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PROPOFOL INDUCED PAIN;

COMPARISON BETWEEN EFFECTS OF LIDOCAINE-PROPOFOL MIXTURE AND METOCLOPRAMIDE PRE-MEDICATION

DR. ABDUL HAMEED CHOHEDRI
Associate Professor of Anaesthesiology
Shiraz University of Medical Sciences,
Department of Anesthesiology, Shiraz, Iran

DR. M. SEYEDI
Shiraz University of Medical Sciences,
Department of Anesthesiology,
Shiraz, Iran

DR. M. MASJEDI,
Assistant Professor of Anaesthesiology
Shiraz University of Medical Sciences,
Department of Anesthesiology,
Shiraz, Iran

ABSTRACT… hameedchohedri@yahoo.com. **Introduction:** Propofol causes pain on injection in 28% - 90% of patients. A number of techniques have been tried for minimizing propofol-induced pain with variable results. **Objectives:** To compare the use of premixed lidocaine-propofol with metoclopramide pretreatment for the reduction of pain during injection of propofol in adult patients. **Design:** A prospective, double blind, randomized, placebo-controlled study. **Setting:** Shiraz University Hospital, Department of Anesthesiology, Shiraz, Iran. **Period:** From Jan 2007 to Dec 2007. **Materials & Methods:** 202 subjects (ASA I-II) scheduled for elective operations under general anesthesia were allocated into three groups and treated as follows: Group A: 20 ml propofol mixed with 20mg lidocaine %1 following 2ml normal saline; Group B: 20 ml propofol mixed with 2ml normal saline following 5 mg metoclopramide; Group C (control group): 20 ml propofol mixed with 2 ml normal saline following 2 ml normal saline. Pain intensity was graded by a single, blinded observer and recorded as either severe, moderate, mild or no pain according to the response of the patients to the injection. **Results:** The incidence of pain was 72% in placebo group compared to 58.7% in the metoclopramide and 28.8% in the lidocaine group. **Conclusion**: Propofol-lidocaine admixture is more effective than metoclopramide pre treatment in decreasing the pain of propofol injection.

Key word: Propofol, Lidocaine, Metoclopramide, Pain on injection.

INTRODUCTION

Propofol is widely used for induction and maintenance of anesthesia and possesses many characteristics of an ideal anesthetic[1]. It is known to cause severe, sharp, stinging or burning pain on injection that can be distressing to the patient. This pain is considered to be clinically unacceptable as it can cause agitation and hinder the smooth induction of anesthesia[2].

Since the first clinical trial in 1977[3], pain on injection of propofol remains a significant problem and many various techniques have been used to reduce it including mixing lidocaine with propofol in the same syringe, pretreatment with lidocaine or procaine, cooling or warming or diluting the propofol solution, injection of propofol into a large vein, prior injection of ondansetron, ketamine, opioids, magnesium sulfate, ketorolac or tramadol. In previous studies, metoclopramide pre-treatment and propofol premixed with lidocaine were introduced as two effective and safe methods[4,5,6]. This study compares these two methods (premixed lidocaine [20 mg] with propofol and metoclopramide pretreatment [5mg] for the reduction of pain during the injection of propofol in adult patients.

MATERIALS AND METHODS

After institutional ethics approval, written informed consent was obtained from participants enrolled in this prospective, randomized double-blind study. As an incidence of no pain on injection of propofol 60% has been reported, based on α=0.05 and β=0.2, a minimum sample size of 35 subject/group was calculated so as to detect a 25% decrease in the incidence of no pain on propofol injection between groups. Adult ASA I-II patients with no anticipated difficult airway (Mallampati class I-II) aged between 18-60 years undergoing elective surgery under general anesthesia, who were expected to require at least 100mg propofol were included. They were not priorly premedicated.

The exclusion criteria was: patients of ASA grade III-V, Mallampati class III-IV, history of cardiac conduction defects, anti dysrhythmic medications, allergies to local anesthetics (propofol and metoclopramide), abnormalities of lipid metabolism, epilepsy, pregnancy, analgesic drug consumption in the previous 24 hours, drug abuse, and patients with difficulty in communication or requiring rapid sequence induction.

A member of the anesthesia team took responsibility for the anesthesia and another recorded the pain on injection of propofol. Subjects were randomly allocated to one of three groups by a computer - conducted randomization. The investigator assessing pain scores was blind to the drugs given as all drug syringes were labeled as “study drug”. Patients received no pre-medication. On arrival in the operating theatre, standard monitoring, including pulse oxymetry, non invasive blood pressure and electrocardiogram (ECG) were instituted. In all subjects, a 20-G cannula was inserted into the largest vein on the dorsum of the non-dominant hand and a fast running drip of ringer solution was started. No other drugs were administered prior to propofol injection.

