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Research Article

Prevention of propofol injection pain, using lidocaine in a large volume does it make a difference? A prospective randomized controlled double blinded study

Amir M. Shabana [1]

Anaesthesia and Surgical Intensive Care, Faculty of Medicine, Mansoura University Hospitals, Egypt

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KEYWORDS

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Abstract *Purpose:* Propofol has become one of the most common anesthetic agents used for anesthesia because of its unique pharmacologic properties. Pain during bolus injection is a major drawback of propofol. The target of this study was to study the effect of lidocaine used in a large volume on prevention of propofol injection pain. Our hypothesis is that IV administration of diluted lidocaine in a large volume before propofol injection could be more effective in prevention of both immediate and delayed types of pain associated with propofol injection than the most commonly used method of mixing lidocaine with propofol (30 mg lidocaine/added to the 20 ml propofol syringe).

Methods: 100 Patients with age range (20–60) years and classified ASA1 and ASA2 undergoing general anesthesia for elective surgery were included in this study. Patients were classified into two groups, the first (study) group, in which 30 mg lidocaine diluted into a total volume of 20 ml using normal saline was given IV after venous occlusion with rubber tourniquet followed by propofol injection. In the second (control) group, 30 mg lidocaine was mixed with propofol and given to the patient as commonly used.

Results: This study showed a highly significant reduction in the propofol injection pain in the study group compared to the control group.

[1] Tel.: +20 10507450200, +968 96892324606.
E-mail address: nuranahmed@yahoo.com

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Conclusion: lidocaine when given diluted in a large volume after venous occlusion has dramatically reduced propofol injection pain in adults.

1. Introduction

Propofol has become one of the most common anesthetic agents used for sedation, induction, and maintenance of anesthesia because of its unique pharmacological properties. Pain during bolus injection is a major drawback of propofol. Propofol belongs to a group of phenol that can irritate the skin, mucous membrane, and venous intima. Pain on injection of propofol can be immediate or delayed [1]. Immediate pain may be caused by direct irritation of afferent nerve ending within the veins, whereas delayed pain probably results from an indirect effect via the kinin cascade. Bradykinin, by producing local vasodilatation and hyper-permeability, may increase the contact between the aqueous phase propofol and the perivascular free nerve ending resulting in pain on injection. This pain has a 10–20 s delayed onset.

There are many methods to prevent or to reduce the pain of propofol injection. Mixing lidocaine with propofol is the most commonly used method among all methods and techniques studied for prevention of propofol injection pain.

In this work, we will study the effect of diluted lidocaine pretreatment after venous occlusion with tourniquet on Propofol-Lipuro® 1% (B. Braun, Melshungen AG, Germany), injection pain. Our hypothesis is that IV administration of diluted lidocaine in a large volume (30 mg lidocaine diluted in a 20 ml normal saline) before propofol injection could be more effective in prevention of both immediate and delayed types of pain associated with propofol injection than the most commonly used method of mixing lidocaine with propofol (30 mg lidocaine/added to the 20 ml propofol syringe). Lidocaine diluted in such volume and injected during venous occlusion may give a chance for larger volume of the drug to spread over larger surface area to block more pain producing nerve endings, not only within the veins, but also bypassing to block perivascular nerve endings, which could prevent both immediate and delayed types of pain caused by propofol respectively.

2. Methods

This prospective randomized controlled double-blind study was conducted on 100 consecutive patients with age range 20–60. A written consent was taken that the research was approved from the responsible authorities.

Patients classified ASA1 and ASA2 undergoing general anesthesia for elective surgery were included. Patients with known history of allergy to either propofol or lidocaine were excluded. Eligible patients were randomly allocated using computer generated-randomized test to one of two equal groups: the study group and the control group.

All patients were premedicated with midazolam tablet 3.75 mg about 30 min preinduction and cannulated with a 20 gauge intravenous cannula on the distal part of the forearm.

On arrival to the operation room, all patients were monitored with electrocardiogram, pulse oximetry, non-invasive arterial blood pressure, and capnography (after endotracheal intubation). Mean arterial blood pressure and heart rate were recorded for statistical comparison between the two groups at baseline, just before intubation, and 1 min after intubation.

