Original Article

Role of hydrocortisone in prevention of pain on propofol injection

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Abstract

Background and Objectives: Pain following intravenous injection of propofol continues to be an intriguing problem. None of the commonly used methods completely attenuate the pain. Inflammatory response to propofol contributes to the pain. Role of hydrocortisone in attenuating pain has not been evaluated. This study was conducted to compare the efficacy of lignocaine and hydrocortisone in attenuation of pain following intravenous injection of propofol.

Materials and Methods: A prospective randomized double-blind, placebo-controlled study was conducted on 72 adult patients belonging to American Society of Anesthesiologists (ASA) physical status I or II, scheduled to undergo elective surgery. They were randomly assigned to four groups of 18 each. Group NS, group LG, group HC10, and group HC25. The groups received 2 ml normal saline, 2 ml 2% lignocaine, 10 mg/2 ml hydrocortisone, and 25 mg/2 ml hydrocortisone, respectively, as pretreatment. Propofol was injected 30 sec later. A blinded researcher assessed the patient's pain level using a four point verbal rating scale.

Results: The four groups were comparable in respect to patient's characteristics. There was no significant difference of hemodynamics changes during propofol induction between all the groups. There was no statistically significant difference in the incidence of pain between patients who received hydrocortisone and the placebo group. The incidence of pain was significantly less in group LG than other three groups.

Conclusion: Use of intravenous low dose hydrocortisone pretreatment of the vein does not attenuate pain following propofol injection.

Key words: Hydrocortisone, injection pain, propofol, steroids

Introduction

Patient satisfaction with perioperative care is assuming more importance in the recent years. Propofol is an intravenous (IV) sedative and hypnotic agent commonly used for anesthesia induction because it rapidly and reliably causes loss of consciousness and is associated with a quick smooth recovery. However, pain on its intravenous injection is a common problem with its use, with an incidence of 40-86%.[1] The mechanisms of pain on propofol injection are not known completely, but a number of factors may be responsible for the pain. Several drugs and techniques have been used to attenuate this pain.[2-6] Lignocaine pretreatment is most commonly used to decrease the injection related pain,[2,3,6] but it has a failure rate between 13-32%.[7,8] One of the mechanisms proposed for pain on propofol injection is release of pro-inflammatory mediators like kinins.[8]

There are few studies on use of pretreatment with steroid based drugs for attenuation of pain on propofol injection. The efficacy of dexamethasone pretreatment for alleviation of propofol injection pain has been studied.[9] There are no studies on the role of hydrocortisone on preventing the pain on propofol injection. This study was undertaken to study the efficacy of two different doses of hydrocortisone 10 mg and 25 mg in comparison with placebo (normal saline) and lignocaine 2%.

Materials and Methods

A prospective, randomized, controlled, double blind study was conducted after approval of the local ethics committee. Informed consent was taken from 72 patients of either gender, aged between 25 and 65 years belonging to American Society

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of Anesthesiologists (ASA) grade I and II scheduled to undergo elective surgery and requiring general anesthesia. Patients with history of allergy to propofol, neurological or cardiovascular disease, and patients with obesity, difficult airway, pregnant patients, and patients on medication with pain modifying drugs were excluded from the study.

Patients were allocated into four groups according to the computer software generated random numbers. Group NS - patients receiving 2 ml (0.9%) normal saline, group LG - patients receiving 2 ml of 2% lignocaine, group HC 10 - patients receiving 10 mg hydrocortisone diluted in 2 ml of normal saline, and group HC 25- patients receiving 25 mg hydrocortisone diluted in 2 ml of normal saline. The drugs were prepared by a different person than the person injecting the drugs. All four drug solutions were looking identical. All patients were explained about the verbal rating scale for assessment of pain on propofol injection.

All patients were premedicated with oral alprazolam 0.25 mg on the night before surgery. On arrival in the operation theatre, an 18G intravenous cannula was placed without the use of local anesthetic infiltration in the largest vein on the dorsum of the hand and lactated Ringer's infusion was started.

Venous occlusion was achieved by using venous tourniquet. The study drug was then injected. Thirty seconds after the administration of study drug occlusion was released and 5 ml of the propofol solution injected over 15 sec. After the injection, crystalloid was administered at maximum gravity flow. The anesthetist blinded to the study drug evaluated the pain according to verbal rating scale (VRS) every five seconds during injection of propofol. The patients were asked to grade any associated pain or discomfort using a four-point verbal rating scale that had been previously described to them. Pain was graded from 0 to 3 in accordance to scale advocated by McCrirrick and Hunter.[10]

0 - no pain or no 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 pain, strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears.

The remainder of the calculated (2 mg/kg) propofol dose was then administered and fentanyl (1 mcg/kg) was given to all patients. Following loss of consciousness injection vecuronium bromide 0.1 mg/kg body weight was administered to facilitate endotracheal intubation. Anesthesia was maintained with isoflurane 0.5-2% and nitrous oxide 60% in oxygen with controlled ventilation. Non-invasive blood pressure (systolic, diastolic and mean) and heart rate were recorded. These parameters were recorded before giving pretreatment solution and after induction of anesthesia at 1, 2, and 3 minutes after propofol injection. Anesthesia was maintained as per the institutional protocol for the scheduled surgery.

The statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 13 (Chicago, IL). The data is expressed as mean with standard deviation (S.D.) and frequency of occurrence with percentages. The categorical variables were compared between the groups using Chi-square test and Fisher exact test when expected frequency was less than 5. The continuous variables were compared between groups using Kruskall - Wallis test. Statistically significant variables were further subjected to Posthoc analysis by non-parametric method. Adjusted *P*-value <0.05 was considered significant.

A pilot study was undertaken on 32 patients with eight patients in each group. The effect size calculated with the incidence of pain on propofol injection was found to be 0.8. The sample size calculated using this data for an alpha error of 0.05 and beta error of 0.2 power of 0.8 was found to be 18 per group.

Results

The four groups were comparable in respect to age (*P* 0.99) and weight (*P* 0.63) [Table 1]. There was no significant difference in hemodynamics changes during propofol induction between groups [Figure 1]. The highest incidence of pain was at 15 sec in all the groups. The overall incidence of pain in group LG was 33.33% as compared to 94.44%, 66.66%, and 94.44 % in the groups NS, HC 10, and HC 25, respectively. There was no statistically significant difference in pain at 5, 10, 15, and 20 sec between the placebo group and groups where hydrocortisone was used as pretreatment [Figure 2]. Group LG had significantly lower incidence of pain. Post hoc analysis revealed that at 5 sec there was significant reduction in pain between group LG and group NS (*P* value 0.008). There was significant difference in pain between group LG and the other three groups at 10, 15, and 20 sec.

Discussion

Propofol is a popular intravenous anesthetic agent because of its rapidity and reliability in causing loss of consciousness associated with quick and smooth recovery. However, pain on injection of propofol is a major drawback. Propofol belongs to the group of sterically hindered phenol that can irritate the skin, mucous membrane, and venous intima. Peripheral veins are innervated with polymodal nociceptors which

Table 1: Comparison of demographic data between the groups

	(Group-NS)		(Group-LG)		(Group-HC 10)		(Group-HC 25)		*P* value
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Age	35.88	13.22	36.16	13.32	34.88	16.21	35.27	11.81	0.992
Weight	57.72	8.00	56.33	8.87	58.11	7.39	60.00	9.35	0.632

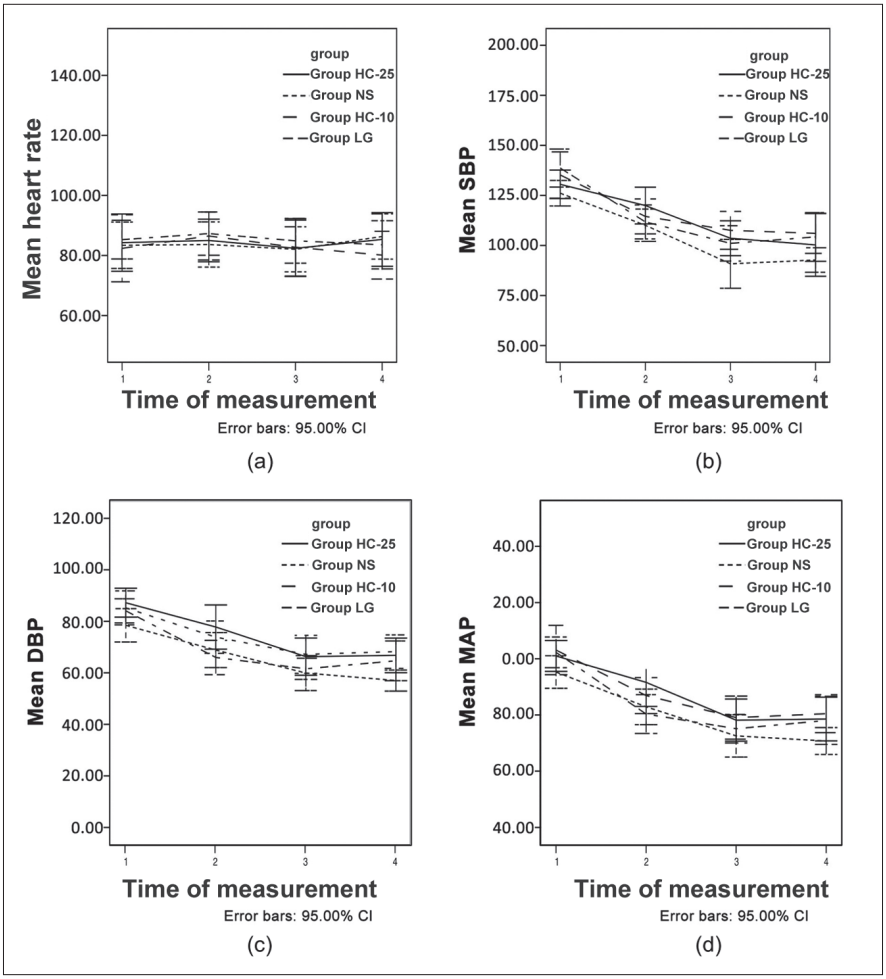

Figure 1: Comparison of hemodynamic changes after propofol injection. (a) Comparison of heart rate between the groups. (b) Comparison of SBP between the groups. (c) Comparison of DBP between the groups. (d) Comparison of MAP between the groups

