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Comparative study of the effect of oral premedication with clonidine versus diazepam on intraocular pressure following intubation under propofol and suxamethonium

Reena Sachin Bhandurge
Assistant Professor, Department of Anaesthesiology, Gautam Buddha Chikitsa Mahavidyalaya & Associated Hospital, Dehradun
Email: reenasimha@yahoo.com

Sarita Fernandes
Professor, Department of Anaesthesiology, Topiwala Nair Medical College, Mumbai

***Abstract*---**Aim: To study the efficacy of clonidine given orally as premedication on attenuation of rise in intraocular pressure, haemodynamic responses to induction aided with suxamethonium, laryngoscopy and subsesequent tracheal intubation, its sedation and antisialogogue effects and compare with oral diazepam premedication. Patients were randomly divided into two groups i.e. each group of 30 patients. One group was assigned to receive oral clonidine 4-5mcg/kg or diazepam 0.2-0.25mg//kg body weight oral premedication 90mins before induction. Patients received this premedication randomly and in double blinded manner. Pulse rate, blood pressure and intraocular pressure of both eyes were recorded prior to premedication in both the groups. The degree of preoperative sedation was determined according to a Ramsay sedation scale. Patients were asked for oral secretions (salivation) and antisialagogue effect was determined. It has been observed that clonidine premedication is superior to diazepam in attenuating the rise in intraocular pressure, pulse rate, blood pressure (systolic, diastolic and MAP) associated with laryngoscopy and intubation aided with suxamethonium. Clonidine is superior to diazepam in decreasing the IOP and maintaining stable haemodynamic responses following i.v. suxamethonium, laryngoscopy and intubation. Diazepam caused more sedation as compared to clonidine. Clonidine exhibits antisialogogue effect which is not seen with diazepam.

***Keywords*---**IOP, clonidine, diazepam, blood pressure

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***Corresponding author**: Bhandurge, R. S.; Email: reenasimha@yahoo.com*
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Introduction

Laryngoscopy and intubation produce considerable rise in blood pressure and IOP (intraocular pressure). The ideal intravenous induction agent should have rapid onset and short duration of action while producing adequate and predictable anaesthesia. It should provide haemodynamic stability and be free of any adverse effects. Propofol 2mg/kg produces decrease in blood pressure and IOP. Suxamethonium stimulates autonomic nervous system ganglia, this leads to increase in blood pressure and heart rate; Increase in intraocular pressure due to cyclopegic action leads to deepening of anterior chamber and increased resistance to outflow of aqueous humor combined with increases in choroidal blood volume and central venous pressure. Due to its rapid onset and short duration of action suxamethonium cannot be replaced from anaesthesiologic armamentarium.[1]

Clonidine is an alfa-2-adrenergic agonist. It is sedative, anxiolytic, antisialogogue, antihypertensive & it also causes decrease in intraocular pressure. It reduces anaesthetic and postoperative analgesic requirements.[2,3] In addition clonidine is effective in blunting tachycardia and hypertension associated with laryngoscopy, subsequent intubation and blunting the rise in intraocular pressure associated with suxamethonium, laryngoscopy and tracheal intubation.[4-6]

Benzodiazepines produce all the pharmacological actions by facilitating the actions of Gamma Amino Butyric Acid (GABA). Premedication with diazepam produces anxiolysis, amnesia and hypnosis. It reduces anesthetic requirement of inhalational agents. Benzodiazepines are also known to blunt the sympathomimetic phenomenon associated with laryngoscopy and intubation. This is probably related to the GABA receptor mediated central inhibitory effects of benzodiazepines.[7]

Laryngoscopy and intubation cause increase in heart rate, blood pressure, intraocular pressure and cause disturbance in cardiac rhythm especially if suxamethonium is employed. The purpose of current study is to study the efficacy of clonidine given orally as premedication on attenuation of rise in intraocular pressure, haemodynamic responses to induction aided with suxamethonium, laryngoscopy and subsequent tracheal intubation, its sedation and antisialogogue effects and compare with oral diazepam premedication.

