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RESEARCH ARTICLE

Effect of small-dose ketamine in the prevention of pain on propofol injection: A prospective randomized controlled study

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ABSTRACT

Background: Propofol is a commonly used intravenous anesthetic agent that produces pain when used for induction. In this study, small doses of ketamine are being used in comparison with lignocaine and placebo for alleviating pain on propofol injection. **Aims and Objectives:** The aim is to assess the effect of ketamine to prevent the pain on injection of propofol and to establish an optimal dose for this purpose. **Materials and Methods:** We conducted a prospective randomized double-blinded study (placebo controlled) in 160 patients belonging to the American Society of Anaesthesiologists grade 1 and 2 who were posted for elective surgeries to be done under general anesthesia. They were allocated randomly into five groups. Patients were administered normal saline (NS) (Group NS), lignocaine 1.5 mg/kg (Group LA), ketamine 0.1 mg/kg (Group KT1), ketamine 0.3 mg/kg (Group KT2), and ketamine 0.5 mg/kg (Group KT3) just before injection of 1% propofol in a dose of 2.5 mg/kg. Pain scores of patients were assessed at intervals of 10 s by an anesthesiologist who was blinded to the test drug. Efficacy of the pretreatment drug was assessed based on pain score and the occurrence of pain. **Results:** The occurrence and intensity of pain were significantly higher in the placebo group (Group NS) compared to other study groups. The occurrence of pain and pain scores were lower in the KT2 and KT3 groups compared with the KT1 and lignocaine groups. **Conclusion:** This study concluded that ketamine administration in a dose of 0.3 mg/kg before propofol injection is beneficial and safe in preventing pain caused by injection of propofol.

KEY WORDS: Ketamine; Lignocaine; Propofol; Pain; Pain Score

INTRODUCTION

Propofol is a commonly used intravenous anesthetic agent for induction in daycare surgeries, short procedures and when a laryngeal mask airway is to be used. It is known for rapid recovery and good quality of anesthesia. The most common problem encountered with its use is discomfort or pain during injection. Pain because of propofol injection has been ranked by anesthesiologists as seventh out of 33 clinical problems as per the findings of Macario *et al.*[1] considering the clinical importance and frequency. The prime factor responsible for the reduced acceptability of this very useful induction agent is the pain during injection which causes distress to the patients. It has been reported that incidence of pain during injection of propofol ranges between 28 and 90%[2,3] in adults and 28 and 85%[4,5] in children. To increase the acceptability and to reduce the pain, various measures have been tried of which administration of lignocaine intravenously is the most common method.

Ketamine is an anesthetic agent producing dissociative anesthesia in clinical doses of 1–2 mg/kg. It is known for its

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potent analgesic and local anesthetic properties.[6,7] It can be beneficial in reducing the pain due to injection of propofol when administered in subanesthetic doses attributed to its local anesthetic property.[8,9]

In this study, we compared the efficacy of low doses of ketamine with lignocaine and placebo for alleviating the pain caused due to propofol injection. This study was also done to find out the optimal intravenous dose of ketamine for this purpose.

MATERIALS AND METHODS

Study Design

This was a prospective placebo controlled randomized double-blinded study done at a tertiary care teaching hospital over 12 months. This study was initiated after obtaining clearance from the Institutional Review Board and Ethics Committee. The study population included patients between 20 and 60 years of age belonging to the American Society of Anesthesiologists (ASA) grade 1 and 2 scheduled for elective surgeries requiring general anesthesia. Patients with any history of heart disease, history of cardiovascular disease, epilepsy, and conditions with raised intracranial pressure, history of allergy to propofol, ketamine, or lignocaine, weighing <40 kg, with anticipated difficult venous access, and pregnant women were excluded from participating in the study.

Study Procedure

Patients were recruited for study after satisfying the eligibility criteria and after obtaining written informed consent. An elaborate pre-anesthetic checkup was done in all the study participants. The initial heart rate, blood pressure, and weight of all patients were noted. A computer-generated table of random numbers was used to divide the patients randomly into five groups of 32 each: Group NS – patients receiving normal saline (NS) 3 ml, Group LA – patients receiving lignocaine 1.5 mg/kg, Group KT1 – patients receiving ketamine 0.1 mg/kg, Group KT2 – patients receiving ketamine 0.3 mg/kg, and Group KT3 – patients receiving ketamine 0.5 mg/kg.

