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A COMPARATIVE STUDY OF INTRAVENOUS INJECTION OF LIGNOCAINE HYDROCHLORIDE AND INTRAVENOUS INJECTION OF PALONOSETRON HYDROCHLORIDE AS PRE-TREATMENT TO REDUCE PAIN ON INTRAVENOUS INJECTION OF PROPOFOL

Anaesthesiology

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ABSTRACT

Background: Propofol is one of the ideal anaesthetics that provides rapid onset of action, rapid recovery, easy titration with minimal side effects. Due to its side effect of causing pain while injecting, patient satisfaction is reduced with propofol. In this study we are comparing Lignocaine and Palonosetron to reduce pain on propofol injection during intravenous induction of anaesthesia.

Material & Methods: Fifty patients of either sex between 18-60 years and ASA physical status I or II randomly allocated into two groups (n=25) to receive either Inj Lignocaine hydrochloride 40mg or Inj palonosetron 0.075mg as pre treatment to reduce pain on propofol injection. The pneumatic tourniquet was placed on same upper arm for 1 min to produce venous occlusion before giving drugs used for pre-treatment.The pain on propofol injection was assessed according to McCririck and Hunter scale: 0 = no pain, 1 = mild pain, 2 = moderate pain and 3 = severe pain.

Results: Comparing pain during propofol injection, 60% in lignocaine group and 68% in palonosetron group did not have pain, 24% in lignocaine group and 20% in palonosetron group had mild pain, 12% in lignocaine group and 8% in palonosetron group had moderate pain, 4% in both groups had severe pain. No significant hemodynamic changes were observed in both groups. Incidence of post operative nausea and vomiting was less in group 2.

Conclusion: Pretreatment with palonosetron is as effective as lignocaine in reducing the pain on injection of propofol with added advantage of reducing the incidence of PONV.

KEYWORDS

Lignocaine, Propofol, Pain on injection, Palonosetron

INTRODUCTION

The World Health Organisation defines pain as "an unpleasantsensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage".

With decreasing postoperative morbidity, the level of patient satisfaction has begun to be of increasing interest throughout the perioperative period. One of the major reasons for lack of patient satisfaction is anaesthetic-induced pain. Propofol is one of the ideal anaesthetics that causes minimal excitation, and it has advantages of ensuring prompt induction, rapid emergence from anaesthesia, titratable level of anaesthesia, absence of cumulation and minimal side effects.[1,2] Due to its side effect of causing pain while injecting, patient satisfaction is reduced with propofol despite of the agent's several advantages. The quality of pain was described as extremely sharp, aching or burning.[3]It has been arranged as the seventh most important problem in current practice of clinical anaesthesia by American anaesthesiologists.[4] Recall of injection pain during induction of anesthesia may have an impact on overall patient satisfaction with anaesthetic care. Although the mechanism of the injection pain caused by propofol remains unclear, it has been postulated that it may be associated with a direct irritant effect or an indirect effect due to the release of pro-inflammatory mediators. This pain is clinically unacceptable as it can cause agitation which interferes with smooth induction of anaesthesia. The incidence of propofol injection pain varies from 3-85% in adults.[5]

The various methods suggested to reduce the pain are injection in larger size veins, cooling[6] or warming[7,8] the propofol solution, pretreatment/ preinjection of various drugs like lignocaine,[2,9,10] opioids like butorphanol,[11] tramadol,[12] remifentanil,[13] metoclopramide,[14] and ketamine.[15]

Intravenous lignocaine, a local anaesthetic, has been well reported to decrease the incidence and severity of pain on propofol injection.[2,9,10] It is considered superior to other drugs but cannot decrease the incidence and severity of pain on propofol injection in all situations.

