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A PROSPECTIVE COMPARATIVE STUDY OF ORAL CLONIDINE AND ORAL MIDAZOLAM AS PREMEDICANTS FOR GENERAL ANAESTHESIA

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ABSTRACT **INTRODUCTION:** Preanaesthetic medication should be effective and pleasant to be taken orally, have analgesic and non-emetic properties, should not impair cardiovascular stability or depress respiration and produce adequate sedation and anxiolysis. We wanted to compare the effectiveness of oral clonidine and oral midazolam as preanaesthetic medicants. **MATERIALS AND METHODS:** It's a prospective, randomised and double blind study was conducted for one year period. Study participants were selected amongst patients selected for surgery under general anaesthesia requiring endotracheal intubation. Before performing the study, we hypothesised that the beneficial effect of oral midazolam and oral Clonidine alone will be evident in at least 25% of the patients, after reviewing related articles. Considering an absolute improvement in the primary outcome by 40 to 50% in the study group can be considered as clinically relevant and based on a Type I error level of 0.05, Type II error level 0.2 and a two-sided test, we needed 25 patients in each group. Therefore, to account for probable dropouts, a number of 30 patients in each group was proposed. 60 patients were randomly divided into 2 groups of 30 each: Group C(n=30): received Tabletclonidine150 mcg (0.15mg) per orally and Group M (n=30): received Tablet midazolam 7.5mg per orally. Patients between 30 to 50 years of age, 40 to 60 kgs of weight of either sex (male or Female) belonging to American Society of Anesthesiologists' physical status (ASAPS)with grade I and grade II, with duration of elective surgery: 45 minutes to 90 minutes done under General anaesthesia with controlled ventilation by orotracheal tube were included in study. **RESULTS:** Oral Clonidine produced significant attenuation of systolic, diastolic & mean arterial pressure, and reduced respiratory rate, than oral midazolam. Oral midazolam was able to attenuate the pulse rate in a better way than oral clonidine. Oral Clonidine produced significant sedation and anxiolysis in comparison to patients who receiving oral midazolam. **CONCLUSION:** Oral clonidine is the better attenuator amongst the two drugs studied as premedicants to attenuate the cardiovascular responses to laryngoscopy and intubation.

KEYWORDS : Clonidine, Midazolam, Premedication, Haemodynamic Response, Anxiolytics, Sedation

INTRODUCTION

The use of pre-operative medication to facilitate induction, maintenance and recovery after anesthesia has been debated over years. Most anesthesiologists agree on the need for efficient pre-medication.[1] The pattern of desired effects of a pre-medication is however, complex and includes relief of anxiety, sedation and relaxation of the patient. Midazolam is a benzodiazepine with a good absorption pattern after oral administration, and a short elimination half-life. Although one study reported anxiolysis with-out side effects after midazolam premedication, other studies indicated that an effective dose of oral midazolam prolonged recovery times.[2] Midazolam has property to produce amnesia. Benzodiazepine is used frequently as premedication before general anesthesia, because of their anxiolytic, sedative and hypnotic properties. Clonidine attenuates sympathoadrenal responses to painful (tracheal intubation or surgery 4) and other stimuli (e.g., sodium nitroprusside induced hypo-tension4).[3] 2- Adrenoceptor agonists activate pre-synaptic 2-adrenoceptors, thus inhibiting release of norepinephrine from sympathetic nerve endings.4 The exact mechanism of the reduction of the anesthetic requirements is unknown but it is presumed that the decrease is caused by actions on both pre- and postsynaptic 2-adrenoceptors in the central nervous system.[5]

The present study was undertaken to compare the effects of Midazolam and clonidine as premedication.

