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Original Article

Anaesthesia Section

Evaluation of Low-Dose Ketamine Pretreatment to Reduce Propofol Injection Pain: A Randomised, Double-Blind, Controlled Trial

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ABSTRACT

Introduction: 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 pretreatment is one of the methods proposed to reduce attenuate propofol injection pain due to its local anaesthetic properties.

Aim: To determine if low-dose ketamine could reduce propofol injection pain in dorsal hand vein. To study haemodynamic effects of this combination of drugs, and to know if any untoward effects like emergence phenomenon occur on administering low-dose ketamine.

Settings and Design: A prospective, randomised, double-blind, placebo-controlled study in a Public Health institute.

Materials and Methods: In this prospective, randomised, double-blind, placebo-controlled study,60 ASA 1 and 2 patients with ages from 18 to 65 years, scheduled for minor gynaecologic surgery under total intravenous anaesthesia were randomly allocated into two groups (A and B). After obtaining written, valid and informed consent, patients in group A received ketamine as the pretreatment before receiving propofol. Those in group B received saline before administration of propofol. Pain scores were measured by the investigator immediately following injection of propofol. All patients' responses were graded by a verbal pain score.

Statistical Analysis: Results were analyzed using t-test, and Chi-square tests.

Results: It was noted that low-dose ketamine was effective in reducing the incidence of pain from 93.3% in the control group to 20% in patients administered ketamine. The intensity of pain was also reduced in the ketamine group, as none of the patients experienced severe pain as compared to 33.30% in control group. Ketamine did not produce any emergence phenomenon or any other side effects at this low dose.

Conclusion: Low-dose ketamine pretreatment is useful in significantly reducing the incidence of pain on injection of propofol. Haemodynamics are preserved for a short interval after administration of propofol, which was more useful when compared to placebo administration. Ketamine does not produce any emergence or side effects in low dose.

Keywords: Local effect, Placebo, Premedication, Verbal pain score

INTRODUCTION

Propofol (2,6-diisopropylphenol) is a drug of choice for short procedures as it results in quicker recovery and earlier return of psychomotor function as compared to thiopentone or methohexital. It is also popular for its anti-emetic properties. Propofol possesses many characteristics of an ideal anaesthetic agent as it produces hypnosis in one arm-brain circulation time with minimal excitation. However, disadvantage of propofol is pain on injection, which is sometimes very unpleasant to patients. Among 33 clinical problems propofol-induced pain ranked seventh, when both clinical importance and frequency were considered [1]. The experience of pain upon the injection of propofol has been widely investigated and is reported to occur in 70% of patients when propofol is injected without any other treatment [2]. In children, the incidence of pain has been found to be around 80% [3]. Many different methods have been proposed to reduce the incidence and severity of this adverse effect of propofol [4-9].

Ketamine has some useful qualities, notably less marked cardio-respiratory depressant effects than other anaesthetic drugs [10], and it has analgesic and local anaesthetic properties [10-12]. Chemical mechanisms for propofol injection pain may involve direct irritation via release of kininogens when propofol comes into contact with the vascular endothelium. The sensory pathway is the afferent free nerve endings between the media and the intima [13]. The local anaesthetic effects of ketamine are caused by antagonism at the N-methyl D-aspartate (NMDA) receptors (which have been found [14] in the vessel endothelium) by opioid mu-receptor antagonism or voltage-sensitive sodium channel interactions. 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 this combination of drugs, and to know if any untoward effects like emergence phenomenon occur on administering low-dose ketamine.

MATERIALS AND METHODS

This study was conducted in the Department of Anaesthesiology of the Topiwala National Medical College and Bai Yamunabai Laxman Nair Charitable Hospital, Mumbai. It was in the form of a prospective, randomized, double-blind, placebo-controlled trial. Based on a previous study [14] in literature, the incidence of pain on injecting propofol was taken to be 80%, and 50% reduction in pain considered clinically significant. The minimum size for each group, assuming a-value of 0.05 and a power value of 90%, was thus calculated to be twenty two. After obtaining approval from the Ethics Committee, sixty patients were recruited by taking their written, valid and informed consent. Patients included were ASA grade 1 or 2, aged 18 to 65 years, weighed between 35 and 75 kg posted for minor gynaecologic surgery. Patients excluded were those with known history of allergy or convulsions, those on sedatives/analgesics/antipsychotics, pregnant and breast-feeding women, patients who required rapid sequence induction and in whom difficult airway was anticipated. Assignment to groups was randomized using toss of coin, into two groups A or B, of 30 each. Group A was to get ketamine as the pretreatment while group B was to be administered normal saline as control. The study was conducted over a period of six months.

