

# Effect of 6% hydroxyethyl starch pre-administration for reduction of pain on propofol injection: A placebo-controlled randomised study

## Address for correspondence:

Dr. Satyajeet Misra,  
Department of Anaesthesiology  
and Critical Care, AIIMS,  
Bhubaneswar - 751 019,  
Odisha, India.  
E-mail: misrasatyajeet@gmail.  
com

**Submitted:** 26-Sep-2021  
**Revised:** 20-Jan-2022  
**Accepted:** 06-Feb-2022  
**Published:** 24-Feb-2022

**Satyajeet Misra, Bikram K. Behera, Alok K. Sahoo**

Department of Anaesthesiology and Critical Care, All India Institute of Medical Sciences (AIIMS), Bhubaneswar, Odisha, India

## ABSTRACT

**Background and Aims:** 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. The objective of this study was to evaluate the effect of 6% hydroxyethyl starch (HES) 130/0.4 pre-administration on propofol injection pain. **Methods:** Adult patients of the American Society of Anesthesiologists physical status I and II patients, 18-65 years old, of either gender and undergoing elective surgery were randomised into two groups. 100 mL bolus of HES or 0.9% normal saline (NS) was administered over three to five minutes through an 18 G cannula placed in the hand or forearm vein, followed by induction with 1% propofol premixed with 2% lidocaine. Pain during propofol injection was assessed every 10 seconds 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 self-reported by patients within 10 seconds with some discomfort; and 3- severe pain accompanied by withdrawing of hand, and behavioural signs. **Results:** 126 patients completed the study. Overall incidence of pain was significantly higher in the NS group vs HES group (53% vs 28%;  $P = 0.004$ ; relative risk 1.54, 95% confidence interval 1.13-2.09). Incidence of severe (8% vs 0%) and moderate pain (16% vs 5%) was higher in the NS group, while the 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 ( $P = 0.002$ ). **Conclusion:** Pre-administration of 100 mL bolus of 6% HES 130/0.4 significantly reduced propofol injection pain.

**Key words:** Adult, adverse effects, injections, pain, propofol

## Access this article online

Website: [www.ijaweb.org](http://www.ijaweb.org)

DOI: 10.4103/ija.ija\_884\_21

Quick response code



## INTRODUCTION

Propofol is the most widely used intravenous agent for induction of anaesthesia. Pain on the intravenous injection of propofol however is a problem.<sup>[1]</sup> The incidence of pain on the intravenous injection of propofol is 30-90%.<sup>[1]</sup> Most patients remember it as one of the unpleasant encounters during operation. Propofol injection pain ranks seventh amongst common important postoperative problems after anaesthesia.<sup>[2]</sup> Pain is due to irritation by the phenol moiety of propofol. The immediate pain is due to irritation of the veins and delayed pain (after 10-20 seconds) is due to kinin release.<sup>[1]</sup> Various techniques to mitigate this pain include administration in a larger vein, pre-mixing with lignocaine, pre-administration of opioids,

sub-anaesthetic doses of ketamine, using a mixture of medium and long chain triglycerides in the carrier emulsion, etc.<sup>[1,3,4]</sup>

However, even with multi-modal techniques, pain on propofol injection is not abolished completely.<sup>[1]</sup> Colloids are used for intraoperative

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** [WKHLRPMedknow\\_reprints@wolterskluwer.com](mailto:WKHLRPMedknow_reprints@wolterskluwer.com)

**How to cite this article:** Misra S, Behera BK, Sahoo AK. Effect of 6% hydroxyethyl starch pre-administration for reduction of pain on propofol injection: A placebo-controlled randomised study. *Indian J Anaesth* 2022;66:107-11.

fluid therapy in anaesthesia,<sup>[5]</sup> and are considered to be safe.<sup>[6]</sup> They are macromolecules that have the capacity to modify endothelial cell junctions and permeability of the vascular endothelium and inhibit endothelial activation by various substances and molecules.<sup>[7,8]</sup> Thus, pre-administration of colloids may prevent contact activation by propofol, which may in turn lead to reduced pain during injection.

