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A prospective comparative study on effects of oral clonidine and oral midazolam as pre-medicants for general anaesthesia

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Abstract---Aim: The purpose of the present research to compare between the effects of oral clonidine and oral midazolam as a pre-medication for initiating General anesthesia. Methodology: A comparative study between midazolam and Clonidine as a premedication for general anesthesia was conducted on 100 patients of each group. The study was performed on Dr. Moopen's Medical College, Wayanad, Kerala. India and duration was from January 2022 to September 2022. All the patients belonged to ASA class I or II. The age of patients ranged from 20 - 60 years. On the day before the operation pre-operative assessment was carried out. Results: Majority of cases in both the groups were in the age group of 20-30 years (56%). Gender wise distribution shows 40% cases were males and 60% were females. The sedation score, apprehension score and excitement score in both the groups before and after induction was statistically significant. There is no significant difference in dose requirement of Thiopentone sodium for induction between midazolam and clonidine group. The amnesia score shows that midazolam produces more potent and perfect amnesia as compared to clonidine. Amnesia score in both the groups was statistically significant.

Conclusion: It was concluded from the present study that midazolam was superior to Clonidine in its sedative and anxiolytic effects.

Keywords---premedication, midazolam, clonidine, benzodiazepine.

Introduction

Premedication plays a pivotal role in general anesthesia. Oral medication is well accepted by children than any another route of administration. They are given to allay anxiety, to produce amnesia, sedation, analgesia, to facilitate smooth induction and to reduce secretion. They should be easily administered, should be safe for the patient, should not prolong the recovery from anesthesia, and should not produce undue depression of cardiovascular, respiratory and central nervous systems.¹ Clonidine is a centrally acting α -2 agonist commonly known as an antihypertensive drug. Due to its sedative, hypnotic and analgesic properties it is used in anesthesia. Its main site of action is on the locus ceruleus in the upper brainstem in the floor of the fourth ventricle.² Midazolam in parenteral form, due to bitter taste is mixed with cola. It has anxiolytic, sedative, hypnotic, anticonvulsant, muscle relaxant, and anterograde amnesic effects. If the receptor occupancy of the midazolam is 20%, it causes anxiolysis, 30 to 50% it causes sedation, more than 60% it causes unconsciousness. It produces dose related ventilatory depression, decreases arterial pressure by decreasing systemic vascular resistance.³ Oral clonidine premedication reduces the minimum alveolar concentration of sevoflurane in children.⁴ In modern anaesthesia, endotracheal Intubation is an essential step for providing balanced anaesthesia and for resuscitative measures in intensive care units. During induction of general anaesthesia two important events take place. One is laryngoscopy, the other one being tracheal intubation. During laryngoscopy, blade of laryngoscope presses against the base of tongue and lifts up the epiglottis. This procedure gives rise to certain impulses resulting in intense sympathetic stimulation causing hypertension and tachycardia.⁵ Compared to endotracheal intubation, laryngoscopy causes more intense stimulation as far as cardiovascular effects are concerned. Thus, the stimuli produced by laryngoscopy and intubation is carried through the afferent pathway through the glossopharyngeal and branches of vagus while the efferent discharge carrying the cardiovascular response is through the cervical sympathetic nerves. This reflex sympathetic stimulation leads to liberation of catecholamines⁶ which are responsible for changes in cardiovascular parameters. An increase in heart rate is associated with increased cardiac work and reduction in coronary filling during diastole. This imbalance between myocardial oxygen demand and supply leads to myocardial ischemia. The changes usually recorded include a rise of systolic blood pressure [SBP] by about 30-50 mm Hg, diastolic blood pressure [DBP]-about 20-30 mm Hg, resulting in rise in mean arterial pressure [MAP]. Heart rate increases by about 20-40 beats per minute. Various cardiac dysrhythmias apart from sinus bradycardia and tachycardia do occur in 5-10% of the patients. However, most of these are benign and transient. Sympathoadrenal stimulation may prove detrimental to the health to a certain group of patients, for example, to those with ischemic heart disease who may suffer acute myocardial infarction. In patients with compromised cardiac status such an increase in heart rate may lead them

into heart failure. In the case of patients with cerebral aneurysm it may result in hypertensive haemorrhage in brain. Therefore, to prevent these casualties one must try to attenuate the sympathoadrenal stimulation. This observation led to use of different techniques and drugs to attenuate cardiovascular responses to laryngoscopy and tracheal intubation like deeper plane of anaesthesia, local anaesthetics,⁷ [applied both locally and intravenously], narcotics,^{8,9} vasodilators, calcium channel antagonists, beta-1 adrenoreceptor blocker,¹⁰ alpha-2 adrenoreceptor agonists, or their combinations with various degrees of success. But no single method has gained widespread acceptance because each method has its own merits and demerits. Many new studies are still being carried out with re-evaluation of older ones.

