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Original Article

Anaesthesia Section

Comparative Study of Lidocaine and Palonosetron Pretreatment in Reduction of Propofol Induced Injection Pain

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ABSTRACT

Introduction: Propofol is very popular as an induction agent in modern day anaesthesia because of its favourable pharmacodynamics and fewer side effects. Any pain pre or post-anaesthesia leads to patient dissatisfaction. The incidence of pain during propofol induction is almost 70%.

Aim: To compare palanosetron and lidocaine to each other as well as with the control group receiving normal saline as placebo in decreasing propofol induced injection pain and to compare patient satisfaction in both the test groups.

Materials and Methods: A total of 150 patients were randomised to constitute three groups. Group L who received 0.5 mg/kg of 2% lidocaine, Group P received palonosetron 0.075 mg, and Group N who received normal saline 0.9% constituted the control group. Patients were given a 5 mL pretreatment solution, containing either lignocaine 0.5 mg/kg, palonosetron 0.075 mg or 0.9% normal saline intravenously. Following pretreatment, venous drainage was occluded at midarm level with a tourniquet. Tourniquet was released after one minute. Propofol injection was given over five seconds at 25% of the total calculated induction dose. Patients were then interviewed about the magnitude of pain and rated as per a pain scale. Descriptive statistics such as range, mean, Standard Deviation (SD) were used to summarise the baseline clinical and demographic profile of the patients. Chi-square test was performed for comparison of categorical data.

Results: Both the study drugs i.e., lidocaine and palonosetron caused significant reduction in pain as compared to the placebo (normal saline) group. Only 20% of patients had pain free induction (at five seconds) in saline group as compared to 64% and 70% in Groups P and L respectively. Comparison among three groups was highly significant with $p<0.001$.

Conclusion: Palonosetron was almost as effective as lidocaine in reducing propofol induced injection pain. Palonosetron has an added advantage because of its antiemetic property so can be chosen as an alternative to lidocaine.

Keywords: Analgesia, Anaesthesia, Antiemetic, Tourniquet

INTRODUCTION

Anaesthesia is an amalgamation of amnesia, analgesia, unconsciousness, and muscle relaxation to allow the performance of surgery or interventional procedures. Analgesia is the primary concern in both intraoperative and postoperative period. One of the significant issues in anaesthesia is pain due to intravenous anaesthetics. Propofol is widely used for intravenous induction because of its rapid onset, short duration, easy titration, and fewer side effects. It is the drug of choice in daycare surgery, sedation in Intensive Care Unit, and ambulatory surgery [1]. Induction of anaesthesia is recalled by most patients as the most painful part in the perioperative period due to the intense burning pain caused by propofol during induction. The incidence of propofol-induced pain is approximately 70%, and it is the seventh most critical problem for American anaesthesiologists in a clinical setting [2]. The mechanisms by which propofol induces pain is not fully understood. These have been attributed mainly to endothelial irritation, osmolar difference, non-physiological pH, and the activation of pain mediators. The cause of immediate pain is irritation of vein endothelium. Mediators such as kininogen released from kinin cascade are responsible for the delayed pain [3].

Both pharmacological and non-pharmacological methods have been tried. Pretreatment with lignocaine, ondansetron, magnesium sulfate, ephedrine, granisetron and opioids such as meperidine, fentanyl, morphine, butorphanol, dexmedetomidine, and topical nitroglycerin have been tried [4-6]. Nonpharmacological methods such as injecting propofol into antecubital veins, injecting cold saline before propofol injection and diluting the propofol solution have also been tried, but none proved perfect for attenuation of pain due to propofol injection [3,6]. As per earlier recommendations, two efficacious interventions to reduce POPI were to either inject propofol in the median cubital vein or pretreatment with lignocaine in addition to venous occlusion whenever small veins were used [6]. Lignocaine and 5-HT3 receptor antagonists have given good results in reducing POPI [2].

Hence, the present study aims to compare palanosetron and lignocaine to each other as well as with the control group receiving normal saline as placebo in decreasing propofol induced injection pain. Assessment of patient satisfaction in both the test group is also made in the present study.