We hypothesised that the pre-administration of 6% hydroxyethyl starch (HES) 130/0.4 will reduce pain on propofol injection. Thus, the aim of this study was to compare the incidence and severity of pain on propofol injection in patients pre-administered either HES or 0.9% normal saline (NS) bolus during induction of anaesthesia.

## METHODS

This prospective randomised placebo-controlled double-blind study was carried out after Institutional Ethics Committee approval. The study was registered in the Clinical Trials Registry of India (CTRI) (CTRI/2020/05/025000) before patient enrolment. The primary objective of the study was to compare the incidence of pain on propofol injection in patients receiving HES bolus vs. NS, and the secondary objective was to compare the severity of propofol injection pain in the two groups.

Adult patients of the American Society of Anesthesiologists physical status I and II, 18-65 years old, of either gender and undergoing elective surgery under general anaesthesia in a tertiary care institute were recruited in this study after obtaining their written informed consent. Exclusion criteria were emergency surgeries, known history of allergy to propofol or HES, hypertensives, diabetics, presence of left ventricular dysfunction, elevated serum creatinine, and those in whom hand or forearm veins were not accessible. The study was conducted over a period of nine months from May 2020 to January 2021.

Randomisation was carried out using a computer-generated random number sequence. Patients were randomised to receive 100 mL bolus of either HES or NS before propofol injection. Allocation concealment was carried out with opaque sealed envelopes which were opened once the patients were received in the theatre.

On arrival in the operating room, an 18 G cannula was inserted either in the hand or forearm veins

under local infiltration anaesthesia. No opioid premedication was given to any patient. The study drugs, HES (Expavon®, Neon Laboratories, India) or NS were drawn up in two 50 mL syringes by an anaesthesiologist not involved in the study and handed over to one of the study investigators who then administered it to the patient over a period of three to five minutes. No tourniquet was applied to the injectant arm. Once the 100 mL bolus was over, an induction dose of 1% propofol (long chain triglycerides propofol, Neorof®, Neon Laboratories, India) premixed with 1 mL of 2% lidocaine (100 mg propofol in 10 mL syringes mixed with 1 mL of 2% lidocaine) was then administered to the patient by the same blinded investigator till loss of verbal contact. After induction and confirmation of mask ventilation, intravenous fentanyl and vecuronium were administered subsequently for tracheal intubation and conduct of surgery.

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.

Given an incidence of 40% pain on injection of propofol mixed with lidocaine,<sup>[9]</sup> we considered a 50% reduction in the colloid pre-treated group to be clinically significant. Accordingly, 62 patients were required in each group to achieve a power of 90% with an alpha error of 5%. Accounting for dropouts, we planned to recruit 130 patients with 65 patients in each group. Moderate-severe pain was considered as significant pain. The number needed to treat (NNT), that is, the number of patients who had to be given HES to prevent propofol injection pain in one patient was also determined.

The normality of data was checked using the Shapiro-Wilk test and found to be normally distributed. Continuous variables in the two groups were expressed as mean (standard deviation) and compared with the unpaired *t*-test. Categorical variables like gender and incidence and severity of pain on propofol injection between the two groups were expressed as numbers (percentages) and compared with Pearson's Chi-square test. Significance was set at  $P < 0.05$  (2-tailed). Data

were analysed by using R (R studio 3.5, Vienna, Austria).

## RESULTS

One hundred and twenty-eight patients were recruited, of which 126 patients completed the study [64 in HES group and 62 in NS group, Figure 1]. One patient in each group was lost to follow up due to protocol violation (study drug was unintentionally known before administration). The age, weight, and other demographic characteristics were comparable in the two groups [Table 1].

Overall, the incidence of pain was significantly higher in the NS group compared to HES group (53% vs 28%;  $P = 0.004$ ; relative risk 1.54, 95% confidence interval 1.13-2.09) [Figure 2]. Incidence of severe (8% vs 0%) and moderate pain (16% vs 5%) was higher in the NS group, while the incidence of mild pain was comparable (29% vs 23%; NS vs HES) [Figure 2]. A significant difference was seen as well in the severity of pain between the two groups (no pain-mild pain vs moderate-severe pain) ( $P = 0.002$ ). The effect size for pain between the groups was large (0.73). NNT in the HES group was 4, that is four patients needed to be administered HES to prevent pain on propofol injection in one patient.

