Original Research Article

Indian Journal of Anesthesia and Analgesia
2019;6(4) (Part - II): 1333-1342
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.6419.38

Pain on Propofol Injection: Comparative Study of Pre-Treatment with Intravenous Lignocaine, Ondansetron and Fentanyl for the Prevention of Pain

Chetan Arun Patil[1], Neha P Kamble[2], Manoj Kumar N Gajbhare[3]

[1]Consulting Anaesthesiologist, Department of Anesthesia, Siddhi Hospital, Nashik, Maharashtra 422007, India. [2]Assistant Professor, Department of Anesthesia, B.J. Government Medical College and Sassoon Hospital, Pune, Maharashtra 411001, India. [3]Associate Professor, Department of Anesthesia, Yashwantrao Chavan Memorial Hospital, Pimpri, Pune, Maharashtra 411018, India.

Abstract

Context: Propofol is a sedative-hypnotic intravenous anaesthetic agent. It causes a high incidence of pain during intravenous injection which leads to patient dissatisfaction. *Aim:* The aim of this study was to determine whether pre-treatment with intravenous lignocaine, ondensetron and fentanyl was effective in reducing propofol induced pain. *Settings and Design:* In a prospective, randomized, double blind study 150 ASA physical status I and II patients, aged 20-60 years, undergoing elective surgery under general anesthesia, were allocated randomly into three groups. *Methods and Material:* Group A received IV lignocaine 42 mg (2 ml), Group B received IV ondansetron 4mg and Group C received IV fentanyl 100 mcg. Mid-arm was occluded before drug injection then released after 1 min followed by propofol injection. Patients were assessed according to Mc Crirrick and Hunter pain scoring system at 0, 5, 10, 15 and 20 seconds. Statistical analysis: ANOVA with Dunnett's post hoc test and chi-square test were used to analyze results. *Results:* Two patients in Group A and one patient in Group B had 'no pain' during the observation period. Group B and Group C have more 'mild pain' than Group A while it is comparable in Group B and C. 'Moderate pain' is comparable between Group A and B while Group A has more 'moderate pain' than Group C and Group B has more 'moderate pain' than Group C. Only one patient in Group A had 'severe pain'. *Conclusion:* Pre-treatment with lignocaine, ondensetron and fentanyl was effective in reducing pain on propofol injection but the superiority of one drug over the other cannot be commented.

Keywords: Fentanyl; Lignocaine; Ondensetron; Pain on injection; Propofol.

How to cite this article:

Chetan Arun Patil, Neha P Kamble, Manoj Kumar N Gajbhare. Pain on Propofol Injection: Comparative Study of Pre-Treatment with Intravenous Lignocaine, Ondansetron and Fentanyl for the Prevention of Pain. Indian J Anesth Analg. 2019;6(4):1333-.

Introduction

Intravenous induction is the most commonly used method for induction of general anesthesia. An ideal intravenous anaesthetic agent should provide hypnosis, amnesia and analgesia without undesirable cardiac and respiratory side effects. Commonly used intravenous anaesthetics are barbiturates (thiopentone) and non-barbiturates (propofol, etomidate, ketamine).

Propofol has a rapid onset (15–45 seconds) and short duration of action (5–10 minutes). Its attractive kinetic properties like titrable level of anesthesia, absence of cumulation, rapid and clear headed recovery, less postoperative nausea and vomiting, greater depression of laryngeal reflexes than other

Corresponding Author: Neha P Kamble, Assistant Professor, Department of Anesthesia, B.J. Government Medical College and Sassoon Hospital, Pune, Maharashtra 411001, India.

E-mail: nehakamble_84@yahoo.com

Received on 19.05.2019, **Accepted on** 19.06.2019

commonly used anaesthetic agents[1] and minimal side effects makes it an ideal agent for induction of anesthesia.[2]

Propofol is known to cause severe, sharp, stinging or burning pain on injection, especially when given in small veins on dorsum of hand. This is clinically unacceptable as it can cause agitation and interfere with smooth induction of anesthesia. The reported incidence varies between 28% and 90% in adults when a vein on dorsum of hand is used.[3] It can be immediate or delayed in nature. The immediate pain probably results from direct irritant effect whereas delayed pain results from indirect effect via the kinin cascade which occurs 10–20 seconds later.[4] Nafamostat mesilate, a kallikrein inhibitor, is effective in decreasing pain on injection of propofol. Its effectiveness has been attributed to the activation of kallikrein- kinin system as the propofol emulsion contacts free nerve endings in the vein. Factor XII is activated which converts prekallikrein to kallikrein, which then cleaves high-molecular weight kininogen to release bradykinin. Bradykinin causes vasodilatation and increased permeability of vein, increasing contact between aqueous phase of propofol and free nerve endings of vein. This will manifest as pain.[5,6]

Drugs like lignocaine, opioids like fentanyl, morphine and butarphanol, magnesium sulphate, paracetamol, ephedrine, metoclopramide and many more have been tried to reduce this pain. Of these the most commonly used methods are pre-treatment with IV (intravenous) lignocaine or IV fentanyl.

Lignocaine reduces pain due its local anaesthetic action,[7] fentanyl, has some peripherally mediated analgesic action within the clinical dosage range,[8] ondansetron[9] due to its multifaceted action as Na channel blocker, a $5HT_3$ receptor antagonist and μ-opioid agonist, can be used to alleviate pain produced by propofol. However the efficacy of ondansetron has never been compared with drugs like lignocaine and fentanyl.

