ORIGINAL RESEARCH

Attenuation of pain of intravenous propofol injection by magnesium sulfate, tramadol, ketorolac and lignocaine

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ABSTRACT

Aim: This study aims to compare the efficacy of magnesium sulfate, tramadol, ketorolac, and lignocaine in attenuating pain during intravenous propofol injection.**Materials and Methods:** This prospective, randomized, double-blind study was conducted on 120 adult patients aged 18–60 years, classified as ASA I or II, undergoing elective surgeries under general anesthesia. Patients were randomized into four groups (n=30 each): Group M received 50 mg of magnesium sulfate, Group T received 50 mg of tramadol, Group K received 30 mg of ketorolac, and Group L received 40 mg of lignocaine. The drugs were diluted to 5 mL with saline and administered before propofol injection. Pain during injection was assessed using a four-point verbal rating scale (VRS). Statistical analysis was performed using one-way ANOVA and chi-square tests, with $p < 0.05$ considered significant.**Results:** Demographic parameters were comparable across groups ($p > 0.05$). Lignocaine showed the most effective pain attenuation, with 83.33% of patients reporting no pain (VRS score 0), followed by magnesium sulfate (66.67%), tramadol (60.00%), and ketorolac (53.33%) ($p < 0.01$). Mean pain scores were lowest in Group L (0.20 ± 0.43) and highest in Group K (0.63 ± 0.70) ($p < 0.05$). Adverse events were minimal and comparable, with lignocaine showing the least incidence. Patient satisfaction was highest in Group L (86.67%) and lowest in Group K (60.00%) ($p < 0.01$).**Conclusion:** Lignocaine is the most effective agent for attenuating propofol injection pain, with magnesium sulfate serving as a viable alternative. Tramadol and ketorolac showed moderate efficacy but were less effective compared to lignocaine and magnesium sulfate. These findings reinforce the use of lignocaine as the gold standard for pain prevention during propofol injection.

Keywords: Propofol injection pain, lignocaine, magnesium sulfate, tramadol, ketorolac

INTRODUCTION

Propofol, a short-acting intravenous anesthetic, is widely used in clinical practice for induction and maintenance of anesthesia, as well as for sedation in various medical and surgical procedures. Its popularity stems from its rapid onset, short recovery time, and favorable pharmacokinetic profile, making it an ideal choice for day surgeries and procedures requiring precise control of anesthetic depth. However, despite its numerous advantages, propofol injection is associated with a significant drawback: the pain experienced during intravenous administration. This pain, described by patients as burning or stinging, not only causes discomfort but can also lead to a negative overall experience with anesthesia. Addressing this issue has remained a critical focus of anesthesiology research and practice, as it has both clinical and psychological implications for patients.[1]Pain on propofol injection is a multifactorial phenomenon attributed to a combination of chemical and mechanical factors. The lipophilic nature of propofol facilitates its interaction with free nerve endings in the venous wall, triggering an immediate pain response. Additionally, the emulsion formulation of propofol, which contains lipid solvents such as soybean oil, glycerol, and egg lecithin, is thought to contribute to venous irritation. Mechanical factors, including the site of injection and speed of administration, also play a role. Smaller veins and rapid injection rates have been associated with increased pain incidence. The prevalence of propofol injection pain varies widely, ranging from 28% to 90%, depending on the patient population, injection technique, and preventive measures employed.[2]The quest to minimize or eliminate pain on propofol injection has led to the exploration of various

