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A study to assess the effect of pretreatment with intravenous palonosetron in preventing pain on propofol injection

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ABSTRACT

Background. Propofol is widely used for induction and maintenance of anaesthesia and possesses many characteristics of an ideal intravenous anaesthetic agent. It is known to cause severe, sharp, stinging, or burning pain on injection, which is considered unacceptable as it can cause agitation and interfere with the smooth induction of anaesthesia. In this study, we compare palonosetron and normal saline for decreasing pain on injection of propofol during intravenous induction of anaesthesia.

Material and methods. One hundred adult patients belonging to ASA physical status I or II, scheduled for elective surgeries under general anaesthesia, were selected and randomly allocated to two groups. Group P received an injection of palonosetron, and Group S received an injection of regular saline as a pretreatment before the propofol injection. Patients were assessed for pain on propofol injection. Haemodynamic parameters and electrocardiography were recorded at the following points of time: prior to induction, after pretreatment, induction, and half-hourly during the surgery.

Results. Comparing pain during propofol injection, 32% of the palonosetron group and 4% of the regular saline group did not experience pain; 54% of the palonosetron group and 20% of the regular saline group suffered mild pain; 12% of the palonosetron group and 48% of the regular saline group developed moderate pain; 2% of the palonosetron group and 28% of the regular saline group experienced severe pain.

Conclusions. Pretreatment with palonosetron 0.075 mg reduced the incidence and severity of propofol-induced pain on injection, with the added advantage of decreased postoperative nausea and vomiting without significant haemodynamic changes.

Introduction

Propofol is the most commonly used intravenous induction agent today. The formulation commonly used is that of 1% propofol, 10% soyabean oil, and 1.2% purified egg phospholipid added as emulsifier, with 2.25% glycerol as a tonicity- adjusting

agent and sodium hydroxide to change pH [1]. It is the drug of choice for induction of anaesthesia in a lot of patients due to its rapid onset, short duration of action, easy titration, and favourable side effects profile [2]. Induction with propofol is associated with pain on injection, apnoea, hypotension, and, rarely, thrombophlebitis of the vein into which propofol is injected [1]. In various studies, the incidence of pain is about 60% on injection of propofol without any preventive measures [3]. The mechanism for pain on injection of propofol is unclear. However, it has been postulated that it could be associated with a direct or indirect irritant effect by releasing pro-inflammatory mediators [4]. The initial component of pain involves immediate stimulation of nociceptors and free nerve endings, mainly associated with the concentration of free drugs within the aqueous phase of the emulsion [5].

Several studies have demonstrated that 5-hydroxytryptamine (5-HT3) receptor antagonists could reduce the incidence of propofol injection pain [4, 6]. Peripheral 5-HT3 receptors are known to be involved in the nociceptive pathway. 5HT3 receptor antagonists could be used as a local anaesthetic based on their effect in blocking sodium channels. Palonosetron is a second-generation 5HT3 receptor antagonist, which reduces pain on propofol injection and decreases postoperative nausea and vomiting. Hence, the study performed to assess and evaluate the effectiveness of palonosetron in reducing the occurrence of propofol–induced pain.

The study's primary objective was to assess the effect of pretreatment with intravenous palonosetron in preventing pain on propofol injection. A secondary objective was to evaluate the safety profile associated with using palonosetron and assess the duration of action in reducing postoperative nausea and vomiting..

Methods

After obtaining institutional ethical committee clearance and written informed consent from patients, a prospective, randomised, controlled single-blind study was conducted on 100 patients aged 18-60 yrs, belonging to ASA (American Society of Anesthesiologists) grade I & II, who were scheduled for surgeries under general anaesthesia. The trial was registered in UMIN UMIN000050665.

Patients who cannot verbally express the severity of pain, ischemic heart disease, previous myocardial infarction, congestive heart failure, congenital long QT syndrome, electrolyte abnormalities, hepatic and renal dysfunction, chronic alcohol abuse and patients on antipsychotic drugs were excluded from the study groups. Patients were randomly allocated to one of the two groups using numbers from www.random.org. Group P – Injection Palonosetron 0.075 mg (2 ml) whereas Group S – Normal Saline (2 ml). Allocation concealment was ensured using sequentially numbered sealed envelopes, opened after moving the patient to the operation table.

