International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Effect of 6% Hydroxyethyl Starch Pre-Administration for Reduction of Pain on Propofol Injection: A Randomized Controlled Trial

Fedry Singh B[1], Valsamma Abraham[2]

Abstract: ***Background: Pain on propofol injection has been a matter of concern over the years. However, even with multi-modal techniques, pain on propofol injection is not abolished completely. Colloids modify the vascular endothelium and prevent contact activation of various substances. Pre administration of colloids may prevent contact activation of vascular endothelium by propofol. Aims and Objectives: To study the effect of 6% HES on the incidence of pain on propofol injection, and occurrence of any adverse reaction. Materials and Methods: This double blinded randomized study included 68 patients of the ASA I and II patients and 18-65 years old who underwent elective surgery. The patients were randomised into two groups: who received either 100ml bolus of 6% HES (n=34) or 100 mL bolus of placebo 0.9% normal saline (n=34). Comparison of demographic characteristics, pain during propofol injection, and adverse effects was done. P-value <0.05 was considered statistically significant. Results: Both groups had similar age, gender, ASA, and weight distribution. Compared to Group B, Group A has a statistically comparable propofol dose distribution (Mean ± SD: 102.79 ± 31.6 mg vs 103.68 ± 31.07 mg, p=0.908). In terms of heart rate compared to placebo, HES group had comparable heart rate before induction at 1, 2, 3, and at 4 minutes. SBP, DBP, and respiratory rate were also comparable. Compared to placebo group, HES group showed significant lesser pain at 10 seconds (0.29 ± 0.58 vs. 1 ± 0.98, p = 0.001); at 20 seconds (0.18 ± 0.46 vs. 0.85 ± 0.89, p = 0.0003); and at 30 seconds (0.12 ± 0.41 vs. 0.59 ± 0.66, p = 0.0003). There were no significant adverse effects in any group. Conclusion: It can be concluded that 6% HES is efficacious and safe for controlling pain on propofol injection. It brings about a significant reduction in the pain as assessed by VAS at various time points without causing any significant side effects.***

Keywords: Adverse reaction, HES, Injection, Pain, Propofol

1. Introduction

Pain during intravenous (IV) drug injection is a common concern in anesthesia practice, especially with the use of propofol. Despite being one of the most used induction agents due to its rapid onset and favourable recovery profile, propofol is notorious for causing pain upon injection. The incidence of this pain ranges widely between 30% and 90%, often making it one of the most unpleasant experiences for patients undergoing anesthesia [1,2]. This discomfort can affect patient satisfaction, induce anxiety, and disrupt smooth induction of anesthesia.

Propofol-related pain is attributed to two main mechanisms: immediate pain caused by direct irritation of the venous endothelium and delayed pain resulting from the release of bradykinin-like substances [3]. These mechanisms cause vasodilation and increased permeability of the vascular endothelium, leading to the stimulation of nociceptors. Several strategies have been employed to reduce this pain, such as changing the site of injection, warming the propofol, administering it rapidly or slowly, and pre-treatment with analgesics or local anesthetics like lidocaine [4]. However, none of these techniques have been universally successful or free from side effects.

Hydroxyethyl starch (HES), a synthetic colloid, has been widely used as a plasma volume expander in various surgical and critical care settings. It is known to modulate vascular endothelium and reduce endothelial activation [5]. These properties make HES a potential candidate for reducing pain associated with propofol injection. Pre-administration of HES might reduce the contact activation and irritation of the endothelium by propofol, thereby mitigating the pain response.

Given the limitations of current strategies and the physiological potential of HES, this study investigates the effect of 6% hydroxyethyl starch pre-administration on the incidence and severity of pain during propofol injection. The study also evaluates the safety profile of HES in this context, aiming to provide an effective and well-tolerated method for improving patient comfort during anesthesia induction.

2. Methodology

Study Design and Setting This was a prospective, double-blind, randomized controlled trial conducted at the Department of Anaesthesia and Critical Care, Christian Medical College and Hospital, Ludhiana. The study period extended over 18 months, from August 2022 to January 2024. Ethical approval was obtained from the Institutional Ethics Committee, and all participants provided written informed consent [6].

