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Original Research Article

Effect of pre-administration of 50 ml and 100 ml 6% hydroxyethyl starch for reduction of pain on propofol injection: a randomized controlled study

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ABSTRACT

Background: Propofol is the drug of choice for induction of anaesthesia but causes pain on intravenous injections. Colloids can prevent contact activation by propofol. This randomized controlled study compared the effects of pre-administration of 50 ml and 100 ml 6% Hydroxyethyl Starch (HES) in attenuating propofol injection pain.
Methods: 180 patients undergoing elective surgery under general anaesthesia were randomized into 3 groups. Group A (Patients received 50 ml HES), Group B (Received 100 ml HES) and Group C (Received 50 ml normal saline). Study drug was administered immediately before administration of propofol. Pain was assessed 15 seconds after administration of propofol using a four-point Verbal Rating Score (VRS). Descriptive statistics, chi-square test, ANOVA and Post hoc Bonferroni test were applied and $p<0.05$ was considered statistically significant.
Results: There was a significant reduction in occurrence of pain in group A and B compared to group C ($p=0.000$). The mean pain score was also significantly higher in group C compared to group A and B ($p=0.000$). On post hoc Bonferroni test for intergroup comparison, there was no significant difference in the pain scores between group A and B ($p=1.000$), whereas both groups had a significantly lower pain scores compared to group C ($p=0.000$ and 0.000 respectively).
Conclusions: Both 50 ml and 100 ml 6% hydroxyethyl starch pre-administration equally and significantly reduces pain on propofol injection.

Keywords: 6% Hydroxyethyl starch, Anaesthesia, Propofol, Propofol injection pain, Randomized controlled study

INTRODUCTION

Propofol (2,6-di-isopropyl phenol), has become the most popular intravenous anesthetic drug for induction, maintenance of anesthesia and sedation.[1] It has rapid onset of action and recovery. It is known as a modulator and activator of type A-Gamma amino butyric acid (GABA-A) receptors in the central nervous system, but it is also reported to affect the function of glycine receptors in spinal cord.[2] Short half-life of propofol allows precise control of sedation levels, facilitating smooth transitions from unconsciousness to wakefulness. Propofol also possesses antiemetic properties, reducing the incidence of postoperative nausea and vomiting. Its lipid formulation enhances solubility, enabling rapid metabolism and elimination, contributing to a quick recovery profile.

Moreover, its minimal accumulation and low incidence of allergic reactions make it suitable for a broad spectrum of patients.[3] These advantageous pharmacokinetic properties make propofol an indispensable tool in modern anaesthesia practice. However, pain on propofol injection is a problem. The incidence of pain following propofol injection varies between 28-90% in adults, if a vein on the

dorsum of hand is used.[4] Most patients remember it as one of the unpleasant encounters during operation. Propofol injection pain ranks seventh among common important post operative problems after anesthesia. The quality of pain is described as extremely sharp, aching or burning.[5] Pain is due to phenol moiety of propofol. Immediate pain is due to irritation of veins and delayed pain (after 10-20 seconds) is due to kinin release.[6] Recent works indicate that transient receptor potential (TRP) channels, especially TRP vanilloid 1 (TRPV1) and TRP ankyrin 1 (TRPA1), which are expressed in peripheral neurons detecting noxious stimuli such as thermal and irritant chemical stimuli are involved in propofol evoked pain sensation.[2]

On literature review, it was found that, most effective non-pharmacological intervention to decrease propofol injection pain is to use an antecubital vein with a relative risk of 0.19 to 0.34.[7] Another commonly used technique is pretreatment with lignocaine. Pretreatment with lignocaine with venous occlusion has a relative risk of 0.39 to 0.69. The NNT with this intervention is 1.6 to 1.9, which means that 1.6 to 1.9 patients need to be exposed to this intervention to prevent pain in one patient.[8] But this technique has not gained much popularity because venous occlusion before induction of anaesthesia is cumbersome.

Other interventions that are efficacious are mixing lignocaine with propofol, pretreatment with ketamine, non-steroidal anti-inflammatory drugs, opioids, corticosteroids, alpha-2 agonists, corticosteroids, cis-atracurium, 5-hydoxytrypatamine (5-HT3) receptor antagonists and use of ice packs before injection.[7] However, even with multimodal techniques, pain on propofol injection is not abolished completely.[1,5] Hydroxyethyl starch is a colloid which is a plasma volume expander. From anesthesia point of view, colloids are used for intra-operative fluid therapy and they are considered to be safe.[8,9]

Colloids are macromolecules that have the capacity to modify endothelial cell junctions and permeability of vascular endothelium and inhibit endothelial activation by various substances and molecules.[10,11] It has been shown that pre-administration of colloid prevents contact activation by propofol, which may in turn lead to reduced pain during injection.[12] In a study conducted by Misra et al it was found that pretreatment with 100 ml hydroxyethyl starch effectively reduced propofol injection pain.[12] So, this ability of hydroxyethyl starch was the basis of our study and we used pretreatment with two different volumes of this colloid, that is 50 ml and 100 ml along with 50 ml of normal saline as control to see whether it was able to prevent propofol injection pain and if so the effective dose also.