Group assignment

Group A received 20 ml propofol mixed with 20mg lidocaine 1% following 2ml normal saline, group B received 20 ml propofol mixed with 2ml normal saline following 5mg metoclopramide, and group C (the controls) received 20 ml propofol mixed with 2ml normal saline following 2ml normal saline.

Identical syringes were prepared and if the volume to be administered was less than 2ml, 0.9% normal saline was added to make a total volume of 2ml. All the patients had a rubber tourniquet applied to the forearm with the sited IV cannula for one minute. The study drugs were injected over 10 seconds and there after the tourniquet was

released and then propofol 0.5 mg/kg was injected at a rate of 4 mg/ sec. This was delivered by a syringe pump (JMS-3000) connected to a three-way tap placed immediately distal to the venous cannula. Consumed drugs were propofol 1% fresenius (Fresenius kabi, Austria GmbH), Lignodic® 1% (IPDIC, Iran) and metoclopramide (OSVAH, Iran). The temperature of injected propofol was not standardized as previous studies have indicated that this does not affect pain on injection. Drug infusion was stopped to assess the degree of pain experienced by the subjects by scoring any verbal response or the observation of any behavioral signs (Mc Crirrick and Hunter, 1990). If there was no verbal or observed pain response, the subject was asked a standard question about comfort at the injection site. Subjects were designated as having pain or no pain on injection as above. Pain on injection was further delineated using a scoring system described by Mc Crirrick and Hunter[7] table I.

Table-I. Assessment of pain (Mc Crirrick and Hunter, 1990)

Pain score	Degree of pain	Response
0	None	Negative response to questioning
1	Mild	Pain reported in response to questioning only, without any behavioral sign
2	Moderate	Pain reported in response to questioning and accompanied by behavioral signs or pain reported spontaneously without questioning
3	Severe	Strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears

Following recording of the intensity of pain on injection, induction of anesthesia proceeded according to the attending anesthetist. Anesthesia was subsequently maintained with an inhalation technique. Extra pyramidal reactions, such as acute dystonic-dyskinetic reactions were monitored after recovery from anesthesia. Demographic data were analyzed using ANOVA. The pain score was analyzed using Kruskal-Wallis rank test. Analysis for inter group difference was performed by Mann-Whitney test. A P value of less than 0.05 was considered significant.

RESULTS

There were no statistically significant differences between the groups with respect to age, gender, weight, and ASA status (Table II). The distribution of pain scores is shown in table III. When the groups were compared, the incidence of no pain on injection of propofol was significantly higher in both lidocaine and metoclopramide groups than in the saline (control) group (P<0.05).

Table-II. Demographic Data

	Placebo	Metoclo pramide	Lidocaine
No. Of Pts	**75**	**75**	**52**
Age (yr)	32.08±8.92	30.92±7.68	31.33±8.28
Sex M/F	38/37	30/45	21/31
Weight(Kg)	71±11.2	72±9.5	69±11.5
ASA I/II	53/22	47/28	38/14
Values are expressed as mean±SD			

The mean pain score was less in patients receiving metoclopramide (1.04) or lidocaine (0.38) than in patients receiving placebo (1.44) (both with a P< 0.05). The mean pain score was also higher in the metoclopramide group in comparison to lidocaine group (p<0.05).

Table-III. Effect of metoclopramide and lidocaine on pain on injection of propofol								
Group	Grade of pain					Modified Grade of Pain		
	None(0)	Mild(1)	Moderate(2)	Severe(3)	None & mild	Moderate & severe	Pain score (mean)	Pain total(n)
Placebo (n=75)	21(28.0%)	15(20.0%)	24(32.0%)	15(200%)	36(48.0%)	39(52.0%)	1.44	54(72%
Metoclopramide (n=75)	31(41.3%)	17(22.7%)	20(26.7%)	7(9.3%)	48(64.0%)	27(36.0%)	1.04	44(58.7%)
Lidocaine (n=52)	37(71.2%)	12(23.1%)	1(1.9%)	2(3.8%)	49(94.2%)	3(5.8%)	0.38	15(28.8%)

None of the patients showed signs/symptoms of extra pyramidal effects of metoclopramide injection upon recovery from anesthesia.

DISCUSSION

Propofol induced pain ranked seventh among the 33 low morbidity clinical outcomes by expert anesthesiologist's analysis, when both clinical importance and frequency were considered[3]. The incidence of pain varies between 40-92% cases especially when injected into a vein on the dorsum of the hand. In our study, 72% of the subjects that received only saline before the infusion of propofol experienced pain, a figure that is consistent with range above.

Since the first clinical trial in 1977[3], pain on injection of propofol remains a significant problem and many various techniques have been used to reduce this, including mixing lidocaine with propofol in the same syringe, pretreatment with lidocaine or procaine, cooling or warming or diluting the propofol solution, injection of propofol into a large vein, prior injection of ondansetron, ketamine, opioids, magnesium sulfate, ketorolac or tramadol. However, none of the pharmacological methods has been proven to be entirely successful[4,5,6]. Therefore the search for a remedy is still an anesthesiological challenge.

