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Research Article

Comparison of Pre-induction Intravenous 6% Hydroxyethyl Starch with Dexmedetomidine for Attenuation of Propofol Injection Pain: A Randomised, Double-blind Controlled Study

Running title: 6% HES versus dexmedetomidine for propofol injection pain

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Abstract

Background. Pain on injection of propofol remains common despite lignocaine admixture. Pre-administration of 6% hydroxyethyl starch (HES) may limit kallikrein–kinin contact activation at the venous endothelium, whereas dexmedetomidine may attenuate pain through α_2-mediated analgesia and sedation.

Objective. To compare the effect of intravenous 6% HES with intravenous dexmedetomidine, each given before a premixed propofol–lignocaine bolus, on the incidence and severity of propofol injection pain.

Methods. In this single-centre, prospective, randomised, double-blind, three-arm controlled study, 177 adults of ASA physical status I–II scheduled for elective surgery under general anaesthesia were allocated to Group H (n = 58; 100 mL of 6% HES), Group D (n = 60; dexmedetomidine 0.5 µg/kg in 100 mL of 0.9% saline) or Group P (n = 59; 100 mL of 0.9% saline). Each infusion was given over 10 min through an 18-G cannula on the dorsum of the hand. Immediately afterwards a sub-induction bolus of propofol 0.5 mg/kg premixed with 1 mL of 2% lignocaine was injected over 30 s. Pain was graded with a four-point Verbal Categorical Score (VCS; primary outcome) and an 11-point Numerical Rating Scale (NRS). Heart rate (HR) and mean arterial

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pressure (MAP) were recorded before the bolus, immediately after it and at 1 min.

Results. The proportion of patients who were pain-free (VCS 0) was 38/58 (65.5%) in Group H, 21/60 (35.0%) in Group D and 9/59 (15.3%) in Group P (Fisher–Freeman–Halton exact test, $p < 0.001$). Any pain (VCS ≥ 1) occurred in 34.5%, 65.0% and 84.7% of patients, respectively. Severe pain (VCS 3) was confined to Group P (5/59; 8.5%). Mean ± SD NRS scores were 0.83 ± 1.39 (H), 1.83 ± 1.68 (D) and 3.51 ± 2.18 (P); corresponding VCS scores were 0.43 ± 0.65, 0.90 ± 0.77 and 1.50 ± 0.86 (Kruskal–Wallis $p < 0.001$ for both scales). Immediate and 1-min HR were lowest in Group D ($p = 0.003$ and $p < 0.001$). MAP did not differ significantly at any time point.

Conclusions. When added to a propofol–lignocaine admixture, pre-administration of 100 mL of 6% HES reduced the incidence and severity of propofol injection pain more than dexmedetomidine 0.5 µg/kg or saline. The findings support further investigation of multimodal strategies for prevention of propofol injection pain; they do not establish HES as a routine substitute for established techniques, and regulatory restrictions on HES must be considered.

Keywords: propofol injection pain; hydroxyethyl starch; dexmedetomidine; lignocaine; Verbal Categorical Score; Numerical Rating Scale; randomised controlled trial.

Introduction

Propofol (2,6-diisopropylphenol) is the most widely used intravenous anaesthetic for sedation and for induction and maintenance of anaesthesia, both inside and outside the operating theatre, because of its rapid onset and smooth recovery. Pain on injection nevertheless remains one of the most frequent and distressing problems of the perioperative period and is a recognised source of patient dissatisfaction.[1] The reported incidence in adults ranges from approximately 28% to 90% when no preventive measure is used, depending on injection site, emulsion formulation and the method of pain assessment.[2]

Propofol is insoluble in water and is formulated as an oil-in-water emulsion containing soybean oil, glycerol and purified egg phosphatide. Injection pain is attributed to irritation of the venous intima by the aqueous phase of propofol and to activation of the plasma kallikrein–kinin cascade. Bradykinin produces local vasodilatation and increased vascular permeability, increasing contact between propofol and perivascular free nerve endings; work with kallikrein inhibitors supports a central role for this pathway.[3] Pain may therefore be immediate, from direct nociceptor irritation, or delayed, from kinin-mediated mechanisms. Because of the high incidence, many pharmacological and non-pharmacological strategies have been tested. Non-pharmacological measures include use of a larger proximal vein rather than a dorsal hand vein, slower injection, dilution of the emulsion and cooling of propofol.[4] Among pharmacological approaches, lignocaine—given either as an admixture or as pretreatment with venous occlusion—remains the most extensively studied and effective single intervention.[5] Other agents evaluated include the 5-HT_3 antagonist ondansetron,[6] the N-methyl-D-aspartate antagonist ketamine[7] and magnesium sulphate,[8] each acting through distinct receptor or membrane-stabilising mechanisms.