Materials and methods

The present prospective study was done during 2007 to 2010 in Topiwala Nair Medical College, Mumbai. Study was undertaken after hospital ethics committee approval. All the patients were assessed on the previous day of the surgery and patient satisfying the inclusion criteria were included in the study. Procedure, its complications and alternative methods were explained to the patient in his own language and patient consent was taken. The subjects were recruited according to the following inclusion and exclusion criteria:

Criteria for Inclusion

a. Age -18-50yrs
b. Male/Female
c. Weight-40-70Kgs
d. ASA-I
e. Conscious patient

Criteria for Exclusion

a. Refusal to give consent
b. Age <18 or >50yrs
c. Weight <40 or >70kgs
d. ASA II, III, IV
e. Drug allergy
f. Ophthalmic complications
g. Myopia and Hypermetropia

Patients were randomly divided into two groups i.e. each group of 30 patients. One group was assigned to receive oral clonidine 4-5mcg/kg or diazepam 0.2-0.25mg//kg body weight oral premedication 90mins before induction. Patients received this premedication randomly and in double blinded manner. We chose Arkamin 100mcg (clonidine) and Calmpose 5mg as these tablets appeared same, both are white in colour, round in shape and of same size. 3 tablets each of either of the two drugs were packed in similar looking packets and were labeled randomly, sixty such packs were made-30 packets of each drugs. The drug administered by an independent person who was blind to the study. Decoding was done at the end of entire study. Pulse rate, blood pressure and intraocular pressure of both eyes were recorded prior to premedication in both the groups.

For monitoring the IOP-the cornea was anaesthetized by instilling 2-3 drops of lignocaine eye drops. The patient was asked to look with the other eye vertically upward to relax accomadation. The eyelids were separated with the fingers avoiding any pressure on the globe and by holding the side arms of the handle of the tonometer;footplate rested vertically on the cornea. The scale reading recorded as soon as the pointer became steady.

The degree of preoperative sedation was determined according to a Ramsay sedation scale. Patients were asked for oral secretions (salivation) and antisialagogue effect was determined using the following scale:

1. Dry
2. Normal
3. Wet.

Patient is preoxygenated with 100% O2 for 8 breathes. Induced with IV propofol 2mg/kg body weight till eyelash reflex disappears or ask the patient to hold pen in hand, give propofol till pen falls from hand. Then pulse rate, IOP of both eyes and blood pressure was recorded. After confirming the ventilation-iv suxamethonium 2mg/kg was administered .After one minute of administration of

suxamethonium again pulse rate, IOP of both eyes and blood pressure was recorded. After disappearance of fasciculations from the toes .Direct larngoscopy was performed, endotracheal intubation was accomplished by suitable size portex endotracheal tube. After 1min of intubation we recorded the pulse rate, blood pressure, respiratory rate, spo2, intraocular pressure. All above parameters repeated after 3min, 5min, 7min, 10mins. Post intubation our study ended. Cases needing greater than two intubation attempts were excluded from the study. The pulse rate, IOP and blood pressure were labeled as follows:

T_0 - Baseline (prior to premedication).
$T_{pre\ op}$ - Upon arrival in operation theatre.
$T_{propofol}$ - After administration of Propofol.
T_{sux} – After administration of suxamethonium.
T_1 - One minute after intubation.
T_3 - Three minutes after intubation.
T_5 – Five minutes after intubation.
T_7 – Seven minutes after intubation.
T_{10} – Ten minutes after intubation.

Statistical analysis

To find out the statistical difference between two groups, tests viz. unpaired 't' test for intergroup comparison and paired 't' test for intragroup comparison were used. p value <0.05 was considered statistically significant.

Results

Patients receiving clonidine were labeled as Group C and those receiving diazepam were labeled as Group D. Each group consisted of thirty patients. The mean age among the diazepam and clonidine group was 34.10±9.98 and 33±9.60 respectively. There were equal distribution of male (19) and female (11) in the study groups.

Comparing between Diazepam & clonidine group there was no significant diff observed in baseline (T0), pre op & after propofol, pulse rate with P >0.05,However there is significant fall of pulse rate in clonidine group as compared to diazepam group at 1,3,5,7& 10 min after intubation (P<0.05) as show in table 1.

