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A DOUBLE BLINDED RANDOMIZED STUDY OF EFFECTIVENESS OF HYDROXYETHYL STARCH PRE-ADMINISTRATION IN REDUCING PAIN ON PROPOFOL INJECTION

Dr. Ketki Jandial[1]* and Dr. Mamta Gupta[2]

[1]Medical Officer, Super Specialty Hospital, GMC Jammu, J&K.
[2]Senior Resident, Department of Anesthesia, GMC Jammu, J&K.

***Corresponding Author: Dr. Ketki Jandial**
Medical Officer, Super Specialty Hospital, GMC Jammu, J&K.

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ABSTRACT

Background: Propofol is an ideal anesthetic agent but the incidence of pain on the intravenous injection of propofol is 30-90%.The immediate pain is due to irritation of the veins and delayed pain may be due to kinin release. Colloids, such as Hyroxyethyl Starch (HES) are used for intra-operative fluid therapy in anaesthesia and are considered to be safe. The aim of this study was to compare the incidence and severity of pain on propofol injection in patients pre-administered either HES 130/0.4 or 0.9% normal saline (NS) bolus during induction of anaesthesia. **Method:** A prospective randomized placebo-control double-blind study was carried out in the Department of Anesthesia, Government Medical College, Jammu, over a period of 6 months. A total of 100 patients, 18-65years old, of either gender, undergoing elective surgery under general anaesthesia, were recruited, with 50 each in two groups: one received 100ml of 6% hydroxyethyl starch (HES) 3 to 5 min before propofol injection, and the other received Normal Saline. **Results:** Both groups were comparable with respect to age, gender, weight and height. None of the patients were lost to follow up. Incidence of pain on injection was significantly lower in group I (14, 28.0%). There were no significant differences in mean arterial pressure and heart rate between the two groups. The effect size for pain between the groups was large (0.73). **Conclusion:** Pre-administration of 6% HES (130/0.4), 3 to 5 min before propofol injection, significantly decreased the pain on injection with propofol.

KEYWORDS: Adult, adverse effects, injections, pain, propofol.

INTRODUCTION

Propofol is the most widely used intravenous (IV) anesthetic agent for induction and maintenance of anesthesia as well as for sedation inside and outside Operation Theater. It is an ideal anesthetic agent, but there is a problem however, the incidence of pain on the intravenous injection of propofol is 30-90%.[1] Propofol is an alkylphenol (2,6 diisopropylphenol); oil at room temperature and insoluble in aqueous solution but is highly lipid soluble. Its pH is 7 and pKa in water is 11; it looks viscous apart from being milky. It was initially prepared with Cremophor EL, but due to anaphylactoid reactions and severe pain on its injection, it was reformulated in an emulsion.[2] This pain ranks seventh amongst post operative problems after anaesthesia.[3] The immediate pain is due to irritation of the veins and delayed pain may be due to kinin release.[1] Various techniques are used to mitigate this pain, which include administration in a larger vein, pre-mixing with lignocaine, pre-administration of opioids, sub-anaesthetic doses of ketamine, using a mixture of medium and long chain triglycerides in the carrier emulsion, etc.[4,5]

Apart from pain on injection, the current lipid formulation has other disadvantages such as bacterial contamination, anaphylaxis, hyperlipidemia, and propofol infusion syndrome when used for sedation for a prolonged period. Hence, search for a better formulation continues till today. In one observational study of 1375 patients, incidence of pain on injection of MCT/LCT propofol was 28.7%, with 16.6% of patients reporting mild pain.[6]

In a recent meta-analysis for POPI, pretreatment with lignocaine and ketamine for MCT/LCT propofol was recommended,[7]

Colloids are used for intra-operative fluid therapy in anaesthesia,[8] and are considered to be safe.[9] They are macromolecules that have the capacity to modify endothelial cell junctions and permeability of the vascular endothelium and inhibit endothelial activation by various substances and molecules.[10,11] Pre-administration of colloids may prevent contact activation by propofol, which may in turn lead to reduced pain

during injection. Hydroxyethyl starch being a synthetic colloid volume expander, is used to maintain vascular volume. HES is a clinically well-tolerated complex polysaccharide that has recently been used in the therapeutic treatment of stroke and vasospasm after subarachnoid hemorrhage. It is available in multiple preparations, and different hydroxyl ethylation ratio.[12]

Studies.[13] having hypothesized that the pre-administration of 6% hydroxyethyl starch (HES) 3 to 5 min before propofol injection, could reduce pain on propofol injection, have yielded encouraging results. However, there are no studies till now which verified such results specific to North Indian population.Thus, the aim of this study was to compare the incidence and severity of pain on propofol injection in patients pre-administered either HES 130/0.4 or 0.9% normal saline (NS) bolus during induction of anaesthesia.