Combination regimens often outperform single agents. Adding nitroglycerin to lignocaine is more effective than lignocaine alone,[9] and opioid pretreatment such as remifentanil is effective, with efficacy influenced by the interval between the opioid and propofol.[10] Increasing the diluent volume of lignocaine has also been shown to reduce incidence and severity of injection pain.[11]

A multimodal strategy that pairs a drug with local anaesthetic activity and a centrally acting sedative or analgesic is therefore attractive. Dexmedetomidine is a highly selective α_2-adrenoceptor agonist with analgesic, sedative and sympatholytic properties and has been studied as

such an adjuvant. Hydroxyethyl starch (HES) colloids are starch-containing macromolecules that can modify endothelial cell junctions and vascular permeability and that may inhibit endothelial activation by inflammatory mediators including kinins. Pre-administration of HES might therefore reduce contact activation by propofol and lessen injection pain.

The present study compared intravenous 6% HES with intravenous dexmedetomidine, each given before a premixed propofol–lignocaine bolus, to determine which intervention more effectively reduces the incidence and severity of propofol injection pain. All three groups received the same lignocaine admixture, so the control arm is a lignocaine-admixture control rather than an untreated placebo.

Materials and Methods

Study design and ethics

This was a single-centre, prospective, randomised, double-blind, three-arm parallel-group controlled study conducted in the Department of Anaesthesiology, Apollo Institute of Medical Sciences and Research, Hyderabad, India. The protocol was reviewed by the Institutional Ethics Committee of Apollo Institute of Medical Sciences and Research at its meeting on 6 November 2024 and approved on 10 December 2024 (Regd No. EC/NEW/INST/1527/2024/11/219). Written informed consent was obtained from all patients before enrolment after the study procedure, its purpose, potential benefits and risks had been explained during the pre-anaesthetic visit. The study was conducted in accordance with the Declaration of Helsinki and the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants.

Participants

Adults aged 18–65 years of either sex, of ASA physical status I or II, scheduled for elective surgery under general anaesthesia were eligible. Exclusion criteria were emergency surgery, known allergy to propofol, lignocaine, dexmedetomidine or HES, ASA physical status III or IV, anticipated difficult venous access on the dorsum of the hand, clinically important cardiac conduction disease or untreated bradycardia (relevant to dexmedetomidine), known or suspected HES contraindication (including sepsis, critical illness, renal impairment, intracranial bleeding or coagulopathy, consistent with current labelling), pregnancy, and refusal of consent.

Randomisation, allocation concealment and blinding

Patients were allocated in a 1:1:1 ratio to Group H, Group D or Group P using sealed opaque envelopes that were opened only after enrolment. An anaesthetist who was not otherwise involved in the study prepared the assigned infusion in two identical 50-mL syringes and handed them to the injecting investigator. The injecting investigator, the pain assessor and the patient were blinded to group assignment. The pain assessor did not prepare or administer the study infusion. Dexmedetomidine can produce recognizable haemodynamic effects, including a reduction in heart rate, which was observed in Group D; such effects could in principle compromise blinding of the injecting clinician, although the pain assessor was a separate investigator who did not administer the study infusion.

Interventions

Group H received 100 mL of 6% hydroxyethyl starch. Group D received dexmedetomidine 0.5 µg/kg diluted to 100 mL with 0.9% sodium chloride. Group P received 100 mL of 0.9% sodium chloride. Each infusion was given intravenously over 10 min immediately before the test bolus of propofol.

Anaesthetic protocol

On arrival in the pre-operative area an 18-G cannula was secured on the dorsum of the left hand. No opioid or other analgesic premedication was given. The dorsal hand vein was chosen deliberately because it is associated with a higher incidence of injection pain and is the conventional

site for evaluating preventive interventions.[12] Standard monitoring (electrocardiography, non-invasive blood pressure and pulse oximetry) was applied.

