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ORIGINAL RESEARCH

Comparison of Intravenous Dexmedetomidine, Ketamine, and Preservative-Free Lignocaine for Attenuation of Propofol Injection Pain: Randomized, Double-Blind Study

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ABSTRACT

Background and aims: Pain on propofol injection (POPI) occurs in 28%–98% of patients and remains a significant clinical drawback. Preservative-free lignocaine is widely used but fails in 13%–32% of cases. This study compared the efficacy of intravenous dexmedetomidine (0.25 mcg/kg), ketamine (0.2 mg/kg), and lignocaine (0.5 mg/kg) in alleviating POPI and their effects on haemodynamic parameters.

Methods: In this prospective, randomised, double-blind study, 150 ASA I–II patients (18–60 years) scheduled for elective surgery were randomised 1:1:1 into Group D (dexmedetomidine), Group K (ketamine), and Group L (lignocaine), n = 50 each. Study drugs were administered over 10 seconds following venous occlusion at 90 mmHg for 60 seconds. POPI severity was assessed using the McCrirrick and Hunter scale at 0, 30, and 60 seconds. Haemodynamic parameters were recorded at baseline, pre-induction, and one-minute post-induction.

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Results: Median POPI scores were 0, 1, and 0 for Groups D, K, and L, respectively, at all time points ($p < 0.001$). Blood pressure and heart rate declined progressively in Group D ($p < 0.001$) and rose progressively in Group K ($p < 0.001$), while Group L maintained haemodynamic stability across all parameters (SBP $p = 0.051$; DBP $p = 0.080$; MAP $p = 0.385$). Peripheral oxygen saturation remained above 97% in all groups with no significant inter-group difference ($p = 0.327$).

Conclusion: Both dexmedetomidine and lignocaine effectively alleviate POPI. Preservative-free lignocaine demonstrates superior haemodynamic stability and remains the preferred agent for routine clinical use. Dexmedetomidine is a viable alternative where mild sympatholysis is clinically acceptable.

Keywords: Propofol, pain on injection, dexmedetomidine, ketamine, lignocaine, general anaesthesia, haemodynamics

INTRODUCTION

Propofol is the most widely used intravenous anaesthetic induction agent, valued for its rapid onset, smooth induction, and antiemetic properties. Despite these advantages, POPI occurs in 28%–98% of adults and was ranked the seventh most important problem in contemporary anaesthetic practice, contributing to patient distress, sympathetic activation, and haemodynamic variability.[1,2]

POPI arises through two mechanisms: immediate activation of TRPA1/TRPV1 channels at vascular free nerve endings and delayed (10–20 seconds) bradykinin-mediated pain via the kallikrein-kinin cascade. Even medium-chain triglyceride reformulations of propofol have not eliminated POPI, which persists in up to 47% of patients.[3]

Pretreatment with preservative-free lignocaine under venous occlusion remains the most evidence-supported strategy, acting via voltage-gated sodium channel blockade,[5,6] yet carries a failure rate of 13%–32%, necessitating evaluation of alternatives. Dexmedetomidine, a selective alpha-2 agonist, attenuates POPI through peripheral enkephalin-like antinociception and prostaglandin-mediated vasodilatation. Ketamine, an NMDA receptor antagonist, acts via dissociative analgesia and sodium channel blockade. This study compared the efficacy of dexmedetomidine (0.25 mcg/kg), ketamine (0.2 mg/kg), and lignocaine (0.5 mg/kg) for POPI attenuation and their haemodynamic profiles.

MATERIAL AND METHODS

This prospective, randomised, double-blind study was approved by the Institutional Ethics Committee (CTRI/2023/12/060528). Written informed consent was obtained from all participants. One hundred and fifty ASA I–II patients aged 18–60 years undergoing elective surgery under general anaesthesia were enrolled. Exclusion criteria included drug hypersensitivity, seizure disorder, psychiatric illness, and substance abuse. Patients were randomised 1:1:1 via computer-generated sequence with allocation concealment using sealed opaque envelopes.

On arrival in the operating room, an 18-gauge peripheral intravenous cannula was inserted in the dorsum of the non-dominant hand, and standard monitoring was established.

An independent anaesthesiologist prepared all drugs in identical 5 mL syringes diluted with normal saline: Group D received dexmedetomidine 0.25 mcg/kg, Group K received ketamine 0.2 mg/kg, and Group L received preservative-free lignocaine 0.5 mg/kg. A pneumatic tourniquet was inflated to 90 mmHg, and the study drug was injected over 10 seconds. After 60 seconds of venous occlusion, the tourniquet was released, and 25% of the total propofol dose (2 mg/kg) was injected over 60 seconds.

