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Original Research Article

COMPARATIVE EFFICACY OF PLASMALYTE, NORMAL SALINE, AND HYDROXYETHYL STARCH PRELOADING IN ATTENUATING PAIN ON PROPOFOL INJECTION: A RANDOMIZED DOUBLE-BLIND CLINICAL TRIAL

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ABSTRACT

Background: Pain on propofol injection (POPI) remains one of the most common and distressing adverse effects during induction of anesthesia, with reported incidences ranging from 28% to 90%. Various pharmacological and non-pharmacological interventions have been investigated to reduce this discomfort; however, the role of different intravenous preload fluids in attenuating POPI remains inadequately explored. This study compared the efficacy of Plasma-Lyte, Normal Saline, and Hydroxyethyl Starch (HES) preloading in reducing the incidence and severity of pain associated with propofol injection.

Materials and Methods: This prospective, randomized, double-blind clinical trial was conducted in 135 adult patients (ASA physical status I–II) undergoing elective surgical procedures under general anesthesia. Participants were randomly allocated into three equal groups (n=45 each): Plasma-Lyte group (PL), Hydroxyethyl Starch group (HES), and Normal Saline group (NS). Patients received 250 mL of the allocated preload fluid before induction of anesthesia. Statistical analysis was performed using ANOVA and Chi-square tests, with $p<0.05$ considered statistically significant.

Results: Baseline demographic and clinical characteristics were comparable among the three groups ($p>0.05$). The overall incidence of propofol injection pain was significantly lower in the HES group (17.8%) compared with the PL group (51.1%) and NS group (42.2%) ($p=0.003$). Pairwise analysis demonstrated significant reductions in pain incidence in the HES group compared with both the PL group ($p=0.002$) and NS group ($p=0.011$).

Conclusion: Preloading with 250 mL of 6% Hydroxyethyl Starch significantly reduces both the incidence and severity of pain on propofol injection compared with Plasma-Lyte and Normal Saline. The analgesic benefit is most pronounced during the early phase of propofol administration.

Keywords: Propofol injection pain; Hydroxyethyl starch; Plasma-Lyte; Normal saline; Preloading; General anesthesia; Randomized controlled trial.

INTRODUCTION

Propofol (2,6-diisopropylphenol) is one of the most widely used intravenous anesthetic agents for induction and maintenance of general anesthesia, procedural sedation, and intensive care unit sedation due to its rapid onset, short duration of action, favorable recovery profile, and antiemetic properties.[1] Despite these advantages, pain on injection remains one of the most common and distressing adverse effects associated with propofol administration. The incidence of propofol injection pain (PIP) has been reported to range from 28% to 90%, making it a significant concern in anesthetic practice.[2] In fact, the pain associated with propofol injection has been ranked among the most

undesirable experiences during induction of anesthesia by patients undergoing surgical procedures.[3]

The pathophysiology of propofol injection pain is multifactorial and not yet fully understood. Two principal mechanisms have been proposed. The first involves direct irritation of the vascular endothelium and free nerve endings by the aqueous phase of propofol emulsion immediately after injection. The second mechanism involves activation of the kallikrein-kinin system, leading to the release of bradykinin, which causes vasodilation and increased vascular permeability. These changes facilitate greater contact of propofol with nociceptive nerve endings, resulting in delayed pain perception.[4,5]

Several factors influence the incidence and severity of PIP, including the site of injection, vein size, injection speed, propofol formulation, temperature of the injectate, and concomitant administration of analgesic or anesthetic agents.[6]

Over the years, numerous strategies have been investigated to reduce PIP. Pharmacological interventions such as lidocaine pretreatment, opioid administration, ketamine, nonsteroidal anti-inflammatory drugs, ondansetron, dexmedetomidine, and magnesium sulfate have demonstrated varying degrees of efficacy.[2,7] Among these, lidocaine pretreatment with venous occlusion is widely regarded as the most effective technique and is often considered the gold standard for preventing propofol injection pain.[2] Nevertheless, the search for simpler and safer alternatives continues because lidocaine administration may not always be feasible and may occasionally be associated with adverse effects.

