Original Article

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Ketamine Pre-treatment to Alleviate the Pain of Propofol Injection - A Prospective, Double-blind, Randomized, Placebo, Controlled Study

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Abstract

Background: Pain during injection is a limiting factor in the use of some anesthetic drugs like propofol.

Objective: The present study was done to find the efficacy of low-dose ketamine pre-treatment in decreasing pain after propofol injection.

Methods: A total of 100 ASA 1 and ASA 2 category patients of both gender aged 18-60 years receiving general anesthesia for elective surgery, were randomly divided into two groups of 50 patients each by shuffle envelope method. Group A patients received 2 ml ketamine (0.2 mg/kg), and Group B patients received 2 ml 0.9% normal saline intravenously. The levels of pain were assessed at 0, 1, and 2 min after administration of propofol by the second observer who was unaware of the group to which the patient had been allocated. A score of 0-3 corresponded to no pain, mild, moderate, and severe pain which were recorded at 0, 1 and 2 min. Data were analyzed using statistical SPSS software.

Results: There was no statistically significant difference in mean dose of propofol used between the groups. The mean pain score at 0, 1, and 2 min was statistically different in between ketamine and control group ($P < 0.05$). At 0 min, mean pain score in ketamine group (Group A) was 0.38 (0.73) as compared to 2.52 (0.71) in control group (Group B). At 1 min, mean pain score in Group A was 0.22 (0.61) while in Group B, was 2.54 (0.71). At 2 min in Group A, it was 0.26 (0.57) while in Group B, it was 2.18 (0.83).

Conclusion: The present study has concluded that low-dose ketamine pre-treatment is effective in reducing the incidence and severity of pain as compared to saline. The pre-treament with ketamine in low dose is also free of hemodynamic consequences.

Key words: General anesthesia, Ketamine, Propofol pain

INTRODUCTION

Propofol is an intravenous (IV) sedative and hypnotic agent commonly used for the induction of anesthesia. Its rapidity and reliability in causing loss of consciousness and quick, smooth recovery are the most favorable features. However, pain on injection when given IV is a common problem with propofol, the incidence of which is between 40% and 86%.[1]

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Mechanism of propofol injection pain is not known completely, but number of factors may be responsible for the pain. Chemically, propofol belongs to the group of sterically hindered phenols. Like the phenols, propofol irritates the skin and mucous membrane.[2] The pain on injection of propofol could be due to other factors too, the osmolality[3] of the solvent used for the preparation, the pH of solution,[4] and concentration of propofol in the aqueous phase of emulsion.[5] Propofol, by an indirect action on the endothelium activates the plasma Kallikrein–Kinin system and releases bradykinin, thereby producing venous

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dilation and hyperpermeability, which increases the contact between the aqueous phase of propofol and free nerve endings, and resulting in pain on injection.[6] To attenuate this pain, several adjuvants have been used, such as addition of lidocaine,[7-9] cooling[10,11] or warming[12] of the drug, diluting propofol solution,[13,14] pre-treatment with ondansetron,[15] metoclopramide,[16] opioids,[17] thiopentone,[18] and fentanyl[19] with varying results. Lidocaine pre-treatment is most commonly used to decrease the injection-related pain.[7-9] Unfortunately, the failure rate is between 13% and 32%.[7,8] Ketamine is an anesthetic agent that has analgesic and local anesthetic properties.[20] It is a phencyclidine derivative that produces dissociative anesthesia in clinical doses of 1-2 mg/kg IV. In the subanesthetic doses, it reduces the propofol injection pain by virtue of its local anesthetic property.[21,22]

In the above scenario, the present study was to look at the efficacy of low-dose ketamine pre-treatment in decreasing pain during injection propofol.

METHODS

The efficacy of low-dose ketamine pre-treatment in decreasing pain during injection propofol was studied for 1 year till required number of patients was enrolled in the study.

Inclusion Criteria

A total of 100 ASA 1 and ASA 2 category patients of both gender aged 18-60 years receiving general anesthesia for elective surgery enrolled for this study, were randomly divided in to two groups of 50 patients each by shuffle envelope method.

