

Efficacy of Ephedrine Versus Lignocaine Pretreatment In Preventing Pain Following Propofol Injection: A Prospective, Randomized, Double-blind, Placebo-controlled Study.

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Citation

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Abstract

Background: Injection pain and hypotension are the two main adverse effects of propofol. The commonly used lignocaine pretreatment for reducing injection pain has a failure rate between 13- 32 %. There are few studies in literature using ephedrine pretreatment for reduction of propofol injection pain and these studies have also looked at the effect of ephedrine in overcoming hypotension and hemodynamic stability, each with varying results. We studied the effect of ephedrine 50µg/kg pretreatment on prevention of propofol injection pain and hemodynamics. **Methods:** This prospective, randomized, double-blind, placebo-controlled study was conducted after obtaining institutional ethical committee approval. Patients (eighty one patients) were randomly allocated to one of three groups. Each group consisting 27 (n= 27) patients were to receive one of lignocaine (Group L, n = 27), normal saline (Group S, n = 27) or ephedrine (Group E, n = 27) as pretreatment. Group L- pretreatment with 2% lignocaine 2 ml. Group S- pretreatment with 0.9% normal saline 2ml, Group E- pretreatment with ephedrine 50 µg/kg body weight diluted in normal saline into a 2 ml normal saline solution. Propofol was injected 30 sec later. A blinded researcher assessed the patient's pain level using a four point verbal rating scale. **Results:** There was no significant difference with respect to patient's characteristics and hemodynamic changes during propofol induction among the three groups. There was a statistically significant difference in the incidence of pain between groups. Patients who received lignocaine pretreatment group had 51.8% pain. The Normal saline pretreatment group had 77.8% pain. Ephedrine pretreatment group had pain as high as 70.4 %. **Conclusion:** Ephedrine used as pretreatment in dose of 50 µg/kg is neither useful to decrease propofol injection pain nor to maintain better hemodynamic.

INTRODUCTION

With the increasing quality and safety of anesthesia and perioperative care patient satisfaction is one of the top priorities of the anesthesiologist. Propofol is an intravenous (IV) sedative and hypnotic agent commonly used for anesthesia induction; injection pain and hypotension are the two main adverse effects of propofol. The pain on injection of propofol interferes with the patient satisfaction, with incidence between 40-86% (1). Propofol belongs to the group of sterically hindered phenols and injection pain is thought to be mediated by endothelial kinin release (2). Ephedrine is proposed to decrease the release of pain mediators from the vascular endothelium (3). There are few studies using ephedrine pretreatment for reduction of propofol injection pain with variable results. This study was

under taken to study the effect of ephedrine 50µg/kg pretreatment on prevention of propofol injection pain and hemodynamic effects.

METHODS

A prospective, randomized, double-blinded, placebo-controlled, study was undertaken after institutional ethical committee approval. Eighty one consented patients of either gender, in age groups 18-50 yrs, with American Society of Anesthesiologists physical status I and II who were scheduled for elective surgery requiring general anesthesia were included in the study. Patients with history of allergy to propofol, patients taking sedatives or analgesics 24 hrs prior to the surgery, neurological or cardiovascular disease, obesity, difficult airway and pregnant female patients were

excluded from the study.

Patients were allocated to one of three groups according to the random numbers generated by statistical software. Each group consisting of 27 (n= 27) patients, was to receive one of the lignocaine (Group L, n = 27), normal saline (Group S, n = 27) or ephedrine (Group E, n = 27) as pretreatment. Group L- pretreatment with 2% lignocaine 2 ml, Group S- pretreatment with 0.9% normal saline 2ml, Group E- pretreatment with ephedrine 50 µg/kg body weight diluted in normal saline into a 2 ml normal saline solution. All syringes of pretreatment solution were prepared by another investigator and so that the investigator who assessed the patient response was unaware of the contents of the syringe.

An 18 gauge intravenous cannula was inserted into a vein on the dorsum of the hand without local anesthetic infiltration approximately 2 hrs before induction of anesthesia. Infusion of normal saline was started to maintain patency of the vein. Before administration of propofol the patient was requested to rate the severity of pain during injection. An anesthetist blinded to the study was asked to evaluate the pain score, using the verbal rating scale (VRS) every 5 seconds during injection of propofol and grade it as 0 to 3 in accordance with scale advocated by McCriffick and Hunter (4) and record the highest degree of pain. The grading criteria of VRS were as follows: 0 = No pain experienced, 1= Mild pain or soreness, 2 = Moderate pain, 3 = Severe pain associated with grimacing, withdrawal movement of forearm or both.

