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Role of Steroids 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.

Methods: A prospective randomized double-blind, placebo-controlled study was conducted on 72 adult patients belonging to ASA physical status I or II, scheduled to undergo elective surgery. They were randomly assigned into four groups of 18 each. Group NS, group LG, group HC10, and group HC25, received 2ml normal saline, 2ml 2% lignocaine, 10mg/2ml hydrocortisone and 25mg/2ml 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 haemodynamics 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 3 groups.

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

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. Its rapidity and reliability in causing loss of consciousness and quick smooth recovery are favorable features. However pain on injection when given intravenously is a common problem with propofol, the incidence of which is between 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. Lignocaine pretreatment is most commonly used to decrease the injection related pain. However, the failure rate is between 13-32% [2,3]. One of the mechanisms proposed for pain on propofol injection is release of pro-inflammatory mediators like kinins. Hydrocortisone is a corticosteroid used for its anti-inflammatory and immunosuppressive effects. There are no previous studies regarding its role on preventing the pain on propofol injection.

This study was undertaken to study the efficacy of two different doses of hydrocortisone 10mg and 25mg in comparison with placebo (Normal Saline) and lignocaine 2%.

Methods

A prospective, randomized, controlled, double blind study was conducted after local ethics approval. Informed consent was taken from 72 patients of either gender, aged between 25 and 65 years, belonging to ASA grade 1 and 2, 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 random numbers generated by computer software. Group NS - patients receiving 2ml (0.9%) normal saline, Group LG - patients receiving 2 ml of 2% lignocaine, Group HC 10 - patients receiving 10 mg Hydrocortisone diluted in 2ml of normal saline and Group HC 25- patients receiving 25mg Hydrocortisone diluted in 2ml of normal saline. The drugs were prepared by a different person than the person injecting the drugs. All four drug solutions were identically looking. All patients were explained about the verbal rating scale for assessment of pain on propofol injection.

All patients were premedicated with oral Alprazolam 0.25mg on the night before surgery. On arrival in the operation theatre, an 18 gauge intravenous cannula was placed without the use of local anesthetic infiltration in the largest vein on the dorsum of the hand lactated Ringers 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 5 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 McCriffick and Hunter; 0-No pain experienced., 1-Mild pain or soreness, 2-Moderate pain and 3-Severe pain associated with grimacing, withdrawal movement of forearm or both.

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The remainder of the calculated (2 mg/kg) propofol dose was then administered and fentanyl (1mcg/kg) was given to all patients. Following loss of consciousness injection vecuronium bromide 0.1mg/kg body weight 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, after induction at 1,2 and 3 minutes after propofol injection. Further anesthesia was continued as per the institutional protocol for the scheduled surgery.

The statistical analysis was performed using 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 the Posthoc analysis by non-parametric method. Adjusted P Value <0.05 was considered significant.

A pilot study was undertaken on 32 patients with 8 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-0.992) and weight

	(Group-NS)		(Group- LG)		(Group –HC 10)		(Group-HC 25)		
	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	MEAN	S.D.	P Value
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

Table 1: Comparison of Demographic Data between the groups.

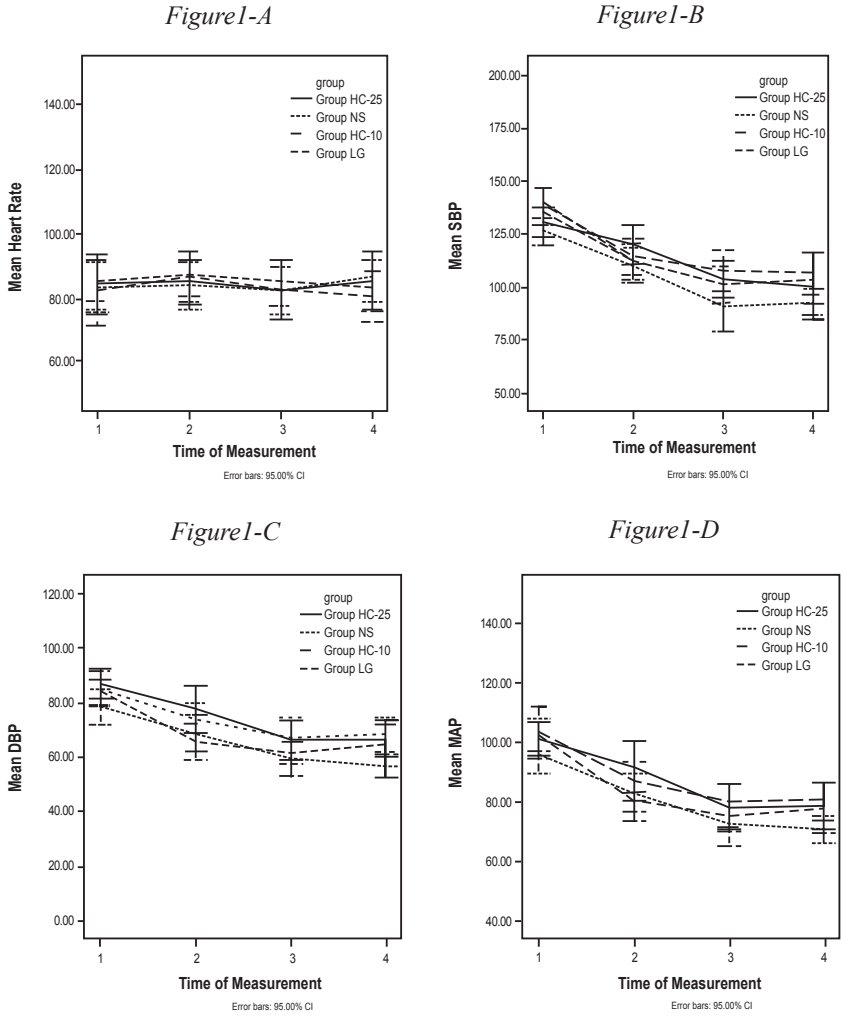

Figure 1: Comparison of Haemodynamic changes following propofol injection
1A: Comparison of Heart rate between Groups
1B: Comparison of SBP between Groups
1C: Comparison of DBP between Groups

