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Research Article

COMPARISON OF INTRAVENOUS LIGNOCAINE, TRAMADOL, AND KETOROLAC FOR ATTENUATION OF PROPOFOL INJECTION PAIN

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ABSTRACT

Objective: This study aims to study and compare the efficacy of lignocaine, tramadol, and ketorolac in minimizing propofol injection pain.

Methods: This is a randomized control research that was conducted on 100 patients between the ages of 18 and 60 years at the department of anesthesiology and critical care. Being planned for elective surgery under general anesthesia with propofol as an inducing drug, with an ASA grade I or II body mass index of 19–30 kg/m^2. Each of the four groups of 25 patients was randomly selected from among all the patients.

Results: The incidence of pain was 20% in the lignocaine group and 28% in the groups treated with tramadol and ketorolac. 92% of patients in the normal saline group felt discomfort during the propofol injection. In comparison to group N (7.46±2.78), the mean pain score in groups L (0.80±1.32), T (0.98±1.70), and K (1.49±1.55) was statistically significant ($p<0.0001$). Group N saw noticeably less side effects than the other groups. Statistics showed that groups L, T, and K were comparable.

Conclusion: We recommend the use of these agents as pre-treatment to propofol to increase the patient acceptability of this ideal anesthetic agent.

Keywords: Ketorolac, Propofol, Lignocaine, Tramadol.

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INTRODUCTION

A number of anesthetic medications, including diazepam, etomidate, and propofol, have limited uses because of injection-related pain. A common induction drug is propofol, which is particularly useful in brief instances, day surgery procedures, and situations requiring a laryngeal mask. Propofol is a chemical member of the sterically hindered phenols group. Propofol irritates the skin, mucous membranes, and venous intima, just like other phenols do [1].

Because of its quick start, brief duration of action, ease of titration, and favorable side effect profile, propofol is the medication of choice for inducing anesthesia in millions of patients each year. One significant restriction on the usage of propofol is the reported pain experienced during injection. When importance and frequency are taken into account, propofol-induced pain has been placed eighth out of 33 clinical concerns. It can occasionally cause significant anguish to the patient.

An injection of propofol may cause acute pain or delayed pain. Propofol injections cause immediate vascular discomfort, which is thought to be caused by the drug's direct irritating action on venous nociceptive receptors or free nerve endings, which then transmit the nerve impulse to the central nervous system through thin, myelinated delta fibers.

The local Kallikrein–Kinin cascade, which causes venous dilatation and hyperpermeability and, most likely, facilitates contact between free propofol and free nerve endings within the vascular wall, is thought to be activated by the delayed pain that manifests after 10–20 s [2].

Many pharmacological and non-pharmacological approaches have been tried to reduce the pain that propofol injections induce. Selecting a bigger vein, accelerating the injection pace, chilling the propofol solution, diluting it with 5% dextrose, and blocking the vein beforehand are examples of non-pharmacological techniques.

Medications that lessen pain include lignocaine, tramadol, dexamethasone, butorphanol, ketorolac, ondansetron, magnesium sulfate, metoclopramide, and thiopentone. These are examples of pharmacological approaches. None of the aforementioned strategies have been able to completely reduce the pain associated with propofol injection, despite some of them showing encouraging results. As a result, research is still ongoing to find the best agent or intervention that would make administering anesthesia with propofol a pleasurable experience.

Due to its local anesthetic qualities, lignocaine, a short-acting local anesthetic, is known to lessen pain during propofol injections. Although it is regarded as the gold standard, it is not always successful in preventing pain. The kinin cascade may be stabilized by lignocaine. It has been discovered to work better when premixed with propofol rather than injected alone. This could be because less pre-injected lignocaine was available to stabilize the kinin cascade because it was washed away in circulation before the propofol bolus. Smith and Power proposed that IV nonsteroidal anti-inflammatory drugs (NSAIDs) lessen the pain associated with propofol injections by blocking the vein wall's prostaglandin production pathways [3].