Immediately after the 100-mL study infusion, a sub-induction dose of propofol 0.5 mg/kg premixed with 1 mL of 2% lignocaine (20 mg) was injected over 30 s by the blinded investigator. Premixing lignocaine with propofol is an established method of attenuating injection pain and was applied equally in all groups so that any incremental effect of HES or dexmedetomidine could be isolated.[13] Pain during this bolus was assessed for 30 s by a second blinded investigator. The remaining induction dose of propofol (1.5 mg/kg), fentanyl 2 µg/kg and atracurium 0.5 mg/kg were then given and the trachea was intubated with an appropriately sized tube. Subsequent anaesthetic management followed institutional practice and was not part of the study analysis.

Outcomes

The primary outcome was the distribution of propofol injection pain on the Verbal Categorical Score (VCS), a four-point ordinal scale: 0 = no pain; 1 = mild pain with no behavioural sign; 2 = moderate pain accompanied by a behavioural sign; 3 = severe pain with a strong vocal response together with facial grimacing, arm withdrawal or crying. The proportion of patients who were completely pain-free (VCS 0) was the principal clinically interpretable contrast.

The secondary pain outcome was the 11-point Numerical Rating Scale (NRS; 0 = no pain, 10 = worst imaginable pain), recorded at the same time. Haemodynamic secondary outcomes were HR and MAP at three time points: after the study infusion and before the propofol bolus ("before"), immediately after the bolus, and 1 min after the bolus. Age, sex, height, weight and body-mass index (BMI) were recorded as baseline variables. Adverse events during the observation window, including clinically important bradycardia, hypotension, rash or other suspected drug reaction, were recorded.

Sample size

An a priori sample-size calculation was not separately documented in the approved protocol file available at revision, and no expected proportion, α, power or dropout allowance is therefore reported as a prospective calculation. All consecutive eligible patients were enrolled until 177 participants had been randomised (Group H, n = 58; Group D, n = 60; Group P, n = 59). All randomised patients completed the induction-phase assessment and were included in the analysis. The achieved sample detected the observed overall difference in VCS distribution at $p < 0.001$, but this post-hoc observation does not replace a formal prospective power calculation, which is acknowledged as a limitation.

Statistical analysis

Data were analysed with SPSS version 24 (IBM Corp., Armonk, NY, USA). Continuous demographic and haemodynamic variables are presented as mean ± standard deviation (SD) and were compared with one-way analysis of variance (ANOVA). When the overall ANOVA was significant, post-hoc pairwise comparisons were performed using Tukey's honestly significant difference (HSD), which adjusts for multiple comparisons.

VCS is an ordinal four-level variable. Because two cells of the 3 × 4 table were empty and the expected frequency of severe pain was approximately 1.6–1.7 in each group, the primary categorical analysis was the Fisher–Freeman–Halton exact test of independence. The Pearson chi-square statistic ($\chi^2 = 50.99$, df = 6) is reported only as a descriptive measure. Pairwise comparisons of the pain-free proportion (VCS 0) were performed with the chi-square test or Fisher exact test as appropriate; a Bonferroni correction was applied for the three pairwise contrasts (two-sided $\alpha = 0.0167$). NRS and VCS scores, which

are skewed and bounded, are presented as mean ± SD for description only; both were compared among groups with the Kruskal–Wallis test. The categorical VCS distribution remained the principal analysis of injection pain. A two-sided p-value < 0.05 was considered statistically significant for overall tests.

Results

Participant flow

One hundred and seventy-seven patients of ASA physical status I–II were enrolled and randomised to Group H (6% HES; n = 58), Group D (dexmedetomidine 0.5 µg/kg; n = 60) or Group P (0.9% saline control; n = 59). All randomised patients completed the induction-phase assessment and were included in the analysis.

Baseline characteristics

The groups were comparable for age and height (p > 0.05). Body weight and BMI differed statistically (p = 0.029 and p = 0.023). The absolute differences were small (highest versus lowest mean weight 4.15 kg; highest versus lowest mean BMI 1.94 kg/m²). Although statistically significant, the absolute differences were small; nevertheless, residual confounding cannot be completely excluded because the primary analysis was not adjusted for weight or BMI (Table 1).

Table 1. Baseline demographic characteristics (mean ± SD).