MATERIALS AND METHODS

It's a prospective, randomised and double blind study was conducted for one year period. Study participants were selected amongst patients selected for surgery under general anaesthesia requiring endotracheal intubation. Before performing the study, we hypothesised that the beneficial effect of oral midazolam and oral Clonidine alone will be evident in at least 25% of the patients, after reviewing related articles. Considering an absolute improvement in the primary outcome by 40 to 50% in the study group can be considered as clinically relevant and based on a Type I error level of 0.05, Type II error level 0.2 and a two-sided test, we needed 25 patients in each group. Therefore, to account for probable dropouts, a number of 30 patients in each group was proposed. 60 patients were randomly divided into 2 groups of 30 each: Group C(n=30): received Tabletclonidine150 mcg (0.15mg) per orally and Group M (n=30): received Tablet midazolam 7.5mg per orally. Patients between 30 to 50 years of age, 40 to 60 kgs of weight of either sex (male or Female) belonging to American Society of Anaesthesiologists physical status (ASAPS) with grade I and grade II, with duration of elective surgery: 45 minutes to 90 minutes done under General anaesthesia with controlled ventilation by orotracheal tube were included in study.

The Exclusion Parameters were patients belonging to American Society of Anesthesiologists physical status (ASAPS) with the grade III, IV and V, any history of allergy, hypersensitivity or contraindication to any of the both study drugs, history of any anticholinergic drug was given before or at the time of induction or during maintenance of anaesthesia. It was a prospective, randomised and double blind study. All the patients were assigned into one of the two groups by using blinded envelopes were prepared with the help of a random number chart. A fellow anesthesiologist who was not involved in the present study was given the study drug in powder form with sips of water, about 90 minutes prior to the induction of anaesthesia. The investigator and the patients were unaware of the nature of the study drug. After detailed history, thorough physical examination and necessary preoperative investigations, Informed written consent was taken from the all selected study patients. Tablet Ranitidine (150mg) and Alprazolam (0,5mg) were given per orally at the night before the surgery. Nil per orally for 6 to 8 hours prior to surgery. Inj. Ondansetron (4mg) I/V was given 30 minutes prior to induction. All patients were monitored with standard monitoring technique. After securing I/V access intravenous fluid (ringer's lactate) was started. Inj. Tramadol (50mg) I/V was given slowly. Pre oxygenation for 5 minutes. Induction was done with inj. Thiopentone (4 mg/Kg). Laryngoscopy and orotracheal intubation was done when adequate jaw relaxation was achieved in a single attempt with Inj.Vecuronium (0.5 mg/Kg). And mechanical ventilation continued. Maintenance of anaesthesia was done with Oxygen & Nitrous oxide (1:2), inj. Vecuronium (0.025 mg/Kg) and intermittent Isoflurane inhalation. At the end of surgery patients were reversed adequately and extubated. Assessment of pulse rate (beats/minute), systolic, diastolic & mean bloods pressure (mm Hg), degree of sedation (Ramsay sedation score)8and anxiolysis (Hamilton anxiety Rating Scale)9 were done at different time period was done by the investigator at seven different time points [Just before the administration of the any study drug which was 90 minutes before to the induction of anaesthesia (1), Just before to induction of anaesthesia (2), three minutes after the orotracheal intubation (3), after that in every 10 minutes for 3 such reading (4,5,6) and three minutes

after the orotracheal extubation (7)].

Statistical Analysis:
Analysis was done only after the Intra Operative Patient Record Sheet of the last subject was in, data was entered, and the computer database cleaned and locked. Data were summarized by routine descriptive statistics. Numerical variables were compared between groups by Student's unpaired t test and Mann-Whitney U test.

RESULTS

Among the total 60 cases 39 were male and 21 were female. The total sex ratio (M: F) is 1.86:1. The mean age was 37.7± 6.67 in Group C, 40.5± 6.92 in Group M. Body weight distribution was 53.1± 5.65 in Group C, 52.8± 5.20 in Group M. They were comparable regarding age and weight and small difference between those mean ages and weight was found to be statistically insignificant (p>0.05). Patients of group C [Clonidine] were having statistically significant fall in systolic blood pressure (SBP) about 90 minutes after the administration of oral clonidine [time point-2] (p<0.01). About 3 min. after the laryngoscopy and orotracheal intubation [time point-3], there was a peak increase of systolic blood pressure in both the groups those were statistically highly significant (p<0.001). This increase was highest in Group M [8.89 %] and was lowest in Group C [7.54 %]. Both clonidine and midazolam produced a statistically significant increase in systolic blood pressure at 13 minutes after intubation [time point-4]. With Clonidine and midazolam, the systolic blood pressure returned to basal value within 23 minutes after intubation [time point-5]. At 33 minutes after intubation [time point-6] and 3 minutes after extubation [time point-7] it came down below the basal level which is statistically significant.

