like modification of the drug composition[3],

cooling or warming the preparation[4], dilution of solution[5], separation or filtration of the formula, and modification of the site of injection and of the infusion rate of formula or carrier fluid.

The more popular pharmacological suggestions include adding lidocaine to propofol[6], pretreatment with IV metoclopramide[7], opioids[8], magnesium, thiopentone[9], dexamethasone[10], with or without using tourniquet. All have been tried with variable results.

It has been established that serotonin ($5HT_3$) receptor antagonists like ondansetron produced numbness when injected beneath the skin[11]. It has also been demonstrated that ondansetron successfully allayed pain following propofol injection without any detrimental effects, in a significant number of people[12]. Granisetron is commonly used in our setup to avoid post operative nausea and vomiting in patients after general anesthesia. Granisetron is a more refined serotonin ($5HT_3$) antagonist with better efficacy, longer duration of action and lesser side effects when compared to ondansetron. We hypothesized that IV granisetron pre-treatment, reduces pain on propofol injection.

METHODS

The study was performed in the department of Anesthesiology, at Kasturba medical college associated hospitals, at Attavar, Ambedkar circle and Government Wenlock hospital, Mangalore from September 2012 to July 2014.

The study is a double blind, randomized, clinical trial. The study participants were patients with age group 18-60 years, either sex of ASA physical status 1 and 2 undergoing elective surgical procedures under general anesthesia. Patients who refused to give consent, patients with ASA 3 or 4 status, history of allergy to any of the study drug, hemodynamically unstable patient, those who had analgesics as premedication, participants with difficult IV cannulation and pregnant women were not included in the study.

The sample size required for correctly rejecting the null hypothesis with the power of 80% and 95% confidence interval was calculated and was determined that 52 participants were required in each of the two groups receiving either intravenous granisetron (2mg/2ml) or intravenous lignocaine (40mg/2ml).

After approval from the institute's scientific and ethics committee and after obtaining written and informed consent the participant took part in the study. Participants were assessed pre-operatively to check against the exclusion criteria of the study. The participant received premedication with tablet Lorazepam 2mg, the night before surgery. After shifting to operation room, venous cannulation was done under aseptic precautions in a large peripheral vein using an 18G cannula and connected to normal saline or ringer lactate at 10-l5ml/kg/hr. Participant was then connected to the monitor to record heart rate, blood pressure and saturation during the procedure.

Venous occlusion of the arm was maintained with a tourniquet tied 12-15 cms proximal to the puncture site. The tourniquet was tightened to a point where the intravenous fluid stopped flowing, thus ensuring venous occlusion. Participants were randomized to receive intravenously either granisetron 2ml (1mg/ml) or 2ml of 2% lignocaine (preservative free) based on the random number table. The intravenous infusion was then closed during the period of occlusion to prevent backflow of blood or the injected drug into the infusion line. After 1 minute of giving the study drug occlusion was released and the participant received propofol 2mg/kg. The first 2ml bolus was

given over 4 seconds and within 15 seconds the patient will be asked to rate his pain sensation. The same propofol formulation was used in all the patients. An anesthetist blinded to the study protocol was made to evaluate the pain during injection of propofol using a four point verbal rating (McCrirrick and Hunter) scale[4] used in the earlier studies.

RESULTS

Statistical analysis was done using SSPS 17 software. There were no statistically significant difference among the variables like mean age, sex, weight and ASA physical status (Table: 1) in both groups. Students' unpaired test was used for the analysis of mean age and weight. Chi square was used for analysis of ASA grade and sex distribution among the two groups. P value <0.05 was considered statistically significant.

The incidence of 'no pain' was significantly higher in the lignocaine group (78.8%) as compared to granisetron group (53.8%). The severity of pain was also greater in the granisetron group with 46.2% complaining of mild to moderate pain, as compared to 21.2% in the lignocaine group. There was however, no incidence of severe pain in either group. (Table: 2)

The mean pain scores (determined by Mann Whitney test) were also significantly lower in the lignocaine group as compared with granisetron group. (Table: 3)

There were no incidences of adverse reaction to lignocaine, granisetron or propofol among the participants. There were also no cases with rapid loss of consciousness after propofol injection or inability to draw pain scores.