Table 1: Demographic characteristics

Demographics	Group 6% HES (n=64)	Group 0.9% NS (n=62)
Age (years)	44.7 (10.6)	44.7 (12.9)
Weight (kg)	61 (11.7)	59.8 (13.9)
Gender (M:F)	19:45	22:40
Propofol induction dose (mg)	125 (26)	131 (32)
Loss of verbal response (seconds)	55 (4.5)	56 (5)

Values are mean (standard deviation) or number of patients

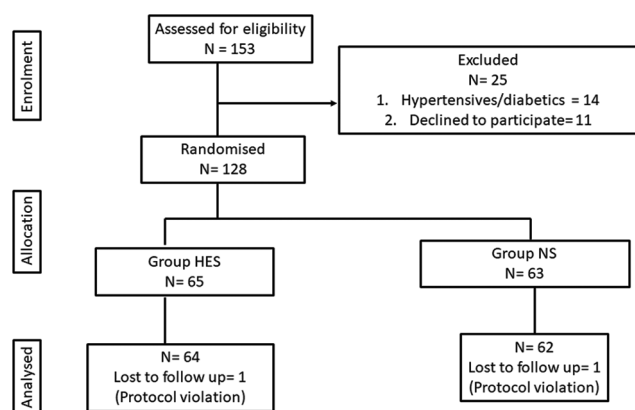


Figure 1: CONSORT flow chart showing the enrolment of patients in the study

## DISCUSSION

The finding of this study was that pre-administration of 100 mL HES reduced the incidence as well as the severity of pain on propofol injection in adults. The most effective non-pharmacological intervention in decreasing the pain on propofol injection is using an antecubital vein with a relative risk of 0.19 to 0.34.<sup>[9]</sup> Pretreatment with lidocaine in association with venous occlusion has a relative risk ranging from 0.39 to 0.69.<sup>[9]</sup> The NNT value with this intervention is 1.6-1.9, that is, 1.6 to 1.9 patients need to be exposed to this treatment to prevent pain in one patient.<sup>[9]</sup> Despite this, it is not widely accepted since the process of venous occlusion before induction of anaesthesia is cumbersome.<sup>[9]</sup>

Six other interventions that are efficacious are lidocaine-propofol admixture and pretreatment with lidocaine, ketamine, opioids, and non-steroidal anti-inflammatory drugs with relative risks of pain ranging from 0.43 to 0.67.<sup>[9]</sup> Besides these drugs, even steroids (methylprednisolone)<sup>[10]</sup> and 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) antagonists (ramosetron, ondansetron)<sup>[11]</sup> have been studied for decreasing propofol injection pain. A recent review has found pretreatment with two drugs, the use of opioids, and 5-HT<sub>3</sub> antagonists to be more effective than placebo in decreasing propofol injection pain.<sup>[12]</sup>

Amongst opioids, meperidine 40 mg administered with tourniquet has an NNT of 2.7 in adults.<sup>[9]</sup> Our results for the NNT with HES are similar to injection pain relief with opioid pretreatment such as alfentanil (NNT 4.3 with 10 µg/kg), and fentanyl (NNT 4 with 100-150 µg) which were typically administered

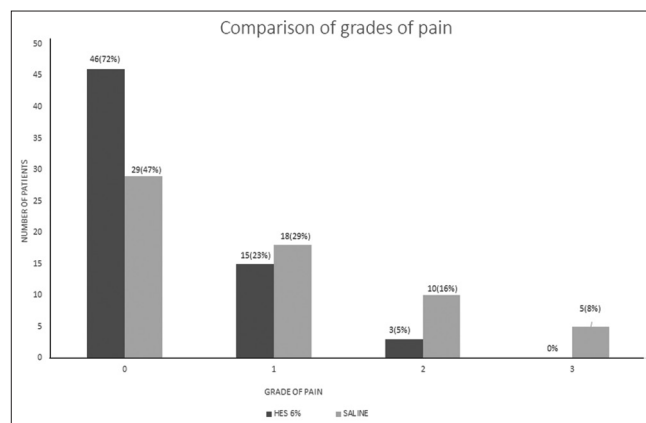


Figure 2: Incidence and severity of pain on propofol injection between the groups. 0- no pain; 1- mild pain; 2- moderate pain; 3-severe pain. HES- 6% hydroxyethyl starch; NS- 0.9% saline

a few minutes before propofol.<sup>[9]</sup> Therefore, HES pre-administration may offer an opportunity to avoid opioids for decreasing pain on propofol injection in patients, especially those undergoing short surgical day care procedures.

