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A Comparitive Study of Effect of Two Different Doses of Oral Midazolam Premedication on Induction Dose and Characteristics of Propofol

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Abstract
Background*- The objective of our study was to evaluate the effect of two different doses of oral midazolam premedication on propofol induction dose and characteristics.*
Methods*- 60 ASA I and II patients, falling between the age group of 20-50yrs were randomly divided in to two groups, group A and group B, who received 7.5mg and 15mg midazolam orally 45 mins before the surgery respectively. Before induction, degree of sedation was assessed by Ramsay sedation score. Propofol 1% infusion was started at a rate of 300 ml/hr (50 mg/min) and patients were assessed for 3 clinical endpoints-loss of eye lash reflex, dropping of hand and loss of response to trapezius squeeze.*
Results*- The mean dose of propofol for induction in group A was 2.81±0.41 mg/kg and in group B was 2.14±0.36 mg/kg .The difference between the two groups was statistically very highly significant with p value of <0.001.No significant difference was noted with respect to degree of sedation, changes in the heart rate and means arterial pressure, oxygen saturation between the two groups (p>0.05).*
Conclusion*- Our study concluded that 15mg midazolam premedication offers more benefits than 7.5mg midazolam by reducing induction dose of propofol without any undesirable effects like excess sedation, bradycardia and hypotension.*
Key words*- Propofol, midazolam, premedication, Ramsay sedation score*

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I. Introduction:

Propofol is the most frequently used intravenous anaesthetic today. Propofol is used for induction and maintenance of anaesthesia, as well as for sedation in and outside the operating room.

Though propofol has replaced thiopental as inducing agent because of its smooth induction, rapid and more complete awakening after induction, it produces significant cardio respiratory depression at doses used for induction.[1,2]

Studies have shown that the induction dose of propofol can be reduced without compromising its beneficial effects by midazolam premedication. Also it has been shown that midazolam acts in synergy with propofol[3-5].

Since no similar study has been conducted in our hospital, so we have undertaken this study in which the effects of two different doses of oral midazolam premedication on induction dose and characteristics of propofol are compared.

II. Materials And Methods:

Place of study: Government Medical College, Kota and attached group of hospitals
Time of study: From January-2016 to December-2016
Design of the Study: The type of study was randomized, prospective, double blind study.
Inclusion Criteria: Adult patients of either sex, of ASA grade I or II, falling between the age group of 20-50 yrs with the weights ranging from 40-70kg, presenting for elective surgery under general anesthesia were included in the study, after obtaining a written and informed consent.

Exclusion criteria:

1. Patients with the history of asthma
2. Patients with history of cardiac or hepatic disorders

3. Patients who were taking centrally acting drugs like benzodiazepines, antidepressants.
4. Patients who were on beta blockers.
5. Patients with history of allergy to propofol or midazolam.
6. Pregnant women.

The patients (subjects) were randomly divided in to 2 groups.

Anaesthesiologist 1 blinded to the induction sequence administered the oral midazolam premedication to both the groups.

1. Group A - received 1 oral midazolam tablet (7.5mg) 45 min before surgery.
2. Group B - received 2 oral midazolam tablets (15mg) 45mins before surgery.

In the operating room, i.v. line was secured with 18G cannula and pulseoximeter, non invasive blood pressure and ECG monitors were connected.

Base line heart rate, blood pressure, SpO2 were recorded before induction and were repeated at intervals of 60s for the remainder of the study. Hypotension was defined as decrease in mean arterial pressure more than 25% of baseline and will be treated with iv fluids and mephenteramine 6mg bolus i.v. and bradycardia was defined as heart rate less than 50/min and was treated with atropine 0.6mg bolus i.v.

Anaesthesiologist 2 blinded to the premedication doses conducted the induction sequence. Before induction, the degree of sedation was assessed with the help of Ramsay sedation scale.

After this, infusion of 1% propofol (mixed with xylocard 2mg/ml of propofol) was started at a rate of 300ml/hr (50mg/min)[4] and patients were assessed for 3 clinical end points.