Exclusion Criteria

The following participants were excluded from the study:

i. Unwilling participants.
ii. Participants with severe respiratory, cardiovascular, neurological, or renal disease (ASA physical status 3 and 4).
iii. Participants with a history of allergy to any of the study drugs.
iv. Hemodynamically unstable participants.
v. Participants having chronic analgesic use before surgery.
vi. Participants with difficult and/or more than one trial of venous cannulation with 18G IV cannula satisfactorily in any large peripheral vein of the hand.
vii. Pregnant women.
viii. Participants with morbid obesity
ix. Participants with psychological disorders.

After the approval from the hospital ethics committee, written informed consent was obtained from all the patients. All patients were made familiar with verbal pain score. Intensity of pain during injection was assessed using a four-point verbal response scale (Table 1).

Primary outcome variables: The primary outcome variables were the incidence of pain on pre-treatment of ketamine drug injection in each group.

Sample Size Calculation

Sample size was determined based on the results of the pilot study. The power analysis (taking $\alpha = 0.05$ and $\beta = 0.90$) showed that we need to enroll minimum of 50 patients in each group. On this basis of that we have chosen 50 patients in each group. Total 100 patients were selected and were randomized equally into 2 groups with the help of shuffle envelope method.

Group A patients received 2 ml ketamine (0.2 mg/kg) IV and Group B patients received 2 ml 0.9% normal saline IV.

A thorough evaluation of each patient was done before taking up for surgery. A detailed history including history of major illness or diseases in the past was taken. General physical examination and systemic examination of each patient were performed to check the general well-being of each patient and to exclude any major medical disorder. All routine biochemical, hematological, and radiological investigations were performed in all patients and were checked against the exclusion criteria of this study. In the operating room, after cleansing of the local area with 70% alcohol, venous cannulation was done in a large peripheral vein of the hand using an 18G polyurethane IV cannula, and IV drip with Ringer's lactate was started at 100 mL/h. To ensure blinding, coded syringes containing test drugs were prepared by an anesthesiologist not involved in evaluation of

Table 1: Comparison of Group ketamine (A) *n* (50) and Group control (B) *n* (50)

Variables	Mean (SD)		*P* value
	Group ketamine (A) *n* (50)	Group control (B) *n* (50)	
Age (year)	37.72 (8.86)	35.32 (7.88)	0.15
Weight (kg)	64.10 (8.15)	63.50 (7.88)	0.79
Dose of propofol mean (SD)	39.56 (4.97)	39.68 (5.39)	0.98
Comparison of pain at 0, 1, and 2 min between group ketamine and control			
Time interval	**Pain score**		
	Mean (SD)	**Mean (SD)**	
0 min	0.38 (0.73)	2.52 (0.71)	0.01
1 min	0.22 (0.61)	2.54 (0.71)	0.01
2 min	0.26 (0.57)	2.18 (0.83)	0.01

the pain score. All patients were fasted for at least 6 h before surgery. All patients were pre-medicated with oral alprazolam 0.25 mg and ranitidine 150 mg approximately 2 h before induction of anesthesia. On arrival of the patient in the operating room, routine monitoring was applied, and baseline hemodynamic values were recorded. An 18-gauge IV cannula was inserted on dorsum of the non-dominant hand without use of local anesthetic. No other solution was injected before the induction of anesthesia. The study solutions were prepared by an independent anesthesiologist and the investigator did not know the content of the solution.

Injection propofol (2.5 mg/kg[1]) was loaded in a syringe. The venous drainage was occluded manually by rubber tourniquet at mid-arm, 1 min after pre-treatment of study solutions. Occlusion was released and one-fourth of the total calculated dose of propofol was administered over 5 s. The level of pain was assessed at 0, 1, and 2 min after administration of propofol by the second observer who was unaware of the group to which the patient had been allocated.

The patients were asked a standard question about the pain on injection of propofol, the verbal response, and the behavioral signs, such as facial grimacing, arm withdrawal, or tears were noted. A score of 0-3 which corresponds to no pain, mild, moderate, and severe pain was recorded at 0, 1, and 2 min (Table 1). Adverse effects, if any, were noted. Induction of anesthesia was completed with the remaining calculated dose of propofol. Tracheal intubation was facilitated with injection vecuronium, and anesthesia was maintained as per surgical requirement.