5-HT3 receptors have been shown to be located in the nociceptive fibers of the dorsal horn and in the peripheral nervous system and modulates nociceptive pathways.[16] Palonosetron is 5-HT3 receptor antagonist which has a greater binding affinity and longer half-life than other 5-HT3 receptor antagonists.[17] The unique pharmacokinetics of palonosetron is associated with better clinical outcomes including better prevention of chemotherapy induced nausea and vomiting and post-operative nausea and vomiting (PONV) compared with other 5-HT3 receptor antagonists.[18] We presumed that palonosetron could relieve the pain on propofol injection, as it is a more refined 5-HT3 receptor antagonist.

In this study we are comparing Lignocaine and Palonosetron to reduce pain on propofol injection during intravenous induction of anaesthesia.

MATERIALS AND METHODS

The study was undertaken in Krishna Institute of Medical Sciences, Hospital and Research Centre, Karad, during the period of December 2016 to July 2018 after obtaining ethical committee clearance as well as informed written consent from all patients.

STUDY DESIGN:

- Prospective, comparative, randomized study

SAMPLE SIZE :

- To detect a difference of 30% reduction in incidence of pain between both groups (Group lignocaine and Group palonosetron) for α error of 0.05 and Power of 80%, we included sample size of 50 patients based on previous studies.[19] Thus 25 patients will be randomly allocated into each group.

METHOD OF COLLECTION OF DATA

Fifty patients posted for various elective surgical procedures were studied in a randomized prospective manner.

The study population was divided into 2 groups of 25 each,

- Group 1: Received 2ml (40 mg) of intravenous injection of Lignocaine hydrochloride as pretreatment
- Group 2: Received 2ml (0.075 mg) of intravenous injection of Palonosetron hydrochloride as pretreatment.

Inclusion Criteria:

1. Patients posted for various elective surgical procedures under general anaesthesia.
2. Age group of 18-60 years of either gender with ASA physical status I and II.

Exclusion Criteria:

1. Patients with history of drug abuse.
2. Patients undergoing emergency surgeries.
3. Difficulty in communication.
4. The suspected presence of abnormalities of the heart, lungs, liver, kidney and peripheral vessels.
5. Infection of the arm.

TECHNIQUE :

Each patient was visited one day prior to the proposed surgery for pre-anesthetic check up. All routine investigations were done. The anaesthetic procedure was explained to patients. Informed written consent was taken to include them in the study. All patients were prescribed 5 mg of Diazepam orally one night prior to surgery. Patients were kept NBM from 12 am one night prior to the surgery.No patients were given analgesics within 12 hours preoperatively.No drugs will be administered to any patients prior to the induction of anesthesia. A 20 gauge IV cannula was inserted at the dorsum of hand after ECG, non Invasive blood pressure and pulse oximeter monitoring were instituted. A pneumatic tourniquet was placed on same upper arm with pressure inflated to 80 mm of Hg for 1 min to produce venous occlusion. Drugs used for pretreatment were palonosetron 0.075mg in 2ml and lignocaine 40mg (2ml). Patients were already informed about the scale for propofol injection pain advocated by Mc Crirrick and Hunter. After intravenous injection of drug, tourniquet was released and initially ¼ of the total calculated dose of propofol was administered and patients were assessed for pain intensity upto 15seconds of initiation of induction. All patients were assesed for postoperative nausea and vomiting.

The following parameters were studied:

- Pain score upto 15seconds of initiation of induction.
- HR,BP,SPO2 & ECG recordings before induction, during induction, intra operatively at 5min, 10min, 15min and post operatively.
- Side effects like PONV.