Variable	Group H (n = 58)	Group D (n = 60)	Group P (n = 59)	F	p
Age (years)	36.38 ± 12.33	38.83 ± 12.10	38.44 ± 12.64	0.666	0.515
Height (m)	1.62 ± 0.06	1.63 ± 0.05	1.64 ± 0.05	0.841	0.433
Weight (kg)	68.79 ± 9.48	71.78 ± 6.99	67.63 ± 9.42	3.62	**0.029***
BMI (kg/m²)	26.02 ± 3.87	27.09 ± 3.68	25.15 ± 3.93	3.83	**0.023***

*BMI, body-mass index; F, one-way ANOVA statistic. *Statistically significant (p < 0.05).*

Haemodynamic parameters

HR and MAP recorded after the study infusion and before the propofol bolus did not differ significantly among groups on the overall ANOVA (Table 2). Immediate post-injection HR and HR at 1 min did differ (p = 0.003 and p < 0.001), with the lowest rates in Group D, consistent with the known sympatholytic effect of dexmedetomidine. MAP did not differ significantly at any of the three time points.

Tukey HSD post-hoc pairwise tests (Table 3) showed that immediate HR was lower in Group D than in Group H (mean difference −5.58 beats/min; p = 0.002) and Group P (−5.06 beats/min; p = 0.005). At 1 min, HR was higher in Group P than in Group H (4.60 beats/min; p = 0.013) and Group D (7.72 beats/min; p < 0.001). A small difference in pre-injection MAP between Group P and Group H (−2.63 mmHg; p = 0.044) is of doubtful clinical importance and sits at the margin of the nominal 0.05 threshold after multiple testing.

Table 2. Heart rate and mean arterial pressure at three time points (mean ± SD).

Variable	Group H (n = 58)	Group D (n = 60)	Group P (n = 59)	F	p
HR before (beats/min)	89.19 ± 10.50	91.98 ± 10.04	91.66 ± 10.58	1.27	0.283
HR immediate (beats/min)	94.29 ± 10.44	88.72 ± 8.11	93.78 ± 10.55	5.92	**0.003***
HR at 1 min (beats/min)	89.52 ± 10.47	86.40 ± 7.70	94.12 ± 11.23	9.12	**<0.001***
MAP before (mmHg)	75.93 ± 7.05	75.55 ± 7.02	73.31 ± 6.86	2.43	0.091
MAP immediate (mmHg)	75.93 ± 7.83	73.63 ± 6.62	75.29 ± 7.27	1.58	0.208
MAP at 1 min (mmHg)	74.34 ± 7.49	72.58 ± 6.74	75.07 ± 7.39	1.86	0.157

*HR, heart rate; MAP, mean arterial pressure. "Before" is after the study infusion and immediately before the propofol test bolus. *Statistically significant (p < 0.05).*

Table 3. Tukey HSD post-hoc pairwise comparisons of HR and MAP (only contrasts with p < 0.05).

Variable	Comparison	Mean difference	p
HR immediate	Group D − Group H	−5.576 beats/min	**0.002***
HR immediate	Group D − Group P	−5.063 beats/min	**0.005***

HR at 1 min	Group P − Group H	4.601 beats/min	**0.013***
HR at 1 min	Group P − Group D	7.719 beats/min	**<0.001***
MAP before	Group P − Group H	−2.626 mmHg	**0.044***

*Only statistically significant pairwise contrasts are shown. *Statistically significant ($p < 0.05$).*

Incidence and severity of propofol injection pain

VCS category distribution differed significantly among the three groups (Fisher–Freeman–Halton exact test, $p < 0.001$; Pearson $\chi^2 = 50.99$, df = 6, reported descriptively; Figure 1 and Table 4). The proportion of patients completely free of injection pain (VCS 0) was highest in Group H (38/58; 65.5%), intermediate in Group D (21/60; 35.0%) and lowest in Group P (9/59; 15.3%). Pairwise contrasts of the pain-free proportion, with Bonferroni-adjusted two-sided $\alpha = 0.0167$, were: Group H versus Group P, risk difference 50.3 percentage points, relative risk 4.30 ($p < 0.001$); Group H versus Group D, risk difference 30.5 percentage points, relative risk 1.87 ($p = 0.0009$); Group D versus Group P, risk difference 19.7 percentage points, relative risk 2.29 (chi-square $p = 0.013$; Fisher exact $p = 0.019$). After Bonferroni correction, the H versus P and H versus D contrasts remained statistically significant. The D versus P contrast was significant on the unadjusted chi-square test ($p = 0.013$) but did not remain significant after Bonferroni correction (Fisher exact $p = 0.019$).

