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Research Article

Effect of 6% Hydroxyethyl Starch Pre-Administration for Reduction of Pain on Propofol Injection: A Placebo-Controlled Randomised Study

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A B S T R A C T

Introduction: Pain on intravenous propofol injection is a common and distressing complication, affecting up to 90% of patients and negatively impacting the induction experience. While various pharmacological agents have been used to mitigate this pain, the role of colloid preloadingsuch as 6% hydroxyethyl starch (HES) has not been extensively studied. This study aimed to evaluate the efficacy of 6% HES, in reducing the incidence and severity of pain during propofol injection.

Materials and Method: This was a prospective, randomised, placebo-controlled, double-blind study conducted from October 2023 to June 2024, involving 126 adult patients (ASA I/II) undergoing elective surgery under general anaesthesia. Patients were randomly allocated into two groups: Group A (n=64) received 100 mL of 6% HES, and Group B (n=62) received 100 mL of normal saline over 3–5 minutes before induction. Pain on propofol injection (1% propofol mixed with 1 mL of 2% lidocaine) was assessed every 10 seconds before loss of verbal contact using a four-point verbal response scale.

Results: The incidence of pain was significantly lower in the HES group (28%) compared to the saline group (53%) ($p = 0.004$). Severe pain occurred in 0% of HES patients versus 8% in the saline group, and moderate pain in 5% vs 16%, respectively. The difference in pain severity was statistically significant ($p = 0.002$), with a large effect size (Cohen's $d = 0.73$) and a number needed to treat (NNT) of 4.

Conclusion: Pre-administration of 6% HES effectively reduces both the incidence and severity of pain on propofol injection and may serve as a safe, simple, and clinically useful strategy.

Keywords: Propofol Injection Pain, Hydroxyethyl Starch, Anaesthesia Induction, Hes 130/0.4, Colloid Preloading, Analgesia

Introduction

Propofol is a widely used intravenous anaesthetic agent, favoured for its rapid onset of action, short duration, and smooth recovery profile. It is extensively used for induction and maintenance of general anaesthesia, procedural sedation, and in intensive care settings. Despite its numerous advantages, one of the most common and distressing drawbacks associated with propofol administration is the pain experienced during intravenous injection. The incidence of pain on propofol injection (PIP) has been reported to range from 30% to as high as 90%, particularly when administered into small peripheral veins. This painful sensation, which can vary from mild discomfort to severe burning, often leaves a negative impression on patients, particularly during elective procedures where anxiety levels are already high.[1,2] The mechanism underlying PIP is multifactorial. It is believed to be due to the activation of the kallikrein-kinin system, which results in the release of bradykinin, a potent vasodilator that increases vascular permeability. This allows the aqueous phase of propofol—which contains phenol groups known to irritate endothelial linings—to directly interact with free nerve endings in the vessel wall, leading to the characteristic pain. Other contributing factors include the speed of injection, size and location of the vein, and the temperature and formulation of the propofol solution.[3] Several pharmacological and non-pharmacological strategies have been explored over the years to minimise or eliminate this injection pain. These include pretreatment with lidocaine, opioids (e.g., fentanyl, remifentanil), nonsteroidal anti-inflammatory drugs (NSAIDs), ketamine, magnesium sulphate, dexmedetomidine, cooling or warming of the propofol, and changes in injection site or technique.[4] Among these, lidocaine pretreatment has remained the most common and effective method.[5] However, even with lidocaine, pain is not eliminated in all patients, especially when the drug is administered without venous occlusion.[6] In recent years, attention has turned toward novel methods to attenuate PIP, including the use of colloid pre-administration. One such agent is 6% Hydroxyethyl Starch (HES 130/0.4), a synthetic colloid solution commonly used for intravascular volume expansion. Beyond its volume-expanding properties, HES has been proposed to exert endothelial stabilising effects, which may mitigate vascular irritation caused by propofol. By modifying endothelial cell activation and reducing capillary permeability, HES may decrease the interaction between the aqueous phase of propofol and the nociceptors in the vessel wall.[7,8] This, in theory, could result in a reduction in both the incidence and severity of injection pain. Emerging studies suggest that pre-administration of HES may effectively attenuate PIP. Misra et al. demonstrated a significant reduction in both incidence and severity of pain using 6% HES when compared to normal saline placebo.[1] Other studies have supported these findings, indicating a consistent benefit with HES preloading.[2,9–11] Therefore, the current study was designed as a prospective, randomised, placebo-controlled trial to assess whether pre-administration of 100 mL of 6% hydroxyethyl starch(130/0.4) can significantly reduce pain during propofol injection when compared with 100 mL of normal saline placebo inpatients undergoing elective surgeries.