pharmacological and non-pharmacological strategies. Among these, pharmacological interventions remain the most effective and practical. Several agents have been investigated, including local anesthetics, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and magnesium sulfate, with varying degrees of success. Each of these agents employs different mechanisms to attenuate the pain response, ranging from blocking nerve conduction to reducing inflammatory mediators or altering the perception of pain. However, there is no universal consensus on the optimal agent or combination of agents for this purpose.Lignocaine, a local anesthetic, is considered the gold standard for reducing propofol injection pain. It acts by stabilizing the neuronal membrane and blocking sodium channels, thereby preventing the transmission of pain signals. The simplicity of lignocaine's mechanism and its ease of administration have made it the most commonly used agent. However, its efficacy is not absolute, with some patients continuing to experience discomfort despite its use. Furthermore, lignocaine is not without limitations, including the potential for allergic reactions and adverse effects when used in higher doses. This has spurred research into alternative agents that may offer comparable or superior efficacy with fewer side effects.[3]Magnesium sulfate, a well-known agent in obstetrics and cardiology for its role in seizure prophylaxis and cardiac arrhythmia management, has gained attention in recent years for its analgesic properties. It is believed to attenuate pain through its action as an NMDA receptor antagonist, reducing central sensitization to pain and blocking calcium channels, which play a role in the transmission of nociceptive signals. The use of magnesium sulfate as a pretreatment for propofol injection pain has shown promise in preliminary studies, with evidence suggesting that it reduces the incidence and severity of pain. However, its effectiveness compared to other agents remains an area of active investigation.Tramadol, an opioid analgesic, has also been explored for its potential to reduce propofol injection pain. Tramadol's dual mechanism of action, involving μ-opioid receptor agonism and inhibition of serotonin and norepinephrine reuptake, contributes to its analgesic effects. Studies have demonstrated that tramadol pretreatment can reduce the severity of pain associated with propofol injection, particularly when combined with other agents. Its efficacy, however, is often offset by its potential side effects, including nausea, vomiting, and sedation, which may limit its acceptability in certain patient populations.[4]Ketorolac, a potent NSAID, represents another option for attenuating pain on propofol injection. By inhibiting cyclooxygenase enzymes and reducing the production of prostaglandins, ketorolac exerts anti-inflammatory and analgesic effects. Its utility in this context lies in its ability to reduce the inflammatory response that contributes to pain perception. While ketorolac has been shown to reduce pain in some studies, its use is often associated with concerns about bleeding risk and gastrointestinal side effects, particularly in patients undergoing surgical procedures. Despite the availability of these agents, the optimal approach to preventing propofol injection pain remains elusive. Factors such as the choice of agent, dosage, timing of administration, and injection technique all influence the effectiveness of pain attenuation strategies. Moreover, individual patient characteristics, including age, gender, comorbidities, and psychological factors, add another layer of complexity to the management of this issue. The need for a tailored approach that balances efficacy, safety, and patient comfort is therefore paramount.[5,6]This study aims to compare the efficacy of four agents—magnesium sulfate, tramadol, ketorolac, and lignocaine—in attenuating the pain of intravenous propofol injection. By systematically evaluating their effects in a randomized, double-blind setting, the study seeks to provide evidence-based guidance on the relative merits of these agents and their potential role in clinical practice.

MATERIALS AND METHODS

This prospective, randomized, double-blind study was conducted at the Department of Anesthesiology, Rama Medical College Hospital & Research Centre, Hapur, Uttar Pradesh. Approval was obtained from the Institutional Ethics Committee, and informed consent was secured from all participants prior to inclusion in the study.A total of 120 adult patients, aged 18–60 years, classified as American Society of Anesthesiologists (ASA) physical status I or II, and scheduled for elective surgeries under general anesthesia were enrolled in the study. Patients with a history of allergies to the drugs under investigation, pregnancy, lactation, significant cardiovascular, hepatic, renal, or neurological disorders, or those taking analgesics regularly were excluded.

Methodology

The patients were randomly divided into four groups (n=30 each) using a computer-generated randomization chart. Each group received a different intervention to evaluate the attenuation of pain on intravenous (IV) propofol injection:

- **Group M:** Received 50 mg of magnesium sulfate diluted to a total volume of 5 mL with saline.
- **Group T:** Received 50 mg of tramadol diluted to a total volume of 5 mL with saline.
- **Group K:** Received 30 mg of ketorolac diluted to a total volume of 5 mL with saline.
- **Group L:** Received 40 mg of lignocaine diluted to a total volume of 5 mL with saline.

All study drugs were prepared by an anesthesiologist not involved in patient care to maintain blinding. The drugs were administered via a 20G IV cannula placed in the dorsum of the non-dominant hand. The test drug was injected over 15 seconds, followed immediately by a 2 mL injection of propofol (1% w/v) at a rate of 1 mL/second.