Intravenous fluid preloading before induction of anesthesia is a routine clinical practice aimed at maintaining hemodynamic stability and optimizing intravascular volume status. Different intravenous fluids possess distinct physicochemical properties that may influence endothelial function, vascular tone, and nociceptive responses. Consequently, the choice of preload solution may affect the incidence and severity of propofol injection pain. Among the commonly used fluids, Normal Saline (NS), Plasmalyte, and Hydroxyethyl Starch (HES) are frequently employed in perioperative settings.

Normal Saline (0.9% sodium chloride) remains one of the most widely administered crystalloid solutions worldwide because of its availability, low cost, and familiarity among clinicians. However, its relatively acidic pH and supraphysiological chloride concentration have been associated with endothelial dysfunction and alterations in vascular reactivity.[8] In contrast, Plasmalyte is a balanced crystalloid solution containing electrolytes in concentrations that closely resemble plasma composition. It has a physiological pH and lower chloride content, which may contribute to improved endothelial preservation and reduced vascular irritation compared with normal saline.[9]

Hydroxyethyl Starch is a synthetic colloid solution that expands plasma volume more effectively than crystalloids owing to its larger molecular structure and prolonged intravascular retention. Previous studies have suggested that pre-administration of HES may significantly reduce both the incidence and severity of propofol injection pain. The proposed mechanisms include endothelial coating, dilution of free aqueous propofol concentration, and modulation of local inflammatory responses within the venous endothelium.[10,11] Misra et al. demonstrated that pretreatment with 6% HES significantly decreased the occurrence of propofol injection pain compared with placebo, highlighting its potential utility as a preventive strategy.[11]

Although several studies have independently evaluated the effectiveness of HES and saline in attenuating PIP, direct comparisons among balanced crystalloids such as Plasmalyte, unbalanced crystalloids such as Normal Saline, and colloid solutions such as Hydroxyethyl Starch remain limited. Given the differences in electrolyte composition, osmolality, pH, and intravascular persistence among these fluids, their relative efficacy in reducing propofol-induced pain warrants systematic investigation. Furthermore, identifying the most effective preload solution could provide a simple, cost-effective, and easily implementable strategy for enhancing patient comfort during anesthesia induction without requiring additional pharmacological interventions.

Despite numerous interventions to reduce propofol injection pain, the role of different intravenous preloading fluids has not been adequately explored. Hydroxyethyl starch, Plasma-Lyte, and normal saline differ in their physicochemical properties and intravascular effects, which may influence the pain experienced during propofol injection.

We hypothesized that preloading with hydroxyethyl starch would be more effective than Plasma-Lyte or normal saline in reducing the incidence and severity of propofol injection pain.

Therefore, the present randomized double-blind clinical trial was designed to compare the efficacy of Plasmalyte, Normal Saline, and Hydroxyethyl Starch preloading in attenuating pain associated with propofol injection. By evaluating the incidence and severity of injection pain among these commonly used intravenous fluids, this study aims to provide evidence-based guidance for optimizing perioperative patient comfort and improving the quality of anesthetic care.

MATERIALS AND METHODS

Study Design and Ethical Approval: This prospective, randomized, double-blind, interventional clinical trial was conducted in the Department of Anaesthesiology, Paras Hospitals, Gurugram, India, between June 2022 and June 2023. The study protocol received approval from the

Institutional Ethics Committee, and written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Study Population: A total of 135 adult patients scheduled for elective surgical procedures under general anaesthesia were enrolled in the study. Eligible participants were aged between 20 and 60 years and belonged to the American Society of Anesthesiologists (ASA) physical status I or II category.

Inclusion Criteria:

- Age between 20 and 60 years.
- ASA physical status I or II.
- Patients scheduled for elective surgery under general anaesthesia.

