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A Comparative Study of Lignocaine, Pethidine, Ketamine and Placebo for Prevention of Pain on Propofol Injection

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ABSTRACT

Background: Pain caused by propofol injection is a common occurrence. **Aims and Objectives**: The aim of this study was to compare and evaluate the efficacy of three drugs, lignocaine, pethidine and ketamine for prevention of pain during propofol injection. **Materials and Methods:** This double blind, placebo-controlled, parallel multi-arm study was done after written informed consent and ethics clearance. Hundred patients of ASA I and II, 18-65 years of age, and with body mass index 18-30 kg/m^2 were included. Exclusion criteria were significant cardiovascular or hepatic diseases, renal insufficiency, and a history of allergy to the study drugs. Group A (Normal Saline), Group B (Ketamine 25 mg), Group C (Lignocaine 20 mg) and Group D (Pethidine 25 mg) were pre-treated with 2 ml of the study agents before propofol injection. The primary outcome was the incidence of pain with propofol injection and the secondary outcomes were the induction time, pain scores at various time intervals, the incidence of recall of pain after surgery, haemodynamic changes and adverse effects. **Results:** There were highly significant differences ($p<0.001$) in the incidences of pain during propofol injection in group A and the other three groups. The difference in incidence of pain was also significant between Group C and other groups. The differences in the pain scores ($p<0.001$) and recall of pain ($p<0.05$) between group A and the other three groups were significant. **Conclusion:** Lidocaine may be considered as a good choice for the purpose of reduction of pain during propofol injection.

Keywords: Propofol; Lidocaine; Ketamine; Meperidine; Pain

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INTRODUCTION

Propofol is a wonderful drug as an induction agent and for short duration procedure. It induces rapid and smooth anaesthesia with minimal side effects. However, pain on propofol injection reported in 28-90% of patients, is one of the major drawbacks to its use.[1] The osmolality of the solvent used in propofol preparation, its pH, or the concentration in aqueous phase of the emulsion are factors responsible for the pain.[2]

Pain caused by the anaesthetic agent is an important part of patient dissatisfaction. Hence different methods have been used to decrease this pain. Addition of local anaesthetics, diluting propofol solution has been attempted but incidence still remains at 30%.[3] A lot of agents such as lignocaine, opioids, ondansetron, ketamine, dexamethasone have been used for prevention of injection pain.[4] But different workers have varying opinion regarding the mode of prevention of propofol injection pain.[5] Hence, we planned to study the effect of lignocaine, pethidine, ketamine and placebo on prevention of pain during propofol injection.

The present study aimed to compare and evaluate the efficacy of three drugs, lignocaine, pethidine and ketamine for prevention of pain during propofol injection so that a suitable remedy can be established.

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MATERIALS AND METHODS

This double blind, placebo-controlled, parallel multi-arm study was done after ethics clearance and written and informed consent from patients. The principles outlined in the Declaration of Helsinki were followed. Hundred patients of ASA I and II, aged 18-65 year, and with body mass index 18-30 kg/m^2 were randomly assigned into one of the four study groups (n= 25 each) under investigation. Exclusion criteria were significant cardiovascular or respiratory disease, hepatic diseases, renal insufficiency, psychiatric illness, history of allergy to agents under investigation and those taking sedative and analgesic drugs.

Premedication with alprazolam 0.25 mg, the night before and the morning of surgery was done. Baseline heart rate, blood pressure, SpO2, ECG and pain status were recorded. Before induction of anaesthesia, patients were told that they would be receiving intravenous (IV) anaesthesia that might cause pain in the forearm. They were instructed to inform the investigator of the amount of pain they experienced by using verbal rating scale (0-3), where score of 0 was given for no pain, 1 for mild pain (reported only in response to questioning without any behavioural sign), 2 for moderate pain (reported in response to questioning, accompanied by a behavioural sign or pain reported spontaneously without questioning) and 3 for severe pain (strong vocal response accompanied by facial grimacing, arm withdrawal or tears).

