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Palonosetron Pretreatment is not as Effective as Lignocaine for Attenuation of Pain on Injection of Propofol

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Abstract

Objective: 5-HT3 receptor antagonists are known to possess local anesthetic properties and are commonly used for the alleviation of pain following propofol injection. Palonosetron, a newer molecule, has shown contradictory results for this property. The aim of this study was to compare the effect of palonosetron pretreatment in alleviating propofol injection pain with that of lignocaine. Their comparative effect on various hemodynamic parameters was also evaluated.

Methods: A total of 100 adult patients were randomly assigned to one of two groups: group L received lignocaine 40 mg in 5 mL of 0.9% saline pretreatment solution and group P received 0.075 mg palonosetron in 5 mL 0.9% of saline pretreatment solution. After 2 minutes, the tourniquet was released and one-fourth of the total calculated dose of propofol was administered, after which the pain assessment was made. The Students t-test was used for comparing the difference of mean between the two groups after testing for equality of variance using F-statistics. Categorical variables were expressed as a percentage, and the Chi-square test was performed to assess the independence of attributes. Repeated-measure analysis of variance was used to compare the change in heart rate and mean arterial pressure over three time points between the two groups.

Results: The proportion of pain reported by the subjects in the lignocaine group was significantly lower as compared to the subjects in the palonosetron group (p=0.001). No significant difference of mean heart rate and mean arterial pressure was observed between the two groups following these interventions.

Conclusion: The efficacy of palonosetron in alleviating the pain on injection of propofol was significantly less than that of lignocaine.

Keywords: Alleviation, pain, palonosetron, propofol

Introduction

Even after more than 35 years since the introduction of propofol (2,6-di-isopropyl phenol) in clinical anesthesia and after approximately 200 clinical trials, pain on injection remains a concern for clinicians. Out of the various pharmacological and non-pharmacological interventions for alleviation of this pain, lignocaine pretreatment remains the gold standard (1). Also, it has been observed that formulations containing medium-chain triglycerides (MCT) cause lesser pain on injection (2).

5HT3 receptor antagonists have been found to be effective in alleviating propofol injection pain (3). They bind to μ-receptors and act as agonists, and ensure that peripheral 5-HT3 receptors are involved in the nociceptive pathway. Palonosetron, a 5HT3 receptor antagonist antiemetic, has superior efficacy and longer duration than ondansetron. We postulated that similar to the other members of this group, palonosetron pretreatment can reduce the incidence and severity of propofol injection pain in addition to performing its antiemetic action.

This study evaluated the efficacy of palonosetron and lignocaine pretreatment for alleviation of pain on injection of propofol containing MCT formulation.

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Methods

The study was registered after obtaining approval from the institutional ethics committee, Indira Gandhi Institute of Medical Sciences, Patna, India (No. 1185 / Acad dated 16.11.2016). We included 100 adult patients aged 18-60 years of either sex, having a physical status of I and II (as described by the American Society of Anesthesiologists). All the included patients were scheduled to undergo general surgical procedures, were able to comprehend the study protocol and were willing to participate in it, and in whom propofol was indicated for induction of anesthesia. Written informed consent was obtained from all patients.

Exclusion criteria were; a known sensitivity to lignocaine, propofol or palonosetron; concomitant analgesic or sedative medication; presence of infection on the dorsum of the left hand; and refusal of the patient to participate in the study.

A randomized, double-blind method of evaluation was used. All patients received 0.25 mg alprazolam and 150 mg ranitidine orally on the evening prior to the experiment.

No premedication was administered. A 20-gage cannula was placed into the largest vein on the dorsum of the left hand after placing the routine monitors (i.e., lead II electrocardiogram, noninvasive arterial pressure, and pulse oximeter). Patients were allocated into one of two groups by using a random computer-generated list and a sealed envelope. The patient and the clinician were blinded to the group assignment.