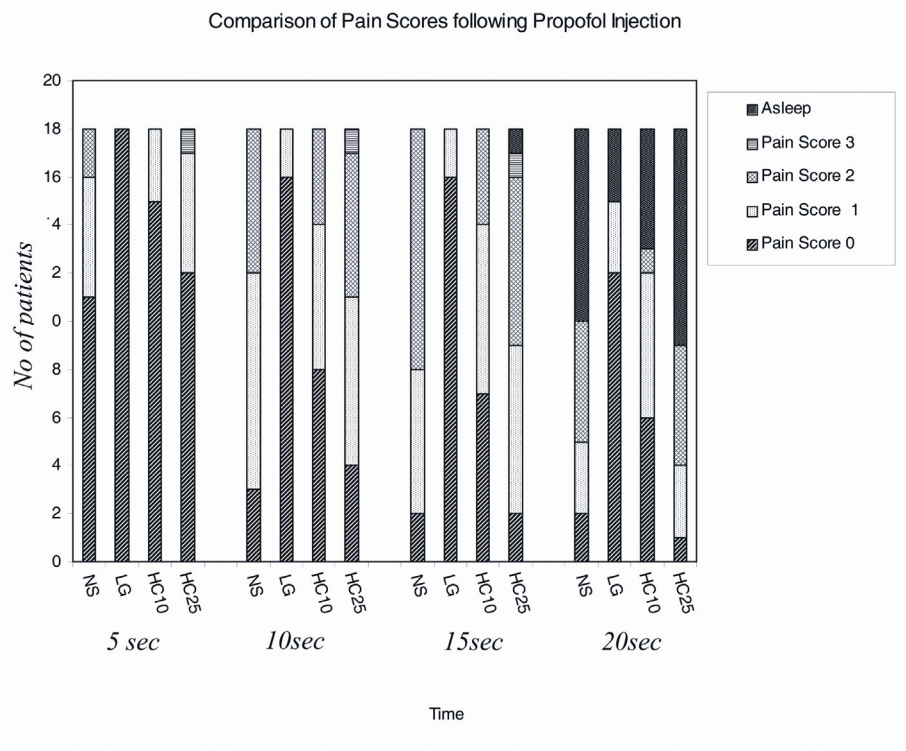

Figure 2: Bar diagram showing Comparison of Pain Scores after Propofol injection.

(p-0.632) (Table 1). There was no significant difference in haemodynamics 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 sec, 10 sec, 15 sec 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 is significant difference in pain between group LG and group NS (P value 0.008). There is significant difference in pain between group LG and the rest of the 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, which has been reported to occur in 40-86% [1]. of patients, 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 mediate the pain response to the injection of certain anaesthetic agents [4]. Aetiology 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 with in 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 [5-7]. Scott et al. [3] speculated that the pain on injection is caused by activation of the kallikrein-kinin system either by propofol or 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 [8]. This pain has a 10-20s delayed onset.

Several methods for prevention of pain have been tried with varying degrees of success like addition of lignocaine, [2,3,9] cooling [10,11] or warming [12] of the drug, diluting propofol solution [5,13], pretreatment with ondansetron [14], metoclopramide [15], opioids [16], thiopentone [17], paracetamol [18], dexamethasone [19] and dexmedetomidine [20]. Analgesic effect of lignocaine may occur because of a local anesthetic effect or an inhibitory effect on the enzymatic cascade which leads to release of kinins [3]. However literature reports the failure rate between 13-32% [2,3]. A Dedic et al. [21] 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.

In another study Hye-Joo Kang et al. [22] concluded that the younger age patients, the patients with a peripheral IV site and female patients are more sensitive to pain on the injection of propofol.

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. Glucocorticoids can prevent or suppress inflammation in response to multiple inciting events. Multiple mechanisms are involved in the supprression 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 chemoattractive factors, diminished secretion of lipolytic and

proteolytic enzymes, 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 & monocytes,endothelial cells,basophils,fibroblasts and lymphocytes and inhibit different proinflammatory mediators [23] like prostaglandins & leukotrienes, cytokines including interleukin and tumor necrosis factor etc.

There are very few studies on use of pretreatment with steroid based drugs for attenuation pain on propofol injection. M Singh et al. [19] studied the efficacy of dexamethasone pretreatment for alleviation of propofol injection pain. Dexamethasone in a dose of 0.15mgkg decreased the incidence of propofol injection pain significantly when administered 1 min before injection of propofol. But it was associated with perineal itching and pain in some cases which precludes its routine administration for alleviation of propofol injection pain.

We have studied the efficacy of pretreatment with hydrocortisone in attenuation of pain on propofol injection. There was no significant reduction of pain with either 10mg 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 10mg hydrocortisone shows lower incidence of pain as compared to pretreatment with 25 mg hydrocortisone though there was no statistically significant difference between the two. Difference of effectiveness of hydrocortisone in two different doses could be due to the dilution of the drug.

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 that was allowed. Hydrocortisone might not be effective on immediate pain [8]. Its effect on delayed pain may not be possible to elicit as patient would be asleep. The pain on injection of propofol is multifactorial. The use of steroid as a sole agent may not be sufficient to attenuate the pain of multiple etiology.

Conclusion

Pretreatment with low dose hydrocortisone as a sole agent may not be sufficient to attenuate the pain of multiple etiologies.

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