ORIGINAL RESEARCH

Analysis of Efficacy of Low-Dose Ketamine for Prevention of Pain Associated with Propofol Injection

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ABSTRACT
Background: To analyse the efficacy of low-dose ketamine for prevention of pain associated with propofol injection. **Materials & Methods:** A total of 40 subjects were enrolled. The age group included was between 20-55 years. The two treatment groups were included as Group A: pretreatment done with ketamine 100µg/kg with 20 subjects and group B: pretreatment with normal saline (1ml). The subjects with diabetes, allergic to ketamine or propofol, cardiovascular diseases etc. were excluded. Consent was taken. The results were analysed using SPSS software. **Results:** None of the patients in Group A reported experiencing moderate or severe pain at any of the three intervals, in contrast to patients in Group B (saline group). **Conclusion:** The administration of 100 micrograms per kilogram of intravenous ketamine, coupled with the use of a tourniquet as a pretreatment before propofol, proved effective in substantially the intensity of pain.

Keywords: Propofol, Pain, Low-dose ketamine.

INTRODUCTION

Propofol is a novel ultra-short-acting intravenous anesthetic agent with rapid effects[1], the main adverse reaction of which is injection pain. Obvious pain can be caused by peripheral intravenous injection.[2] Propofol injection pain ranks 7th among the 33 major problems of clinical concern, with the incidence rates of 28%-90%.[3] Propofol, which activates inhibitory GABA receptors, allows rapid recovery and is considered suitable for deep sedation in outpatients undergoing day surgery.[4] However, this drug has a few drawbacks including the possibility of patient movement in the middle of a procedure and vascular pain at the time of administration because it has no analgesic effect. Furthermore, it may cause respiratory or circulatory depression due to sympathoinhibition.[5] In contrast to propofol, ketamine, which competes with excitatory NMDA receptors, possesses the property of maintaining an analgesic and sympathomimetic effect and airway reflex.[6] Additionally, prior administration of ketamine is reported to relieve vascular pain that occurs during propofol administration.[7] Nevertheless, ketamine also has drawbacks, including the possibility of postoperative hallucination and vomiting.[8] In contrast, propofol acts to suppress postoperative vomiting and prevent nightmares caused by ketamine.[4]

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 theater. Propofol is almost an ideal IV anesthetic agent, but pain in its injection still remains a problem. The pain may not be a serious complication, but most patients remember it as one of their unpleasant encounters with anesthetists. In one survey, pain on propofol injection (POPI) stands as the seventh most important problem in the current practice of clinical anesthesia.[9] Propofol is an alkylphenol (2,6 diisopropylphenol); oil at room temperature and insoluble in aqueous solution but is highly lipid soluble. It was initially prepared with Cremophor EL, but due to anaphylactoid reactions

and severe pain on its injection, it was reformulated in an emulsion. Current formulation of 1% (weight/volume) propofol is available in 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide; also disodium edetate (0.005%) is added as a bacterial growth retardant. In this formulation, the oil droplets containing most of propofol are large enough to reflect and refract white light significantly, and hence it appears milky. Its pH is 7 and pKa in water is 11; it looks viscous apart from being milky. This formulation causes pain on injection in 28%–90% of patients.[10]

Widely available propofol is in long chain triglyceride (LCT) emulsion. The commonly used LCT emulsion of propofol is Diprivan (AstraZeneca). Another preparation of propofol is available in a combination of medium chain triglyceride (MCT) and LCT emulsion. Commonly available MCT/LCT propofol emulsions are Propoven (Fresenius) and Propofol-Lipuro (B Braun). MCT/LCT propofol has low free propofol content and is expected to reduce pain on injection; the free propofol content is less by 30%–45% compared to LCT propofol.[11] In one observational study of 1375 patients, incidence of pain on injection of MCT/LCT propofol was 28.7%, with 16.6% of patients reporting mild pain.[12] In another study, propofol formulation 6% in Lipofundin MCT/LCT 10% had a similar incidence of pain on injection as LCT propofol containing intralipid 10%.[13] Lipofundin MCT/LCT 10% is a 10% fat emulsion consisting of MCT and LCT, whereas intralipid 10% contains only LCT.[13] In several other studies, less pain is reported with MCT/LCT preparation compared to LCT preparation. Hence, this study was conducted to analyse the efficacy of low-dose ketamine for prevention of pain associated with propofol injection.

MATERIAL AND METHODS

The present study was conducted for evaluating microbiological Profile of Asymptomatic Bacteriuria in Pregnancy. A total of 500 pregnant subjects were screened in the present study. Socio-demographic data were obtained. Clean-catch midstream urine was collected from each patient into a sterile universal container. Samples were cultured on dried plates of blood agar and cysteine lactose electrolyte deficient agar. Plates were incubated aerobically of 37°C overnight. Colony counts yielding bacterial growth of 105/ml or more of pure isolates were regarded as significant for infection. The isolated organisms from culture plates were identified by standard laboratory techniques. All the results were recorded in Microsoft excel sheet and were subjected to statistical analysis using SPSS software.

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RESULTS

The statistical analysis of pain scores, as assessed by the McCrirrick and Hunter evaluation scale, revealed highly significant differences between Group A and Group B at P5, P10, and P15 intervals (p value < 0.0001). None of the patients in Group A reported experiencing moderate or severe pain at any of the three intervals, in contrast to patients in Group B (saline group). McCrirrick and Hunter evaluation score mean values were also highly significant at all time intervals between both the groups.