Table 1: Pulse rate

PULSE RATE/MIN	GROUP			Unpaired T-Test		
		Mean	Std. Deviation	T Value	P Value	Significance
T0	Diazepam	81.33	9.223	-0.850	0.399	Non-Sig
	Clonidine	83.00	5.502			
T Pre-op	Diazepam	75.07	8.530	1.088	0.281	Non-Sig
	Clonidine	73.07	5.349			
T Propofol	Diazepam	73.40	7.686	0.669	0.506	Non-Sig
	Clonidine	72.27	5.192			
Tsuxamet	Diazepam	84.67	6.915	5.260	0.000	Sig

	Clonidine	76.53	4.890			
T1min	Diazepam	94.50	5.244	9.501	0.000	Sig
	Clonidine	81.90	5.026			
T3min	Diazepam	92.47	5.244	11.036	0.000	Sig
	Clonidine	78.07	4.856			
5min	Diazepam	90.33	5.358	10.581	0.000	Sig
	Clonidine	76.47	4.776			
7min	Diazepam	85.87	5.355	9.306	0.000	Sig
	Clonidine	74.13	4.361			
T10min	Diazepam	84.80	5.189	10.081	0.000	Sig
	Clonidine	73.07	3.704			

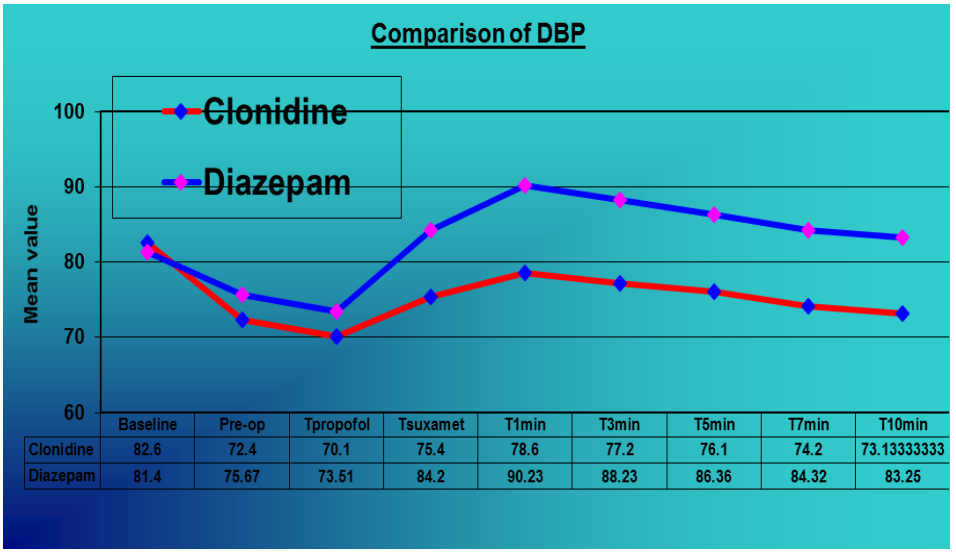
<0.05 –Significant, >0.05-Non – Significant

Comparing between Clonidine &Diazepam Group there is no significant difference in SBP AT T0 ,Tpre-op & Tpropofol with p>0.05, However there is significant rise SBP in Diazepam Group at Tsux, T1, T3, T5, T7& T10 with p<0.05 as shown in table 2.

