

PREVENTION OF PROPOFOL INJECTION PAIN WITH SMALL-DOSE KETAMINE

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Abstract

Purpose: Propofol is a popular IV anesthetic induction drug that causes pain when given IV, the incidence of which is between 28%-90%. We plan to determine the optimal dose of ketamine in the prevention of propofol injection pain and compare it with lidocaine, the commonly proposed pre-treatment.

Methods: In a double-blind randomized study 500 Patients (ASA I, II) scheduled for elective strabismus surgery under general anesthesia were randomly allocated into five groups. After obtaining the informed consent., patients received normal saline (Group NS), lidocaine 1mg.kg⁻¹ (Group L), and different doses of ketamine 50-75-100 µg.kg⁻¹ (Group K50-K75-K100 respectively), immediately before the injection of 2.5 mg.kg⁻¹ propofol. Each patient's pain scores were measured at five seconds intervals by a blinded anesthesiologist. Statistical analysis were made by SPSS vs 11.5.

Results: 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.

Conclusion: Administration of ketamine 100 µg.kg⁻¹ immediately before propofol injection is a safe and effective method in preventing propofol injection.pain.

Key words: ketamine, propofol, lidocaine, pain on injection

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Introduction

Propofol is one of the most popular IV anesthetic induction drugs that causes pain when given IV^{1,2}. Several methods have been used to reduce this pain: adding lidocaine, warming or cooling the solution, dilution of propofol, injection through large bore veins, changing the speed of injection, using tourniquet and previous injection of lidocaine, benzodiazepines, ondansetron, metoclopramide, opioids, thiopental², flurbiprofen³, ephedrine⁴ and ketamine¹. Lidocaine pre-treatment has been commonly proposed to decrease propofol induced pain, but its failure rate is between 13-32%⁴.

Ketamine (a phencyclidine derivative) has potent analgesic effects and local anesthetic properties. It seems likely that the reduction in propofol injection pain was the result of a peripheral action which attenuated the afferent pain pathways. Ketamine as a NMDA receptor antagonist may activate these receptors either in the vascular endothelium or in the central nervous system⁵. Although unpleasant dreams and emergence reactions seem to be associated with it, it has some unique advantages notably, less cardiorespiratory depression than other anesthetics, which makes it a good choice in specific conditions⁵. Few studies have evaluated the advantages of ketamine to reduce propofol-induced pain suggesting the effectiveness of ketamine in adults and children^{5,7-10}. Although lack of efficacy of the ketamine-propofol admixture in pediatrics was reported⁶.

The purpose of this study is to determine the safe and optimal dose of IV ketamine and comparing it with IV lidocaine, as a pre-treatment for propofol-induced pain on injection during induction of general anesthesia.

Materials and Methods

Ethics Committee approval was obtained and all patients signed informed consent before enrollment in the study.

In a prospective, randomized, placebo-controlled, double-blinded study, 500 ASA I-II patients of 18-40 years old scheduled for elective strabismus surgery, were enrolled. Patients taking sedatives or analgesics in the past 24 hours before surgery and those with history

of allergic reactions to anesthetic drugs, neurologic or cardiovascular disease and pregnant patients, were excluded from the study.

In all patients, a 20-gauge teflon catheter was inserted into a vein of the dorsum or wrist of the hand at approximately 60 minutes before the induction of anesthesia and 5cc.kg⁻¹ ringer lactate solution was infused.

Patients were randomly allocated into one of 5 treatment groups (100 each):

- Group NS received 5 ml 0.9% NS,
- Group L received 1mg.kg⁻¹ lidocaine,
- Groups K50, K75, K100 received 50μg.kg⁻¹, 75μg.kg⁻¹ and 100μg.kg⁻¹ ketamine respectively. Study drugs were diluted with NS 0.9% up to 5cc and were prepared by an investigator not involved in drug injection or assessment of patients' responses.

All study drugs were slowly administered before propofol injection in 15 seconds. Immediately propofol (1%) 2.5mg.kg⁻¹ was injected slowly over 30 seconds. A blinded anesthesiologist before the administration of propofol asked the patient to rate any sensation of pain every 5 seconds during propofol injection graded as 0-3 VRS (Verbal Rating Scale) and recorded the highest score of pain. The grading criteria of VRS were as follows: 0 = no pain, 1 = mild pain or soreness, 2 = moderate pain and 3 = severe pain associated with grimacing, withdrawal, movement or both.