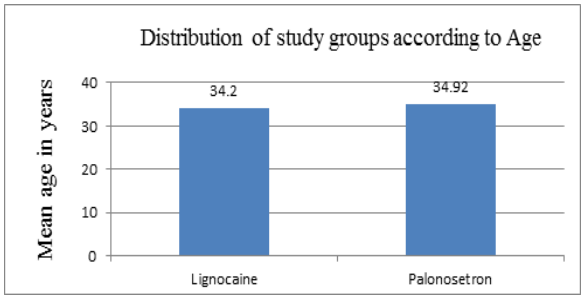
Table 1: McCririck and Hunter pain scale :

Pain Score	Degree Of Pain	Response
0	None	Negative response to questioning
1	Mild	Pain reported only in response to questioning without any behavioural signs
2	Moderate	Pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning
3	Severe	Strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears

RESULTS :

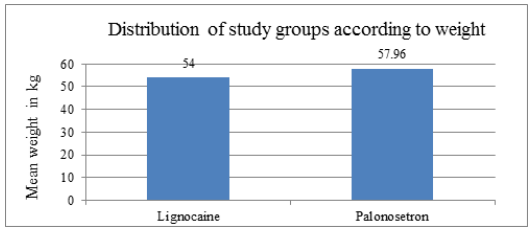
Table 2 : Demographic Data

	Type of drug used		P value
	LIgnocaine (1)	Palonosetron(2)	
Age (yr)	34.2 ± 11.84	34.92 ± 10.44	0.82
Weight (kg)	54 ± 4.90	57.96 ± 5.11	0.17
Gender (M/F)	15/10	15/10	
ASA physical status (I/II)	8/17	11/14	



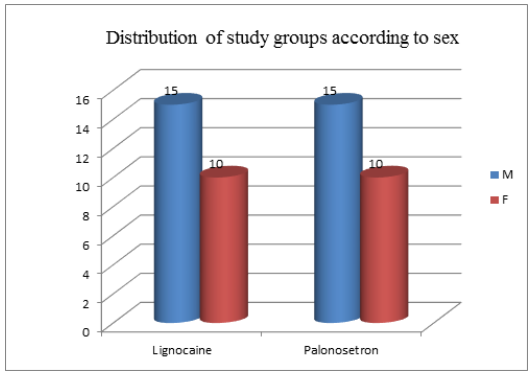
Graph 1 : Age wise distribution in both groups

- After applying student unpaired 't' test, mean age in group 1 was 34.2 ± 11.84 and 34.92 ± 10.44 in Group 2. There was no significant difference in mean age between two groups. (p>0.05)



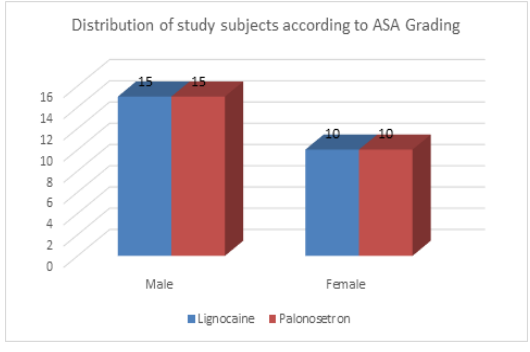
Graph 2 : Weight wise distribution in both groups

- After applying student unpaired 't' test, mean weight in group 1 was 54 ± 4.90 and 57.96 ± 5.11 in Group 2. There was no significant difference in mean weight between two groups. (p>0.05)



Graph 3 : Sex wise

- Males and females were equally distributed in both groups. (Chi-square test). distribution in both groups

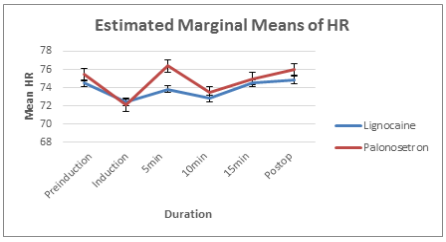


Graph 4: Comparision of ASA physical status in both study groups

- In our study 32% and 44% of patients belong to ASA I physical status in lignocaine group and in palonosetron group respectively. 68% and 56% of patients belong to ASA II physical status in lignocaine group and in palonosetron group respectively. The difference between two groups is stastically insignificant.

