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COMPARISON OF LIGNOCAINE AND KETAMINE PRETREATMENT IN REDUCING PAIN OF PROPOFOL INJECTION. A DOUBLE-BLIND, PROSPECTIVE, AND RANDOMIZED STUDY.

Anaesthesiology

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ABSTRACT

Background and Aims: Intravenos injection of propofol during anesthetic induction induces pain. Several drugs have been studied to alleviate this pain. Ketamine has been shown to reduce injection pain. Aim of this study was to assess the efficacy of ketamine pretreatment to alleviate the propofol injection pain and compare it with lignocaine **Settings and design:** This was a prospective, randomized, double-blinded study. **Methods:** 110 patients of age 18-60 yrs with weight between 35-75kg of ASA grade I and II, undergoing various elective surgeries under GA, were selected and randomly divided in two groups K and L with 55 patients in each group. Patients in group K, received ketamine (0.1mg/kg) pretreatment 60 sec before 3 ml of 1% propofol bolus, and patients in group L received lignocaine Hcl (1mg/kg) 60 sec before propofol bolus.. The patients were asked about the pain on injection. For analysis of pain a score of 0-3 of verbal pain score (VPS) was used. **Results:** In Group K 92.7% of the subjects had no pain (VPS score = 0), 7.3% had mild pain (VPS = 1) and none of the subjects had moderate pain (VPS = 2), while in Group L 85. 5% subjects had no pain (VPS score = 0), 10.9% had mild pain (VPS = 1) and 3.6% subjects with moderate pain (VPS score = 2). Application of Chi square test however showed that this difference in VPS score among study groups was not statistically significant. (p=0.278) HR, SBP, DBP, MAP, all were low in both the groups after 1 min of administration of study drug , but the changes were not statistically significant(P>0.05). No significant change in SBP, DBP & MAP after propofol bolus in both the groups. **Conclusion:** Ketamine in a dose of 0.1mg/kg administered just before propofol can reduce the incidence and intensity of propofol induced pain without significant adverse hemodynamic effects. So we can use ketamine as an effective and safe alternative to lignocaine

KEYWORDS

Pain, Ketamine, Propofol, Lignocaine, Verbal pain Score (VPS), Pain on Propofol Injection(POPI).

INTRODUCTION

Propofol is the most widely used intravenous (IV) anesthetic agent for induction and maintenance of anesthesia as well as for sedation inside and outside operation theatre. Propofol is almost an ideal IV anesthetic agent, but pain on its injection still remains a problem, most patients remember it as one of the unpleasant encounters with anesthetists. In one survey, pain on propofol injection (POPI) stands seventh most important problem in the Current practice of clinical anesthesia.[1] Lignocine is most commonly used drug to relive POPI, but it does not provide complete relieve from POPI, protection is not complete, with a failure rate of between 32% and 48%.[2] Also some patients may have history of hypersensitivity to local anesthetic, so in that case we must have some alternative to lignocaine, so our study was done to find efficacy of ketamine in reducing POPI and compare it with lignoaine hydrocloride.

METHOD

This study was carried out in the Department of Anaeshtesiology and critical care of a tertiary care centre National Institute of Medical Sciences and Research, Jaipur, after obtaining approval from ethical committee of hospital and written informed consent from all patients.

Study type: It was a prospective, double blind, randomized study.

Study population: Patients visiting the institute for elective surgery under general Anaesthesia.

Study groups: Based on a computer generated randomization table, a total of 110 patients were randomly divided in two groups K and L with 55 patients in each group.

Group K: Received ketamine 0.1 mg/kg
Group L: Received lignocaine Hcl (2%) 1 mg/kg

Sample Size:
A total of 110 patients were randomly divided in two groups of 55 each. Sample size was determined, using the formula mentioned below for equivalence trial where
N = Size per group;
δ = A clinically acceptable margin;
S = Pooled standard deviation of both comparison groups and
z = Standard normal deviate.
55 patients per group were required for the study, with type I error (α) =0.05, type II error (β) =0.20, power of study 80% and 95% confidence limit.

$$N = 2 \times \left(\frac{z_{1-\frac{\alpha}{2}} + z_{1-\beta}}{\delta} \right)^2 \times s^2$$

Inclusion Criteria:

1. Patients with ASA class I and II
2. Patients with age between 18 and 60 years, weighed between 35 and 75 kg.
3. Patients who give informed written consent.
4. Patients scheduled for elective surgery under general anesthesia.