Table 2: Systolic blood pressure

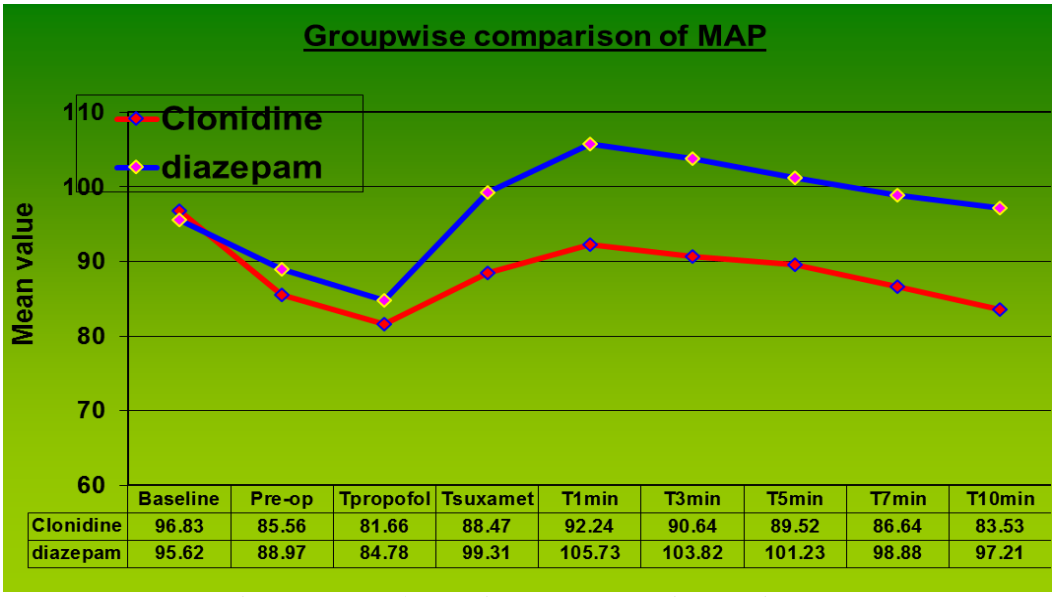
Time Interval		Mean	SD	T Value	P Value	Significance
Baseline	Diazepam	124.33	9.353	-0.474	0.637	Non-Sig
	Clonidine	125.67	12.229			
Pre-op	Diazepam	115.33	9.371	1.672	0.100	Non-Sig
	Clonidine	111.20	9.778			
Propofol	Diazepam	108.33	10.519	1.473	0.146	Non-Sig
	Clonidine	104.67	8.668			
Tsuxamet	Diazepam	128.67	5.020	6.718	0.000	Sig
	Clonidine	115.20	9.764			
T1min	Diazepam	136.33	4.985	7.723	0.000	Sig
	Clonidine	119.80	10.614			
T3min	Diazepam	134.27	5.913	7.620	0.000	Sig
	Clonidine	117.33	10.639			
5min	Diazepam	130.40	7.247	7.073	0.000	Sig
	Clonidine	115.07	9.406			
7min	Diazepam	127.60	7.780	6.207	0.000	Sig
	Clonidine	113.27	9.972			
T10min	Diazepam	125.60	7.361	6.460	0.000	Sig
	Clonidine	110.73	10.232			

Comparing between Diazepam & clonidine group there was no significant difference observed in baseline (T0), pre op & after propofol, DBP with P >0.05. However there is significant fall of DBP in clonidine group as compared to diazepam group at 1,3,5,7& 10 min after intubation (P<0.05) as shown in graph 1.



Graph 1: DBP among the study groups

Comparing between Diazepam & clonidine group there was no significant diff observed in baseline (T0), MDP with P >0.05,However there is significant fall of MAP in clonidine group as compared to diazepam group a pre op & after propofol, Tsux, T1,T3,T5,T7& T10 min after intubation (P<0.05) as shown in graph 2.



Graph 2: Comparison of MAP among the study groups

Comparing between Diazepam & clonidine group there was no significant diff observed in baseline (T0), IOP with P >0.05,However there is significant fall of IOP in clonidine group as compared to diazepam group at pre op &after propofol, Tsux, T1,T3,T5,T7& T10 min after intubation (P<0.05) as shown in table 2.