Table 3: Comparison of heart rate changes in study groups

	GROUP 1,2	Mean	Std. Deviation	P Value
PREIND HR	1	74.48	4.194	0.48
	2	75.44	5.339	
IND HR	1	72.40	3.686	0.73
	2	72.08	2.985	
5 MIN HR	1	73.84	5.352	0.12
	2	76.40	6.164	
10 MIN HR	1	72.80	3.958	0.56
	2	73.48	4.331	
15MIN HR	1	74.48	2.815	0.58
	2	74.96	3.285	
POSTOP HR	1	74.84	3.771	0.33
	2	76.00	4.610	

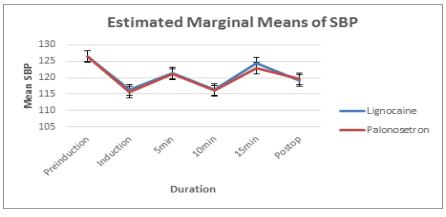


Graph 5 : Comparison of heart rate changes in study groups

- The heart rate in both groups were compared before induction, during induction, intraoperatively at 5min, 10min, 15min and post operative period.
- After applying General Linear Model for repeated measures, there was no statistical significant variations in heart rate between both groups. (p>0.05)

Table 4: Comparison of systolic blood pressure in study groups

	GROUP 1,2	Mean	Std. Deviation	P value
PREIND SBP	1	126.56	6.285	0.96
	2	126.48	5.839	
IND SBP	1	116.24	9.786	0.81
	2	115.60	9.747	
5 MIN SBP	1	121.40	8.005	0.77
	2	121.04	8.488	
10 MIN SBP	1	116.40	6.831	0.84
	2	116.00	7.483	
15MIN SBP	1	124.48	5.332	0.27
	2	122.88	4.910	
POSTOP SBP	1	119.08	6.224	0.74
	2	119.64	6.123	

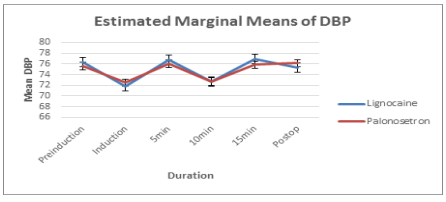


Graph 6 : Comparison of systolic blood pressure in study groups

- The systolic blood pressure in both groups were compared before induction, during induction intra operatively at 5min, 10min, 15min and post operative period.
- After applying General Linear Model for repeated measures, there was no statistical significant variations in systolic BP between both groups. (p>0.05)

Table 5 : Comparison of diastolic bp between study groups

	GROUP 1,2	Mean	Std. Deviation	P value
PREIND DBP	1	76.32	4.100	0.46
	2	75.56	3.083	
IND DBP	1	71.84	5.257	0.63
	2	72.48	4.012	
5 MIN DBP	1	76.72	3.889	0.52
	2	76.00	4.143	
10 MIN DBP	1	72.72	3.868	0.94
	2	72.64	4.680	
15MIN DBP	1	76.96	4.128	0.36
	2	75.84	4.441	
POSTOP DBP	1	75.36	4.786	0.55
	2	76.12	4.146	

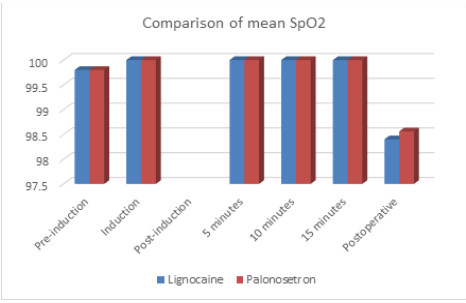


Graph 7 : Comparison of diastolic blood pressure in study groups

- The diastolic blood pressure in both groups were compared before induction, during induction, intra-operatively at 5min, 10min, 15min and post operative period.
- After applying General Linear Model for repeated measures, there was no statistical significant variations in diastolic BP between both groups. (p>0.05)