All patients were visited the evening before surgery and the whole procedure was explained. They were instructed to rate any pain sensation every 10 s while administering propofol before surgery. They were kept nil orally for 6 h before surgery. They received tablet Diazepam 0.2 mg/kg body weight, tablet Pantoprazole 40 mg the night before surgery, and morphine 0.1 mg/kg, promethazine 12.5 mg, and glycopyrrolate 0.2 mg intramuscular 45 min before surgery as per institutional protocol. The anesthesia machine and circuit checked, laryngoscope blades of different sizes checked and kept ready, working suction checked, various sizes of facemasks, oropharyngeal and nasopharyngeal airways, and stylets kept ready. All emergency drugs were kept ready.

When patients arrived in the reception area, they were reassured again. On the dorsum of hand, intravenous line was secured with 18 G cannula on a large vein 15 min before anesthetic induction and an intravenous fluid Ringer lactate solution was administered to the patient. The patients were transferred to the operation theatre. Monitors were attached and baseline parameters were measured. The solutions of drugs were prepared in identical plastic syringes 10 min before induction by a doctor who is not related to the study and labels were hidden to make sure that the doctor who recorded the patient response was blinded to the test drug. The patients were pre-oxygenated with 100% oxygen for 3 min using the anatomical facemask and closed circuit. The respective test drug was administered over 5 s followed immediately by injection of 1% solution of propofol in a dose of 2.5 mg/kg slowly over 30 s through a three-way tap keeping the IV infusion line closed. Ringer lactate was administered at maximal flow afterwards.

Before propofol injection, every patient was asked by an anesthesiologist, who was unaware of the test drug being administered to immediately rate any pain sensation every 10 s during injection, using a 0–3 verbal rating scale (VRS) suggested by McCrirrick and Hunter.[2] Pain scores during 0–10, 11–20, and 21–30s were noted and recorded.

The grading criteria of VRS were as follows:

- 0 – No perception of pain (negative report when asked).
- 1 – Mild pain or soreness (no behavioral signs and pain reported only on enquiry).
- 2 – Moderate pain (pain reported without enquiry or pain reported on enquiry + a behavioral sign).
- 3 – Severe pain (strong vocal response or response along with tears, arm withdrawal, or facial grimacing).

Once the patient became unconscious after propofol injection, vecuronium 0.12 mg/kg was given to aid endotracheal intubation. Intermittent positive pressure ventilation was given using 6 L/min oxygen with isoflurane 1.5–2% by facemask. After 3 min of vecuronium injection, direct laryngoscopy and endotracheal intubation was done. After intubation, maintenance of anesthesia was done using nitrous oxide-oxygen in 2:1 ratio and isoflurane 0.5 volume% using Datex-Ohmeda S5 Avance anesthesia workstation. The surgical procedure started after intubation. Fentanyl 2 mcg/kg was given for analgesia.

Vital signs were noted initially, before administration of the test drug and just before intubation. Peripheral oxygen saturation was also recorded. The patients were monitored during the procedure with peripheral nerve stimulator and top up doses of vecuronium supplemented based on train of four response. After surgery, reversal of the neuromuscular blockade was done using intravenous neostigmine 0.05 mg/kg body weight along with glycopyrrolate 0.01 mg/kg body weight. Patients were extubated on table after the reversal was complete.

Postoperatively, all patients were monitored in the post-operative ward. Patients were observed for any behavioral abnormalities such as presence of any delirium, illusions, or hallucinations which were reported at the earliest.

Statistical Analysis

Sample size calculation was done and a group size of 32 was adequate to achieve a study power of 90% with 5% Type 1 error. Data were expressed as mean ± standard deviation. Comparison between groups was done using Chi-square test and analysis of variance. Mann–Whitney U-test was done for comparing the pain score in between the groups. $P < 0.05$ was considered as statistically significant.