Participants A total of 68 patients were enrolled based on the following inclusion criteria: aged 18 to 65 years, ASA physical status I or II, scheduled for elective surgery under general anesthesia, and with accessible veins on the hand or forearm. Exclusion criteria included hypersensitivity to propofol, egg lecithin, or HES; pregnancy; emergency surgeries; neurological disorders affecting pain perception; and any known cardiovascular or renal dysfunction [7].

Randomization and Blinding Patients were randomly assigned to one of two groups using a computer-generated randomization sequence. Group A received a 100 mL bolus of 6% hydroxyethyl starch (Voluven, Fresenius Kabi India Pvt Ltd), and Group B received a 100 mL bolus of 0.9% normal saline (placebo). Allocation concealment was ensured using opaque sealed envelopes. Both the patient and the investigator

administering the propofol were blinded to group allocation [8].

Intervention Protocol Upon arrival in the operating room, an 18G intravenous cannula was inserted into a vein on the dorsum of the hand or forearm. The allocated study fluid was administered over 3–5 minutes using a microvolume set. After the fluid infusion, an induction dose of 1% propofol premixed with 2% lidocaine (100 mg propofol in 10 mL mixed with 20 mg lidocaine) was administered slowly until loss of verbal response. No opioids were given prior to the administration of propofol [9].

Pain Assessment Pain during injection was assessed every 10 seconds after the start of propofol administration until loss of verbal contact. A 4-point pain scale was used:

- 0: No pain
- 1: Mild pain (complaint on questioning only)
- 2: Moderate pain (spontaneous complaint)
- 3: Severe pain (verbal complaint with physical withdrawal)

The assessments were conducted by a second investigator blinded to group allocation [10].

Hemodynamic and Adverse Effect Monitoring Heart rate, blood pressure (systolic and diastolic), and respiratory rate were recorded before induction and at 1-minute intervals up to 4 minutes after propofol injection. Any adverse events such as hypotension, bradycardia, or allergic reactions were documented [11].

Sample Size Calculation The sample size was calculated assuming a 35% reduction in pain incidence with HES compared to saline, with 80% power and a significance level of 0.05. The required sample was 34 patients per group [12].

Statistical Analysis Data were analyzed using SPSS version 25.0 (IBM Corp, Armonk, NY). Continuous variables were expressed as mean ± standard deviation (SD) or median (IQR) and analyzed using the independent t-test or Mann-Whitney U test. Categorical variables were analyzed using chi-square or Fisher's exact test as appropriate. A p-value of <0.05 was considered statistically significant [13].

3. Results

A total of 68 patients were analyzed, with 34 in each group (Group A: 6% HES; Group B: Normal Saline). Demographic and baseline clinical characteristics were comparable between the two groups.

Table 1: Demographic Characteristics

Variable	Group A (HES)	Group B (Saline)	p-value
Age (years, mean ± SD)	43 ± 14.76	41.1 ± 15.83	0.608
Gender (m/f)	18/16	16/18	0.628
Weight (kg, mean ± SD)	61.1 ± 13.37	59.3 ± 11.79	0.553
ASA (I/II)	20/14	18/16	0.625

No statistically significant differences were observed in the demographic profiles.

Hemodynamic Parameters Heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and respiratory rate were monitored. No statistically significant differences were observed at any time point.

Table 2: Heart Rate at different Time Intervals (mean ± SD)

Time Interval	Group A (HES)	Group B (Saline)	p-value
Before Induction	86.74 ± 14.97	87.71 ± 15.29	0.792
1 min	83.47 ± 14.23	84.18 ± 14.31	0.839
2 min	80.18 ± 14.99	81.15 ± 14.71	0.788
3 min	77.74 ± 14.37	79.12 ± 14.48	0.694
4 min	74.59 ± 14.25	75.56 ± 14.02	0.778

Pain Scores Pain was evaluated at 10, 20, 30, and 40 seconds after propofol injection. A significant reduction in pain was observed in the HES group at 10, 20, and 30 seconds ($p < 0.01$).

