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To Compare the Efficacy of Intravenous Ketamine Versus Preservative Free Lidocaine in Alleviating Propofol Injection Site Pain – A Double Blinded Randomised Control Study

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ABSTRACT

Background: Propofol is a widely used intravenous anaesthetic that is known to cause distressing local pain at the site of injection. Several methods to attenuate this pain with varying efficacy have been described. Ketamine and Lidocaine pretreatment is one of the methods proposed to reduce Propofol injection pain due to its local anaesthetic properties.
The present study is conducted to determine the effectiveness of IV Ketamine 10mg in comparison with 21.3mg of preservative free 2% IV Lidocaine pretreatment on the incidence and severity of pain on Propofol injection.
Primary Objective: To grade the injection pain at the local site during Propofol injection for induction of general anesthesia.
Secondary Objective
1.Haemodynamic changes after injection of study drug
2.Effect on attenuation of intubation response after injection of study drug, if any.
3.Adverse events during the intraoperative period after the injection of study drug.
Study Design: Prospective, randomized, double-blind study.
Materials and Methods: After ethical committee approval 120 patients fulfilling inclusion criteria were randomized into two groups of 60 each. After obtaining informed written consent and after applying standard tourniquet, Group I received Inj Ketamine 10mg IV and Group II received Inj preservative free Lidocaine 2% 21.3mg IV. Sixty seconds after receiving pretreatment drug, tourniquet was released and 25% of precalculated dose of Inj Propofol IV was given. Each patient's pain scores was measured at five seconds interval by a blinded anaesthesiologist.
Statistical Analysis: The data was analysed using Independent t test and Chi square test.
Result: Two clinically and demographically similar groups of 60 (Ketamine = Lidocaine = 60) patients were studied. In the Ketamine group, 93.3% of patients experienced no pain during Propofol injection compared to 80% in the Lidocaine group. Mild pain was reported by 6.7% of patients in the Ketamine group, and none experienced moderate pain. In contrast, in the Lidocaine group, 11.7% of patients experienced mild pain and 8.3% experienced moderate pain. The difference in pain perception between the two groups was statistically significant ($p = 0.04$). However, there was no statistically significant difference between the groups with respect to haemodynamic parameters and intubation response.
Conclusion: Pre-treatment with 10mg Ketamine significantly reduces the incidence of Propofol injection pain when compared to 1ml 2% preservative free Lidocaine.

Keywords*: Propofol injection pain, preservative-free Lidocaine pretreatment, Ketamine pretreatment, venous occlusion.*

INTRODUCTION

Propofol, a substituted isopropyl phenol (2,6-diisopropylphenol), is widely employed as an inducing agent in contemporary surgical procedures due to its quick onset of action, quick recovery of awareness, and low residual CNS effects. It has fewer adverse effects and is wellknown for its antiemetic, sedative-hypnotic, antipruritic, and anticonvulsant qualities[1].

By directly irritating the vascular endothelium, Propofol causes pain at the injection site. This triggers the release of mediators like kininogen from the kinin cascade, which activates nociceptive receptors at the free nerve terminals between the intima and media layers of the venous wall. Pain is characterised as being incredibly sharp, agonising, or scorching. Adults experience pain at rates ranging from 28% to 90%. When injected, it can induce varying degrees of discomfort[1].

Ketamine is a drug with analgesic effects used commonly in the induction of anaesthesia. It is a N-methyl D-aspartate receptor antagonist with strong analgesic effects even at lower concentrations. The local anaesthetic effects of Ketamine are produced by antagonism at the NMDA receptors which have been found in the vessel wall endothelium by voltage sensitive sodium channel interactions. Hence, Ketamine given as pretreatment could act as a preemptive analgesic preventing sensitization of the local nerve endings by noxious inputs[2].

Lidocaine is a drug with analgesic effects used commonly as a local anesthetic agent. It prevents transmission of nerve impulses by inhibiting passage of sodium ions through ion selective sodium channels in nerve membranes. Hence, Lidocaine given as pretreatment could act as a preemptive analgesic preventing sensitization of local nerve endings by noxious inputs[3].