Both groups were subjected to the same anesthetic management. In the study group, a 30 mg lidocaine diluted with sterile saline into a total volume of 20 mL was injected intravenously after venous occlusion. We used a very simple fast non-invasive method for occlusion of venous out flow through the use of the tourniquet used for non-invasive BP measurement limiting inflation pressure to just above 50 mmHg (seen on monitor), using a clamp in order to be sure that venous outflow was completely restricted.

The tourniquet was placed around the middle of the arm [2], which was maintained 90 s after lidocaine injection, and then after release of the tourniquet, propofol in a dose of 2 mg/kg was injected slowly over 30 s.

In the second group (control), tourniquet was applied similarly like the study group and a total volume of 20 mL of sterile normal saline without any drug addiction was served as a placebo, so the anesthesia providers administering the propofol would still remain blinded to the mixed or unmixed propofol. After tourniquet release, propofol mixed with 30 mg lidocaine (total volume 20 ml) was injected in a dose of 2 mg/kg over 30 s.

Each dose was prepared by one of the researchers in the operating room immediately prior to induction but was given by the attending anesthesia providers, who were blinded to the content of each syringe.

Assessment of pain during and within 1 min after propofol injection was done objectively using the withdrawal response score proposed by Shevchenko and his colleagues [3] according to Table 1. A researcher who was unaware of group assignment assessed the pain according to the score grading.

After propofol injection, and pain assessment, fentanyl 1 μg/kg and tracrium 0.5 mg/kg were given. Intubation was done 3 min after tracrium administration; anesthesia was maintained by a mixture of nitrous oxide and oxygen supplemented with isoflorane. Muscle relaxation was maintained by increments of tracrium. At the end of the procedure, muscle relaxant was reversed by neostigmine and atropine.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 17). While intergroup parametric data were compared by the independent sample-*t* test, nonparametric data were compared by Mann Whitney test.

Table 1 The withdrawal response score.

Degree of movements	Patient response
0	No response or withdrawal
1	Movement at the wrist only
2	Movement/withdrawal involving arm only
3	Generalized response-withdrawal or movement in more than one extremity, cough or breath holding

Table 2 Total number of cases associated with pain in both groups represented by absolute number and percentage and the highest score recorded in each group.

Group	No of cases with pain	Highest score recorded	Incidence of pain (%)
Study	2	1	4
Control	12	3	24

Table 3 Demographic data and operative time in both study and control groups. Values for age, weight, and operative time are mean (SD) and for sex represented by absolute number of cases.

	Study group	Control group
Age (yr)	32.4 (11.9)	33.5 (10.8)
Weight (kg)	75.3 (13.9)	78.1 (9.8)
Operative time	93.2 (50.4)	96.9 (47.9)
Sex	55 M 5 F	54 M 6

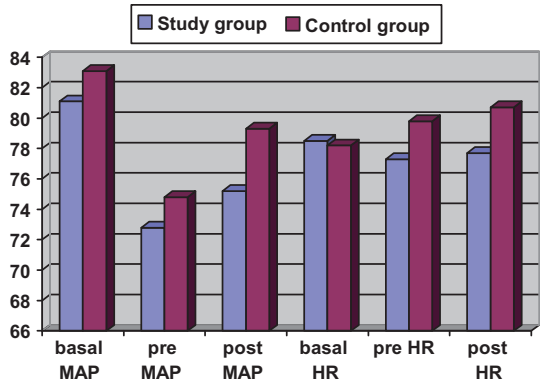

Figure 1 Mean arterial blood pressure (MAP) and heart rate (HR) measurements in study and the control groups, where pre = preintubation and post = postintubation.

Significance level was set at $p < 0.05$. Incidence of propofol injection pain was also presented by percent (%) in both groups.

3. Results

This study showed a highly significant reduction in the withdrawal movements in the study group (median score 0.22) compared to the control group (median score 1.5) with p value 0.001. The incidence of pain in the study group was 4% (2 patients) and the number of patients who recorded highest score was 1, while in the control group, the incidence of pain with propofol injection was 24% (12 patients) and the number of patients who recorded highest score were three (Table 2). All patients tolerated 50 mmHg tourniquet cuff pressure for 2 min without discomfort.

The groups' demographic data did not significantly differ (Table 3). Table 3 demonstrates the operation list and the number of cases. Basal and preintubation mean arterial blood pressure measurements showed no statistical significance between the two groups. There was a significant reduction of the postintubation mean arterial blood pressure in the study group (mean = 75.2) compared to that of the control group (mean = 79.3) with p value 0.037. Basal, preintubation, and postintubation heart rate measurements showed no statistical significance between the two groups (Fig. 1).