Unlike other studies where propofol was administered alone,<sup>[13,14]</sup> in the current study, propofol was administered with lidocaine. But failure rates with lidocaine combined with propofol are 13-32% and thus, the protective effect of lidocaine cannot be universally assumed.<sup>[15]</sup> The incidence of propofol injection pain was 0% in only three clinical trials.<sup>[1]</sup> One study used three drugs (fentanyl, lignocaine, and sevoflurane),<sup>[16]</sup> another study used a very high dose of ketamine (1 mg/kg),<sup>[17]</sup> while the third study used a combination of 40 mg of lidocaine with 2 µg/kg of remifentanyl before propofol injection.<sup>[18]</sup> However, the potpourri of anaesthetic and analgesic drugs used to reduce pain on propofol injection may themselves have undesirable effects like hypotension which may become more significant than the pain on propofol injection.

Activation of various nociceptive receptors like 5-HT<sub>3</sub> receptors,<sup>[19]</sup> human transient receptor potential ankyrin 1 (TRPA1),<sup>[20]</sup> as well as irritation of the venular endothelium by the phenol moiety of propofol,<sup>[1]</sup> have been implicated in propofol injection pain. It is possible that the pre-administration of HES may have led to modulation of the venous endothelium, thereby preventing contact activation of the various nociceptive receptors by propofol. This modulation of the endothelium by starches has been demonstrated in many in-vivo and in-vitro experimental models.<sup>[7,8,21]</sup>

In a porcine model of cerebral ischaemia, intravenous 10% HES 257/0.47 administration just after ischaemia (600 mg/kg) and continued during the period of reperfusion (600 mg/kg/h), significantly reduced the number of leucocytes adhered to the cerebral venular endothelium at 1- and 2-h following reperfusion.<sup>[6]</sup> This reduced leucocyte adherence was associated with decreased capillary permeability. Similarly, isovolaemic haemodilution with 6% HES 200/0.62 to a 30% haematocrit resulted in a 40% decrease in the number of post-ischaemic neutrophils adherent to postcapillary skeletal muscle venules during the two hours of reperfusion.<sup>[22]</sup> In-vitro studies also support this decreased adhesion of molecules secondary to inhibition of contact activation by colloids.<sup>[21]</sup>

This study has some limitations. A total of 100 mL boluses of HES were arbitrarily used. The effect of different starches may be different and thus, our results will be applicable to only 6% HES (130/0.4). The actual mechanism of action of HES in this context needs determination. The pain was rated on a Likert scale where there may have been some overlap between the severity of pain. The assessment would have been more accurate had we used a numerical rating scale (NRS), but it was felt that with patients being put to sleep, the NRS scale may also not be accurate and so we relied on a simple assessment.

## CONCLUSION

Pre-administration of 100 mL of 6% HES 130/0.4, 3 to 5 min before propofol injection, significantly decreases the pain on injection with propofol in comparison to normal saline.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Desousa KA. Pain on propofol injection: Causes and remedies. *Ind J Pharmacol* 2016;48:617-23.
2. Macario A, Weinger M, Truong P, Lee M. Which clinical anesthesia outcomes are both common and important to avoid? The perspective of a panel of expert anesthesiologists. *Anesth Analg* 1999;88:1085-91.
3. Kundra P, Vinayagam S. Perioperative intravenous lidocaine: Crossing local boundaries and reaching systemic horizons. *Indian J Anaesth* 2020;64:363-5.
4. Singla B, Malde AD. A prospective observational study of injection pain in children with medium plus long chain triglyceride and long chain triglyceride propofol premixed with lignocaine. *Indian J Anaesth* 2018;62:214-8.
5. Joosten A, Delaporte A, Ickx B, Touihri K, Stany I, Barvais L, *et al.* Crystalloid vs colloid for intraoperative goal directed fluid therapy using a closed loop system: A randomized double-blinded controlled trial in major abdominal surgery. *Anesthesiology* 2018;128:55-66.
6. Martin C, Jacob M, Vicaut E, Guidet B, Van Aken H, Kurz A. Effect of waxy maize-derived hydroxyethyl starch 130/0.4

