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Research Article

EFFECT OF PROPOFOL TEMPERATURE (4°C VS ROOM TEMPERATURE) ON ATTENUATION OF INJECTION PAIN FOLLOWING PRETREATMENT WITH DEXMEDETOMIDINE

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ABSTRACT

Propofol is a widely used intravenous anesthetic agent known for its rapid onset and smooth recovery profile. However, pain on injection is a common side effect that can cause significant discomfort for patients. This study aimed to evaluate the effect of propofol temperature and dexmedetomidine pretreatment on injection pain. In this prospective, randomized, double-blind study, 120 patients scheduled for elective surgery under general anesthesia were randomly assigned to receive either propofol at 4°C or room temperature, with dexmedetomidine pretreatment in both groups. Pain was assessed using a 4-point verbal rating scale. The cold propofol group had significantly lower pain scores compared to the room temperature group (p=0.001), with 40% reporting no pain versus 23.3% in the room temperature group. Hemodynamic parameters remained stable and were similar between groups. Administering propofol at 4°C with dexmedetomidine pretreatment appears to be an effective method for reducing injection pain without compromising safety.

Keywords*: Propofol injection pain, Cold propofol (4°C), Dexmedetomidine, Pain attenuation, Induction of anesthesia.*

INTRODUCTION

Propofol (2,6-diisopropylphenol) has become one of the most commonly used intravenous anesthetic agents since its introduction into clinical practice in the 1980s [1]. Its popularity stems from its favorable pharmacokinetic profile, characterized by rapid onset of action, short duration of effect, and quick recovery [2]. These properties make propofol ideal for both induction and maintenance of anesthesia, as well as for sedation in various clinical settings.

Despite its many advantages, propofol is associated with a significant drawback: pain on injection. The incidence of pain during propofol administration has been reported to range from 28% to 90% of patients [3]. This pain can be moderate to severe in intensity and is often described as burning or stinging sensation. For many patients, it represents one of the most distressing aspects of the perioperative experience [4].

The mechanism of propofol-induced pain is multifactorial and not fully understood. Several theories have been proposed, includingDirect irritation of afferent nerve endings or free nerve endings by the lipid solvent in the propofol formulation [5].Activation of the kinin cascade, leading to bradykinin production and subsequent stimulation of nociceptors [6].Activation of transient receptor potential (TRP) channels, particularly TRPA1 and TRPV1, which are involved in pain sensation [7].

Given the high incidence and potentially distressing nature of propofol injection pain, numerous strategies have been investigated to mitigate this side effect. These include:Pharmacological interventions: Pre-treatment or admixture with various agents such as lidocaine, opioids, ketamine, and metoclopramide [8].Non-pharmacological methods: Altering injection speed, using larger veins, and diluting propofol [9].Temperature modification: Both warming and cooling of propofol have been studied [10,11].

Among these strategies, temperature modification of propofol has shown promise in several studies. The rationale behind cooling propofol is based on the hypothesis that lower temperatures may reduce the activation of pain receptors or slow the release of pain mediators [12]. Additionally, cold temperatures may have a local anesthetic-like effect on nerve endings.

Dexmedetomidine, a highly selective α2-adrenergic agonist, has gained popularity in anesthesia practice due to its sedative, anxiolytic, and analgesic properties [13]. Its use as a premedication agent has demonstrated efficacy in reducing propofol injection pain in some trials [14]. The combination of dexmedetomidine pretreatment with cold propofol administration represents a novel approach that has not been extensively studied.Given these considerations, there is a clear need for well-designed studies to evaluate the efficacy and safety of this combined approach.

AIMS

The primary aim of this study was to evaluate the effect of propofol temperature (4°C vs room temperature) on attenuation of injection pain following pretreatment with dexmedetomidine.

MATERIAL AND METHODS

Study Design and Setting: This prospective, randomized, double-blind study was conducted at Mahatma Gandhi Medical College and Hospital in Jaipur, India between September 2022 and March 2024. The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants.