All study patients were randomly allocated into four groups of 25 each using a list of computer-generated random number and sequentially numbered opaque sealed envelopes were prepared. An anaesthesia technician not participating in the drug administration or data collection prepared drugs. The anaesthesiologist who administered the drugs was not involved in the encoding of the data, and the observers who recorded all pain scores and patients were blinded to the used drug.

Group A: 2 ml of Normal Saline.
Group B: 2 ml of Ketamine 25 mg.
Group C: 2 ml of Lignocaine 20 mg.
Group D: 2 ml of Pethidine 25 mg.

On the operation table, the patient had IV access on the dorsum of hand by using 20-gauge catheter and attached to an infusion of acetated Ringer's Lactate. Pulse, BP, SpO2 and ECG were noted. IV infusion was stopped and the arm with IV line was elevated for 15 seconds for gravity drainage of venous blood. A tourniquet was tied at this forearm to obstruct the venous flow only. Then 2 ml of the study drugs under investigation was administered intravenously over 10 seconds and occurrence of any pain was noticed. After one minute, the tourniquet was released and the required amount of propofol (2mg/kg) was administered intravenously. The occurrence and severity of pain was assessed as per noted below after 25% of the desired volume of propofol was injected. At the same time the changes in pulse, BP, SpO2, etc. was noted. The changes in haemodynamic and pain scores were also recorded after 5 and 10 minutes of propofol injection. After propofol, fentanyl 2 mcg kg^{-1}, and vecuronium 0.1 mg kg^{-1} body weight were also administered and intubation was done. Anaesthesia was maintained using isoflurane (0.6-1.2%), air and oxygen. Injection paracetamol 15 mg kg^{-1} TDS was given to all patients, the first dose intraoperatively. Ondansetron 4 mg iv was injected about 30 minutes before the anaesthesia was reversed.

Patients were followed up for 2 hours in recovery room and asked for recall, if there was pain during injection of propofol in recovery room and incidence of pain was graded as 0 when there was no recall of pain and 1 if there was recall of pain.

The primary outcome was the incidence of pain associated with propofol injection after pre-treatment with each of the study drugs and the secondary outcomes were the induction time, the incidence of recall of pain after surgery, pain scores at various time intervals, incidence of spontaneous expression of pain, the hemodynamic changes and any associated adverse effect.

Considering 70% reduction in pain as clinically significant 20 patients were calculated as the minimum sample size for each group assuming alpha error of 0.05 and a power of study as 80%. To allow for the drop outs a sample size of 25 for each was taken. The results were analysed by using analysis of variance (ANOVA test). The data were expressed as means and standard deviation. Unpaired student t test for intergroup comparison of parametric data was used. For ordinal data e.g. VRS scores, Chi-square test was used. P value <0.05 was considered as statistically significant.

RESULTS

All the groups were comparable as far as the age distribution, sex, BMI or ASA status of patients are concerned (Table 1). There were highly significant differences in the incidences of pain during propofol injection in group A (Placebo) and the other three groups ($p=0.006$). Differences in the incidences of pain between groups B and D were insignificant, although the differences in pain between groups B and C and that between groups C and D were significant (Table 2). Mean induction time i.e., the time lapse between the injections of propofol to loss of consciousness of all the four groups were comparable (Table 2).

Table 1: Demographic Profile

Variables	Group A(n=25)	Group B(n=25)	Group C(n=25)	Group D(n=25)	P-value
Age(years)	41.2±4.94	36.04±8.55	38.44±8.397	38.0±8.40	0.135(ANOVA)
Sex M/F	11/14	9/16	10/15	8/17	0.849(Chi-square test)
ASA 1/2	20/5	19/6	17/8	18/7	0.79(ChiSquare)
BMI(kg/m^2)	25.51±8.02	22.15±8.28	23.41±10.47	24.51±8.12	0.57(ANOVA)

Data are presented as mean±SD and counts. Abbreviations: M, Male; F, Female; ASA, American Society of Anaesthesiologists; BMI, body mass index

