Journal of Rawalpindi Medical College (JRMC); 2017;21(3): 241-244

Original Article

Comparison of Ephedrine Versus Lidocaine in Reducing the Frequency of Pain on Propofol Injection during Elective Surgeries

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Abstract

Background: **To compare the ephedrine with lidocaine for reducing frequency of pain on propofol injection during elective surgeries.**

Methods: **In this randomized controlled trial 80 patients were observed by taking 40 patients in each group, i.e. group A: ephedrine group and group B:lidocaine group. Patients with ASA–I (normal healthy patient), II (mild systemic disease with no functional limitation) aging between 20 and 40 years and opting for elective surgical procedures were included. The pain intensity was classified in four levels from no pain to severe pain. The frequencies of pain intensity were recorded during the injection period before the loss of consciousness according to the verbal rating scale (VRS) explained to patients at the preoperative visit. Chi square test was used to compare the frequency of pain in two groups, where p-value <0.05 was considered statistically significant. Effect modifiers i.e. the age, gender and ASA were controlled by stratification. The post stratification Chi-square test was applied keeping the p-value <0.05 as significant.**

Results: **In Group A, 35% complained of severe pain, 42.5% had moderate pain, 22.5% had mild pain and no patients reported absence of pain as per our operational definition. In Group B 47.5% reported no pain during propofol injection, 40% complained of mild pain, 12.5% had moderate and no patients reported severe pain. The p-value is 0.00.**

Conclusion: **Pretreatment with lidocaine resulted in significantly better pain control during propofol infusion than pretreatment with ephedrine.**

Key Words: Propofol, Procedural sedation, Ephedrine, Lidocaine

Introduction

Propofol (2,6-diisopropylphenol) is one of the most commonly used intravenous anaesthetic agent. It is preferred for its rapid onset, short duration of action, early recovery and minimal organ toxicity. It is commonly used for induction and maintenance of general anesthesia and sedation in intensive care units for its simplicity, stability and safety.

Two main side effects of propofol use are pain on injection and hypotension. Incidence of pain on injection is 80-90% if injected in vein of dorsum of hand.[1] Exact mechanism of pain is not known but many are proposed. Immediate pain results from action of phenol on vein and delayed pain by stimulation of nerve endings between intima and media by endothelium releasing kininogens.[1] To date, many methods are proposed to eliminate its pain like adding lidocaine, injecting into larger veins like antecubital,changing temperature, diluting solution with 5% dextrose or intralipid[2], varying speed of injection[3], prior medication with metoclopramide, clonidine, ephedrine, magnesium sulphate, opioids, thiopentol, ketamine, paracetamol, flurbiprofen axetil, nitroglycerine and nitrous oxide, oxygen mixture[4]. New preparations like the one with sodium metabisulphite and one with 1% propofol in 16% polyoxyethylated castor oil also decrease pain. But none of these has resulted in reliable attenuation of pain, though lidocaine pretreatment is considered most effective so far.[5]

Lidocaine is a local anesthetic agent. It reduces propofol injection pain by 30%.[5]Its exact mechanism of action is not known but is thought to be decreased neuronal conduction in peripheral nerves by attenuating the neuronal membrane's permeability to sodium ions or due to alteration in propofol's pH by adding HCl to it.[3,5] Pain by lidocaine pretreatment with prior venous occlusion has failure rate of 24-37% and augments hypotension associated with propofol.[5]

Ephedrine is a sympathomimetic, used for its effects to counter hypotension and bradycardia. It has both direct and indirect actions; direct by acting on alpha and beta receptors (more on beta) and indirect by

releasing norepinephrine from sympathetic nerve terminals. Cheong et al suggested in 2002 that ephedrine by its indirect action can reduce effect on bradykinin responsible for propofol injection pain.[6] Incidence of this pain reduction is 65%.[2] It is also a venodilator and increases contact between propofol in aqueous phase and free nerve endings. It is also buffered with HCl resulting in altered pH and decreased pain.[4] Agarwal et al. found that ephedrine pretreatment did not reduce pain so there are conflicting evidences about ephedrine's role in reducing propofol injection pain. But as pain reduction by ephedrine is 65% as compared to lidocaine 30% with additional benefit of heamodynamic stability so aim of this study is to compare ephedrine with lidocaine for reducing pain on propofol injection during elective surgeries.[4]