Table 6 : Comparison of mean SpO2 according to type of drug

Time of recording of SpO2	Type of drug		P value
	Lignocaine (1) (n=25)	Palonosetron (2) (n=25)	
Pre-induction	99.8 ± 0.40	99.8 ± 0.40	-
Induction	100	100	-
Post-induction			
5 minutes	100	100	-
10 minutes	100	100	-
15 minutes	100	100	-
Postoperative	98.4 ± 1.04	98.56 ± 1.15	0.60



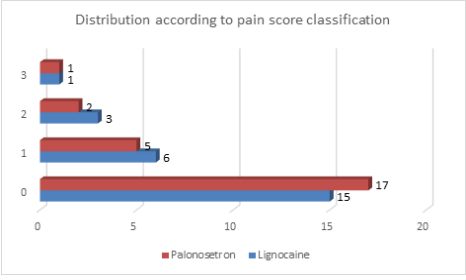
Graph 8 : Comparison of SpO2 changes in study groups

- There is no statistically significant difference in mean SpO2 between two groups during pre-induction, induction, post-induction and post-operative period. (p>0.05)

Table 7 : Distribution of study subjects according to Pain score

Pain score upto 15 secs of initiation of induction	Types of drug		Total
	Lignocaine (1) (n=25)	Palonosetron (2) (n=25)	
0	15 (60%)	17 (68%)	32 (64%)
1	6 (24%)	5 (20%)	11 (22%)
2	3 (12%)	2 (8%)	5 (10%)
3	1 (4%)	1 (4%)	2 (4%)
Total	25	25	50

(Fisher exact test, p=0.87)



Graph 9 : Distribution of study subjects according to Pain score

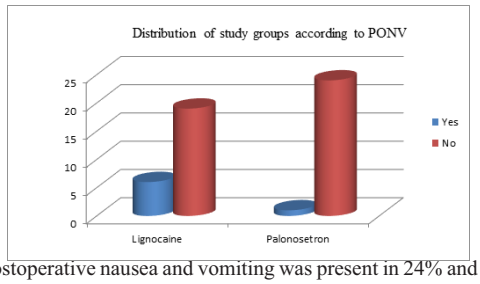
- In lignocaine group out of total 25 subjects 60%, 24%, 12% and 4% subjects were having pain score 0 (no pain), 1(mild), 2(moderate) & 3 (severe) respectively. Similarly in palonosetron group out of total 25 subjects 68%, 20%, 8% and 4% subjects were having pain score 0 (no pain), 1(mild), 2(moderate) & 3 (severe) respectively. There was no statistically significant difference in this observed proportions between two groups.

Table 8 : Distribution of study subjects according to PONV

PONV	Type of drug used		Total
	Lignocaine (1) (n=25)	Palonosetron (2) (n=25)	
Yes	6 (24%)	1 (4%)	7

No	19 (76%)	24 (96%)	43
Total	25	25	50

chi-square test = 4.1, p=0.04



- Postoperative nausea and vomiting was present in 24% and 4% of study subjects of lignocaine and palonosetron group respectively. This difference in proportion of postoperative nausea and vomiting is statistically significant. (p = 0.04)

STATISTICALANALYSIS

- Data analysis was done using Chi-square test for distribution of gender, ASA physical status and PONV; Student unpaired 't' test was used for distribution of age and weight. (Openepi software, Version 3)
- Fisher's exact test was used for distribution of pain score.
- General linear model for repeated measures was used for comparision of heart rate, systolic BP, diastolic BP. (SPSS; Windows version 22.0, SPSS Inc, Chicago, IL).
- Results were considered statistically significant when p value was <0.05.

DISCUSSION

There is no such drug called 'ideal induction agent' for induction of anaesthesia. Every drug has its own pros and cons. Researchers from around the globe make continuous efforts to develop an induction agent which will fulfill all qualities of an ideal induction agent.