The present study is conducted to determine the effectiveness of pretreatment with IV Ketamine 10mg in comparison with 1ml of preservative free 2% IV Lidocaine on the incidence and severity of pain on Propofol injection.

MATERIALS AND METHODS

Patients meeting inclusion criteria were included in the study after detailed explanation of technique of procedure. Written informed consent was taken. Standard NPO guidelines were followed. Intravenous access was secured with 18G cannula on the dorsum of the hand, Inj Pantaprazole 40 mg IV was given on the morning of surgery and baseline vitals were recorded. Intra-operatively, all the standard monitors (NIBP, ECG leads, SPO2 probe, EtCo2) were connected and monitored. Patients were allocated to each of the two groups using Systemic Random Sampling technique which include:
GROUP I - Pretreatment with 10mg of Ketamine
GROUP II - Pretreatment with 1ml of preservative free 2% Lidocaine.

Prior to induction of anaesthesia, premedication was given Inj Glycopyrrolate 0.2mg IV, Inj Midazolam 1mg IV, Inj Fentanyl 2mcg/kg IV. The primary anaesthesiologist inducing the case was efficiently blinded. Venous occlusion was performed with a standard tourniquet placed on the forearm 10 cm distal to elbow joint after elevating the arm for 30 seconds for gravity drainage of venous blood.

Patients in GROUP I received a pretreatment bolus with 10mg Ketamine and GROUP II received pretreatment bolus with 1ml of preservative free 2% Lidocaine. Sixty seconds after pretreatment bolus, venous occlusion was released and both group received Inj Propofol 2mg/kg precalculated dose. All drugs were injected at the rate of 1ml/s. The study drugs were prepared by secondary anaesthesiologist not involved in the observation. After injection of 25% of the calculated dose of Propofol, patients were asked to grade the pain as per

McCrirrick and Hunter scale (4 point verbal pain scale) by the primary anaesthesiologist.

After assessment of pain intensity the rest of the dose of Propofol was given and anaesthesia was continued and managed. Snapshot of trends was taken to assess haemodynamic changes and intubation response.

RESULTS

The baseline demographic and clinical characteristics of participants in both the Ketamine and Lidocaine groups were comparable. The mean age of participants in the Ketamine group was 38.65 ± 13.45 years, while in the Lidocaine group it was 39.03 ± 13.5 years, with no statistically significant difference ($p = 0.87$).

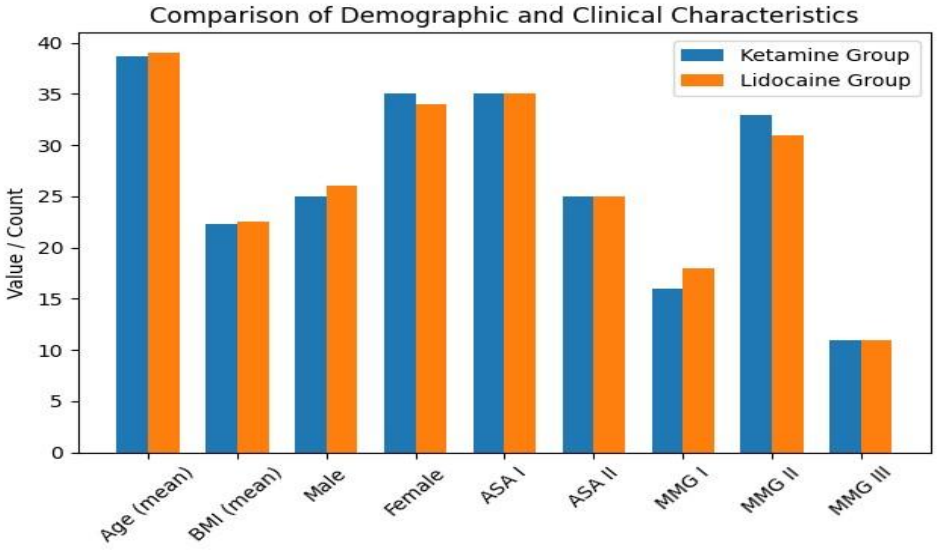
Similarly, the mean BMI was 22.30 ± 1.41 kg/m² in the Ketamine group and 22.50 ± 1.44 kg/m² in the Lidocaine group ($p = 0.44$), with the range being 20 to 24 in both groups. In terms of sex distribution, the Ketamine group had 25 males (41.7%) and 35 females (58.3%), while the Lidocaine group had 26 males (43.3%) and 34 females (56.7%). This