METHODS

A prospective randomized placebo-control double-blind study was carried out in the Department of Anesthesia, Government Medical College, Jammu, conducted over a period of 6 months. A total of 100 patients were selected, 50 each in two groups. Randomization was carried out using a computer- generated random number sequence. Patients were randomized to receive 100 mL bolus of either HES or NS before propofol injection. Allocation concealment was carried out with opaque sealed envelopes which were opened once the patients were received in the theatre. The primary objective of the study was to compare the incidence of pain on propofol injection in patients receiving HES bolus vs. NS, and the secondary objective was to compare the severity of propofol injection pain in the twogroups. Due approval was obtained from Institutional Ethics Committee, and written informed consent was obtained from each patient before enrollment.

Inclusion Criteria: Adult patients of the American Society of Anesthesiologists physical status I and II, 18-65 years old, of either gender, undergoing elective surgery under general anaesthesia, were recruited.

Exclusion criteria: Emergency surgeries, known history of allergy to propofol or HES, hypertensive, diabetics, presence of left ventricular dysfunction, elevated serum creatinine, and those in whom hand or fore arm veins were not accessible.

On arrival in the operating room, an 18 G cannula was inserted either in the hand or forearmveins. No opioid premedication was given to any patient. The study drugs HES (Expavon®, Neon Laboratories, India) or NS were coded, drawn up in two 50 mL syringes, presented to the anesthetist not involved in the management of the patient and handed over to one of the study investigators who then administered it to the patient over a period of three to five minutes. The study drug and saline were pre-heated to 37°C before administering them to the patient. The patients were randomized into two groups of 50 patients each, as follows:

Group II: Patients received 100 ml 6% hydroxyethyl starch (HES) 3 to 5 minutes before propofol injection.

Group I: Patients received 100 mL normal saline 3 to 5 minutes before propofol injection.

Once the 100 mL bolus was over, an induction dose of 1% propofol was thenadministered to the patient by the same blinded investigator till loss of verbal contact. After induction and confirmation of mask ventilation, intravenous fentanyl and vecuronium were administered subsequently for tracheal intubation and conduct ofsurgery.

Pain during propofol injection was assessed every 10 seconds before the loss of verbal contact as 0- no pain; 1-mild pain evident only on questioning after 10 seconds without any obvious discomfort; 2-moderate pain which was self-reported by patients within 10 seconds withsome discomfort;and3-severepain which was accompanied by withdrawing of hand, facial grimace/wincing and/ orhowling/crying. Moderate-severe pain was considered as significant pain.

Given an incidence of 80% pain on injection of propofol we considered a 50% reduction in the colloid pre-treated group to be clinically significant. Accordingly, 48 patients were required in each group to achieve a power of 90% with an alpha error of 5%. Accounting for dropouts, we planned to recruit 100 patients with 50 patients in each group.

M S Excel 2010 software was used to analyze the data. Data wasexpressed as mean (standard deviation) and compared with the unpaired *t*-test. Categorical variables like gender and incidence and severity of pain on propofol injection between the two groups were expressed as numbers (percentages) and compared with Pearson's Chi-square test. $P < 0.05$ was considered significant.

RESULTS

Both groups were comparable with respect to age, gender, weight and height (Table 1). There was no statistically significant difference in any given parameter between the two groups. None of the patient was lost to follow up.

Table 1: Demographic data

Group	Group I	Group II
N	50	50
Age (years)	46 ± 15	45 ±17
Weight (kg)	62.8 ± 12.2	61.3 ±12.4
Height (cm)	161 ± 9	164 ±10
gender (M/F)	22/28	24/26
Propofol induction dose (mg)	129 ± 24	133 ± 29
Loss of Verbal Response (Seconds)	54	57

Data are presented as either number of patients or as mean ± SD.