Table 2: IOP among the study groups

		Mean	Std. Deviation	T Value	P Value	Significance
Baseline	Diazepam	16.600	2.6094	-1.442	0.155	Non-Sig
	Clonidine	17.570	2.6027			
Pre-op	Diazepam	16.563	2.5979	4.000	0.000	Sig
	Clonidine	14.187	1.9599			
Propofol	Diazepam	14.177	1.9838	-5.320	0.000	Sig
	Clonidine	12.01	0.8310			
Tsuxamet	Diazepam	21.033	2.2227	10.557	0.000	Sig
	Clonidine	15.497	1.8195			
T1min	Diazepam	23.117	1.8495	10.518	0.000	Sig
	Clonidine	17.240	2.4380			
T3min	Diazepam	22.000	1.8990	10.031	0.000	Sig
	Clonidine	16.200	2.5346			
5min	Diazepam	21.123	1.7917	13.584	0.000	Sig
	Clonidine	14.833	1.7951			
7min	Diazepam	18.490	1.5198	10.217	0.000	Sig
	Clonidine	14.310	1.6468			
T10min	Diazepam	17.430	1.8084	7.537	0.000	Sig
	Clonidine	14.110	1.5968			

According to the Mann-Whitney test the diazepam group patients were significantly more sedated than clonidine group (table 3).

Table 3: Comparison of Sedation Score in study group

Sedation Score (N=30)	Mean Rank	Sum of Ranks	Mann-Whitney test	p value	Significance
Diazepam	45.5	1365	0	<0.05	Sig
Clonidine	15.5	465			

Discussion

General anaesthesia should ideally provide cardiovascular stability, low intraocular pressure especially in patients in patients with open eye injuries, glaucoma and patient posted for eye surgeries. It should also provide adequate level of sedation, antisialogogue effect and anaesthesia. Suxamethonium causes bradycardia; it increases the blood pressure, intraocular pressure, intragastric pressure, intracranial pressure; it may also cause cardiac dysrhythemiasdue due to the action of suxamethonium at cardiac muscarinic cholinergic receptors where the drug mimics the physiologic effects of acetylcholine. Clonidine a centrally acting antihypertensive agent has been shown to supresssupress central noradrenergic activity.[8,9] Hence we decided to study the effect of clonidine during laryngoscopy and intubation after induction with propofol and suxamethonium on haemodynamic and intraocular pressure changes and compare with oral diazepam.

To study the effect of IV Propofol, suxamethonium, laryngoscopy and intubation response we measured pulse rate, blood pressure- systolic blood pressure, diastolic blood pressure, mean arterial pressure and intraocular pressure both in right and left eye at the time T0-T10. While young healthy patients tolerate changes associated with IV Suxamethonim, laryngoscopy and tracheal intubation, such changes may be detrimental in patients with limited myocardial reserve, glaucoma and patient with open eye injuries. The pulse rate is important as an increase in pulse rate decreases the diastolic time for coronary blood flow and increase in myocardial oxygen consumption.

Ocular perfusion pressure is defined as mean arterial pressure minus intraocular pressure. In patients with glaucoma a rise in intraocular pressure decreases the ocular perfusion pressure and in patient with an open eye injuries suxamethonium causes deeping of anterior chamber, increase in choroidal blood volume and central venous pressure leading to expulsion of eye contents. Hence we also observed mean arterial pressure.

Pulse Rate

Inter group comparison showed significant difference in both groups at the time T3,T5,T7&T10 (p=0.00). Group C patients had significantly low pulse rate which was sustained through the operations. Magnitude of changes in pulse rate was small in Group C as compared to the Group D throughout the surgery. Our study results compare favorably with the studies conducted by Ghignone et al[8] and other authors[10,11] in which Clonidine pretreated patients had pulse rate values significantly less than in the Diazepam group. Propofol may either reset or inhibit the baroreceptor reflex, reducing the tachycardia response to hypotension

Blood Pressure

Inter group comparison showed significant difference in both groups at the time T3,T5,T7&T10 (p=0.00). Group C patients had significantly low systolic blood pressure which was sustained throughout the operations. Propofol produces decrease in systemic blood pressure is often accompanied by corresponding changes in cardiac output and systemic vascular resistance. The relaxation of the vascular smooth muscle produced by Propofol is primarily due to inhibition of sympathetic vasoconstrictive activity. Magnitude of changes in systolic blood pressure was small in Group C as compared to the Group D throughout the surgery. Our study results compare favourbly with the studies conducted by Ghignone et al in which Clonidine pretreated patients had low and stable blood pressure throughout the surgery as compared to diazepam pretreated patients.[8,9] Similar results were reported w.r.t. diastolic and mean arterial blood pressure.