Table 2: Time of Induction and Incidence of Pain

Variables	Group A(n=25)	Group B(n=25)	Group C(n=25)	Group D(n=25)	P-value
Induction time(Sec)	26.24±2.264	26.12±4.186	24.6±3.64	25.16±3.49	>0.05(ANOVA)
Incidence of pain during Propofol injection n(%)	21(84)	13(52)	9(46)	15(60)	P(AB)<0.001*** P(AC)<0.001*** P(AD)<0.001*** P(BC)<0.05** P(CD)<0.05** P(BD)>0.05*
Incidence of Recall of pain n(%)	18(72%)	9(36%)	4(16%)	11(44%)	P(AB)=0.009** P(AC)<0.05) ** P(AD)<0.05** P(BC)>0.05* P(CD)>0.05* P(BD)>0.05*

*Insignificant; ** Significant; *** Highly Significant;

The differences in the pain scores between group A and the other three groups were highly significant ($p<0.001$). The differences in the pain scores between groups B and D were insignificant ($p>0.05$), though the differences in the pain scores between groups B and C and the same between groups C and D were significant ($p<0.05$) (Figure 1).

The differences of recall of pain between group A (placebo) and the other three groups was significant ($p<0.05$), although there were no significant differences between the same among other three groups ($p>0.05$) (Table 2).

The incidences of spontaneous expression of pain in different groups were negligible. Two patients in group A showed grimacing and 3 cried; 1 patient in Group B showed grimacing and 1 cried; and 2 patients in group D showed grimacing. None of the patients in group C showed any incidence of spontaneous expression.

There was insignificant change in heart rate, mean arterial pressure and SpO2 at different points of time among patients of the groups. The most common adverse effect was hypotension. There were also few incidences of post-operative nausea and vomiting (PONV), hallucination, headache, etc. but overall, these incidences were negligible.

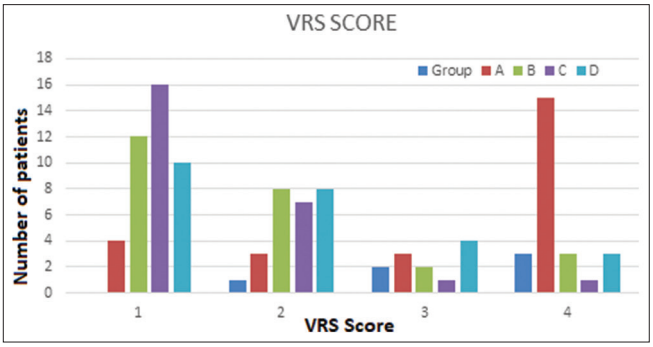

Figure 1: Mean values of Pain Score in the Four Groups

DISCUSSION

Propofol as an intravenous anaesthetic agent has increased rapidly because of high quality of anaesthesia and rapid recovery. However, pain on its injection is distressing feature. Pain of injection at the induction of anaesthesia can cause agitation and hinder the smooth induction of anaesthesia and thus an effective method of prevention would be beneficial. Several methods of prevention of pain have been tried with varying degrees of success.

Several authors have found that lignocaine in propofol reduced the pain of injection.[6] Gupta et al. in a randomised, double blind study between lignocaine, pethidine, dexamethasone and placebo conducted for prevention of propofol injection pain have shown the incidence of pain after giving lidocaine before the injection of propofol to be 40 % as compared to 75% in case of placebo.[7] In the present study similar results were seen, i.e. 36% patients complained of pain after giving lidocaine as compared to 84% in placebo group.