Any pain (VCS ≥ 1) occurred in 20/58 (34.5%) of Group H, 39/60 (65.0%) of Group D and 50/59 (84.7%) of Group P. Moderate pain (VCS 2) was present in 5/58 (8.6%) of Group H, 15/60 (25.0%) of Group D and 30/59 (50.8%) of Group P. Severe pain (VCS 3) occurred only in Group P (5/59; 8.5%); no patient in Group H or Group D reported severe pain.

Table 4. *Verbal Categorical Score (VCS) by group, n (%).*

VCS category	Group H (n = 58)	Group D (n = 60)	Group P (n = 59)	All (n = 177)
0 — no pain	38 (65.5%)	21 (35.0%)	9 (15.3%)	68 (38.4%)
1 — mild	15 (25.9%)	24 (40.0%)	15 (25.4%)	54 (30.5%)
2 — moderate	5 (8.6%)	15 (25.0%)	30 (50.8%)	50 (28.2%)
3 — severe	0 (0%)	0 (0%)	5 (8.5%)	5 (2.8%)
Any pain (VCS ≥ 1)	**20 (34.5%)**	**39 (65.0%)**	**50 (84.7%)**	**109 (61.6%)**

Primary analysis: Fisher–Freeman–Halton exact test, $p < 0.001$. Pearson $\chi^2 = 50.99$, df = 6 (descriptive). Groups are shown in the order H, D, P throughout.

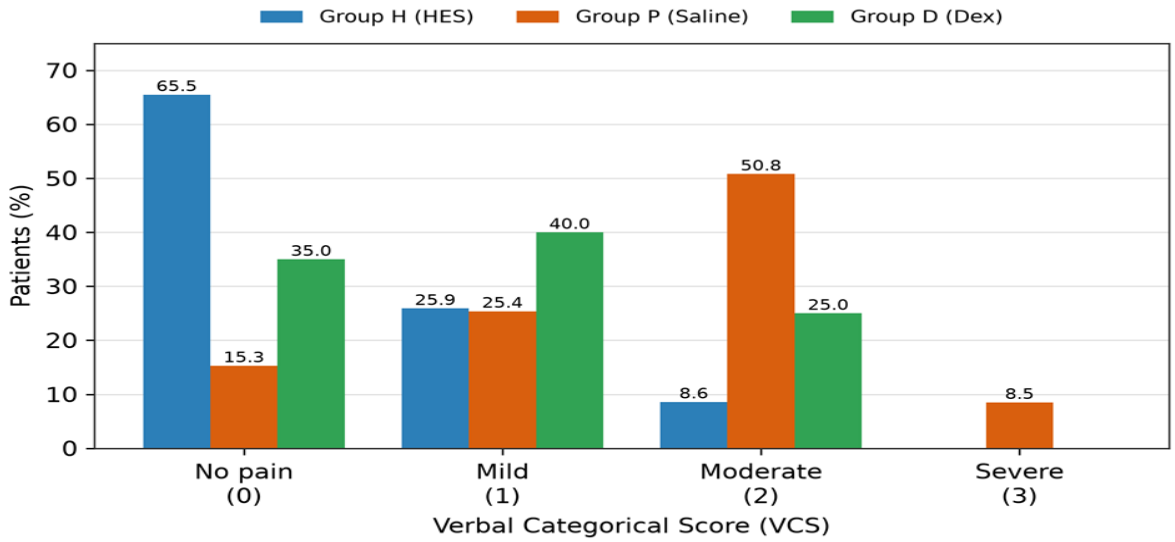

Figure 1. Distribution of Verbal Categorical Score categories across groups (percentage of patients). Fisher–Freeman–Halton exact test $p < 0.001$ (Pearson $\chi^2 = 50.99$ reported descriptively).

Pain scores on NRS and VCS

Mean scores on both scales differed among groups (Kruskal–Wallis test, overall $p < 0.001$ for each; Figure 2). Group H had the lowest mean NRS (0.83 ± 1.39) and VCS (0.43 ± 0.65). Group D was intermediate (NRS 1.83 ± 1.68; VCS 0.90 ± 0.77). Group P had the highest scores (NRS 3.51 ± 2.18; VCS 1.50 ± 0.86). VCS is an ordinal scale; the categorical distribution in Table 4 remains the principal analysis, and the mean ± SD values are descriptive only. Standard deviations that exceed the mean in Group H indicate right-skew, as expected when most patients report zero pain. The lignocaine admixture alone (Group P) did not abolish injection pain in this dorsal-hand, 30-s bolus model.