Exclusion Criteria:

Patients were excluded if they had any of the following:

- Age <20 years or >60 years.
- ASA physical status III or higher.
- Known hypersensitivity or allergy to any study fluid or study medication.
- Refusal to participate in the study.
- Significant cardiovascular, pulmonary, hepatic, or renal disease.
- Inaccessible veins on the dorsum of the hand or forearm.
- Pregnancy or lactation.
- Uncontrolled hypertension.
- Diabetes mellitus.
- Emergency surgical procedures.

Randomization and Blinding

Participants were randomly allocated in a 1:1:1 ratio into three study groups using a computer-generated randomization sequence. Allocation concealment was ensured using sequentially numbered opaque sealed envelopes.

The study was conducted in a double-blind manner. An anaesthesiologist not involved in data collection prepared and administered the study fluids. The investigator responsible for pain assessment and data recording remained blinded to group allocation throughout the study period.

Study Groups:

Each group consisted of 45 patients.

- Group PL (n = 45): Received 250 mL of Plasma-Lyte®.
- Group HES (n = 45): Received 250 mL of 6% Hydroxyethyl Starch 130/0.4.
- Group NS (n = 45): Received 250 mL of 0.9% Normal Saline.

Sample Size Estimation:

The sample size was calculated based on the primary outcome, namely the incidence of pain on propofol injection (POPI). Assuming a clinically significant difference of 30% in the incidence of POPI among the three study groups, with a two-sided alpha error of 0.05 and a study power of 80% ($\beta = 0.20$), the minimum required sample size was estimated to be 40 patients per group. To compensate for potential dropouts and protocol violations, 45 patients were recruited into each group, resulting in a total sample size of 135 participants.

Study Procedure: After arrival in the operating room, standard ASA monitoring, including continuous electrocardiography, non-invasive blood pressure monitoring, and pulse oximetry, was instituted. Following infiltration of the skin with local anaesthetic, intravenous access was secured using a 20-gauge peripheral intravenous cannula inserted into a vein on the dorsum of the hand or forearm.

Patients were randomly assigned to receive the allocated preload solution (250 mL of Plasma-Lyte®, 250 mL of 6% Hydroxyethyl Starch 130/0.4, or 250 mL of 0.9% Normal Saline), which was administered intravenously over 5–10 minutes by an anaesthesiologist who was not involved in outcome assessment.

No opioid premedication was administered to any patient prior to induction of anaesthesia.

Anaesthesia was induced using 1% propofol premixed with 1 mL of 2% lignocaine, administered intravenously according to the standard induction dose based on body weight. From the start of propofol injection, patients were asked about pain at the injection site every 10 seconds until loss of verbal contact. Pain assessment was performed by a blinded investigator using the predefined pain scale. The incidence and severity of pain on propofol injection and the time to loss of verbal response were recorded.

Outcome Measures

Primary Outcome: The primary outcome was the incidence of pain on propofol injection following preloading with Plasma-Lyte, Hydroxyethyl Starch, or Normal Saline.

Secondary Outcome: The secondary outcome was the severity of pain experienced during propofol injection after administration of the respective preload fluid.

Pain Assessment

Pain on propofol injection was evaluated using a four-point Likert scale:

- 0 = No pain
- 1 = Mild pain – Evident only on questioning
- 2 = Moderate pain – Self reported by patients
- 3 = Severe pain – Accompanied by facial grimace/ wincing, withdrawing of hand, and/ or howling /crying

Pain scores were recorded at 10-second intervals (10, 20, 30, 40, 50, and 60 seconds) until loss of verbal response. The time to loss of verbal response was also documented.

Data Collection: Demographic variables including age, sex, body weight, height, ASA physical status, diagnosis, and type of surgery were recorded. Pain scores and timing of loss of verbal response were entered into a predefined data collection form and

subsequently transferred to a Microsoft Excel 2019 database for analysis.

Statistical Analysis: Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 28.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages.

Comparisons of continuous variables among the three study groups were performed using one-way analysis of variance (ANOVA). Categorical variables, including the incidence and severity of pain on propofol injection, were analyzed using the Chi-square test or Fisher's exact test as appropriate. Pairwise post hoc comparisons were undertaken when statistically significant differences were observed.

A two-tailed p-value <0.05 was considered statistically significant for all analyses.