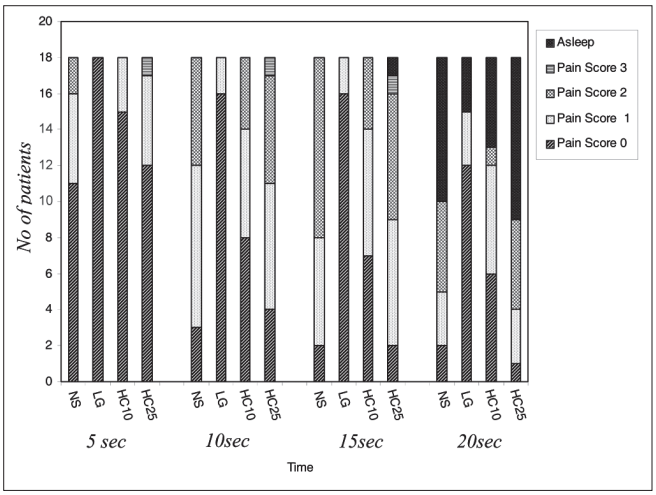

Figure 2: Comparison of pain scores after propofol injection

mediate the pain response to the injection of certain anesthetic agents.[11] Etiology of the injection pain caused by intravenous administration of propofol is not clear. The immediate pain may be caused by direct irritation of afferent nerve ending within the veins. It has been reported that the pain may be due to the activation of nociceptors by the osmolality or pH of the solution, amount of free agent in the aqueous phase of emulsion or activation by the release of endogenous mediators.[12-14] Scott *et al*., speculated that the pain on injection is caused by activation of the Kallikrein-Kinin system either by propofol or the lipid solvent, thereby 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.[8] This pain has a 10-20 sec delayed onset.

Several methods for prevention of pain have been tried with varying degrees of success like addition of lignocaine,[2,7,9] cooling[10,15] or warming[16] of the drug, diluting propofol solution,[12,17,18] pretreatment with ondansetron,[4] metoclopramide,[5] opioids,[6] thiopentone,[19] paracetamol,[20] dexamethasone,[9] and dexmedetomidine.[21]

Glucocorticoids can prevent or suppress inflammation in response to multiple inciting events. Multiple mechanisms are involved in the suppression of inflammation by glucocorticoids. They inhibit the production by multiple cells of factors that are critical in generating the inflammatory response. As a result, there is decreased release of vasoactive and chemo-attractive factors, diminished secretion of lipolytic and proteolytic enzymes, and decreased extravasation of leukocytes to areas of injury. Glucocorticoids can also reduce expression of proinflammatory cytokines, such as COX-2(cyclooxygenase 2) and NOS2 (nitric oxide synthase 2). They act on macrophages and monocytes, endothelial cells, basophils, fibroblasts and lymphocytes, and inhibit different proinflammatory mediators[22] like prostaglandins and leukotrienes, cytokines including interleukin and tumor necrosis factor etc. Since one of the proposed mechanisms for pain on propofol injection is mediated through the inflammatory pathway, it was hypothesized that pretreatment with steroid would attenuate the pain on propofol injection.

There are very few studies on use of pretreatment with steroid based drugs for attenuation pain on propofol injection. Singh *et al.*,[9] studied the efficacy of dexamethasone pretreatment for alleviation of propofol injection pain and found that dexamethasone in a dose of 0.15 mg/kg decreased the incidence of propofol injection pain significantly when administered 1 min before injection of propofol. However, it was associated with perineal itching and pain in some cases which precludes its routine administration for alleviation of propofol injection pain.

In addition to the local factors, several systemic factors can influence the pain experienced on propofol injection. Dedic *et al.*,[23] concluded that combined premedication regimen with midazolam, diclofenac sodium, and acetaminophen orally aimed at preoperative anxiety reduction and peri- and postoperative analgesia causes a significant reduction in experience of pain on propofol injection. We did not administer any analgesics for premedication to avoid interference with pain perception.

There was no significant reduction of pain with either 10 mg or 25 mg of hydrocortisone as pretreatment when compared to placebo. The incidence of pain following lignocaine pretreatment was 33.33%. There was significantly higher incidence of pain with hydrocortisone than lignociane. Pretreatment with 10 mg hydrocortisone was associated with lower incidence of pain as compared to pretreatment with 25 mg hydrocortisone; however, this was not statistically significant.

Certain methodological limitations could have contributed to the lower efficacy of hydrocortisone. It was administered 30 sec prior to administration of propofol which may be a short contact time. Hydrocortisone might not be effective on immediate pain.[8] Its effect on delayed pain is not possible to elicit as patient would be asleep by then.

Conclusion

The pain on injection of propofol is multifactorial. The use of steroid as a sole agent may not be sufficient to attenuate this pain of multiple etiology.

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