difference was not statistically significant (p = 0.85). The ASA physical status classification was identical in both groups, with 35 participants (58.3%) categorized as ASA I and 25 participants (41.7%) as ASA II (p = 1.0).

The Mallampati grading also showed a similar distribution across the two groups, with MMG I in 26.7% and 30.0%, MMG II in 55.0% and 51.7%, and MMG III in 18.3% in both the groups, respectively (p = 0.91).
This comparability strengthens the internal validity of the study, ensuring that any differences observed in pain relief efficacy, haemodynamic changes, or adverse events can be attributed to the study interventions—intravenous Ketamine or preservative-free Lidocaine—rather than to confounding factors.

Table 1: Demographic and Clinical Characteristics of Participants between Ketamine and Lidocaine Groups

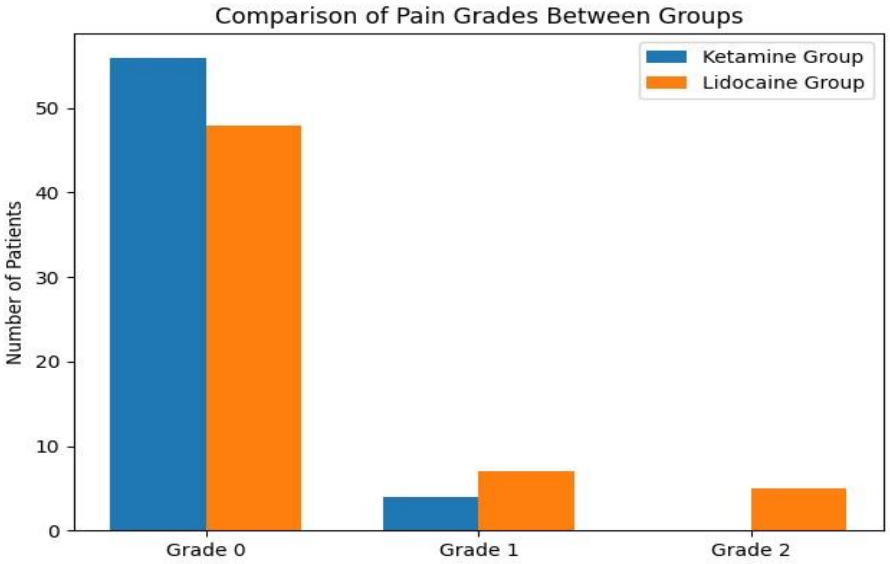
Variable	Ketamine Group (n=60)	Lidocaine Group (n=60)	P-value
Age (years)	38.65±13.45	39.03±13.5	0.87(NS)
Range	18-59	18-59	
BMI (kg/m²)	22.30±1.41	22.50±1.44	0.44(NS)
Range	20-24	20-24	
Sex			
Male	25 (41.7%)	26 (43.3%)	0.85(NS)
Female	35 (58.3%)	34 (56.7%)	
ASA PS			
I	35 (58.3%)	35 (58.3%)	1.0(NS)
II	25 (41.7%)	25 (41.7%)	
MMG			
I	16(26.7%)	18(30.0%)	0.91(NS)
II	33 (55.0%)	31(51.7%)	
III	11(18.3%)	11(18.3%)	



The comparison of injection pain scores between the two groups reveals that a higher proportion of patients in the Ketamine group (93.3%) experienced no pain (Grade 0) compared to the Lidocaine group (80.0%). Only 6.7% of patients in the Ketamine group reported mild pain, and none experienced moderate pain. In contrast, the Lidocaine group had 11.7% with mild pain and 8.3% with moderate pain. The p-value of 0.04 indicates a statistically significant difference between the groups regarding pain perception during the injection of Propofol. This suggests that Ketamine is more effective than preservative-free Lidocaine in alleviating Propofol injection site pain.