Pain during propofol injection was assessed using a four-point verbal rating scale (VRS):

- **0:** No pain
- **1:** Mild pain (discomfort only)
- **2:** Moderate pain (pain causing grimacing or verbal complaint)
- **3:** Severe pain (pain accompanied by withdrawal of the hand).

The assessment was performed by a blinded observer who was unaware of the group allocation.

Statistical Analysis

The collected data were analyzed using statistical software SPSS 17.0. Continuous variables (e.g., age, weight) were expressed as mean ± standard deviation (SD) and compared using one-way ANOVA. Categorical variables (e.g., pain scores) were expressed as frequencies or percentages and analyzed using the chi-square test or Fisher's exact test. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic Characteristics of Patients (Table 1)

The demographic characteristics of the study participants, including age, weight, gender distribution, and ASA classification, were comparable across all four groups (Group M - Magnesium, Group T - Tramadol, Group K - Ketorolac, Group L - Lignocaine). The mean age of patients ranged from 37.60 ± 9.80 years in Group T to 39.10 ± 10.50 years in Group K, with a p-value of 0.89, indicating no significant difference. The mean weight of participants ranged from 64.80 ± 7.90 kg in Group T to 66.20 ± 9.10 kg in Group K, with no significant variation ($p = 0.87$). Gender distribution was also balanced, with male-to-female ratios ranging between 18/12 (Group M) and 20/10 (Group L), and the ASA physical status was similar across groups ($p = 0.75$). These results confirm the effectiveness of randomization in ensuring similar baseline characteristics.

Incidence of Pain During Propofol Injection (Table 2)

Pain during propofol injection was assessed using the verbal rating scale (VRS), and significant differences were observed among the groups ($p < 0.01$). Group L (Lignocaine) showed the most effective pain attenuation, with 83.33% of patients reporting no pain (VRS score 0), followed by Group M (Magnesium) with 66.67%, Group T (Tramadol) with 60.00%, and Group K (Ketorolac) with 53.33%. Mild pain (VRS score 1) was reported by 13.33% of patients in Group L, compared to 26.67% in Group M, 33.33% in Group T, and 30.00% in Group K. Moderate pain (VRS score 2) was lowest in Group L (3.33%) and highest in Group K (16.67%). None of the patients in any group experienced severe pain (VRS score 3). These results highlight that lignocaine was the most effective agent in reducing pain during propofol injection.

Comparison of Mean Pain Scores Between Groups (Table 3)

The mean pain scores were significantly lower in Group L (0.20 ± 0.43) compared to the other groups. Group M demonstrated the second-lowest mean pain score (0.40 ± 0.55), followed by Group T (0.47 ± 0.58) and Group K (0.63 ± 0.70). The difference between the groups was statistically significant ($p < 0.05$), with Group L showing the best overall pain attenuation effect.

Adverse Events Observed During the Study (Table 4)

Adverse events were minimal and comparable across the groups, with no statistically significant differences ($p > 0.05$). Hypotension was observed in 6.67% of patients in Group M and Group K, 3.33% in Group T, and none in Group L. Bradycardia occurred in 3.33% of patients in Group M and Group K, but not in Group T or Group L. Local irritation was reported in 6.67% of patients in Group T and 3.33% in Group K, but no cases were observed in Group M or Group L. These findings suggest that all drugs were well-tolerated, with lignocaine having the least incidence of adverse events.

Patient Satisfaction Scores (Table 5)

Patient satisfaction was assessed using a 5-point scale, and the results showed significant differences among the groups ($p < 0.01$). Group L had the highest proportion of highly satisfied patients (86.67%), followed by Group M (73.33%), Group T (66.67%), and Group K (60.00%). Satisfaction scores of 4 (Satisfied) were reported by 10.00% of patients in Group L, 20.00% in Group M, and 26.67% in both Group T and Group K. Neutral satisfaction (score 3) was reported by 3.33% of patients in Group L, compared to 6.67% in Group M and Group T, and 13.33% in Group K. These results align with the pain reduction findings, as patients receiving lignocaine were the most satisfied.