Different methods have been used to decrease the discomfort of pain for drug pre-treatment by brief venous retention with tourniquet, which was used before propofol injection that isolates the forearm veins from the rest of the circulation. It presented a useful model for studying the peripheral actions of a drug in the absence of a central effect. Briefly, applied venous tourniquet did not cause pain by itself. Although this technique was straightforward in elective surgery and adult participants, its clinical applicability in emergency induction and children remains doubtful.

Statistical Analysis

Data were analyzed using statistical software (SPSS -13). Data from categorical variables were presented as proportions and percentages. Data from continuous variables were presented as mean (SD). Unpaired *t*-test was used to see the difference between the two groups; $P < 0.05$ was considered to be statistical significant.

RESULTS

Out of 100 patients, 50 in each group, no local complication (e.g. pain, edema, wheal, flare) was noted at local site at the time of administration of injection and up to 24 h.

With respect to demographic characteristics such as weight and age, no statistically significant difference between the groups was noted (Table 1 and Figures 1 and 2).

The mean propofol dose required in ketamine group was 39.56 ± 4.97 mg compared to 39.68 ± 5.39 mg in group control. There was no statistically significant difference in mean dose of propofol between the groups (Table 1 and Figure 3).

The mean pain score at 0, 1, and 2 min was statistically different in between ketamine and control group ($P < 0.05$) ($P < 0.05$) (Table 1 and Figure 4).

In ketamine group (A) at 0 min, out of 50 patients, 38 patients experienced no pain (76%), 5 patients mild pain (10%), 7 patients moderate pain (14%), and 0 patient severe pain. In control group (B), 1 patient experienced no pain (2%), 3 patients mild pain (6%), 15 patients moderate pain (30%), and 31 patients experienced severe pain (62%) (Table 2 and Figure 5).

In ketamine Group (A) at 1 min, out of 50 patients, 43 patients experienced no pain (86%), 4 patients mild pain (8%), 2 patients moderate pain (4%), and 1 patient experienced severe pain (2%). In control Group (B),

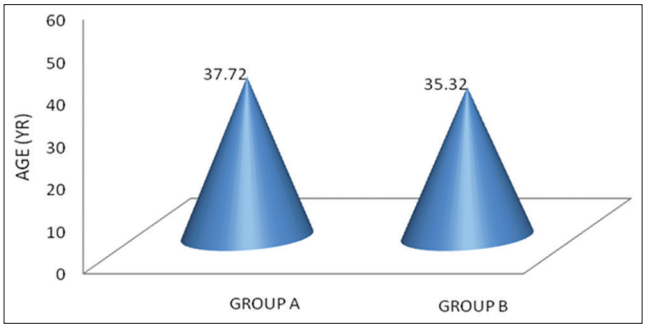

Figure 1: Comparison of age between the two groups

Table 2: Incidence of pain at 0, 1, 2, and 3 min

Pain score	Incidence of pain at 0 minute		Incidence of pain at 1 minute		Incidence of pain at 2 minute	
	Group A *n* (%)	Group B *n* (%)	Group A *n* (%)	Group B *n* (%)	Group A *n* (%)	Group B *n* (%)
0	38 (76)	1 (2)	43 (86)	0 (0)	40 (80)	2 (4)
1	5 (10)	3 (6)	4 (8)	3 (6)	7 (14)	7 (14)
2	7 (14)	15 (30)	2 (4)	15 (30)	3 (6)	21 (42)
3	0 (0)	1 (2)	1 (2)	32 (64)	0 (0)	20 (40)

