

Effect of low dose ketamine pretreatment on propofol injection pain: A randomised double blind, controlled trial

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Article Info

Received: 6th June, 2019

Accepted: 9th July, 2019

Published Online: 22nd August, 2019

Keywords: Propofol, Pain, Ketamine, Premedication.

Abstract

Introduction: Propofol being the most commonly used induction agent for general anaesthesia causes pain on injection as a side effect with an incidence of 28-90%. Ketamine is one of the drugs that have shown to reduce the incidence and severity of pain. The study aimed to know the efficacy of ketamine at 2 different doses on propofol injection pain.

Materials and Methods: After institutional ethical committee clearance and written informed consent 90 adult patients of ASA grade I/II aged between 20-60 years scheduled for various elective surgical procedures under general anaesthesia were randomly divided into 3 groups as group K100, group K200 and group S. Group K100 and K200 received 100 and 200µg/kg iv ketamine respectively and group S received 2ml normal saline over 15 seconds just before the injection of propofol over 30 seconds. Incidence of pain and its severity was measured in each patient using verbal rating scale as 0-3 grade while injecting propofol corresponding to no, mild, moderate, severe pain. Hemodynamic parameters were also recorded at specific time intervals. Data was collected and analyzed using appropriate statistical tests.

Results: The demographic data had no statistical difference among the groups. The incidence of pain in group K100, K200 and group S was 50%, 23.3%, 83.3% respectively which was significant statistically with $P < 0.001$. The severity of pain was less in K200 with none having moderate to severe pain where as K100 group has mild to moderate pain and in group S 26.7% patients had severe pain which was significant statistically with $P < 0.001$. The median pain scores were 1, 0 and 2 in K100, K200 and group S respectively with $P < 0.001$.

Conclusion: Premedication with ketamine is a simple safe effective method to reduce propofol injection pain. 200µg/kg decreases the incidence and severity more effectively.

Introduction

Propofol is the most commonly used induction agent in the era of day care surgeries under general anaesthesia due to rapid onset, short duration of action, antiemetic properties and fewer side effects.¹ Although Propofol injection pain is a minor complication of anaesthesia, at times it can cause distress to the patient. The incidence of this pain varies between 28% and 90% in adults.²

Methods to reduce this pain are cooling or warming the solution, diluting the solution, injection into larger vein, addition of lidocaine, pretreatment with ephedrine, ondansetron, opioids, thiopental or ketamine.³⁻⁷ Failure rate of commonly used lidocaine is between 32 to 48%.^{4,8}

Ketamine, a potent analgesic is a phencyclidine derivative with NMDA receptor antagonistic action. Studies have shown that ketamine can reduce propofol injection pain by virtue of its local anaesthetic properties^{9,10} and only few studies have been done to evaluate the effective dose that can reduce the incidence and severity of pain. We decided to evaluate ketamine in decreasing the incidence and severity of propofol injection pain at 2 different doses

and also to know the hemodynamic effects of combination of these drugs in comparison with control group in a prospective randomized placebo controlled double blind study.

Materials and Methods

Sample size was calculated based on the observations from previous studies. Keeping the power of study as 80% and an alpha error as 5%, a minimum of 28 cases were required in each group to detect an improvement in injection pain by 25%. Hence 90 ASA grade I/II patients were selected and divided into 3 groups of 30 each using random number table as group K100, K200 and group S.

After informed written consent from the patients and institutional ethical committee clearance, 90 adult patients with ASA grade I/II aged between 20-60 years scheduled for various elective surgical procedures under general anaesthesia were selected and divided into 3 groups as mentioned above.

Patients with known hypersensitivity/contraindication to study drugs, uncontrolled diabetes mellitus/hypertension,

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<http://doi.org/10.18231/ijca.2019.087>

severe renal/hepatic/respiratory/cardiac disease, pregnant females, patients with neurological, psychiatric, neuromuscular disorders, alcohol or substance abuse were excluded from the study.

Allocation to study group was done by an anaesthetist not involved in the study. Study drugs were administered and monitored by an anaesthetist conducting the case who was unaware of the patient’s study group. All patients were kept fasted overnight and were given tab. Alprazolam 0.5mg and tab. Ranitidine 150mg on the previous night before surgery.

On the day of surgery no patients were given any premedication. On arrival of patient to the operation theatre new intravenous line using 20G Teflon catheter was inserted on to the dorsum of the hand and 5ml/kg normal saline infusion was started. Multichannel monitors like SPO₂, NIBP, ECG were connected and baseline reading of the above parameters were recorded.

Group S received 2ml of normal saline, Group K100 and K200 received 100µg/kg and 200µg/kg ketamine diluted to 2ml using saline respectively to maintain blinding.