Our aim is to compare the efficacy of lignocaine, ondansetron and fentanyl in reducing pain on injection of propofol, to detect an agent with minimal side effects and the hemodynamic changes due to these drugs.

Materials and Methods

After approval by the Hospital Ethics Committee, we studied 150 patients of either sex, aged 20-60 years, scheduled for elective surgery under general anesthesia.

All patients who belong to the ASA physical status class I and II were enrolled for this prospective randomized, double-blind study. Patients were not included if they refused to participate in the study, a history of allergy to the study medications, hemodynamically unstable patients, presence of infection on the dorsum of hand, difficult IV cannulation. Also excluded were patients of ASA physical status III and IV, pregnant and diabetic patients, patients with pre-existing cardiac conduction defects, patients receiving analgesics and patients with difficulty in communication.

In a pilot study on 20 patients we found that all patients complained of pain during propofol injection. The incidence of moderate to severe pain was highest at 15 seconds. So the number needed to bring down the incidence of pain by 50%, keeping the type I error at 5% and power of study at 95% was 44. We used a web based sample size calculator. To round it off we have taken the number of patients in each group as 50.

Randomization list was generated by random number function using the Microsoft Excel 2003 spreadsheet, resulting in a list of 150 assigned to participants receiving the drugs. Randomization was conducted using sequentially numbered, opaque and sealed envelope. Patients were divided in three groups, 50 patients in each group.

Group A: IV Lignocaine 42 mg (2 ml) diluted to 5 cc.

Group B: IV Ondansetron 4mg diluted to 5cc.

Group C: IV Fentanyl 100 mcg diluted to 5cc.

The study drug was prepared in identical looking (5ml) coded syringes by an anaesthesiologist not involved in the study. The drug administrator and the person making the observations were blind to the study drug.

A complete pre-anaesthetic evaluation was done. After explaining the anaesthetic procedure to the patients, written informed consent was taken to include them in the study. They received the study medication as per randomization. During the preoperative rounds all patients were explained about the pain scoring method advocated by Mc Crirrick and Hunter*.

All patients were kept fasting 6 hours before surgery. They were advised to take tablet alprazolam 0.5 mg and tablet ranitidine 150 mg night before surgery. In the operating room,

non-invasive blood pressure, electrocardiogram and pulse oximeter were attached and baseline vital parameters were noted. Intravenous access was established with an 18-G cannula on the dorsum of the non-dominant hand. No analgesic or sedative drugs were given before induction. Venous occlusion of the arm proximal to the puncture site was maintained with a blood pressure cuff inflated to 40 mmHg. The study drugs were injected over 30 seconds and venous occlusion was released after 1 min of completion of study drug injection. Propofol (2 mg/kg) was administered through the intravenous cannula. During the first 25% of the calculated propofol dose, the patient was assessed according to four- point pain score at 0, 5, 10, 15 and 20 seconds. Following which, general anesthesia was continued with the remainder of the calculated dose of propofol. Vecuronium 0.1 mg/kg intravenous was used to facilitate tracheal intubation. Anesthesia was maintained with isoflurane 1% and 60% nitrous oxide with oxygen on controlled ventilation with intermittent bolus of vecuronium.

Intraoperative analgesia was maintained with incremental doses of intravenous fentanyl 50 mcg. At the end of surgery, inhalational agents were discontinued and neuromuscular blockade was reversed with neostigmine 0.5 mg/kg with glycopyrrolate 0.1 mg/kg intravenously. The participants were extubated and transferred to the recovery area after confirmation of satisfactory recovery criteria. All observations were recorded by an anaesthesiologist not involved in the study.

Mc Crirrick and Hunter scale of pain assessment on injection with propofol

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

The following observations were made:

Age, sex, ASA grade, body mass index (BMI).

Pain scores at 0, 5, 10, 15 and 20 seconds after propofol injection.

Heart rate and oxygen saturation was monitored continuously, recorded at baseline, 0, 5, 10, 15 and 20 seconds after propofol injection.

Mean arterial blood pressure at baseline, after 20 seconds, 5, 10, 15 and 20 minutes.

Any adverse effects.

Statistics Analysis

Data represented as mean ± SD (n = 50). All the results were analyzed statistically by one-way and two-way ANOVA with Dunnett's post hoc test and Chi square test by using Graphpad Prism 7.0 (GraphPad Software, Inc., CA, USA). P <0.05 was considered as significant.

Results

All the three groups were comparable (p > 0.05) with respect to demographic parameters and ASA Physical Status class as shown (Fig. 1 and 2).

There was no statistically significant difference in the mean pulse rate recorded at baseline and at 0 seconds but a statistically significant difference was noted at 5, 10, 15 and 20 seconds when compared with baseline pulse rate (p < 0.05) (Table 1, Fig. 3) There was a statistically significant difference in the mean blood pressure recorded at baseline and that recorded after 20 seconds, 5, 10, 15 and 20 minutes (p < 0.05) (Table 2, Fig. 4).

No significant changes were noted in the SpO_2 between the studied groups (p > 0.05) (Fig. 5).

The incidence of pain when compared amongst the groups was statistically insignificant (Table 3, Fig. 6). Chi – square test {χ^2 – Test} was used for the comparison of incidence of pain. Comparison of Group A with Group B and Group C gives p value as 0.0956 and 0.514 respectively, while comparison of Group B with Group C gives p value as 0.1333 which is statistically insignificant.