POPI severity was assessed by a blinded observer using the McCrirrick and Hunter scale at 0, 30, and 60 seconds (0 = no pain; 1 = mild; 2 = moderate/arm withdrawal; 3 = severe with tears). Haemodynamic parameters (SBP, DBP, MAP, HR, SpO2) were recorded at baseline, pre-induction, and one-minute post-induction. The sample size was based on Aditya et al.,2, requiring a minimum of 44 patients per group (80% power; $\alpha = 0.05$); 50 were enrolled per group to account for dropouts. Data were analysed using SPSS v25.0. Kruskal-Wallis and Friedman tests compared pain scores; RM-ANOVA and Mixed ANOVA assessed haemodynamic trends. A p-value < 0.05 was considered significant.

RESULTS

All 150 enrolled patients completed the study without dropout or protocol deviation. Baseline demographics were comparable across groups (Table 1).

Median POPI scores at all three time points were 0 for Groups D and L and 1 for Group K. Intra-group variation was not significant across all groups. Inter-group differences were highly significant at all time points ($p < 0.001$, Kruskal-Wallis test) (Table 2).

SBP and DBP declined progressively in Group D ($p < 0.001$), rose progressively in Group K ($p < 0.001$), and remained stable in Group L (SBP $p = 0.051$; DBP $p = 0.080$). Inter-group differences were highly significant ($p < 0.001$) (Table 3).

Table 1: Baseline Demographic and Clinical Characteristics

Parameter	Group D (n=50)	Group K (n=50)	Group L (n=50)	*p*-value
Age (years), mean ± SD	36.2 ± 11.8	32.8 ± 11.2	35.4 ± 11.5	0.301†
Weight (kg), mean ± SD	55.6 ± 11.68	57.4 ± 11.85	55.3 ± 9.28	0.588†
Female, n (%)	40 (80.0%)	39 (78.0%)	40 (80.0%)	0.952‡
ASA I (n; %) ASA II (n; %)	18 (36%) 32 (64%)	18 (36%) 32 (64%)	14 (28%) 36 (72%)	>0.05‡

† One-way ANOVA; ‡ Chi-square test. SD = Standard Deviation; ASA = American Society of Anaesthesiologists.

Table 2: Median McCrirrick and Hunter Scale Scores Across Groups and Time Points

Study Group	n	0 sec	30 sec	60 sec	Intra-group p (Friedman test)
Group D (Dexmedetomidine)	50	0	0	0	0.874#
Group K (Ketamine)	50	1	1	1	0.942#
Group L (Lignocaine)	50	0	0	0	0.956#
Inter-group p (Kruskal-Wallis)		<0.001*	<0.001*	<0.001*	

*Median McCrirrick and Hunter scale scores. *Significant ($p < 0.05$); #Not Significant.*

Table 3: Mean Systolic and Diastolic Blood Pressure Across Groups at Different Time Points

Variable / Group	n	Baseline (mmHg)	At 0 min (mmHg)	At 1 min (mmHg)	Intra-group p (RM-ANOVA)
SBP – Group D	50	127.14	121.66	117.82	<0.00*
SBP – Group K	50	118.40	122.56	124.34	<0.001*
SBP – Group L	50	125.12	124.14	123.14	0.051#
SBP Inter-group (Mixed ANOVA) p<0.001*					
DBP – Group D	50	95.88	92.74	89.20	<0.001*
DBP – Group K	50	88.50	91.96	93.30	<0.001*
DBP – Group L	50	93.06	92.96	92.22	0.080#
DBP Inter-group (Mixed ANOVA): p<0.001*					

*SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; *Significant ($p < 0.05$); #Not Significant*

MAP declined significantly in Group D (95.88 → 89.20 mmHg; $p < 0.001$) and rose significantly in Group K (88.50 → 93.30 mmHg; $p < 0.001$), consistent with their respective sympatholytic and sympathomimetic profiles. Group L showed the most stable MAP (93.06 → 92.22 mmHg; $p = 0.385$). HR showed similar divergent trends. Inter-group differences were highly significant for both MAP and HR ($p < 0.001$) (Table 4).