With this background and in search for the ideal dose, we conducted a randomized controlled study to compare the effects of pre-administration of 50 ml and 100 ml 6% Hydroxyethyl Starch (HES) in attenuation of propofol injection pain during induction of anesthesia.

METHODS

This randomized controlled study was conducted from May 2022 to June 2024 on patients undergoing elective surgery under general anesthesia. The study was carried out after obtaining clearance from the Institutional Ethics Board, Imphal (REB No- A/206/REB-Comm(SP)/RIMS/2015/ 826/167/2022) and after being registered to Clinical Trial Registry of India (CTRI/2023/03/050378).

Individuals belonging to age group 18-60 years and ASA physical status I and II were included, whereas those with neurological deficits, history of allergy to 6% hydroxy ethyl starch and propofol, those taking any analgesic before surgery, those with diabetes, hypertension, cardiac disease, hepatic, renal, pulmonary disease and convulsion, those with anticipated difficult venous access, patients with pregnancy and breastfeeding, those with chronic pain syndromes and patients having problems in communication were excluded from the study.

Sample size was calculated based on the proportions of pain experienced on propofol injection in normal saline and hydroxyethyl starch groups (53% and 28% respectively) in a study conducted by Misra et al, considering 80% power and 95% confidence interval.[12] Calculated sample size was 60 in each group.

180 eligible participants were randomized into three groups by block randomisation technique with a block size of six, using an internet generated randomisation sequence. Group A: Patients received 50 ml hydroxyethyl starch. Group B: Patients received 100 ml hydroxyethyl starch. Group C: Patients received 50 ml normal saline. Blinding was done at the level of participant and investigator. The study drugs were prepared and administered by an anaesthetist, not involved in the study according to the web-based block randomization without the knowledge of the investigator.

Eligible participants were enrolled after explaining the purpose and procedure of the study. It was informed that they will receive some drugs at the beginning of anaesthesia which may or may not cause pain during injection and they will be blinded to the group assigned. On arrival at the pre-anaesthetic room, an 18G intra-venous cannula was inserted into a vein on the dorsum of the patient's non-dominant hand. No opioid pre-medication was given to the patients. Inside the operation theatre, the study drug (50 ml hydroxyethyl starch or 100 ml hydroxyethyl starch or 50 ml normal saline) was prepared by an anaesthetist and he/she administered the drug to the patient according to the web-based block randomization list without the knowledge of the investigator over 3 to 5 minutes.

The investigator remained outside the operation theatre until the study drug was administered. The investigator then administered one-fourth of the total calculated dose

(2 mg/kg body wt.) of propofol over 20 seconds. The pain was assessed by the investigator 15 seconds later according to the four-point Verbal Rating Score1(VRS) (0-none, 1-mild, 2-moderate, 3-severe).[13] Induction of anaesthesia was achieved with propofol and the study was taken as complete at this point and further anaesthetic technique was not influenced by this study. The anaesthetic procedure was then continued according to the standard protocol.

Data were analysed using SPSS version 26 (IBM, Armonk, New York, USA). Descriptive data like sex, ASA grade and pain were presented as frequency and percentage, while age and weight were presented in terms of mean and standard deviation. Chi-square test was used to compare proportion of sex and ASA physical status and, ANOVA to compare the means of age and weight across the three study groups.

Chi square test was applied to find association between the study groups and incidence of pain. ANOVA was employed for intergroup comparison of mean pain score. Post-hoc Bonferroni test was used for multiple pairwise comparison of mean pain score across groups. A p-value<0.05 was considered as statistically significant.

Written informed consent was obtained from each participant. Privacy and confidentiality were maintained throughout the study by limiting the identifying variables to the minimum and by using unique Medical Records Department number. Data collected were not linked to identify the individual in any way or data collection were made available only to the principal investigator and co-investigator and were kept under lock in the department. Presentation of data were made collectively without identifying the individuals.

RESULTS

The mean age of the participants was 38.13±11.70 years and the median age was 37.50 years (IQR: 29, 47), with a minimum of 18 years and a maximum of 60 years. Majority (n=103, 57.2%) of the participants were males. Majority (n=150, 83.3%) of the participants belonged to ASA physical status I.