Participants: A total of 120 patients were enrolled in the study based on the following criteria:

Inclusion criteria:

- Age 18-55 years
- ASA physical status I-II
- Scheduled for elective surgery under general anesthesia

Exclusion criteria:

- History of allergy to propofol or dexmedetomidine
- Neurological or psychiatric disease
- Use of analgesic medication within 24 hours before surgery
- Pregnancy or breastfeeding
- Inability to communicate or understand pain scales

Randomization and Blinding: Patients were randomly allocated into two groups of 60 each using a computer-generated randomization sequence. Group allocation was concealed in sealed opaque envelopes until the time of intervention.

Group A: Dexmedetomidine + Propofol at 4°C Group B: Dexmedetomidine + Propofol at room temperature

The anesthesiologist preparing and administering the medications was aware of the group allocation but was not involved in data collection. Patients and the researcher assessing outcomes were blinded to group assignment.

Intervention: In the operating room, standard monitors (ECG, non-invasive blood pressure, pulse oximetry) were applied and baseline vital signs recorded. An 18G intravenous cannula was inserted into a vein on the dorsum of the hand in all patients.

Dexmedetomidine 0.5 µg/kg was administered intravenously over 5 minutes in both groups using an infusion pump. After completion of dexmedetomidine infusion, propofol 0.5 mg/kg was injected slowly over 30 seconds.

In Group A, propofol was cooled to 4°C prior to administration by storing it in a refrigerator and confirming the temperature with a digital thermometer. In Group B, propofol was kept at room temperature (approximately 22-25°C).

Outcome Measures: Primary Outcome: Pain was assessed within 10 seconds of propofol injection using a 4-point verbal rating scale: 0 = No pain 1 = Mild pain (pain reported only in response to questioning without any behavioral signs) 2 = Moderate pain (pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning) 3 = Severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears)

Secondary Outcomes:

1. Hemodynamic parameters: Heart rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation were recorded at the following time points:
    - Baseline (before dexmedetomidine administration)
    - Immediately before propofol injection
    - 5 seconds after propofol injection

- 40 seconds after propofol injection

2. Adverse effects: Any occurrences of bradycardia (HR < 50 bpm), hypotension (SBP < 90 mmHg), desaturation (SpO2 < 92%), or other adverse events were recorded.

3. Patient satisfaction: 24 hours postoperatively, patients were asked to rate their satisfaction with the induction experience on a 5-point Likert scale (1 = very dissatisfied, 5 = very satisfied).

Sample Size Calculation: Based on previous studies, we estimated that a sample size of 54 patients per group would be required to detect a 30% difference in the incidence of pain between groups, with a power of 80% and a significance level of 0.05. To account for potential dropouts, we enrolled 60 patients per group.

Statistical Analysis: Statistical analysis was performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation and compared using independent t-test or Mann-Whitney U test, depending on the distribution of data. Categorical variables were presented as frequencies and percentages and analyzed using chi-square test or Fisher's exact test as appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

Demographic and Baseline Characteristics: A total of 120 patients were enrolled and randomized, with 60 patients in each group. All patients completed the study protocol and were included in the final analysis. The demographic and baseline characteristics were comparable between the two groups (Table 1).

Table 1: Demographic and baseline characteristics

Characteristic	Group A (n=60)	Group B (n=60)	p-value
Age (years), mean ± SD	37.7 ± 12.0	39.7 ± 12.7	0.386
Gender (M/F)	29/31	24/36	0.358
Weight (kg), mean ± SD	62.0 ± 8.4	60.7 ± 7.4	0.395
ASA status (I/II)	39/21	46/14	0.317
Hypertension, n (%)	12 (20.0)	10 (16.7)	0.637
Diabetes mellitus, n (%)	2 (3.3)	2 (3.3)	1.000

Primary Outcome: The incidence and severity of pain on propofol injection was significantly lower in Group A (cold propofol) compared to Group B (room temperature propofol) (p=0.001) (Table 2). In Group A, 40% of patients reported no pain, compared to only 23.3% in Group B. The incidence of moderate pain was also lower in Group A (10% vs 30%).

