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Research Paper

Premedication With Melatonin and Midazolam in Elective Surgeries Under General Anaesthesia - A Clinical Comparative Study

Medical Science

KEYWORDS : midazolam, melatonin, premedication, preoperative anxiety

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ABSTRACT

Preoperative anxiety is as an unpleasant state of tension playing a critical role during intraoperative and post-operative events, may have adverse consequences extended hospital stay,delayed recovery and sleep disturbances. Benzodiazepines alleviate anxiety but may impair psychomotor performance, suppress the duration of rapid eye moment sleep. An alternative drug, melatonin (Nacetyl5methoxytryptamine) causes preoperative anxiolysis by exerting its hypnotic effects through activation of MT1 and MT2 melatonin receptors.

METHODS: After approval from ethical committee, with simple random sampling technique,60 patients fulfilling the inclusion and exclusion criteria divided into two groups of 30 each as follows. Group A: received oral melatonin 6mg, night before surgery and 6mg, two hours before surgery. Group B: received oral midazolam 7.5mg , night before surgery and 7.5mg, two hours before surgery. VAS anxiety scores, VAS orientation score, sedation score, Digit symbol substitution test and Traeger dot test before and after giving the premedication, were studied. Induction dose of propofol and side effects,if any, also studied.

RESULTS: 2 hrs after premedication , VAS anxiety scores with melatonin were 1.13±1.22 whereas with midazolam it was 2.17±.87 , hence p value was significant (<0.0001), sedation scores for group A were 1.10±.31 and group B 1.40±.50 had significant p value of 0.0007. Also TDT and DSST were significant in Group A with p value of 0.04 for both tests.

CONCLUSION: Anxiety was better relieved by melatonin . Midazolam provides better sedation but it impairs psychomotor functions which remains intact with melatonin.

INTRODUCTION:

Preoperative anxiety is a universal reaction experienced by patients who are admitted to the hospital for surgery.

Surgery is a threatening experience, with a multiple stressful components. The unfamiliar and cold environment of the operation theatre makes surgery a potentially unpleasant and uncomfortable experience. This in particular may cause acute distress and high level of anxiety in patients.[1] According to Peplau, 'anxiety is an energy source inextricably related to human development from infancy to death and is required for biological and emotional growth.[2]

Preoperative anxiety may also serve a critical role in the chain of events that control the postoperative pain response. Increased anxiety before a surgery is associated hypertension, dysrrhythmias, apprehension, and nervousness increased requirements for postoperative analgesia and may cause patients to refuse planned surgery. Anaesthesiologists can help their patients overcome their anxiety and avoid its untoward effects.

In clinical practice, melatonin was mainly used for its hypnotic effects in patients suffering from insomnia. In the recent past, a few studies on its anxiolytic effect as a premedicant in perioperative setting, has been explored and compared with either placebo or benzodiazepine such as midazolam, hence this study was designed.

MATERIALS AND METHODS

I) Source of data:

This clinical study consisting of 60 adult patients slated to undergo elective surgeries under general anaesthesia was undertaken at J.S.S. Medical College & Hospital, Mysore.In this randomized, clinical comparative study, we studied 60 ASA Grades I and II patients aged 18 – 55 years, undergoing elective surgeries under general anaesthesia. Approval was taken from the ethical committee and written informed consent was taken from all the patients. They were randomly divided into two groups, Group A and Group B, each consisting of 30 patients.

Sample size calculated using the formula :

Sample size $\eta = \frac{2(z\alpha + z\beta)^2\sigma^2}{d^2}$

Group A: received oral melatonin 6mg, night before surgery and 6mg, 2 hours before surgery.

Group B: received oral midazolam 7.5mg, night before surgery and 7.5mg, 2 hours before surgery

II) Selection of patients: -

A] ***Inclusion criteria*:**

Patients of age group 18 to 55 yrs with ASA grade I and II , undergoing elective surgeries under general anaesthesia, giving informed consent were undertaken for the study.