Aim of the present study

The purpose of the present research to evaluate and compare the effects between oral clonidine and oral midazolam as a pre-medication for initiating general anesthesia.

Methodology

A comparative study between midazolam and Clonidine as a premedication for general anesthesia was conducted on 100 patients of each group. All the patients belonged to ASA I or II. Study was performed at Dr. Moopen's Medical College, Wayanad, Kerala, India and duration was from January 2022 to September 2022. The age of patients ranged from 20-60 years. On the day before the operation pre-operative assessment was carried out. A complete systemic examination was done, to rule out any major systemic dysfunction. Routine investigations like hemoglobin estimation, renal function tests, RBS, X-ray chest, ECG were done in all cases. No sedation was given the night before operation. Written Informed consent was taken up for anesthesia and surgery. Patients were divided in two groups: Group I: Oral. Midazolam 0.25mg/kg. 60 minutes before surgery; Group II Tab. Clonidine 4µg/kg oral, 60 minutes before surgery. Pulse rate, blood pressure, state of excitement, apprehension and sedation were noted at the time of giving premedication. Technique: Pulse rate, blood pressure, state of excitement, apprehension and sedation were noted before induction of anesthesia. Patients were given Inj. Glycopyrrolate 0.001 mg/kg intravenously before induction. All patients were given general anesthesia with Inj. Thiopentone sodium (2.5%) intravenous and inj. Suxamethonium 2 mg/kg intravenous. Inj. Thiopentone sodium was given up to the loss of eyelash reflex and given dose was noted. Anesthesia was maintained on O₂+N₂O+isoflurane+ non-depolarizing muscle relaxant (vecuronium 0.1 mg/kg). At the end of surgery, neuromuscular blockade was reversed with inj. Neostigmine 0.05 mg/kg intravenous and inj. Glycopyrrolate 0.001mg/kg intravenous. Pulse rate and blood pressure were measured during laryngoscopy and intubation and 5 min., 10 min. and 15 min. after intubation. Post-operatively, recovery score was noted just after reversal and up to 2 hours according to recovery score mentioned in proforma. Post operative sedation and amnesia were also noted.

Results

Majority of cases in both the groups were in the age group of 20-30 years (56%). Gender wise distribution showed 40% cases were males and 60% were females. Majority of cases in both groups were between 41-50 kg (56%). The sedation score, apprehension score and excitement score in both the groups before and after induction was statistically significant ($p < 0.001$). Midazolam and clonidine both caused significant reduction in thiopentone dose required to induce anesthesia. There is no significant difference in dose requirement of thiopentone sodium for induction between midazolam and clonidine group. (Table 1) There is statistically significant difference in systolic blood pressure and heart rate between before pre-medication and induction but no statistically significant difference between before induction and during laryngoscopy in clonidine group while in Midazolam group there is no statistically significant difference between before pre-medication and induction, but significant difference in blood pressure and heart rate between before induction and during laryngoscopy. Blood pressure: Baseline systolic, diastolic and mean arterial blood pressure difference in both the groups were not statistically significant. In group 1, mean SBP, DBP, MAP one minute post intubation remained low compared to baseline values. But in group 2 there was a statistically significant increase in SBP, DBP, and MAP from baseline. Thus, increase in blood pressure in group 2 was statistically significant ($P < 0.05$) in the intergroup comparison. (Table 2)