Patients received a 5 mL pretreatment solution of either 40 mg lignocaine in saline (group L), or 0.075 mg palonosetron in saline (group P) intravenously for a period of 10 seconds while the venous drainage was occluded by placing a pneumatic tourniquet (pressure inflated to 70 mmHg) on the upper arm. The patients were asked if they felt any pain during the administration of pretreatment solution. An independent clinician who was blinded to the contents of the solutions prepared the solution administration. The occlusion was released after 2 minutes (3). One-fourth of the total calculated dose of propofol (2 mg kg^{-1} body weight) was administered for a period of 5 seconds. The drugs used in the study were preservative-free and stable at room temperature.

Main Points:

- Lignocaine or palanosetron pretreatment alleviates severe pain on injection of propofol formulation containing medium chain triglyceride.
- Palonosetron pretreatment reduces the incidence of pain on injection of propofol, but to a significantly lesser degree than lignocaine.
- Palonosetron has a different molecular structure, it interacts at different 5HT3 receptor sites, is a longer-acting agent and displays the characteristics of a delayed-onset action as compared to older molecules of this group. These factors might explain our findings.
- As compared to lignocaine, palonosetron pretreatment does not significantly reduce the incidence of pain on injection of 1% propofol.
- However, palonosetron pretreatment may be used for this purpose in situations where lignocaine is to be avoided.

No analgesic or sedative was administered before the propofol injection. Another independent clinician, who was blinded to the group allocation, assessed the level of pain after the injection of propofol. The patients were asked a standard question, "Is the injection comfortable?" Their verbal responses and behavioral signs, such as facial grimacing, withdrawal of arms, tears, etc. were noted (4). A score of 0 to 3 (no, mild, moderate, or severe pain, respectively) was recorded. Mean arterial pressure and heart rate before the interventions (baseline), after the administration of study drugs (time 1), and after the administration of propofol (time 2) were recorded. Adverse effects, if any, were noted. The rescue medication selected were atropine for bradycardia (less than 50 beats per minute) and mephentermine for hypotension (mean arterial pressure less than 20% of the baseline value). Anesthetic induction was continued with propofol after administering fentanyl. Tracheal intubation was facilitated with vecuronium and anesthesia was maintained with isoflurane and nitrous oxide in oxygen along with intermittent positive pressure ventilation.

Statistical analysis

The primary end-point of this study was to evaluate the incidence and severity of pain on injection of propofol and the effectiveness of drugs in pain attenuation. The secondary end-point was to assess effect of the study drug on hemodynamic parameters, i.e., the mean arterial pressure (MAP) and heart rate (HR).

Power Analysis and Sample Size System (PASS) [NCSS, Utah, USA] version 11 software was used for the calculation of the sample size using the primary end-point of the study, i.e., the incidence of pain. On the basis of the result of a study (5), the sample size was estimated to detect a difference of 30% in the proportion of incidence of pain in the patient (30%) and control groups (60%), with a power of 80% and an alpha error of 5%. The sample size came to 50 for each group.

All statistical analyses were performed using the Stata Version7 (Stata Corp, Texas, USA) software. Data were entered using MS Excel Version 10. Continuous variables were presented as mean with 95% confidence interval. The Students' *t*-test was used for comparing the difference in the mean be-