At time point-7 maximum decrease was observed in Clonidine group. There was a peak increase in diastolic blood pressure (DBP) at the 3 min after laryngoscopy and intubation [time point-3] in both groups. This increase was highly significant [p<0.001] in both the groups when compared to basal value. This peak increase was slightly higher in Group M [9.41 %], and lower in Group C [9.15 %]. But there was significant decrease of diastolic blood pressure at the time point -6 & 7 in both Groups. There was a peak increase in mean arterial pressure (MAP) at the 3 min after laryngoscopy and intubation [time point-3]. This increase was highly significant in both the Groups when compared to basal value [p<0.001]. This peak increase was slightly higher in Group M [8.86 %], and lower in Group C [8.45 %]. Both Clonidine and midazolam produced a significant decrease in mean arterial pressure [MAP] at the time point -6 and 7 which was the statistically significant.

Table 1: Percentage (%) of Mean of Mean Arterial Pressure [MAP] Increase [+] or Decrease [-] in Comparison to Time Point-1 [Basal Level] in Group C and Group M

S.No		Time Points					
		2	3	4	5	6	7
1	Group C	1.51	8.45	4.18	0.20	-3.32	-6.04
2	Group M	1.56	8.86	6.05	1.77	-1.04	-4.80

Patients of clonidine Group were having significant rise of pulse rate at just before induction and 3 min., 13 min., 23min. & 33 min. after laryngoscopy and intubation [time point-2, 3, 4, 5 & 6]. These rises were statistically significant. Patients of midazolam Group were having significant rise of pulse rate at just before induction and 3 min., 13 min., & 23 min. after laryngoscopy and intubation [time points-2, 3, 4, & 5]. These rises were statistically significant. There was significant reduction in pulse rate at time point-7. Increase in pulse rate in both groups at just before induction and 3 min., 13 min., & 23 min. after laryngoscopy and intubation [time points-2, 3, 4, & 5] was highest in Clonidine Group & lowest in midazolam Group. Thereafter there was a gradual decrease in pulse rate in both the groups & in midazolam Group decrease from base line value was observed.

Table 2: Percentage (%) of Mean of Pulse Rate [PR] Increase [+] or Decrease [-] in Comparison to Time Point-1 [Basal Level] in Group C and Group M

S.No		Time Points					
		2	3	4	5	6	7
1	Group C	6.52	16.19	12.55	8.78	3.89	0.38
2	Group M	5.58	13.03	8.93	4.59	-0.37	-4.84

Table 3: Changes of Respiratory Rate [RR] in the Group C [Clonidine] Patients (n = 30) and Group M (Midazolam) at Different Time Points

With Clonidine	Time Points	
	RR1 (Breaths/Min)	**RR2 (Breaths/Min)**
Range	12-26	10-24
Mean ± SD	17.1 ± 3.48	15.1 ± 3.44
SE	0.64	0.63
P Value		0.001
With Midazolam		
Range	12-24	11-22
Mean ± SD	16.2 ± 2.99	15.0 ± 2.92
SE	0.55	0.53
P Value		0.0032

Patients of clonidine group were having statistically significant sedation at 90 minutes after the administration of oral clonidine [time point-2] (p=0.002). Patients of midazolam group were having also sedation at 90 minutes after the administration of oral midazolam [time point-2], but that was statistically insignificant (p=0.116).

Table 4: Changes of Sedation Score [Sed Sco] in the Group C [Clonidine] and Group M (Midazolam) Patients at Different Time Points

With Clonidine	**Time Points**	
	SedSco1	**SedSco2**
Range	0-2	0-3
Mean ± SD	0.5 ± 0.73	1.1 ± 0.94
Median ± SD	0 ± 1	1 ± 2
SE	0.13	0.17
P Value		0.001
With Midazolam	**Time Points**	
	SedSco1	**SedSco2**
Range	0-2	0-3
Mean ± SD	0.5 ± 0.57	0.7 ± 0.83
Median ± SD	0 ± 1	1 ± 1
SE	0.55	0.53
P Value		0.116

Patients of clonidine group were having statistically significant anxiolysis at 90 minutes after the administration of oral Clonidine [time point-2].Patients of midazolam group were having little anxiolysis at 90 minutes after the administration of oral midazolam [time point-2] but that was statistically insignificant (p=0.008). But Patients of group M were having little anxiolysis at 90 minutes after the administration of oral midazolam[time point-2] and that was statistically insignificant (p=0.554).