Propofol provides rapid onset of action and rapid recovery making it useful for day care procedures.[1] It provides excellent amnesia, sedation, anxiolysis with state of general well being at sub hypnotic doses. It is found to have antiemetic action as an additional advantage. It provides muscle relaxation and suppresses the upper airway reflexes making it the drug of choice in hypertensive patients, patients with epilepsy or hyperactive airway where attenuation of stress response to laryngoscopy and intubation is desirable.

Propofol has become very popular in ICU sedation, daycare surgeries, cardiac anaesthesia, pediatrics anaesthesia and neuroanaesthesia because of its attractive clinical profile .But propofol is also associated with side effects like hypotension, myoclonus, apnoea, and pain on injection.[20]

Pain that is produced at the injection site during injection of propofol is the most extensively studied side effect. The incidence of propofol injection pain varies from 30-85% of patients.[2] The initial formulation of 2% emulsion with soya oil, ethanol, castor oil were studied. It was reformulated in 10% w/v soya bean oil, glycerol and egg phosphatide because of high rate of occurence of pain and other reactions.[20] Klement and Arndt reported that its acidic pH and high osmolality leads to pain.[5] Other drugs with high osmolality like diazepam, etomidate, etc also cause pain on injection.

Scott et al suggested that vein size is also an important aspect in causation of pain on propofol injection.[6] They reported that patients did not complaint of pain when propofol was injected in the antecubital veins.[21] This is due to the drug being injected in the blood stream having no contact with sensitive walls of veins. Moreover drug is buffered by the blood. Brigg et al reported that 39% incidence of pain when injecting propofol into a vein on dorsum of palm compared with 3% incidence in forearm or ante cubital fossa veins.[22]

In our study, we preferred a larger size vein which was located on the dorsum of hand as it is not always feasible to select the vein in antecubital fossa as the IV site in antecubital fossa is relatively uncomfortable to patients and has a tendency to get occluded.

Another important aspect for pain on propofol injection is high rate of injection which leads to rapid clearance of drug preventing release of kininogens from vascular endothelium.[6] Similarly the speed of carrier IV fluid infusion is also important as the contact area will be smaller between vascular endothelium and propofol so fewer kininogen molecules may be produced.

In a study conducted in 1985, it was concluded that slowing the speed of propofol injection provided more comfort.[23] Though there were conflicting views regarding the speed of propofol injection and pain, in our study, 1/4th of the total calculated induction dose of propofol (2.5mgkg^{-1}) was given slowly over 5 seconds in both the groups to determine the efficacy of pre-treatment in alleviating the injection pain.

Intravenous lignocaine injection has been commonly used to attenuate pain on propofol injection. Several doses of lignocaine were studied. It is reported that lignocaine 0.1mg kg^{-1} significantly lessened the incidence of propofol injection pain and there was no improvement when dose of lignocaine was increased.[2] In an attempt to determine optimal dose of lignocaine necessary to alleviate propofol injection pain, Than et al concluded that a propofol emulsion containing 0.05% lignocaine is effective in alleviating pain on propofol injection.[24] Singh et al concluded that pre-treatment with lidocaine 40 mg significantly reduced the incidence of pain on propofol injection.[25] However, we used a dose of 40mg lignocaine in our study considering it to be an effective dose. Gehan et al had previously shown that lignocaine 0.1mg kg^{-1} significantly lessened pain on propofol injection and 84% patients experienced no pain during the procedure.[2] Another randomized, double blind, placebo controlled study had shown that lidocaine 30mg and 40mg groups had 7% patients who complaint of pain which was significantly less than a 33% incidence in the lidocaine 10mg group ($p< 0.05$).[26] Pain of propofol injection was also found to be reduced when 10mg lignocaine was added to 19 ml of emulsified propofol.[27] Another study to find out the optimal dose of lignocaine showed that 20mg lignocaine decreased the incidence and severity of propofol injection pain (only 32% had pain) during induction. This shows similar results to another study which showed that pre treatment with lignocaine 20mg with or without venous occlusion for 60 seconds significantly reduced pain during injection of propofol.[10]

Our study also made use of venous occlusion for 60 seconds which gave us a better result with 40mg of lignocaine in decreasing pain of propofol injection.