After administration of drug, 48 (96%) patients in Group A, 49 (98%) patients in Group B and all patients [50 (100%)] in Group C experienced pain (p=0.7675) (Table 4). Pain score was compared in all the groups at 0, 5, 10, 15 and 20 seconds (Table 5, Fig. 7).

The mean pain score (MPS) in Group A, B and C was 1.46 ± 0.61, 1.42 ± 0.53, 1.48 ± 0.50 respectively (Fig. 8). Chi – square test was used for the comparison of pain scores in the study groups (Fig. 9). Comparison of 'MPS 0'(no pain) in Group A with Group B and C gives P value as 2.037 and

0.555 respectively, while comparison of Group B with Group C gives p value as 0.0964 which is statistically insignificant.

Comparison of 'MPS 1'(mild pain) in Group A with Group B and C gives p value as 0.036 and 0.015 respectively which is statistically significant while comparison of Group B with Group C gives p value as 0.534 which is statistically insignificant.

The 'MPS 2' (moderate pain) in Group A when compared with Group B (p = 0.074) was statistically insignificant and that with Group C (p = 0.0005) was significant while comparison of Group B with

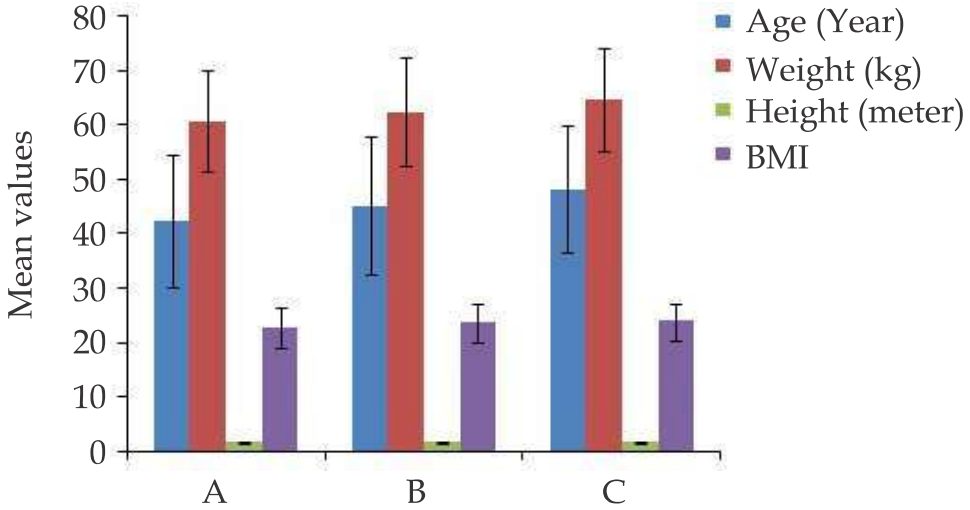

Fig. 1: Graphical representation of average age, weight, height and BMI of the patients in different drug treated group [Mean ± SD (n=50)]. Column width.

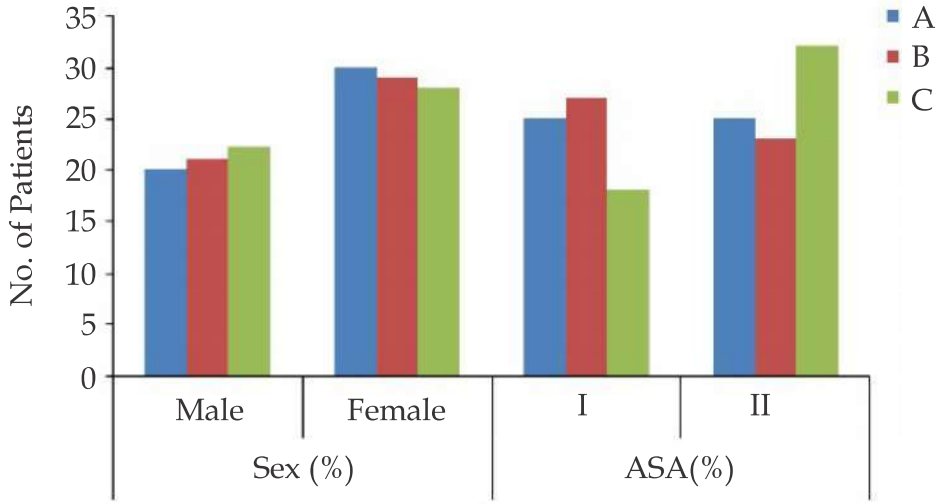

Fig. 2: Graphical representation of Gender and ASA stage wise distribution of patients in different drug treated group [Data represented as n (%). Statistical analysis for the Gender of patients X^2=0.1642, p = 0.9212.Statistical analysis for ASA Physical Status X^2=3.589, p = 0.1662. Chi square test was performed for the statistical analysis]. Column width.