One NSAID medication that can be used to reduce discomfort following surgery is ketorolac. In addition, it is a cyclooxygenase (COX) inhibitor that stops the production of prostaglandins. The COX pathway may be the cause of injection discomfort from propofol [2,4]. Right now, the most often prescribed opioid worldwide is tramadol. It is a medication with central action that works well to treat moderate to severe pain. A weak agonist of the μ receptor with central action is tramadol. It increases serotonin release and decreases the absorption of adrenaline. Numerous investigations have been conducted to evaluate a broad spectrum of medications for reducing discomfort during propofol injection. In this study, we assessed and contrasted tramadol, lignocaine, and ketorolac's ability to reduce pain following a propofol injection.

METHODS

It is randomized control study done at the Department of Anaesthesiology and Critical Care, Gandhi Medical College, Secunderabad, 18 months (from January 2021 to June 2022).

Inclusion criteria

Patients aged between 18 and 60 years. Belonging to ASA grade I or II, body mass index between 19 and 30 kg/m^2.

Exclusion criteria

Individuals who struggle with communication, expectant or nursing mothers, those with a history of epilepsy, cardiac conduction problems, antiarrhythmic medications or analgesics, lipid metabolic disorders, bronchial asthma history, allergy history to propofol, NSAIDs, eggs, and morbid obesity.

Gandhi Medical College's Institutional Ethical Committee granted the study approval in Secunderabad. Every patient who was part of the trial gave written informed consent. One hundred adult patients who were scheduled for elective surgery under general anesthesia with propofol as the inducing agent, classified as ASA grade I and II, participated in the study. Each of the four groups of 25 patients was randomly selected from among all the patients.

Table 1: Age distribution among study subjects

Age group	Group L (%)	Group T (%)	Group K (%)	Group N (%)
11–20	0 (0)	0 (0)	1 (4)	1 (4)
21–30	6 (24)	5 (20)	3 (12)	4 (16)
31–40	9 (36)	10 (40)	9 (36)	8 (32)
41–50	7 (28)	8 (32)	11 (44)	10 (40)
51–60	3 (12)	2 (8)	2 (8)	2 (8)
Gender				
Male	12 (48)	10 (40)	11 (44)	12 (48)
Female	13 (52)	15 (60)	14 (56)	13 (52)
ASA Grade				
I	16 (64)	19 (76)	20 (80)	18 (72)
II	9 (36)	6 (24)	5 (20)	7 (28)

Table 2: Incidence of pain among study groups

Group	Number of patients with pain on propofol injection	Percentage
Group L	5	20
Group T	7	28
Group K	7	28
Group N	23	92

Table 3: Mean score of pain among study groups

Group	Mean±SD
Group L	0.80±1.32
Group T	0.98±1.70
Group K	1.49±1.55
Group N	7.46±2.78

Group L: Received a 60 mg intravenous injection of lignocaine. Group T: Received a 50 mg intravenous injection of tramadol. Group K: 10 mg of ketorolac was administered intravenously. Group N: Received a 3 mL intravenous injection of normal saline.

A thorough history was obtained the night before the procedure, and a preoperative clinical examination was performed. Standard tests included blood urea, serum creatinine, RBS, hemoglobin, chest X-ray (PA view), electrocardiogram, and blood urea concentration. Patients were given nothing by mouth starting at 0 h. Before the procedure, no pre-medication was administered.

The patient's usual saline infusion was initiated as soon as they arrived in the pre-operative room and an 18 Gauge intravenous cannula was inserted into the biggest vein on the dorsum of their hand. Standard ASA monitors were connected once the patient was moved to the operating room, and it was informed to them that the intravenous anesthetic they would be receiving would cause discomfort during the injection.

The patient was directed to use a Visual Analog Scale (VAS) ranging from 0 to 10 to rate their level of pain for the investigator. Being painless 10: The most agonizing agony.

