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Comparative Evaluation of Intravenous Granisetron Hydrochloride and Intravenous Lignocaine Hydrochloride to Alleviate the Pain on Propofol Injection

Jenish C Patel[1], Jayshree M Thakkar[2], Damini Makawana[3], Sanobar Khokhar[4], Saeed Vora[5], B C Shah[6]

[1]Junior Lecturer [2]Associate Professor [3]Associate Professor [4]1st Year Resident [5]Ex Resident [6]Professor, Department of Anaesthesia, Gujarat Cancer and Research Institute, Ahmedabad, Gujarat 380016, India.

Abstract

Propofol is one of the most commonly used induction agent. Pain on injection still remains a considerable concern for anaesthesiologist. The aim of the study was to assess the efficacy of granisetron HCL and ligocaine HCL to alleviate the pain on propofol injection. *Methods:* Fifty patients aged 18-50 years, ASA grade 1-2, posted for elective surgeries under general anaesthesia were randomly divided into two groups. Group G received 2 ml (1 mg/ml) granisetron while group X received 2 ml (2%) ligocaine intravenously before propofol injection. Manual venous occlusion was done for 1 minute after pre-treatment drug. 2 ml of total calculated dose of propofol was given over a period of 4 seconds. Patients were asked about the pain on injection with use of verbal rating score chart after 15 seconds. HR, SBP, DBP, SpO_2 was measured 0, 1, 3 minute after propofol injection. *Results:* HR, SBP and DBP were significantly raised in granisetron group as compared to lidocaine group. Average pain score in group G was 2.1 while in group X it was only 0.8, which was statistically significant. ($p<0.05$). *Conclusion:* We conclude that lignocaine HCL is better than granisetron for alleviating pain after propofol induction.

Keywords: Pain; Propofol; Lignocaine Hcl; Granisetron Hcl.

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Introduction

Pain is a vital function of the nervous system which warns the body of potential or actual tissue damage. The pain pathway begins with the specialized pain receptors (nociceptors) which are spread throughout the body. These nociceptors are stimulated by a number of stimuli like mechanical forces, thermal injuries as well as chemical substances. The noxious stimuli are converted into electrical stimuli and transported to spinal dorsal horn via A and C fibres. In the spinal cord these stimuli are carried via spinothalamic tracts into the thalamus and from there into the cerebral cortex. There are other accessory ascending & descending tracts which modulate the degree of

Corresponding Author: Jayshree M Thakkar, Associate Professor, Department of Anaesthesia, Gujarat Cancer and Research Institute, Ahmedabad, Gujarat 380016, India.

E-mail: drjmthakkar@yahoo.com

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pain perception. Moreover, tissue damage causes release of PGs, TX, Serotonin and other chemical mediators which further sensitize the nociceptors and reduce the threshold of pain sensitivity.

Propofol (2, 6, di-isopropyl phenol) is a chemically phenol base anesthetic agent. Pain during injection of propofol is a very unpleasant and irritating event. Incidence of pain during propofol injection varies between less than 10% in large veins at the cubital fossa to 90% in veins at the dorsum of hand [1]. The immediate vascular pain on injecting propofol is attributed to the direct irritant effect of propofol on nociceptors at the intimal layer of vessel.

The delayed pain (after 10-20 sec) is probably due to activation of Kallikrien- Kinin system. Many factors affect the incidence of pain on injection like age of patient, site and size of veins, temperature, PH of the formulation, speed of injection, concentration in the aqueous phase and the buffering effect of blood.

Lignocaine is an amide based local anaesthetic [2] which blocks the Na^+ channel in the nociceptors and prevents the transmission of the noxious stimulus from nociceptor to the pain fibres. Moreover, as it is a weak base, it releases H^+ ion on contact with a lipid like propofol and thus decreases PH. Thereby decreasing concentration of free propofol molecules. These two mechanisms help to decrease pain at propofol injection.

Granisetron is a 5-HT3 receptor antagonist [3]. It blocks the effect of serotonin on the nociceptors and thus reduces the intensity of pain on propofol injection.

