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Original Article

Anaesthesia Section

Comparsion of Intravenous Lignocaine, Tramadol and Keterolac for Attenuation of Propofol Injection Pain

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ABSTRACT

Introduction: Propofol possesses many characteristics of an ideal intravenous anaesthetic agent, providing a smooth induction and a rapid recovery. However, it has been reported to evoke considerable pain on injection in 10-100% of patients. The cause of pain upon intravenous injection of propofol remains a mystery.

Aim: To study and compare the efficacy of Lignocaine, Tramadol and Ketorolac in minimizing the propofol injection pain.

Materials and Methods: Hundred adult patients (ASA grade I and grade II) scheduled for elective surgery under general anaesthesia with propofol as an inducing agent were considered for the study. Patients were randomly divided into 4 groups of 25 patients each Group L (lignocaine) Group T (tramadol) Group K (ketorolac) and Group N (normal saline). Pain scores were measured by the investigator immediately following injection of propofol. All patients' responses were graded by a verbal pain score.

Results: All the results were tabulated and analysed using the one-way ANOVA and z-test. There was no statistically significant difference among group L (24%), T (28%) and K (28%) for pain on injection, but significant difference of all 3 groups was there when compared with group N.

Conclusion: Intravenous lignocaine, tramadol and ketorolac all 3 drugs significantly reduce propofol injection pain. However, lignocaine appears to be more acceptable cause of less pain and fewer side effects as compared to tramadol and ketorolac.

Keywords: Tourniquet, Analgesic, Injection pain

INTRODUCTION

Propofol (2,6 di-isopropyl phenol is a popular intravenous anaesthetic induction agent, especially for brief cases, day surgery or when laryngeal mask airway is to be used. Propofol can be used in Total Intravenous Technique (TIVA) for maintenance of anaesthesia and sedation [1]. It is an ideal intravenous anaesthetic agent, providing a smooth induction and a rapid recovery. However, it has been reported to evoke considerable pain on injection in 10-100% of patients [2].

Propofol induced pain ranked 7th among the 33 low morbidity clinical outcomes by expert anaesthesiologist when both clinical importance and frequency were considered [3]. Pain during injection may be severe enough to cause life-threatening complications. Ahed Zeidan reported a case report of profound pain due to propofol injection triggering severe bronchospasm in a smoker [4]. Morishima et al., reported a myocardial ischemia attack due to profound pain during propofol injection [5].

It is well known that intravenous injection of propofol is associated with pain. The incidence ranges from 28-90% and may be recalled as an unpleasant experience by the patient [6]. Factors which appear to affect the incidence of pain of propofol injection are: the site of injection; size of vein; speed of injection; propofol concentration in aqueous phase; buffering effect of blood [7].

The methods for prevention of propofol injection pain studied are site of injection (use of large vein), use of aspirin and or non-steroidal anti-inflammatory drugs, premedication with an opiate, speed of injection of propofol, speed of carrier intravenous fluid, the use of local anaesthetic (lignocaine, most widely used), dilution of propofol, different temperatures, opiates, metoclopramide, glyceryl trinitrate, thiopentone, ketamine, different syringe material and aspiration of blood [8].

The cause of pain on injection of propofol still remains a question. Administration of lignocaine, either before or premixed with propofol remains the most widely used method. Lignocaine may act by stabilizing the kinin cascade. It has been found to be more effective if premixed with propofol and not injected prior to propofol. This may be due to pre-injected lignocaine being washed away in blood before the propofol bolus leaving less lignocaine available for stabilizing of kinin cascade [9]. Pain of propofol may be due to release of a kininogen from the vein wall with triggering of a local kinin cascade [9]. Smith and Power postulated that IV NSAIDS inhibits prostaglandin synthesis pathways in the vein wall and thus reduce propofol injection pain [10]. It has been suggested that propofol needs to be within the vein for a longer period to produce the postulated localized anti-prostaglandin effect and reduce release of kininogen [11].

Ketorolac is a non-steroidal anti-inflammatory drug that is effective in postoperative analgesia. It is also a potent Cyclo-Oxygenase (COX) inhibitor that blocks the prostaglandin production. The mechanism of propofol injection pain could be through the COX pathway [7].

