Original Article

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Anaesthesia Section

Efficacy of 6% Hydroxy Ethyl Starch Pre Administration to Alleviate Pain following Propofol Injection: A Randomised Control Study

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ABSTRACT

Introduction: Propofol is widely used intravenous induction agent owing to its rapid onset and short duration of action; however, Pain on Propofol Injection (POPI) remains a common adverse effect, with reported incidence between 28-90%. Despite the evaluation of multiple preventive strategies, including lignocaine, opioids, and formulation modifications, none have achieved complete effectiveness in eliminating POPI. Colloids, particularly Hydroxyethyl Starch (HES), may reduce pain through their effects on endothelial permeability and inhibition of contact activation.

Aim: To evaluate the efficacy of pre-administration of 50 mL of 6% HES 130/0.4 compared with 0.9% Normal Saline (NS) in alleviating POPI.

Materials and Methods: This double-blinded randomised control study was conducted at Dhiraj General Hospital, Sumandeep Vidyapeeth, Waghodia, Vadodara, Gujarat, India, from March 2025 to July 2025. A total of 84 patients of either gender belonging to the American Society of Anaesthesiology (ASA) physical status grade I or II were randomised into two groups. Group HES received 50 mL 6% HES, and group NS received 50 mL 0.9% normal saline via 20-G intravenous cannula over 3-5 min before propofol. Pain during propofol injection was assessed every 10 seconds before loss of verbal contact. Data were analysed with the Unpaired t-test. A p-value <0.05 was considered significant, and a p-value <0.001 was considered highly significant.

Results: Both groups were comparable with respect to demographic variables, including age, weight, gender distribution and ASA physical status. The dose of propofol required for induction was also comparable between the HES and NS groups (136.10±21.25 vs. 131.67±16.22 mg; p-value=0.28). The incidence of pain on propofol injection was significantly lower in the HES group, with 78.57% of patients reporting no pain compared to 28.57% in the NS group (p-value <0.001). Pain grade 1 (14.29% vs. 38.09%; p-value=0.01), grade 2 (4.76% vs. 19.05%; p-value=0.04), and grade 3 (2.38% vs. 14.29%; p-value=0.04) were significantly more frequent in the NS group. Haemodynamic parameters showed no significant difference between groups.

Conclusion: Administration of 50 mL 6% HES before propofol injection results in significantly less incidence of pain compared to 0.9% NS. Thus, authors conclude that it is effective to alleviate POPI.

Keywords: Angialgia, Colloid, General anaesthesia, Induction agent, Inflammation

INTRODUCTION

Propofol (2,6-diisopropylphenol) is the most commonly used induction agent, as it has a quick onset of action as well as a short duration of action. It is also used for sedation inside and outside the operating theatre. But, Pain on Propofol Injection (POPI) is experienced by the patients as one of the unpleasant encounters during the operation. The incidence of POPI is 28-90% and in current practice, it is the 7th most important problem in anaesthesia [1,2].

There is no gender discrimination in the incidence of propofol injection pain. Compared to other intravenous anaesthetic agents, propofol has a high incidence of pain on injection. The incidence of pain with thiopentone is about 7% [3] and with methohexitone it is between 12% and 64% [4,5]. Diazepam in the organic solvent propylene glycol (Valium) has an incidence of pain on injection of about 37% but it becomes 0 when diazepam is reformulated in soya bean oil (Diazemuls) [4]. Pain on injection is very low with midazolam at 1% [4]. The incidence of pain with etomidate administration varies between 24% and 68% [6,7].

POPI occurs due to the phenol moiety present in the propofol formulation. All phenols irritate the skin and mucous membrane, so propofol, as an alkylphenol, is expected to cause pain. POPI has also been described as angialgia by some, meaning that the pain is due to vascular involvement [8]. POPI is immediate as well as delayed after 10–20 seconds [9]. The immediate pain is due to irritation of the vein endothelium, whereas delayed pain is due to the release of mediators such a kininogen from the kinin cascade [10].

Various techniques have been tested to alleviate this pain. These include administration in a larger vein, increasing speed of propofol injection or carrier fluid; premixing or pretreatment with lignocaine; pre-administration of opioids, non steroidal anti inflammatory drugs or metoclopramide; subanaesthetic doses of ketamine or thiopentone, using a mixture of medium and long chain triglycerides in the carrier emulsion, etc., [2,10,11,12]. However, even with multimodal techniques, POPI is not alleviated completely [2].