Following the patient's instructions, the IV infusion was stopped, and the IV line-attached arm was raised for 15 s to allow the venous blood to drain naturally. To cause venous occlusion, a pneumatic tourniquet was applied to the arm with pressure raised to 70 mmHg. For 3 min, patients received 100% oxygen preoxygenation. The study was conducted in a double-blind manner. The anesthesiologist who recorded the pain score was blinded to the pre-treatment medication during the study.

An investigator made sure of this by filling the syringe with the medication before giving it to the anesthesiologist.

Every medication was made in a 3 mL amount and diluted using regular saline. Every injection was administered at a rate of 0.5 mm/s using an intravenous cannula. The tourniquet was released 1 min after the drug under study was injected, and an intravenous infusion of propofol (2.5 mg/kg) at a rate of 0.5 mL/s was then administered to induce anesthesia. Before the patient passed out, their pain was measured using the VAS. If more anesthesia was thought to be required, it was administered. In addition, the presence or absence of redness in the arm was noted.

Statistical analysis

All the results were tabulated and analyzed using the one-way ANOVA and z-test.

RESULTS

The age group of 31–40 years old comprised the majority of patients in all four study groups: L, T, and K (36%, 40%, and 36%, respectively). In Group N, however, 40% of the patients belonged to the age range of 41–50 years old (Table 1).

In comparison to male patients, the percentage of female patients was marginally higher in each of the four study groups (52%, 60%, 56%, and 52% in Groups L, T, K, and N, respectively) (Table 2).

Table 4: Comparison of side effects among study groups

Group	Side effects (%)							
	Pain	Redness	Nausea	Vomiting	Headache	Bradycardia	Hypotension	Swelling
L	5 (20)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (8)
T	6 (24)	2 (8)	3 (12)	0 (0)	0 (0)	1 (4)	1 (4)	0 (0)
K	7 (28)	3 (12)	2 (8)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)
N	24 (96)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
p-value	0.02	0.001	0.026	0.034	0.01	0.001	0.041	0.038

Table 5: Comparison between groups for incidence of side effects among pre-treatment drug

Group	Z value	p-value	Significance
L versus T	0.77	>0.05	Not significant
L versus K	0.41	>0.05	Not significant
L versus N	1.79	0.001	Significant
T versus K	0.37	>0.05	Not significant
T versus N	2.36	0.002	Significant
K versus N	2.09	0.003	Significant

In Groups L, T, K, and N, the majority of patients (64%, 76%, 80%, and 72% in Groups L, T, K, and N, respectively) were classified as ASA grade I.

The incidence of pain was 20% in the lignocaine group and 28% in the groups treated with tramadol and ketorolac. 92% of patients in the normal saline group felt discomfort during the propofol injection.

The mean pain score in group L (0.80±1.32), T (0.98±1.70), and K (1.49±1.55) was statistically significant when compared to group N (7.46±2.78) (p<0.0001) (Table 3).

Group N saw noticeably less side effects than the other groups. Comparable groups were L, T, and K. Group N comprised the majority of patients with pain (96%), whereas group L had the lowest percentage of patients with pain (20%). Three patients in group K and two patients in group T (8%), respectively, showed signs of redness. The highest number of patients experiencing nausea among the four trial groups three was found in group T. Not one of the research subjects vomited. The only patient with a headache in the ketorolac group was 1. Tramadol was given to a patient who experienced bradycardia and hypotension. No patients in groups T, K, or N experienced swelling at the injection site; only two patients in the lidocaine group did. Two patients in the lidocaine group had swelling at the injection site, while no other patients in groups T, K, and N had swelling (Table 4).

DISCUSSION

A popular induction drug is propofol, an intravenous sedative and hypnotic. It is a fast-acting substance that consistently induces unconsciousness and loss of respiratory reflexes, facilitating a swift and easy recuperation from anesthesia. Propofol's well-known injection-related pain is still a drawback for this medication when used in clinical settings, despite its well-established superior anesthetic qualities [5].