MATERIALS AND METHODS

The study was a prospective, randomized, double-blinded study conducted in Department of Anaesthesiology, at a Tertiary Care Centre, Mayo Institute of Medical Sciences, Barabanki, from September 2016 to September 2017. After obtaining Institutional Review Board approval, written informed consents were taken from 150 patients belonging to American Society of Anaesthesiologists (ASA) I and II, aged 20–50 years, who were to undergo operation under general anaesthesia. Patients were randomly assigned into three groups of 50 patients each by computer generated randomisation to receive pretreatment with either i.v. lignocaine (0.5 mg/kg), i.v. Palonosetron 0.075 mg or 5 mL of 0.9% normal saline in control group. Pretreatment drugs (5 mL solution) were prepared in identical syringes by an independent anaesthesiologist not involved in the study. The treating anaesthesiologist was blinded to the pretreatment drug administered to each subject.

Patients with neurological deficit, history of allergy to study drugs or propofol, taking any analgesic before surgery, history of diabetes, hypertension, patients with known cardiac problems, other systemic

disorders of lungs and liver, pregnant patients, morbid obesity, and emergency surgery were excluded from the study. Thorough, check-up and routine investigations were carried out which comprised of haemoglobin, total leukocyte count, differential leukocyte count, Bleeding Time (BT), Clotting Time (CT), routine urine tests, serum creatinine, chest X-ray, and electrocardiogram. Patients with optimal results were selected for the study. Before the surgery fasting for 8 hours was maintained. Premedication was tablet diazepam 10 mg at night and 5 mg hours before surgery was given with sips of water. The 18 gauge needle cannula was placed in a suitable vein on the dorsum of non-dominant hand without any local infiltration, and intravenous fluid (Ringer-lactate) was infused at 100 mL/hour. After five minutes, the fluid infusion was stopped, and the arm was elevated for 15 seconds to drain the venous blood. Multi-para monitor was used to measure heart rate, noninvasive blood pressure, SpO_2, ECG and end-tidal carbon dioxide. Patients were not given any analgesic drug before propofol injection. Tourniquet was applied to the forearm to increase the local concentration of the drug by causing venous occlusion.

All patients received 5 mL volume of the test drug intravenously over 10 seconds. Tourniquet was removed after one minute. Without any delay one-fourth of the calculated dose (2 mg/kg) of propofol was injected over 20 seconds. Then, patients were assessed for pain severity. The pain intensity grading was done by using a verbal rating scale and was assessed at 5, 10, 15 and 20 seconds. After 20 seconds this scale has no role as the patient most likely would be under the effect of propofol [7]. Grade 0-None (negative response to question). Grade 1-Mild pain (pain reported only in response to question without any behavioural sign). Grade 2-Moderate pain (pain reported in response to question and accompanied by behavioural sign and pain reported spontaneously without question). Grade 3-Severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal, and tears).

The observer and the patient were both blinded to the drug being given to the patient. Induction was continued with the rest of the calculated propofol dose, and for analgesia, fentanyl 2 μg/kg was given to all patients. Intubation was done with appropriate size endotracheal tube after giving vecuronium. Anaesthesia was maintained with isoflurane and nitrous oxide-oxygen (66–33%). Muscle relaxation was antagonised by glycopyrrolate (10 mics/kg) and neostigmine (50 mics/kg). Postoperatively after 24 hours, all patients were asked if they could recall the pain following injection during induction of anaesthesia. These patients were also asked to rate their satisfaction with the overall anaesthetic care experience (very satisfied, satisfied, neutral, or dissatisfied).

STATISTICAL ANALYSIS

The estimated sample size was calculated based on the difference between moderate-to-severe pain incidence (35 vs. 2.5%) reported by Ryu HB and Kim SJ (α=0.05/3, β=0.2, dropout rate 30%); it was calculated that 50 patients were required per group [8].

The data collected were tabulated and analysed by the Statistical Package for Social Sciences (SPSS) version 21.0. Continuous data were analysed by Student's t-test. The results were expressed as number or means±Standard Deviation (SD).

Chi-square test was performed for comparison of categorical data, and a p-value of less than 0.05 was deemed to be statistically significant.

RESULTS

There were no dropouts in the study. Demographic characters of the study group such as age, height, weight, sex, and ASA classification were comparable in both the groups with a p-value >0.05 [Table/Fig-1]. The number of patients with grade 0 pain at 5, 10, 15 and 20 seconds in N, P and L groups revealed highly significant results (p<0.001). Comparison of grade 0 pain in P and L groups at all time intervals revealed no significant results [Table/Fig-2-5].