Colloids are commonly used in intraoperative fluid therapy as a volume expander [13], and it is considered safe [14]. They are macromolecules that modify endothelial cell junctions and permeability of the vascular endothelium, thus inhibiting activation of the endothelium by various substances and molecules [15,16]. Pre-administration of colloids prevents contact activation by propofol, which may in turn lead to reduced pain. HES is a complex polysaccharide. It is available in multiple preparations, each with different pharmacological characteristics based on concentration, molecular weight, degree of substitution, and C2/C6 hydroxyethylation ratio [17].

Most of the studies have compared 100 mL of HES with either NS or 2% lignocaine [18-22]. The present study was designed to evaluate the efficacy of pre-administration of 50 mL of 6% HES 130/0.4 compared with 0.9% NS in alleviating POPI.

MATERIALS AND METHODS

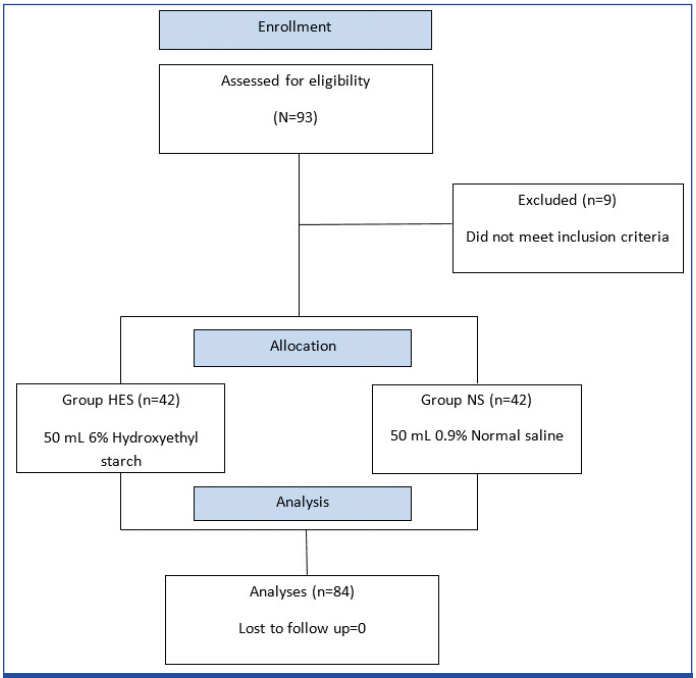
This double-blinded randomised control study was conducted at Dhiraj General Hospital, Sumandeep Vidyapeeth, Waghodia, Vadodara, Gujarat, India, after obtaining permission from the institutional ethical committee (SVIEC/ON/Medi/RP/Feb/25/55) from March 2025 to July 2025. The study was registered in Clinical Trial Registry- India (CTRI) with registration number- C/TRI/2024/12/077542. Recruitment of patients was done only after the CTRI registration. The purpose of the study was informed, and written informed consent was taken from all the patients included in the study.

Same size calculation: Given an incidence of 80% pain on propofol injection, a 50% reduction in the colloid pretreated group was considered clinically significant. Based on this, a sample size of 84 patients per group was calculated to achieve 90% power with a 5% alpha error.

Inclusion criteria: Adult patients aged between 18 to 60 years of either gender and belonging to ASA grade I and II undergoing elective surgery under general anaesthesia were included in the study.

Exclusion criteria: Patients belonging to ASA grade III, IV and V, with severe cardiorespiratory compromise, uncontrolled diabetes and hypertension and raised creatinine level were excluded from the study. Patients were also excluded if hands or forearm veins were not accessible.

Randomisation was carried out by a computer-generated random number table [Table/Fig-1]. Patients were randomised to receive a 50 mL bolus of either HES (group HES) or NS (group NS) before propofol injection. Allocation was carried out with opaque, sealed envelopes, which were opened once the patients had arrived in the theatre. Odd numbers were allocated to group HES, and even numbers to group NS. The study was double-blinded as the participant and the investigator administering the drug and assessing the pain were blinded to the drug given [Table/Fig-1].



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) diagram.

Study Procedure

Patients were kept nil by mouth for 8 hours for solid foods and 2 hours for clear liquids before the surgery. After the arrival of the patient in the operating theatre, a 20-G venous cannula was inserted into either hand or the forearm vein. Multipara monitor, including electrocardiography leads, an automated non invasive blood pressure cuff and a pulse oximetry probe were applied. Baseline Heart Rate (HR), Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were recorded

Premedication in the form of an inj. glycopyrrolate 0.004 mg/kg i.v. and inj. ondansetron 0.08 mg/kg i.v. was given. An opioid analgesic was not given at that time, as it can lead to bias. inj. tramadol 2 mg/kg was given after loss of verbal response by the patient [23].

