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"A CLINICAL STUDY TO COMPARE THE EFFICACY OF INTRAVENOUS ONDANSETRON WITH INTRAVENOUS LIGNOCAINE TO ALLEVIATE PAIN ON PROPOFOL INJECTION DURING GENERAL ANAESTHESIA"

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ABSTRACT

Background: Propofol has the significant disadvantage of causing pain or discomfort during intravenous (IV) injection. The aim of this prospective, observational study was to assess the efficacy of IV Ondansetron with IV lignocaine to alleviate pain on propofol injection during general anaesthesia. The primary objective was to compare the incidence and severity of pain during injection of propofol in ondansetron and lignocaine group and the secondary objective was to evaluate the hemodynamic stability and incidence of adverse effects in both the groups.

Materials and Methods: 210 patients belonging to ASA grade I and II were assigned into 3 groups (70 each). Group L received 2 ml of 2% lignocaine, group O received 2 ml of Ondansetron and group N received 2 ml of 0.9% normal saline. Venous occlusion was done by compressing mid forearm with a tourniquet before injection, the study drugs were injected over 5 seconds and thereafter the occlusion was removed after 1 minute. The first calculated dose of propofol was then injected over 5 s. Patients were observed and asked 15 s later to rate immediately any sensation of pain in the arm and pain was scored on a four-point scale: 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. Paired Student's t-test, chi-square test/one way ANOVA test were used to analyze results.

Results: Pain was reduced significantly in group'L' where majority (94.20%) experienced mild pain only as compared to other two groups and the difference was significant statistically ($p<0.05$).

Conclusion: Pre-treatment with Lignocaine provides an effective method of reducing the incidence of pain on Propofol injection.

KEYWORDS : Ondansetron, lignocaine, propofol

Introduction:

Ever since its inception in clinical practice, Propofol undoubtly has enjoyed unsurpassed popularity as an IV induction agent. Propofol with its alluring pharmacokinetic properties like absence of cumulation, titrable level of anesthesia, rapid and clear headed recovery and negligible side effects is an ideal agent for anesthesia induction.[1]but often, it has the significant disadvantage of causing pain or discomfort on injection especially when given in small veins on dorsum of hand. Among 33 clinical problems, Propofol induced pain ranked seventh when both clinical importance and frequency were considered.[2,3]

Lignocaine is a popular local anesthetic and has proven to be one of the most efficient treatments for reduction of Propofol induced vascular pain.

Ondansetron is a specific serotonin 5 Hydroxytryptamine 5 HT_3 receptor antagonist which has been exhibited to successfully relieve pain following Propofol injection without any adverse effects in a significant number of patients. [4]

Numerous pharmacological strategies have been used to minimize the incidence of pain on Propofol injection including pretreatment with lignocaine, ondansetron, ketorolac, ketamine, topical nitroglycerin application with Propofol, diluting Propofol with 5% dextrose or 10% intralipid and using medium and small chain triglycerides. [5, 6, 7, 8] with variable results and the search for an ideal agent to decrease pain on Propofol injection still continues.

In the present study, an effort therefore has been made to compare ondansetron with lignocaine to alleviate pain on Propofol injection.

Material and methods: After obtaining institutional ethical committee approval and informed written consent,. 210 adult patients belonging to ASA I and II class, scheduled for elective surgery under general anesthesia were allocated to either of the three groups, for this prospective, observational, placebo-controlled study.

Group I: 70 patients who received 2% lignocaine – 2ml (42 mg) as pretreatment

Group II: 70 patients who received 4mg ondansetron (2ml) as pretreatment.

Group III: 70 patients who received 0.9% normal saline (2ml) as pretreatment

The sample size was calculated according to confidence interval approach formula for hospital/institutional study. Patients with a history of allergic response to Propofol, 5HT3 antagonists, lignocaine (preservative free) or egg, patients with difficulty in communication, neurological disorders or altered sensorium or those on anti-psychotropic medications were excluded from this study.

All patients were subjected to a thorough pre-anaesthetic evaluation, in which procedure was explained to the patients and all patients were educated about the visual analogue scale (VAS) pain score of 0-10.. A common conduct of anaesthesia was followed in all patients which included alprazolam 0.25 mg orally at night before surgery and ranitidine 150 mg orally at night and on the morning of surgery. Standard monitoring included pulse oximetry, non-invasive blood pressure, end-tidal CO_2 and three-lead electrocardiogram.

