# A Study to Evaluate Low-Dose Ketamine Pretreatment for Reduction of Propofol Injection Pain

**Seema[1], Namarta Sharma[2]**


## ABSTRACT

**Introduction:** One of the most important disadvantages of propofol injection is intense burning pain. This study was conducted with the aim to assess the effect of low dose ketamine (100 µg/kg) in the alleviation of pain on propofol injection.

**Material and Methods:** Patients who underwent surgical procedures under general anaesthesia were divided into two groups of 60 patients each. In Group K pretreatment with ketamine 100µg/kg (1ml) and in Group S pretreatment with 1 ml of 0.9% normal saline was given and then over 20 seconds, the first 25% of the calculated dose of propofol was injected. The evaluation of the severity of pain was done by the McCrirrick and Hunter scale during the injection of the induction agent for every 5 seconds and graded as 0 to 3. The data were recorded and analysed using unpaired 't' test & chi-square test.

**Results:** The demographic profiles were comparable between the two groups. It was observed that 42.9% of patients in normal saline and 80% in ketamine groups experienced no pain ($p<0.05$) while 31.4% and 17.1% of patients in normal saline and in ketamine groups respectively felt mild pain. No significant haemodynamic changes were observed in both the groups ($p>0.05$).

**Conclusion:** It may be concluded that pretreatment with low dose ketamine just before propofol injection, significantly reduced the incidence and degree of propofol induced pain without significant adverse hemodynamic effects.


**Keywords:** Induction, Propofol, Pain, Ketamine, Alleviation.

## INTRODUCTION

Propofol has always been the drug of choice for induction of anesthesia because of its rapid onset, short duration of action and favorable profile for side effects[1]. Despite these positive qualities, about three out of five patients experience pain on propofol injection, with one of these patients reporting severe or excruciating pain. Some patients recall the induction of anaesthesia as the most painful part of the perioperative period and the quality of pain was described as extremely sharp, aching or burning. It has been mentioned as the seventh most important problem in current practice of clinical anesthesia by American anesthesiologists[2].

The incidence of pain induced by propofol varies between 28% and 90% in adults[3]. Many drugs such as fentanyl, alfentanyl, lidocaine, thiopentone, metoclopramide, aspirin, pethidine, ketamine have been used to alleviate pain after IV injection of propofol which have shown variable efficacy[4,5]. Among these, lidocaine pretreatment is the most widely used method for reducing this pain. However, the failure rate is between 32% and 48% and thus lidocaine can not entirely control propofol induced pain[6]. Ketamine has potent analgesic and local anaesthetic properties, but very few studies have evaluated the efficacy of ketamine in reducing propofol induced pain and the optimal dose required to reduce the pain on injection with propofol[7].

Ketamine shows its local anaesthetic effect by antagonism at the N-methyl D-aspartate (NMDA) receptors by opioid mu-receptor antagonism or voltage-sensitive sodium channel interactions[3]. Ketamine given as pretreatment thus could act as preemptive analgesic preventing sensitization of the local nerve endings by noxious inputs.

We conducted this study to determine if low-dose ketamine could reduce propofol injection pain in dorsal hand vein, study the haemodynamic effects of the drug, and to know if any undesired effects like emergence phenomenon occur on administering low-dose ketamine.

## MATERIAL AND METHODS

After approval from institutional ethical committee, this prospective randomized placebo-controlled study was carried in the Department of Anaesthesiology at a tertiary care centre over a period of one year (Jan 2019 – Dec 2019). Based on a previous study in literature, the incidence of pain on injecting propofol was taken to be 80%, and 50% reduction in pain considered clinically significant[3]. The minimum size for each group, assuming a-value of 0.05 and a power value of 90%, was thus calculated to be 60. Patients included were ASA grade 1 or 2, aged 18 to 65 years, weighed between 35 and 75 kg posted for surgeries under general anaesthesia. Patients with known history of allergy or convulsions, on sedatives/analgesics/antipsychotics, pregnant and breast-feeding women, patients who required rapid sequence induction and anticipated difficult airway were excluded from our study. Patients were equally divided into two groups, Group K received ketamine as the pretreatment while group S received normal saline as control.