DISCUSSION

In this study, pretreatment with lignocaine has significantly reduced pain levels (78.8%) when compared with granisetron (53.8%). The mean pain scores were also lower with lignocaine (1.24) than with granisetron (1.62). Pain on injection of propofol remains a common problem and various methods have been tried to decrease this pain, including mixing lidocaine with propofol in the same syringe, pretreatment with lignocaine or procaine, cooling or warming or diluting the propofol solution. Most of the commonly attempted solutions to the problem aim at using a regular premedication drug prior to propofol injection which could serve both the purposes. Several drugs including opioids, antiemetics, prokinetics, local anesthetics have been tried with varying efficacy. Lignocaine has been the most widely used drug for this purpose and hence become a measure of comparison in several studies.

Lignocaine is more effective in reducing pain on injection of propofol when it is given as a mixture than when administered as pretreatment before the propofol injection[1,13,14]. The addition of lidocaine may result in destabilization of the propofol solution. But applying the emulsion in a 9:1 mixture of propofol-lidocaine for a short duration (less than 30min), has less effect[15]. Since the effect of mixing granisetron in propofol has not been established we have considered giving it as pretreatment. Moreover tourniquet-controlled pretreatment with lignocaine was superior to admixing lignocaine with propofol for reducing propofol injection pain intensity[1,5].

Studies comparing other $5HT_3$ antagonists like ondansetron also had relieved pain in 75% of the subjects[12]. Ondansetron was said to have local anesthetic action due to its ability to block Na channels[11]. It caused numbness when

injected under the skin. Peripheral $5HT_3$ receptors are thought to be involved in nociceptive pathways. Ondansetron also demonstrated binding at opioid μ-receptors with agonistic activity[16]. The binding of ondansetron to these additional receptor subtypes other than their target receptor may underlie the local anesthetic effect and also adverse effect compared to the newer and more specific $5HT_3$ antagonists like granisetron[17]. Ahmed *et al*, in 2012 found that granisetron was successful in reducing pain on propofol injection by 85% compared with patients receiving saline[18]. Our study shows that granisetron did reasonably reduce pain in more than 50% of the patients. Also there were no participants with severe pain scores in the granisetron group. On the contrary more refined $5HT_3$ antagonists like ramosetron were found to be equally efficacious as lignocaine in reducing pain on propofol injection[19].

The differences in these results can only be attributed to the fact that mechanism for pain on propofol injection is still incompletely understood. The mechanism for propofol injection pain is by affecting an enzymatic cascade[1], possibly the plasma kallikrein-kinin system leading to bradykinin generation. While some use aqueous free propofol[20] as the mediator, the other implicates the lipid solvent[21] for bradykinin generation. A study by Sim JY *et al* showed no evidence of raised plasma bradykinin levels caused by propofol-induced pain. In addition, agents known to reduce propofol-induced pain did not decrease aqueous free propofol concentrations[22]. Probably, lignocaine's ability to modulate G-protein coupled receptors could explain its better efficacy in reducing pain[23]. Recent study by Ando *et al* shows that prostanoids were responsible for pain due to propofol injection[24]. Thus multiple interplay of mechanisms mediate pain due to propofol injection and no method seems to completely abolish it.

CONCLUSION

From our study pre-treatment with lignocaine is proved to be more effective in controlling pain on propofol injection than granisetron. However granisetron does reduce pain in more than 50% subjects making it an alternative choice due to its additional property to prevent postoperative nausea, vomiting.

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Table 1. Showing comparison of the demographic variables among the two groups

Patient variables	Lignocaine group	Granisetron group	p-value
Mean age (sd)	40.65 (11.482)	38.75 (13.705)	0.444 (NS)
Mean weight (sd)	61.90 (8.923)	62.31(9.283)	0.822 (NS)
Sex M/F	25/27	21/31	0.430 (NS)
ASA physical status I/II	40/12	43/9	0.464 (NS)

Sd- Standard deviation from mean, NS- not significant.

Table 2. Comparison of pain score between the two groups

		Group		
		Lignocaine	Granisetron	Total
Pain score	No pain	41	28	69
		78.8%	53.8%	66.3%
	Mild pain	9	16	25
		17.3%	30.8%	24.0%
	Mod pain	2	8	10
		3.8%	15.4%	9.6%
Total		52	52	104
		100.0%	100.0%	100.0%

Chi square test p- value 0.018 (significant).

Table 3. Comparison of mean pain scores between the two groups

Group	Mean	S.d	Mann Whitney test p value	
Lignocaine	1.25	.519	.005	Highly
Granisetron	1.62	.745		Significant