The IV access was secured with 18 g cannula in a suitable vein on dorsum of non-dominant hand without any local infiltration. Baseline parameters i.e. heart rate, NIBP, SpO2, end-tidal $C0_2$ and ECG were monitored at 1 and 3 minutes after injecting Propofol. No analgesic drug was given to the patient before injecting Propofol. Venous occlusion was done by compressing the forearm *with a tourniquet* to increase the local concentration of the drug. The study drugs (lignocaine and ondansetron were injected over 5 seconds and thereafter the occlusion was removed after 1 minute and then one fourth of the calculated dose (2.5 mg/kg) of Propofol (1%w/v in lipid base) was injected over 5 seconds and 15 seconds later, patient was asked to rate immediately any sensation of pain during injection of Propofol. The level of pain was measured by another anaesthesiologist who was unaware of the group to which patients had been allocated. Assessment included standard questions such as pain on injection, verbal rating scale and behavioural signs.

Results:

Table – 1: Demographic data

	Group	N	Ratio	Mean±SD	P value
Age	L	70	-	39.50+_11.66	0.233
	O	70	-	41.47+-9.56	
	N	70	-	38.52+-9.64	
Gender (M:F)	L	70	30:39	---	0.568
	O	70	36:33	---	
	N	70	35:35	---	
Bodyweight (Kg)	L	70	-	65.15+-10.10	0.084
	O	70	-	66.60+-9.81	
	N	70	-	63.12+-7.46	

All three groups were comparable with regards to age, sex distribution and body weight and the difference was not significant statistically (P > 0.05) **Table-1.**

Table-2: Comparison of groups according to baseline heart rate and MAP

	Group	N	Mean ± SD	F value	P value
Baseline Heart rate	L	70	73.3623 ± 8.17092	2.359	0.097
	O	70	71.2174 ± 5.40933		
	N	70	71.2571 ± 6.04017		
MAP Baseline	L	70	77.1739 ± 8.44351	2.785	0.064
	O	70	74.6957± 6.87986		
	N	70	74.6143± 6.26999		

There were no significant variations in either baseline heart rate or MAP among different groups (P>0.05) as assessed by using one-way ANOVA test. **Table-2**

Table-3: Comparison of groups as changes in heart rate and MAP after injecting Propofol

	Group	N	Mean ± SD	F value	P value
Heart rate after injection	L	70	69.5371 ± 7.78115	13.176	<0.0001 *
	O	70	72.7246 ± 6.14023		
	N	70	75.2248 ± 5.3698		
MAP after injection	L	70	76.3982 ± 8.15805	7.568	0.001*
	O	70	76.7246 ± 6.44635		
	N	70	80.6522 ± 6.83961		

Table-4: Post Hoc Tests:

Dependent Variable	(I) Injection	(J) Injection	Mean Difference (I-J)	Std. Error	Sig.
Heart Rate after Injection	Lignocaine	Ondansetron	3.92754*	1.22304	0.004*
		0.9% Normal saline (Control)	7.66025*	1.15354	.<0.0001*
	Ondansetron	0.9% Normal saline (Control)	5.16749*	1.15354	<0.0001*
MAP after Injection	Lignocaine	Ondansetron	2.49275	1.15768	0.082
		0.9% Normal saline (Control)	10.92360*	1.21867	<0.0001*
	Ondansetron	0.9% Normal saline (Control)	6.99607*	1.21867	<0.0001*

There is significant variation in heart rate among different studied groups (P<0.05) after Injection {By Using One Way ANOVA Test} and according to post Hoc Test for pair wise comparison {by Using Turkey's HSD Test}. The heart rate is high in 0.9% Normal Saline (Control) and low in lignocaine and ondansetron group.

There is significant variation in MAP among different groups (P<0.05) after Injection with Propofol ; {By Using One Way ANOVA Test } and according to post Hoc Test for pair wise comparison {by Using Turkey's HSD Test};The MAP is high in 0.9% Normal Saline (Control) and lower in lignocaine and ondansetron Injection. **Table 3-4.**

Table-5: Comparison of groups according to verbal pain response score

	Group	N	Mean Rank	K Value	P value
Verbal Pain Score	L	70	35.00	150623	<0.0001*
	O	70	122.82		
	N	70	154.95		
	Total	210			

Table - 6: Incidence of severity of pain following Propofol injection

	Group L (%)	Group O (%)	Group N (%)
No Pain	5 (7.15)	0 (0)	0(0)
Pain	65 (92.85)	70(100)	70(100)
1 (mild pain)	65 (92.85)	02(2.85)	01(1.42)
2 (moderate pain)	0(0)	49(70.00)	23(32.85)
3 (severe pain)	0(0)	19(27.14)	46(65.71)