Opioids can inhibit the release of excitatory and pro-inflammatory compounds from sensory nerve endings. Tramadol is a centrally acting weak μ receptor agonist. It inhibits nor-adrenaline re-uptake and promotes serotonin release. Endogenous or exogenous opioids activate the opioid receptors and thus increase potassium currents and decrease calcium currents in sensory neuron cell bodies leading to inhibition of signal transmission [6].

Mangar et al., showed that lignocaine given after inflation of the tourniquet 50mmHg virtually abolishes the transient pain associated with propofol injection [12].

AIM

To study and compare the efficacy of Lignocaine, Tramadol and Ketorolac in minimizing the propofol injection pain.

MATERIALS AND METHODS

The present study was a prospective, randomized double blinded, single centre study. It was conducted for a period of 1 year after approval of the Hospital Academic Council. A written informed consent was obtained from all patients included in the study. The study was conducted on a total of 100 adult patients belonging to ASA grade I and II scheduled for elective surgery under general anaesthesia with propofol as an inducing agent.

All the patients were randomly divided into 4 groups of 25 patients each.

Group L : Received injection Lignocaine 60 mg i.v.

Group T : Received injection Tramadol 50 mg i.v.

Group K : Received injection Ketorolac 10 mg i.v.

Group N : Received injection Normal saline 3 ml i.v.

Inclusion Criteria

For the study, a patient who is scheduled for elective surgery under general anaesthesia and conforms with the below criteria was included in the study-

1. Age between 18-60 years,
2. ASA grade 1 and 2,
3. BMI between 19-30 kg/m^2

Exclusion Criteria

Patients with the following conditions were excluded.

- Patients with difficult communication.
- Pregnant/lactating mothers.
- Patients with history of epilepsy.
- Patients with history of cardiac conduction defects.
- Patients on antiarrhythmic drugs or analgesics.
- Patients with disorders of lipid metabolism.
- Patients with history of bronchial asthma.
- Patients with history of allergy to Propofol/NSAIDS/Egg.
- Patients with morbid obesity.

A complete history was taken and clinical examination was conducted pre-operatively a night before the surgery was planned. Routine investigations like Hb, RBS, blood urea, serum creatinine, serum electrolytes, Chest X-ray (PA view) and Electrocardiogram (ECG) was done. Patients were kept nil by mouth from 22:00 hours. No pre-medication was given prior to the surgery.

On arrival to the pre-operative room 18 gauge intravenous cannula was placed into the largest vein on the dorsum of the hand of the patient and the normal saline infusion was started. After shifting to operating room the patient was explained that he/she would be receiving intravenous anaesthetic that might cause pain on injection. The patient was instructed to inform the investigator of the amount of pain he/she experienced using a visual analogue scale (VAS) from 0-10 with

0 : Being no pain

10 : Most excruciating pain

After instructing the patient the intravenous infusion was stopped and the arm with the intravenous line was elevated for 15 seconds for gravity drainage of the venous blood. A pneumatic tourniquet was placed on the arm with pressure inflated to 70mmHg to produce venous occlusion.

Patients were pre-oxygenated with 100% oxygen for 3 min. The study was conducted in a double blind manner. During the study the anaesthetist recording the pain score was kept blinded about the pretreatment drug. This was ensured by the investigator prefilling the syringe with the drug before handing it over to the anaesthetist.

All drugs were prepared in 3ml volume, diluted with normal saline. All the injections were given at the port immediately proximal to the intravenous cannula at the rate of 0.5 ml/sec. 1 min after the injection of the drug under study; the tourniquet was deflated, followed immediately by intravenous injection of propofol (2.5 mg/kg) at the rate of 0.5 ml/sec for the induction of anaesthesia. Pain score using VAS were assessed before the patient became unconscious. Additional anaesthetics were given if deemed necessary. Moreover, the absence or presence of redness in the arm was observed and recorded.

STATISTICAL ANALYSIS

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

RESULTS

There was no significant difference in the demographic data between the four groups [Table/Fig-1]. All groups were statistically comparable as regard to age (p-value >0.10). There was no significant difference between male and female(sex) ratio and weight in all the groups.