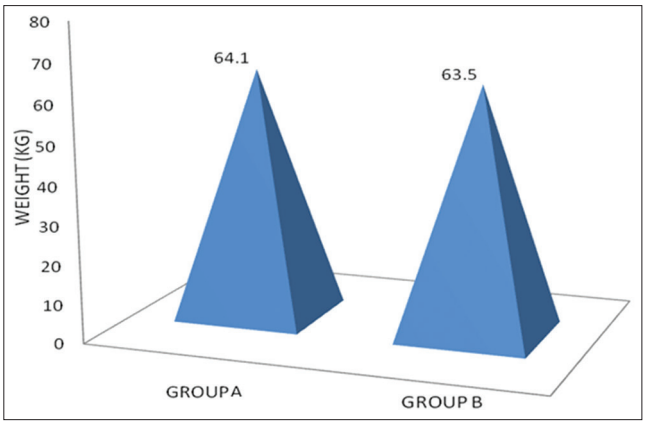

Figure 2: Comparison of weight between the two groups

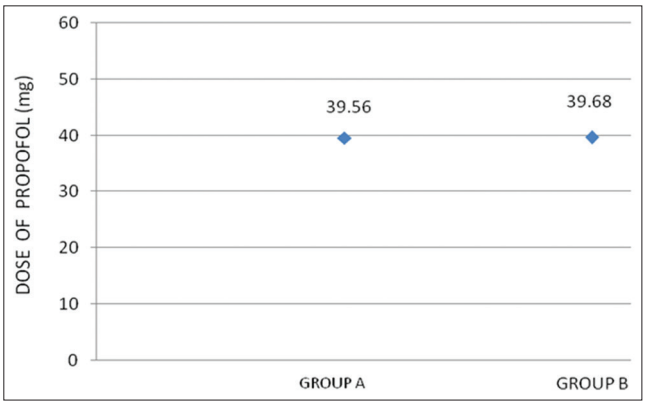

Figure 3: Comparison of dose of propofol between the two groups

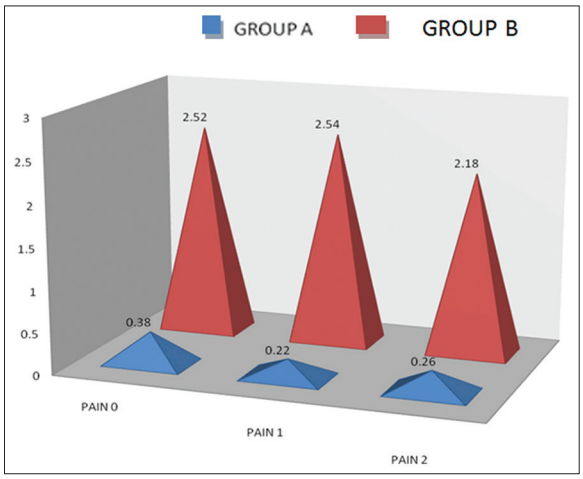

Figure 4: Comparison of mean pain score at 0, 1, and 2 min between ketamine and control group

0 patient experienced no pain, 3 patients mild pain (6%), 15 patients moderate pain (30%), and 32 patients experienced severe pain (Table 2 and Figure 6).

In ketamine Group (A) at 2 min, out of 50 patients, 40 patients experienced no pain (80%), 7 patients mild pain (14%), 3 patients moderate pain (6%), and 0 patient