Materials and Methods

This was a prospective, randomised, placebo-controlled, double-blind study conducted after obtaining approval from the Institutional Ethics Committee. The study was carried out over a period of nine months, from October 2023 to June 2024. A total of 126 adult patients were enrolled and randomly assigned into two groups:

- **Group A (n = 64):** Received 100 mL of 6% Hydroxyethyl Starch (HES 130/0.4)
- **Group B (n = 62):** Received 100 mL of 0.9% Normal Saline (NS)

Randomisation and drug preparation were performed by an anaesthesiologist not involved in patient care or outcome assessment to maintain blinding.

Inclusion Criteria

1. Adults aged between 18 and 65 years
2. Either gender
3. American Society of Anaesthesiologists (ASA) physical status I or II
4. Scheduled for elective surgery under general anaesthesia

Exclusion Criteria

Patients were excluded if they had:

1. Emergency surgical indications
2. Known allergy to propofol or hydroxyethyl starch
3. Hypertension or diabetes mellitus
4. Left ventricular dysfunction
5. Elevated serum creatinine
6. Poor peripheral venous access in hand or forearm veins

Study Procedure

Upon arrival in the operating room, an 18G intravenous cannula was inserted in a hand or forearm vein under local infiltration anaesthesia. The study solution (either 6% HES or 0.9% NS) was drawn into two 50 mL syringes and administered as a 100 mL bolus over 3–5 minutes by a blinded investigator. Subsequently, induction was carried out with 1% propofol premixed with 1 mL of 2% lidocaine (100 mg propofol in 10 mL + 1 mL lidocaine). The propofol-lidocaine mixture was injected until loss of verbal contact was achieved. Following induction, fentanyl and

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vecuronium were administered intravenously to facilitate tracheal intubation and maintenance of anaesthesia.

Assessment of Pain

Pain associated with propofol injection was assessed systematically at 10-second intervals prior to the loss of verbal response. This evaluation was conducted by a second investigator who was blinded to the group allocation in order to maintain objectivity. A standardised four-point verbal response scale was employed to grade the severity of pain: a score of 0 indicated no pain; 1 denoted mild pain that was only reported by the patient upon questioning, without any visible discomfort; 2 represented moderate pain, which was spontaneously reported by the patient within 10 seconds and was accompanied by visible signs of discomfort; while a score of 3 corresponded to severe pain, characterised by withdrawal of the hand, facial grimace, or audible expressions such as howling or crying.

Statistical Analysis

Data analysis was performed using appropriate statistical methods. The distribution of continuous variables was first evaluated for normality using the Shapiro-Wilk test. Variables that were found to be normally distributed were summarised as mean and standard deviation (SD) and compared between the two study groups using the unpaired t-test. Categorical variables, including gender distribution and the incidence and severity of pain during propofol injection, were expressed as counts and percentages. These categorical data were analysed using the Pearson's Chi-square test. A p-value of less than 0.05 was considered indicative of statistical significance for all analyses conducted in this study.

Results

Out of the 128 patients initially enrolled in the study, a total of 126 completed the protocol as intended. One patient from each group was excluded due to protocol violation, where the identity of the study drug was inadvertently revealed before administration. As a result, 64 patients in the 6% hydroxyethyl starch (HES) group and 62 patients in the normal saline (NS) group were included in the final analysis. The randomisation and blinding process were thus largely preserved, ensuring the validity of outcome comparisons. The demographic profiles and baseline characteristics of the patients were comparable between the two groups. The mean age was 44.7 years in both the HES and NS groups. Average body weight was 61 kg in the HES group and 59.8 kg in the NS group. The gender distribution was also similar, with 19 males and 45 females in the HES group, and 22 males and 40 females in the NS group (Table 1). The mean induction dose of propofol was 125 mg in the HES group and 131 mg in the NS group. Time to loss of verbal response was nearly identical, recorded as 55 seconds in the HES group and 56 seconds in the NS group. These similarities in baseline parameters indicate appropriate randomisation and suggest that any observed differences in outcomes are unlikely to be due to demographic variability.

The overall incidence of pain on injection of propofol was significantly lower in patients who received pre-administration with 6% HES compared to those who received 0.9% normal saline. Pain was reported in 28% of patients in the HES group, whereas 53% of patients in the NS group experienced pain, a difference that was statistically significant ($p = 0.004$) (Table 2) The relative risk of experiencing pain was calculated to be 1.54, with a 95% confidence interval of 1.13 to 2.09, indicating a substantial reduction in risk with HES. When analysed by severity, no patients in the HES group experienced severe pain, compared to 8% in the NS group. Moderate pain was observed in 5% of the HES group and 16% of the NS group. The incidence of mild pain was comparable between the groups, reported in 23% of HES patients and 29% of NS patients. When severity levels were pooled into two categories—no/mild pain versus moderate/severe pain—a statistically significant difference emerged between the groups ($p = 0.002$). The effect size for this difference was large (Cohen's $d = 0.73$), suggesting a clinically meaningful impact of HES pre-administration (Table 3). Additionally, the number needed to treat (NNT) was calculated to be 4, indicating that four patients would need to receive HES to prevent pain on propofol injection in one individual.