Table 1: Effect of different drug treatment on the pulse rate at different time interval after the administration of drug

Group	Pulse rate (Beats/min)					
	Baseline	0 Sec	5 Sec	10 Sec	15 Sec	20 Sec
A	89.3 ± 14.3	89.7 ± 14.5	94.2 ± 14.8	98.7 ± 14.8##	102.6 ± 15.7##	106.5 ± 16.4##
B	88.3 ± 9	88.1 ± 9.2	94.1 ± 9.5#	101.2 ± 9.8##	106.7 ± 9.61##	112.2 ± 10.6##
C	87.5 ± 9.1	87 ± 9.2	90.9 ± 9.5	102.7 ± 9.5##	112.4 ± 9.2##	123.63 ± 8.7##

Mean ± SD (n=50), ##P<0.01 compared to baseline

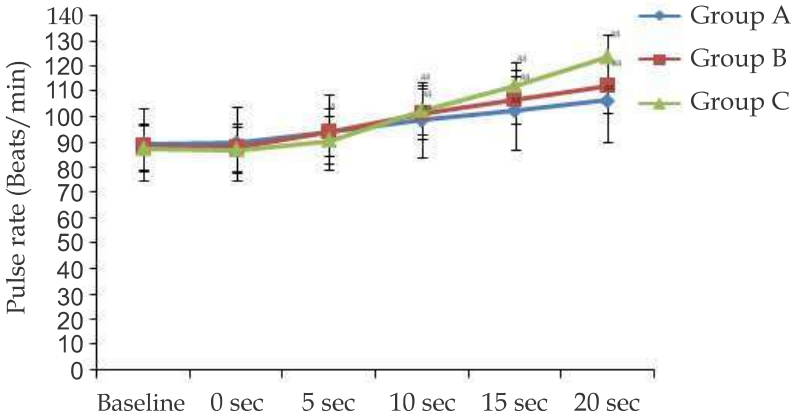

Fig. 3: Effect of different drug treatment on the pulse rate at different time interval after the administration of drug [Mean ± SD (n=50), ## p <0.01 compared to baseline]. Column width.

Table 2: Effect of different drug treatment on the mean blood pressure at different time interval after the administration of drug

Group	Mean blood pressure (mm Hg)					
	Baseline	**20 Sec**	**5 min**	**10 min**	**15 min**	**20 min**
A	101.88 ± 9.62	93.48 ± 7.05##	92.33 ± 7.18##	94.05 ± 7.11##	93.25 ± 7.18##	93.18 ± 9.97##
B	99.14 ± 10.06	92.5 ± 6.63##	91.86 ± 6.61##	94.08 ± 6.33##	92.95 ± 6.24##	93.3 ± 8.69##
C	102.14 ± 7.71	93.25 ± 7.41##	91.37 ± 7.24##	93.99 ± 6.73##	92.2 ± 7.18##	92.81 ± 9.19##

Mean ± SD (n=50), ##P <0.01 compared to baseline

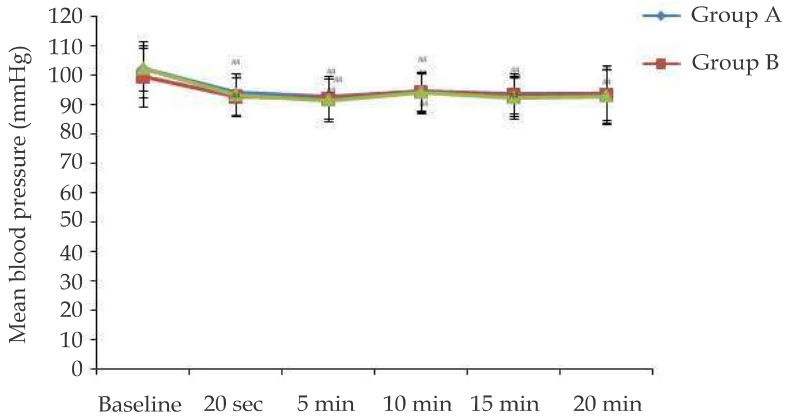

Fig. 4: Effect of different drug treatment on the mean blood pressure at different time interval after the administration of drug [Mean ± SD (n=50), ## p <0.01 compared to baseline] Column width.

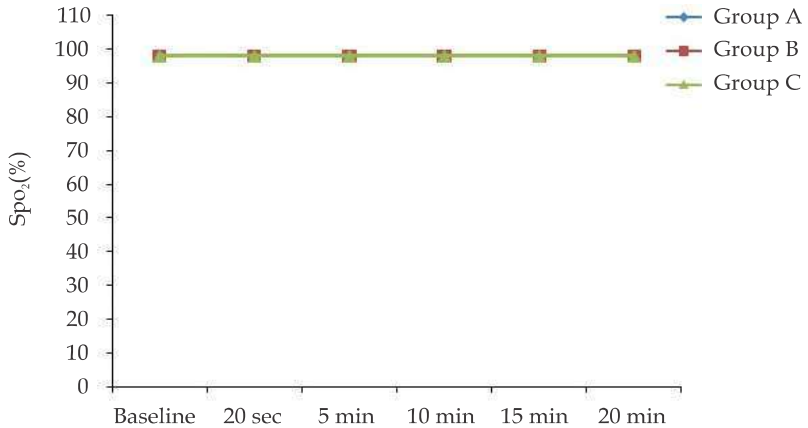

Fig. 5: Effect of different drug treatment on the percentage of SpO_2 at different time interval after the administration of drug [Mean ± SD (n=50)] Column width.