Studies involving propofol injections into an intravenous catheter in the back of the hand or the forearm cephalic vein revealed a 68–72% incidence of pain. It is believed to be correlated with the aqueous phase's concentration of propofol. The activation of nociceptors and nerve endings is the initial part of pain following a propofol injection. The delayed component of pain manifests after a minute and is mediated by bradykinins through the plasma Kallikrein–Kinin system. Bradykinins increase the interaction between the aqueous phase and free nerve endings, creating hyperpermeability and local vasodilatation that in turn generate pain. According to Özaktay *et al*. [6], prostanoids, in particular prostaglandin E2, may mediate pain. Pain obstructs patient happiness and creates negative recollections of the induction process.

The osmolality of the preparation solvent, the pH of the solution, and the concentration of propofol in the aqueous phase are the additional parameters that cause pain.

Numerous strategies have been studied in an effort to reduce the pain related to propofol injections. Large forearm vein injections also lessen discomfort, most likely by minimizing drug-endothelium contact. It is common practice to provide lignocaine either with or before injecting propofol. After researching the best dosage of lidocaine for propofol pain, Gajraj and Nathanson [7] came to the conclusion that 30 mg of lidocaine is the best amount for attenuating propofol discomfort.

As a centrally acting receptor agonist, tramadol increases the release of serotonin while blocking the absorption of norepinephrine. Using a tourniquet to isolate the arm vein from the rest of the circulation – akin to a modified bier's block – offers a helpful model for examining a drug's peripheral effects when there is no central effect. In our investigation, venous occlusion was created by applying a pneumatic tourniquet to the arm with an inflated pressure of 70 mmHg, which allowed the predrug to stay in the vein for a minute.

According to Destro *et al*., [8] ketorolac must be in the vein for a longer period to have the hypothesized localized anti-prostaglandin impact and decrease kininogen release.

The incidence of pain in group N in the current investigation, where propofol was administered without prior therapy, was found to be 92% with a VAS of 7.46±2.78. This was similar to studies conducted by Mangar and Holak [9], which found 90%, and Bashir *et al*. [10], which showed 96.7%.

With a mean VAS of 0.72±1.62, the incidence of pain during propofol injection following lignocaine (60 mg) pre-treatment is 24% in the current study. According to Ganta and Fee [11], 21% of patients had pain with propofol administration following lignocaine. Lignocaine acts on excitable membranes in the arm to reversibly block peripheral nerve pathways.

In the current investigation, 28% of patients had propofol injection pain following a 50 mg tramadol pre-treatment, with a mean VAS of 0.98±1.70. The results are comparable to the result shown by Madan *et al*. [12] (28%), Pang *et al*. [13], were 23%, Wong *et al*., was 30% [6], Goel *et al*. [14] was 25% and Bashir *et al*. [10], was (26.7%).

According to Mok Martin *et al*. [15], tramadol caused a transient local sensory block. Tramadol's analgesic efficacy in lowering the pain associated with propofol injections may be explained by its local anesthetic action (Table 5). Since the majority of studies utilized 1 mg/kg of tramadol, we used 50 mg, which is similar to 1 mg/kg. Our findings about the efficacy of tramadol pre-treatment for pain from propofol injection are in line with those of other studies. In our study, the mean VAS was 1.49±1.55 and the incidence of pain on propofol injection after ketorolac 10 mg pre-treatment was found to be 28%. Following pre-treatment with ketorolac, the incidence of propofol injection discomfort was reported by Madan *et al*. [12] (28%) and Goel *et al*. to be 25% [14].

Since a tourniquet was not employed to retain the ketorolac, the incidence of propofol injection pain was not significantly reduced by ketorolac pre-treatment in the Smith and Power research [16]. According to Yull *et al*. [17], administering 10 mg of ketorolac together with venous occlusion for 2 min lowers the likelihood of experiencing significant discomfort after receiving a propofol injection. The incidence of pain did not reduce with the same dose of ketorolac in the absence of venous blockage. It has been proposed, therefore, that NSAIDs probably require time to inhibit the route; thus, the drug's activity may require keeping it in the vein for a while.