Table 2: Propofol Injection Pain Score between Ketamine and Lidocaine Groups

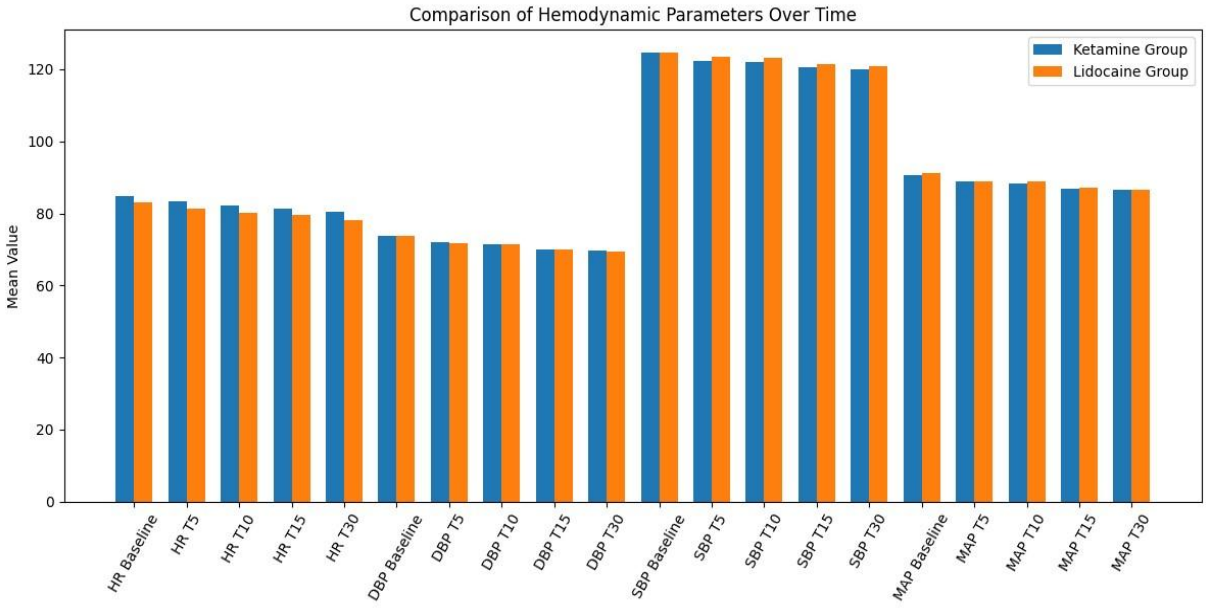
Pain Grade	Ketamine Group (n=60)	Lidocaine Group (n=60)	p-value (Chi-square)
Grade 0	56(93.3%)	48(80.0%)	0.04(S)
Grade 1	04(6.7%)	07(11.7%)	
Grade 2	0(0.0%)	05(8.3%)	
Total	60	60	