RESULTS

This study was performed in a total of 160 patients (ASA 1 and 2) posted for elective surgeries requiring general anesthesia. Patients were randomly distributed into five groups. Patients were administered NS (Group NS), lignocaine 1.5 mg/kg (Group LA), ketamine 0.1 mg/kg (Group KT1), ketamine 0.3 mg/kg (Group KT2), and ketamine 0.5 mg/kg (Group KT3) just before injection of 2.5 mg/kg of 1% propofol.

The mean age of patients in our study population was 41.14 years and majority of them were females (67.5%). The age and gender distribution were similar in all study groups.

Comparison of Pain Score at 1–10 s

At 1–10 s, the incidence of pain in the patients who received saline (NS) was 100%, 78.2% in the patients who received lignocaine (LA) group, 81.3% in the ketamine 0.1 mg/kg (KT1) group, 31.2% in the ketamine 0.3 mg/kg (KT2) group, and 28.1% in the ketamine 0.5 mg/kg (KT3) group. Statistically significant differences were noted between LA group and KT2 group, LA group and KT3 group, KT1 and KT2 groups, and KT1 and KT3 groups. There was no statistically significant difference between LA and KT1 groups and KT2 and KT3 groups. None of the patients in the LA, KT1, KT2, and KT3 groups experienced severe pain. In the KT3 group, none of the patients had even moderate pain while in KT2 group, 1 patient (3.1%) experienced moderate pain, but the difference is statistically insignificant [Table 1].

Comparison of Pain Score at 11–20 s

At 11–20 s, the incidence of pain in patients in the NS group was 100%, 90.6% in the LA group, 81.2% in the KT1 group, 46.9% in the KT2 group, and 25% in the KT3 group. On statistical analysis, significant differences were seen between LA and KT2 groups, LA and KT3 groups, KT1 and KT2 groups, and KT1 and KT3 groups. Differences in pain scores between LA and KT1 and KT2 and KT3 groups were statistically insignificant. No patients in lignocaine, KT1, KT2, and KT3 groups experienced severe pain. Only 1 patient (3.1%) each in lignocaine and KT1 groups and no patient in KT2 and KT3 groups experienced even moderate pain [Table 2].

Comparison of Pain Score at 21–30 s

At 21–30 s, the overall incidence of pain was less than at 1–10 s and 11–20 s in the four test groups and in the control group (NS), it was 100%. The incidence of pain was found to be 21.9% in the lignocaine group and 15.6% in the KT1 group. None of the patients in KT3 group (9.4%) experienced any pain at 21–30 s. Statistically significant differences were noted between lignocaine and KT2 and lignocaine and KT3

Table 1: Comparison of pain score at 1–10 s

Pain	Group				
	NS	LA	KT1	KT2	KT3
Nil	0 (0)	7 (21.9)	6 (18.8)	22 (68.8)	23 (71.9)
Mild	0 (0)	14 (43.8)	15 (46.9)	9 (28.1)	9 (28.1)
Moderate	13 (40.6)	11 (34.4)	11 (34.4)	1 (3.1)	0 (0)
Severe	19 (59.4)	0 (0)	0 (0)	0 (0)	0 (0)

χ^2=97.77, P<0.01 (Kruskal–Wallis test); between LA and KT1, P>0.05 (Mann–Whitney U-test); between LA and KT2, P<0.01 (Mann–Whitney U-test); between LA and KT3, P<0.01 (Mann–Whitney U-test); between KT1 and KT2, P<0.01 (Mann–Whitney U-test); between KT1 and KT3, P<0.01 (Mann–Whitney U-test); between KT2 and KT3, P>0.05 (Mann–Whitney U-test)

Table 2: Comparison of pain score at 11–20 s

Pain	Group				
	NS	LA	KT1	KT2	KT3
Nil	0 (0)	3 (9.4)	6 (18.8)	17 (53.1)	24 (75)
Mild	0 (0)	28 (87.5)	25 (78.1)	15 (46.9)	8 (25)
Moderate	18 (56.3)	1 (3.1)	1 (3.1)	0 (0)	0 (0)
Severe	14 (43.8)	0 (0)	0 (0)	0 (0)	0 (0)