B] ***Exclusion criteria:***

Patients having upper gastrointestinal disorder advanced liver disease, uremic patients, cardiovascular disease and hypotension ,morbidly obese patients having BMI>35kgm^{-2},patients with ASA grade 3 and 4 , patients with history of alcohol or abusing benzodiazepenes within last 3 months, patients receiving anti emetics within 24 hrs preceding surgery, patients with h/o psychiatric disorders or on any antipsychotic drugs and patients with language or communication difficulties.

III) Methods:-

Preoperative evaluation was conducted on the previous day of surgery. Detailed history was noted. General and systemic examinations of cardiovascular, respiratory and central nervous system and routine laboratory investigations were done.

Group A received Tab. Melatonin 6mg and group B received Tab midazolam 7.5mg on the previous night of surgery. Baseline heart rate ,blood pressure levels and room air saturation were obtained on the morning of surgery two hours before premedication. VAS anxiety scores, VAS orientation score, sedation score and amnesia scores were recorded . Trieger Dot Test (TDT) and a Digit Symbol Substitution Test (DSST) in order to obtain baseline values for

psychomotor ability and cognitive skills were conducted[8].Once these tests were completed, the subjects were given either melatonin 6mg or midazolam 7.5mg as a premedication.

Patients were reassessed two hours after premedication just before surgery for Heart Rate, Blood pressure, VAS anxiety scores, VAS orientation score, sedation score, Amnesia scores, DSST and TDT .

General anaesthesia with controlled ventilation was used. All vitals were recorded in the operation theatre. During induction, the dose of IV propofol at which the patient's ability to respond to commands like 'open your eyes' and when the eyelash reflex lost, were assessed.[8]Postopertively, in the recovery room, same parameters were reassessed to find out degree of sedation and any psychomotor impairment.

Assessments Used In the Study

Visual Analogue Scale

A validated scale which involves the patient rating his/her anxiety by placing a mark on a straight line of a certain length (Kindler et al., 2000; Caumo et al., 2001). One end of the line is "no anxiety" and the other end is "worst anxiety possible.For this study, 10 cm VAS scale was used.[7]

2)Trieger Dot Test (TDT):

The degree of psychomotor impairment was assessed using the Trieger Dot Test. This validated test involves connecting a series of dots to complete a particular shape. By having the subject complete this test before and after administration of melatonin, the extent of psychomotor impairment can be assessed by analyzing the number of dots missed, extraneous deviation of the lines, and time required to complete the test[16]

3)Digit Symbol Substitution Test (DSST):

The degree of cognitive impairment was assessed using the Digit Symbol Substitution Test. The subject's task in this validated test was to draw in certain shapes that correspond to a set of numbers within a certain time period. For this study, the time limit was for 60 seconds. By completing this test before and after administration of melatonin, the extent of cognitive impairment was assessed.[8]

4) VAS Orientation Scores VAS(OS):

Orientation was assessed using orientation scores-

Score 0 – not oriented
Score 1 – orientation in either time or space
Score 2 – orientation in both time and space.[8]

5) Sedation scores (SS):

Level of sedation was recorded using sedation scores

Score 0 – alert
Score 1 – arouses to voice
Score 2 – arouses to tactile stimulation
Score 3- lack of responsiveness.[8]

6) Amnesia scores:

Degree of amnesia was studied using amnesia scoring. The subjects were shown 5 different pictures of fruits and animals before premedication. Two hours after premedication and post surgery patients were asked to recall the images. Number of images recalled were recorded.[16]

STATYSTICAL ANALYSIS

The descriptive statistics was used to summarize the data by measuring mean, median, standard deviation and proportions.

Inferential statistics was done using independent t test and chi-square test. All $p<0.05$ is considered significant.

All the measurements are done using SPSS version 21.0. The graphs were made using Microsoft Excel.

Chi-square test and independent t tests were done.

RESULTS

VAS anxiety scores 2 hours after premedication were 1.13±1.22 and 2.17±0.87 in group B. ($p<0.0001$) which means there significant reduction in anxiety scores two hours after premedication in melatonin group.

Sedation scores 2 hours after premedication were 1.10±0.31 in group A and 1.40±0.50 in group B. ($p=0.0007$) which is significantly less in melatonin group. Patients with melatonin premedication were significantly less sedated.

Heart rate, two hours after premedication had range of 85.47±8.34 in melatonin group, and 89.03±6.93 in midazlam group, p value 0.08 was statistically insignificant.

