THE EFFECTS OF REMIFENTANİL, LIDOCAINE, METOCLOPRAMIDE, OR KETAMINE PRETREATMENT ON PROPOFOL INJECTION PAIN

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Abstract

Background: Propofol injection pain is a frequent and a well-known complaint distressing for the patients. Although the ethiology of this pain remains obscure, the ideal method for the prevention of propofol injection pain is still controversial. Local anesthetics, opioids, nonsteroidal anti-inflammatory drugs, ketamine, metoclopramide, droperidol have been tested. We aimed to conduct a study comparing various drugs with saline, lidocaine and together at the same time.

Methods: In this randomized, double-blind, prospective trial a total of 250 patients (ASA I-II) undergoing elective surgery with general anesthesia were randomly allocated into five groups. After premedication of 3 mg midazolam im, patients received either 2 mL (0.02 mg) of remifentanil (n=50, Group R), 2mL (40 mg) of lidocaine (n=50, Group L), 2 mL (10mg) of metoclopramide (n=50, Group M), or 2mL (100 µg/kg) of ketamine (n=50, Group K) and 2 mL of saline. Pain intensity was evaluated through the use of a verbal rating scale, 0=none, 1=mild pain, 2= moderate pain, and 3=severe pain.

Results: Pretreatment with remifentanil 0.02 mg, % 2 lidocaine 40 mg, metoclopramide 10 mg, and ketamine 100 µg/kg yields propofol induced pain 38%, 76%, 76%, and 58% respectively. Pretreatment with lidocaine or metoclopramide equally and significantly reduced the incidence and severity of propofol induced pain (76%).

Conclusion: Lidocaine and metoclopramide were equally and the most effective treatments in attenuating pain during intravenous injection of propofol compared to pretreatment with remifentanil and ketamine.

Keywords: Lidocaine; metoclopramide; propofol injection pain

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Introduction

Propofol is most commonly used intravenous (iv) anesthetic drug. Pain induced during propofol injection is a common problem and can be very distressing to the patient. The incidence of this pain varies between 28% and 90% in adults and may be severe[1,2]. Many drugs such as alfentanyl, fentanyl, lidocaine, thiopenthal or metoclopramide have been used to alleviate this pain after iv injection of propofol with variable efficacy [2,3,4,5]. Among them, lidocaine pretreatment is the most popular method for reducing this pain[4,7]. However, the failure rate is between 32% and 48% and thus lidocaine can not entirely control propofol induced pain. Metoclopramide is a benzamide with both central and peripheral antiemetic actions[7]. In addition to this pharmacologic property, metoclopramide has also local anesthetic properties similar to those of lidocaine[1,5]. Ketamine has potent analgesic and anesthetic properties, but few studies have evaluated the utility of ketamine for reducing propofol induced pain on injection[3]. The use of opioids, especially short acting drugs such as alfentanil and remifentanil, was also observed to decrease pain induced by propofol[10].

Remifentanil is a selective μ opioid agonist, with a rapid and short effect. It has been reported that very low doses of remifentanil may prevent propofol injection pain[11,12].

To date, there are only a few studies comparing the effects of different drugs in same cases, mostly different doses of particular drugs were compared and optimal doses to prevent pain induced by propofol injection were reported. We, therefore, performed a prospective, randomized, placebo-controlled, double-blind clinical trial to evaluate and compare the efficacy of remifentanil, lidocaine, metoclopramide and ketamin on propofol injection pain. The aim was to show any superiority of study drugs.

Materials and Methods

The study population consisted of 250 patients (ASA physical status I or II) undergoing elective surgery with general anesthesia. All patients provided written informed consent, and the study protocol was approved by the Ethics Committee of our hospital.

Patients with a history of allergy, renal or hepatic problems, thrombophlebitis or chronic pain for which they were taking sedative or analgesic medication and those weighing less than 50 kg were excluded from study.

All patients were pre-medicated with 3 mg midazolam im 45 min before induction of anesthesia. Upon arrival to the operating room, an 20 gauge teflon catheter was inserted into a vein on the dorsum of the patient's non-dominant hand and an infusion of Ringer's lactate solution was started at a rate of 5 ml/kg/h. Monitoring consisted of pulse oximetry, electrocardiography (lead II) and non invasive blood pressure were applied (Drager Infinity Delta, ABD). Blood pressure was monitored on the opposite extremity of IV cannula.