The study drug was given by blinded anaesthetist over 15seconds followed by injection of 2mg/kg Propofol 1% at room temperature over 30 seconds. Before the administration of propofol, every patient was asked by him/her to rate any sensation of pain every 5seconds during propofol injection using a 0-3 verbal rating scale (VRS) published by McCrirrick and Hunter.⁵ Any sensation of pain and highest pain score was recorded. The grading of VRS was as follows 0=no pain, 1=mild pain/soreness, 2=moderate pain, 3=severe pain associated with grimacing, withdrawal movements of forearm or both. After the propofol injection and patient was induced, inj. Fentanyl 2µg/kg, inj. Midazolam 1mg and inj. Vecuronium bromide

0.1mg/kg were administered to facilitate controlled ventilation and 6L/min oxygen with isoflurane 1% was administered during ventilation via facemask. Trachea was intubated after 3 minutes and anaesthesia was maintained with isoflurane 1-1.5% and NO₂ 50% in O₂ as per surgical requirements. NIBP, HR,SPO₂ were recorded at the start of the monitoring, after study drug injection, just before intubation and 1,2,3,5,10 and 15 minutes after intubation and data was recorded. The change in HR of ± 20 beats and 20% rise/fall in BP from baseline was considered clinically significant in our study. After surgical procedure and extubation a blinded anaesthetist observed the patients in the post anaesthesia care unit and checked for any abnormal behavioural responses including hallucinations, illusions, delirium and was told to report immediately if any such responses are present and the study was concluded.

Statistical Analysis

Data was entered into Microsoft Excel and analysis were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 20.0; SPSS Inc, Chicago). Mean and standard deviation (SD) for continuous variables, frequencies and percentages for categorical Variables were calculated. Categorical Variables like Gender were analyzed using chi-square test of independence. Comparison of mean of quantitative variables like Heart rate were analyzed using ANOVA. P value <0.05 was considered statistically significant.

Results

90 patients were enrolled in the study and all patients completed the study. The demographic variables were comparable in our study with no significant statistical difference.

Table 1: Comparison of Age, Sex and Weight between three Groups

Parameter	Group			P Value
	K100 (n=30) Mean (SD)	K200 (n=30) Mean (SD)	NS (n=30) Mean (SD)	
Age in Years	36.23(11.67)	34.83(10.68)	39.27(13.75)	0.354
Sex Male/Female	11/19 36.7/63.3%	14/16 46.7/53.3%	6/24 20/80%	0.089
Weight (kg)	59.80(10.61)	59.23(9.46)	57.40(12.98)	0.684
ASA gradeI/II	30/0	30/0	29/1	0.364

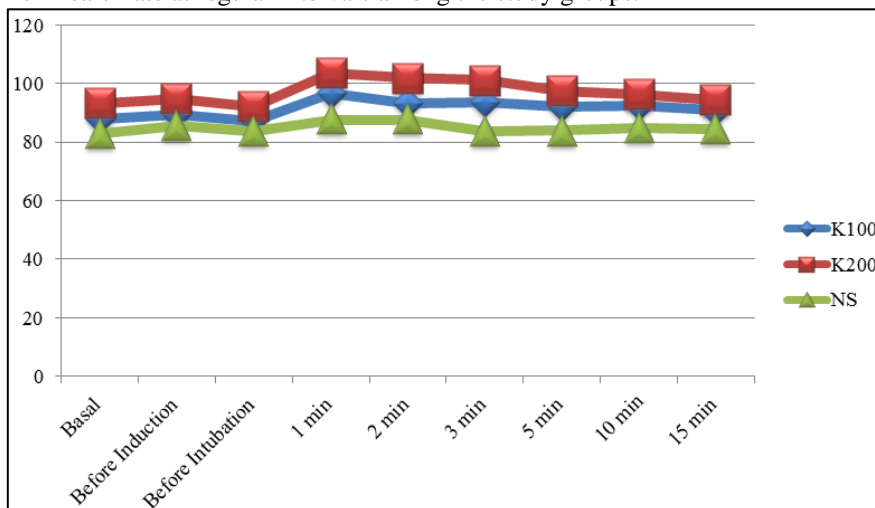
P <0.05 is considered statistically significant

Table 2: Incidence of Propofol injection pain and severity scores

Severity of Pain	Group			P value
	K100 (n=30) n (%)	K200 (n=30) n(%)	NS (n=30) n (%)	
None(=0)	15(50.0)	23(76.7)	5(16.7)	<0.001
Mild (=1)	8(26.7)	7(23.3)	7(23.3)	<0.001
Moderate(=2)	7(23.3)	0	10(33.3)	<0.001
Severe(=3)	0	0	8(26.7)	<0.001
Any pain/ Discomfort	15	7	25	<0.001
Percentage %	50	23.3	83.3	<0.001
Median pain score	1	0	2	<0.001

The incidence of pain or any discomfort was 50%, 23.3% and 83.3% with median pain scores of 1, 0 and 2 in K100, K200 and group S respectively with P value <0.001 which is statistically significant. The severity of pain was less in ketamine group when compared to saline group with P<0.001 which is statistically significant.