A 20 gauge venous cannula was inserted into a vein on the dorsum of the patient's non-dominant hand in the first attempt and a bivalve to facilitate injections was attached. It was connected to an infusion of saline 0.9% at 5ml/kg/hr. After the three-way tap was closed to saline, the pretreatment drug was injected. 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 and was thus blinded to it. The patients were unaware of the study drug used. After 30 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 question 'do you feel anything uncomfortable in your hand or arm' was addressed to each patient when propofol was injected. It was graded as per verbal pain score. Pain score [14] was graded as follows:

0 – No pain.

1 – Mild pain (discomfort in the hand or arm which is acceptable to the patient)

2 – Moderate pain (discomfort in hand or arm which is unacceptable)

3 – Severe pain (grimace or limb withdrawal)

Heart rate and blood pressure were noted before pretreatment and after pretreatment with ketamine, and at 0, 1, 2 and 3 minutes after propofol bolus. Change in heart rate of +/- 20 beats and 20% rise or fall in blood pressure from the baseline was considered clinically significant in our study.

Continuous data was reported as mean ± standard deviation. Comparison of age, sex, weight and ASA between the groups was obtained by Student's t-test. Categorical data was reported as numbers and percentages and analysed using Chi-square test or Fisher's exact test as appropriate. The value p <0.05 was considered statistically significant.

RESULTS

The groups were comparable with respect to age, weight, height, sex, and physical status. 80% (24)of the patients in the study group had no pain as compared to 6.7% (2) in the control group. Mild and moderate pain occurred in 16.70% (5) and 3.30% (1) respectively in group A compared

Pain Score	Group A (ketamine) n = 30	Group B (saline) n =30
0	24 (80 %)	2(6.7 %)*
1	5(16.70 %)	4 (13.30 %)*
2	1 (3.30%)	14 (46.70%)*
3	0 (0%)	10 (33.30%)*
Chi square test applied	p- value	Significance
Pearson Chi square	1.07 E-08	Significant

[Table/Fig-1]: Comparison of pain score between the two groups.
*0 – No pain, 1 – mild pain, 2 – moderate pain, 3 – severe pain
*p< 0.05 for intergroup differences

Time intervals	GroupA Ketamine		Group B Saline		Unpaired T-test applied		
	Mean	SD	Mean	SD	T-value	p-value	Significance
Before pretreatment	78.37	13.18	87.77	15.92	1.990	0.051	NS
After pretreatment	90.70	13.16	87.17	15.24	-0.961	0.340	NS
After propofol bolus	89.43	11.87	86.13	14.10	-0.981	0.331	NS
After propofol bolus (1 min)	83.37	12.75	81.80	13.24	-0.467	0.642	NS
After propofol bolus (2 min)	78.03	9.42	79.30	12.85	0.435	0.665	NS
After propofol bolus (3 min)	75.47	9.50	76.47	12.41	0.350	0.727	NS

[Table/Fig-2]: Comparison of pulse rate (beats/min) at different time intervals between the two groups.

Time intervals	GroupA Ketamine		Group B Saline		Unpaired T-test applied		
	Mean	SD	Mean	SD	T-value	p-value	Significance
Before pretreatment	118.20	15.73	118.33	12.62	0.036	0.971	NS
After pretreatment	126.73	11.44	118.07	11.53	-2.923	0.005	Significant
After propofol bolus	125.73	11.75	116.27	11.58	-3.143	0.003	Significant
After propofol bolus (1 min)	117.20	11.83	108.33	9.13	-3.250	0.002	Significant
After propofol bolus (2 min)	109.80	11.13	107.00	9.52	-1.047	0.300	NS
After propofol bolus (3 min)	109.00	12.13	105.00	9.38	-1.429	0.158	NS

[Table/Fig-3]: Comparison of systolic blood pressure (mmHg) at different time intervals between the two groups.

to 13.30% (4) and 46.70% (14) respectively in group B ($p<0.05$) as depicted in [Table/Fig-1]. The incidence of severe pain (limb withdrawal) was 0% in group A and 33.30% (10) in the group B. Heart rate as seen in [Table/Fig-2] shows a rise in pulse rate in group A by 10 beats per minute after ketamine pretreatment, which though clinically not significant, was statistically significant. In group B there was no change when compared with baseline.The difference between the two groups was not statistically significant. Comparison of systolic blood pressure (mmHg) at different time intervals between the two groups. When the systolic blood pressure after ketamine pretreatment was compared with baseline, in group A there was rise by 6.7% which was statistically significant but not clinically significant. In group B there was no change. When the two groups were compared to each other the difference in systolic blood pressure was significant at pretreatment and upto 1 minute after propofol bolus [Table/Fig-3].