The same level of pain alleviation as ketorolac 10 mg IV with venous occlusion was obtained by pre-treatment with either 15 or 30 mg of the drug, according to Huang *et al*. [18]. However, 23.3% of patients still experienced injection pain. When compared to normal saline without a tourniquet, Kaya *et al*. [19] on 100 women revealed that the administration of lidocaine with venous occlusion for 60 s considerably reduced the occurrence and degree of pain during the propofol injection.

Another study by Johnson *et al*. [20] found that all groups receiving lidocaine experienced a considerable reduction in pain, with the amount of pain relief being directly correlated with the quantity of lidocaine administered.

The current conclusion is in line with research conducted by Sumalatha *et al*. [21], who examined how lignocaine, ondansetron, and ramosetron affected the attenuation of pain caused by a propofol injection. According to the study's findings, pre-treatment with intravenous ramosetron 0.3 mg is superior than ondansetron and equally efficient in avoiding propofol-induced pain when compared to 0.5 mg/kg of 2% lignocaine.

In comparison to a placebo, pre-treatment with tramadol 60 s before propofol injection and the propofol-lidocaine mixture considerably reduced the discomfort associated with propofol administration in children, according to a study by Borazan *et al*. [22] involving 120 ASA I and II patients. According to Sasaki *et al.* findings [23], applying a tourniquet simultaneously with preinjected lidocaine enhanced its analgesic effects. For the best prevention of propofol-induced vascular discomfort, lidocaine should be given before propofol injection, according to a meta-analysis by Picard and Tramèr [24].

According to Tsai *et al*. [25], tramadol blocks the conduction of motor and sensory nerves by means of voltage-gated sodium channels, which in turn induces axonal blockage. The Pang *et al*. group [13]. Tramadol caused substantially more local skin responses and transient minor injection pain than lidocaine ($p<0.05$). When compared to normal saline, both tramadol and lidocaine significantly reduced the occurrence and intensity of propofol injection discomfort ($p<0.05$).

In a different study conducted by Patilbuwa and Yarramalle [26], the average VAS score for metoclopramide, ketamine, and lignocaine was measured. The results showed that metoclopramide had a score of 3.120±1.666, and ketamine had a score of 2.320±0.945. This suggests that lignocaine ($p<0.01$) reduces pain more effectively than ketamine. Our study's findings are also similar to those of other research that found that administering 40 mg of lidocaine as a pre-treatment increased the incidence of propofol injection pain to 21.7%.

This result is in line with research conducted by Kaya *et al*. [19], who reported less pain from propofol injections than we did. Their findings may have been influenced by the fact that they used a tourniquet to obstruct the vein for 60 s, injected propofol sporadically, and titrated the drug before injection.

The incidence of side effects (pain and local redness) of lignocaine pre-treatment in this study was 8%. It is comparable to the results of Madan *et al*. [12] (12%), Pang *et al*. [13] 14% and Mok Martin *et al*. [15] 14%. In our study, the incidence of tramadol injection side effects (pain and local redness) was 16%; of these, 12% of patients reported pain, and 1 patient reported local redness at the injection site. The incidence of side effects (pain and local redness) at the site of tramadol injection is comparable to the result shown by Goel *et al*. [14] 15%, Mok Martin *et al*. [15], 22%, Madan *et al*. [12], 23.2% (redness - 13.2%).

Most injectable NSAIDs cause pain and redness at the injection site. Ketorolac side effects were 12% in frequency, with 8% being pain and 4% being soreness and redness. This incidence is similar to that reported by Goel *et al*. [14], Yull *et al*. [17], (15% complained of pain, 5% complained of redness at the local location, and 5% complained of both pain and redness). Compared to tramadol and ketorolac, lignocaine seems to be more tolerable despite not being much different in terms of adverse effects.

CONCLUSION

There was a statistically significant difference in side effects between the study groups (<0.05). Thus, pretreatment with any of these three medications greatly lessens the discomfort associated with propofol injections. However, lignocaine was more tolerable than tramadol and ketorolac because it caused less pain and had fewer adverse effects. To improve patient acceptance of this perfect anesthetic, we advise using these medications before administering propofol.

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