All patients were assessed preoperatively, given study details, and informed about the anaesthetic procedure they were to undergo. Patients were kept fasting for 8 hours prior to their scheduled surgery. Alprazolam 0.5 mg and Ranitidine 150 mg were given orally the previous night of surgery. On the day of surgery, intravenous (IV) access was established, and an IV infusion of Ringer lactate was started.

All the patients were premedicated with an injection of Glycopyrrolate 0.005 mg/kg IV, an injection of Midazolam 0.03 mg/kg, followed by respective study drugs and anaesthesia was induced with propofol as mentioned below.

Patients were informed regarding pain on propofol injection. Patients in each group received respective drugs, followed by anaesthesia induction with propofol after 3 minutes, as already mentioned.

Patients were preoxygenated, and the venous drainage of the limb was occluded after giving the study drug by applying a tourniquet inflated to 70 mmHg for 1 min, after which 25 % of the total calculated dose of propofol injection (2 mg/kg) was given over 5 seconds and assessed for degree of pain [7].

Monitoring included electrocardiography (ECG), peripheral oxygen saturation (SpO2), non-invasive blood pressure (NIBP), end-tidal carbon dioxide (EtCO2), and train of four (TOF). Monitors were connected to patients, baseline haemodynamic parameters were recorded, and Qt interval was noted during premedication, pretreatment of the study drug and half hourly till the end of surgery. Patients were induced

with remaining propofol followed by vecuronium 0.1 mg/kg IV. After 3 minutes, intubation was done with an appropriate-sized endotracheal tube. An injection of fentanyl 2 µ/kg was given after intubation. Anaesthesia was maintained with oxygen at 33%, nitrous oxide at 66%, and isoflurane at 1-2%, which was titrated to maintain haemodynamic parameters within 20% of basal readings. Adequate muscle relaxation was ensured by maintaining TOF count < 2 with intermittent injections of vecuronium 0.02 mg/ kg. At the end of the surgery, muscle relaxation was reversed with Glycopyrrolate 10 mcg/kg and Neostigmine 0.05 mg/kg IV, and patients were extubated when the TOF ratio was > 0.9.

In both groups, haemodynamic parameters (heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, SpO2) were continuously monitored and recorded every 5 min till the end of surgery. Haemodynamic changes and intraoperative blood loss guided intraoperative fluid management. Postoperatively, intravenous fluids, antibiotics and other medications were administered per standard institutional protocol.

Nausea and vomiting were monitored during the immediate postoperative period, early (0-2 hrs), and late postoperative period (2-24 hrs), and an injection of ondansetron 4 mg intravenously was administered if there was nausea and vomiting.

The patients who suffered postoperative nausea and vomiting received ondansetron postoperatively as a rescue measure.

The sample size was calculated based on a previous study [9]. Pain incidence on propofol injection without preventive measures was about 60% [9]. With α value of 0.05 and power of 80%, the sample size calculated will be 43 patients to detect at least a 50% difference between the regular saline and palonosetron groups concerning propofol-induced pain. For an α value of 0.01 and better validation, each group comprised 50 patients.

Data was entered into a Microsoft Excel data sheet and analysed using SPSS version 22 software. The present study applied descriptive and inferential statistical analysis. Results on continuous measurements were presented as mean ±SD (Min-Max), and categorical measurements were presented in number (%). Student t-test (two-tailed, independent) was used to find the significance of study parameters on a continuous scale between two groups (Intergroup analysis) on metric parameters. The Chi-square/ Fisher Exact probability test was used to find the significance of study parameters on a categorical scale between two or more groups.

Statistical software: The statistical software, namely SPSS 15.0, was used to analyse the data, and Microsoft Word and Excel were used to generate graphs and tables.

Results

Figure 1 shows that a hundred patients were considered for the analysis. There were no dropouts. Demographic characteristics and duration of surgery in both groups were comparable. In both the palonosetron and regular saline groups, the age distribution ranged from 18-60 years, with a mean age for the palonosetron group being 40.14 ± 10.09 and for the regular saline group being 41.50 ± 9.68. The difference in age between both groups is not statistically significant. The sex difference between the groups is statistically insignificant. The mean weight in the palonosetron group is 52.10, and the mean weight in the regular saline group is 50.76. The difference between the two groups in the distribution of patients' weight is insignificant (see **Table 1**).

