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PREVENTION OF PROPOFOL PAIN: A RANDOMIZED CONTROLLED STUDY

[1]Dr. Shweta Shelke, [2]Dr. Ajit Gaikwad, [3]Dr. Prashant Bhalekar and *[4]Dr. Deepak Phalgune

[1]MBBS, Senior Resident, Dept. of Anaesthesia, Poona Hospital & Research Centre, Pune.
[2]MBBS, DNB (Anaesthesia), Consultant Anaesthesiologist, Dept. of Anaesthesia Poona Hospital & Research Centre. Pune.
[3]MBBS, DA, DNB (Anaesthesia), Senior Registrar, Dept. of Anaesthesia, BJ Government Medical College and Sassoon General Hospitals, Pune.
[4]MBBS, MD (P & SM), PhD, Research Consultant, Poona Hospital & Research Centre, Pune.

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***Corresponding Author**
Dr. Deepak Phalgune
MBBS, MD (P & SM), PhD, Research Consultant, Poona Hospital & Research Centre, Pune.

ABSTRACT

Background and Aims: Propofol is the most widely used intravenous anaesthetic agent for induction and maintenance of anaesthesia. However, pain is a major disadvantage with a reported incidence of approximately 70%. Several interventions have been applied to prevent this pain, with variable success. The primary objective of the present study was to compare the efficacy of lidocaine, ketamine and combination of lidocaine and ketamine in reduction of pain of propofol injection. **Methods:** Ninety patients, aged 18–60 years, scheduled to undergo elective surgeries under general anaesthesia were randomly assigned to three groups of 30 each. Group L patients received 40 mg of Inj. lidocaine, Group K patients received Inj. ketamine 10 mg, whereas Group LK received Inj. lidocaine 40 mg mixed with Inj. ketamine 10 mg. with venous occlusion. Sixty seconds later, the tourniquet was released and 20% dose of propofol was given over 10 seconds. Pain was assessed with 4-point verbal rating scale (VRS). Analysis of variance (ANOVA) and Chi-square test/Fisher's exact test were used to compare quantitative and qualitative variables respectively. **Results:** The overall incidence and intensity of pain were significantly less in Groups LK and L compared to Group K. The percentage of patients whose VRS was 0 was significantly higher in group LK (25/ 30 – 83.3%) compared to group

K (15/ 30- 50.0%) and Group L (20/30- 66.7%). (*P* = 0.009). **Conclusion:** Lignocaine and ketamine in combination significantly reduced pain of propofol injection with no untoward side effects as compared to lignocaine or ketamine alone.

KEYWORDS: Lidocaine, ketamine, pain, propofol, verbal rating scale.

INTRODUCTION

Propofol is the most widely used intravenous (IV) anaesthetic agent for induction and maintenance of anaesthesia as well as for sedation inside and outside operation theatre. Propofol is an ideal IV anaesthetic agent. When propofol is used without any intervention to reduce the pain, the incidence of pain is approximately 70%. This is a major disadvantage of the use of propofol.[1] Several interventions have been applied to prevent this pain, with variable success. These include physical methods such as venous occlusion, changing speed of propofol injection, changing temperature of propofol, pre-administration of opioids, ondansetron, metoclopromide, ketamine, and several other agents, and venous occlusion. The administration of lignocaine is the most frequently used method to reduce pain. It is administered before propofol injection, or added to the propofol emulsion as a mixture. This can be done with or without a tourniquet.[2]

Lignocaine added to or given before injection of propofol is widely employed, although protection is not complete, with a failure rate of between 13% and 44%.[1] Cooling the propofol to 4°C reduces its injection pain possibly by delaying the activation of enzymatic cascade of pain mediators.[3] Injecting into a large forearm vein also reduces the pain, probably by reducing contact between drug and endothelium. Diluting propofol with intralipid and the application of eutectic mixture of local anaesthetic cream to the skin before venepuncture have also been reported to reduce the incidence of propofol injection pain.[4] Metoclopromide has been shown to be as effective as lignocaine in reducing propofol injection pain. Opioids may also reduce the incidence of pain, and alfentanil has shown to reduce the incidence of pain following propofol injection from 84% to 36%.[5] Pre-treatment with some IV induction agents like ketamine, thiopentone and even propofol itself in sub-anaesthetic doses have shown some promise in reducing the incidence and severity of propofol injection pain but not with ketamine pre-mixed with propofol.