Patients were connected to standard monitoring and thirty seconds after the administration of pretreatment solution, 1% solution of propofol 2 mg/kg bodyweight was injected at 1mL/s through a 3 way tap directly connected to the IV catheter with the IV infusion line closed titrating with the verbal response. After the injection of propofol, normal saline was administrated at maximum gravity flow. Following the loss of consciousness fentanyl 1µg/kg was administered and vecuronium bromide 0.1mg/kg body weight was administered to facilitate orotracheal intubation. Prior to intubation, anesthesia was administered with 50 % oxygen, 50% nitrous oxide and Isoflurane 2% given by face mask. Non-invasive blood pressure (systolic, diastolic and mean) and heart rate were recorded before giving pretreatment solution, and at 1, 2, and 3 minutes after propofol injection. Three minutes after administration of vecuronium orotracheal intubation was performed by an experienced anesthetist (more than 3 yrs experience). Further

anesthesia management was continued as per the discretion of attending anesthesiologist.

STATISTICAL ANALYSIS

The data obtained was subjected to statistical analysis using Minitab software for Windows. The various variables were compared between groups using Kruskal-Wallis test. Statistically significant variables i.e. pain response was further subjected to the Posthoc analysis by non-parametric method. Adjusted P Value <0.05 was considered significant.

RESULTS

No case was excluded from study after randomization. All three groups were comparable in demographic data (age, sex, weight). There were no statistically significant difference in demographic data among the three groups (Table: 1)

Figure 1

Table 1

	Group: L (n=27)	Group :S(n=27)	Group: E (n=27)
Age (yr)	36.07 ± 8.81	38.63 ± 9.10	37.15 ± 11.40
Sex (M/F)	18/9	19/8	17/10
Weight (Kg)	64.41 ± 10.74	62.00 ± 10.10	62.11 ± 13.80

Values are mean ± SD (range); all three groups were comparable in demographic data.

Hemodynamic data

There was no statistically significant difference in hemodynamic parameters (heart rate, systolic, diastolic and mean arterial blood pressure) among the three groups (Fig: 1)

Figure 2

Figure: 1

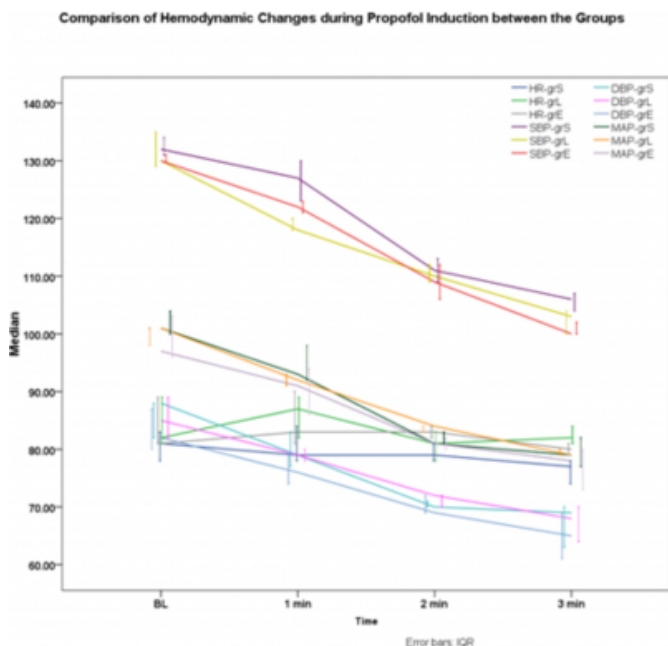


Figure: 1. Changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial blood pressure (MAP) in three groups, L = lidocaine, S = saline, E = ephedrine. BL = before induction, 1, 2, and 3 min = 1, 2, and 3 min after propofol injection.

There were no statistically significant difference of hemodynamic parameters (P value < 0.05)

Assessment of injection pain following pretreatment done at 5sec, 10 sec, 15 sec and 20sec after starting administration of propofol (Fig:2). Statistical analysis revealed no significance at 5 sec (P value of 0.303),and significant difference at 10sec, 15sec, and 20sec .P values of 0.025, 0.009 and 0.006 respectively.