In our study, 52% of patients in the palonosetron group and 46% of patients in the regular saline group belong to ASA I, 48% of patients in the palonosetron group and 54% of patients in the regular saline group belong to ASA II (see **Table 1d**). The difference between the two groups regarding the distribution of ASA physical status is insignificant. The mean duration of surgery in the palonosetron group was 2.33 ± 0.7 hrs, and in the regular saline group, it was 2.59 ± 0.75 hrs (see **Table 1e**).

Comparing pain during propofol injection, 32% of the palonosetron group and 4% of the regular saline group did not suffer pain; 54% of the palonosetron group and 20% of the regular saline group experienced mild pain; 12% of the palonosetron group and 48% of the regular saline group developed moderate pain; and 2% of the palonosetron group and 28% of the regular saline group experienced severe pain. Palonosetron

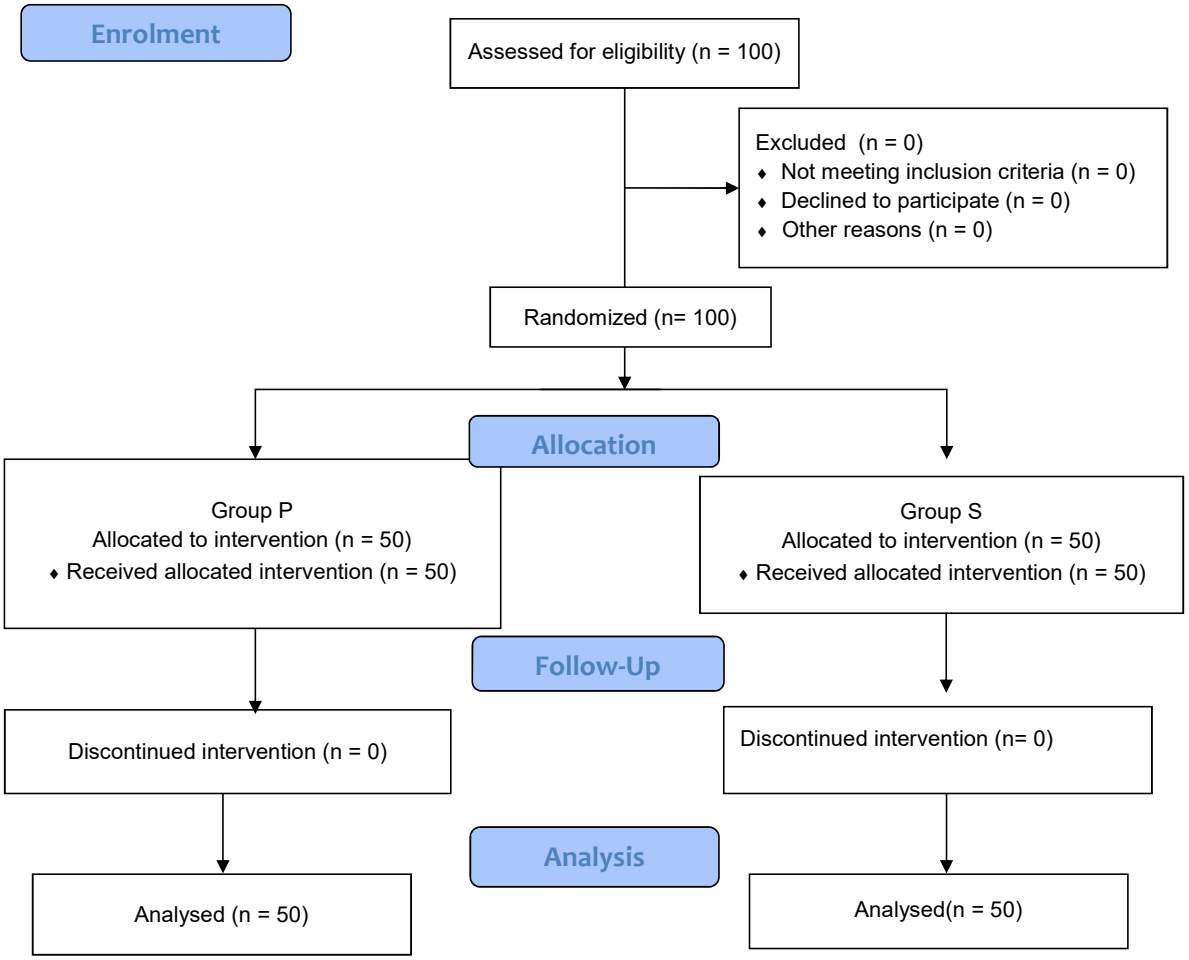

Figure 1. CONSORT Flow Diagram.