Discussion

Clonidine, an imidazoline derivative is a selective α_2 adrenergic receptor agonist. It is a potent antihypertensive drug. It produces a fall in heart rate and blood pressure associated with decreased cardiac output but unchanged peripheral resistance. Clonidine is rapidly absorbed after oral administration and bioavailability is almost 100%. Peak plasma concentration develops within 60-90 minutes after an oral dose. The plasma half-life varies from 12-24 hours. The duration of hypotensive effect after a single oral dose is about 6-12 hours. Midazolam, an imidazole-benzodiazepine derivative, is having anxiolytic, hypnotic, anticonvulsant, muscle relaxant, and anterograde amnesic effects. In normal individuals, midazolam produces reductions in systolic (5%) and diastolic (10%) blood pressure, and increase in heart rate (18%). Midazolam is absorbed rapidly and completely after oral administration. Maximum plasma concentrations are reached within 60-90 minutes after an oral dose. The increased sympathetic activity caused by stimulation of upper respiratory tract has been supported by the observation that increase in arterial pressure during endotracheal intubation is associated with an increase in plasma noradrenaline level.¹¹ After intubation there is gradual return of blood pressure and pulse rate to pre-laryngoscopic value due to fatigue of the receptor. Various methods have been used to attenuate the cardiovascular responses to laryngoscopy and endotracheal intubation. The effects of intravenous and oral practolol in hypertensive patients showed a significant attenuation of cardiovascular responses following laryngoscopy and intubation.¹² The effect of Esmolol, a ultrashort acting beta blocker introduced in the late eighties, with an elimination half-life about 9 minutes was found to be much satisfactory so far the attenuation of cardiovascular responses to laryngoscopy and intubation are concerned.¹³ Intravenous lignocaine 1.5 mg/kg

administered 90 seconds before laryngoscopy and viscous lidocaine 25 ml [4%] given as mouth wash 12 minutes before laryngoscopy were found to be equally protective.¹⁴ The sedative and anaesthetic sparing properties of alpha 2 adrenergic agonists is due to their actions on locus ceruleus. The brain stem nucleus that regulates a wide variety of physiological process including sleep-wakefulness regulation is inhibited by alpha 2 adrenergic agonists via a G protein mediated mechanism that involves inhibition of adenylate cyclase. M Tanaka et al.¹⁵ studied the effect of oral clonidine premedication in attenuating hypertensive response to ketamine. Rudra A et al.¹⁶ studied the evaluation of clonidine as a premedicant during ketamine anaesthesia and revealed that, clonidine provide acceptable level of sedation, similar anxiolysis as diazepam ($p>0.1$), good antisialagogue effect and better cardiovascular stability. In the present study, we observed the post operative recovery score as well as post-operative sedation in both the groups. Our observations correlated with F. Bonnet et al who observed that clonidine does not delay recovery from anesthesia.. In contrast to our study R. Aantaa et al¹⁷ concluded that time needed to regain consciousness was increased significantly after midazolam 0.08mg/kg and not after Dexmedetomidine.

Conclusion

It was concluded from the present study that midazolam was superior to Clonidine in its sedative and anxiolytic effects, had a potent amnesia and does not attenuate hemodynamic response to laryngoscopy and intubation and does not prolong recovery time.

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Tables

Table 1- Sedation, apprehension score in both groups

Variables		Midazolam	Clonidine	P Value
<i>Sedation Score</i>	Before premedication	0	0	p<0.001
	Before Induction	1.80 ± 0.80	1.12 ± 0.711	
<i>Apprehension score</i>	Before premedication	-0.52 ± 0.299	-0.52 ± 0.223	p<0.005
	Before Induction	-0.12 ± 0.256	-0.3 ± 0.288	

Table 2- The haemodynamic changes before induction, during laryngoscopy and intubation and at 5 minutes after extubation

Midazolam group							
	<i>Baseline</i>	<i>Before induction</i>	<i>P value</i>	<i>During laryngoscopy and intubation</i>	<i>P value</i>	<i>5 min after extubation</i>	<i>P value</i>
<i>Mean</i>	86.93±9.4	96.8±9.3	<0.0	130.66±11	<0.0	123.66±10	<0.0

<i>Pulse rate (per min)</i>	9	1	01	.35	01	.57	01
<i>Mean BP(mm Hg)</i>	98.66±6.9 1	91.8±6.0 8	<0.0 01	132.06±4. 37	<0.0 01	125.13±4. 56	<0.0 01
Clonidine Group							
<i>Mean Pulse rate (per min)</i>	85.93±7.6 9	76.0±7.9 3	<0.0 01	97.86±7.7 1	<0.0 01	87.33±7.1 3	<0.0 5
<i>Mean BP(mm Hg)</i>	100.46±7. 34	89.66±6. 54	<0.0 01	114.93±7. 69	<0.0 01	104.66±6. 58	<0.0 01