Randomization was carried out using the table of random numbers. Patients were randomly assigned to five groups to receive either 2 mL (0.02 mg) of remifentanil (n=50, Group R), 2mL (40 mg) of lidocaine (n=50, Group L), 2 mL (10mg) of metoclopramide (n=50, Group M), or 2mL (100 μg/kg) of ketamine (n=50, Group K) and 2 mL of saline. A rubber tourniquet was used to perform 1 minute of venouse occlusion before administration of the study drugs and then 25% of total calculated dose of propofol (2 mg/kg) was injected into the dorsal vein of the hand through a 20-gauge IV cannula a rate of 1mL/s. During a 10 second pause before the induction of anesthesia, patients were questioned by a blinded investigator about the pain intensity on injection. Pain intensity was evaluated through the use of a verbal rating scale, 0=none (negative response to questioning), 1=mild pain (pain reported only in response to questioning without any behavioural signs), 2=moderate pain (pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning), 3=severe pain (strong vocal response or response accompanied by facial grimacing arm withdrawal, or tears).

Thereafter, induction of anesthesia continued with the remainder of the calculated dose of propofol. Atracurium 0.5 mg/kg iv was administered for muscle relaxation and to facilitate tracheal intubation, and anesthesia was maintained with sevoflurane 1% to 3% and nitrous oxide 66% in oxygen, with controlled ventilation (Drager Primius Delta, ABD).

Incidence and intensity of pain (as assessed by mean pain scores) were determined in each of the 5 study groups. Within 24 hours after the operation, the injection site was checked for pain, edema and wheal flare response by a researcher to group assignment.

The primary aim of this study was to compare by proportions of differences in incidence of propofol injection pain among groups. A sample size of 48 per group was required to detect at least 25% difference between any of two groups with a power of 80% at the 5% significance level. The difference of 25% was taken from both pilot study and clinical experience. Sample size estimation was performed by using NCSS and PASS 2000 software.

Statistical analysis was carried out using SPSS 15.0 statistical program. Analyses of variance were performed on the demographic data, using the ANOVA test for continuous variables (ie, age, weight) and the $\chi 2$ test for discrete variables (sex, ASA status). $\chi 2$ test was used to calculate difference in insidence of propofol induced pain among the groups. Statistical significance was set at $p < 0.05$. The Bonferroni correction was applied for all possible multiple comparisons regarding for the difference in insidence of propofol induced pain ($p < 0.005$).

Results

A total of 250 patients were successfully performed in the course of the study. There were no statistically significant differences among the groups with regard to age, weight, gender and ASA classification (p is greater than 0.05; Table 1).

When compared with the saline group, the remifentanil (p is equal to 0.003), lidocaine (p is less than 0.001), metoclopramide (p is less than 0.001), and ketamine (p is less than0.001) groups all showed significantly less frequency and severity of pain (p is less than 0.005; Table 2). The overall comparison of the groups revealed that; lidocaine is equal to metoclopramide which is greater than ketamine which is greater than remifentanil which is greater than saline.

When the lidocaine group was compared to the other groups; metoclopramide group was found equally effective (p is equal to 1), ketamine group showed no significant difference (p is equal to 0.056), remifentanil group was found significantly less effective (p is less than 0.001) in relief of pain associated with propofol injection (lidocaine is equal to metoclopramide which is equal to ketamine which is greater than remifentanil).

Discussion

Our results showed that pretreatment with remifentanil 0.02 mg, 2% lidocaine 40 mg, metoclopramide 10 mg, and ketamine 100 μg/kg yields propofol induced pain 38%, 76%, and 58% respectively. Pretreatment with lidocaine or metoclopramide equally and significantly reduced the incidence and severity of propofol induced pain (76%).

Avoiding pain on propofol injection is highly desirable, as pain appears to be a limiting factor to an otherwise useful anesthesia. Propofol induced pain on injection is related to the amount of free propofol present in the aqueous phase[11]. The contact of free propofol with free nerve endings of vessels activates the plasma kinin-kallikrein system, which locally liberates pain mediators[1,2]. Pain on injection of propofol can be immediate or delayed; immediate pain probably results from a direct irritant effect whereas delayed pain likely is the result of an indirect effect via the kinin cascade[2,4].

Table 1
Demographic Data Collected from the Patients of the Study
mean ± SD

Groups	n	Age (yrs)	Weight (kg)	Gender (F/M)	ASA (I/II)
Remifentanil	50	45.64±13.89	70.58±13.71	31 / 19	31 / 19
Lidocaine	50	45.22±16.4	76.02±13.90	22 / 28	27 / 23
Metoclopramide	50	49.3±16.2	73.14±13.65	27 / 23	29 / 11
Ketamine	50	47.2±14.6	75.24±15.81	30 / 20	20 / 30
Saline	50	46.2±16.1	74.43±13.96	23 / 27	22 / 28

Although the etiology of this pain remains obscure, the ideal method for the prevention of propofol injection pain is still controversial. The literature reveals that pretreatment may prevent propofol injection pain. Numerous methods, pharmacological treatments, different doses and combinations, alternative methods of administration and physical interventions were tested to reduce its incidence and intensity. Propofol has been warmed or cooled, injected faster or more slowly, with or without a tourniquet, diluted or not.