After the propofol injection and patients' loss of consciousness, atracurium 0.5mg.kg⁻¹, fentanyl 1.5μg.kg⁻¹, midazolam 0.02 mg.kg⁻¹ were administered and 3 minutes after atracurium injection the trachea was intubated and anesthesia was maintained with propofol infusion of 100μg.kg⁻¹.min⁻¹. Non-invasive blood pressure monitoring (MAP), HR monitoring by ECG and O₂ saturation with pulse oximetry were used in all patients. Patients were assessed regarding emergence reactions like delusion and agitation in the recovery room by an anesthesiologist blinded to patients' group.

Data were analysed by SPSS (v11) and were expressed as mean ± SD. Statistical comparison between groups were made by Chi2 and One-way analysis of variance. For ordinal data of pain score, medians were compared by Man-Whitney test. A P<0.05 was considered significant in all tests.

Table 1
Patients' characteristics

| Group | NS (N=100) | L (N=100) | K50 (N=100) | K75 (N=100) | K100 (N=100) |
|------------|---------------|--------------|----------------|----------------|-----------------|
| Age(yr) | 28.9±7.4 | 29.7±6.8 | 29.4±7.8 | 29.7±8.8 | 30.7±6.6 |
| Sex(F/M) | 45 / 55 | 49 / 51 | 52 / 48 | 44 / 56 | 51 / 49 |
| Weight(kg) | 53±8.9 | 50±6.9 | 49.4±11 | 53.7±9 | 55.9±7 |

NS=Normal Saline, L=Lidocaine, K50=Ketamine50µg.kg-1, K75=Ketamine75µg.kg-1 and K100=Ketamine100µg.kg-1. Data are presented as mean±sd and number of patients.

Results

Patients demographic characteristics including age, gender and weight in each group are presented in Table 1. There were no significant differences among groups.

The incidence and intensity of pain in all study groups were significantly lower than placebo group (Group NS) (P<0.005) (Table 2). Patients in K100 Group had significantly lower pain incidence and median pain score compared with K50 and L groups (P<0.0001) (Table 2).

None of patients in K100 and K75 groups had severe pain or score 3 VRS. There were no significant differences in hemodynamic parameters between groups and no adverse events such as arrhythmias and allergic reactions during induction or intubation were seen. None of the patients had post anesthesia emergence reactions during recovery.

Discussion

The incidence of propofol caused pain on injection has been reported to be between 28-91% in adults (88% in present study). Even small dose of propofol administered for sedation may induce pain varied between 33-50¹%.

Although the mechanism of this pain remains obscure, the endothelium irritation, osmolality changes, non pharmacologic pH⁵ and activation of pain cascade mediators like kinin have been suggested to be involved⁴.

Different methods have been used to reduce this pain incidence and intensity, the most popular is the use of lidocaine either by mixing or pre-treatment². In this study the incidence of pain in lidocaine group was reported to be 65% which is somewhat higher than previous studies 55¹% and 43²%. Moreover ketamine doses of 100 µg.kg⁻¹ were more effective than IV

Table 2
Incidence and Intensity of pain on injection of Propofol in different study groups

| | NS | L | K50 | K75 | K100 |
|--------------------------|-----|-----|-----|-----|------|
| Intensity of pain | | | | | |
| None (Score 0) | 12 | 35 | 40 | 45 | 55 |
| Mild (Score 1) | 34 | 39 | 35 | 39 | 42 |
| Moderate(Score 2) | 40 | 19 | 21 | 16 | 3 |
| Severe (Score 3) | 14 | 7 | 4 | -- | -- |
| Any pain (%) | 88% | 65% | 60% | 55% | 45% |
| Median pain score | 1 | 1 | 1 | 1 | 0 |

NS=Normal Saline, L=Lidocaine, K50=Ketamine 50µg/kg, K75=Ketamine 75µg/kg, K100=Ketamine100µg/kg. Data are presented as number (or %) of patients.

lidocaine 1mg.kg^{-1} (the commonly popular pre-treatment).

In the present study we observed that small dose ketamine ($50\text{-}75\text{-}100\ \mu\text{g.kg}^{-1}$) administered just before propofol injection, reduced both the incidence and intensity of propofol injection pain without significant adverse hemodynamic effects, which strongly suggests this analgesic action is brought locally, not through the central nervous system because the dose used by us is much lower than the dose one would choose for a central analgesic effect. In addition, sympathetic activation caused by ketamine may attenuate the hypotension induced at induction with propofol, in

comparison to lidocaine¹⁰.

In conclusion, our findings suggest that a dose of $100\ \mu\text{g.kg}^{-1}$ ketamine administered just before propofol can reduce the incidence and intensity of propofol injection pain without significant adverse effects.

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