χ^2=108.05, P<0.01 (Kruskal–Wallis test); between LA and KT1, P>0.05 (Mann–Whitney U-test); between LA and KT2, P<0.01 (Mann–Whitney U-test); between LA and KT3, P<0.01 (Mann–Whitney U-test); between KT1 and KT2, P<0.01 (Mann–Whitney U-test); between KT1 and KT3, P<0.01 (Mann–Whitney U-test); between KT2 and KT3, P>0.05 (Mann–Whitney U-test)

Table 3: Comparison of pain score at 21–30 s

Pain score	Group				
	NS	LA	KT1	KT2	KT3
Nil	0 (0)	25 (78.1)	27 (84.4)	32 (100)	32 (100)
Mild	7 (21.9)	7 (21.9)	5 (15.6)	0 (0)	0 (0)
Moderate	19 (59.4)	0 (0)	0 (0)	0 (0)	0 (0)
Severe	6 (18.8)	0 (0)	0 (0)	0 (0)	0 (0)

χ^2=123.05, P<0.01 (Kruskal–Wallis test); between LA and KT1, P>0.05 (Mann–Whitney U-test); between LA and KT2, P<0.01 (Mann–Whitney U-test); between LA and KT3, P<0.01 (Mann–Whitney U-test); between KT1 and KT2, P<0.05 (Mann–Whitney U-test); between KT1 and KT3, P<0.05 (Mann–Whitney U-test); between KT2 and KT3, P>0.05 (Mann–Whitney U-test)

groups ($P < 0.01$) and also between KTI and KT2 and KT1 and KT3 groups ($P < 0.05$) [Table 3].

Abnormal Behavioral Response

Postoperatively, all patients were monitored for emergence problems. Two patients (6.3%) in the KT2 group and three patients in the KT3 group (9.4%) exhibited abnormal behavioral response. There was no statistically significant difference noted between the groups. No active interventions were required for emergence reactions [Figure 1].

DISCUSSION

In this study, five groups of patients with 32 patients in each group scheduled for elective surgeries requiring general anesthesia were studied at a tertiary care teaching hospital over a period of 12 months. Patients received NS (Group NS), lignocaine 1.5 mg/kg (Group LA), ketamine 0.1 mg/kg (Group KT1), ketamine 0.3 mg/kg (Group KT2), and ketamine 0.5 mg/kg (Group KT3), just before the injection of propofol in a dose of 2.5 mg/kg. The age and sex distribution were similar in five study groups with no statistically significant difference.

The best method to measure pain is by verbal response or using the visual analogue scale (VAS). The VAS is found to be sensitive to minute changes in effect over time when compared to categorical measures.[10] In this study, 4-point VRS (published by McCrirrick and Hunter)[2] was used. The 4-point VRS was simple for patient use. For VAS, appropriate hand-eye coordination which is required might not be present in all patients while the state of consciousness rapidly changes during anesthetic induction. Injection of propofol with placebo caused pain in 100% of patients, with severe pain in 59.4% of patients at 1–10 s, 43.8% of patients in 11–20 s, and 18.8% of patients at 21–30 s. Pain on injection of propofol was reported to vary between 28 and 90%[2,3] in adults, but in this study, the incidence was higher (100%). Injection of propofol with lignocaine 1.5 mg/kg pretreatment caused pain in 78.2% of patients at 1–10 s, 90.6% of patients at 11–20 s, and 21.9% of patients at 21–30 s. The use of intravenous lignocaine either as a bolus dose or by mixing it with propofol was commonly used, but the failure rate is high.