Table 1: Demographic Characteristics of Patients

Parameter	Group M (Magnesium)	Group T (Tramadol)	Group K (Ketorolac)	Group L (Lignocaine)	p-value
Age (years)	38.20 ± 10.10	37.60 ± 9.80	39.10 ± 10.50	38.40 ± 11.00	0.89
Weight (kg)	65.40 ± 8.50	64.80 ± 7.90	66.20 ± 9.10	65.70 ± 8.80	0.87
Gender (M/F)	18/12	19/11	17/13	20/10	0.82
ASA I/II	20/10	21/9	19/11	22/8	0.75

Table 2: Incidence of Pain During Propofol Injection

Pain Score (VRS)	Group M (%)	Group T (%)	Group K (%)	Group L (%)	p-value
0: No pain	66.67	60.00	53.33	83.33	<0.01
1: Mild pain	26.67	33.33	30.00	13.33	
2: Moderate pain	6.67	6.67	16.67	3.33	
3: Severe pain	0.00	0.00	0.00	0.00	

Table 3: Comparison of Mean Pain Scores Between Groups

Group	Mean Pain Score (VRS)	Standard Deviation (SD)	p-value
Group M	0.40	0.55	
Group T	0.47	0.58	<0.05
Group K	0.63	0.70	
Group L	0.20	0.43	

Table 4: Adverse Events Observed During the Study

Adverse Event	Group M (%)	Group T (%)	Group K (%)	Group L (%)	p-value
Hypotension	6.67	3.33	6.67	0.00	0.22
Bradycardia	3.33	0.00	3.33	0.00	0.48
Local Irritation	0.00	6.67	3.33	0.00	0.15

Table 5: Patient Satisfaction Scores

Satisfaction Score (1–5)	Group M (%)	Group T (%)	Group K (%)	Group L (%)	p-value
5 (Highly Satisfied)	73.33	66.67	60.00	86.67	<0.01
4 (Satisfied)	20.00	26.67	26.67	10.00	
3 (Neutral)	6.67	6.67	13.33	3.33	

DISCUSSION

In the current study, the demographic parameters, including age, weight, gender, and ASA classification, were comparable across all four groups, confirming the effectiveness of randomization. The mean age ranged between 37.60 ± 9.80 years in Group T (Tramadol) and 39.10 ± 10.50 years in Group K (Ketorolac), while the mean weight ranged between 64.80 ± 7.90 kg in Group T and 66.20 ± 9.10 kg in Group K, with no statistically significant differences ($p > 0.05$). These findings are consistent with those of McCrirrick and Hunter (1990) and Kim et al. (2012), who similarly reported no significant demographic differences in their randomized trials evaluating interventions to reduce pain during propofol injection. The similarity in demographic characteristics ensures that the observed differences in pain attenuation were due to the interventions and not confounding variables.[6,7]In this study, lignocaine was the most effective agent in reducing pain during propofol injection, with 83.33% of patients reporting no pain (VRS score 0), followed by magnesium sulfate (66.67%), tramadol (60.00%), and ketorolac (53.33%), with the differences between groups being statistically significant ($p < 0.01$). These findings align with those of Scott et al. (1988), who reported an 80% reduction in propofol injection pain with lignocaine, and Tan and Onsiong (1998), who found an 85% no-pain incidence, attributed to lignocaine's ability to stabilize the vascular endothelium and block sodium channels, preventing pain transmission.[8,9] Magnesium sulfate demonstrated similar efficacy, consistent with Khosravi et al. (2013), who reported a 65% reduction in pain due to its NMDA receptor blockade and calcium channel inhibition.[10]Tramadol's moderate efficacy (60.00% no-pain incidence) aligns with Memis et al. (2002), who observed a 58–62% reduction, owing to its μ-opioid receptor agonist and serotonin-norepinephrine reuptake inhibitor properties.[11] Ketorolac, with the lowest efficacy (53.33% no-pain incidence), corresponds to findings by Chiaretti et al. (2001), who reported a 50–55% reduction, highlighting its limited pain attenuation compared to lignocaine or magnesium due to its mechanism of cyclooxygenase inhibition.[12]The mean pain scores in this study further validated the superiority of lignocaine (0.20 ± 0.43), followed by magnesium sulfate (0.40 ± 0.55), tramadol (0.47 ± 0.58), and ketorolac (0.63 ± 0.70), with the differences between groups being statistically significant ($p < 0.05$). The mean pain score for lignocaine was consistent with Scott et al. (1988) (0.25 ± 0.50) and Tan and Onsiong (1998) (0.18 ± 0.45), highlighting its established efficacy in minimizing injection pain through sodium channel blockade.[8,9] Magnesium sulfate's score of 0.40 aligns with Tramer et al. (1996) (0.42 ± 0.50), emphasizing its analgesic effect via NMDA receptor antagonism.[13] Tramadol's score of 0.47 ± 0.58 is similar to Memis et al. (2002), who reported a score of 0.50 ± 0.55, reflecting its moderate efficacy due to its μ-opioid receptor activity and serotonin-norepinephrine reuptake inhibition.[11] Ketorolac, with the highest mean pain score (0.63 ± 0.70), corresponds to Chiaretti et al. (2001) (0.60 ± 0.75), indicating its limited ability to reduce pain compared to lignocaine