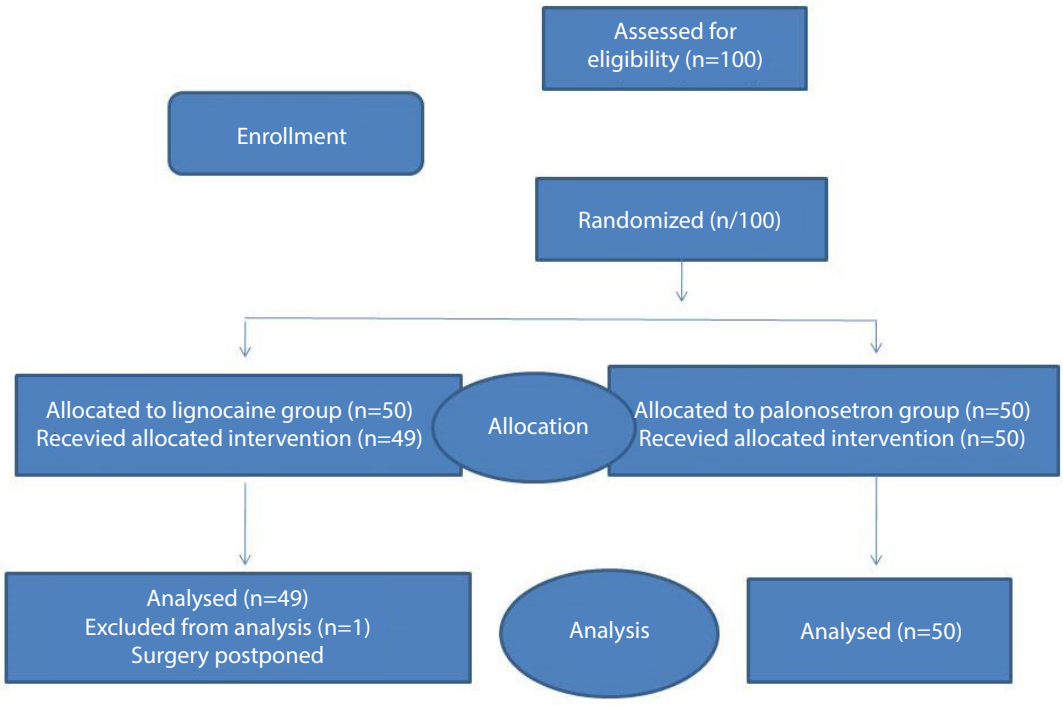

Figure 1. CONSORT flow diagram of the study patients

Table 1. Demographic profile of both groups

Characteristics	Group L (n=49)	Group P (n=50)	Test Statistics	p
Gender				
Male	24	21	$\chi 2$=0.4862	0.547
Female	25	29		
Age (In years)	35.9 (32.67-39.1)	35.1 (32.3-37.9)	Students' t-stat=0.346	0.730
ASA Grade I	48	48	$\chi 2$=0.3233	0.508
ASA Grade II	1	2		
Weight (in kgs)	57.5 (54.8-60.3)	56.9 (54.2-59.6)	Students' t-stat=0.339	0.7350

All data are represented as mean with 95% confidence interval; ASA: American Society of Anesthesiologists.

Table 2. Assessment of pain after administration of propofol

Pain score*	Degree of pain	Group L (n=49)	Group P (n=50)	Test statistics	p
0	None	47	34	$\chi 2$=11.6884	0.001
1	Mild	2	15		
2	Moderate	0	1		
3	Severe	0	0		
	Overall incidence	4%	32%		

*Response Pain score

0=Negative response to questioning

1=Pain reported in response to questioning only, without any behavioral sign

2=Pain reported in response to questioning and accompanied by a behavioral sign, or pain reported simultaneously without questioning

3=Strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears

tween two groups after testing for equality of variance using F-statistics. Categorical variables were expressed as percentage, and the Chi-square test was performed to assess the independence of attributes. Repeated-measure analysis of variance (ANOVA) was used to compare the change in HR and MAP over three time points and between the two groups.

Table 3. Comparison of heart rate between two groups over time

Source	Partial sum of square	Degree of freedom	Test statistics	p
Model	44700.67	102	F-stat=19.05	0.0001
Group	27.55	1	F-stat=0.06	0.8067
Time	225.02	2	F-stat=4.89	0.0085
Group* Time	57.993	2	F-stat=1.26	0.2858
Residual	4462.86	194		
Group/Time	**Group L (n=49) Mean (95% CI)**	**Group P (n=50) Mean (95% CI)**	**Students' t-statistic**	**p**
On Baseline	91.46 (87.77-95.16)	92.08 (88.47 - 95.68)	0.2328	0.8164
Time 2	91.75 (88.11 - 95.39)	90.3 (86.57 - 94.02)	0.5496	0.5838
Time 3	90.16 (86.38 - 93.93)	89.18 (85.88 - 92.47)	0.3868	0.6968