The mean body mass index (BMI) of the participants was 22.87±3.45 kg/m^2 and the median BMI was 22.15 kg/m^2 (IQR: 20, 25), with a minimum of 16.53 kg/m^2 and a maximum of 30.69 kg/m2. Age, BMI, gender, ASA grade was comparable across the three different study groups (Table1, Table 2). Proportion of participants with pain was significantly more in group C (50 ml NS) (p value=0.001) (Figure 1). The mean pain score was significantly higher for group C (p value=0.001) (Table 3).

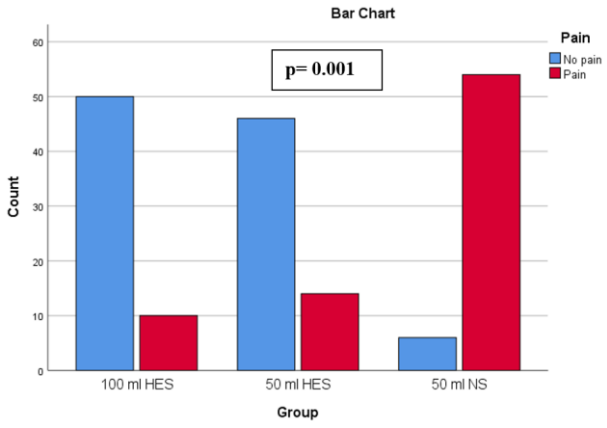

Figure 1: Occurence of pain following propofol injection across the three groups (n=180).

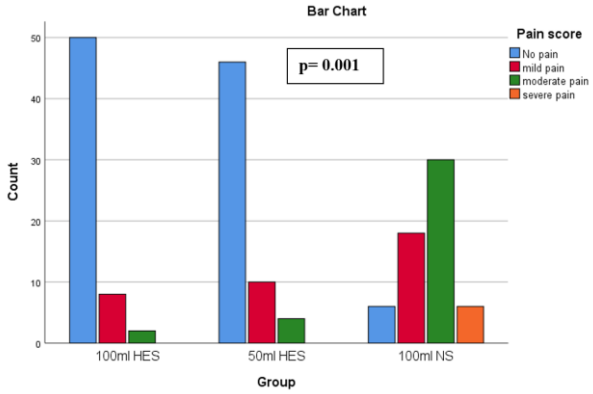

Figure 2: Severity of pain following propofol injection across the three groups (n=180).

Post hoc Bonferroni test was applied for intergroup comparison of mean pain score and it was found that the mean pain score was significantly more for 50 ml NS when compared to 100 ml HES (p=0.001) and 50 ml HES (p=0.001), but there was no significant difference in pain score between 100 ml HES and 50 ml HES (p=0.998) (Table 4).

Table 1: Age and BMI distribution of the study participants between the groups (n=180).

Characteristics	Group A (100 ml HES)	Group B (50 ml HES)	Group C (50 ml NS)	P value*
Age (Mean±SD)	37.83±12.02	37.43±10.69	39.13±12.45	0.710
BMI (Mean±SD)	22.84±3.34	22.18±3.34	23.60±3.58	0.078

*ANOVA.

Table 2: Gender and ASA distribution of the study participants between the groups (n= 180).

Variable	Group n (%)			P value*
	A (100 ml HES)	B (50 ml HES)	C (50 ml NS)	
Gender				
Male	27 (26.2)	37 (35.9)	39 (37.9)	0.060
Female	33 (42.9)	23 (29.9)	21 (27.2)	
ASA physical status				
I	48 (33.1)	51 (35.2)	46 (31.7)	0.510
II	12 (34.3)	9 (25.7)	14 (40.0)	

*Chi-square.

Table 3: Mean pain score comparison across groups (n=180).

Groups	Mean±SD	P value*
A (100 ml HES)	0.20±0.48	0.001
B (50 ml HES)	0.30±0.59	
C (50 ml NS)	1.60±0.81	

*ANOVA.

Table 4: Intergroup pain score comparison (n=180).

Group X	Group Y	Mean difference (X-Y)	P value*
100 ml HES	50 ml HES	-0.100	0.998
100 ml HES	50 ml NS	-1.400	0.001
50 ml HES	50 ml NS	-1.300	0.001

*Post hoc Bonferroni test.

DISCUSSION

Propofol is a widely used intravenous anaesthetic agent renowned for its rapid onset and offset of action, making it a favoured choice for induction and maintenance of anaesthesia during surgical procedures.[14] However, pain on intravenous injection is one of its major drawbacks.