Table 3: Effect of different drug treatment on the incidence of pain at different time interval after the administration of drug

Group	Incidence of Pain n (%)				
	0 Sec	5 Sec	10 Sec	15 Sec	20 Sec
A	0 (0)	7 (14)	24 (48)	45 (90)	48 (96)
B	0 (0)	1 (2)	35 (70)	49 (98)	49 (98)
C	0 (0)	0 (0)	17 (34)	46 (92)	50 (100)

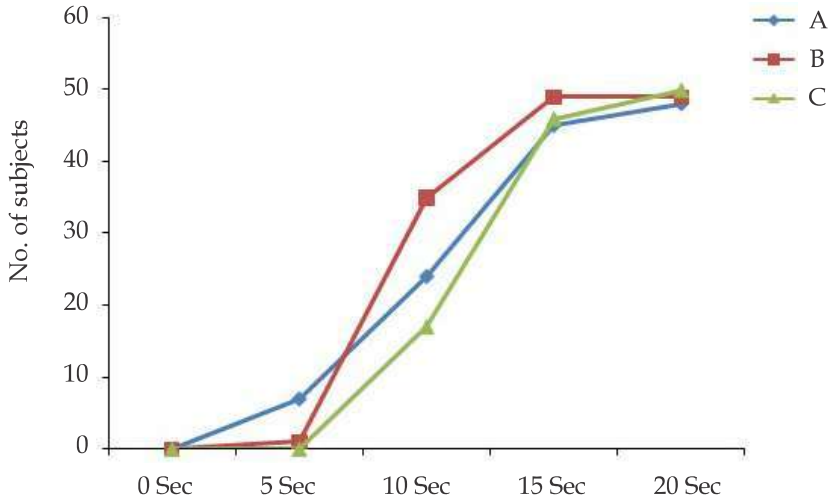

Fig. 6: Effect of different drug treatment on the incidence of pain at different time interval after the administration of drug. Column width.

Table 4: Number of patients experiencing pain after the administration of drug

Sr. No.	Group	Number of patients complaining of pain n(%)	Number of patients free from pain n(%)
1	A	48 (96)	2 (4)
2	B	49 (98)	1 (2)
3	C	50 (100)	0 (0)
	p Value	0.7675	
	X^2 value	0.5292	

Data represented as n (%), X^2=0.5292, p = 0.7675
Chi square test was performed for the statistical analysis

Table 5: Number of patients experiencing different levels of pain at different time interval after the administration of drug

Sr. No.	Group	Pain Level	No. of patients complaining of pain at different time interval n(%)				
			0 Sec	5 Sec	10 Sec	15 Sec	20 Sec
1	A	Mild	0 (0)	7 (14)	18 (36)	28 (56)	24 (48)
		Moderate	0 (0)	0 (0)	6 (12)	17 (34)	23 (46)
		Severe	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)
2	B	Mild	0 (0)	1 (2)	35 (70)	37 (74)	27 (54)
		Moderate	0 (0)	0 (0)	0 (0)	12 (24)	22 (44)
		Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
3	C	Mild	0 (0)	0 (0)	17 (34)	45 (90)	26 (54)
		Moderate	0 (0)	0 (0)	0 (0)	1 (2)	24 (48)
		Severe	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Data represented as n (%)
Statistical analysis for mild pain level on 10, 15 and 20 sec X^2=7.399, p= 0.1162
Statistical analysis for moderate pain level on 10, 15 and 20 sec X^2=19.87, p= 0.0005
Chi square test was performed for the statistical analysis

Group C (p = 0.010) was statistically significant. Only one patient (2.08%) had 'MPS 3' (severe pain) in Group A which is statistically insignificant.

There were few adverse events observed in all the groups during the study period [Table 7].

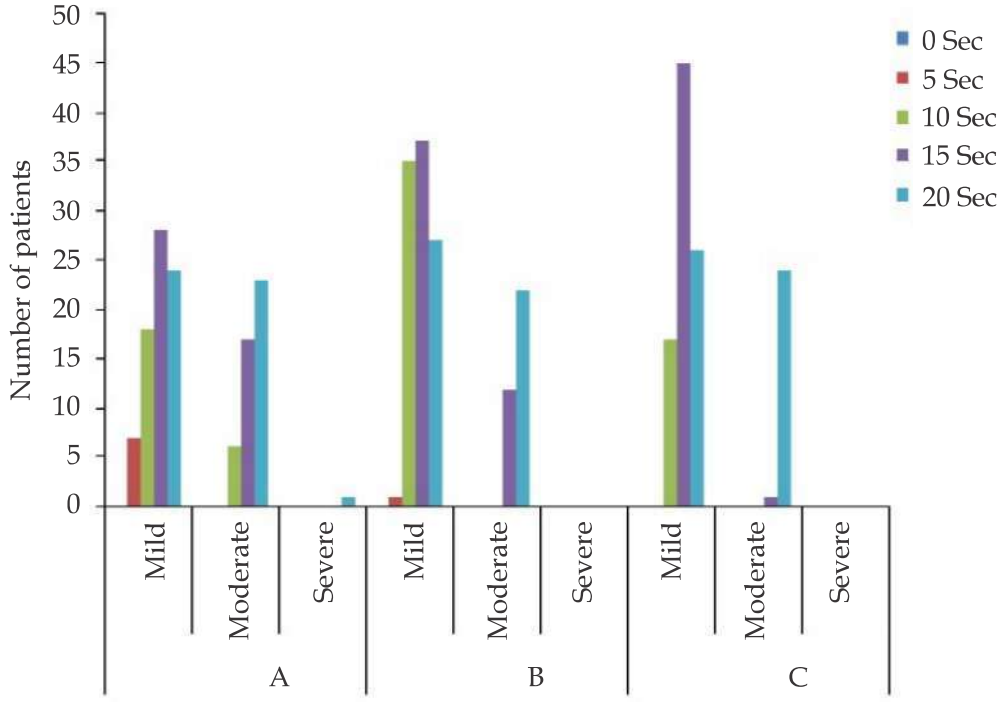

Fig. 7: Number of patients experiencing different level of pain at different time interval after the administration of drug. Column width.