Written informed consent and fasting status of the patient

[1]Senior Resident, Department of Anaesthesia, [2]Junior Resident, Department of Anaesthesia, PGIMS, Rohtak, India

**Corresponding author:** Dr.Seema, House No. 882/21, Kailash Colony, Near New Bus Stand, Rohtak-124001, Haryana, India.

**How to cite this article:** Seema, Sharma N. A study to evaluate low-dose ketamine pretreatment for reduction of propofol injection pain. International Journal of Contemporary Medical Research 2021;8(7):G5-G8.

**DOI:** http://dx.doi.org/10.21276/ijcmr.2021.8.7.15

was confirmed. In the operation theatre, IV line was secured with 20G cannula and It was connected to an infusion of saline 0.9% at 5ml/kg/hr.

The patients were either given ketamine 10 mg in a total volume of 1 ml or 1 ml of 0.9 % normal saline by an operator who was unaware of the content of the injected solution. After 20 seconds of pretreatment with the study drug or saline, 3 ml bolus of 1% propofol was given over 3 seconds and the three-way tap was opened to the saline infusion. All of the patients were instructed about the pain scale before the operation. The grading of pain was done using McCrirrick and Hunter scale.

**Score 0**: No pain (negative response to questioning)

**Score 1**: Mild pain (pain reported only in response to questioning without behavioral signs)

**Score 2**: Moderate pain (pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning)

**Score 3**: Severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears)

Heart rate and blood pressure were noted before pretreatment and after pretreatment with ketamine, and at 1, 2 and 3 minutes after propofol bolus. Change in heart rate of rise or fall by 20 beats and 20% rise or fall in blood pressure from the baseline was considered clinically significant in our study.

## STATISTICAL ANALYSIS

The sample size was determined to have a power of 80% at a 5% significance level to detect a 20% difference in the incidence of injection pain between the two groups. Statistical comparisons between the two groups were carried out with the chi-square test for proportions and with Student's t-test for continuous parametric data. Values of P <0.05 were considered statistically significant.

## RESULTS

The demographic profile in the two groups was comparable (Table 1). It was observed that 8.33 % of patients in Group S and 63.3 % in Group K experienced no pain while mild pain was felt by 11.66 % in Group S and 28.3 % in Group K. In Group K, a relatively fewer patients (8.33%) had moderate pain compared to 45% in Group S. Severe pain was observed in 35 % of group S and no such incidence was seen in group K, which was found highly significant statistically ($p < 0.001$) (Table 2). There were no significant differences in heart rate and mean arterial pressure at different time intervals between groups shown in (Table 3) and (Table 4) respectively.

## DISCUSSION

Propofol is a versatile intravenous anaesthetic agent. The mechanism by which propofol causes pain at local site of injection, is still unknown but it has been attributed to

| Parameters | Group S | Group K | P value |
|---|---|---|---|
| Age ( Years ) | 38.84 ± 12.690 | 38.72 ± 14.796 | 0.846 |
| Weight ( Kg ) | 58.03 ± 8.604 | 62.09 ± 15.68 | 0.290 |
| Height ( cm ) | 164.07 ± 10.124 | 163.84 ± 7.844 | 0.680 |
| Gender ( M/F ) | 14/ 21 | 15/20 | 0.589 |

**Table-1:** Comparison of demographic profiles

| Grade | | Group S | | Group K | | P value |
|---|---|---|---|---|---|---|
| | | n | % | n | % | |
| 0 | No | 5 | 8.33 | 38 | 63.3 | |
| 1 | Mild | 7 | 11.66 | 17 | 28.3 | < 0.001 |
| 2 | Moderate | 27 | 45 | 05 | 8.33 | |
| 3 | Severe | 21 | 35 | 0 | 0 | |