Various theories have been suggested to explain the cause of propofol injection pain. Recently, kallikrein-kinin cascade has been implicated, which is triggered by release of kininogen from the vein wall following drug injection[8]. Also, pain may be a direct irritant effect of the aqueous phase phenol on the vein.

Many factors appear to affect pain occurrence[9]. These include the site of injection, the speed of injection, the propofol concentration in the aqueous phase, the buffering effect of the blood, the speed of any IV carrier fluid, the syringe material, and the concomitant use of drug such as local anesthetic. Administration of lidocaine - either before or pre-mixed with propofol - is the most widely used method. Lidocaine is more effective when it is added to the propofol and not injected before it[10].

So the admixture of the lidocaine-propofol used in our study is the best form thus studied to effectively control such pain. The addition of lidocaine may lead to destabilization of the propofol solution. When applying the emulsion in a 9:1 mixture of propofol lidocaine within a short time frame (< 30min), this effect is negligible. In a recent study by Tan and Hwang[11], the induction dose

of propofol with or without lidocaine were similar, indicating no relevant clinical destabilization of the emulsion when lidocaine is pre-mixed. Which explains the safety and clinical relevance of the method used in our study.

The use of tourniquet can reduce the incidence of pain. The failure rate with use of lidocaine is 13% - 32%. Mangar and Holak[12] showed that the free flow of lidocaine provided some analgesia but was not sufficient to predictably prevent pain and that application of a tourniquet, by obstructing the venous return, increased the duration of contact of lidocaine in the venous system distal to the occlusion, thus enhancing the analgesic effect of lidocaine. Scott et al[13] suggest a relationship between timing of administration of the drugs and the incidence of pain. They studied the effect on the incidence of pain at different intervals between the administration of lidocaine and propofol. In our study, this failure rate was found to be 28.8%, which is consistent to that of Managar[12] and Scott[13].

On the other hand, metoclopramide has been shown to be effective for reducing the incidence of pain on injection of propofol[4], probably because of its local anesthetic action. Recently, Liaw and coworkers have compared different techniques that include metoclopromide with the use of tourniquet, which was found to be the most useful method for reducing propofol induced pain on injection[14]. Metoclopramide is a benzamide with both central and peripheral actions. With its ability to block dopaminergic receptors at the chemorecoptor trigger zone, it increases lower esophageal sphincter tone and enhances gastric and small bowel motility and thereby reduces emetic episodes. In addition to this, it is a weak local anesthetic in its own right. In the first report by Ganta and coworkers, intravenous injection of metoclopromide 5 mg before the induction of anesthesia with propofol, reduced the incidence of pain on injection[15]. Similarly, a mixture of propofol to which metoclopromide 20 mg is added was effective for reducing the incidence of injection pain.

Maroof and Coworkers have demonstrated the analgesic efficacy of metoclopramide 10mg administered intravenously, using a venous tourniquet for one minute before propofol injection for reducing propofol-induced pain on injection[5]. A comparative study has been reported that intravenous retention of metoclopramide with a tourniquet is the most useful method for reducing the incidence of pain on injection of propofol[14]. In a study, Fujii and coworkers have shown that metoclopramide in a dose of 5 or 10 mg with venous occlusion for one minute effectively decreases the incidence of pain caused by propofol injection[4].

So the dosage of 5 mg used in this study would be effective in reducing pain while, on the other hand, rather in theory, avoid the side effects that may be possibly seen with higher doses sited above. The conspicuous lack of extrapyramidal effects could be explained by dose used in the study, despite the relatively older patient population studied. Also, Fujii et al showed IV administration lidocaine 40 mg with metoclopramide 5 mg or lidocaine 40 mg with metoclopramide 10 mg was associated with lower incidence, but not lower mean pain intensity scores of pain on injection of propofol than LID/MET 40/2.5 or LID/ Saline before induction of anesthesia[16]. Older patients require less metoclopramide, with venous occlusion for 1 minute, to reduce pain on injection of propofol than do younger patients[17]. In previous studies, metoclopramide pre-treatment and propofol premixed with lidocaine were introduced as two effective and safe methods[5,6,10]. This was also seen with both the drugs in our study.

Analysis of results in a study by Fujii [4] was based on "No pain" group but, given the number to subjects in "Mild pain" group possibly skews the results. So, we

might have compared "no pain + mild" and "moderate + severe" groups like Fujii[4]. But according to the allowing capability of our sample size in each group, we could safely use Chi-square test and conclusively demonstrate that the difference between these two groups is significant (P<0.001).

CONCLUSION

It is concluded in this study, after comparing the two methods, that lidocaine pre-mixed with propofol is more effective in reducing propofol induced pain on injection than metoclopramide pre-treatment.

Mixture of lidocaine-propofol is superior to pre-treatment with metoclopramide to prevent pain on injection of propofol.

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