Table 1a. Demographic characteristics in the study groups included. Age distribution of cases in study groups.

Age in years	Group P	Group S
<20	2(4%)	0(0%)
20-30	7(14%)	7(14%)
31-40	16(32%)	15(30%)
41-50	17(34%)	16(32%)
51-60	8(16%)	12(24%)
Total	50(100%)	50(100%)
Mean ± SD	40.14 ± 10.09	41.50 ± 9.68

Samples are age-matched with P = 0.493, student t-test.

Table 1b. Demographic characteristics in the study groups included. Sex distribution of cases in study groups.

Gender	Group P	Group S	Total
Female	31(62%)	23(46%)	54(54%)
Male	19(38%)	27(54%)	46(46%)
Total	50(100%)	50(100%)	100(100%)

Table 1c. Demographic characteristics in the study groups included. Comparison of weight, height and bmi in study groups.

	Group P	Group S	Total	P value
Weight (kg)	52.10 ± 4.81	50.76 ± 5.13	51.43 ± 4.99	0.181
Height (cm)	152.18 ± 3.57	153.44 ± 3.82	152.81 ± 3.74	0.092+
BMI (kg/m^2)	22.52 ± 2.01	21.54 ± 2.28	22.03 ± 2.19	0.025*

Table 1d. Demographic characteristics in the study groups included. Comparison of asa physical status in study groups.

ASA Grade	Group P	Group S	Total
Grade I	26(52%)	23(46%)	49(49%)
Grade II	24(48%)	27(54%)	51(51%)
Total	50(100%)	50(100%)	100(100%)

P = 0.548

Table 1e. Demographic characteristics in the study groups included. Comparison of duration in study groups.

Duration of Surgery (hours)	Group P	Group S	Total
<2	9(18%)	4(8%)	13(13%)
2-4	41(82%)	46(92%)	87(87%)
Total	50(100%)	50(100%)	100(100%)
Mean ± SD	2.33 ± 0.70	2.59 ± 0.75	2.46 ± 0.73

P = 0.076+

significantly reduced pain on propofol injection (p < 0.001) (see **Table 2a**).

There was no significant change in pain score in Males and females in both Group P (P value 0.556) and Group S (P value 0.947) (see **Table 2b**).

The baseline heart rate was comparable between the groups. There was an increase in heart rate after study drug administration in Group P (87.44 ± 8.42) compared to Group S (84.44 ± 8.74), but clinically, it was insignificant (P value -0.083+).

The Systolic Blood Pressure was comparable between the groups at baseline, but after the study drug and after induction with propofol, the intragroup comparison showed a decrease in Systolic Blood Pressure in both Group P and Group S, which was statistically significant (p-value <0.001**), but clinically, it was insignificant which was treated with IV fluids. Intergroup comparison showed no significant change in systolic blood pressure in either group. The Diastolic Blood Pressure was comparable between the groups at baseline, after the study drug and after induction. The intragroup comparison showed hypotension in both groups after induction with propofol from 1-5 min (P value <0.001**), which was statistically significant but clinically insignificant (see **Figure 2**).

24% of patients in the palonosetron group had early postoperative nausea and vomiting compared to 78% in the regular saline group, and 26% of patients in the palonosetron group had late postoperative nausea and vomiting compared to 90% in the regular saline group. 76% of patients in the palonosetron group and 22% in the regular saline group did not have postoperative nausea and vomiting in the early postoperative period. 74% in the palonosetron

Table 2a. Assessment of pain on propofol injection.

McCrirrick and Hunter Pain Scale	Group P	Group S	P value
Negative response to questioning (No pain)	16 (32%)	2 (4%)	0.0001**
Pain reported in response to questioning only without behavioral signs (Mild pain)	27 (54%)	10 (20%)	0.0002**
Pain reported to questioning and accompanied by behavioural signs, or pain reported spontaneously without questioning (Moderate pain)	6 (12%)	24 (48%)	0.00004**
Strong facial grimacing, arm withdrawal or tears (Severe Pain)	1 (2%)	14 (28%)	0.0004**
Total	50 (100%)	50 (100%)	
Mean ± SD	1.14 ± 0.76	2.00 ± 0.81	

P < 0.001**

Table 2b. Sex distribution in pain on propofol injection.