Patients and Methods

This randomized controlled trial was conducted at Department of Anaesthesia, Holy Family Hospital, Rawalpindi, from August 2014 to February 2015. A total of 80 patients were observed by taking 40 patients in each group. Group A: ephedrine group. Group B:lidocaine group. The sample size was calculated by using WHO sample size calculator following are the calculations: Level of significance: 5% Power of test: 80% Anticipated population proportion A is 65%[12] Anticipated population proportion B is 30%[10]. Patients with ASA–I (normal healthy patient), II (mild systemic disease with no functional limitation), age ranged 20-40 years and elective surgical procedures were included while patients patients with difficulty in communication e.g. psychiatric illness, dementia, aphasia etc, with history of adverse response or allergy to propofol, lidocaine or ephedrine,neurologic disease and cardiovascular disease were excluded. Cases in which vasopressor drugs are contraindicated e.g. thyrotoxicosis, diabetes mellitus, and hypertension of pregnancy and Patients receiving monoamine oxidase Inhibitors therapy were excluded. Patients were allocated to two groups "A"or "B" using computer generated random numbers. In both groups heart rate, non-invasive blood pressure, oxygen saturation and electrocardiography was monitored. Intravascular access in antecubital vein with one 18G cannula was established. Intravenous fluids administered to each patient as per requirement of patient and procedure. All the patients were preoxygenated with 100% oxygen via face mask for 3 minutes. Syringes of the pretreatment drugs, intravenous ephedrine 30 microgram/kg labeled as A and intravenous lidocaine 0.5 mg/kg labeled as B prepared. The coded syringes were identical and the drugs prepared by the personnel not involved in the study. Drugs were handed over to the anesthetists for pretreatment who was unaware of the identity of the drug. So investigator who assess the patient response was also ignorant of the nature of the solution. All drugs were used within 15 minutes after preparation. Patients were randomly assigned into two groups to receive either drug. One minute after the administration of the test solution, the 1% solution of propofol at 2 mg/kg was given through the IV catheter while the running of IV infusion temporarily ceased. After the injection of propofol the crystalloids were administered. Patients were informed regarding the possible stinging sensation on administration of a drug at the start of the anesthesia and they were asked about their pain during the injection period before the loss of consciousness according to the verbal rating scale (VRS) explained to patients at the preoperative visit. Furthermore, a blinded anesthesiologist evaluated the pain score during propofol injection. Means and SD were calculated for continuous variables i.e. age, weight and height. Frequency and percentage were calculated for categorical variables i.e. gender, ASA and pain on injection. Chi square test was used to compare the frequency of pain in two groups, where p-value <0.05 was considered statistically significant. Effect modifiers i.e. the age, gender and ASA were controlled by stratification. The post stratification Chi-square test was applied keeping the p-value <0.05 as significant.

Results

The patients included in the study were ASA-I and ASA-II. In group A, 25 (62.5%) patients were ASA I and 15 (37.5%) patients were ASA II. In group B, 22 (55%) patients were ASA I while 18 (45%) patients were ASA II. In overall study population, 47 (58.75%) patients were ASA I while 33 (41.25%) were ASA II. Mean and standard deviation of their age, weight and height were calculated within each group as well as of the whole population (Table 1).Thirteen patients from group A complained of severe pain while no patient from group B complained of severe pain (Table 2).

The p-value was found to be 0.00 (<<0.05). Post-stratification Chi-square tests were applied and P-value was found to be 0.00 (<<0.05). The results showed significant difference in the observed outcomes with pretreatment with lidocaine resulting in significantly better pain control than ephedrine during propofol infusion regardless of considered

effect modifiers, i.e. age, gender, height and ASA classification (Table 3).