4. Discussion

This study clearly demonstrated a highly significant reduction in the propofol injection pain evidenced by marked decrease in the withdrawal movements in the study group (median score 0.22) compared to the control group (median score 1.5) with p value 0.001. We used an objective method for assessment of pain because it may be more reliable than subjective methods especially in patients under sedation, and pain-related withdrawal movements occur even after loss of consciousness during induction of anesthesia which gives us time to assess pain.

Propofol is now widely used for both anesthesia and sedation because of its high quality of anesthesia with rapid recovery in addition to the very useful antiemetic property. Pain on injection with propofol is a common well recognized problem, and it can be very distressing to the patient. Propofol belong to group of phenol that can irritate the skin, mucous membrane, and venous intema [1]. Pain on injection of propofol can be immediate or delayed. Immediate pain may be caused by direct irritation of afferent nerve ending within the veins, whereas delayed pain probably caused by activation of the kallikrein–kinin system either by propofol or by the lipid solvent, there by generating kinins, probably bradykinin. Bradykinin, by producing local vasodilation and hyper-permeability, may increase the contact between the aqueous phase propofol and the free nerve ending resulting in pain on injection. This pain has a 10–20 s delayed onset.

The incidence of propofol injection pain without use of any analgesic intervention according to previous published studies [4–6] is approximately 80%. The younger the patient, the higher is the incidence and severity of propofol injection pain [7].

There are different factors that may augment this type of pain including site of injection, the temperature of the propofol solution, size of the vein, and speed of injection. In this study, we had tried to control and fix these factors in both groups as much as possible. Different methods and techniques were tried in order to attenuate propofol injection pain including warming [8] or cooling of propofol [9] and using larger antecubital and forearm veins [10]. Furthermore, multiple agents have been administered as either pretreatment or given concurrently including: thiopentone [6], ondansetron [1], alfentanil [11], remifentanil [12], metoclopramide [13], magnesium sulfate [5], and ketamine [14]. Among these studies, two of the most commonly accepted techniques are the administration of lidocaine immediately prior to the injection of propofol or mixing lidocaine with the propofol itself.

Propofol-Lipuro® 1% is newer formulation (B. Braun, Melshungen AG, Germany) that was produced as a trial to prevent propofol injection pain which is evidenced by Sun and his colleagues [15]. However, based on other studies [16,17], it can be said that Propofol-Lipuro® offers some advantage over the older drug Diprivan® 1% (AstraZeneca, Cheshire, UK) concerning injection pain. This advantage might probably be smaller than what was previously sug-

gested. Furthermore, measures, e.g., preinjecting or mixing lidocaine, preinjecting opioids, or use of large veins at forearm or even antecubital fossa seem indicated with Propofol-Lipuro® too.

In a quantitative systematic review, Picard and Tramer [4] compared three different methods of using lidocaine in prevention of propofol pain. The first was lidocaine bolus injection before propofol injection. Second was mixing lidocaine with propofol, and the third by giving lidocaine after venous occlusion with tourniquet. They reported that using the tourniquet was the most effective method.

We studied lidocaine pretreatment because propofol pain may hinder smooth induction of anesthesia which is associated with patient agitation and enhancement of the stress response, so pretreatment for prevention of this pain become the standard technique in anesthesia practice. Overbaugh et al. [18] concluded that lidocaine more effectively reduces pain on injection of propofol when it is administered as a mixture than when given as a pretreatment before the propofol injection. Our technique is different because of using markedly diluted lidocaine under tourniquet which may explain the different result between our study and Overbaugh et al. study [18]. The present study was both cost and time effective as it can be used during the period of preoxygenation.

In this study, the reduction of the preintubation and postintubation measurements of mean arterial blood pressure and heart rate in the study group compared to the control one could be explained by attenuation of the stress response as a result of reduction of the propofol injection pain in the study group.

5. Conclusion

Pretreatment with lidocaine diluted in a large volume under venous tourniquet dramatically reduced propofol injection pain in adult patients; this method is easy to apply, with no time wastage, without adding cost. Also we can say that reduction of propofol injection pain was associated with smooth anesthesia induction and attenuation of the stress response.

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