Efficacy of various drugs such as lignocaine, tramadol, ketorolac and ketoprofen have been compared in reducing the propofol-induced pain.[6] Each of these methods has its own

advantages and disadvantages. We have also to keep in mind various side effects of drugs while using these methods, also combinations of various drugs may lead to untoward reactions which can be fatal to the patients. Combination of several interventions have been only partially successful, leaving a large number of patients with unmitigated pain. The primary objective of the present study was to compare the efficacy of lidocaine, ketamine and combination of lidocaine and ketamine in reduction of pain of propofol injection whereas secondary objectives were to compare incidence of psycho mimetic reactions, and untoward side effects.

MATERIAL AND METHODS

This prospective, double-blind randomised controlled study was conducted between April 2016 and October 2017. After approval from the scientific advisory committee and institutional ethics committee, written informed consent was obtained from all the patients. Patients aged 18 to 60 years of either sex scheduled to undergo elective surgeries under general anaesthesia, belonging to American Society of Anaesthesiologist (ASA) grade I and II were included. Pregnant or lactating women, patients with severe diabetes (HB1Ac >8%), psychiatric or neurological problems likely to affect communication, and patients with severe kidney or liver disease, patients using regular analgesic medication for chronic pain and patients who underwent emergency surgeries were excluded from this study.

Out of 100 patients assessed for eligibility, after exclusion 90 patients were randomly divided into three equal groups of 30 each, using computer generated randomization code. We used sealed envelope for randomization with block size four. Group L patients received 40 mg of Inj. lidocaine, Group K patients received Inj. ketamine 10 mg, whereas Group LK received Inj. lidocaine 40 mg mixed with Inj. ketamine 10 mg. with venous occlusion. The randomization code was provided to operation theater nurse who prepared the study medication by adding normal saline to above mentioned medication in 5 mL volume in identical syringes and put them into concealed envelopes according to the allocation orders. This was done under the supervision of a senior anaesthesiologist. Researcher and patients were blind as to their group assignment.

Pre anaesthesia check-up was done one day prior to surgery. The patients were evaluated for any systemic diseases and laboratory investigations were recorded. Lignocaine sensitivity test was done preoperatively. Details of the procedure were explained to the patients. The patients were educated about 4-point verbal rating scale (VRS).[7]

In the operation theatre, adequate IV access was confirmed. Standard monitors were attached. Non-invasive blood pressure, pulse-oximeter, electrocardiogram, and end tidal CO_2 (ET CO_2) were monitored after intubation. A 20 G angio-catheter was placed in a vein on the dorsum of the hand and ringer lactate infusion was started. Before anaesthetic induction, the blood pressure and heart rate was measured to find the baseline values. Ondansetron 4 mg and fentanyl 100 µg was given. Then with an elastic tourniquet placed on the forearm without prior exsanguination, the veins were occluded, and the test medication was administered.

Sixty seconds later, the tourniquet was released and 20% dose of propofol was given over 10 seconds. Patients were asked to report any discomfort and the pain score was recorded as per 4-point VRS before patient lost consciousness. After recording the scale remaining dose of the propofol was given. After the patient fell asleep, suxamethonium 2 mg/kg was given and patient intubated with appropriate sized cuffed oral endotracheal tube (ETT). ETT placement was confirmed.

Before induction of anaesthesia, all patients were given IV glycopyrrolate 0.2 mg, IV ondensetron 4 mg, and IV ranitidine 50 mg. In all patients, anaesthesia was induced with IV fentanyl 2 µg / kg, IV propofol 2-2.5 mg / kg followed by IV atracurium 0.5 mg / kg. Orogastric tube was placed for deflating the stomach. This was removed at the end of surgery.

Anaesthesia was maintained with a total one litre of gas in equal air and O_2 ratio and sevoflurane 1.0% - 2.5% with controlled ventilation. ET CO_2 was maintained between 30 and 35 mm Hg. Inj. atracurium loading dose of 0.5 mg/kg was given and then in supplemental doses of 0.1 mg/kg was used. Heart rate, mean arterial blood pressure, ECG, SpO2, ET CO_2 concentration were monitored.

When the patient's spontaneous respiratory efforts appeared, muscle relaxation was reversed with IV neostigmine 50 µg / kg and IV glycopyrolate 0.004 mgm / kg. Each patient was further observed for 15 minutes and shifted to the post-anesthesia care unit (PACU). During recovery, patients were observed for any psycho mimetic reactions, untoward side effects and were asked about dreaming or hallucinations 6-8 hours later.