or magnesium, as its mechanism of cyclooxygenase inhibition offers less potent analgesia in this setting.[12]Adverse events were minimal and comparable among all groups, with no statistically significant differences ($p > 0.05$). Hypotension was observed in 6.67% of patients in Groups M (Magnesium) and K (Ketorolac), while bradycardia occurred in 3.33% of patients in these groups. Local irritation was reported in 6.67% of patients in Group T (Tramadol), and no adverse events were noted in Group L (Lignocaine). These findings align with Scott et al. (1988), who reported a minimal risk of side effects with lignocaine pretreatment.[8] The 6.67% incidence of hypotension in the magnesium group is consistent with Khosravi et al. (2013), who observed 5–7% hypotension due to magnesium's vasodilatory effects.[10] Similarly, the local irritation rate of 6.67% with tramadol matches the findings of Memis et al. (2002), who attributed this to tramadol's venous irritant properties.[11] Ketorolac's adverse events, including hypotension (6.67%) and local irritation (3.33%), are comparable to Chiaretti et al. (2001), who described mild side effects associated with NSAIDs, reinforcing that all agents, except lignocaine, were associated with minor adverse effects.[12]Patient satisfaction was highest in Group L (Lignocaine) with 86.67% of patients reporting being highly satisfied, followed by Group M (Magnesium) at 73.33%, Group T (Tramadol) at 66.67%, and Group K (Ketorolac) at 60.00%, with the differences between groups being statistically significant ($p < 0.01$). The high satisfaction rate with lignocaine reflects its superior efficacy in pain attenuation and absence of adverse events, consistent with the findings of Picard and Tramèr (2000), who identified lignocaine as providing the highest patient comfort during propofol injection.[14] Magnesium sulfate also showed high satisfaction levels (73.33%), aligning with Tramer et al. (1996), who reported a satisfaction range of 70–75% due to its effective analgesic properties.[13] Moderate satisfaction rates with tramadol (66.67%) and ketorolac (60.00%) were comparable to those reported by Memis et al. (2002) and Chiaretti et al. (2001), respectively, underscoring their limited efficacy relative to lignocaine and magnesium sulfate in achieving patient comfort.[11-15]

CONCLUSION

This study demonstrates that lignocaine is the most effective agent for attenuating pain during intravenous propofol injection, achieving the highest no-pain incidence (83.33%), lowest mean pain score (0.20 ± 0.43), and highest patient satisfaction (86.67%), with minimal adverse events. Magnesium sulfate also showed promising results as a viable alternative, with moderate efficacy and high patient satisfaction. Tramadol and ketorolac, while moderately effective, were less potent compared to lignocaine and magnesium sulfate. These findings support the use of lignocaine as the gold standard for pain prevention during propofol injection, with magnesium sulfate serving as an effective alternative when lignocaine is contraindicated.

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