The haemodynamic response to endotracheal intubation was assessed by comparing heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) immediately after intubation and 5 minutes post-intubation in the Ketamine and Lidocaine groups. The results revealed no statistically significant differences between the two groups across all measured parameters ($p > 0.05$ for all). Immediately following intubation, the heart rate in the Ketamine group was slightly higher (80.26 ± 10.24 bpm) compared to the Lidocaine group (77.53 ± 9.63 bpm), though this difference was not statistically significant ($p = 0.13$). A similar non-significant trend was seen 5 minutes post-intubation, where the heart rate remained marginally higher in the Ketamine group (77.06 ± 9.95 bpm) than in the Lidocaine group (74.05 ± 9.29 bpm), with a p-value of 0.08. Systolic and diastolic blood pressures, as well as MAP, were also comparable between the two groups at both time points. For instance, the mean SBP immediately post-intubation was 115.8 ± 9.11 mmHg in the Ketamine group and 116.2 ± 9.37 mmHg in the Lidocaine group ($p = 0.85$). Similarly, MAP values showed almost identical readings between the groups, with a p-value of 0.93 immediately after intubation and 0.59 at 5 minutes post-intubation.

Table 3: Hemodynamic Parameters Comparison Ketamine and Lidocaine Groups

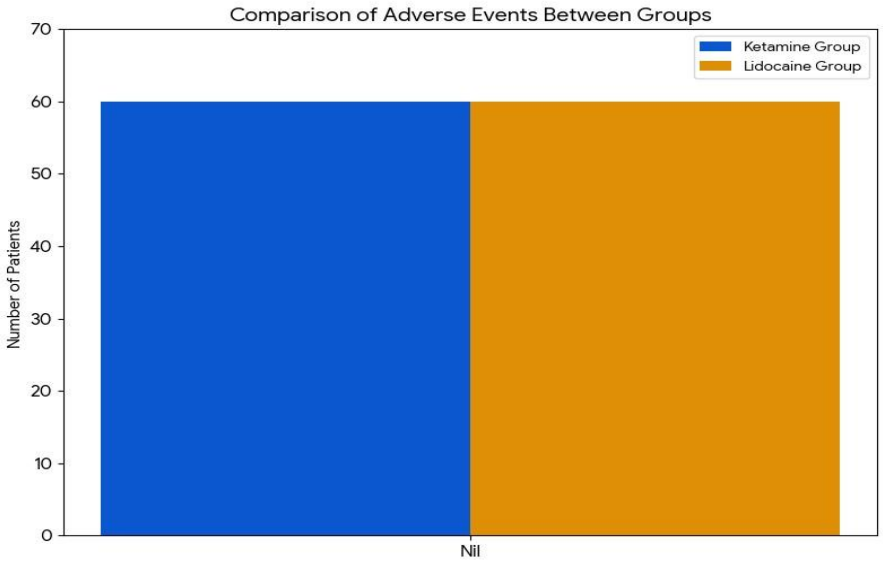
Parameter	Time	Ketamine Group	Lidocaine Group	p-value
Heart Rate (bpm)	Baseline	84.75±10.27	83.06±9.34	0.35(NS)
	T5	83.26±10.13	81.21±9.54	0.26(NS)
	T10	82.21±9.98	80.26±9.60	0.27(NS)
	T15	81.45±9.95	79.45±9.61	0.26(NS)
	T30	80.36±9.82	78.18±9.56	0.22(NS)
DBP (mmHg)	Baseline	73.81±6.90	73.70±7.06	0.92(NS)
	T5	71.95±6.90	71.71±6.92	0.85(NS)
	T10	71.51±6.81	71.40±7.01	0.92(NS)
	T15	70.11±7.02	69.91±6.87	0.87(NS)
	T30	69.75±6.92	69.26±6.91	0.70(NS)
SBP (mmHg)	Baseline	124.5±8.76	124.7±12.4	0.91(NS)
	T5	122.3±8.67	123.5±8.83	0.44(NS)
	T10	122.1±8.83	123.3±8.81	0.44(NS)
	T15	120.5±8.98	121.4±8.81	0.57(NS)
	T30	119.9±9.1	120.8±8.94	0.59(NS)
MAP	Baseline	90.73±7.26	91.13±7.29	0.76(NS)
	T5	88.73±7.26	88.98±7.11	0.84(NS)
	T10	88.35±7.21	88.73±7.13	0.77(NS)
	T15	86.88±7.44	87.10±7.04	0.87(NS)
	T30	86.55±7.50	86.41±7.16	0.92(NS)