Table 3: Comparison of Pain scores (Median [IQR])

Time	Group A (HES)	Group B (Saline)	p-value
10 seconds	0 (0-0)	1 (0-2)	0.001
20 seconds	0 (0-0)	1 (0-2)	0.0003
30 seconds	0 (0-0)	0.5 (0-1)	0.0003
40 seconds	0 (0-0)	0 (0-0)	0.99

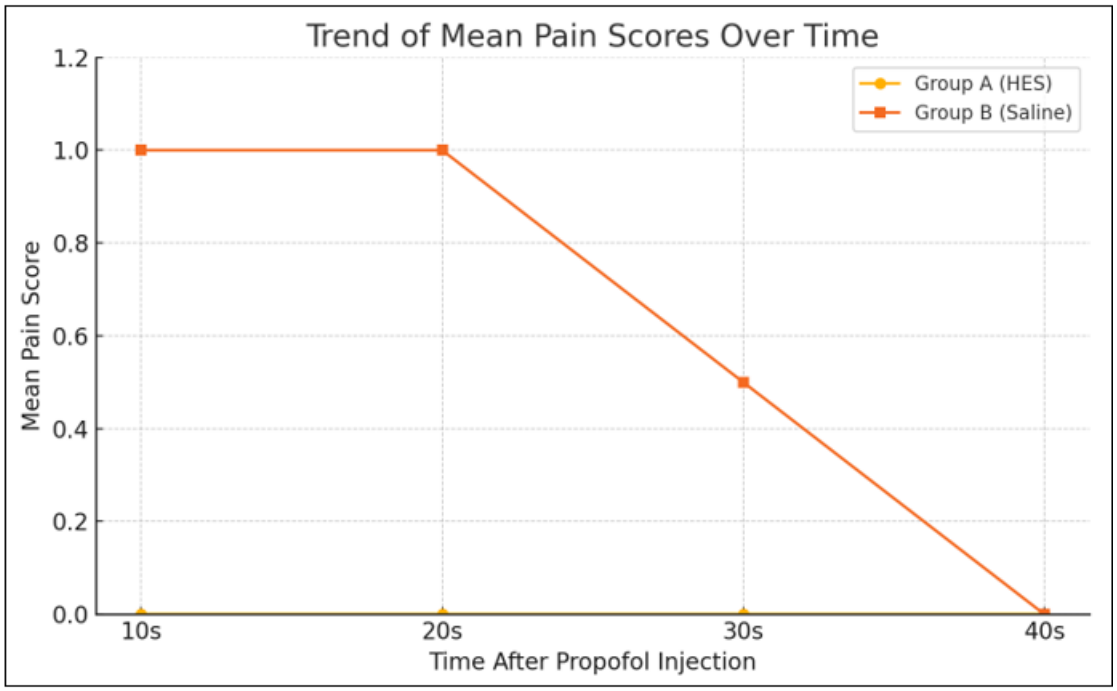

Figure 1: Trend of Mean Pain Scores over time

4. Discussion

The present randomized controlled study aimed to evaluate the efficacy and safety of pre-administration of 6% hydroxyethyl starch (HES) in reducing pain associated with propofol injection. The findings demonstrated that patients receiving HES reported significantly less pain at 10-, 20-, and 30-seconds post-injection compared to those receiving normal saline, indicating that HES effectively attenuates propofol-induced injection pain.

These results are consistent with prior studies, such as those by Misra et al. and Jandial et al., which also showed a significant reduction in pain intensity with HES pre-treatment. The mechanism is thought to involve the modulation of vascular endothelial response, reducing contact activation and nociceptor stimulation caused by propofol. HES may alter the endothelial permeability or surface characteristics, thereby diminishing the irritant effect of the phenol group in propofol responsible for early and delayed pain phases.

Furthermore, this study confirmed that pre-treatment with HES does not adversely affect hemodynamic stability. Throughout the induction period, heart rate, systolic and diastolic blood pressure, and respiratory rates remained comparable between both groups. This finding supports the safety profile of HES, especially when used in limited volumes like 100 mL. Larger volumes (>1000 mL) of HES have been associated with renal injury in critically ill patients; however, such complications were not observed in this elective surgical cohort.

In terms of methodology, the study's double-blind, randomized design, standardized dosing, and use of an objective pain scale ensure robustness and reduce bias. The absence of confounding from opioid premedication and the use of a uniform propofol-lidocaine mixture further strengthen the internal validity.