Graph 1: Comparison of Heart Rate at regular intervals among the study groups.



In our study there is significant difference in change in Heart rate at regular intervals measured up to 15min post intubation with P<0.05. But it is not significant clinically as defined earlier.

Table 3: Comparison of SBP between three Study Groups

SBP	Group			P Value
	K100(n=30) Mean (SD)	K200(n=30) Mean (SD)	NS(n=30) Mean (SD)	
Basal	129.53(17.34)	126.13(16.50)	128.97(15.79)	0.697
After premedication	125.30(17.89)	126.67(15.88)	119.13(33.50)	0.429
Before Intubation	125.30(22.86)	106.50(16.65)	108.03(20.70)	0.866
1 min	122.70(19.00)	131.90(18.96)	126.37(19.78)	0.182
2 min	118.80(20.40)	118.20(15.11)	117.03(16.11)	0.923
3 min	116.43(17.88)	115.40(14.89)	116.13(14.45)	0.967
5 min	112.87(15.01)	114.77(17.67)	115.83(17.00)	0.783
10 min	115.33(15.83)	116.80(15.24)	114.93(19.51)	0.904
15 min	118.40(19.24)	117.57(14.22)	119.27(16.60)	0.926

Table 4: Comparison of DBP between three study groups

DBP	Group			P Value
	K100(n=30) Mean (SD)	K200(n=30) Mean (SD)	NS(n=30) Mean (SD)	
Basal	81.00(14.01)	79.13(8.68)	80.40(8.95)	0.795
After premedication	78.90(12.26)	80.60(10.23)	77.73(11.32)	0.616
Before Intubation	70.07(16.82)	63.57(11.14)	65.23(18.22)	0.255
1 min	81.10(16.08)	82.50(12.71)	82.23(14.01)	0.923
2 min	76.67(16.46)	73.93(13.49)	76.53(10.78)	0.688
3 min	76.10(15.87)	71.83(11.87)	72.63(12.51)	0.434
5 min	71.20(16.17)	72.20(12.27)	77.33(14.79)	0.219
10 min	75.10(13.56)	74.00(14.63)	75.60(16.10)	0.912
15 min	75.63(13.74)	74.17(14.53)	77.80(20.16)	0.690

Table 5: Comparison of MAP between three study groups

MAP	Group			P Value
	K100(n=30) Mean (SD)	K200(n=30) Mean (SD)	NS(n=30) Mean (SD)	
Basal	97.23(14.24)	92.13(11.96)	94.23(11.47)	0.295
After premedication	95.07(13.19)	92.50(13.78)	93.30(12.51)	0.743
Before Intubation	83.53(18.55)	75.40(13.21)	80.23(18.97)	0.186
1 min	95.40(16.55)	97.03(14.78)	97.43(14.77)	0.864
2 min	91.73(18.15)	87.87(13.46)	90.53(10.36)	0.567
3 min	90.70(15.86)	84.60(13.03)	88.70(11.71)	0.217
5 min	86.63(13.48)	84.07(13.73)	90.20(14.79)	0.240
10 min	91.13(17.99)	86.23(15.08)	88.00(15.26)	0.496
15 min	89.63(14.24)	85.33(14.50)	90.90(14.20)	0.293

Systolic, Diastolic blood pressures and Mean Arterial Pressures measured at regular intervals till 15min post intubation showed no statistically significant difference in our study. None of the patients required any active intervention.

There were no other side effects observed during the course of the study in any of the groups including emergence delirium.