A total of 180 participants undergoing elective surgery under general anaesthesia were studied, by randomizing them into three groups. Group A (100 ml hydroxyethyl starch), Group B (50 ml hydroxyethyl starch) and Group C (50 ml normal saline). The difference in baseline characteristics (age, sex, BMI& ASA physical status) observed between the groups were not found to be statistically significant, concluding that the groups were comparable demographically.

In this study, 83.3% and 76.7% of the study participants who received 100 ml and 50 ml HES respectively did not experience pain while injecting propofol which was significant statistically while comparing with the control group in which 90% of the patients experienced pain while injection. This result was similar to that of the study conducted by Misra S et al, where he compared 100 ml HES pre-treatment to alleviate the propofol injection pain with normal saline placebo.[12] In his study 72% of the participants in study group did not experience pain while propofol injection. But in control group, only 53% of participants experienced pain while propofol injection. This difference might be because of the premixing of propofol with lignocaine in the above-mentioned study, as lignocaine itself can alleviate propofol injection pain. But in our study, we used propofol without lignocaine to avoid this confounding factor. There was also significant reduction in the mean pain scores in our study groups compared to control groups. This was similar to the study conducted by Adithya K et al, where he compared the effects of intravenous dexmedetomidine and lignocaine to attenuate propofol injection pain.[15]

While doing pairwise group comparison using post hoc Bonferroni test, it was found that there was significant reduction in mean pain scores for both the groups when compared to normal saline but no significant difference in pain score was observed between 100 ml and 50 ml HES groups. So, similar to the study done by Misra et al 100 ml HES attenuated propofol injection pain in our study, but there was an added finding that, 50 ml HES is as effective as 100 ml HES in attenuating propofol injection pain.[12]

Considering the levels of pain, there was also significant reduction in mild, moderate and severe pain in study groups comparing the normal saline, this was also in line with the findings of Misra et al except that incidence of mild pain was similar between 100 ml HES and normal saline in his study.[12] This could be again explained by the use of lignocaine admixture with propofol.

The occurrence of pain in this study was similar to the trial conducted by Madhu et al where he compared effect of low dose ketamine pre-treatment on propofol injection pain.[16]

The incidence of pain among study groups (100 and 200 µg/kg iv ketamine) were 50%, 23.3% and control normal saline was 83.3%. The results yielded similar results with Burman et al evaluating efficacy of ephedrine, Banu et al, evaluating granisetron, Rasool et al evaluating pethidine and dexamethasone, Shivanna et al evaluating methylprednisolone, Sumalatha et al evaluating ramosetron, Singh et al evaluating tramadol and butorphanol, Karki et al evaluating ice gel pack for attenuation of propofol injection pain.[9,14,17-21] So, hydroxyethyl starch pre-treatment is as effective as the above-mentioned techniques in attenuation of propofol injection pain.

One advantage of hydroxyethyl starch is that the side effects and interactions with other drugs are minimal making it a safer alternative in attenuating propofol injection pain.[9] Other drugs used conventionally can have undesirable side effects like hemodynamic variation etc. which may become more significant than pain on propofol injection. The mechanism by which hydroxyethyl starch attenuates propofol injection pain may be by endothelial modulation, thereby preventing contact activation of nociceptive receptors of propofol (5-HT3, TRPA1) and also by preventing irritation of venular endothelium by phenol moiety.

Many in vivo and in vitro models have demonstrated this endothelial modulation.[10,11,22] The result also shows that the use of tourniquet was not required with hydroxyethyl starch making the technique easier. Even though premixing propofol with lignocaine is a convenient and commonly used technique, it also has a failure rate of 13-32 %.[23] So, combining this with our study technique can bring down the pain to almost nil. The only concern is the cost associated with HES. But considering the effectiveness of 50 ml HES, if appropriate aseptic precautions are followed, one bottle of HES can be utilised for 10 patients, especially in a center where multiple cases are done under general anaesthesia, making it a cost-effective technique.

The use of block randomization ensured a balanced distribution of participants at any point of time across different study groups during the course of the study. But the assessment of pain using verbal rating score, a subjective scale which would have led to some overlap between the severity of pain, is a limitation of the study.[13]

CONCLUSION

From this randomized controlled study, to compare the effect of 50 ml and 100 ml 6% hydroxyethyl starch pre-administration for reduction of pain on propofol injection, it is concluded that, both 50 ml and 100 ml 6% hydroxy ethyl starch pre-administration equally and significantly reduces pain on propofol injection. Considering the safety profile, ease of availability and ease of administration without a tourniquet, the routine use of 6% hydroxyethyl starch before propofol injection can be recommended to provide pain free administration of propofol, thereby increasing patient comfort.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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