

Original Research Article

Prevention of propofol injection induced pain: A comparison of acetaminophen with lidocaine

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Abstract: Propofol is a commonly used intravenous anaesthetic and is often the induction agent of choice. However pain on injection is a major drawback. Interventions to mitigate the pain have included selecting larger hand veins for injection, cooling or warming the drug pre-treatment with drugs like lidocaine, ephedrine, ondansetron, metoclopramide, opioids, thiopental, ketorolac, nifedipine, nonsteroidal anti-inflammatory drugs etc. As an alternative to these, acetaminophen is being used to decrease propofol –injection pain. The Aim was to study the efficacy of acetaminophen in decreasing the pain on injection of propofol and compare it with lidocaine. A randomised, double blind controlled study 150 patients aged 18-60 years classified as ASA physical status I or II scheduled for elective surgery, were assigned to one of the three groups. After securing a 20G I.V cannula in largest superficial vein on the dorsum of the hand, Lactated Ringer solution was started at the rate of 100ml /hr. After 5 minutes the infusion was stopped. A Pneumatic tourniquet was applied to the upper arm and the limb elevated for 15 seconds for drainage of venous blood. Tourniquet pressure was raised to 70 mm Hg. Patients were pretreated over 5 seconds with one of the study drugs i.e. 50mg (5ml) of acetaminophen (group A) or 50mg (5ml) lidocaine (group L) or (5ml) normal saline (groups).After 2 minutes, occlusion was released and one fourth of the total calculated dose(2mg/kg) of propofol was injected over 5 seconds. The pain that occurred during propofol injection was assessed on a four point verbal rating scale (none=0 mild=1 moderate=2 severe=3). In Results Group A (acetaminophen) - 30% had mild, 16% moderate and 4% severe pain after injection of propofol. 50% had no pain at all. Group L (Lidocaine) - 12% had mild, 2% moderate, none experienced severe pain. 86% were pain free. Group S (normal saline) - 54% had mild, 14% moderate and 4% severe pain. 28% were pain free. In Conclusion we concluded that lidocaine is superior to acetaminophen in reducing the pain on injection of propofol.

Keywords: Propofol, Pain on injection, Acetaminophen, Lidocaine

INTRODUCTION

Propofol is a commonly used intravenous anaesthetic and sedative. The ability to formulate propofol in a biocompatible vehicle having minimal side effects and an appropriate pharmacokinetic /pharmacodynamic profile is critical to its use as an intravenous agent [1]. One of the drawbacks associated with current formulations is pain on injection, with a reported incidence of 28%-90% [2]. Some patients recall the induction of anaesthesia as the most painful part of the perioperative period [3]. Triggering of the local kallikrein –kinin cascade, the concentration and pH of the injected drug and stimulation of the nociceptive receptors at the nerve endings between the intima and media layers of the vein have been implicated as causative mechanisms of propofol – injection pain [4]. Interventions to mitigate this pain

include selecting a larger hand vein for injection , cooling or warming the drug [5], pretreatment with drugs like lidocaine[6],ephedrine, ondansetron, Metoclopramide, opioids, thiopental, ketorolac [7], nifedipine [8], nonsteroidal anti-inflammatory drugs etc.

Acetaminophen (N acetyl-p-amino-phenol) has antipyretic and analgesic effects but lacks anti-inflammatory effects. The analgesia most likely arises from central action although the exact site in the CNS is not well defined. It has weak peripheral effects which are attributed to blocking impulse generation within the bradykinin sensitive chemoreceptors. We compared the efficacy of acetaminophen with that of lidocaine which has been commonly used for attenuating propofol-injection pain.

MATERIALS AND METHODS

This was a prospective, randomized double blind, single centre study conducted after obtaining Institutional Ethics committee approval and written informed consent from the patients. 150 patients aged 18-60years, of either gender, belonging to American Society of Anaesthesiologists physical status I, and requiring elective surgery under general anaesthesia were recruited for the study. Patients were excluded if they had any known allergy to the study drugs, were unco-operative, had difficulty communicating, were on concomitant use of pain modifying drugs or had peripheral vascular disease.

Patients were allocated to one of the below mentioned groups using computer generated randomisation.

Group A: Patients pretreated with i.v. Acetaminophen (50mg, 5ml).