Figure 3

Figure: 2

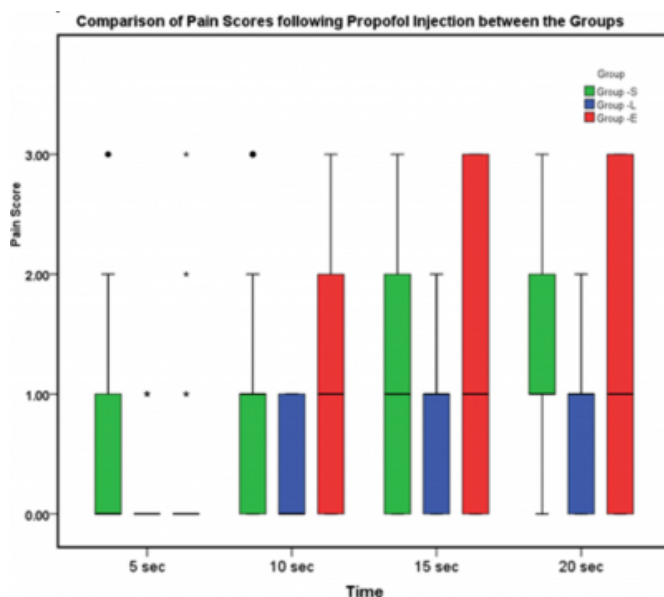


Figure: 2. Pain score following injection of propofol in three groups. L = lidocaine, S = saline,

E = ephedrine during induction. 5, 10, 15 and 20sec = 5, 10, 15 and 20 sec after propofol injection. The grading criteria of VRS were as follows: 0 = No pain experienced, 1= Mild pain or soreness, 2 = Moderate pain, 3 = Severe pain associated with grimacing, withdrawal movement of forearm or both.

In our study, patients who received lignocaine pretreatment had an incidence of pain of 51.8% compared to normal saline pretreatment patients (77.8%). However the incidence of pain in patients who received ephedrine pretreatment was as high as 70.4 %. There was statistically significant difference in pain scores between lignocaine group and normal saline group, and also between lignocaine group and ephedrine group. A higher number of patients in the ephedrine group complained of severe pain but no patient in the lignocaine group complained of severe pain (Table :2) There was no statistically significant difference in the pain between ephedrine group and normal saline group.

Figure 4

Table: 2. nIncidence and Intensity of Pain (Verbal Rating Scale) on Injection of Propofol

Intensity of pain	Group -L (n =27)	Group- S(n=27)	Group-E (n=27)
None (0)	13	6	8
Mild(1)	12	10	6
Moderate (2)	2	6	5
Severe(3)	0	5	8
Any pain	14/27 = 51.85%	21/27 = 77.77%	19/27 = 70.37%
Median pain score	1	1	3

Data are expressed in number of patients

Pain score following injection of propofol in three groups. L = lidocaine, S = saline,

E = ephedrine during induction. There was a statistically significant difference in pain scores between group L and S & L and E, there was no statistically significant difference between group S and E.

DISCUSSION

Pain on injection of propofol has been reported since the initial studies (5) and is still a limitation of this otherwise excellent IV anesthetic agent. Chemically propofol belongs to the group of sterically hindered phenols (6). Hence, like the phenols, it irritates the skin, mucous membrane and venous intima and can cause injection pain. Propofol injection pain is thought to be mediated by endothelial kinin release (2). The trigger for this kinin release is unclear.

Although the etiology of this pain remains obscure, several methods have been used to attenuate this pain and lignocaine pre-treatment is most commonly used to decrease the injection related pain (7-9). However literature reports the failure rate between 13- 32 % (7, 8). Ephedrine acts directly on both alpha and beta receptors and indirectly by releasing endogenous norepinephrine. It is proposed to decrease the release of pain mediators from the vascular endothelium (3).

There are few studies using ephedrine pretreatment for reduction of propofol injection pain and have looked at the effect of ephedrine in overcoming hypotension and hemodynamic stability each with varying results. The study done by Mi A Ceoing using ephedrine pretreatment had shown reduction of pain with ephedrine comparable with lignocaine at various doses of ephedrine pretreatment (10) (The incidence of pain with placebo was 86.6%, lignocaine 43.3%, Ephedrine 30µg/kg 35.6%, Ephedrine 70 µg/kg 43.3%, Ephedrine 110 µg/kg 40%, Ephedrine 150 µg/kg 42.8% respectively). Increase in the dose of ephedrine did not result in decrease in pain severity experienced by the patient. Also considering that increasing the dosage could

produce adverse hemodynamic effects, they have recommended use of ephedrine in the dose of 30-70 µg /kg range (10). Austin JD et al have concluded adding 30 mg of ephedrine to 20 mL of 1% propofol is as effective as adding lidocaine in preventing injection pain (preventing injection pain with lignocaine 68.6%, Ephedrine 15 mg 64.7%, and Ephedrine 30 mg 61.1% respectively) and it results in a more stable hemodynamic profile (11).