Table 2: Incidence and severity of pain on propofol injection

Pain score	Group A (n=60)	Group B (n=60)	p-value
No pain	24 (40.0%)	14 (23.3%)	0.001
Mild pain	30 (50.0%)	28 (46.7%)	
Moderate pain	6 (10.0%)	18 (30.0%)	
Severe pain	0 (0%)	0 (0%)	

Secondary Outcomes:

1. Hemodynamic Parameters: There were no significant differences in hemodynamic parameters between the two groups at any time point (Tables 3-6). Heart rate, blood pressure, and oxygen saturation remained stable throughout the study period in both groups.

Table 3: Comparison of heart rate (bpm) between groups

Time	Group A	Group B	p-value
Baseline	78.4 ± 8.2	78.2 ± 9.0	0.882
Before propofol	80.8 ± 6.3	81.6 ± 7.6	0.573
5s after propofol	76.5 ± 7.1	77.2 ± 8.3	0.612
40s after propofol	73.0 ± 6.0	71.9 ± 4.5	0.297

Table 4: Comparison of systolic blood pressure (mmHg) between groups

Time	Group A	Group B	p-value
Baseline	127.5 ± 8.0	125.3 ± 8.6	0.149
Before propofol	127.1 ± 6.5	125.0 ± 9.0	0.153
5s after propofol	122.3 ± 7.8	120.5 ± 8.7	0.246
40s after propofol	116.8 ± 7.1	114.1 ± 5.3	0.121

Table 5: Comparison of diastolic blood pressure (mmHg) between groups

Time	Group A	Group B	p-value
Baseline	79.7 ± 6.9	79.9 ± 5.6	0.862
Before propofol	79.8 ± 4.8	79.2 ± 4.6	0.484
5s after propofol	76.4 ± 5.5	75.8 ± 6.1	0.572
40s after propofol	72.2 ± 5.2	72.1 ± 4.7	0.883

Table 6: Comparison of oxygen saturation (%) between groups

Time	Group A	Group B	p-value
Baseline	99.8 ± 0.4	99.7 ± 0.5	0.225
Before propofol	99.9 ± 0.3	99.8 ± 0.4	0.124
5s after propofol	99.8 ± 0.4	99.7 ± 0.5	0.225
40s after propofol	99.7 ± 0.5	99.6 ± 0.6	0.312

2. Adverse Effects: No cases of clinically significant bradycardia, hypotension, or desaturation were observed in either group. Two patients in Group A and three patients in Group B reported mild shivering, but this did not reach statistical significance ($p = 0.648$).
3. Patient Satisfaction: Patients in Group A reported higher satisfaction scores compared to Group B, although the difference was not statistically significant (4.5 ± 0.6 vs 4.3 ± 0.7, $p = 0.082$).

DISCUSSION

This study aimed to evaluate the effect of propofol temperature (4°C vs. 25°C) on injection pain attenuation following dexmedetomidine pretreatment. The results demonstrate that administering propofol at 4°C significantly reduces injection pain compared to room temperature propofol, without compromising hemodynamic stability.

The demographic characteristics, including age, gender, weight, ASA status, and comorbidities, were comparable between the two groups. This similarity in baseline characteristics strengthens the validity of the observed differences in pain outcomes. The lack of significant differences in these factors suggests that the pain reduction effect can be primarily attributed to the temperature intervention rather than variations in patient demographics. This is consistent with previous studies, such as Ahmad S et al. [14], who also found no significant demographic differences between groups when studying the effects of propofol temperature on injection pain.

A key finding of this study was the statistically significant difference in pain levels between the two groups. Group A (propofol at 4°C) had a higher proportion of participants reporting no pain or mild pain compared to Group B (propofol at 25°C). This outcome aligns with previous studies investigating the impact of propofol temperature on injection pain. Lu et al. [15] reported that the combination of dexmedetomidine pretreatment and propofol at 4°C resulted in lower pain incidence and intensity compared to other pretreatment strategies. Similarly, Patel et al. [16] found that cooled propofol led to a higher incidence of mild to moderate pain compared to other pharmacological interventions.