Other agents used to reduce pain of propofol includes Opioids [4], Ketamine [5], NSAIDS [6], Nitrous oxide [7], Steroids [8], ondansetron [9], thiopental sodium [10], $MgSO_4$ [11], NTG [11] etc. Ondansetron exhibits property of local anaesthetic. So, granisetron is also 5-HT3 receptor antagonist and may be exhibits local anaesthetic properties [12].

Aim of our study was to evaluate the comparison of granisetron and preservative free lignocaine in alleviating the pain of propofol after intravenous injection.

Material and Methods

After approval from institutional ethical committee, fifty patients aged between 18-50 years of age, of both sexes, belonging to ASA grade I & II, who were scheduled to undergo elective surgeries under general anaesthesia were randomly divided into two groups.

Informed consent from all patients were taken and explained about the procedure. Patients with history of allergy to lignocaine, propofol or granisetron were excluded. Patients belonging to ASA grade III, IV, those undergoing emergency surgery and those who could not communicate properly were also excluded.

Routine preanaesthetic evaluation was performed. All routine investigation was done. On arrival in the operating room, the baseline readings of HR, NIBP, SpO_2 and ECG of all patients were recorded. 20 G IV Cannula was inserted into a vein on the dorsum of patient's non-dominant hand & RL infusion started.

Verbal rating score was recorded during propofol injection.

Patients in Group G received 2 ml of (1 mg/ml) granisetron, while in Group X 2 ml 2% lignocaine were given over 5 seconds. Both drugs were given 5 min after IV cannulation.

At the time of propofol injection, manual occlusion at midarm was applied for 1 min and then released. Next propofol injection of 2 ml bolus was given over 4 second. 15 seconds after this small bolus dose, patients were asked to rate any pain sensation during the injection.

An anesthesiologist blinded to the study recorded the pain using the verbal rate scale:

0 = None (Negative response to questioning)

1 = Mild Pain (Pain reported only on questioning and no behavioural signs)

2 = Moderate Pain (Pain reported on asking with behavioural signs or pain reported spontaneously)

3= Severe Pain (Strong vocal response with facial grimacing, arm withdrawal or tears from eyes.)

After recording this, patients were induced with Glycopyrrolate 4 mcg/kg, Fentanyl 2 mcg/kg, Propofol 2.5 mg/kg and Succinyl choline 2 mg/kg IV. After IPPV with 100% O_2 tracheal intubation was done with appropriate sized portex endotracheal tube.

HR, NIBP, SpO_2 and ECG were recorded before propofol injection and at 0, 1 & 3 min after propofol.

Maintenance was done with N_2O, O_2, and vecuronium bromide 0.1 mg/kg IV and Isoflurane as volatile anaesthetic agent. At the end of surgery patients were reversed with neostigmine bromide 0.05 mg/kg and glycopyrrolate 5 mcg/kg IV and shifted to ICU.

Statistical analysis: Group X and Group G study results were statistically analysed by using unpaired

students 'T' test on graph pad software. P value < 0.05 was considered as statistically significant.

Results

All data were recorded and expressed in terms of mean±standard deviation. p value < 0.05 was considered significant. Statistical software from www.Graphpad/instate3 site was used.

Tables 1 shows both groups were comparable with respect to age distribution and gender and statistically not significant (p> 0.05).

Table 2 shows a different trend in both groups. The average HR at 0, 1 & 3 min after propofol injection were 79.6±7.73, 78.16±5. 83 and 76.76±5.88 in the lignocaine group while they were 80.4±9.06, 90.76±9.14 and 92.8±8.18 in the granisetron group was statistically significant (p < 0.0001) and was due to pain induced tachycardia.

Table 3 shows that the systolic blood pressure (SBP) at 0,1 & 3 minute after propofol injection were 122.9±9.88, 118.6±10.01 and 115.0±9.4 mm of Hg in the lignocaine group, while in the granisetron group, it was 126.4±9.87, 132.4±10.9 & 134.2±11.79 mm of Hg. The rise in SBP was more in the granisetron group and the difference in both groups was statistically significant (p < 0.0001).

Table 4 shows the diastolic blood pressure (DBP) in lignocaine group at 0, 1& 3 min were 72.7±7.09, 68.72±6.47 & 66.24±5.54 mm of Hg while DBP in granisetron group were 75.12±6.95, 79.04±8.64 and 82.0±8.92 mm of Hg. The DBP was significantly lower (p< 0.0001) in lignocaine group which shows better control of propofol pain during injection.