ASA: All groups were statistically comparable as regard to ASA grading [Table/Fig-2].

Incidence of pain: The incidence of pain was statistically significant in group L, T and K when compared with group N. However, there was no statistically significant difference among group L, T and K [Table/Fig-3].

Mean Score of Pain: The mean pain score in group L (0.72 ± 1.62), T (0.96 ± 1.65) and K (1.28 ± 2.13) was statistically significant when compared to group N (7.00 ± 1.78) (p-value < 0.0001). However, there was no statistically significant difference in group L, T and K [Table/Fig-4].

Side Effects: The side effects were significantly less in group N as compared to other groups. Groups L, T and K were statistically comparable, but had a significant difference when each was compared to group N [Table/Fig-5].

DISCUSSION

The pain on propofol injection which occurs in 26%-90% of patients may be severe enough to add to patients stress from anaesthesia and surgery and most probably will be recalled in the

	Group L	Group T	Group K	Group N	
Age (Years)					
11-20	0 (0)	0 (0)	2 (8)	1 (4)	F-ratio -0.05, p-value >0.10 C.D. - NS
21-30	7 (28)	6 (24)	4 (16)	5 (20)	
31-40	8 (32)	9 (36)	9 (36)	7 (28)	
41-50	8 (32)	8 (32)	7 (28)	10(40)	
51-60	2 (8)	2 (8)	3 (12)	2(8)	
Mean ± SD	37.52 ± 9.68	38.40 ± 7.94	38.36 ± 11.24	38.44 ± 9.19	
Sex					
Male	10 (40)	10 (40)	11 (44)	11 (44)	χ^2-value 0.16 p-value >0.10 CD-NS
Female	15 (60)	15 (60)	14 (56)	14 (56)	
Weight (kg)					
Mean ± SD	58.44 ± 4.98	57.04 ± 4.53	58.40 ± 6.83	58.40 ± 6.83	F-ratio 0.33 p-value >0.01 C.D. -NS.

[Table/Fig-1]: Demographic profile.

ASA Grade	Group L	Group T	Group K	Group N	
I	17 (68)	20 (80)	14 (56)	15 (60)	χ^2-value-3.74 p-value > 0.10 CD-NS
II	8 (32)	5 (20)	11 (44)	10 (40)	

[Table/Fig-1]: ASA profile.

Group	Number of pts. with Pain on Propofol Injection	Total pt. in Group	%
L	6	25	24%
T	7	25	28%
K	7	25	28%
N	24	25	96%

[Table/Fig-3]: The incidence of pain on propofol injection.

Group	Mean ± SD	
L	0.72 ± 1.62	F-ratio 69.71 p-value < 0.0001 C.D.-1.02
T	0.96 ± 1.65	
K	1.28 ± 2.13	
N	7.00 ± 1.78	

[Table/Fig-4]: Mean score of pain in different groups.

Group	Side Effects							
	Pain		Pain+Redness		No Side Effects		Redness	
	No. of pts	%	No. of pts.	%	No. of pts.	%	No. of pts.	%
L	3	12%	0	0%	22	88%	0	0%
T	4	16%	0	0%	22	88%	1	4%
K	3	12%	1	4%	21	84%	0	0%
N	0	0%	0	0%	25	100%	0	0%

Group	Z value	p-value	
L Vs T	0.77	>. 01 NS	Non Significant
L Vs K	0.41	>. 01 NS	Non Significant
L Vs N	1.79	<0 . 1	Significant
T Vs K	0 .37	>. 01 NS	Non Significant
T Vs N	2.36	<. 05	Significant
K Vs N	2.09	<. 05	Significant

[Table/Fig-5]: Comparisons between groups for incidence of side effects among pre-treatment drug.

recovery room. Some patients recall the induction of anaesthesia as the most painful part of the perioperative period [8]. Several interventions have been investigated to alleviate the pain associated with propofol injection. Injecting into a large forearm vein also reduces the pain, probably by reducing contact between drug and endothelium. Lignocaine added to or given before injection of propofol is widely employed. Gajraj et al., studied the optimal dose of lidocaine for propofol pain and concluded that 30mg lidocaine is the optimal dose for attenuation of propofol pain [13].