RESULTS

The flow of participants through the study is presented in [Figure 1]. A total of 135 patients were screened for eligibility, all fulfilled the inclusion criteria, underwent randomization, completed the allocated intervention, and were included in the final analysis.

[Table 1] Baseline demographic and clinical characteristics were comparable among the three study groups. No statistically significant differences were observed with respect to age, sex distribution, body weight, height, BMI, or ASA physical status (all $p > 0.05$), indicating successful randomization and homogeneity of study participants before intervention.

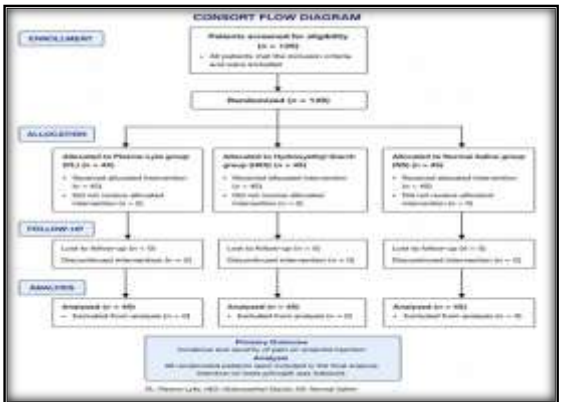

Figure 1: CONSORT Flow Diagram.

Table 1. Baseline demographic and clinical characteristics of study participants

Characteristic	Plasma-Lyte (n=45)	Hydroxyethyl Starch (n=45)	Normal Saline (n=45)	p-value
Age (years), Mean ± SD	38.6 ± 10.8	39.2 ± 11.3	40.1 ± 10.5	0.781
Weight (kg), Mean ± SD	65.4 ± 8.7	66.8 ± 9.2	67.1 ± 8.9	0.642
Male, n (%)	24 (53.3)	23 (51.1)	25 (55.6)	0.913
Female, n (%)	21 (46.7)	22 (48.9)	20 (44.4)	
ASA I, n (%)	27 (60.0)	29 (64.4)	28 (62.2)	0.894
ASA II, n (%)	18 (40.0)	16 (35.6)	17 (37.8)	
Height (cm), Mean ± SD	164.8 ± 7.9	165.2 ± 8.1	164.6 ± 7.5	0.947
BMI (kg/m²), Mean ± SD	24.1 ± 2.8	24.5 ± 3.1	24.7 ± 2.9	0.713

Table 2: Comparison of overall incidence of pain on propofol injection

Variable	PL (n=45)	HES (n=45)	NS (n=45)
No Pain	22 (48.9%)	37 (82.2%)	26 (57.8%)
Pain Present	23 (51.1%)	8 (17.8%)	19 (42.2%)

Pairwise Comparison	p-value
Overall comparison	0.003*
PL vs HES	0.002*
PL vs NS	0.398
HES vs NS	0.011*

[Table 2] compares the overall incidence of pain on propofol injection among the three study groups. The Hydroxyethyl Starch group demonstrated the lowest incidence of pain (17.8%), whereas the Plasma-Lyte and Normal Saline groups exhibited pain incidences of 51.1% and 42.2%, respectively. The overall difference among groups was statistically significant ($p = 0.003$). Pairwise analysis revealed significantly lower pain incidence in the Hydroxyethyl Starch group compared with both Plasma-Lyte and Normal Saline groups, indicating superior efficacy of Hydroxyethyl Starch in attenuating propofol injection pain.

Table 2: Time-wise incidence of pain on propofol injection

Time after Injection	PL n (%)	HES n (%)	NS n (%)
10 sec	21 (46.7)	7 (15.6)	14 (31.1)
20 sec	16 (35.6)	4 (8.9)	14 (31.1)
30 sec	14 (31.1)	4 (8.9)	12 (26.7)
40 sec	3 (6.7)	3 (6.7)	6 (13.3)
50 sec	1 (3.3)	0 (0.0)	0 (0.0)

[Table 3] illustrates the temporal pattern of pain following propofol administration. The incidence of pain progressively decreased over time in all groups. However, patients receiving Hydroxyethyl Starch consistently experienced the lowest pain incidence during the early stages of injection (10–30 seconds), which correspond to the period of maximum discomfort. Significant reductions in pain were observed during the first 30 seconds in the Hydroxyethyl Starch group compared with the other groups, suggesting a rapid protective effect against propofol-induced vascular irritation.