Adjusted R-Squared=0.8615

*Group × Time =Interaction effect

Table 4. Mean arterial pressure of subjects in two groups over time

Source	Partial sum of square	Degree of freedom	Test statistics	p
Model	28332.98	102	F-stat=20.40	0.0001
Group	659.30	1	F-stat=2.60	0.1098
Time	3084.35	2	F-stat=113.27	0.0001
Group*Time	44.17	2	F-stat=1.62	0.20
Residual	2641.75	194		
Group/Time	**Group L (n=49) Mean (95% CI)**	**Group P (n=50) Mean (95% CI)**	**Students' t-statistic**	**p**
On Baseline	98.79 (95.84-101.75)	95.2 (92.35-98.04)	1.7629	0.0811
Time 2	97.59 (94.67-100.59)	94.12 (94.57-96.70)	1.789	0.0766
Time 3	90.61 (87.93-93.29)	88.72 (86.12-91.31)	1.0191	0.3167

Adjusted R-Squared=0.9147

*Group × Time =Interaction effect

Results

The study included 99 patients (Figure 1). Demographic data were comparable among the two groups (Table 1). None of the patients experienced pain or discomfort during the injection of the pretreatment solution. The assessment of pain of each group is shown in Table 2. The overall incidence of pain was 4% in the lignocaine group and 32% in the palonosetron group. Pain intensity was significantly less in patients receiving lignocaine for pretreatment than in those receiving palonosetron (p=0.001). A dose of 0.075 milligrams of palonosetron during pretreatment reduces the incidence of pain on injection of propofol, but to a significantly lesser degree than 0.8% lignocaine. However, no patient in either the lignocaine pretreatment group or the palonosetron pretreatment group complained of severe pain.

No significant difference of mean HR was observed between the two groups at baseline, at time 1, and at time 2 (Table 3). The mean HR within each group significantly decreased over time in both groups (p=0.008). The between-group interaction and time in response to the HR was not found to be significant (p=0.2858) (Table 3).

No significant difference of MAP was observed between the two groups at baseline, at time 1, and at time 2 (Table 4). The MAP within each group significantly decreased over time in both groups (p=0.001). The between-group interaction and time in response to MAP was not found to be significant (p=0.20) (Table 4).

Discussion

The mechanisms attributed to pain on injection of propofol are endothelial irritation, a difference in osmolarity, non-physiological pH, and the activation of pain mediators (6). The kallikrein-kinin system is activated in the plasma by contact with propofol, which generates bradykinin. Consequently, the aqueous-phase propofol comes into contact with more free nerve endings outside the endothelial layer of the vessel and aggravates the severity of pain on injection. It has also been proposed that the nonselective ligand-gated cation channels like transient receptor potential (TRP), ankyrin1 (TRPA1), and TRP vanilloid 1 (TRPV1) are the main mediators of propofol-induced pain and the release of neuropeptides (7). This induces vascular leakage and dilatation, which contrib-

utes to neurogenic inflammation in the periphery and central sensitization in the spinal dorsal horn.

Formulations containing MCT are associated with fewer incidences of mishap and severity of pain on injection (8) as compared to the traditional emulsions containing only long chain triglyceride. This is because the concentration of free propofol is reduced in the aqueous phase.

Although lignocaine pretreatment is the most effective strategy, the use of lignocaine may not always be desirable. Anaphylactic shock has been reported to develop immediately after intravenous administration of lignocaine was added to propofol treatment (9). Further, adding lignocaine may destabilize the propofol emulsion, which results in a potential risk of pulmonary fat embolism if the droplet size exceeds 5 μm (10).

5-HT receptors are located in the central and peripheral nervous system and modulate transmitted nociceptive stimulations (11). A recent meta-analysis showed that 5HT3 receptor antagonists can effectively reduce the incidence and severity of propofol injection pain and may become an alternative to lignocaine (3).

The main findings of this study were, firstly, no patient in either the lignocaine pretreatment group or the palonosetron pretreatment group complained of severe pain, and secondly, palonosetron pretreatment reduced the incidence of pain on injection, but to a significantly less degree than lignocaine. None of the patients in either group experienced severe pain. This finding is in agreement with Ryu and Kim (5), who reported that no patient complained of severe pain when they compared palonosetron pretreatment with placebo. However, they did not disclose the formulation of propofol used in their study. In our case, we preferred to use the MCT formulation that is known to cause lesser pain on injection. Pretreatment with lignocaine and palonosetron might have further influenced the decreased severity of pain, resulting in the absence of severe pain in either group.