Table 4: Mean Arterial Pressure and Heart Rate Across Groups at Different Time Points

Variable / Group	n	Baseline	At 0 min	At 1 min	Intra-group p (RM-ANOVA)
MAP (mmHg) – Group D	50	95.88	92.74	89.20	p<0.001*
MAP (mmHg) – Group K	50	88.50	91.96	93.30	p<0.001*
MAP (mmHg) – Group L	50	93.06	92.96	92.22	p=0.385#
MAP Inter-group (Mixed ANOVA): p<0.001*					
HR (bpm) – Group D	50	91.22	86.28	82.62	p<0.001*
HR (bpm) – Group K	50	87.46	90.08	91.40	p<0.001*
HR (bpm) – Group L	50	90.46	89.72	89.06	p=0.008*
HR Inter-group (Mixed ANOVA): p<0.001*					

*MAP = Mean Arterial Pressure; HR = Heart Rate; bpm = beats per minute; *Significant (p<0.05); #Not Significant*

Table 5: Mean Peripheral Oxygen Saturation Across Groups at Different Time Points

Study Group	n	Baseline (%)	At 1 min (%)	Intra-group p (RM-ANOVA)
Group D	50	99.18	99.72	<0.001*
Group K	50	99.40	97.80	0.440#
Group L	50	99.12	99.44	<0.001*
Inter-group p (Mixed ANOVA): p=0.327#				

*SpO2 = peripheral oxygen saturation; *Significant (p < 0.05); # Not Significant*

SpO_2 remained above 97% across all groups at all time points. Inter-group differences were not statistically significant (p = 0.327), with no clinically meaningful respiratory compromise observed in any group (Table 5).

DISCUSSION

Dexmedetomidine (0.25 mcg/kg) and preservative-free lignocaine (0.5 mg/kg) each achieved a median POPI score of 0, while racemic ketamine (0.2 mg/kg) scored 1 — significantly inferior to both ($p < 0.001$). Lignocaine was the only agent maintaining haemodynamic stability across all parameters.

The equivalence of dexmedetomidine and lignocaine is consistent with Sapate et al.,[4] Singh et al.,[7] and Aditya et al.2 At the highest level of evidence, Ji et al. confirmed in a meta-analysis that dexmedetomidine below 1 mcg/kg is not superior to lidocaine (pooled RR 1.28; 95% CI: 0.82–2.00).[9] In apparent contrast, Biswal et al. reported 54.74% POPI incidence with the same dose,[10] likely because they used 70 mmHg tourniquet pressure for 30 seconds versus 90 mmHg for 60 seconds in the current study – underscoring venous occlusion technique as an independent determinant of efficacy.

The inferior performance of ketamine (0.2 mg/kg) reflects sub-analgesic dosing; the threshold begins at 0.3–0.5 mg/kg. Studies finding ketamine superior to dexmedetomidine, such as Thukral et al., used 0.5 mg/kg.[11] Additionally, the R(−) enantiomer is three to four times less potent than S(+)-ketamine, leaving an effective S(+) dose of only ~0.1 mg/kg — insufficient for vascular sodium channel blockade. Esketamine dose-response data support this: POPI incidences of 29% and 9% were achieved with 0.15 and 0.3 mg/kg, respectively, the latter superior even to lidocaine.[13,14]

The haemodynamic superiority of lignocaine is supported by Jalota et al.'s meta-analysis of 177 RCTs (n = 25,260), which ranked lignocaine under venous occlusion among the two most efficacious single interventions for POPI,[15] and by Ranjini et al., who confirmed identical findings in a direct three-arm comparison.[16] Notably, dexmedetomidine's sympatholytic effect may confer a secondary advantage in patients requiring attenuation of the laryngoscopy stress response.

Limitations include: sub-analgesic ketamine dose; single-centre design; absence of a placebo arm; predominantly female cohort (79.33%); and lack of patient recall assessment. Future work should evaluate esketamine versus lignocaine under standardised conditions. Zeng et al.'s observation that ciprofol carries a pooled injection-pain risk ratio of 0.15 versus propofol raises the broader question of whether substituting induction agents may be the most practical long-term solution.[17]

CONCLUSION

Intravenous pretreatment with dexmedetomidine (0.25 mcg/kg) and preservative-free lignocaine (0.5 mg/kg) each effectively alleviates POPI with a median McCrirrick and Hunter score of 0. Racemic ketamine (0.2 mg/kg) was significantly inferior ($p < 0.001$). Preservative-free lignocaine maintains superior haemodynamic stability and remains the preferred agent for routine clinical use. Dexmedetomidine offers a viable alternative where mild sympatholysis is clinically acceptable.

AUTHORS' CONTRIBUTIONS

Conceptualization and design: SAK, PTS

Literature search: SAK, MS

Data collection: SAK, MS

Data analysis: SAK

Manuscript drafting and critical revision: SAK, MS, PTS

Proofreading and approval of the manuscript: SAK, MS

FUNDING

No external funding was received to prepare the manuscript.

DECLARATION OF CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

ETHICAL CLEARANCE

Approved by the Institutional Ethics Committee of the Shimoga Institute of Medical Sciences, Shivamogga, India (No: SIMS/ IEC/ 762/ 2022-23); Approval date: April 20, 2023.

The study was registered with the Clinical Trials Registry – India.

(CTRI No: CTRI/2023/12/060528)

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