Table 4: Comparison of pain severity at 10 seconds following propofol injection

Comparison	p-value
Overall comparison	0.031*
PL vs HES	0.009*
PL vs NS	0.261
HES vs NS	0.173

[Table 4] presents the comparison of pain severity among the study groups at 10 seconds following propofol administration. A statistically significant difference in pain severity was observed among the groups (p = 0.031). Post hoc analysis demonstrated significantly lower pain severity in patients receiving Hydroxyethyl Starch compared with Plasma-Lyte. Although pain severity was also lower in the Hydroxyethyl Starch group compared with Normal Saline, the difference did not reach statistical significance. These findings suggest that Hydroxyethyl Starch not only reduces pain incidence but also mitigates pain intensity.

Table 5: Distribution of mild pain among study groups

Mild Pain	PL (n=45)	HES (n=45)	NS (n=45)
Present	18 (40.0%)	8 (17.8%)	17 (37.8%)
Absent	27 (60.0%)	37 (82.2%)	28 (62.2%)

[Table 5] shows the frequency of mild pain experienced by patients in each study group. Mild pain was observed most frequently in the Plasma-Lyte and Normal Saline groups, whereas the Hydroxyethyl Starch group demonstrated a significantly lower proportion of patients experiencing mild pain (17.8%). The difference among groups was statistically significant (p = 0.045), further supporting the superior analgesic effect of Hydroxyethyl Starch preload in reducing patient discomfort during propofol administration.

Table 6: Time-wise Incidence of Moderate–Severe Pain Following Propofol Injection

MODERATE-SEVERE PAIN ON PROPOFOL	Group			p value	PL vs HES	PL vs NS	HES vs NS
	PL	HES	NS				
	Frequency (%)	Frequency (%)	Frequency (%)				
10 sec	5 (11.1%)	0 (0%)	1 (2.2%)	0.026	0.021	0.203	1.000
20 sec	3 (6.7%)	0 (0%)	1 (2.2%)	0.165	0.242	0.616	1.000
30 sec	2 (4.4%)	0 (0%)	1 (2.2%)	0.360	0.494	1.000	1.000
40 sec	0 (0.00%)	0 (0.00%)	1 (2.20%)	0.843	-	1.000	1.000
50 sec	0 (0.00%)	0 (0.00%)	0 (0.00%)	-	-	-	-
60 sec	0 (0.00%)	0 (0.00%)	0 (0.00%)	-	-	-	-

The incidence of moderate-to-severe pain following propofol injection differed across the three preloading groups, particularly during the early observation period. At 10 seconds, moderate-to-severe pain was reported in 5 patients (11.1%) in the Plasma-Lyte (PL) group and 1 patient (2.2%) in the normal saline (NS) group, whereas no patient in the hydroxyethyl starch (HES) group experienced moderate-to-severe pain. The overall difference among the groups at 10 seconds was statistically significant (p=0.026). Pairwise analysis showed a significant difference between the PL and HES groups (p=0.021), while the differences between PL and NS (p=0.203) and between HES and NS (p=1.000) were not statistically significant.

At 20 seconds, the incidence decreased to 6.7% in the PL group and remained 2.2% in the NS group, with no cases in the HES group. At 30 seconds, moderate-to-severe pain was observed in 4.4% of patients in the PL group and 2.2% in the NS group. By 40 seconds, no patient in either the PL or HES group reported moderate-to-severe pain, whereas one patient (2.2%) in the NS group continued to experience pain. None of these differences from 20 to 40 seconds were statistically significant. No moderate-to-severe pain was observed in any of the three groups at 50 or 60 seconds.