Group L: Patients pretreated with i.v. lidocaine (50mg, 5ml)

Group S: Patients pretreated with normal saline (5ml)

Patients did not receive any pre-medication. On arrival in the operation theatre a 20G I.V cannula was inserted in largest superficial vein on the dorsum of non - dominant hand after attaching NIBP cuff, pulse oximeter and cardio scope. Lactated Ringer solution at the rate of 100ml /hr was started. After 5 minutes the infusion was stopped. Pneumatic tourniquet was applied to the upper arm of the hand with the i.v. Line. The arm was elevated for 15 seconds for drainage of venous blood. Tourniquet pressure was raised to 70 mmHg and patients were pretreated over 5 seconds with one of the study drugs. After 2 minutes, occlusion was released and one fourth of the total calculated dose (2mg/kg) of propofol was injected over 5 seconds. Propofol-lipuro, an emulsion of propofol 1% in a mixture of long-chain and medium chain triglycerides was used. The pain that occurred during propofol injection was assessed on a four point verbal rating McCrirrick and Hunter Scale [9] (none=0, mild=1, moderate=2 severe=3).

The anesthesiologist who prepared the study drug and the investigator who evaluated the pain were both not involved in the study.

Mc Crirrick and Hunter pain intensity scale

PAIN SCORE	DEGREE OF PAIN	RESPONSE
0	NONE	Negative response to questioning
1	MILD	Pain reported in response to questioning only without any behavioral signs
2	MODERATE	Pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning
3	SEVERE	Strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears.

Heart rate, systolic and diastolic blood pressure, mean arterial pressure (MAP) and arterial oxygen saturation were recorded as baseline, immediately after injection of pretreatment drugs and immediately after propofol injection. An increase or decrease in haemodynamic parameters by greater than 20% was considered clinically significant. Additional propofol was administered as required and choice of anaesthesia thereafter was left to the discretion of the anesthesiologist involved in the case. The injection site was checked for any edema, redness or allergic reaction.

Statistical Analysis:

On the basis of previous studies, the expected incidence of pain was 8% in the lidocaine group, 22% in the acetaminophen group and 64 % in the saline Group [10]. A power analysis indicated that a sample

size of 50 was sufficient to detect a large statistical difference with an alpha=0.05 and power 1-beta=0.8

The data was entered into the Microsoft excel sheet and analyzed using SPSS 15 and Sigma plot 11 software. Comparison within study groups was done with the help of paired T test and between groups by one-way ANOVA. Association among the study group was assessed with the help of Chi-Square test. p value of < 0.05 was considered significant.

RESULTS

There were no intergroup differences with respect to age, gender, weight and baseline hemodynamic parameters. The data on the incidence and severity of pain after injection of propofol among the three groups is presented in Table 1.

Table-1: Comparison of the Incidence and Severity of Pain after Propofol Injection (Among Group Acetaminophen, Group Lignocaine and Group Saline)

STUDY DRUG		PAIN SCORE(after propofol injection)				Total
		No pain	Mild	Moderate	Severe	
Acetaminophen	Count	25	15	8	2	50
	Percent	50.0%	30.0%	16.0%	4.0%	100.0%
Lignocaine	Count	43	6	1	0	50
	Percent	86.0%	12.0%	2.0%	0.0%	100.0%
Normal Saline	Count	14	27	7	2	50
	Percent	28.0%	54.0%	14.0%	4.0%	100.0%
Total	Count	67	63	16	4	150
	Percent	44.7%	42.0%	10.7%	2.7%	100.0%
Chi-Square Tests	Value	Df	P value	Association is		
Pearson Chi-Square	36.930	6	< 0.001	Significant		

DISCUSSION

Pain on injection of propofol can be immediate or delayed. The immediate pain could be the result of a direct irritant effect, but the kinin cascade is probably the cause of delayed pain [11]. The lipid solvent for propofol activates the plasma kallikrein-kinin system which results in bradykinin production that increases local vein permeability and dilation. The aqueous-phase propofol diffuses into more free nerve endings outside the endothelial layer of the vessel which is more permeable and dilated because of bradykinin effect, thereby intensifying pain on injection.

Lidocaine pretreatment is most commonly used to decrease pain due to injection of propofol. However it was reported that addition of lidocaine may destabilize the emulsion formulation of propofol with a potential risk of causing pulmonary fat embolism [12]. Lee and colleagues [13] showed that acetaminophen selectively suppresses peripheral PGE2 release and increases COX-2 gene expression in a clinical model of acute inflammation. In our study after pretreatment with acetaminophen, the overall incidence of propofol pain was 50%. Amongst these 30% experienced mild, 16% moderate and 4% severe pain. 50% of patients were absolutely pain free. The study by S.Ozkan *et al.* concluded that i.v. acetaminophen when given using tourniquet is as effective as i.v. lidocaine on propofol associated pain. Further, acetaminophen administration with tourniquet seemed to be superior to acetaminophen without use of a tourniquet. This could be because of higher doses of acetaminophen used that is 100mg [14] whereas the dose used in our study was 50mg. The study by Khaled *et al.*; to compare the effect of pretreatment with 1% lidocaine(4ml), acetaminophen(4ml) and a mixture of 2%