Intraocular Pressure

The differences in mean intraocular pressure between the baseline value and following the administration of clonidine I Group C was found to be 3.4. This shows that clonidine pretreated patients had lower intraocular pressure while arriving in operation theatre as compared to their baseline. In intergroup comparison there is significant rose in IOP in Group D compared to Group D

(P=0-000). The IOP compared to baseline was significantly high in subsequent levels in Group D at time T1,T3,T5,T7 (P<0.05). Inter group comparison showed significant difference in both groups at the T3,T5,T7&T10.

The reduction in the B.P does not seems to have a cause effect relationship with the reduction in IOP.[12] Some other mechanisms are likely to have contributed to the fall in IOP. These include reduction in aqueous humor production by:

1) Direct vasoconstriction (at as low as 1ng/ml) of the afferent blood vessels of the cilliary process and by inhibiting peripheral cholenenergic transmission.[13]
2) By central reinforcement of atonic inhibitor on neurons of Edinger Westpal complex, which results in a reduction of the parasympathetic outflow to ciliary plexus, thus of aqueous humor sd secretion.[14]

By contrast, the prevention of the IOP response during laryngoscopy and intubation aided with suxamethonium observed in Group C is most likely explained by the attenuation of the associated hemodynamic response. While in Group D a sudden increase in hemodynamic parameters overcomes the auto regulation of uveal blood flow and to result in an increase choroidal blood volume. A central mechanism is also responsible for increasing in IOP.

Our results compare favorably with the study conducted by Ghignone et al[8] in which clonidine pretreated patients has sustained decrease in intra ocular pressure which did not rise above the base line values throughout the surgery. Ghignone et al. in his study described that the intraocular pressure values T4 and T5 remained low in both the groups but in Group C the values remained significantly low as compared to Group D.

After analyzing the above parameters and their values it has been observed that clonidine premedication effectively attenuates the changes in intraocular pressure, pulse rate, blood pressure- systolic and diastolic, MAP and RPP associated with laryngoscopy and intubation aided with suxamethonium. While diazepam was unable to completely attenuate these responses.

Sedation Score

In this study 16.70% patients experienced sedation score of Grade 1 (alert) in Group C. 83.30% patients experienced sedation score of Grade 2 (drowsy but easily arousable by verbal commands to an alert state). Group D patients experienced Grade 2 sedation in 23.30% patients and Grade 4 in 76.70% patients. No patients experienced Grade 5 sedation score. It shows that the patients receiving clonidine premedication have adequate sedation. Group D patients experienced high sedation score which may be due to the high dose administered to them-0.2- 0.25 mg/kg of body weight. Wright et al[15] evaluated the use of oral clonidine 0.3 mg as routine premedicant. Clonidine produced significant reduction in anxiety and sedation and reduction in the sleep dose of methohexitone. Tachycardia in response to intubation was attenuated by clonidine.

Antisialogogue Effect

All patients in Group C experienced dryness of mouth. This effect is due to the side effects of associated with clonidine-xerostomia and decrease in secretions. Though this effect may be uncomfortable to patients, it is helpful for intubation. Group D patients have normal salivary secretions because diazepam does not elicit this kind of effect. No patients experienced increased salivary secretions. Our results compare favorably with the study conducted by Ghignone et al[8] in which clonidine pretreated patients has sustained decrease in intra ocular pressure which did not rise above the base line values throughout the study.

After analyzing the above parameters it has been observed that clonidine premedication is superior to diazepam in attenuating the rise in intraocular pressure, pulse rate, blood pressure (systolic, diastolic and MAP) associated with laryngoscopy and intubation aided with suxamethonium.

Conclusion

Clonidine is superior to diazepam in decreasing the IOP and maintaining stable haemodynamic responses following i.v. suxamethonium, laryngoscopy and intubation. Propofol induction reduced the blood pressure and IOP but it effects were reversed after i.v. suxamethonium, laryngoscopy and intubation. Diazepam caused more sedation as compared to clonidine. Clonidine exhibits antisialogogue effect which is not seen with diazepam.

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