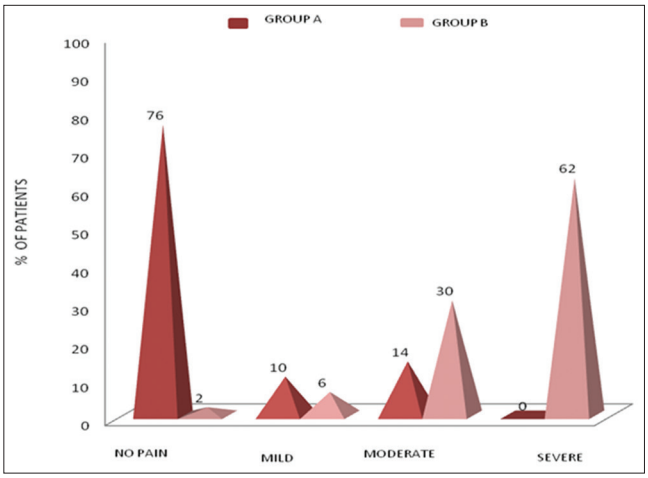

Figure 5: Incidence of pain at 0 min

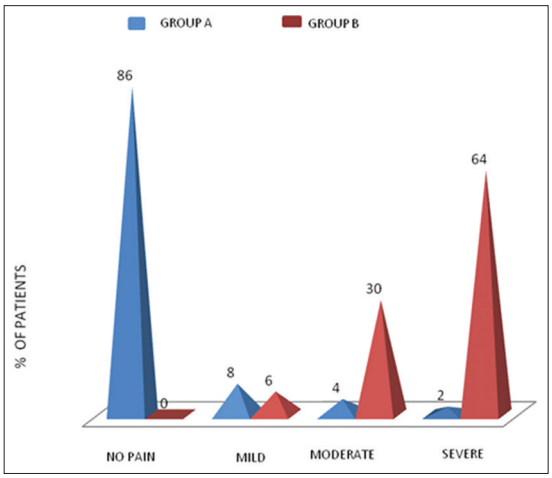

Figure 6: Incidence of pain at 1 min

experienced severe pain (0%). In control Group (B), 2 patients experienced no pain (4%), 7 patients mild pain (14%), 21 patients moderate pain (42%), and 20 patients experienced severe pain (40%) (Table 2 and Figure 7).

No statistically significant difference in hemodynamic variables was found at 0, 1, and 2 min after administration of propofol between ketamine group and control (Table 3 and Figures 8-10).

DISCUSSION

Pain has been often described as an unpleasant sensory and emotional experience associated with tissue or cell damage and it gives a warning that such damage is taking place. Pain on injection of IV drugs is usually not considered as a serious complication of anesthesia but it may be distressing to the patients and can reduce the acceptability of an otherwise useful agent. Although the pain on injection of propofol is not considered as a serious complication, yet it is common problem, the incidence of which is between

Table 3: Comparison of hemodynamic variable in Group ketamine and control

Time interval	Mean (SD)		*P* value
	Group ketamine	Group control	
Heart rate (beats/min)			
0 min	80.86 (9.81)	79.04 (10.79)	0.38
1 min	83.64 (9.03)	81.20 (9.21)	0.18
2 min	82.92 (9.49)	80.50 (10.45)	0.23
Systolic blood pressure			
0 min	127.80 (6.29)	126.74 (5.69)	0.38
1 min	129.88 (8.83)	129.48 (8.91)	0.82
2 min	125.90 (5.60)	126.20 (5.75)	0.79
Diastolic blood pressure			
0 min	78.02 (9.37)	75.92 (7.85)	0.23
1 min	78.76 (9.55)	78.74 (9.11)	0.99
2 min	78.38 (7.01)	77.98 (7.35)	0.78

SD: Standard deviation

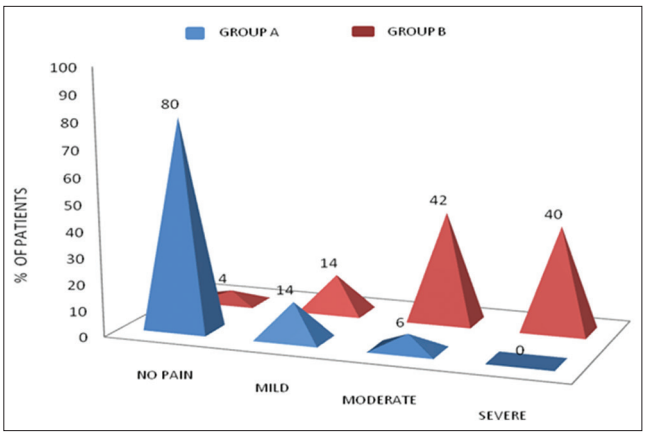

Figure 7: Incidence of pain at 2 min

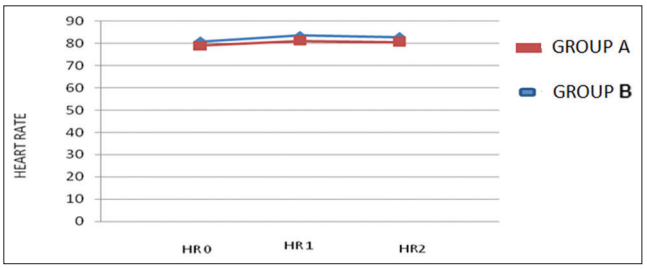

Figure 8: Comparison of heart rate at 0, 1, and 2 min in between group ketamine and saline group

40% and 86%.[1] As the quality of an anesthetic is judged by any recall of discomfort or pain at the time of anesthetic induction and its interference with patient satisfaction, efforts are underway to reduce the severity of the pain or discomfort.