Table 5: Changes of Anxiety Score [Anx Sco] in the Group C [Clonidine] Patients and Group M (Midazolam) Patients at Different Time Points

With Clonidine	**Time Points**	
	AnxSco1	**AnxSco2**
Range	0-3	0-2
Mean ± SD	0.8 ± 0.99	0.4 ± 0.56
Median ± SD	1 ± 1	0 ± 1
SE	0.18	0.10
P Value		0.008
With Midazolam	**Time Points**	
	SedSco1	**SedSco2**
Range	0-3	0-2
Mean ± SD	0.7 ± 0.8	0.6 ± 0.63
Median ± SD	0.5 ± 1	0.5 ± 1
SE	0.15	0.11
P Value		0.554

Oral clonidine as preanaesthetic medication was unable to attenuate the pulse rate, but it produced significant attenuation of systolic, diastolic & mean arterial pressure and reduced respiratory rate too. Oral midazolam as preanaesthetic medication was able to attenuate the pulse rate in a better way than oral clonidine. It produced less significant attenuation of systolic, diastolic and mean arterial pressure throughout the study period. But it reduced respiratory rate significantly. It was also found that oral clonidine produced significant sedation and anxiolysis in comparison to those patients who were pre-medicated with oral midazolam. Therefore, all parameters indicated

that preanaesthetic medication with oral clonidine may be superior to oral midazolam. This result corroborates with the findings of similar study conducted by Paris Andrea.

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.[7] 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.[8] Approximately 50% of the administered drug is metabolised in the liver whereas the rest is excreted unchanged in urine. Midazolam, an imidazobenzodiazepine derivative, is having anxiolytic, hypnotic, anticonvulsant, muscle relaxant, and anterograde amnesic effects.[9] In normal humans, 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. Due to substantial first-pass effect, absolute bioavailability is 30-50%. 60-80% of the dose is excreted in the urine as α-hydroxymidazolam. In young healthy adults, the elimination half-life is between 1.5 and 2.5 hours.[10]

Mrinmoy Das, Manjushree Ray and Gauri Mukherjee [2007] found in their study that clonidine has been shown to reduce perioperative haemodynamic instability. The aim of the study was to investigate the clinical efficiency of oral clonidine premedication in prevention of haemodynamic response associated with pneumoperitoneum. Pradipta Bhakta, B. R. Ghosh, Manjushree Roy and Gouri Mukherjee [2007] conducted a study for evaluation of intranasal midazolam for preanaesthetic sedation in paediatric patients. They concluded that 0.2 mg/Kg intranasal midazolam is an effective method of producing anxiolysis and sedation in paediatric patients. Paris, Andrea [2009] conducted a study for effects of clonidine and midazolam premedication on Bispectral index and recovery after elective surgery. They took, in a randomized, double-blind study, effects of clonidine (150 µg orally), midazolam (7.5 mg orally) and placebo administered 60-90 min prior to estimated anaesthesia induction time were investigated in 60 healthy ASA I or II patients. They indicated that Clonidine augmented haemodynamic stability and partially blunted stress responses as determined by adrenocorticotropic hormone plasma levels. In addition, clonidine did not delay postoperative recovery. Therefore, surrogate parameters indicated that preanaesthetic medication with clonidine may be superior to midazolam in healthy individuals. Oral midazolam as a premedicant was able to attenuate the pulse rate in a better way than oral clonidine. But it reduced respiratory rate significantly too. It was also found that oral Clonidine produced significant sedation and anxiolysis in comparison to oral midazolam.

CONCLUSION

Preanaesthetic medication forms an integral part of anaesthetic management. From the present study it could be concluded that oral clonidine is the better attenuator of cardiovascular responses to laryngoscopy and intubation. Oral Clonidine produced significant sedation and anxiolysis in comparison to oral midazolam. Therefore, oral clonidine could be regarded as drug of choice as a premedicant among the two drugs studied here.

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