An anaesthesiologist not involved in the study prepared either 50 mL of 6% HES or 0.9% NS, depending upon which group the patient was allocated. Another anaesthesiologist gave the 50 mL solution over 3 to 5 min. after completing that inj. Propofol was injected in a dose of 2 mg/kg till the loss of eyelash reflex.

Pain during propofol injection was assessed every 10 seconds by a second blinded investigator 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 with some discomfort; and 3- severe pain which was accompanied by withdrawing of hand, facial grimace/wincing and/or howling/crying [20].

HR, SBP and DBP were also recorded before and 10 seconds after propofol injection.

After confirming proper bag and mask ventilation inj. succinylcholine 2 mg/kg was given, and patients were intubated.

STATISTICAL ANALYSIS

Data were collected and organised in Microsoft Excel 2010. The normality of data was checked using the Shapiro-Wilk test and found to be normally distributed. Categorical data like gender, ASA grading and incidence and severity of pain on propofol injection between the two groups were presented as percentages and frequency (%) and compared with Pearson's Chi-square test. Continuous data were presented as mean and standard deviation and compared with the unpaired t-test. $p<0.05$ was considered significant, and p-value <0.001 was considered highly significant.

RESULTS

A total of 93 patients were assessed for eligibility to participate in the study. Out of which 9 patients were excluded from the study as they did not meet the inclusion criteria, and 84 patients were included in the study (42 in group HES and 42 in group NS).

Both groups were comparable with respect to age, weight, gender, and ASA grade, and there was no statistically significant difference between the two groups, as shown in [Table/Fig-2]. Dose of propofol required for loss of eyelash reflex was also comparable between the two groups (136.10±21.25 in group HESS and 131.67±16.22 in group NS with p-value of 0.28).

Parameters		Group HES n (%)	Group NS n (%)	p-value
Age (years) (mean±SD)		41.40±13.96	37.17±12.46	0.12
Weight (kg) (mean±SD)		68.29±9.30	65.14±8.11	0.12
Gender	Male	18 (42.86%)	21 (50%)	0.51
	Female	24 (57.14%)	21 (50%)	
ASA grade	I	28 (66.67%)	24 (57.14%)	0.37
	II	14 (33.33%)	18 (42.86%)	
Propofol dose (mg) (mean±SD)		136.10±21.25	131.67±16.22	0.28

[Table/Fig-2]: Demographic characteristics and dose of propofol.
(Pearson's Chi-square test for gender and ASA grade, unpaired t-test for age, weight, propofol dose)

The percentage of patients having pain grade 0 (no pain) was significantly higher in group HESS (78.57%) compared to group NS (28.57%), with a p-value of <0.001, which is statistically highly

significant. Percentage of patients having grade 1 pain (14.29% vs 38.09%; p-value=0.01), grade 2 pain (4.76% vs 19.05%; p-value=0.04) and grade 3 pain (2.38% vs 14.29%; p-value=0.04) in the group HESS and group NS, respectively and was statistically significant with higher incidence of POPI in group NS [Table/Fig-3].

Pain grade	Group HES n (%)	Group NS n (%)	p-value	p-value
0	33 (78.57%)	12 (28.57%)	<0.001	<0.001
1	6 (14.29%)	16 (38.09%)	0.01	
2	2 (4.76%)	8 (19.05%)	0.04	
3	1 (2.38%)	6 (14.29%)	0.04	

[Table/Fig-3]: Comparison of pain grading between two groups.
(Pearson's Chi-square test)

The difference between preinduction and postinduction haemodynamic parameters (HR, SBP, DBP), was not statistically significant is shown in [Table/Fig-4].

Parameters	Group HES (mean±SD)	Group NS (mean±SD)	p-value
Δ in HR	-6.79±3.94	-6.98±4.68	0.83
Δ in SBP	7.90±4.96	8.86±3.25	0.28
Δ in DBP	4.38±2.13	4.19±3.27	0.77

[Table/Fig-4]: Comparison of preinduction and postinduction haemodynamic parameters.
(Δ in HR=difference in heart Rate, Δ in SBP=difference in Systolic Blood Pressure, Δ in DBP=difference in Diastolic Blood Pressure); (Unpaired t-test)

DISCUSSION

The pain on propofol injection is described as a burning or stinging feeling in the skin, which can be distressing to patients, leading to discomfort and anxiety [18].