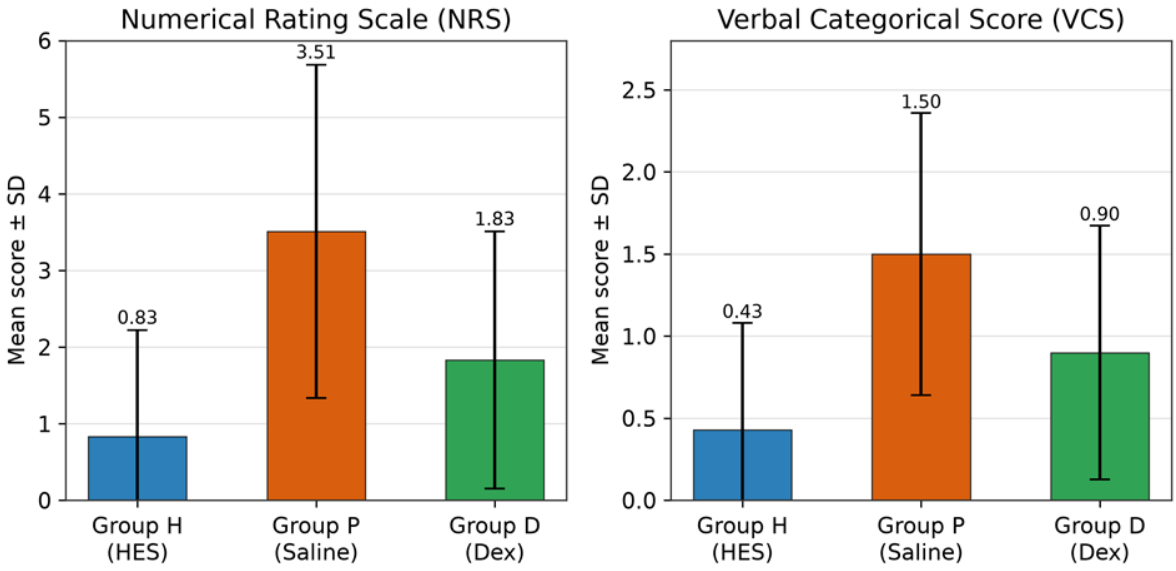

Figure 2. Mean ± SD Numerical Rating Scale and Verbal Categorical Score by group. Kruskal–Wallis $p < 0.001$ for both scales. Error bars represent one standard deviation.

Safety

No patient in the HES or dexmedetomidine arms reported severe injection pain. No hypersensitivity, clinically important bradycardia requiring treatment, or other adverse events were observed during the observation window. The lower HR in Group D was not accompanied by a significant difference in MAP but could theoretically have unblinded the injecting clinician.

Discussion

In this randomised, double-blind, three-arm study, pre-administration of 100 mL of 6% HES before a premixed propofol–lignocaine bolus produced the largest reduction in both the incidence and the severity of propofol injection pain. Almost two-thirds of patients in the HES group were free of pain, none had severe pain, and the absolute reduction in any-pain incidence versus the lignocaine-admixture control was 50.3 percentage points. Dexmedetomidine 0.5 µg/kg produced an intermediate effect: better than saline plus lignocaine, but clearly inferior to HES on both VCS and NRS. The haemodynamic pattern matched the pharmacology of dexmedetomidine, with lower HR immediately and 1 min after the bolus and no significant MAP difference.

These pain results are consistent with Misra et al., who found that 100 mL of 6% HES 130/0.4 given shortly before propofol reduced injection pain compared with saline, including when propofol was premixed with lignocaine.[14] Subsequent randomised comparisons of HES with lignocaine or saline have generally reported a higher pain-free rate after HES, although study size, HES volume (50 mL versus 100 mL), cannula site and co-

administration of lignocaine have varied. The proposed mechanism is dual: modification of endothelial junctions and permeability, with reduced kallikrein–kinin contact activation and less bradykinin-mediated stimulation of perivascular nociceptors. A further proposed mechanism is physical coating of the venous intima by the starch macromolecule, which may limit direct contact between aqueous-phase propofol and free nerve endings; this explanation is offered as a hypothesis rather than as a directly demonstrated effect in the present study. The present protocol cannot separate those two actions.