Table 1.Demographic and Baseline Characteristics of the Study Population

Parameter	Group A (6% HES, n = 64)	Group B (0.9% NS, n = 62)	p-value
Age (years), mean	44.7	44.7	> 0.05
Weight (kg), mean	61.0	59.8	> 0.05
Gender (M:F)	19:45	22:40	> 0.05
Propofol induction dose (mg)	125	131	> 0.05
Time to loss of verbal contact (sec)	55	56	> 0.05

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Table 2.Incidence of Pain on Propofol Injection

Pain Presence	Group A (6% HES)	Group B (0.9% NS)	Relative Risk (RR)	95% CI	p-value
Pain Present	18 (28%)	33 (53%)	1.54	1.13–2.09	0.004
Pain Absent	46 (72%)	29 (47%)	—	—	

Table 3.Severity of Pain on Propofol Injection

Severity Grade	Group A (6% HES)	Group B (0.9% NS)	p-value
No Pain (0)	46 (72%)	29 (47%)	-
Mild Pain (1)	15 (23%)	18 (29%)	-
Moderate Pain (2)	3 (5%)	10 (16%)	-
Severe Pain (3)	0 (0%)	5 (8%)	-
Moderate + Severe	3 (5%)	15 (24%)	0.002
Effect Size (Cohen's d)	-	-	0.73
Number Needed to Treat (NNT)	-	-	4

Discussion

In this prospective, randomised, doubleblind study involving 126 adult patients, preadministration of 100 mL of 6% HES (130/0.4) significantly reduced the incidence and severity of pain on propofol injection compared to placebo (normal saline). The overall incidence of pain was 28% in the HES group versus 53% in the saline group (p = 0.004; RR 1.54; 95% CI 1.13–2.09). Notably, severe pain occurred in none of the HES recipients versus 8% of controls, while moderate pain was reported by 5% with HES versus 16% with saline. Mild pain incidence was similar (23% vs 29%). These findings strongly support the analgesic potential of HES preloading. Sumalatha et al.[12] compared intravenous pre-treatment with lidocaine (0.5 mg/kg), ramosetron (0.3 mg), and ondansetron (4 mg) in 150 patients. The incidence of no pain was 76% in lignocaine, 72% in ramosetron, and 34% in ondansetron (P ≤ 0.001). Mild-to-moderate pain occurred in 56% with ondansetron, 26% with ramosetron, and 20% with lignocaine.[2] In comparison, our study achieved 72% of patients with no pain in the HES group (because 28% reported pain), paralleling the analgesic efficacy of both lignocaine and ramosetron seen in that study. Their study performed a systematic review and meta-analysis summarizing multiple pharmacological modalities for PIP prevention. Agents such as lidocaine and $5HT_3$ antagonists showed lowered pain incidence but to varying degrees depending on dosage and protocol.[12,13] In this study, fentanyl, morphine, meperidine, and lidocaine were compared in peripheral veins—lidocaine emerged significantly better in reducing pain.[13] Our study's results are comparable to lidocaine but achieved using a colloid preadministration strategy without opioids. A study by Collis et al. demonstrated that HES and other plasma volume substitutes can inhibit endothelial cell activation in vitro, reducing leukocyte adherence and vascular permeability, which may mitigate inflammatory nociception.[2, 14] Further it is reported that HES inhibited post- ischaemic leukocyte adherence better than dextran in animal models.[14] Which further supports the hypothesis: HES may modulate the venous endothelial response to propofol, thereby lowering contact activation of nociceptive receptors and reducing injection pain. While lignocaine and ramosetron remain effective, the use of HES offers a non-pharmacological, volume-based pretreatment that avoids introducing additional anaesthetic drugs or altering induction protocols. The NNT of 4 is clinically meaningful and compares favourably with other interventions like lidocaine (typical NNT ~3–5 depending on dose).[12, 13] Additionally, HES is already used for volume management by anaesthesiologists, making it a good option in operative settings.

Conclusion

Pre-administration of 100 mL of 6% HES significantly reduced the incidence (28% vs. 53%) and severity of propofol injection pain compared to saline. With a large effect size and favourable NNT of 4, HES offers a safe, simple, and effective method to improve patient comfort during anaesthesia induction. Further studies are needed to compare its efficacy with standard agents.

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Limitations of the Study

This single-centre study excluded patients with comorbidities, limiting generalisability. Pain assessment was subjective, and long-term effects of HES were not evaluated.

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