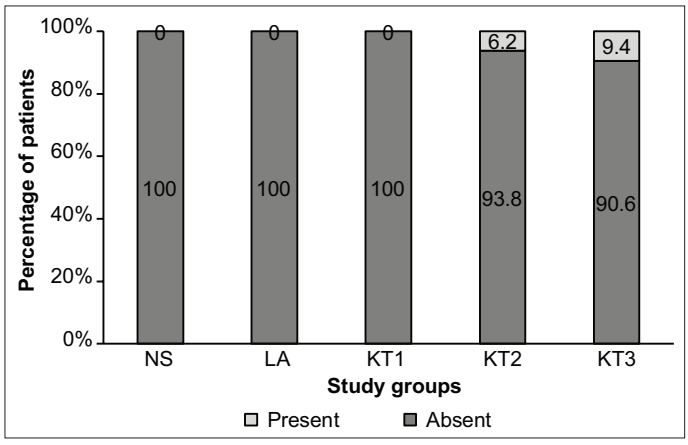

Figure 1: Percentage distribution of groups according to abnormal behavioral response

This study was done to assess the efficacy of low dose of ketamine (0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg) in prevention of pain produced by injection of propofol. Drug was injected just before injection of propofol to avoid the bias if sedation was caused by ketamine. In our study, with 0.1 mg/kg ketamine, the incidence of pain was 81.3%; with 0.3 mg/kg ketamine, the incidence of pain was 31.2%; and with 0.5 mg/kg ketamine, the incidence of pain was 28.1%. In this study, ketamine was administered just before the injection of propofol which eliminated even the possibility of immediate pain on injection. Statistically significant difference in pain scores were noted between lignocaine and KT2, LA and KT3, KT1, KT2, and KT1 and KT3 groups at 1–10 s,11–20 s, and 21–30 s. Difference in pain scores between LA and KT1 and KT2 and KT3 groups was statistically insignificant ($P > 0.05$). None of the patients in LA, KT1, KT2, KT3 groups experienced severe pain which shows that all these drugs and their respective doses decrease injection pain due to propofol. Patients receiving 0.3 mg/kg and 0.5 mg/kg ketamine did not even complain of moderate pain except one patient in KT2 group at 1–10 s, but it was statistically insignificant. From the comparison of pain scores, it was clear that the reduction in pain on propofol injection in those patients receiving ketamine in doses of 0.3 mg/kg and 0.5 mg/kg is much better than those patients receiving LA and ketamine 0.1 mg/kg. It is also clear that no statistically significant difference in pain scores exists between patients receiving ketamine 0.1 mg/kg and LA. Postoperatively, all patients were monitored for emergence problems. There was no statistically significant difference between the groups with respect to emergence problems.

The incidence of pain with lignocaine in our study was higher than that in the previous studies.[10-12] The effect of ketamine pretreatment on propofol injection pain was studied in 1998 by Tan *et al*. and they found that the incidence of pain was decreased from 84% to 26%.[13] In 2003, a study was done by Barbi *et al*. to see if pretreatment with ketamine would reduce infusion line pain with propofol in 122 children undergoing gastroscopy and they found that the incidence of propofol infusion pain was significantly reduced in patients pretreated with ketamine (80% vs. 37%, $P = 0.0001$). They finally concluded that pre-treatment with ketamine 0.5 mg/kg was very effective in preventing propofol infusion pain.[14] In a study done by Koo *et al*.,[15] in 2006, small dose of ketamine was used to decrease the pain on injection of propofol and they reached at a conclusion that ketamine 0.1 mg/kg just before propofol injection was the optimal dose and timing

to reduce propofol injection pain. No statistically significant differences were found between the pain scores in patients receiving lignocaine and ketamine 0.1 mg/kg similar to our study. Results of this study are comparable with the previous studies. Bano *et al*.[16] stated that pre-treatment with ketamine 0.5 mg/kg after using a rubber tourniquet just 1 min before propofol administration decreased injection pain without causing hemodynamic changes. In our study, a tourniquet had not been used.

Our study showed that ketamine 0.1 mg/kg is not more effective than lignocaine in reducing pain on propofol injection. Administration of ketamine in 0.3 mg/kg and 0.5 mg/kg doses immediately before propofol injection is effective in relieving pain on propofol injection. Administration of 0.3 mg/kg ketamine just before propofol injection is a reliable and effective method in the prevention of pain on injection of propofol. A 0.3 mg/kg is the ideal dose of ketamine pretreatment for prevention of injection pain due to propofol and is not associated with adverse outcomes.

CONCLUSION

This study concluded that ketamine administration in a dose of 0.3 mg/kg before propofol injection is beneficial and safe in preventing pain caused by injection of propofol.

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