Degree of pain	Group P		Group S	
	Males	Females	Males	Females
No pain	5	11	1	1
Mild pain	11	16	6	4
Moderate pain	2	4	12	12
Severe pain	1	0	8	6
Total	19	31	27	23

Group P p-value: 0.556; Group S p-value: 0.947

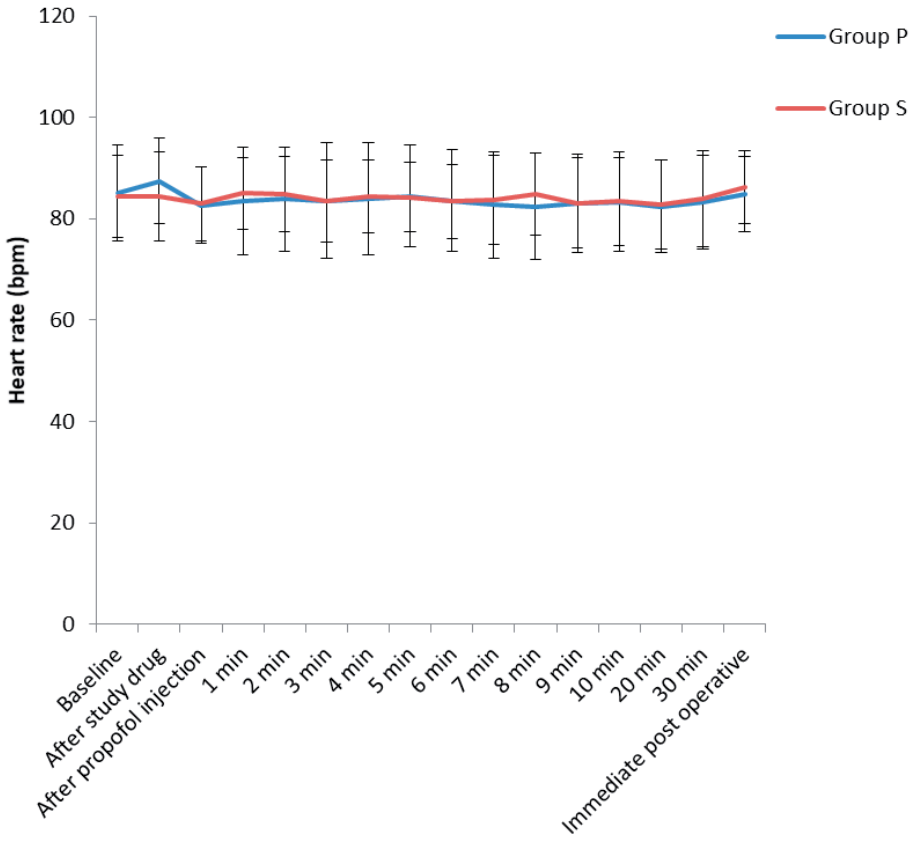

Figure 2a. Haemodynamic parameters in both groups. Line diagram showing changes in heart rate in study groups.