The overall incidence of injection pain was significantly lower in group I (14, 28.0%) compared with group II (29, 58.0%), P=0.003. The severity of injection pain, which was graded as none, mild, moderate or severe, showed a statistically significant benefit for Group II over group I (P=0.007). Incidence of severe (10%) and moderate pain (18%) was higher in the NS group (Group II).(Table2).

Table 2: The incidence and severity of propofol-injection pain.

	Group I	Group II	P Value
No pain	36 (72.0%)	21 (42.0%)	0.007
Mild	10 (20.0%)	15 (30.0%)	
Moderate	4 (8.0%)	9 (18.0%)	
Severe	0 (0.0%)	5 (10.0%)	
Overall Pain	14 (28.0%)	29 (58.0%)	0.003

Group I: HES6% hydroxyethylstarch; Group II: NS0.9%saline

There were no significant differences in mean arterial pressure and heart rate between the two groups. There were no emergence reactions. The effect size for pain between the groups was large (0.73).

DISCUSSION

Several methods have been tried to reduce the incidence of pain of propofol injection with variable success. The methods used to reduce this pain include the addition of lignocaine, using solutions at different temperatures, dilution of propofol, different sites of injection and various ways of combining ephedrine, ondansetron, metoclopramide, opioids, thiopentone or ketamine with the propofol injection.[14,15,16]

The most effective non-pharmacological intervention in decreasing the pain on propofol injection is using an antecubital vein with a relative risk of 0.19 to 0.34. Still, it is not widely accepted since the process of venous occlusion before induction of anaesthesia is cumbersome.[7] When the injection is carried out in a large vein, pain experienced is less probably due to injection in the midstream leading to minimal contact of propofol with the endothelial wall of the vein. The injected propofol can mix with blood freely and can have a buffering effect. Scott et al.[15] noticed that slow injection causes more pain than the fast injection since slow injection may increase the concentration and duration of exposure of propofol to the vein wall and rapid injection may clear the drug quickly from vein and replace it with blood. It has been demonstrated by several investigators that increased concentration of propofol in aqueous phase increases pain.[17] Doenicke et al. demonstrated that by increasing lipid content of propofol, pain could be reduced mainly due to decreased concentration of propofol in aqueous phase.[18] Reducing propofol concentration to 0.5% from 1% also decreased the incidence of pain. However, the potpourri of anaesthetic and analgesic drugs used to reduce pain on propofol injection may themselves have undesirable effects like hypotension which may become more significant than the pain on propofol injection.

Propofol being an alkylphenol is expected to cause pain in spite of the fact that it is almost isotonic. The immediate pain is due to irritation of vein endothelium whereas delayed pain is due to the release of mediators such a kininogen from kinin cascade.[19] HES pre-administration may offer an opportunity to avoid opioids for decreasing pain on propofol injection in patients, especially those undergoing short surgical day care procedures.[7] It is possible that the pre-administration of HES may have led to modulation of the venous endothelium, thereby preventing contact activation of the various nociceptive receptors by propofol.[11] In-vitro studies also support this decreased adhesion of molecules secondary to inhibition of contact activation by colloids.[20] Postischemic treatment with HES concomitantly attenuates increases in leukocyte adherence and vascular permeability during early reperfusion after global cerebral ischemia. The mechanistic basis of anti-adherent actions of HES is unclear and may include the reduction or modulation of the expression of adhesion molecules.

The likely mechanism of the analgesic efficacy of the propofol-ketamine mixture may be the lower pH of the mixture compared with propofol alone. Koo et al reported that a propofol-ketamine mixture (ketamine 100μg/kg) did not reduce propofol injection pain compared with saline pre-treatment.

The present study did not find any adverse outcome or emergence reactions, either with the pre-administration of HES or with the use of normal saline.

Propofol is rarely given without analgesia in clinical

practice because of the high incidence of injection pain, and our focus was to find a mechanism of pain reduction. Besides, a total of 100 mL boluses of HES were arbitrarily used. The effect of different starches may be different and thus, our results will be considered applicable to only 6% HES (130/0.4).

CONCLUSION

In our study, during the trail pre-administration of 100 mL of 6% HES (130/0.4), 3 to 5 min before propofol injection, significantly decreased the pain on injection with propofol in comparison to normal saline. The results may be encouraging, but more such studies with different demographical set up, and needed to be performed.

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