Table 1: Demography of the study Population

	Group A			Group B		
	Male	Fem-ale	Total	Male	Fem-ale	Total
No	17	23	40	20	20	40
Age (years)	30.82 ± 7.03	30.35 ± 7.08	30.56 ± 6.98	33.95 ± 9.5	33.55 ± 6.13	33.75 ± 7.89
Height (cm)	170.7 ± 13.7	152.6 ± 13.8	166.0 ± 14.2	163.7 ± 10.9	159.8 ± 14.4	161.6 ± 13.2
Weigh t (kg)	62.74 ± 9.56	56.08 ± 8.33	58.85 ± 9.36	65.95 ± 10.34	56.0± 10.31	60.98 ± 11.37

Table 2: Group wise frequency of pain intensity

	Group A		Group B	
	No	Percentage	No	Percentage
No pain	2	5	19	47.5
Mild pain	9	22.5	16	40
Moderate pain	16	40	5	12.5
Severe pain	13	32.5	0	0

Table 3: Pain frequency and percentages after treatment in both groups

Pain	Group A (Ephedrine)	Group B (Lidocaine)	p- value
Yes	2 (5%)	21 (52.5%)	0.000 (≤ 0.05)
No	38 (96%)	19 (47.05%)	

Discussion

The practice of acute care medicine often requires the performance of procedures that can cause pain and anxiety. Procedural sedation reduces the discomfort, apprehension, and potential unpleasant memories associated with such procedures and facilitates performance of the procedure. Procedural sedation involves the use of short-acting analgesic and sedative medications to enable clinicians to perform procedures effectively, while monitoring the patient closely for potential adverse effects.

Propofol is an intravenous anaesthetic that is commonly used for sedation of the agitated adult intensive care unit (ICU) patient. It is particularly useful when rapid sedation and rapid awakening is desirable (e.g., patients who require frequent neurological examinations) because it has a short duration of effect.[7,8] Propofol is a highly lipophilic phenol derivative that is insoluble in water. It is administered by continuous infusion in the ICU and not by intermittent infusion because it is associated with dose- and rate-dependent hypotension.[9] Other main side effect of propofol use is pain during infusion. Incidence of pain on injection is 80-90% if injected in vein of dorsum of hand.[1] Although, under the assumption of independent efficacy a third practical alternative could be pretreatment of the hand vein with lidocaine or ketamine and use of a propofol emulsion containing medium and long chain triglycerides.[10,12]

The choice of drugs to be compared in this study, i.e. ephedrine and lidocaine followed from already existing studies, which show that ephedrine, by its indirect action, can reduce effect on bradykinin responsible for propofol injection pain.[1,6] Furthermore, it has been reported that the two most efficacious interventions to reduce pain on injection of propofol were use of the antecubital vein, or pre-treatment using lidocaine in conjunction with venous occlusion when the hand vein was chosen. Although not the most effective intervention on its own, a small dose of opioids before induction halved the risk of pain from the injection and thus can generally be recommended unless contraindicated.[10] Dependence of pain intensity during injection of microemulsion propofol on the amount of dose of lidocaine has been investigated in literature and it is established that increasing lidocaine dosage, within a dose range, significantly reduces pain during injection of microemulsion propofol.[3,13]

Chi-square test was applied and p-value was found to be 0.000 (<0.05) implicating significant difference in the observed outcomes with pretreatment with lidocaine resulting in significantly better pain control than ephedrine during propofol infusion. The data was stratified with respect to effect modifiers like age, gender and ASA. The post stratification Chi-square test was applied and p-value was found to be 0.000 (<0.05). Hence the significance of pain control treatment difference was found to be invariant of effect modifiers.

The present study shows ephedrine not to be the most effective approach for reduction of pain caused by propofol injection. This is analogical to available literature, where it is reported that the low dose ketamine or ephedrine pretreatment may prevent hypotension due to propofol induction but, despite the reduction in injection pain intensity after ketamine, both drugs were found to be ineffective in lowering the injection pain incidence.[11,14] The study also found lidocaine to be effective measure in reducing the pain during propofol injection. Similar results have been deduced in other studies too, where lidocaine is found

to be the most effective measure to reduce the pain caused by the propofol injection.[10] It is also known that increasing the dosage of lidocaine results in higher reduction in pain.[3,15]

The natural intuition that may follow as a result of comparison of ephedrine and lidocaine is to consider their combination as a pain reducing measure. The idea has already been addressed in literature and shows that pretreatment with combination of small-dose ephedrine and lidocaine could reduce the incidence and intensity of propofol-induced pain and also result in more stable hemodynamic profile, but however, the combination of two drugs failed to work better in further reduction of pain.[1]

Conclusion

Pretreatment with lidocaine results in significantly better pain control during propofol infusion than pre-treatment with ephedrine.

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