DISCUSSION

Propofol is a versatile intravenous anaesthetic. The mechanism by which propofol causes pain at local site of injection, is unknown but it has been attributed to release of kininogen from the vein wall with triggering of local kinin cascade. 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. Utility of ketamine is limited due to contraindication in patients who have high predisposition to laryngospasm or apnoea (e.g. active pulmonary infection, very young patients), severe cardiovascular disease, CSF obstructive states like severe head injury, central congenital or mass lesions, intraocular pressure pathology like glaucoma and acute globe injury, previous psychotic illness, hyperthyroidism or thyroid medication use, and porphyria but the low cost, ease of administration, effectiveness, relatively better side effect profile, and ease of availability in hospitals make ketamine an otherwise attractive option. It also has local anaesthetic effect and this property can be harnessed to attenuate pain on injection of propofol [15]. The incidence of propofol injection pain in our study was reduced from 93.3 % in control group to 20% in ketamine pretreatment group,and these results are significant when compared with other techniques of propofol injection pain relief [2]. The incidence of severe pain was completely abolished with ketamine.The higher incidence of pain in our study could be attributed to the gender of the patients as females generally have a lower threshold for perceiving pain [9]. Our observations were consistent with those seen by CH Tan et al., [14] where they found ketamine pretreatment reduced the incidence of pain from 84% to 26%. A study done by Ozkocak et al., [16] the intensity of pain was lowered but the incidence was as high as 76% in the ketamine group. Some studies have been done with application of tourniquet after injection [17]. 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 [18]. Another

study done by Zhao GY et al., used a lower dose of ketamine (0.3 mg/kg) and recorded a reduction in the frequency and intensity of propofol injection pain without severe adverse effects [19].

Administration of ketamine 100 μg/kg immediately before propofol injection provided the optimal dose and timing to reduce propofol-induced pain on injection was demonstrated by Koo SW et al., [6]. By giving ketamine as a pretreatment it could act as a preventive analgesia to prevent sensitization of the local nerve endings from noxious inputs.

Thus, this drug is useful for pain relief due to its local action. A comparison between peripheral ketamine pre-treatment and ketamine added to propofol was done, the results supported pH changes as a more important cause for the decrease in propofol injection pain with the addition of ketamine to propofol than a peripheral effect of ketamine [20].

We have used direct questioning in addition to observation of pain responses, to assess the severity of pain. This patient participation has reduced observer bias, thus proving to be a superior technique in assessing pain.

The study done by CH Tan et al., did not comment extensively on the haemodynamic changes after using the combination of ketamine and propofol though both these drugs have effect on haemodynamics [14]. We have tried to study these effects, and also to look for any added advantage or disadvantage using this technique. Furuya and colleagues [21] found that administration of ketamine 0.5 mg/kg, one minute prior to propofol induction prevented an excessive decrease or increase in arterial pressure after intubation. The mechanism causing the decrease in arterial pressure and heart rate induced by propofol, include inhibition of myocardial contractility, decrease in peripheral vascular resistance and sympathetic inhibition leading to a decrease in vascular resistance and cardiac output [22]. Ketamine has the effect of sympathetic stimulation leading to increase in arterial pressure and heart rate [15]. Administration of low doses of ketamine was thought to have some benefit especially in patients with hypovolaemia, ischemic heart disease and ischemic cerebral vascular disease who are prone to a greater decrease in arterial pressure with propofol [16]. Ketamine produces a dose-related rise in the rate-pressure product with a transient rise in the cardiac index but without significantly altering the stroke index [15]. It produces sympathomimetic actions primarily by direct stimulation of structures of central nervous system. Recent studies have shown ketamine directly dilates vascular smooth muscle, while causing sympathetically-mediated vasoconstriction. The net effect is that systemic vascular resistance is not significantly altered by ketamine [15]. In our study it was noted that after pretreatment with ketamine there was a transient rise in heart rate and systolic blood pressure, which returned to baseline after one minute of propofol bolus and subsequently fell below baseline. It was noted that the haemodynamic changes, though in some instances were statistically significant, were never clinically significant. This could be due to use of low doses of ketamine (10 mg) and propofol (30 mg). Haemodynamic effects caused by propofol injection were prevented by low-dose ketamine, but only transiently, thus offering temporary haemodynamic advantage.

CONCLUSION

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

LIMITATIONS

This study had an absence of comparison with other standard techniques of pre treatment advocated to reduce propofol injection pain.

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