Exclusion Criteria:

1. Patients with known history of allergy to study drug.
2. Patients with history of convulsions
3. Patients on treatment with sedatives, analgesics, antipsychotic and Antihypertensive.
4. Pregnant and breast feeding women.
5. Patients who required rapid sequence induction.
6. Patients with difficult airway.
7. Patients undergoing emergency surgery.

Pre-anaesthetic assessment of patients was done on pre-operative day. Written informed consent for the drug to be used was taken. All patients were kept nil per oral for 6 hours before surgery. No pre-medication was advised to the patients. In the operation theatre, after proper identification, monitoring of vital parameters, with Philips monitor i.e. pulse, BP, oxygen saturation, respiratory rate was recorded as baseline vitals.

A 20 gauge venous cannula with a three way valve was inserted into a vein on the dorsum of the patient's non-dominant hand. It was connected to an infusion of saline 0.9% at 5ml/kg/hr. After the three-

way valve was closed to saline, the pretreatment drug was injected. The patients were given ketamine 0.1mg/kg in group K and 1mg/kg of 2% lignocaine Hcl was given to patients of group L, by an operator who was unaware of the content of the injected solution and was thus blinded to it. The patients were also unaware of the study drug used. After 1 minute of pretreatment with the study drug, 3 ml bolus of 1% propofol was given over 3 seconds and the three-way valve was opened to the saline infusion. All of the patients were instructed about the verbal pain score 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** (VPS) 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 recorded before pretreatment (T0) and after1 minute of pretreatment with ketamine, and lignocaine (T1) and at 0 (P0), 1 (P1), 2 (P2) and 3 (P3) minutes after propofol bolus.

Statistical analyses

Statistical analyses were done using computer software (SPSS Trial version 23 and primer). Comparison of age, sex, weight and ASA between the groups was obtained by Student's t-test. Categorical data were reported as numbers and percentages and analysed using Chi-square test. The value $p < 0.05$ was considered statistically significant. Continuous variables were summarized as mean and SD, where as Nominal/categorical variables as proportions. Unpaired't' test was used for continuous variables while chi-square test was used for nominal/categorical variables.

RESULT

Out of total 110 subjects, 70% were females while 30% were males. This difference was not statistically significant (p=0.298) and the two groups were comparable in their gender composition. 53.6% were ASA I while 46.4% were ASA II. Both the groups were comparable regarding distribution based on ASA grade (p=0.085). The patients in both the groups were evenly matched based on age and weight distribution.

Table 1: Comparison of mean age (years) of study groups

Group	N	Mean	Std. Deviation
Group K	55	39.87	2.22
Group L	55	36.02	1.43
t = 1.458 ; at 108 degree of freedom; p = 0.148 (NS)			

Table 2: Gender distribution of study subjects

Gender	Group K		Group L		Total	
	N	%	N	%	N	%
Female	36	65.5	41	74.5	77	70
Male	19	34.5	14	25.5	33	30
Total	55	100	55	100	110	100
Chi square = 1.082 ; at 1 degree of freedom; p = 0.298 (NS)						

Table 3: Comparison of mean weight (Kg) of study groups

Group	N	Mean	Std. Deviation
Group K	55	60.20	7.79
Group L	55	61.67	10.37
t = -1.098 ; at 108 degree of freedom; p = 0.274 (NS)			

Table 4: Distribution of study subjects according to ASA grade

ASA grade	Group K		Group L		Total	
	N	%	N	%	N	%
Grade I	34	61.8	25	45.5	59	53.6
Grade II	21	38.2	30	54.5	51	46.4
Total	55	100	55	100	110	100
Chi square = 2.961 ; at 1 degree of freedom; p = 0.085 (NS)						

No significant difference was observed in subjects of both the groups on the basis of general examination findings i.e. HR, SBP, DBP, and MAP. This ensures that any significant observation made during the study was attributed to the effect of study drugs only. HR, SBP, DBP, MAP, all were low in both the groups after 1 min of study drug administration, but the changes were not statistically significant. Heart rate was slightly lower in lignocaine group after propofol bolus at 0,1,2,3 min, as compared to ketamine group, but changes were not significant. No significant change in SBP, DBP & MAP after propofol bolus in both the groups

Table 5: Comparison of Heart rate (HR) and Mean Blood Pressure (MBP) among study groups