Isolating the arm vein from rest of the circulation by a tourniquet, similar to a modified bier's block presents a useful model for studying the peripheral actions of a drug in the absence of central effect [14]. In our study we used a pneumatic tourniquet that was placed on the arm with pressure inflated to 70mmHg to produce venous occlusion to allow the pre drug to be retained in the vein for 1 minute.

Dexter et al., suggested that ketorolac needs to be within vein for a longer time to produce the postulated localized anti-prostaglandin effect and reduce release of kininogens [15].

In the present study incidence of pain in group N in which propofol was injected without pre-treatment is found to be 96% with VAS of 7.00±1.78 which was comparable with studies done by Mangar et al., (90%), Bashir et al., (96.7%) [12,16].

In the present study, incidence of pain on propofol injection after lignocaine (60 mg) pretreatment is 24% with a mean VAS of 0.72 ± 1.62. The incidence of propofol injection pain after lignocaine shown by Ganta et al., was 21% [17], and WH Wong et al., was 27% [6]. Lignocaine reversibly blocks peripheral nerve pathways through the action on excitable membranes in the arm.

In the present study, the incidence of propofol injection pain after tramadol 50 mg pre-treatment was 28% with mean VAS of 0.96 ± 1.65. The results are comparable to the result shown by Wei-Wu Pang et al., were 23% [18], WH Wong et al., was 30% [6], Goel et al., was 25% [19] and Bashir et al., was (26.7%) [16].

Martin et al., found that tramadol produced a local sensory block of short duration. This local anaesthetic activity of tramadol might account for its analgesic effect in reducing propofol injection pain [20]. We used 50 mg tramadol (equivalent of 1 mg/kg) as most studies used 1 mg/kg of tramadol [6,16]. Our results are consistent with the findings of other studies regarding the effectiveness of pre-treatment of tramadol for propofol injection pain.

The incidence of pain on propofol injection after Ketorolac 10 mg pre-treatment in our study was found to be 28% and a mean VAS of 1.28 ± 2.13. The incidence of propofol injection pain after pre-treatment with ketorolac as shown by YW Huang et al., is 23.3% [7], Goel et al., is 25% [19].

In the study by Smith et al., ketorolac pre-treatment did not significantly reduce the incidence of propofol injection pain as tourniquet was not used for retention of ketorolac [10]. Yull et al., reported that administration of 10 mg ketorolac with venous occlusion for 2 minutes reduces the incidence of severe pain on propofol injection. The same dose of ketorolac without venous occlusion did not decrease the incidence of pain. Therefore, it has been suggested that NSAIDs presumably need time to inhibit the pathway and hence holding the drug within the vein for some time is necessary for its action [11].

Huang et al., observed that pre-treatment with either 15 or 30 mg ketorolac without venous occlusion achieved the same pain relief effect of ketorolac 10 mg IV with venous occlusion. However, injection pain still occurred at a rate of 23.3% [7].

The incidence of side effects (pain and local redness) of lignocaine pre-treatment in this study was 12% as 3 out of 25 patients complained of pain at injection. It is comparable to results of Wei-Wu-Pang et al., 14% [18] and Martin et al., 14% [20].

The incidence of side effects (pain and local redness) of tramadol injection in our study was 20% in which 4 patients complained of pain and 1 patient showed local redness at site of injection. 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., 15% [19], Martin et al., 22% [20], Singh et al., 23.2% (redness -13.2%) [21].

Pain and redness at injection site are common with most injectable NSAIDs [11]. The incidence of side effect of ketorolac was 16% of which 12% was pain and 4% pain and redness. This incidence is comparable with those shown by Dexter (21%) [15], Yull et al., (6% redness and 6% pain) 11, Goel et al., (15% complained of pain and 5% complained of redness at local site and 5% complained of pain and redness) [19]. Though not significantly different lignocaine appears to be more acceptable due to fewer side effects as compared to tramadol and ketorolac.

CONCLUSION

Thus, pre-treatment with any of these 3 drugs significantly reduce propofol injection pain. However, lignocaine was more acceptable because of less pain and fewer side effects then tramadol and ketorolac. We recommend the use of these agents as pre-treatment to propofol to increase the patient acceptability of this agent ideal anaesthetic agent.

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