While previous strategies to mitigate injection pain—such as the use of lidocaine, ketamine, opioids, and warming techniques—have shown partial success, they come with limitations including hemodynamic alterations or delayed recovery. The use of HES as a non-pharmacologic adjuvant may offer a safer and simpler alternative, particularly in short-duration surgical cases or ambulatory settings.

The clinical relevance of these findings is notable. Pain on injection, although not a major anesthetic complication, can significantly affect patient experience and perioperative satisfaction. Implementing a low-risk strategy like HES preloading could improve patient comfort without adding procedural complexity or cost.

5. Conclusion

This randomized controlled trial clearly demonstrates that pre-administration of 6% hydroxyethyl starch (HES) significantly reduces the incidence and severity of pain associated with propofol injection in adult patients undergoing elective surgeries. The HES group experienced consistently lower pain scores at 10-, 20-, and 30-seconds post-injection, with statistical significance compared to the control group receiving normal saline. Importantly, these benefits were achieved without compromising hemodynamic stability or inducing any adverse effects, thereby affirming the safety and tolerability of this intervention in clinical practice.

The underlying mechanism of pain reduction is likely related to the protective modulation of vascular endothelium by HES, which minimizes contact activation and the subsequent nociceptive response triggered by propofol. As injection pain remains a distressing yet underappreciated perioperative complaint, this study adds to the growing body of evidence supporting proactive strategies to enhance patient comfort and satisfaction.

Given its ease of administration, cost-effectiveness, and favourable safety profile when used in appropriate volumes, 6% HES can be considered a practical and efficient measure for improving patient experience during anesthetic induction. Broader implementation of this technique, especially in day-care and short surgical procedures, holds promise for enhancing anesthesia quality without additional pharmacologic burden.

Future large-scale, multicentric studies comparing HES with other commonly used interventions like lidocaine or ketamine could further validate these findings and aid in establishing standard protocols. Nevertheless, the results from this trial support the clinical utility of 6% HES as a simple, safe, and effective pre-treatment option for alleviating propofol injection pain.

References

[1] Jalota L, Kalira V, George E, et al. Prevention of pain on injection of propofol: systematic review and meta-analysis. BMJ. 2011; 342: d1110.
[2] Picard P, Tramèr MR. Prevention of pain on injection with propofol: a quantitative systematic review. Anesth Analg. 2000; 90(4): 963- 969.
[3] Nathanson MH, Gajraj NM, Russell JA. Prevention of pain on injection of propofol: a comparison of lignocaine with alfentanil. Anaesthesia. 1996; 51(6):502-505.
[4] Doenicke AW, Roizen MF, Rau J, et al. Reducing pain during propofol injection: the role of the carrier and lidocaine. Anesth Analg. 1996;82(3): 472- 474.
[5] Misra S, Kalra A, Saroa R, et al. Comparative study of pre-treatment with hydroxyethyl starch and normal saline to reduce pain on propofol injection. Anesth Essays Res. 2018;12(2):467-471.
[6] Schulz KF, Altman DG, Moher D; for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.
[7] Singh M, Bhatia N, Mohan A, et al. Propofol injection pain: incidence, mechanism, and prevention. J Anaesthesiol Clin Pharmacol. 2014; 30(3): 377-384.
[8] Jalota L, Kalira V, George E, et al. Prevention of pain on injection of propofol: systematic review and meta-analysis. BMJ. 2011; 342: d1110.
[9] Canbay O, Celebi N, Sahin A, et al. Efficacy of intravenous lidocaine and ketamine on propofol injection pain. Br J Anaesth. 2008;100(1):95-98.
[10] Ramesh VJ, Rajagopalan S, Anandan H, et al. Hemodynamic stability and adverse effects of 6% HES versus crystalloids. Indian J Crit Care Med. 2020;24(4):248-254.
[11] Chow S, Shao J, Wang H. Sample Size Calculations in Clinical Research. 2nd ed. CRC Press; 2007.
[12] Altman DG. Practical Statistics for Medical Research. 1st ed. Chapman & Hall; 1990.