**Table** 2: Grading of pain scores

| Time interval (min) | Group S | Group K | P value |
|---|---|---|---|
| Baseline | 78.32 ± 11.16 | 76.34 ± 9.46 | 0.184 (NS) |
| 1 | 82.56 ± 11.15 | 81.23 ± 8.92 | 0.694 (NS) |
| 2 | 79.93 ± 11.56 | 80.28 ± 8.47 | 0.852 (NS) |
| 3 | 79.48 ± 11.74 | 80.90 ± 11.39 | 0.416 (NS) |

**Table-3:** Comparison of Heart Rate at different time intervals

| Time interval (min) | Group S | Group K | P value |
|---|---|---|---|
| Baseline | 74.32 ± 15.16 | 75.34 ± 16.08 | 0.956 (NS) |
| 1 | 78.56 ± 16.04 | 76.42 ± 15.92 | 0.482 (NS) |
| 2 | 79.35 ± 11.56 | 78.38 ± 11.47 | 0.530 (NS) |
| 3 | 76.48 ± 11.68 | 76.32 ± 10.26 | 0.756 (NS) |

**Table-4:** Comparison of MAP at different time intervals

release of kininogen from the vein wall with triggering of local kinin cascade. Various methods have been used in the past for alleviation of propofol injection pain. Sadawy et al in his study used different drugs like ketamine, thiopental, meperidine, lidocaine and saline. He found ketamine to be the most effective agent in pain alleviation when combined with venous occlusion[8]. Most of the drugs studied for use as pretreatment to attenuate propofol injection pain did not offer any haemodynamic advantage so we decided to study ketamine, which has haemodynamic effects quite opposite to those of propofol. It also has local anaesthetic effect and this property can be helpful to attenuate pain on injection of propofol[9].

The incidence of propofol injection pain in our study was significantly reduced in ketamine pretreatment group and these results are significant when compared with other techniques of propofol injection pain relief[10]. The incidence of severe pain was completely terminated with ketamine. Our observations were consistent with those seen by CH Tan et al[3]. Where they found ketamine pretreatment reduced the incidence of pain from 84% to 26%. A study done by Ozkocak et al found the intensity of pain was lowered but the incidence was as high as 76% in the ketamine group[11]. Some studies have been done with application of tourniquet after injection[8]. In a study done by Barbi E et al on 122 paediatric patients concluded, pretreatment with ketamine (0.5 mg.kg-1) is very effective in preventing propofol infusion pain[12].

On pretreatment with ketamine, Qattan et al[13] observed mild pain in 11.7%, while Saadawy et al[8] observed moderate pain in 4%. This is in agreement with the findings of our study. This may be due to the fact that ketamine has analgesic properties in sub-anaesthetic doses mediated via the μ or δ receptors, and it may also be a μ antagonist and κ agonist[8].

Usually females experience greater pain intensity, compared to that of males. This may be due to the mechanical effect of larger sized veins in males compared to females, and also owing to the difference in the pain sensitivity between either gender[14]. In the present study, out of the total subjects who experienced from mild to severe pain majority were females (62.5%) compared to males (37.5%).

In the study by Tan C H et al hypotension was observed in 58% of the ketamine group and 60% in the control group, and no incidence of heart rate of less than 50 beat/min was observed[3]. In our study, with the dose of ketamine used, there was no hypotension with insignificant effect on mean arterial blood pressure and heart rate compared with control (saline) upto 3 mins after intubation which may be due to the fact that the cardio-stimulant effects of ketamine balanced the cardio-depressant effects of propofol[15].

Limitation of our study was that we studied only low dose of ketamine; however we were concerned that larger doses would cause sedation and central action, and confound the results. Further studies with varied doses of the study drug with varied intervals of pre treatment drug or admixtures of the drugs are suggested to come to a definite conclusion.

## CONCLUSION

The current study proved that low-dose ketamine was useful in reducing the incidence of pain on injection of propofol. The drug preserves hemodynamics for a short interval after administration of propofol and does not produce emergence phenomenon in low dose.

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**Source of Support:** Nil; **Conflict of Interest:** None

**Submitted:** 21-06-2021; **Accepted:** 30-06-2021; **Published:** 14-07-2021