Table 1: Comparison of pain score of 2 groups according to McCrirrick and Hunter scale

	Number					
Score	**At p5 interval**		**P10 interval**		**P15 interval**	
	Group A	**Group B**	**Group A**	**Group B**	**Group A**	**Group B**
0	20	10	16	5*	16	6*
1	0	6	4	7*	4	8*
2	0	4	0	3*	0	2*
3	0	0	0	5*	0	4*
Total subjects with pain	0	10	4	15*	4	14*

*P value < 0.0001 Highly Significant

Table 2: Comparison of mean pain score between groups

Mean values	Group A	Group B
Baseline	0	0
P5	0	0.5
P10	0.12	1.33
P15	0.15	1.39

DISCUSSION

The injection pain of propofol is manifested as immediate pain or delayed pain (delayed by 10-20s).[14] To prevent the immediate pain, ketamine was injected 30s before propofol injection. Pre-injecting or mixing low-dose ketamine both decreased the incidence rate of injection pain, exceeding the outcomes using 0.2 mg/kg lidocaine pre-injection. Meanwhile, the hemodynamics was not obviously affected. Nevertheless, ketamine has well-documented

side effects such as delayed recovery, postoperative nausea and vomiting, and mental excitement. [15] Hence, this study was conducted to analyse the efficacy of low-dose ketamine for prevention of pain associated with propofol injection.

In the present study, the statistical analysis of pain scores, as assessed by the McCrirrick and Hunter evaluation scale, revealed highly significant differences between Group A and Group B at P5, P10, and P15 intervals (p value < 0.0001). A study by Zahedi H et al, determined the optimal dose of ketamine in the prevention of propofol injection pain and compare it with lidocaine, the commonly proposed pre-treatment. patients received normal saline (Group NS), lidocaine 1 mg x kg(-1) (Group L), and different doses of ketamine 50-75-100 microg x kg(-1) (Group K50-K75-K100 respectively), immediately before the injection of 2.5 mg.kg(-1) propofol. The incidence and intensity of pain in all study groups were significantly lower than placebo group (Group NS) (P < 0.005). Patients in the K100 Group had significantly lower incidence of pain and lower pain scores compared with the K50 and L Groups (P < 0.0001). There were no significant differences in hemodynamic parameters between groups. Administration of ketamine 100 microg x kg(-1) immediately before propofol injection is a safe and effective method in preventing propofol injection pain. [16]

In the present study, none of the patients in Group A reported experiencing moderate or severe pain at any of the three intervals, in contrast to patients in Group B (saline group). McCrirrick and Hunter evaluation score mean values were also highly significant at all time intervals between both the groups. Koo SW et al, established the optimal dose of ketamine to prevent the pain of injection with propofol. Two hundred forty 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. 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. Administration of ketamine 100 microg/kg immediately before propofol injection provided the optimal dose and timing to reduce propofol-induced pain on injection. [17] Complications of deep sedation with propofol-ketamine combination include vomiting and mental abnormalities, including hallucination. Although propofol has demonstrated an anti-nausea effect through dopamine D2 receptor antagonism, it is reported that the frequency of nausea after propofol-ketamine anesthesia increases as the ketamine dose increases. [18] It has been reported that mental abnormalities due to ketamine intravenous injection are not observed when the dose is < 1 mg/kg; [19] however, a previous study reported that 10% of patients experienced hallucinations after sedation with propofol-ketamine 0.1 mg/kg. [20] To relieve the injection pain of propofol, researchers have been devoted to the following two aspects. First is the combination of several drugs. [21] For instance, Zhang et al. evaluated the pain on injection of propofol via different combinations of fentanyl, sufentanil or remifentanil in gastrointestinal endoscopy. [22] They found that propofol and sufentanil group was the most suitable program for painless gastroscopy. Second is the use of M/LCT as the solvent. West et al. compared and systematically assessed the effects of several anesthesia methods, and reported that using M/LCT effectively mitigated the injection pain of propofol. [23] Zhao GY et al, evaluated the efficacy of ketamine in preventing propofol injection pain in children. Patients were randomly assigned to 4 groups. Group S (control) received normal saline as a placebo; Group K1, Group K3, and Group K5 received 0.1 mg/kg, 0.3 mg/kg, and 0.5 mg/kg of ketamine, respectively. Fifteen seconds after the ketamine injection, patients were injected with propofol at a rate of 12 mL/min until loss-of-eyelash reflex. Pain was evaluated blindly at the time of induction using a 4-point scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. Adverse effects were recorded. Characteristics of induction of anesthesia, such as dose of propofol and time from propofol injection to loss of consciousness (induction duration), were noted. 39 (84.8%) Group S (control) patients had pain. Pretreatment with ketamine reduced the frequency of pain significantly to 56.5%, 17.0%, and 14.9% in Groups K1, K3, and K5, respectively. Furthermore, the frequency of moderate and severe pain in Group K1 (21.8%), Group K3 (6.4%), and Group K5 (4.3%) was significantly (P < 0.001, respectively) reduced compared with Group S (76.1%). Moreover, the dose of propofol for induction in Group K5 was smaller than in Group S, Group K1, and Group K3 (P < 0.05). One patient in Group K5 had emergence agitation. Pretreatment with a small dose of ketamine (0.3 mg/kg) reduced the frequency and intensity of propofol injection pain without severe adverse effects. [24]

CONCLUSION

The administration of 100 micrograms per kilogram of intravenous ketamine, coupled with the use of a tourniquet as a pretreatment before propofol, proved

effective in substantially diminishing the intensity of pain.

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