Parameters	Normal saline	Palonosetron	Lignocaine	p-value
Age (Years) Mean±SD	32.64±8.91	31.74±7.45	32.36±7.21	0.844
Weight (kg)	57.8±9.25	57.00±9.64	55.3±9.1	0.395
Height (cm)	162.9±6.85	163.5±4.97	165.5±5.2	0.063
ASA (1:2)	41:9	39:11	43:7	0.581
Sex (M:F)	38:12	40:10	36:14	0.644

[Table/Fig-1]: Comparison of demographic variables in three groups.
p<0.05 is significant; Chi-square test used to calculate p-values; M: Male, F: Female

Pain score	Normal saline	Palonosetron	Lignocaine
0	10	32	35
1	14	13	9
2	24	4	4
3	2	1	2

[Table/Fig-2]: Pain scores of patients at five seconds.
Chi-square test statistics among groups N, P and L equals 41.086 with p-value <0.001 (Highly Significant)
Chi-square test statistics between P and L groups 1.194 with p-value 0.754 (Not Significant)

Pain score	Normal saline	Palonosetron	Lignocaine
0	8	32	33
1	10	12	13
2	26	4	3
3	6	2	1

[Table/Fig-3]: Pain scores of patients at 10 seconds.
Chi-square test statistics among groups N, P and L equals 52.25 with p-value <0.001 (Highly Significant)
Chi-square test statistics between P and L groups 0.531 with p-value 0.91(Not Significant)

Pain score	Normal saline	Palonosetron	Lignocaine
0	6	22	28
1	8	24	19
2	24	3	2
3	12	1	1

[Table/Fig-4]: Pain scores of patients at 15 seconds.
Chi-square test statistics among groups N, P and L equals 70.95 with p-value <0.001 (Highly Significant)
Chi-square test statistics between P and L groups 1.5 with p-value 0.68 (Not Significant)

Pain score	Normal saline	Palonosetron	Lignocaine
0	6	20	19
1	10	25	25
2	26	3	4
3	8	2	2

[Table/Fig-5]: Pain scores of patients at 20 seconds.
Chi-square test statistics among groups N, P and L equals 52.36 with p-value <0.001 (Highly Significant)
Chi-square test statistics between P and L groups 0.1685 with p-value 0.98 (Not Significant)

Postoperative recollection of injection pain was similar in the two Groups P and L, and there were no statistically significant differences in patient satisfaction ratings, with a p-value of 0.32. Saline group N recorded more than double patients who had recall of propofol pain during induction. Patient satisfaction was also poor in the saline group, and differences were statistically significant [Table/Fig-6].

	Normal saline	Palonosetron	Lignocaine
Recall of pain	42	12	10
Patient satisfaction			
Very satisfied	2	25	32
Satisfied	8	15	14
Neutral	10	8	3
Dissatisfied	30	2	1

[Table/Fig-6]: Incidence of recall of propofol injection pain and patient satisfaction.
Chi-square test statistics among groups N, P and L equals 80.36 with p-value <0.001 (Highly Significant)
Chi-square test Statistics between P and L groups 3.50 with p-value 0.32 (Not Significant)

DISCUSSION

The incidence of pain with intravenous propofol administration is as high as 85-90% [9]. Propofol belongs to the class of phenols that can irritate the skin, mucous membrane, and venous intima [10]. A recent study of Ando R and Watanabe C has shown that propofol causes vascular pain that occurs due to prostanoids, particularly Prostaglandin E2 (PGE2) [11]. Pain due to propofol injection can be immediate or delayed. Immediate pain is primarily attributed to the direct irritant effect, whereas delayed pain occurring around half a minute is caused by the kinin cascade. Plasma kinin-kallikrein system is activated by the lipid solvent for propofol which produces bradykinin thus increasing local vein permeability [12]. The permeability of the endothelial layer increases due to bradykinin effect so aqueous phase propofol diffuses into free nerve endings thereby intensifying pain on injection [13]. A quantitative systematic review in 2000 has concluded that i.v. lidocaine (0.5 mg/kg) given with a rubber tourniquet on forearm, 30-120 seconds before propofol injection prevents pain in 60% of the patients [14]. This finding is similar to the present study where POPI in lidocaine group was prevented in 57.5% of patients (averaging values at 5,10,15,20 seconds). Another systematic review in 2011 concluded two effective interventions to reduce POPI. They recommend use of a large vein (antecubital vein) or pretreatment with lidocaine in conjunction with venous occlusion if hand veins are used [2]. The 5-HT3 receptor antagonists have also been tried in alleviating POPI. Ye et al., have reported that ondansetron acts via a dual mechanism of 5-HT3 antagonisms and a 15-fold-higher potency as a local anaesthetics than lidocaine [15]. In 1999, first report stating that ondansetron was effective in reducing POPI was published [4]. Of various types of 5-HT3 receptor antagonists, palonosetron inhibits receptor function by causing internalisation of the receptor. Palonosetron effectively reduces the occurrence of acute (0-24 hours) and delayed (24-120 hours) emesis as compared with its older counterparts [16,17]. The improved clinical efficacy of palonosetron is due to its high binding affinity and longer half-life [7].