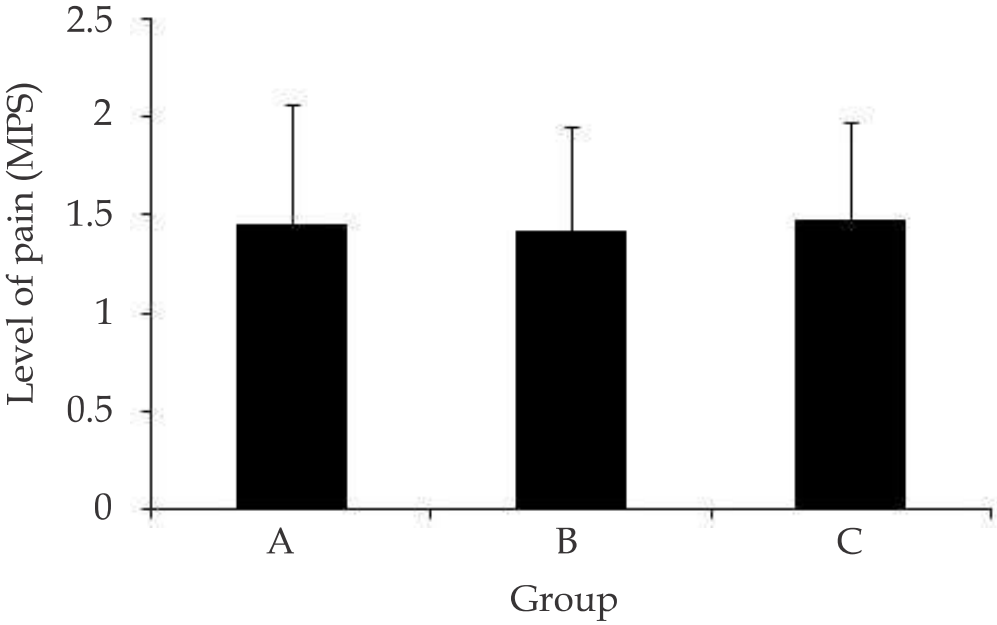

Fig. 8: Effect of different drug treatment on the level of mean pain score [Mean ± SD (n=50)]. Column width.

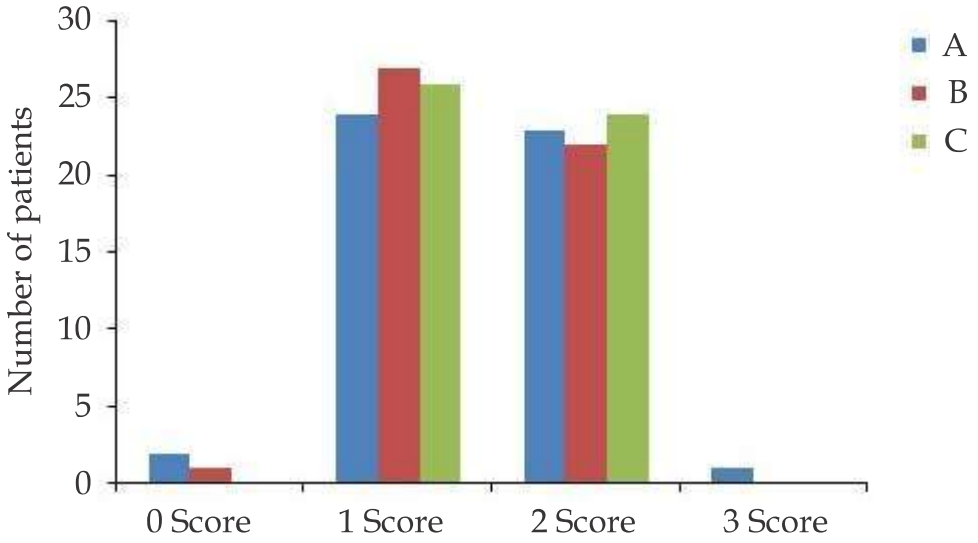

Fig. 9: Number of patients experiencing different level of pain after the drug administration [Data represented as n (%). X^2=4.269, p = 0.6404. Chi square test was performed for the statistical analysis]. Column width.

Table 6: Number needed to treat (NNT)

Groups	NNT	ARR	RRR
Lignocaine	4.5	0.22	0.31
Ondansetron	4.1	0.24	0.34
Fentanyl	4.5	0.22	0.31

ARR: Absolute Risk Reduction, RRR: Relative Risk Reduction

Table 7: Adverse events during the study

	Groups			
Adverse event	A	B	C	*p* value
Redness	1	0	0	>0.05
Hypotension	0	0	0	
Wheal	0	0	1	
Pruritus	0	1	0	

Discussion

All the three groups were comparable with respect to demographic parameters and ASA Physical Status (p > 0.05) [Figs. 1, 2].