Dexmedetomidine's intermediate position is biologically plausible. Its α_2-mediated analgesia and sedation would be expected to blunt the affective component of injection pain, and the lower HR confirms that a pharmacologically active dose was delivered. It is not, however, primarily directed at the local kallikrein–kinin pathway that is thought to drive delayed propofol pain. Lu et al. likewise found that dexmedetomidine combined with cooled propofol–lignocaine attenuated but did not abolish injection pain.[15] The 0.5 μg/kg dose infused over 10 min is a conventional loading dose; larger or smaller doses were not tested.

Two design features are essential for interpretation. First, every patient received 20 mg of lignocaine mixed with the test bolus. Group P is therefore a lignocaine-admixture control, not an untreated placebo. The residual any-pain rate of 84.7% in that arm, using a dorsal hand vein and a 30-s injection, shows that lignocaine admixture alone was insufficient in this model—an observation that agrees with systematic reviews in which lignocaine reduces but does not eliminate pain.[5,13] Second, HES was given as a 10-min, 100-mL infusion immediately before the bolus, so any effect is that of pretreatment plus residual intravascular colloid, not of mixing HES with propofol. Other published strategies remain relevant context. Premixing lignocaine with a long-chain-triglyceride propofol emulsion produces less injection pain than some alternative emulsions.[16] Vein pretreatment with magnesium sulphate has been reported as not justified.[17] Lipid content of the emulsion influences both pain and pharmacodynamics.[18] The combination studied here—local anaesthetic admixture plus an endothelial-directed colloid—addresses two different proposed mechanisms and performed better than admixture plus a central α_2 agonist.

Regulatory and safety context must temper any recommendation to adopt HES for this indication. Hydroxyethyl starch products carry restrictions or boxed warnings in several jurisdictions because of signals for renal injury, coagulopathy and mortality in critically ill and septic patients.[19] The present population was ASA I–II elective surgical patients given a single 100-mL dose, which is far smaller than typical resuscitation volumes, and no adverse events were reported in the brief observation window. That is not evidence of long-term renal or haemostatic safety, and HES should not be used in patients who fall under current contraindications. Whether a non-HES colloid or a crystalloid of equal volume would reproduce the analgesic effect is unknown and is a logical next trial.

Limitations

This was a single-centre study. A prospective sample-size calculation was not documented. Allocation used sealed opaque envelopes. Pain scores are subjective; the assessor was blinded, but no objective surrogate of pain was recorded. Observation stopped at 1 min after the test bolus, so delayed pain after the full induction dose was not captured. Weight and BMI showed small but statistically significant baseline differences and were not adjusted for in the analysis. Two cells in the 3 × 4 VCS table were empty (no severe pain in Groups H and D), which is why the Fisher–Freeman–Halton exact test was used as the primary categorical analysis. The findings apply to adult ASA I–II patients receiving a dorsal-hand propofol–lignocaine bolus and may not generalise

to antecubital injection, other propofol emulsions or higher-risk patients.

Conclusion

In adults receiving a premixed propofol–lignocaine induction bolus through a dorsal hand vein, pre-administration of 100 mL of 6% HES reduced the incidence and severity of injection pain more than dexmedetomidine 0.5 µg/kg or a saline infusion of equal volume. Dexmedetomidine had an intermediate analgesic effect and lowered heart rate without a significant change in MAP.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed by the Institutional Ethics Committee of Apollo Institute of Medical Sciences and Research, Hyderabad, at its meeting on 6 November 2024 and was approved on 10 December 2024 (Regd No. EC/NEW/INST/1527/2024/11/219). Written informed consent was obtained from all patients before enrolment after the study procedure, its purpose, potential benefits and risks had been explained during the pre-anaesthetic visit.

Availability of data and materials

The anonymised individual-patient dataset supporting the findings of this study is available from the corresponding author on reasonable request, subject to institutional policy.

Competing interests

The authors declare that they have no competing interests.

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. Study drugs were taken from routine hospital stock.

Authors' contributions

D.O.: concept, design, conduct, statistical interpretation, manuscript drafting and corresponding author. U.G.: conduct, data acquisition and critical revision. R.S.S.: supervision, methodological oversight and critical revision. All authors approved the final manuscript.

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