All the patients experienced pain except 5 patients in lignocaine group. More number of patients experienced only mild pain in the lignocaine group(94%) as compared to other two groups which was statistically significant(P<0.05). Moderate pain was observed more in the Ondansetron group (48%) as compared to other two groups which was also statistically significant (P< 0.05). Severe pain was observed more in the Ondansetron group(19%) as compared to the lignocaine group which was also significant statistically (P<0.05).**Table-6.**

Table -7: Intergroup comparison of side effects after injecting Propofol

	Group	N	N%	Total	Total %	Chi-square	P value
Myoclonus	L	06	8.57	15	7..14	8.924	0.012*
	O	0	0				
	N	09	12.85				
Rash	L	03	4.28	08	3.80	4.964	0.088
	O	00	0				
	N	05	7.14				

Discussion: Propofol stands the drug of choice for anesthesia induction by virtue of its amicable pharmacokinetic profile. Despite these positives, many patients experience pain or discomfort on propofol injection and is sometimes recalled by the patients as the most painful part of the perioperative period. As a result, various interventions have been investigated to alleviate the pain associated with propofol injection.[9]

Pain after propofol injection distinctively occurs immediately or later after the drug injection with a delayed response of 10-20 seconds.[10]The reasons for the pain include endothelial irritation, osmolality differences, unphysiological PH and the activation of pain mediators.[11] Overall pain on propofol injection ranges from 25-100% at veins on dorsum of hand and only 3-26% when injected into proximal veins, probably by reducing contact between drug and endothelium.[12,13,14]

To overcome this pain on injection, it has been suggested to inject it in large veins.[15] some have suggested decreasing speed of injection, dilution in 5% dextrose or 10% intralipid or pretreatment with narcotics or thiopentone before Propofol administration.[16]All these investigators have performed their studies on various methods but no one has come out with a single method applicable in all patients with success.

Metoclopramide has been demonstrated to be as effective as lidocaine in reducing propofol injection pain.[17] Ondansetron had been shown to relieve pain by its multifaceted actions as a Na channel blocker, a 5HT3 receptor antagonist, and mu opioid agonist.[18, 19] Ondansetron pretreatment may be used to minimize the incidence of pain on propofol injection with an added positive of prevention of PONV.[4]

In our study, lignocaine was found to be convincingly effective as compared to ondansetron in reducing pain on propofol injection (P< 0.05). Other investigators have also found lignocaine to be the most effective method to decrease propofol induced pain.[20,21]

In present study, pediatric and geriatric patients were not taken because of their anticipated uncooperation and problems encountered during choice of vein. We did not administer any other premedication in form of sedatives or narcotic agents as they could have interfered with pain assessment.

According to groups the test drug were given as pretreatment in 2ml solution over 5 seconds followed by venous occlusion at arm for 1 minute as per recommendation of various authors. [4, 22] After pretreatment test dose of Propofol (1/4th of calculated induction dose) was injected over 5seconds.

It has been suggested that the speed of injection directly correlates with pain on injection, accordingly speed of test drug and Propofol

were kept constant as 5 seconds.[16] Initial test dose of Propofol given was only 1/4th dose to exclude those patients having sedation score more than 3 and to evaluate verbal pain score.

The mean change in pulse rate and systolic blood pressure were comparable in lignocaine and Ondansetron group ($p>0.05$) but when compared to normal saline group, the difference was significant statistically ($p<0.05$). This cardiovascular stability may be secondary to membrane stabilizing action which blocks the sensitivity of myocardium to further stimulation mediated by sympathetic stimulation due to any cause such as pain. Similar observations were made by other investigators as well.[4,23]

With regard to adverse effects, 6 patients in lignocaine group developed myoclonus while none of the patient developed it in the ondansetron group, the difference being significant statistically ($p<0.05$). In lignocaine group 3 patients developed rash while none of the patient developed it in the ondansetron group, although the difference observed was not significant statistically ($p>0.05$)

One limitation of our study could be that we injected drugs manually. Instead, drugs could have been injected using a syringe infusion pump.

Conclusion

In our study, lignocaine was found to be significantly effective as compared to ondansetron in reducing propofol induced pain. Llignocaine pre-treatment provides an efficient method of reducing the incidence of pain on propofol injection.

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