Table 5 shows the pain score (VRS) at 15 second. After propofol bolus (2 ml/4s) injection. The pain score in lignocaine group is 0.8±0.81 while in granisetron group it is 2.1±0.68. Now this is statistically significant (p < 0.0001). This means that lignocaine was more effective in blunting pain of propofol injection as compared to granisetron.

Hence the incidence of moderate to severe pain was quite high in granisetron group compared to the lignocaine group (p < 0.0001).

Table 1: Demographic Data

	Age (Yrs.)	p value	Sex (M:F)
Group G	42.5(3.5355)	1.0000	23:02
Group X	40.0(4.2426)	1.0000	18:07

All the data were represented as mean±SD.

Table 2: Changes of heart rate (bpm) at 0, 1, 3 min

Time	Group X	Group G	P value
O Min	79.60(±7.73)	80.40(±9.06)	0.7385
1 Min	78.16(±5.83)	90.76(±9.14)	0.0001(s)
3 Min	76.76(±5.88)	92.80(±8.18)	0.0001(s)

Table 3: Changes of SBP (mmHg) at 0, 1, 3 min

Time	Group X	Group G	P value
0 Min	122.96(±9.88)	126.48(±9.87)	0.2138
1Min	118.64(±10.01)	132.40(±10.96)	0.0001(s)
3 Min	115.04(±9.40)	134.24(±11.7)	0.0001(s)

Table 4: Changes of DBP (mmHg) at 0, 1, 3 min

Time	Group X	Group G	P value
0 Min	72.72(±7.09)	75.12(±6.95)	0.2329
1 Min	68.72(±6.47)	79.04(±8.64)	0.0001(s)
3 Min	66.24(±5.54)	82.00(±8.92)	0.0001(s)

Table 5: Pain score (VRS) at 15 sec

Time	Group X	Group G	P value
15 sec	0.8(0.81)	2.1(0.68)	0.0001(s)

Discussion

Nowadays anaesthesiologists are expected to provide their services with safe and uncomplicated technique to patient. The patient also expects painless, safe and uncomplicated anaesthesia for their operative procedures.

Propofol [13] (2-6-di isopropyl phenol) is one of the most popular anaesthetic induction agent for inducing general anaesthesia for surgery as well as for sedation in various procedures with many advantages and low incidence of side effects. The rapid action, smooth induction as well as quick recovery make it an ideal anaesthetic agent. But pain on injection limits its use, it is a common problem and can be very distressing to the patient.

Propofol preparation we use is a 1% (wt/vol) aqueous emulsion containing 10% w/v soybean oil, 2.25% glycerol and 1.2% purified egg phosphatide lecithin. The pH is 7 and pka of the drug in water is 11.

Scott RP et al. observed that the pain on injection is caused by activation of the Kallikrein-kinin system or by the lipid solvent in propofol by generating kinins, mainly bradykinin, local vasodilation & hyper permeability, increase the contact between the aqueous phase propofol and the free nerve ending. This pain has a delayed onset up to 10-20 seconds. They found that lignocaine mixed propofol was more effective than pre-

treatment with lignocaine in decreasing propofol injection pain. They found significant decrease in pain incidence from 46.7% to 13.5% by mixing lignocaine 10 mg with propofol as compare to pre-treatment with lignocaine 10 mg 30 second before propofol injection (46.7% to 40%) [14].

A 4 point verbal rate scale (VRS) was chosen in this study rather than visual analogue score (VAS). VAS required hand-eye coordination and it's not possible during the rapidly changing state of consciousness. So we used VRS in our study to quantity pain intensity. Dhananjay Kumar Singh et al. [11] and Ahmed et al. [17] also used 4 point verbal rate scale in their study.

Lignocaine is commonly used to decrease the pain on propofol injection [15,16,4]. Ondansteron has long been used for propofol pain by virtue of its mu opioid agonism, 5-HT_3 antagonism and Na^+channel blocking action [9]. We compared a novel drug granisetron which is a 5-HT_3 antagonist like ondansetron and expected to have some effects like it.