The analgesic effect of lignocaine may occur because of a local anaesthetic effect or an inhibitory effect on the enzymatic cascade which leads to release of kinin.[8] Different concentrations of lignocaine were used in different studies. Optimal dose of lidocaine using control, 20 mg, 30 mg and 40 mg lidocaine was studied. It was found that increasing the lidocaine dose significantly reduced pain.[9] Sharon et al. used 1 ml of 0.5% (5 mg) lignocaine, 1% (10 mg) lidocaine and 2% (20 mg) lidocaine mixed with 19 ml propofol and they supported the use of 20 mg of lignocaine to minimise discomfort due to propofol injection.[10] In our study concentration of lignocaine was 2 ml of 1% (20 mg) and 64% patients had no pain on propofol injection, which was statistically significant when compared to placebo group.

Pethidine is a synthetic opioid with proven local anaesthetic effect. Local anaesthetic effect is most likely due to its structural similarity to cocaine.[11] Lyon et al., found that pethidine (25 mg) is a suitable candidate prior to the injection of propofol with very low incidence of moderate and severe pain (<20%).[12] Similarly, in our study the incidence of severe pain was 12% using pethidine. Pang et al. compared the analgesic effect of fentanyl, morphine, meperidine (pethidine) and lidocaine in peripheral veins and found that lidocaine 60 mg or meperidine 40 mg effectively reduces pain on propofol injection but 74% patients complained of skin erythema distal to tourniquet after meperidine injection.[13] Our findings resemble the study. We used 25 mg in 2 ml solution of pethidine, 40% patients had no pain on propofol injection, in contrast to 16% in placebo. None of the patients complained of skin erythema after getting pethidine. We used lower doses of pethidine which could be the reason that we did not meet this adverse effect.

The IV anaesthetic ketamine possesses analgesic properties and has been used in combination with propofol for general anaesthesia. The analgesic effects of ketamine are seen at plasma concentrations significantly lower than those producing hypnosis (0.2 microgram/ml versus 1.5-2.5 microgram/ml, respectively).[14] In our study we used 25 mg of ketamine in 2 ml of normal saline and it effectively reduced pain on propofol injection. Pre-treatment with the N-methyl-D-aspartic acid antagonist ketamine was also effective in reducing the risk of pain from propofol injection in various other studies.[15,16]

Injection of propofol without any drug (group A) caused pain in 84% of patients, 60% complaining of severe pain. But in contrast incidence of pain in groups C, B, and D was, 36%, 52% and 60% and percentage of patients having severe pain was 4%, 12%, and 12% respectively. There was no significant difference between pethidine and ketamine regarding the incidence of pain. But the difference was significant when we compare Group C(lignocaine) with groups A, B or D.

Patients were followed up for two hours in the recovery room and asked for recall if there was pain during injection of propofol. The incidence of recall of pain was reported in 72% in group A (Placebo), 36% in group B (Ketamine), 16% in group C (Lidocaine) and 44% in group D (Pethidine). Thus, there was significant difference in the recall of pain in Group A as compared to the other three groups although there were no significant differences between the same among other three groups. Subsequent use of other anaesthetic agent could have resulted in loss of memory of pain in many patients. In this respect our study was similar to that of Gupta et al.[7]

There were no statistically significant differences in the hemodynamic responses among the four study groups. Ketamine induced tachycardia and hypertension were not evident in the hemodynamic response of patients treated with propofol-ketamine combination.[16] It appears that the sympathomimetic effects of ketamine may be attenuated when administered in combination with propofol. There were few incidences of PONV, and hallucination in ketamine and pethidine groups but these were not significant statistically (P>0.05).

The limitation in our study was that occlusion at mid forearm which was done manually, may vary from person to person. This was overcome to some extent by assigning this work of occluding the forearm to the same person in almost all cases.

CONCLUSION

Lidocaine 20 mg, ketamine 25 mg and pethidine 25 mg significantly reduce the incidence of pain during propofol injection more than placebo. Lidocaine may be considered as a good choice for the purpose of reduction of pain during propofol injection.

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Author's Contribution:
SN-Concept and design of the study; prepared first draft of manuscript and further revised the manuscript; **EO-** Interpreted the results; reviewed the literature and helped in manuscript preparation; **AA-** Statistically analysed and interpreted, preparation of manuscript and revision of the manuscript.

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