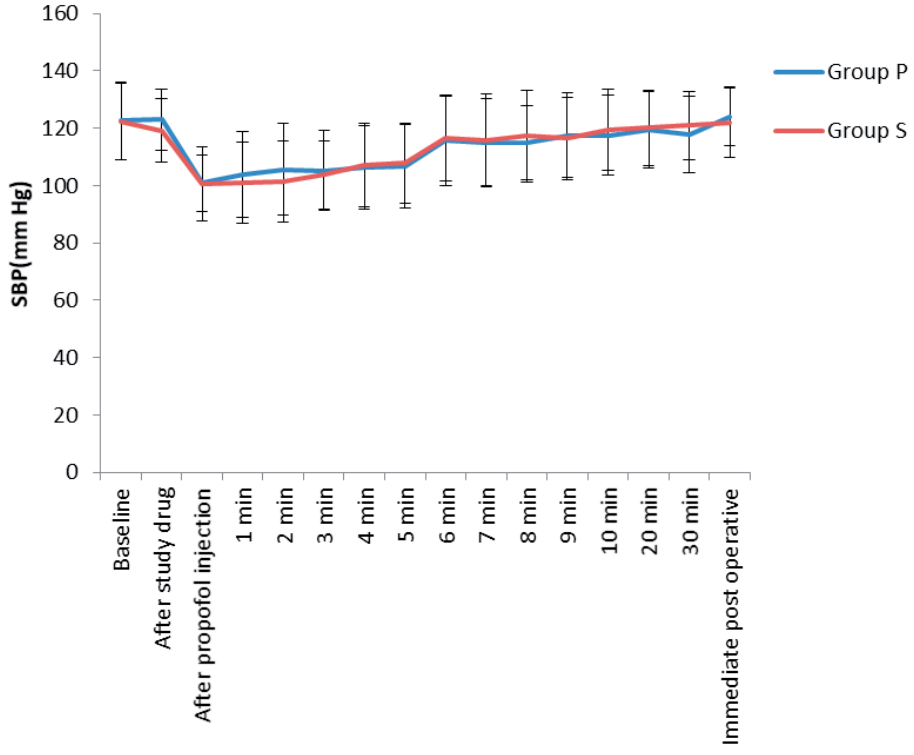

Figure 2b. Haemodynamic parameters in both groups. Line diagram showing changes in systolic blood pressure in study groups.

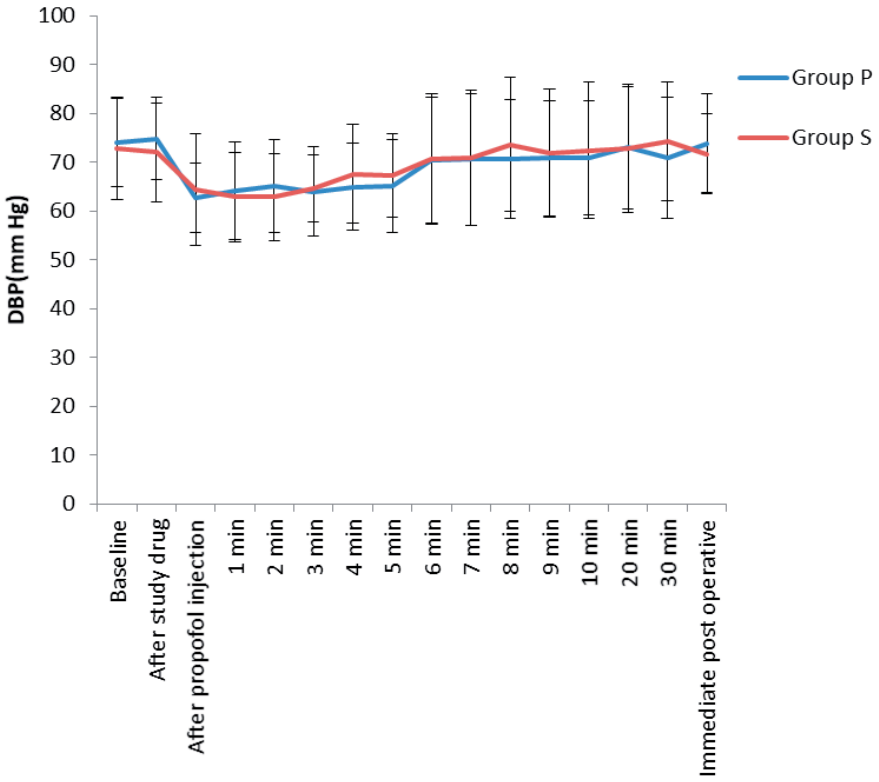

Figure 2c. Haemodynamic parameters in both groups. Line diagram showing changes in diastolic blood pressure in two groups.

Table 3. Comparison of postoperative nausea and vomiting in study groups.

PONV	Group P (n = 50)	Group S (n = 50)	Total (n = 100)	P value
Early				
– No	38(76%)	11(22%)	49(49%)	<0.001**
– Yes	12(24%)	39(78%)	51(51%)	
Late				
– No	37(74%)	5(10%)	42(42%)	<0.001**
– Yes	13(26%)	45(90%)	58(58%)	

Table 4. Comparison of qtc interval in both the groups.

Qtc. interval (msec)	Group P	Group S	P value
Premedication	376.60 ± 15.73	368.20 ± 11.37	0.003**
Pretreatment	374.60 ± 13.43	376.00 ± 10.69	0.566
Induction	368.40 ± 10.57	371.80 ± 10.04	0.102
Every 30 min	370.80 ± 9.66	371.60 ± 15.83	0.761

group and 10% in the regular saline group did not have late postoperative nausea and vomiting (see **Table 3**).

The antiemetic action of palonosetron was more than 24 hours postoperatively.