King Sy, Davis Fm, Wells JE et al. [2], in 1992 studied various dose of lignocaine and concluded that significant reduction in the pain from 73% with saline to 32% with 20 mg lidocaine 1 ml (1%).

G. Gehan et al. [15], studied optimal dose of lignocaine for preventing pain on propofol injection. They compared the different doses of lignocaine mix with with propofol 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg and control group. They concluded that lignocaine 0.1 mg/kg significantly reduced the incidence of pain and there was no improvement as dose was increased. Haemodynamic changes were similar in all four groups and no significant cardiac event present due to lignocaine.

Agarwal et al. [10] in their study compared the efficacy of pre-treatment with thiopental 0.25 mg/ kg and 0.5 mg/kg and lignocaine 40 mg for prevention of propofol induced pain. They found 77% patients complained of pain in the group pre-treated with normal saline as compared with 39%, 37%, 3% in groups pre-treated with lignocaine 40 mg, thiopental 0.25 mg/kg and 0.5 mg/kg respectively. ($p<0.05$)

We also used 40 mg lignocaine and pain relief was in 40% of patients.

Sarita Fernandes et al. [18] also concluded that lidocaine is superior to acetaminophen in reducing the pain on injection of propofol.

Ahmed et al. [17] in 2012 in their study observed that pain reduced from 60% to 15% by pre-treatment with granisetron when the venous drainage was occluded manually at mid arm by assistant for 1 minute after IV injection.

We also used mid arm occlusion technique for our study.

Many other authors have compared lignocaine and granisetron with other drugs to relieving pain of propofol injection.

Ye JH, Mui WC, Ren J et al. [12] in 1997 studied that ondansteron exhibits the properties of a local anaesthetic. It acts as a Na^+ channel blocker, a 5 HT_3 receptor antagonist and mu opioid agonist.

Granisetron is a more $5HT_3$ antagonist so relieved pain by a similar mechanism. We used granisetron 2 ml (1 mg/ml) for our study. Ahmed et al. [17], Swati et al. [19] and Dhananjay Kumar Singh [19] also used same dose of granisetron.

Swati et al. [19] also concluded that there was 100% no pain in granisetron group than saline group which was highly significant. While we compared granisetron and lignocaine and observed that lignocaine has good pain relief.

Dhananjay Kumar Singh et al. [11] studied that granisetron reduced the incidence of propofol injection pain most effectively than nitroglycerine followed by magnesium sulphate. They found that granisetron reduced the incidence of propofol injection pain to 40% from 88% in placebo at 15 seconds.

B P Manjula et al. [20] used lignocaine 30 mg and granisetron 2 mg as pre-treatment before propofol injection. They concluded that there was 76% in lignocaine group and 62% in granisetron group did not have pain, 12% and 20% had mild pain, 12% and 18% had moderate pain in lignocaine and granisetron group respectively.

R cork et al., studied in 2008 [21] a comparison of the verbal rating scale and the visual analogue scale for pain assessment. They found an excellent correlation between the two (Pearson coefficient $r = 0.906$ & $p < 0.001$)

The average heart rate (HR), SBP, DBP at 0, 1, 3 min after propofol injection were raised in granisetron group than lignocaine group. Ahmed et al. [17] also noticed that there was transient rise in HR in patients suffering from pain of VRS score 2-3 in both the groups but no changes in blood pressure. The haemodynamic data from this study are difficult to compare because of variation in study.

All studies showed that 5- HT3 antagonists (granisetron, ondansetron etc.) and local anaesthetic

(lignocaine) both reduced the pain of propofol injection.

In our study we use 2 ml (2%) lignocaine. Our study also showed good results with lignocaine in reducing the pain of propofol injection.

In our study the HR, SBP, DBP were significantly raised in granisetron group as compared to lignocaine group. Moreover in our study we found that average pain score with granisetron was 2.1 while with lignocaine it was 0.8 our results show that pre-treatment with lignocaine is more effective than pre-treatment with granisetron in relieving pain of propofol injection.

Conclusion

Propofol is very commonly used agent for induction of anaesthesia due to its smooth induction and excellent emergence. Pain on propofol injection is very common complaint which can be relieved by number of drugs. We conclude from our study that lignocaine hydrochloride is better than granisetron for alleviating pain of propofol injection.

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