On the basis of a previously published study,[8] a sample size of 28 patients in each group was calculated by a formula[9] with 80% power and 5% probability of Type I error to reject null hypothesis. We included 30 patients in each group.

Data collected were entered in Excel 2007 and analysis of data was done using Statistical Package for Social Sciences (SPSS) version 20, IBM, USA. The comparison of quantitative variables between the groups such as mean age, mean weight, mean heart rate, mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP) was done using analysis of variance (ANOVA). Comparison of qualitative variables such as gender, ASA grade, VRS, incidence of psycho mimetic reactions, and incidence of untoward side effects was done by using chi-square test or Fisher's exact test. The confidence limit for significance was fixed at 95% level with p-value < 0.05.

RESULTS

Out of 100 patients assessed for eligibility, 10 were excluded because of severe diabetes mellitus (5), patients using regular analgesic medication for chronic pain (3), refused to participate (2). Ninety patients were randomly allotted into 3 groups. In all, data for 90 patients (30 patients in each group) were analyzed and compared.

As shown in table 1, all the three groups were comparable with respect to mean age, sex distribution, mean weight, and ASA physical status. As depicted in table 2, mean heart rate, mean SBP, and mean DBP were comparable in all the three groups. The percentage of patients whose VRS was 0 was significantly higher in group LK (25/ 30 – 83.3%) compared to group K (15/ 30- 50.0%) and Group L (20/30- 66.7%) with p value 0.009. There was no incidence of psycho mimetic reactions, and untoward side effects in all the three groups.

Table 1: Demographic profile.

Demographic characteristic	Group L (N = 30)	Group K (N = 30)	Group LK (N = 30)	p value
Mean age in years (SD)	40.3 (± 12.4)	40.5 (± 13.1)	41.3 (± 12.9)	0.999
Gender, no (%) Male Female	 13 (43.3) 17 (56.7)	 15 (50.0) 15 (50.0)	 17 (56.7) 13 (43.3)	0.999
Mean weight in kg (SD)	63.5 (± 10.8)	66.2 (± 11.5)	64.2 (± 11.4)	0.999
ASA Grade (%) I II	 22(73.3) 8(26.7)	 24(80.0) 6(20.0)	 24(80.0) 6(20.0)	0.999

Table 2: Comparison of outcome variables.

	Group L (N = 30)	Group K (N = 30)	Group LK (N = 30)	p value
VRS (%) 0 1 2 3	 20 (66.7) 5 (16.7) 5 (16.7) 0 (0.0)	 15 (50.0) 4 (13.3) 9 (30.0) 2 (6.7)	 25 (83.3) 5 (16.7) 0(0.0) 0(0.0)	0.009
Mean heart rate per minute (SD)	81.6 (± 8.5)	81.4 (± 8.2)	77.1 (± 5.9)	0.017
Mean SBP in mm of Hg (SD)	128.1 (± 6.1)	129.3 (± 7.0)	127.8 (± 8.5)	0.999
Mean DBP in mm of Hg (SD)	78.4 (± 5.9)	79.1 (± 5.0)	79.4 (± 5.6)	0.999
Incidence of psychomimetic reactions (%) Yes No	 0(0.0) 30(100.0)	 0(0.0) 30(100.0))	 0(0.0) 30(100.0)	0.999
Incidence of untoward side effects (%) Yes No	 0(0.0) 30(100.0)	 0(0.0) 30(100.0))	 0(0.0) 30(100.0)	0.999

DISCUSSION

In the present study percentage of patients whose VRS was 0 was significantly higher in group LK compared to group K and Group L. Hwang I et al., reported that the incidence and severity of pain was significantly lower in lidocaine and ketamine (LK) group than lodocaine (L) group or ketamine (K) group at 10 seconds after the injection of microemulsion propofol 30 mg ($P < 0.05$). They further stated that the incidence and severity of pain was significantly lower in Group LK and Group K than Group L when remaining dose of propofol was given.($P < 0.05$). They stated that pre-treatment with IV lidocaine 40 mg plus ketamine 25 mg with a rubber tourniquet on the forearm 1 minute before the injection of micro emulsion propofol is more effective than lidocaine 40 mg or ketamine 25 mg alone in preventing pain from the injection of micro emulsion propofol.[8] Jalota L et al. reported in a systematic review and meta-analysis that the use of the antecubital vein, or pre-treatment using lidocaine in conjunction with venous occlusion were the two most efficacious interventions to reduce pain of injection of propofol when the hand vein was chosen.[10] The findings of our study are similar to the above studies.