	Heart rate(bpm)				Mean Blood Pressure(mmHg)			
Time point	Group K	Group L	t	P value	Group K	Group L	t	P value
Baseline (T0)	90 ± 13.1	85.7 ± 11.7	1.819	0.072	95.1 ± 13.3	96.8 ± 12.3	-0.698	0.487
After study drug (T1)	89.9 ± 15	85.4 ± 11	1.801	0.075	93.4 ± 11.6	93.9 ± 10.1	-0.201	0.841
Propofol bolus (P0)	91.3 ± 15.7	83.3 ± 13.3	2.887	0.005	91.8 ± 11.9	89.6 ± 9.8	1.058	0.292
Propofol bolus (P1)	89.9 ± 16.1	79.7 ± 11.7	3.823	<0.001	88.6 ± 11.1	86 ± 10.7	1.258	0.211
Propofol bolus (P2)	96.1 ± 14.9	85.5 ± 12.2	4.073	<0.001	88.6 ± 15.4	88.7 ± 12	-0.014	0.989
Propofol bolus (P3)	87.7 ± 12.9	81.4 ± 10.9	2.766	0.007	83.5 ± 12	83.3 ± 12.2	0.079	0.937

For verbal pain score, in Group K most (92.7%) of the subjects had no pain (VPS score = 0), 4 (7.3%) had mild pain (VPS = 1) and none of the subjects had moderate pain (VPS = 2), while in Group X 47 (85.5%) subjects had no pain (VPS score = 0), 6 (10.9%) had mild pain and 2 (3.6%) subjects with moderate pain (VPS score = 2). Application of Chi square test however showed that this difference in VAS score among study groups was not statistically significant. (p=0.278) Most of the patients in Group Ketamine (92.7%) & in Group lignocaine (85.5%) had no pain or discomfort and this difference was not statistically significant.

Table 6: Distribution of study subjects according to VPS score

VPS score	Group K		Group L		Total	
	N	%	N	%	N	%
None (0)	51	92.7	47	85.5	98	89.1
Mild (1)	4	7.3	6	10.9	10	9.1
Moderate (2)	0	0	2	3.6	2	1.8
Total	55	100	55	100	110	100
Mean VPS ± SD	0.07 ± 0.26		0.15 ± 0.39			
Chi-square = 2.563 with 2 degrees of freedom; P = 0.278 (S)						

DISCUSSION

Various pharmacological[3-5] and non-pharmacological[6,7] methods to decrease pain due to propofol injection have been tried, the most efficacious method has not been identified yet[8]. The most popular is the use of lidocaine either by mixing it with propofol or by pretreatment with a bolus injection of lidocaine[9-11]. However, protection is not complete, with a failure rate of between 32% and 48%[10-12].

In our study lignocaine hydrochloride (lignocaine Hcl) 1mg/kg, and ketamine 0.1mg/kg was used as i.v. pretreatment and after 60sec it was followed by 1% propofol injection 3ml ,both lignocaine and ketamine were found to reduce POPI significantly with no significant change in haemodynamic parameters.

Depue K[13], Jalota Leena et al[9] and Massad I M[11] used lignocaine 1mg/kg with venous occlusion to reduce POPI. Koo SW[14] and Wang M[15] found that a small dose 0.1 mg/kg of ketamine was very effective.

It is postulated that low dose of ketamine may be effective due to its peripheral local anesthetic effect where as with high-dose central analgesic and sedative effect may be playing a role. Based on these studies 1mg/kg lignocaine and 0.1mg/kg of ketamine were chosen in this study. Both the groups were comparable regarding gender (p=0.298) and ASA distribution(p=0.085) The mean weight of subjects in Group K was 61.67 ± 7.79 Kg while in Group L it was 60.20 ± 10.37 Kg, (p=0.274). Mean age of Group K (39.87 years) while in Group L (36.02 years), (p=0.148) i.e. the two groups were comparable in relation to their weight and age. No significant difference was observed in subjects of both the groups on the basis of baseline heart rate (P=0.072) and baseline MAP (p=0.487), so we can say that both the groups were comparable on the basis of baseline haemodynamic parameters and any significant observations made during the study were attributed to the effect of study drugs only and not on any pre

medication difference in the study group.

Saadawy I[16] did a randomized, placebo controlled, double blind study to compare the analgesic efficacy of iv pretreatment with ketamine 0.4 mg/kg; thiopental 0.5 mg/kg; meperidine 0.5 [corrected] mg/kg; lidocaine 1 mg/kg; saline 3 ml. they found that all treatment groups had a significantly lower incidence of pain than placebo group ($p < 0.05$). However, it was observed that pretreatment with ketamine was the most effective in attenuating pain associated with propofol injection ($p < 0.05$). For painless injection of propofol, routine pretreatment with ketamine 0.4 mg/kg along with venous occlusion was recommended.