In the present study, we used ketamine in a dose of 0.2 mg/kg, which is much lower than the dose producing central analgesic effects. As a non-competitive NMDA receptor agonist, ketamine may activate NMDA receptors either in the vascular endothelium or in the central nervous system. It seems likely that the reduction in injection pain was the result of a peripheral action which attenuated the efferent pain pathway by its local anesthetic action.

The present study was designed to ascertain whether the low dose of ketamine could attenuate the pain produced by propofol and 1 min was allowed for its action to begin. We chose 1 min interval because previous investigators have found 20 mg lidocaine with a venous occlusion for 10, 20, or 30 s to be significantly better than placebo, suggesting that venous occlusion is important.

Mangar and Holak[23] demonstrated that administering lidocaine after a tourniquet was inflated to 50 mmHg for 1 min virtually abolished the pain associated with propofol injection. The tourniquet isolates the arm veins from the rest of the circulation and increases the action of locally acting substances.

The pain was monitored using pain score at 0, 1, and 2 min after administration of propofol by an independent observer. We have not used VAS score in the present study because of the probable impairment of reading and motor coordination skills of the patients after propofol injection. The mean pain score at 0 min was 0.38 compared to 2.52 in group control. The mean pain score was more in control group as compared to ketamine group and was statistically significant. The mean pain score at 1 min was 0.22 compared to 2.54 in group control. The mean pain score was more in control group as compared to ketamine group and was statistically significant at 1 min. The mean pain score at 2 min was 0.26 compared to 2.18 in group control. The mean pain score was more in control group as compared to ketamine group and was statistically significant at 2 min. The present study has shown a significant difference in pain score at 0, 1 and 2 min.

Ozkoçak *et al.* have done a similar study in which they have compared the effect of saline 2 mL, ketamine 0.5 mg/kg, and ephedrine 70 μg kg on propofol injection pain. They have used pain using numerical scale (0-10) as compared to the present study in which pain scale (0-3) was used. The mean pain score in their study was 2.1 in group ketamine, 4.9 in group saline, and 4.6 in group ephedrine. Their study has shown significant decrease in pain score in ketamine group compared to other two groups. The dose of ketamine used in their study was 0.5 mg/kg as compared to 0.2 mg/kg in the present study. The pain was monitored at regular time interval in the present study as compared to Ozkoçak *et al.* study in which it was at a point of time.[24]

Saadawy *et al.* have done similar study to assess efficacy of ketamine (0.4 mg/kg), thiopental (0.5 mg/kg), meperidine

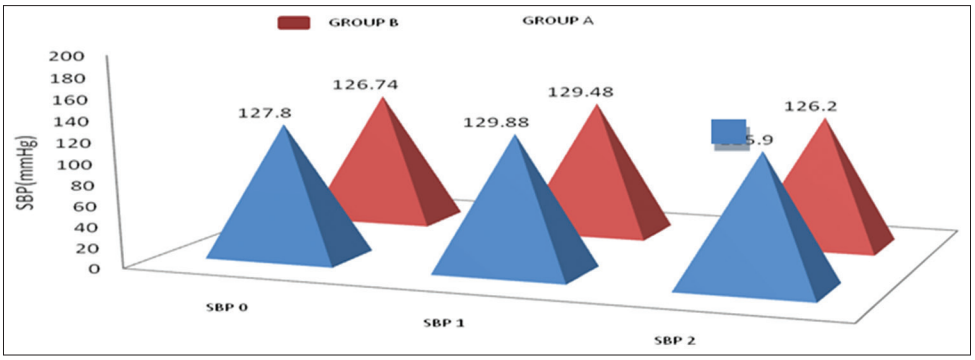

Figure 9: Comparison of systolic blood pressure at 0, 1, and 2 min in between group ketamine and saline group