Lignocaine has been extensively used, either separately or as preformed mixture to alleviate pain on propofol injection. Picard *et al.*[10] in a meta-analysis have found the NNT (number needed to treat) of 40 mg of lignocaine to be 1.6. Lignocaine in a dose of 0.5 mg/kg was effective in reducing pain in 60% cases when administered with a rubber tourniquet on the forearm 30-120 seconds before the injection of propofol. Fentanyl (100 mcg) has been shown to provide more analgesia than placebo.[11] Ondansetron has provided results comparable to tramadol 50 mg.[12] Since fentanyl and ondansetron are the two drugs routinely used in our set up for all the surgeries done under general anesthesia, we felt the necessity of testing their ability to attenuate pain from propofol injection and comparing its efficacy with that of lignocaine. This would save us from using a separate drug which will avoid the expenses and adverse effects as well. The doses fentanyl, lignocaine and ondansetron have been the same as used by Pang *et al.*[8] and Zahedi *et al.*[13]

We have chosen the dorsum of the non-dominant hand for the injections. Although Kang *et al.*[14] have shown that injection in the vein on dorsum of hand was more painful (61.2%) than in antecubital fossa (22.5%) (p < 0.01), we have still chosen this site in our study as it was not possible to attach the tourniquet with the IV line at any other site. However, since we did not take any placebo group the decision was not of ethical concern.

We have observed changes in the pulse rate and SpO_2 at the baseline, at the start of propofol injection and thereafter at 5, 10, 15 and 20 seconds during propofol injection. However recording of blood pressure with non-invasive method was not possible at the above mentioned intervals. So we have taken the baseline reading (before starting of propofol injection) and thereafter at the end of 20 seconds, 5, 10, 15 and 20 minutes. Following which changes in the heart rate and blood pressure would be construed as resulting from pain.

Baseline mean pulse rate was comparable between the three groups. The intra-group analysis of pulse rate showed a significant increase in the pulse rate at 5, 10, 15 and 20 seconds of propofol injection in all the groups compared to baseline ($p < 0.05$) [Table 1, Figure 3]. This could have been a response as a result of pain on injection of propofol despite of pre-treatment with lignocaine, ondansetron and fentanyl. However the mean pulse rate was comparable between the three groups at 5, 10, 15 and 20 seconds ($p > 0.05$). Similarly, there was a statistically significant increase in the mean blood pressure recorded at baseline and that recorded after 20 seconds, 5, 10, 15 and 20 minutes of propofol injection ($p < 0.05$) [Figure 4]. No significant changes were noted in S_pO_2 over the baseline reading [Fig. 5]. In the earlier studies many authors have not commented on hemodynamic changes during propofol injection. Ray *et al.*[15] in their study have observed hemodynamic changes, but have not commented on their trend. Mahmood *et al.*[16] and Canbay *et al.*[17] found no significant changes in hemodynamic parameters. They have used ketamine, dexamethasone and lignocaine as their study drugs.

All patients in Group C experienced some form of pain at some time during the study period. However two patients in Group A and one patient in Group B did not experience any pain during any time of the observation period (Table 4). There was no statistically significant difference in the incidence of pain in the three groups. Therefore it is not possible for us to comment on the superiority of one drug over the other as far as the incidence of pain is concerned. Ray *et al.*[15] in their study have documented a significant difference in the incidence of pain between the lignocaine and fentanyl pre-treatment group (14.3 vs. 42.9). They have calculated the NNT (number needed to treat) for fentanyl and lignocaine to be 4 and 2 respectively.

The incidence of 'MPS 1' (mild pain) increased with time, with peak at 15 seconds and then declining at 20 seconds. [Table 5] There was a statistically significant difference in the incidence of 'mild pain' at 15 seconds in Group A and Group B ($p = 0.0362$), so also in Group A and Group C ($P = 0.0156$). Incidence of mild pain in Group B and C was comparable. The incidence of 'MPS 2' (moderate pain) at 15 seconds was comparable between Group A and Group B ($p = 0.0742$) however the same in group C was significant ($p = 0.0005$) when compared with the other two groups. No patient in Group B and C had severe pain at any time period.

Our study cannot be compared with the other studies with regard to severity of pain, since they have taken pain as an all or none phenomenon. We have taken a four point verbal categorical scoring system in accordance with the study of Mahmood *et al.*[16] as it was simple to use by the patients. Visual analogue scale (VAS) was not appropriate to the present study as appropriate hand-eye coordination might not be present in all patients during the rapidly changing state of consciousness of anesthesia induction.

The incidence of moderate and severe pain in our pilot study was 100% at 15 seconds. We aimed at 50% reduction in its incidence with our test drugs. All the three drugs were able to successfully attenuate moderate and severe pain due to propofol injection but not mild pain, which means patients did not remain completely pain free.

The mechanism of pain produced by propofol has been shown to be the high concentration of free propofol in the aqueous phase[18,19] of an emulsion and the lipid carrier.[20] A kinin cascade has been suggested which describes a slight delay before pain is experienced. We have experienced this phenomenon in our patients where maximum pain has been experienced at 15 seconds. The immediate pain which is due to the local irritant action of the drug on vein has not been inhibited by these drugs. Whereas the delayed effect, which is due to the kinin cascade, was effectively attenuated.