In our study we observed that ketamine is equally effective to lignocaine Hcl , but not better than lignocaine Hcl , as we have used a lower dose i,e 0.1mg/kg , as compared to 0.4 mg/kg in above study.

Tan CH[17] did a controlled, randomised double blind study to compare the prior intravenous administration of ketamine 10mg (1ml) or 0.9% saline (1ml) on propofol injection pain. 100 patients of ASA status 1 or 2 presenting for gynaecological surgery were studied. Following an initial 5ml bolus of propofol into a dorsal hand vein, 30sec after the treatment, 84% of the saline control patients experienced mild or severe pain compared to 26% of those who were given ketamine pretreatment ($p<0.05$). There were no emergence reactions defined as dreams, hallucinations, delayed recovery and looking dissociated from surroundings in either treatment group.

Similarly in our study ketamine significantly reduces POPI, 7.3% patients were pain free in group ketamine, as compared to above study where 26%patient had no pain, it may be because we used 60 sec duration for pretreatment, as compared to 30 sec in above study.

Koo SW[15] did a study to establish optimum dose of ketamine to prevent POPI. 240 patients presenting for elective surgery were randomly allocated into eight groups; five groups during the first part of the study and three groups during the second part. In Part 1, patients received saline (Group S), lidocaine (Group L), ketamine 10 microg/kg (Group K10), 50 microg/kg (Group K50), or 100 microg/kg (Group K100), respectively, immediately followed by propofol 2.5 mg/kg. In Part 2, the optimal dose of ketamine (100 microg/kg) was administered 3 min before propofol (Group Pre), mixed with propofol solution (Group KP), or after oral midazolam premedication (Group M). An anesthesiologist blinded to the study group monitored each patient's pain score at 5-s intervals. The results showed that In Part 1, the incidence and intensity of pain were the lowest in the K100 and L groups ($P < 0.001$). In Part 2, the patients in the K100 and M groups had significantly lower pain scores compared with the KP and Pre groups ($P < 0.05$). During induction, there were no significant intergroup differences in mean arterial blood pressure and heart rate in all groups. The study concluded that administration of ketamine 100 microg/kg immediately before propofol injection provided the optimal dose and timing to reduce propofol-induced pain on injection. In Our study we got similar results, ketamine 0.1 mg/kg reduces propofol induced pain with no significant changes in haemodynamic parameters.

F Bano, et al[18] compared the effects of lidocaine (2 ml of 1% lidocaine) and ketamine (0.5 mg/kg in volume of 2 ml) pretreatment on POPI and hypotension due to propofol induction.

Anesthesia was induced with propofol, 15 sec after injection of 25% of the calculated dose of propofol, severity of injection pain was evaluated. HR & NIBP were recorded .Incidence of pain after propofol injection was lower in ketamine group but found statistically insignificant. SBP &, DBP were significantly higher in ketamine group after induction with propofol. The maximum fall in SBP from baseline in ketamine group was 16% and 29.1% in lidocaine group, while maximum decrease in DBP in ketamine group was found to be 12.66% vs. 26.47% in lidocaine group. There was no significant change in heart rate from baseline in either group. They concluded that Ketamine pre-treatment with venous occlusion is an effective method in reducing pain and providing hemodynamic stability after propofol induction.

In our study we used less dose of ketamine (0.1mg/kg) and that is why heamodynamically there were no significant changes, as compared to the above study which had used higher dose of ketamine (0.5mg/kg) along with venous occlusion. Hypotension, defined in our study as a fall of systolic blood pressure of greater than 20% of baseline value, occurred in 58% of the ketamine group compared to 60% of the control group. None of the patients experienced a heart rate of less than 50 beat.min−1.

CONCLUSION

Ketamine in a dose of 0.1mg/kg administered just before propofol can reduce the incidence and intensity of propofol induced pain without significant adverse hemodynamic effects. So we can use ketamine as an effective alternative to the most widely used drug lignocaine without any undue side effects. Our results of comparisons suggest a possible strategy that is both efficacious and easy to apply in clinical practice and thus when interventions seem similarly efficacious, choices for intervention can be made on factors such as cost, personal choice, and simplicity of application.

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