Fujii Y and Nakayama M reported that for pain control during propofol injection combined lignocaine 20 mg and ketamine 5 mg, with manual venous occlusion was more effective than lignocaine 20 mg alone.[11] In a study conducted by Sethi N et al. propofol was premixed with normal saline in Group A, and in Group B propofol was premixed with 20 mg lignocaine. In Group A, the incidence of pain was 63% as compared to 15% in Group B ($X^2 = 48.242$, $p < 0.001$).[12] Euasobhon P et al performed meta-analysis. They reported that the overall incidence of pain and high-intensity pain following propofol injection in the control group were 64% (95% CI 60% to 67.9%) and 38.1% (95% CI 33.4% to 43.1%), respectively while those in the lidocaine group were 30.2% (95% CI 26.7% to 33.7%) and 11.8% (95% CI 9.7% to 13.8%). They further stated that for reduction of pain on propofol injection, lidocaine admixture and pre-treatment were both effective (lidocaine admixture OR 0.19, 95% CI 0.15 to 0.25, 31 studies, 4927 participants, high-quality evidence). They opined that both lidocaine admixture and pre-treatment were effective in reducing pain on propofol injection as per the currently available data from randomized controlled trials.[13]

There are some limitations of the present research. The duration of study was very short and there are chances that psycho mimetic effects may occur later in the postoperative recovery period. Hence, a longer duration of patient observation in the PACU should be done. The VRS requires more concentration and coordination on the part of the patient, and may be prone to some error in the immediate post-propofol injection period. Other pain assessments scales might give more precision.

CONCLUSION

Lignocaine and ketamine in combination significantly reduced pain of propofol injection with no untoward side effects as compared to lignocaine or ketamine alone.

REFERENCES

1. Picard P, Tramèr MR. Prevention of pain on injection with propofol: A quantitative systematic review. Anesthesia & Analgesia, 2000; 90: 963-9.
2. Gehan G, Karoubi P, Quinet F, Leroy A, Rathat C, Pourriat JL. Optimal dose of lignocaine for preventing pain on injection of propofol. British Journal of A naesthesia, 1991; 66: 324–6.
3. McCrirrick A, Hunter S. Pain on injection of propofol: the effect of injectate temperature. Anaesthesia, 1990; 45: 443-4.

4. Stokes DN, Robson N, Hutton P. Effect of diluting propofol on the incidence of pain on injection and venous sequelae. British Journal of Anaesthesia, 1989; 62: 202-3.
5. Fletcher JE, Seavell CR, Bowen DJ. Pretreatment with alfentanil reduces pain caused by propofol. British Journal of Anaesthesia, 1994; 72: 342-4.
6. Sumalatha GB, Dodawad RR, Pandarpurkar S, Jajee PR. A comparative study of attenuation of propofol-induced pain by lignocaine, ondansetron, and ramosetron Indian Journal of Anaesthesi, 2016; 60: 25–29.
7. Jensen MP, Turner JA, Romano JM. What is the maximum number of levels needed in pain intensity measurement? Pain., 1994; 58: 387–92.
8. Hwang I, Noh JI, Kim SI, Kim MG, Park SY, Kim SH et al. Prevention of pain with the injection of microemulsion propofol: a comparison of a combination of lidocaine and ketamine with lidocaine or ketamine alone. Korean journal of anesthesiology, 2010; 59: 233-7.
9. Harvey Motulsky. Intuitive Biostatistics. New York: Oxford University Press, 1995.
10. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O et al. Prevention of pain on injection of propofol: systematic review and meta-analysis. British Medical Journal, 2011; 342: d1110.
11. Fujii Y, Nakayama M. Efficacy of Lignocaine plus Ketamine at Different Doses in the Prevention of Pain Due to Propofol Injection. Clinical Drug Investigation, 2005; 25: 537-42.
12. Sethi N, Jayaraman L, Sethi M, Sharma S, Sood J. Prevention of propofol pain: a comparative study. Middle East Journal of Anaesthesiology, 2009; 20: 71-4.
13. Euasobhon P, Dej-Arkom S, Siriussawakul A, Muangman S, Sriraj W, Pattanittum P, et al. Lidocaine for reducing propofol-induced pain on induction of anaesthesia in adults**.** The Cochrane Database of Systematic Reviews, 2016 18; 2: CD007874.