Overall, HES demonstrated complete absence of moderate-to-severe propofol injection pain throughout the 60-second observation period, whereas PL showed the highest early incidence, which progressively declined with time.

Table 7: Overall Incidence of Moderate–Severe Pain

Moderate–Severe Pain	PL (n=45)	HES (n=45)	NS (n=45)	Overall p-value
Present, n (%)	5 (11.1%)	0 (0%)	2 (4.4%)	0.057
Absent, n (%)	40 (88.9%)	45 (100%)	43 (95.6%)	
Total	45 (100%)	45 (100%)	45 (100%)	
Pairwise comparisons				
Comparison	**p-value**		**Interpretation**	
PL vs HES	0.056		Not significant	
PL vs NS	0.434		Not significant	
HES vs NS	0.494		Not significant	

The overall incidence of moderate-to-severe pain was highest in the Plasma-Lyte group, where 5 of 45 patients (11.1%) experienced pain. In comparison, moderate-to-severe pain was reported in 2 of 45 patients (4.4%) receiving normal saline, while none of the 45 patients receiving hydroxyethyl starch experienced moderate-to-severe pain. Consequently, the proportion of patients remaining free from moderate-to-severe pain was 88.9% in the PL group, 95.6% in the NS group and 100% in the HES group. The overall difference among the three groups approached, but did not reach, conventional statistical significance (p=0.057).

Among the five patients experiencing moderate-to-severe pain in the PL group, four had moderate pain and one had severe pain. In the NS group, one patient experienced moderate pain and one experienced severe pain, whereas no moderate or severe pain was observed in the HES group. Pairwise comparisons also showed no statistically significant difference between PL and HES (p=0.056), PL and NS (p=0.434), or HES and NS (p=0.494).

These findings indicate that HES was associated with the lowest observed incidence of moderate-to-severe propofol injection pain, followed by normal saline, while Plasma-Lyte showed the highest incidence. However, the overall difference in cumulative incidence did not achieve statistical significance.

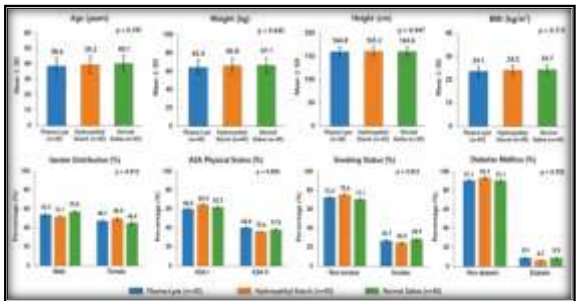

Figure 2: Comparison of baseline demographic and clinical characteristics among patients receiving Plasma-Lyte, Hydroxyethyl Starch, and Normal Saline preloading

[Figure 2] illustrates the baseline demographic and clinical characteristics of patients allocated to the Plasma-Lyte, Hydroxyethyl Starch, and Normal Saline groups. The mean age, body weight, height, and body mass index (BMI) were comparable across all three groups, with no statistically significant differences observed (all p > 0.05). Similarly, the distribution of male and female participants, as well as ASA physical status classifications (ASA I and ASA II), was balanced among the study groups. These findings indicate that the groups were homogeneous at baseline and that randomization was successful in minimizing selection bias. Consequently, any subsequent differences observed in the incidence or severity of pain on propofol injection are unlikely to be attributable to demographic or clinical disparities among the groups.

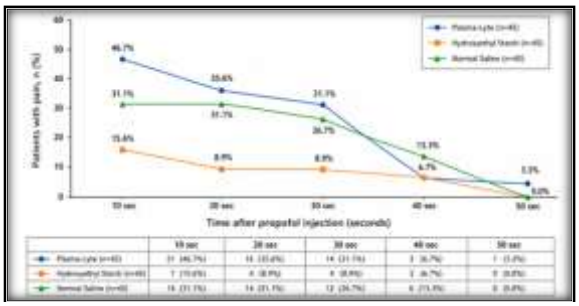

Figure 3: Temporal trend in pain incidence following propofol administration across the three study groups