Discussion

Propofol has become the most popular induction agent of choice due to its rapid onset, antiemetic action, blunt airway reflexes, short duration of action, fast recovery of psychomotor functions and has extra hepatic metabolism with fewer side effects. Being phenol derivative one of the disadvantage is that it causes pain on injection which is ranked 7th among the 33 clinical problems when both clinical importance and frequency were considered.¹¹ The incidence of pain varies between 28 to 90%² in adults and between 40-86% when injected to hand vein.¹² The exact mechanism of pain after propofol injection is not known but such type of pain originates from secretion of kininogen from walls of veins and stimulation of kinin cascade.¹³

Failure rate of commonly used lidocaine in attenuating propofol injection pain is between 32-48%. Ketamine an N-Methyl D-Aspartate (NMDA) receptor antagonist is a potent analgesic and has local anaesthetic properties. It decreases the incidence of propofol injection pain due to its local anaesthetic properties which attenuates the efferent pain pathway.¹⁴

Most of the previous studies have evaluated 100µg/kg ketamine as a premedication to decrease the incidence and severity of propofol injection pain in comparison with lidocaine, ondansetron, ephedrine, acetaminophen, metaclopramide. The incidence of any pain in studies done by Seung-Woo Koo et al,¹⁵ Hamid Zahedi et al,¹⁶ Vida Ayotollahi et al¹⁷ was 46.7%, 45% and 25.7% respectively which is same as that with lidocaine premedication. Hence we decided to compare 2 different doses of ketamine 100µg/kg and 200µg/kg with a control group to find the effective dose of ketamine in decreasing the incidence and severity of propofol injection pain.

Study done by Seung Woo Koo et al¹⁵ have evaluated that administration of ketamine immediately before propofol injection provided the optimal timing to reduce pain during the induction sequence. Hence we decided to follow the same method in our study.

The demographic data were comparable between the groups with no statistical difference. In our study the incidence of pain was reduced from 83.3% group S to 50% in K100 and 23.3% in K200 group which is statistically significant with P<0.001. The severity of pain assessed by VRS was less in K200 and K100 group when compared to group S. None of the patients in K200 had moderate to severe pain but had only mild pain in 23.3%. None of the K100 patients had severe pain but 23.3% had moderate pain where as 33.3% patients had moderate pain and 26.7% had severe pain in the group S which is statistically significant with P<0.001. The median pain score was 0, 1 and 2 in K200, K100 and group S respectively which is statistically significant with P<0.001.

The study done by Seung Woo et al¹⁵ showed that the incidence of pain after 100µg/kg ketamine and in control group was 46.7% and 86.7% which is comparable with our study with a median pain score of 0 and 1 respectively. Pretreatment with 10mg ketamine (100-150µg/kg) in 1ml normal saline 30seconds before propofol injection was found to significantly reduce the incidence of pain during the later from 84% to 26% in a study done by Tan CH et al¹⁹ which is also comparable with our study.

In a study done by Pakhare Vandana et al¹⁸ the incidence of pain on 100µg/kg ketamine was 76% which is more than that of our result. In a similar study done by Ashok Chaudhari et al¹⁹ the incidence of pain with 200µg/kg ketamine and control group was 26% and 94% at zero minute. None of the patients had severe pain in ketamine group where as 52% of control group had severe pain which is almost double than that is observed in our study. They suggested 200µg/kg intravenous ketamine pretreatment to alleviate pain on propofol injection.

In a study done by Vida Ayotollahi et al¹⁷ the incidence of pain on propofol injection was 25.7% in K100 group and 74.3% in saline group which is less than that of our study. 5.7% and 17.1% patients had severe pain in ketamine and saline group respectively where as in our study none had

severe pain in K100 group and 26.7% had severe pain in group S.

Another study done by Deepa Ravindra et al²⁰ showed that 10mg ketamine was effective in reducing the incidence of Propofol injection pain from 93.3% in the control group to 20% in patients treated with ketamine. The intensity of pain was also reduced in ketamine group with none experiencing severe pain as compared to 33.3% in control group.

Hemodynamic parameters like Heart rate(HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Pressure(MAP) showed no clinically significant difference as defined earlier up to 15minutes post intubation though there was statistically significant difference with $P < 0.05$ was present in terms of change in Heart Rate (HR) among the 3 groups. The increase in HR in K200 group can be attributed to stimulation of sympathetic nervous system by ketamine. There was no statistically significant difference in blood pressure changes among the groups. None of the patients required any active intervention.

No side effects and emergence reactions like dreams, hallucinations, delayed recovery, and looking dissociated from surroundings were observed in any of the patients.

From the observations done by previous studies and our study we conclude that low dose ketamine pretreatment is a safe, simple, effective method in significantly decreasing the incidence and severity of propofol injection pain. We suggest a dose of 200µg/kg iv ketamine pretreatment just before propofol injection to alleviate pain without significant adverse hemodynamic effects.

Source of Funding: None.

Conflict of Interest: None.

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How to cite this article: Madhu KP, Yathish SK, Rao RSR. Effect of low dose ketamine pretreatment on propofol injection pain: A randomised double blind, controlled trial, *Indian J Clin Anaesth* 2019;6(3):450-4.