Palonosetron is a commonly used antiemetic drug. It is a novel second generation 5-HT3 receptor antagonist. It is more effective in preventing the occurrence of acute (0-24 hr) and delayed (24-120 hr) emesis as compared to the older first-generation 5-HT3 receptor antagonists. [17] 5-HT3 receptors are located in the chemoreceptor trigger zone of the area postrema of the central nervous system. Peripherally, they are located in the vagal nerve endings. Sensory nerve endings of neurons releases pain mediators such as substance P.

5-HT3 receptor antagonists bind to opioid μ-receptors and thereby act as agonists that blocks sodium channels. This leads to their analgesic effect.[28] Therefore it can be hypothesized that they may be effective in reducing the occurrence of propofol-induced pain. Therefore, the use of 5-HT3 receptor antagonists for the management of diseases causing chronic pain, such as fibromyalgia and peripheral neuropathy is a matter of interest.

We speculated that palonosetron would be effective in reducing the occurrence of pain based on similar mechanisms to other 5-HT3 receptor antagonists.

There are seven types of 5-HT3 receptor antagonists (ondansetron, granisetron, dolasetron, palonosetron, alosetron, tropisetron and ramosetron) that are commercially available.[12]

- A study performed by Lee et al., concluded that following pretreatment with ramosetron 0.3 mg, 40% patients in the ramosetron group did not complain of pain, whereas only 4% of patients in the normal saline group did not complain of pain.[29]
- Ambesh et al. reported that the occurrence of propofol-induced vascular pain was reduced to 25% following pretreatment with ondansetron 4 mg.[30]
- Ahmed et al. reported that following pretreatment with granisetron 1 mg, 60% of patients in the normal saline group complained of

pain, but only 15% of patients in the granisetron group did.[31]

- Singh et al. conclude that pre-treatment with ramosetron 0.3 mg and lidocaine 40 mg equally effective in preventing pain from propofol injection.[25]
- Other drugs tried in the same manner were metoclopramide,[14] opioids[12] and ondansetron[28] and were reported to be effective as well.

In our study, Out of 25 patients in each study group, 60% and 68% patients did not complaint of pain in lignocaine group and palonosetron group respectively, 24% and 20% patients had mild pain in lignocaine group and palonosetron group respectively, 12% and 8% patients had moderate pain in lignocaine group and palonosetron group respectively, 4% patients in both groups had severe pain. Thus both palonosetron 2ml(0.075mg) and lignocaine 2ml(40mg) significantly reduced propofol injection pain. The difference between both groups is statistically insignificant.

A study conducted by Ryu HB et al shows similar results who reported that 60% patients experienced propofol-induced pain in the normal saline group compared to 27.5% in the palonosetron group.[19] Our results were also comparable with a study conducted by singh T et al who reported that 26 patients in palonosetron group (86.67%) did not complaint of pain as compared with the saline group (43.33%.)[32]

Regarding other side effects, Out of 25 patients, 6 and 1 patients had PONV in lignocaine group and palonosetron group respectively. The difference between both groups is statistically significant. So palonosetron group had an added advantage of having less number of patients with PONV. No evidence of thrombophlebitis in form of pain, oedema, wheal and flare at injection site was reported in either group. However, further comparative studies with lignocaine, which is a gold standard agent for alleviating propofol pain, needs to be undertaken.

CONCLUSION

Palonosetron and lignocaine are equally effective in reducing pain on propofol injection. No significant haemodynamic changes are caused by either drugs. Palonosetron when used for prevention of PONV provides the additional benefit of reducing propofol injection induced pain.

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