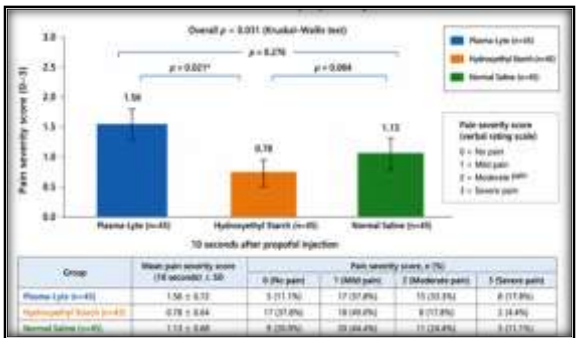

Figure 4: Comparison of pain severity scores at 10 seconds after propofol injection

[Figure 3] illustrates the temporal changes in the incidence of pain following propofol injection among patients preloaded with Plasma-Lyte, Hydroxyethyl Starch (HES), and Normal Saline. Pain incidence progressively decreased over time in all three groups; however, marked differences were observed during the early phase of propofol administration.

[Figure 4] compares the severity of pain experienced by patients 10 seconds after propofol administration in the Plasma-Lyte, Hydroxyethyl Starch (HES), and Normal Saline groups. Pain severity was

assessed using a four-point verbal rating scale, where 0 indicated no pain, 1 indicated mild pain, 2 indicated moderate pain, and 3 indicated severe pain.

DISCUSSION

The present randomized double-blind clinical trial evaluated the comparative efficacy of Plasma-Lyte, Hydroxyethyl Starch (HES), and Normal Saline (NS) preloading in attenuating pain associated with propofol injection. The principal findings demonstrated that preloading with 6% Hydroxyethyl Starch significantly reduced both the incidence and severity of propofol injection pain compared with Plasma-Lyte and Normal Saline. Patients receiving HES exhibited the lowest overall incidence of pain (17.8%), whereas higher incidences were observed in the NS (42.2%) and Plasma-Lyte (51.1%) groups. Furthermore, the beneficial effect of HES was most pronounced during the initial 30 seconds following propofol administration, corresponding to the period of maximal nociceptive stimulation.

Pain on propofol injection remains one of the most common adverse events during induction of anaesthesia despite advances in anaesthetic techniques. Previous systematic reviews have reported that the incidence ranges from 28% to 90%, depending on patient characteristics, injection site, propofol formulation, and assessment methods, emphasizing the continued clinical importance of preventing this complication.[2,7] In the present study, pain was observed in 51.1% of patients receiving Plasma-Lyte and 42.2% of those receiving Normal Saline, findings that are consistent with the published literature.

The superior efficacy of Hydroxyethyl Starch observed in the present study is consistent with previous randomized clinical investigations. Misra et al. demonstrated that pretreatment with 6% Hydroxyethyl Starch significantly reduced both the incidence and severity of propofol injection pain compared with placebo.[11] More recently, Sahoo et al. reported that Hydroxyethyl Starch significantly decreased propofol injection pain and demonstrated efficacy comparable to lidocainepretreatment, supporting its potential role as an alternative preventive strategy.[10] Collectively, these findings strengthen the evidence supporting Hydroxyethyl Starch as an effective non-pharmacological adjunct for reducing propofol injection pain.

The mechanisms underlying the beneficial effects of Hydroxyethyl Starch are likely multifactorial. Propofol injection pain is believed to result from direct endothelial irritation, activation of free nerve endings, and stimulation of the kallikrein–kinin system with subsequent bradykinin release, leading to increased vascular permeability and nociceptor activation.[4,6] Nakane and Iwama further demonstrated that inhibition of the kallikrein–kinin pathway reduces propofol injection pain, supporting the proposed pathophysiological mechanism.[12] Hydroxyethyl Starch may therefore reduce endothelial exposure to the aqueous phase of propofol through plasma volume expansion, endothelial coating, and dilution of the free propofol fraction, thereby attenuating pain perception.