Local anesthetics, opioids, non-steroidal anti-inflammatory drugs, ketamine, metoclopramide, and droperidol have been tested.

The most popular is the use of lidocaine either by mixing it with propofol or by pretreatment with a bolus injection of lidocaine[4,7,15]. However, protection is not complete, with a failure rate of between 32% and 48%. When mixed with propofol, lidocaine may act as a stabilizer for the kinin kaskade, and 40 mg of lidocaine has been found to be more effective than 20 mg[15]. A highly significant negative dose response relationship between the dose of lidocaine and the severity of pain, is demonstrable, lidocaine 40 mg (2%) will significantly reduce the incidence and severity of pain with propofol injection, but about 6% of patients will still suffer from unpleasant pain if the dorsum of the hand is used[1].

The best intervention to prevent pain on injection with propofol is still unknown. It has been suggested that remifentanil, metoclopramide and ketamine all alone are effective in preventing pain caused by propofol injection. We present the first study comparing various drugs with saline, lidocaine and together at all.

Opioids, such as fentanyl and alfentanil decreased the frequency and severity of injection pain with propofol. Remifentanil is an ultra short-acting opioid of phenylpiperidine derivative with μ-opioid receptor agonist effects[16]. Similar to the other opioids, site of action of remifentanil may be either central or peripheral[6]. Opioids may also expert local anesthetic effect. Pretreatment with remifentanil is effective in reducing propofol induced-pain, similar to findings for fentanyl and alfentanil, Roehm et al[10] reduced propofol induced pain 50% using remifentanil at an infusion dose of 0.25 μg kg/min. Iyilikçi et al[16] achieved adequate reduction of pain with remifentanil at doses of 10–20 μg, with a better efficacy at the 20 μg dose. It was reported that remifentanil is effective on preventing propofol injection pain and should be used at a dose of at least 0.02 mg for this purpose[12,16].

Metoclopramide is a benzamide with both central and peripheral antiemetic actions[1,5,8.] With its ability to block dopaminergic receptors at the chemoreceptor trigger zone, prevents emetic symptoms. In additions to this pharmacological property, shares structural and physicochemical properties with lidocaine, and metoclopramide is a weak local anesthetic in its own right[13]. Liew et al [13] have evaluated the efficacy of metoclopramide, compared with lidocaine in reducing propofol injection pain, and have shown that both drugs are comparable for the control of pa in during propofol injection. Larger doses (more than 20 mg) of metoclopramide occasionally cause dystonic and extrapyramidal reactions[8].

However, in the present study patients received metoclopramide 10 mg, and none experienced extrapyramidal reactions. Thus, the dose (10 mg) of metoclopramide used in this study appears to be safe.

Pretreatment with ketamine has also been found to alleviate pain on injection of propofol. Ketamine acts on a multitude of receptors. It is a non-competitive N-methyl-D aspartic acid receptor antagonist and opioid μ receptor agoinst in the central nervous system and vascular endothelium[3,9,14.] It is possible that the reduction in injection pain was the result of a local peripheral action. But a ketamine-propofol admixture did not reduce the pain on injection compared with a lidocaine-propofol admixture[14.] Ketamine has analgesic properties and promotes blood pressure stability via sympathetic stimulation. Pretreatment with ketamine has been proved effective in preventing propofol infusion pain in adults[3].

Our randomized, prospective, double-blinded comparison focused on proving efficiency of different drugs. Pretreatments with remifentanil 0.02 mg, 2% lidocaine 40 mg, metoclopramide 10 mg, and ketamine 100 μg/kg were compared to reduce incidence and severity of propofol induced pain. In this respect, we did not conduct a dosing study. But it may be argued that administering different doses would change the results or undesired side effects would occur. However, as previously recommended doses to prevent propofol

injection pain of each drug were administered it is unlikely that this limitation impaired our results.

In the present study, %2 lidocaine 40 mg and metoclopramide 10 mg were equally and the most effective treatments in attenuating pain during intravenous injection of propofol compaired to pretreatments with remifentanil and ketamine. In conclusion, pretreatment with metoclopramide may be an alternative to lidocain in reducing such pain.

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