In the assessment of intraoperative safety profiles between the Ketamine and Lidocaine groups, no adverse events were reported in either group. As shown in Table 4, all 60 participants in both the Ketamine and Lidocaine groups completed the procedure without experiencing any adverse effects such as hypersensitivity reactions, respiratory complications, cardiovascular instability, nausea, vomiting, or emergence phenomena. This finding suggests an excellent safety profile for both study drugs when used in the administered doses and settings. The absence of adverse effects in both groups indicates that intravenous Ketamine and preservative-free Lidocaine are well tolerated and clinically safe for use as pretreatment agents prior to Propofol administration. These results provide confidence in their continued use for pain prevention at the injection site without compromising patient safety during the intraoperative period.

Table 4: Incidence of Adverse Effects in Ketamine and Lidocaine Groups

Adverse Event	Ketamine (n=60)	Lidocaine (n=60)
Nil	60	60



DISCUSSION

A total of 120 patients were observed in this study, the groups were comparable in their socio-demographics, clinical characteristics, and baseline hemodynamic variables. The incidence of Propofol injection pain after pre-treatment was significantly lower in the low-dose Ketamine group than the Lidocaine group (p = 0.04).

In present study, a higher proportion of patients in the Ketamine group (93.3%) experienced no pain (Grade 0) compared to the Lidocaine group (80.0%). Only 6.7% of patients in the Ketamine group reported mild pain, and none experienced moderate pain. In contrast, the Lidocaine group had 11.7% with mild pain and 8.3% with moderate pain.

The p-value of 0.04 indicates a statistically significant difference between the groups regarding pain perception during the injection of Propofol. This suggests that Ketamine is more effective than preservative-free Lidocaine in alleviating Propofol injection site pain.

Hossain et al, conducted a study on attenuation of Propofol injection pain using low dose Ketamine pretreatment with venous occlusion and they observed 10% patients experienced pain and there was no significant hemodynamic variability noted[4].

The study conducted by Kaya et al found that pretreatment with Lidocaine 20 mg plus venous occlusion for 60 seconds significantly reduced the incidence of Propofol-induced pain compared with Lidocaine without venous occlusion[5].

Rajan et al, conducted a study comparing effect of IV Lidocaine and Ketamine pretreatment in alleviating Propofol injection pain and they observed, pre-treatment of 15 mg Ketamine was as effective as 21.3 mg 2% Lidocaine in reducing the severity of Propofol injection pain[6]. In contrary to present study findings, Shetty et al conducted a study on comparison between Lignocaine (0.4mg/kg), Tramadol (1mg/kg), and Ketamine (0.1mg/kg) in Attenuating Propofol Induced Pain and observed the incidence of no pain (score 0) was highest in the Lignocaine group (60%) compared to Ketamine and Tramadol groups (both 10%). Mild pain was most common with Tramadol (65%) and Ketamine (50%), while moderate pain occurred more frequently with Ketamine (40%) than with Tramadol (25%) or Lignocaine (10%). This difference could be attributed to lower dose of Ketamine used[7].

Zahedi et al observed that small dose of Ketamine (50-75-100μgkg-1) administered just before Propofol injection, reduced both the incidence and intensity of Propofol injection pain without significant adverse hemodynamic effects[8].

Gesso et al conducted a study comparing effect of low dose Ketamine and Lignocaine pretreatment in reducing pain on Propofol injection and haemodynamic variability and observed that pretreatment with low dose Ketamine is effective in reducing Propofol injection pain compared to Lignocaine without any significant haemodynamic variability, which is similar to present study[9].

CONCLUSION

We observed that pretreatment with 10mg Ketamine and 1ml 2% preservative free Lidocaine was effective in reducing pain on Propofol injection and concluded, pre-treatment with 10mg Ketamine significantly reduces the incidence of Propofol injection pain when compared to 1ml 2% preservative free Lidocaine.

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