A meta-analysis of Randamised Controlled Trials was conducted in 2016 to study the effectiveness and safety of 5-HT3 receptor antagonists in reducing POPI [18]. It showed no statistical significance between 5-HT3 receptor antagonists and lidocaine in reducing POPI. This is in accordance with the present study where lignocaine and palonosetron showed no statistical difference when compared at 5,10,15,20 seconds of propofol injection. The present study showed that pain free population after palonosetron pretreatment was 53% (averaging the values at 5,10,15,20 seconds). This is almost equivalent to lignocaine group. So, these 5-HT3 receptor antagonists may become substitutes for lidocaine in reducing POPI. In the present study, we compared palonosetron, lignocaine and saline group as pretreatment drugs. We compared patients in all three groups at 5, 10, 15 and 20 seconds after propofol injection following pretreatment with test drugs. Comparing the number of patients in 0 pain group at 5 sec we had only 20% patients in group N as compared to 64% and 70% in groups P and L respectively. Similar observations were made at 10, 15 and 20 seconds, showing a three to four-fold pain-free patients in test Groups as compared to the control group. Incidences in groups P and L were comparable with minor differences. Grade 3 pain was almost two to three times more in control group as compared to P and L groups. Since, propofol-induced pain is maximum at 10-20 seconds we took the present study observations at 15 seconds to compare with other studies [8,19].

Comparing Grade 0 patients in all groups at 15 seconds, we had 12% patients in Group N as compared to 44% and 56% in Groups P and L respectively. So, almost four times number of patients were comfortable with study drugs. In a study conducted by Ryu HB and Kim SJ, 60% of patients experienced pain following propofol injection in the normal saline group compared to 27.5% in the palonosetron group ($p<0.05$) [8]. The higher incidence of propofol pain in palonosetron group in their study could be the result of manual mid-arm occlusion technique as against tourniquet in the present study. However, in a similar study conducted by Singh DK and Singh M, where the use of a tourniquet caused a significant reduction in pain following propofol administration in the palonosetron group, showed concurrence with the present study [19]. Stoltz R et al., demonstrated that palonosetron has a long half-life of approximately 40 hours in contrast to ondansetron, which has a half-life of only five hours [7]. Besides, Park SK and Cho EJ, reported that the incidence of PONV in first 24 hours postoperatively was significantly lower in the palonosetron 0.075 mg group as compared to the ondansetron 8 mg group [20]. Therefore, pretreatment with palonosetron may be considered an effective method of decreasing the occurrence of pain following propofol injection and has the added advantage of preventing postoperative nausea and vomiting without the additional administration of other antiemetics.

LIMITATION

Palonosetron has been proved as a long acting antiemetic upto a period of 72 hours postoperatively [21]. We did not make this observation as the sample size chosen was quite small to study its effect in Post Operative Nausea and Vomiting (PONV).

The present study was based on subjective assessment so it had its own limitations. Only one-fourth of the calculated dose of propofol, to assess patient's response. Pain assessment could have been more accurate with full dose of propofol combined with objective assessments like changes in heart rate, mean arterial pressure and withdrawal response score proposed by Shevchenko Y et al., [22].

CONCLUSION

It can be concluded that palonosetron and lidocaine groups showed similar degrees of pain relief. Both the drugs gave 3-4 fold pain relief as compared to normal saline group. So, palonosetron which is an effective antiemetic can also be used as a substitute to lidocaine in decreasing POPI.

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