The Mean Qtc interval in the palonosetron group was 374.60, and in the regular saline group, it was 376. There was no Qt prolongation intraoperatively and postoperatively (see **Table 4**).

No incidence of Qtc prolongation, giddiness or tinnitus was noted in any patient in our study.

Though palonosetron was a known antiemetic, we assessed its duration of antiemetic actions on postoperative nausea and vomiting.

Discussion

Propofol is a fast-acting agent, and its action wears off quickly, making it useful for daycare procedures [10]. It provides excellent sedation, amnesia, anxiolysis and a state of general well-being with the added advantage of having antiemetic properties. It suppresses the upper airway reflexes in response to laryngoscopy and intubation, which is of great help in patients with hypertension, epilepsy or hyperactive airway. It attenuates stress response to intubation.

Propofol has gained tremendous popularity in daycare surgery, cardiac anaesthesia, neuro

anaesthesia and ICU sedation for its attractive profile. However, it is also associated with side effects like myoclonus, apnoea, hypotension and pain on injection [11].

The incidence of pain on injection of propofol varies from 30-90% of patients in various studies [12]. Klement and Arndt pointed out that its high osmolality and acidic pH lead to pain [13]. Other drugs, like diazepam and etomidate, also have osmolality and cause pain on injection.

Pretreatment of many drugs to decrease propofol pain on injection has been tried in different ways, i.e. either given intravenous before propofol or given with a tourniquet [14] similar to Bier's block or pretreatment drug mixed with propofol. A systematic literature search by Picard et al. found that lignocaine given with a tourniquet was the most effective method to decrease pain [8]. Other drugs which were also tried were metoclopramide [15], opioids [16] and ondansetron [17], which were found to be effective as well. Our study used a tourniquet pressure of 70 mmHg, which was maintained for one minute during pretreatment and released prior to propofol injection. Lee et al., in their study, undertook a similar method [17]. In this study, we avoided any intravenous premedication (than the study drugs), which may cause irritation or analgesia before injection of propofol.

Ryu et al. [18], Singh TH and coworkers [19], and Lee KH et al. [20] in their study found that Palonosetron 0.075 mg was effective in reducing pain on propofol injection, which was comparable to our study as we used the exact dosage and the results were similar.

Most patients in the palonosetron group experienced only mild pain and reported pain only on questioning. The finding is comparable with the study of Ambesh et al., who found that ondansetron decreased pain in almost 50% of patients. Our results also resemble the study by Kang et al., who showed that about 60% of patients did not have pain after pretreatment with ondansetron [21]. Another study conducted using microemulsion propofol found that lignocaine 2% 2 ml (52%) was more effective than ondansetron 4 mg (84%) in reducing injection pain [22]. Memis et al. compared the efficacy of tramadol and ondansetron in minimising pain due to the propofol injection in 100 patients. They showed that 4 mg ondansetron was as effective as 50 mg tramadol in preventing pain from propofol injection [23]. Singh DK, his colleagues, and Ahmed et al. used granisetron in their comparative study and found that the incidence of pain on propofol injection was scarce [6, 24]. Lee and his group used ramosetron and found that it reduces pain on propofol injection [25]. Our study found that propofol injection pain was lesser in the group pre-treated with palonosetron than in the regular saline group.

Our study used propofol as an induction agent, so the incidence of PONV in both groups was scarce. 74% of the palonosetron group and 10% of the regular saline group did not develop late postoperative nausea or vomiting, which was similar to the study done by Gralla et al. [26]. Therefore, the palonosetron group had the added advantage of having less number of patients with PONV (p-value <0.001). In contrast, Lee KH et al. found no significant differences in PONV in their groups [20].

Our study compared the effect of palanosetron and placebo in decreasing propofol-induced pain. We also assessed the duration of the antiemetic potential of palonosetron, which was more than 24 hours. By this study, we infer that a single injection of Palonosetron could address both problems, such as pain on propofol injection, and reduce postoperative nausea and vomiting.

The limitation of the study was that we assessed postoperative nausea and vomiting between an antiemetic palonosetron and a placebo.

Further scope of the study is that palonosetron could be compared with ondansetron or any other antiemetic to know its potency in reducing propofol-induced pain.

Conclusions

Pretreatment with Palonosetron 0.075 mg reduced the incidence and severity of propofol-induced pain on injection, with the added advantage of decreased postoperative nausea and vomiting without significant haemodynamic changes.

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Conflict of interest statement
The authors declare no conflict of interest.

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