lidocaine(2ml) with fentanyl 100µg using tourniquet found that lidocaine-fentanyl reduced pain in 70% of patients while lidocaine alone in 68% patients whereas acetaminophen reduced pain in 54% patients which is in consonance with our study [15]. Our observations reveal that in the lidocaine group, 86% were pain free while 12% experienced mild and 2% moderate pain. This showed that lidocaine was superior to acetaminophen in alleviating propofol injection pain in statistically significant number of cases ($P < 0.001$).

Our findings were similar to those of Canbay *et al.*; who concluded that for reducing propofol injection pain lidocaine was superior to acetaminophen where 8% experienced pain whereas with acetaminophen 22% experienced pain [10]. Although lidocaine injected before propofol acts as a local anaesthetic and reduces pain, its analgesic effect is increased when a tourniquet is used concomitantly. A study by Kaya *et al.*; [16] showed that pretreatment with lidocaine plus venous occlusion for 60 seconds significantly reduced the incidence of pain compared with lidocaine without venous occlusion. Walker BJ *et al.*; found that lidocaine pretreatment with tourniquet was superior to admixing lidocaine with propofol for reducing the pain intensity. Admixture of lidocaine works by reducing the pH of the emulsion, thereby rendering more of propofol un-ionised and driving it from the aqueous phase into the lipid phase [17]. The tourniquet used for venous occlusion isolates the arm vein from the rest of the circulation. This is useful for differentiating the peripheral action of a drug in the absence of its central effect [18].

Gehan and colleagues concluded that the optimal dose of lidocaine was 0.1 mg/kg for prevention

of propofol pain and there was no further improvement as the dose of lidocaine was increased [19]. Borazan and colleagues concluded that when given as venous retention pre-treatments 1 min before propofol, paracetamol 1 mg/ kg and lidocaine 0.5 mg/ kg were equally effective in attenuating pain but acetaminophen 2 mg/ kg was shown to be most effective [20]. We used acetaminophen in a dose of 50 mg and found that 50% of patients experienced pain, one reason for this could be the lower dose used in our study. In our study, after pre-treating with normal saline and subsequent propofol injection 28% were pain free. Of the 72% who experienced pain, 54% had mild, 14% moderate and 4% severe pain.

We found a statistically significant ($p < 0.000$) although not clinically significant increase in pulse rate after acetaminophen pre treatment and subsequent propofol injection ($p < 0.192$). There was a simultaneous rise in Mean Arterial Pressure but this increase was not statistically significant ($P < 0.696$). After lidocaine pretreatment both mean pulse rate ($p < 0.007$) and MAP ($p < 0.003$) decreased to statistically significant levels but was not clinically significant to warrant any intervention. After subsequent propofol injection the mean pulse rate decrease was statistically significant ($p < 0.000$). The fall in MAP after subsequent propofol injection was not statistically significant ($p < 0.768$). This could be because the dose of propofol injected in our study was 1/4th of the total induction dose. Even in the absence of cardiovascular disease, a propofol induction dose of 2 to 2.5 mg/kg produces a 25% to 40% reduction of systolic blood pressure with similar changes in diastolic and mean blood pressure. Lidocaine does not prevent the fall in blood pressure caused by propofol [21]. Pretreatment with normal saline and subsequent propofol injection was found to increase mean pulse rate from baseline values to levels that were significant ($p < 0.021$). MAP also showed a similar trend ($p < 0.029$). This could be probably attributed to pain caused by propofol which was not attenuated by pretreatment with normal saline.

The results of a study conducted by Mohammad *et al* showed that the effects of lidocaine and granisetron in reducing pain after propofol were similar (69.64%) and higher than the other groups *i.e.* magnesium sulphate (51.78%), ondansetron (39.28%) and paracetamol (28.57%). The reduction of MAP was less in the acetaminophen group compared with the others, so they suggested that acetaminophen be used as a premedicant for patients predisposed to hypotension [22]. None of the patients in the three groups experienced any allergic reaction to study drugs.

As per our observations we conclude that lidocaine is superior to acetaminophen in alleviating propofol injection pain. The drawback of the study was

that lidocaine and acetaminophen were used in fixed doses and did not vary with the weight of the patients.

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