- on renal function in surgical patients. *Anesthesiology* 2013;118:387-94.
7. Wisselink W, Patetsios P, Panetta TF, Ramirez JA, Rodino W, Kirwin JD, *et al.* Medium molecular weight pentastarch reduces reperfusion injury by decreasing capillary leak in an animal model of spinal cord ischemia. *J Vasc Surg* 1998;27:109-16.
  8. Kaplan SS, Park TS, Gonzales ER, Gidday JM. Hydroxyethyl starch reduces leucocyte adherence and vascular injury in the newborn pig cerebral circulation after asphyxia. *Stroke* 2000;31:2218-23.
  9. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, *et al.* Prevention of pain on injection of propofol: Systematic review and meta-analysis. *BMJ* 2011;342:d1110.
  10. Shivanna S, Priye S, Singh D, Jagannath S, Mudassar S, Reddy DP. Efficacy of methylprednisolone and lignocaine on propofol injection pain: A randomised, double-blind, prospective study in adult cardiac surgical patients. *Indian J Anaesth* 2016;60:848-51.
  11. Sumalatha GB, Dodawad RR, Pandarpurkar S, Jajee PR. A comparative study of attenuation of propofol-induced pain by lignocaine, ondansetron, and ramosetron. *Indian J Anaesth* 2016;60:25-9.
  12. Bakhtiari E, Mousavi SH, Gharavi Fard M. Pharmacological control of pain during propofol injection: A systematic review and meta-analysis. *Expert Rev Clin Pharmacol* 2021;14:889-99.
  13. Pang WW, Mok MS, Huang S, Hwang MH. The analgesic effect of fentanyl, morphine, meperidine, and lidocaine in the peripheral veins: A comparative study. *Anesth Analg* 1998;86:382-6.
  14. Wall R, Zacharias M. Effects of alfentanil on induction and recovery from propofol anaesthesia in day surgery. *Anaesth Intensive Care* 1990;18:214-8.
  15. Fletcher JE, Seavell CR, Bowen DJ. Pretreatment with alfentanil reduces pain caused by propofol. *Br J Anaesth* 1994;72:342-4.
  16. DeSousa K, Ali MS. Sevoflurane to alleviate pain on propofol injection. *J Anesth* 2011;25:879-83.
  17. Iwata M, Inoue S, Kawaguchi M, Kimura T, Tojo T, Taniguchi S, *et al.* Ketamine eliminates propofol pain but does not affect hemodynamics during induction with double-lumen tubes. *J Anesth* 2010;24:31-7.
  18. Aouad MT, Siddik-Sayyid SM, Al-Alami AA, Baraka AS. Multimodal analgesia to prevent propofol induced pain: Pretreatment with remifentanil and lidocaine versus remifentanil or lidocaine alone. *Anesth Analg* 2007;104:1540-4.
  19. Wang W, Zhou L, Wu LX, Wang T, Zhang CB, Sun L. 5-HT<sub>3</sub> Receptor antagonists for propofol injection pain: A meta-analysis of randomized controlled trials. *Clin Drug Investig* 2016;36:243-53.
  20. Nishimoto R, Kashio M, Tominaga M. Propofol-induced pain sensation involves multiple mechanisms in sensory neurons. *Pflugers Arch* 2015;467:2011-20.
  21. Collis RE, Collins PW, Gutteridge CN, Kaul A, Newland AC, Williams DM, *et al.* The effect of hydroxyethyl starch and other plasma volume substitutes on endothelial cell activation; an *in vitro* study. *Intensive Care Med* 1994;20:37-41.
  22. Menger MD, Thierjung C, Hammersen F, Messmer K. Dextran vs hydroxyethyl starch in inhibition of postischemic leukocyte adherence in striated muscle. *Circ Shock* 1993;41:248-55.