1. The loss of eye lash reflex.
2. Patients' hands were raised every 5sec and the end point was taken as the time (and hence the dose of propofol) at which patients drop their hands.
3. Following this, painful stimulus was applied every 5sec in the form of trapezius muscle squeeze and response in the form of movements was observed[5]. The infusion was stopped as soon as the patient shows no movement to the trapezius squeeze and time was recorded thus completing the study.

Then injection fentanyl (1µg/kg) was given and the tracheal intubation was facilitated by succinyl choline (1mg/kg). The heart rate, blood pressure responses to the intubation were noted. Anaesthesia was maintained with nitrous oxide and oxygen in the ratio of 5:3, 0.25-0.5% halothane and vecuronium 0.04mg/kg bolus and 0.02mg/kg supplemental doses using IPPV and Bain's circuit. Monitoring during anaesthesia was continued with ECG, pulseoximetry and non invasive blood pressure measurements.

At the end of the surgery patients were reversed with neostigmine (0.05mg/kg) and atropine (0.02mg/kg) and extubated tracheally once fully awake.

Data analysis:

Collected data was analyzed by paired and unpaired 't' test. Data was summarized and presented in the form of mean, S.D. percentages and by diagrams. A confidence interval was calculated for the doses at which the end points were achieved. For the analysis of significance Chi-square test was used to obtain other possible association. p value <0.05 is considered statistically significant.

III. Results:

60 patients with ASA physical status 1 and 2 were selected for the study. They were randomly allocated in to two groups of 30 each –Group A (Midazolam 7.5mg) and group B (Midazolam 15mg).

The two groups were compared with respect to age, sex, weight, ASA status, Ramsay sedation score, clinical end points, hemodynamic variables- heart rate, mean arterial pressure, oxygen saturation.

Table 1: Ramsay sedation score

			group		Total
			Group A	Group B	
Ramsay sedation score	1	Count	4	2	6
		%	13.33%	6.67%	10.00%
	2	Count	19	11	30
		%	63.33%	36.67%	50.00%
	3	Count	4	13	17

		%	13.33%	43.3%	28.33%
	4	Count	3	4	7
		%	10%	13.3%	11.67%
Total		Count	30	30	60
		%	100.0%	100.0%	100.0%

X^2=6.84, p=0.021 ns

There was no statistically significant difference between the two groups with respect to Ramsay sedation score.

Table 2:Dose of Propofol

Group	N	Mean	Std. Deviation	t
Propofol Group A dose	30	2.81	0.41	4.64
Group B	30	2.14	0.36	p<0.001 (S)

The mean dose of propofol for induction in group A was 2.81±0.41 mg/kg and in group B was 2.14±0.36 mg/kg .The difference between the two groups was statistically very highly significant with p value of <0.001.

Table 3: Mean Arterial Pressure (mmHg)

	Group	N	Mean	Std. Deviation	p-value
MAP baseline	Group A	30	98.23	13.45	
	Group B	30	98.67	15.21	p=0.01 (S)
MAP 1min	Group A	30	90.21	8.12	
	Group B	30	90.74	12.10	p=0.65(NS)
MAP 2min	Group A	30	84.21	8.32	
	Group B	30	89.67	14.12	p=0.091 (NS)
MAP 3min	Group A	29	80.18	9.32	
	Group B	24	85.36	12.36	P=0.094 (NS)
MAP 4min	Group A	21	79.24	10.24	
	Group B	3	100.00	0.0	p=0.002 (S)

Both the groups were comparable with respect to changes in MAP and there was no statistically significant difference between the two groups.