In our study, 94% of the patients pretreated with lignocaine did not feel any pain. The rest of the patients felt only mild pain. However, in the palonosetron pretreatment group, 30% of the subjects felt mild pain and 2% experienced moderate severity of pain. Although palonosetron pretreatment reduced the incidence of pain on injection, the reduction was significantly less than what was obtained with lignocaine.

Unlike other 5HT3 receptor antagonists, palonosetron has shown conflicting results in alleviating the pain on the injection of propofol. Ryu and Kim (5) have shown that palonosetron reduced injection pain from 60% to 27.5% as compared to the placebo. On the other hand, Lee et al. (12) reported that palonosetron did not reduce the overall incidence of propofol injection pain, although it reduced the incidence of severe pain from 33% to 3% in a patient group as compared to the pain reduction in a control group. Singh et al. (10) found that pretreatment with palonosetron with venous occlusion for 1 minute could effectively reduce the incidence of propofol injection pain. None of these studies mentioned the constituents of the propofol formulation that was used.

While almost all the studies compared lignocaine with a placebo, there is one published study that has compared lignocaine with palonosetron. This study by Yoo et al. (2) is also the only study that has evaluated the effectiveness of palonosetron pretreatment for injection pain caused by MCT propofol. Their study demonstrated that palonosetron pretreatment with venous occlusion does not reduce the incidence of moderate-to-severe or overall pain on the injection of 1% MCT propofol. They compared this with saline pretreatment. They also found that lignocaine pretreatment does not reduce moderate-to-severe pain, although it reduces the overall incidence of propofol injection pain. There were no significant group differences ($p=0.076$) between lignocaine and palonosetron pre-treatment.

However, there was a major difference in the methodology that they used as compared to ours. Like most of the similar studies that have been conducted, we administered only one-fourth of the total calculated dose of propofol to assess the pain response. We also used the most widely used pain score described by McCrirrick and Hunter that incorporates both objective and subjective responses to pain. On the contrary, Yoo et al. (2) administered a full dose of propofol, and by the time a response from the patient was expected, usually they fell asleep. This, in our view, was a major limitation in their methodology. They had defended this by explaining that they felt it was clinically important to evaluate the pain exactly one may expect to encounter in a clinical situation. However, assessing the delayed pain response to a propofol injection is difficult if the patient is asleep following a full-dose propofol injection.

Palonosetron has a different molecular structure and it interacts at different 5HT3 receptor sites as compared to older molecules. It has been proposed that unlike the earlier 5HT3 receptor antagonist molecules, palonosetron has allosteric interactions and cooperates positively with 5HT3 receptors at different sites, which can lead to a different pharmacological profile in clinical studies (13).

Another possible explanation for the results in our study may be that palonosetron is a longer-acting agent and displays the characteristics of a delayed-onset action (12). In this situation, a 2-minute interval after the pretreatment may not have been enough for the local anesthetic action of palonosetron to set in.

While comparing the hemodynamic effects, no significant difference between HR and MAP was observed between the two groups at the baseline, before and after the propofol injection. However, repeated measure ANOVA to compare the HR and MAP between the two groups showed a significant decrease over time in both groups. This may be a reflection of the effect of propofol on hemodynamics. This phenomenon also indicates that there was no incidence of severe pain that may have resulted in an increase in these parameters after the injection of propofol.

However, there was a critical limitation in terms of the relatively small sample size of our study. Further, a placebo group was not included due to ethical issues.

Conclusion

As compared to lignocaine, palonosetron pretreatment does not significantly reduce the incidence of pain on injection of 1% propofol. However, palonosetron pretreatment may be used in situations where lignocaine is to be avoided.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Indira Gandhi Institute of Medical Sciences (No. 1185/Acad dated 16.11.2016).

Informed Consent: Written informed consent was obtained from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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