An important finding of the present study was the significant reduction in pain during the first 30 seconds following propofol administration. This observation suggests that Hydroxyethyl Starch exerts its greatest protective effect during the early vascular phase of propofol injection, when endothelial irritation is maximal. Similar temporal patterns have been reported in previous mechanistic studies evaluating interventions that modify vascular exposure to propofol.[12]

Numerous pharmacological interventions have been investigated to prevent propofol injection pain. Lidocaine remains the most extensively studied agent and is generally regarded as the standard preventive strategy.[13] Other agents, including ketamine, have also demonstrated significant efficacy in randomized clinical trials.[14] Comparative studies evaluating tramadol, remifentanil, and lidocaine have reported varying degrees of effectiveness, indicating that no single intervention completely abolishes propofol injection pain under all clinical circumstances.[15,16] The present findings suggest that Hydroxyethyl Starch preloading may represent a simple and effective adjunctive strategy without requiring additional analgesic medications.

Although Plasma-Lyte possesses a more physiological electrolyte composition and acid-base profile than Normal Saline, no statistically significant difference was observed between these two crystalloid solutions in reducing propofol injection pain. This finding suggests that the balanced electrolyte composition of Plasma-Lyte alone may not substantially influence the local vascular mechanisms responsible for propofol-induced pain. While balanced crystalloids have demonstrated advantages in maintaining acid-base homeostasis and reducing hyperchloremia in critically ill patients,[9] these physiological benefits do not appear to translate into clinically meaningful reductions in acute injection pain.

The present study also demonstrated significantly lower pain severity scores and fewer patients experiencing mild pain in the Hydroxyethyl Starch group compared with the crystalloid groups. Reduction in pain intensity is clinically relevant because unpleasant experiences during anaesthetic induction influence patient satisfaction and the overall perioperative experience. Previous studies have shown that minimizing discomfort during anaesthesia contributes significantly to patient satisfaction and postoperative quality of recovery.[17,18]

Strengths: The present study has several important strengths. It employed a randomized, double-blind design with equal group allocation, thereby minimizing selection, performance, and observer

bias. A standardized anesthetic protocol and systematic assessment of propofol injection pain at predefined time intervals enhanced the internal validity and reproducibility of the findings. The inclusion of both balanced (Plasma-Lyte) and unbalanced (Normal Saline) crystalloid solutions alongside a colloid comparator (6% Hydroxyethyl Starch) enabled comparison of three commonly used preload fluids in routine anesthetic practice. Furthermore, assessment of both the incidence and severity of pain provided a comprehensive evaluation of the clinical effectiveness of each intervention.

Limitations: Several limitations should be acknowledged. First, the study was conducted at a single center and included only ASA physical status I and II patients undergoing elective surgery, which may limit the generalizability of the findings to broader or higher-risk surgical populations. Second, although Normal Saline and Plasma-Lyte were selected because they are commonly used intravenous fluids in clinical practice, other clinically relevant preload fluids were not evaluated, limiting the scope of the comparisons. Third, a preload volume of 250 mL was used uniformly across all study groups to standardize the intervention; however, the optimal preload volume for attenuating propofol injection pain remains uncertain, and different fluid volumes may produce different clinical effects. In addition, the study focused exclusively on immediate propofol injection pain and did not evaluate hemodynamic responses, patient satisfaction, postoperative outcomes, or cost-effectiveness. Future multicenter studies involving larger and more diverse patient populations should evaluate additional intravenous fluids, varying preload volumes, and clinically relevant perioperative outcomes to validate these findings and further elucidate the mechanisms underlying the protective effect of Hydroxyethyl Starch.

CONCLUSION

The present randomized double-blind clinical trial demonstrated that preloading with 6% Hydroxyethyl Starch is significantly more effective than Plasma-Lyte and Normal Saline in attenuating pain associated with propofol injection. Patients receiving Hydroxyethyl Starch exhibited the lowest incidence of pain, reduced pain severity scores, and a significantly lower frequency of mild pain compared with the other study groups. The beneficial effect of Hydroxyethyl Starch was particularly evident during the first 30 seconds following propofol administration, corresponding to the period of maximum pain perception.

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