Table 4: Oxygen saturation

	Group	N	Mean	Std. Deviation	p-value
SpO_2 base line	Group A	30	99.88	0.42	
Group B		30	99.85	0.45	p=0..068 (NS)
SpO_2 1min	Group A	30	99.61	0.18	
	Group B	30	99.68	0.15	p= 0..99 (NS)
SpO_2 2min	Group A	30	99.72	0.42	
	Group B	30	99.87	0.26	p=0.78 (NS)
SpO_2 3min	Group A	29	99.86	0.19	

	Group B	24	99.68	0.24	p=0..81 (NS)
SpO_2 4min	Group A Group B	20 3	99.67 100.00	0.23 0.0	p=0. 64(NS)

The changes in oxygen saturation between the two groups at different time intervals were statistically not significant.

Table 5: Heart rate

	Group	**N**	**Mean**	**Std. Deviation**	**p-value**
HR base line	Group A	30	80.21	16.24	p=0.714 (NS)
	Group B	30	71.65	14.24	
HR 1min	Group A	30	76.34	17.64	p= 0..82 (NS)
	Group B	30	80.23	15.32	
HR 2min	Group A	30	76.35	13.64	p=0.84 (NS)
	Group B	30	76.84	12.45	
HR 3min	Group A	29	75.00	12.45	p=0..876 (NS)
	Group B	24	74.12	13.24	
HR 4min	Group A	21	74.36	16.24	p=0..068 (NS)
	Group B		73.64	14.21	

There was no statistically significant difference between the two groups with respect to heart rate.

IV. Discussion:

Combination of drugs has long been used by anaesthesiologists because no single agent provides all components of general anaesthesia. Also the synergistic action between drugs helps to decrease the dose of a single agent leading to fewer side effects.

Both midazolam and propofol act partially through the same inhibitory transmitter Gamma Amino Butyric Acid located in post synaptic membrane. Their synergy in pharmacologic profiles makes it an excellent combination for co-induction.

Propofol is the most frequently used intravenous anaesthetic today. Though it causes smooth induction, rapid and more complete awakening, it is associated with significant decreases in arterial blood pressure. This decrease in blood pressure is a dose dependent phenomenon[6] and can be avoided by reducing the dose of propofol.

Although in our study we did not observe any significant difference in the degree of sedation between the two groups, group B patients had higher sedation scores compared to group A.

Eren and colleagues[7] compared dexmedetomidine and three different doses of midazolam in preoperative sedation. Dexmedetomidine 1µg/kg and midazolam 0.02mg/kg, 0.04mg/kg, 0.06mg/kg were compared. They observed marked sedation in dexmedetomidine group and midazolam 0.06mg/kg group but of shorter duration in midazolam group because of shorter half-life of midazolam. This study shows midazolam can cause marked but short duration of sedation.

Trivedi and co-workers[8] compared the sedation characteristics of intranasal and sublingual midazolam 0.3mg/kg in 60 paediatric patients reffered for body MRI. They observed that the patients of both the groups were adequately sedated without any adverse effects.

Wilder-Smith and colleagues[9] investigated the propofol requirements for multiple anaesthetic end points in midazolam premedicated patients. They observed that midazolam 0.05mg/kg prior to induction reduced the propofol requirements for multiple end points.

Adachi and others[10] showed that the administration of small doses of midazolam (10µg/kg) decreases the time to achieve hypnosis when compared to placebo. In their study the time required to achieve hypnosis was 180 seconds in midazolam group compared to 262 seconds in placebo group (reduction by 31%).

The mean dose of propofol for induction in group A was 2.81±0.41 mg/kg and in group B was 2.14±0.36 mg/kg .The difference between the two groups was statistically very highly significant with p value

of <0.001.

Our study correlates well with the study conducted by Miller and co-workers[10], where they showed that the amount of propofol required to induce anaesthesia was 1.7mg/kg in the placebo group and 15µg/kg midazolam group where as it was only 1.3mg/kg in midazolam 30µg/kg and 45µg/kg groups, a reduction in the dose of propofol by 25%.

V. Conclusion:

We concluded from our study that oral premedication with midazolam 15mg offers more benefits than midazolam 7.5mg in reducing the propofol dose requirements without any undesirable effects like excess sedation, bradycardia or hypotension.

Conflict of interest:- There is no conflict of interest between authors.

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