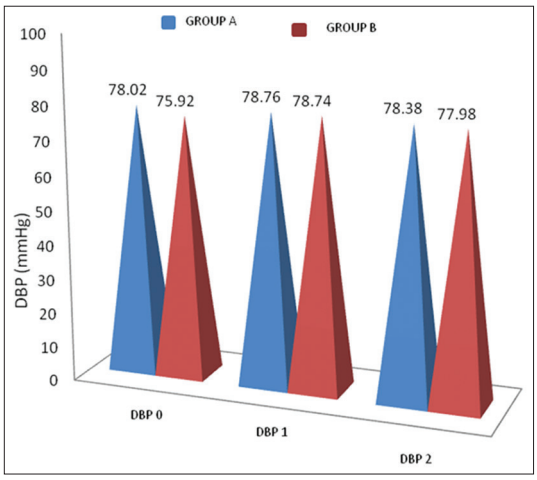

Figure 10: Comparison of diastolic blood pressure at 0, 1, and 2 min in between group ketamine and saline group

(0.4 mg/kg), saline and lidocaine (1 mg/kg) on propofol injection pain. As compared to the present study, they have seen pain at one point of time rather than at different point of times. The incidence of pain in their study was significantly less in ketamine group (8%) as compared to saline group (88%). The dose of ketamine used in their study was 0.4 mg/kg as compared to 0.2 mg/kg in the present study. The present study has shown similar significant different incidence of pain with lower dose of ketamine as compared to their study.[25]

The mean systolic blood pressure in ketamine group at 0, 1, and 2 min was 127.80, 129.88, and 125.90 mmHg, respectively. The control group has shown mean systolic blood pressure 126.74, 129.48, and 126.20 mmHg at 0, 1, and 2 min, respectively. The present study has not shown any effect of 0.2 mg/kg on systolic blood pressure as compared to saline group. Ozkocak *et al.*[24] have found mean systolic blood pressure of 120 mmHg in group ketamine, 123 mmHg in group ephedrine, and 104 mmHg in group saline. They have found significant difference in the mean systolic blood pressure in between ketamine and saline group in their study, ($P < 0.05$). They have stated that ketamine pre-treatment may prevent hypotension due to propofol induction. The present study has not found any significant difference in the systolic blood pressure in between two groups with 1/4th of induction dose of propofol.

The mean diastolic blood pressure in ketamine group at 0, 1, and 2 min was 78.02, 78.76, and 78.38 mmHg, respectively. The control group has shown mean systolic blood pressure 75.92, 78.84, and 77.98 mmHg at 0, 1, and 2 min, respectively. The present study has not shown any effect of 0.2 mg/kg on systolic blood pressure as compared to saline group.

Saadawy *et al.*[25] have found statistical significant difference in ketamine group (85.6 mmHg) as compared to saline group (74.4 mmHg). The present study has not found any significant difference in systolic and diastolic blood pressure in between two groups.

Strengths of the Study

Our study demonstrates that the incidence of pain on low-dose ketamine pre-treatment was effective in reducing the incidence and severity of pain during induction of anesthesia among our study participants.

Limitations of the Study

We had several limitations. Many factors can affect the incidence of pain, which include site of injection, size of vein, speed of injection, buffering effect of blood, temperature of propofol, and concomitant use of drugs such as local anesthetics and opioids, all of which could not be get rid of.

Future Directions of the Study

Further studies are needed to establish the feasibility of this technique in children and emergency induction of anesthesia.

CONCLUSION

Propofol (2,6-diisopropylphenol) used for the induction of anesthesia often causes mild-to-severe pain or discomfort

on injection, for which various methods have been tried, but with conflicting results. The present study concluded that low-dose ketamine pre-treatment is effective in reducing the incidence and severity of pain as compared to saline. The pre-treatment with ketamine in low dose is also free of hemodynamic consequences.

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