The mechanism behind reduced pain with colder propofol is likely multifaceted. Lower temperatures may decrease vein irritation, slow the release of pain mediators, and provide a local anesthetic-like effect [12]. Additionally, the increased viscosity of cold propofol may result in less contact with free nerve endings in the vessel wall, further reducing pain sensation [17]. These mechanisms are supported by Iwata Met al [18], who proposed that cold temperature might reduce the activation of pain receptors and slow the release of pain mediators.

Dexmedetomidine pretreatment likely contributed to the overall low incidence of pain in both groups. As an α2-adrenergic agonist, it possesses analgesic and sedative properties that may synergistically enhance pain relief when

combined with cooled propofol [13]. The combination of dexmedetomidine and cold propofol appears to offer an additive or potentially synergistic effect in pain reduction.

Importantly, the study found no significant differences in hemodynamic parameters between the two groups at any measured time point. Heart rate, blood pressure, and oxygen saturation remained stable throughout the procedure in both groups. This finding is consistent with other studies, such as those by Lu et al. [15] and Patel et al. [16], which reported no significant differences in hemodynamic parameters between different pretreatment strategies. The stability of these parameters across groups indicates that the interventions were well-tolerated and did not result in clinically relevant alterations in cardiovascular or respiratory function. The effectiveness of cold propofol in reducing injection pain, as demonstrated in this study, is supported by previous research. Fletcher et al. [19] showed that warming propofol to 37°C reduced both the frequency and severity of injection-related discomfort compared to room temperature propofol. Our study extends these findings by demonstrating that cooling propofol may have an even more pronounced effect on pain reduction. This is further supported by McCrirrick and Hunter [20], who found that propofol at 4°C resulted in less pain than propofol at room temperature.

The combination of cold propofol and dexmedetomidine pretreatment appears to be a particularly effective strategy for mitigating propofol injection pain. This approach offers several advantages:

1. It is a simple and cost-effective intervention that can be easily implemented in most clinical settings.
2. It does not require additional medications or complex procedures, potentially reducing the risk of adverse effects or drug interactions.
3. The stable hemodynamics observed suggest that this combination can be safely used in ASA I-II patients.

These advantages are particularly relevant when considering the findings of Jalota et al. [21], whose meta-analysis found that the most effective single intervention for reducing propofol injection pain was the use of lidocaine with venous occlusion. Our combined approach of cold propofol and dexmedetomidine pretreatment may offer similar or superior pain reduction without the need for venous occlusion, which can be time-consuming and potentially uncomfortable for patients.

However, some practical considerations should be noted. Proper refrigeration facilities near the operating room and a system for maintaining the correct temperature during transfer and administration are necessary. Staff education on the importance of temperature control and proper handling is also crucial. The present study's findings are also consistent with the growing body of literature on multimodal approaches to reducing propofol injection pain. For example, Kwak et al. [22] found that combining remifentanil pretreatment with lidocaine mixed propofol was more effective than either intervention alone. Similarly, our combination of temperature modification and pharmacological pretreatment represents a multimodal approach that may offer superior results to single interventions.

It's worth noting that our study found no cases of severe pain in either group, which may be attributed to the use of dexmedetomidine in both arms. The absence of severe pain in our study suggests that the combination of dexmedetomidine and temperature modification may be particularly effective in mitigating the most distressing pain experiences associated with propofol injection.

Additionally, we did not explore the potential impact of propofol formulation on injection pain. Future studies could investigate whether the pain-reducing effect of cold temperature varies with different propofol formulations.

CONCLUSION

The present study compared the effectiveness of propofoladministraterd at different temperatures (4°C and room temperature) pretreatment with dexmedetomidine in reducing pain associated with intravenous propofol injection. The study found statistically significant differences in VRS with propofol administered at 4°C being less painful without any clinically relevant hemodynamic instability.

Overall, the present study adds to the growing body of evidence supporting the use of a combination of dexmedetomidine pretreatment and the administration of propofol at a lower temperature (4°C) as an effective approach to mitigate the pain experienced by patients during intravenous propofol injection.

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