Our study was powered to find a 50% reduction in the incidence of pain at 15 seconds. So, all our study drugs have successfully achieved reduction in the pain induced by propofol at 15 seconds to < 50% (34%, 24%, 2% respectively in Group A, B & C for moderate pain at 15 seconds and 0% severe pain in all the groups at 15 seconds). The NNT (number needed to treat) for the three drugs were found to be 4.5, 4.1 and 4.5 respectively for lignocaine, ondansetron and fentanyl [Table 6]. Number needed to treat (NNT) of 4 means 4 out of 10 patients will benefit from treatment to be an effective drug. The expected NNT is < 2. However, since our study was powered to detect 50% reduction only, we cannot comment on the efficacy of drugs based on NNT.

One patient in the Group A had redness at the site of drug injection, one patient had pruritus in Group B and one had a wheal in the Group C. Overall these were very mild reactions and did not need any form of intervention.

Conclusion

We conclude that pre-treatment with the three drugs Lignocaine 42 mg, Ondansetron 4 mg and Fentanyl 100 mcg effectively decreased the incidence of pain on propofol injection at 15 seconds. However the superiority of one drug over the other cannot be commented. All the three drugs were comparable with respect to hemodynamic changes and adverse effects.

Key message: Propofol, an ideal intravenous anaesthetic agent causes pain on injection which interferes with smooth induction of anesthesia. Fentanyl and Ondensetron were compared with Lignocaine to test their ability to attenuate pain from propofol injection. All the three drugs effectively reduced pain on propofol injection but none was found superior over other.

References

1. Mc Leskey CH *et al.* Adverse events in multicenter phase IV study of propofol: evaluation by anaesthesiologist and post anesthesia care unit nurses. Anesth analg. 1993;73(4):3–9.
2. Mcleod., N.Boheimer. Propofol infusion as main agent for day care surgery. Post graduate Medical journal. 1985;61 suppl 3:105–107.
3. Hynynen M, Korttila K, Tammisto T. Pain on IV injection of propofol (ICI 35868) in emulsion formulation: short communication. Acta anesthesiologica Scandinavica. 1985;29:651–2.
4. Klement W, Arndt JO. Pain on injection of propofol, the effects of concentration and diluent. Br J Anaesth. 1991;67:281–84.
5. Iwama H, Nakane M, Ohmori S *et al.* Nafamostat mesilate a kallikrein inhibitor prevents pain on injection with propofol. Br J Anesth. 1998; 81:963–964.
6. Nakane M, Iwama H. A potential mechanism of propofol induced pain on injection based on studies using nafamostat mesilate. Br J Anesth. 1999;83(3):397–404.
7. Mangar D, Holak EJ. Tourniquet at 50 mm Hg followed by intravenous lidocaine diminishes hand pain associated with propofol injection. Anesth Analg. 1992;74:250–2.
8. Pang WW, Mok MS, Huang S, *et al.* The analgesic effect of fentanyl, morphine, meperidine and lidocaine in the peripheral veins: a comparative study. Anesth Analg. 1998;86:382–6.
9. Ambesh SP, Dubey PK, Sinha PK. Ondansetron pre-treatment to alleviate pain on propofol injection: a randomized, controlled, double-blinded study. Anesth Analg. 1999;89(1):197–9.
10. Picard P, Tramer MR. Prevention of pain on injection with propofol: a quantitative systematic review. Anesth Analg. 2000;90:963–9.
11. Ray S, Pal R, Pal S, *et al.* Preclusion of pain on injection with propofol : Evaluating the effects of lignocaine or fentanyl pre-treatment. Anesth Essays Res. 2011;5:33–8.
12. Memis D, Turan A *et al.* The prevention of propofol injection pain by tramadol or ondansetron, European Journal of anaesthesiology. 2002; 19(1):47–51. Cambridge University Press.
13. Zahedi H, Maleki A and Rostami G. Ondansetron Pre-treatment Reduces Pain on Injection of Propofol. *Acta Medica Iranica*. 2012;50(4):239–43.
14. Hye–joo Kang, Mi- Young Kwon *et al.* Clinical factors affecting the pain on injection of propofol Clinical Research Article, Korean J Anesthesiol. 2010 Mar;58(3):239–243.
15. Ray S, Pal R, Pal S, Kirtania J, Sarbapalli D, Sarkar U, *et al.* Preclusion of pain on injection with propofol : Evaluating the effects of lignocaine or fentanyl pre-treatment. Anesth Essays Res. 2011; 5:33–8.
16. Mahmood I, Yasmine M. Prevention of pain on propofol injection; A comparative, randomized, double blind study between lignocaine, ketamine, dexamethasone and placebo. Professional Med J. Sep 2010;17(3):405–410.
17. O Canbay, N Celebi *et al.* Efficacy of intravenous acetaminophen and lidocaine on propofol injection pain. Br J Anaesth. 2008;100(1):95–98.
18. Schaub E, Kern C Landau R. Pain on injection: A double blind comparison of propofol with lidocaine pre treatment versus propofol formulated with long and medium chain triglycerides. Anesth Analg. 2004;99:1699–702.
19. Babl J, Doenicke A, Monch V. New propofol LCT/MCT fat emulsion as solvent: approach to reducing pain on injection of propofol. Eur Hosp Pharm. 1995;1:15–21.
20. Doenicke AW, Roizen MF, Rau J, O'Connor M, Kugler J, Klotz U, Babl J. Pharmacokinetics and pharmacodynamics of propofol in a new solvent. Anesth Analg. 1997;85(6):1399–403.