Agarwal A et al showed that pretreatment with ephedrine 30 µg /kg did not attenuate pain associated with intravenous injection of propofol, nor did it improve hemodynamic stability during induction (12). The study by Khezri MB, et al also showed that the pain scores in Ephedrine 30 µg /kg and Ephedrine 70 µg /kg pre treatment failed to show a significant difference with that of normal saline pretreatment but the MAP was maintained better (13).

In our study, patients who received pretreatment with lignocaine, normal saline and ephedrine had an incidence of pain of 51.8%, 77.8%, 70.4 % respectively. There was statistically significant difference in pain scores between lignocaine group and placebo group, and also between lignocaine group and ephedrine group. A higher number of patients in the ephedrine group complained of severe pain but no patient in the lignocaine group complained of severe pain. There was no statistically significant difference in the pain between the ephedrine group and the normal saline group.

There was no statistically significant difference in the hemodynamic parameters among the three groups. Hence, ephedrine pretreatment using 50µg/kg dose neither had reduction of propofol injection pain nor better maintenance of hemodynamics. This finding was similar to the study done by Ozkicak et al where they concluded that ephedrine 70 µg/kg may prevent hypotension due to propofol induction, but not able to reduce injection pain (The incidences of injection pain in normal saline group 84%, and in ephedrine group 80%, respectively) (14).

The lack of hemodynamic benefits in our study could be due to the small dosage of ephedrine used (50 µg/kg) as pretreatment in our study. However GamlinF et al, found no benefit even with addition of 10 mg of ephedrine given in combination with propofol to prevent hypotension (15) .Hence ephedrine (50µg/kg) pretreatment neither reduces the pain nor alter the haemodynamics compared to lignocaine 2ml 2% pretreatment.

CONCLUSION

Ephedrine used as pretreatment in dose of 50 µg/kg was neither useful to decrease propofol injection pain nor to maintain better haemodynamics. Hence we suggest the usage of the most commonly used and extensively studied drug lignocaine, may be administered as pretreatment to reduce incidence of propofol injection pain.

References

1. Angst MS, Mackey SC, Zupder et al. Reduction of Propofol injection pain with a double lumen IV Set. *J clin Anesth* ; 9:462-6 :1997.
2. Klement.W and Arndt. Pain on I.V injection of some anaesthetic agents is evoked by the unphysiological osmolarity or pH of their formulation. *BJA*; 66; 189-195, 1991
3. Hemmingsen C, Poulsen, Risbo A. Prophylactic ephedrine during spinal anaesthesia: *BJA* 63:340-42:1989.
4. McCrirrick and Hunter. Pain on injection of propofol: The effect of injectate temperature. *Anaesthesia* , volume 45:443-444:1990.
5. Kay B, RollyG, ICI 35868, a new IV induction agent *Acta analgesia* :28:303-16,1977.
6. Fragen R:Diprivan (propofol):A historical perspective. *Semin Anesth* 7:1, 1988.
7. Scott RP, Saunders DA, Norman J. Propofol : clinical strategies for preventing the pain of injection. *Anaesthesia* 43:492-4.1988.
8. King SY, Davis FM, Well JE et al. Lidocaine for the prevention of pain due to injection of Propofol, *Anesh Analg* 74:246-249.1992.
9. Picard P, Tramer MR. Prevention of pain on injection with Propofol : a quantitative systematic review. *Anaesthesia Analgesia*; 90:963-9:2000.
10. Mi A Ceong , KyoS Kim, and WonJ.Choi. Ephedrine reduces the pain from propofol injection. *Anesthesia Analgesia* 95; 95:1293-6: 2002.
11. Austin JD, Parke TJ. Admixture of ephedrine to offset side effects of propofol: a randomized, controlled trial. *J Clin Anesth.* 2009 Feb; 21(1):44-9.
12. Agarwal A, Dhiraaj S, Raza M, Singhal V, Gupta D, Ranjan R, Singh PK, Singh U. Pain during injection of propofol: the effect of prior administration of ephedrine. *Anaesth Intensive Care.* 2004 Oct; 32(5):657-60.
13. Khezri MB, Kayalha H. The effect of combined ephedrine and lidocaine pretreatment on pain and hemodynamic changes due to propofol injection. *Acta Anaesthesiol Taiwan.* 2011 Jun; 49(2):54-8. Epub 2011 Jun 24.
14. Ozkoçak I, Altunkaya H, Ozer Y, Ayoğlu H, Demirel CB, Çiçek E. Comparison of ephedrine and ketamine in prevention of injection pain and hypotension due to propofol induction. *Eur J Anaesthesiol.* 2005 Jan; 22(1):44-8.
15. Gamlin.F, Vucevic.M et al Haemodynamic effects of propofol in combination with ephedrine. *Anaesthesia* May; 51(5): 488-91, 1996.

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