Many factors that affect POPI are evaluated. Not only the intrinsic drug property (e.g., emulsion composition, pH of the formulation, temperature, injection volume and osmolarity), but the injection procedure itself could contribute to injection pain [24-26], which includes the speed of pushing the medication during injection, propofol concentration in the aqueous phase, speed of i.v. carrier fluid, use of local anaesthetics, and the buffering effect of blood [25,27,28].

In the present study, we evaluated the effect of HES to alleviate propofol-induced pain. Both groups were comparable with respect to demographic profile (age, weight, gender, ASA status). Dose of propofol given in both the groups were also comparable between both the groups. This result was comparable to the study done by Jindal K and Gupta M [20]. In their study, group HES patients received 129±24 mg propofol and group NS patients received 133±29 mg propofol, which was statistically not significant. The result was also similar to the study done by Reddy A and Raghavendra A [22]. In their study, 126 mg propofol was used in the HES group and 130 mg propofol was used in the NS group, which was not statistically significant (p-value=0.81).

In this study, the proportion of patients having grade 0 pain was significantly higher in the HES group compared to the NS group (78.57%, 28.57% respectively, p-value <0.001). Proportion of patients having grade 1 pain (mild pain) was 14.29% vs 38.09% p-value=0.01, grade 2 pain (moderate pain) 4.76% vs 19.05% p-value=0.04 and grade 3 pain (severe pain) 2.38% vs 14.29% p-value=0.04; on propofol injection in HES and NS group, respectively. A similar study was also conducted by Misra S et al., [21]. They have used 100 mL HES and NS. Their results showed a higher overall incidence of pain in the NS group vs the HES group (53% vs 28%; p-value=0.004). Incidence of severe (grade 3) (8% vs 0%) and moderate (grade 2) pain (16% vs 5%) was higher in the NS group. Incidence of mild pain was comparable (29% vs 23%; NS vs HES). A significant difference was seen in the severity of pain between the groups (p-value=0.002). These results are comparable to the current study, except for mild pain, which was comparable in their study, while there was a statistically significant difference in the current study. This may be due to a difference in study design. They have pre-administered either 100 mL of HES or NS, followed by an induction dose of 1% propofol premixed with 2% lidocaine, while the authors have not added lidocaine to propofol. The present study results are also comparable with the study done by Sahoo TK et al., [18]. In their study, the overall incidence of pain in the HES and NS groups was 33.63% and 70.8% respectively, and the proportion of patients with no POPI (grade 0) was significantly higher in the HES group (66.37%) than the placebo (11.5%) group (p-value <0.001). Results of this study are also compatible with the study done by Jindal K and Gupta M [20]. In their study, the overall incidence of injection pain was significantly lower with HES (28.0%) compared with NS (58.0%), p-value=0.003. The severity of injection pain, which was graded as none, mild, moderate or severe, showed a statistically significant difference with less pain in the HES group compared to the NS group (p-value=0.007).

In the present study, there was no statistically significant difference between preinduction haemodynamic parameters (HR, SBP and DBP). In the study done by Sahoo TK et al., there was no statistically significant difference in SBP (group HES-14.55±13.34, group NS-17.23±23.22, p-value=0.423) and DBP (group HES-9.17±10.05, group NS-10.95±14.99, p-value=0.072), while there was a statistically significant difference in HR (group HES=.17±11.45, group NS=9.69±14.64, p-value <0.0001). The difference might be due to a change in methodology, as they have used fentanyl while we have used tramadol.

Limitation(s)

This study has certain limitations. The study was conducted in a single centre, which may restrict the applicability of the results. Pain assessment was based on patient responses during induction, which are subjective and may be influenced by individual pain thresholds and anxiety levels. The study focused only on immediate pain on propofol injection and did not evaluate potential long-term effects. Future studies with multicenter cohorts, objective pain assessment tools, and evaluation of long-term outcomes are recommended to validate and expand upon these results.

CONCLUSION(S)

Pre-administration of 50 mL of 6% hydroxyethyl starch was found to significantly reduce the incidence of pain associated with propofol injection when compared with 0.9% normal saline. This demonstrates that hydroxyethyl starch has a clinically relevant role in improving patient comfort during the induction of anaesthesia. The intervention is simple, safe, and feasible in routine anaesthetic practice, making it a practical option for reducing propofol-induced injection pain. In conclusion, pre-administration of 6% hydroxyethyl starch can be considered an effective strategy to alleviate pain on propofol injection.

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