P value for TDT after two hours of premedication was ($p=0.04$) .P value for DSST after two hours of premedication was ($p=0.04$) .TDT scores and DSST scores were significantly better in melatonin group 2 hours after premedication.

In group A dose of propofol administered for induction of general anaesthesia was 90.67±12.58 mg whereas in group B it was 99.33±2.54.$p<0.0001$,which was statistically significant.

There was significant reduction in propofol dose requirements in case of melatonin

Heart rate in case of melatonin 84.40±16.32 and 120.67±144.09 for midazolam. p value was insignificant ($p=0.2$).Systolic blood pressure for melatonin 116.50±8.77 and for midazolam was 118.33±12.21, ($p=0.5$) was not significant, indicating that there was no difference on the effect of both drugs on blood pressure.Diastolic Blood pressure for melatonin 74.03±6.76 and 118.33±12.21 for midazolam.p = 0.08 was not significant.

VAS anxiety scores for melatonin .70±1.12 and for midazolam were .67±1.06, p= 0.9, was not significant. Hence postoperatively, there was no difference between the anxiety scores in both the groups. Post surgery, sedation scores in group A were 1.10±0.31 and in group B were 1.57±0.57, $p<0.0001$ was statistically significant. Patients in melatonin group were less sedated and orientation scores in group A were 2.00±.00 and in group B 1.80±.41. ($p=0.01$).

Patients in melatonin group were significantly better oriented .Postoperatively, TDT for both groups, ($p=0.6$), which was statistically insignificant, indicating that there was no difference between the psychomotor performance in subjects of either groups.DSST post surgery were also insignificant ($p=0.5$).Amnesia scores postsurgery were also insignificant ($p=0.3$)

DISCUSSION

Anxiety in the perioperative period is defined as an emotional state with diffuse apprehensive feelings, uncertainities, unpleasant sensations of a vague and unspecified nature associated to alienation and insecurity. Several studies have reported that melatonin given as preoperative premedication is associated with sedation and preoperative anxiolysis without cognitive dysfunction including the memory recall.

In our study we investigated the sedative, anxiolytic and amnesic effects of 6 mg melatonin compared with 7.5mg We selected the dose of oral melatonin as 6mg in the night and 6 mg in the

morning, two hours before surgery because we wanted the maximum effectiveness of oral melatonin within safe limits.

In our study we studied Anxiety scores and orientation scores using visual analogue scale, Digit symbol substitution test, Treiger Dot test, Sedation scores, Amnesia scores by showing them five different pictures and dosage of propofol required for induction of general anaesthesia.We did not include a control group receiving placebo as depriving the patients of premedication may be unethical if active drugs are availableas incidence of perioperative anxiety is high. These results were similar and comparable to the present study

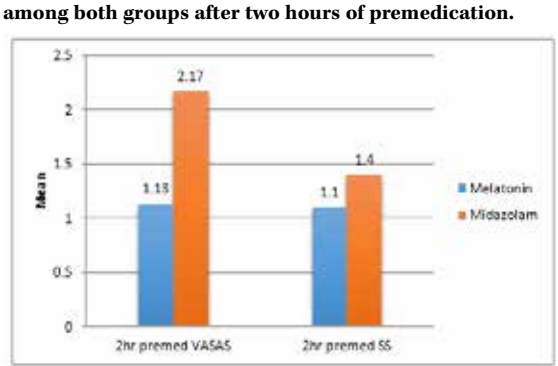
We conducted a study on 60 patients of ASA grade I and II divided into two groups, Group A receiving melatonin and Group B receiving midazolam with similar demographic data in terms of age, sex and weight. We used the DSST and TDT for assessing cognitive and psychomotor function and a number of higher mental functions including sensory perception, vigilance, visual acuity, ability to alter eye fixation quickly, fine muscular coordination, and mental concentration. The TDT is a neuropsychological test of visual attention and task switching. It can provide information about visual search speed, scanning, speed of processing, mental flexibility, and executive functioning.

There was no significant difference between the demographic profile of both the groups. There was highly significant decrease in the anxiety scores (p <0.0001)and sedation scores(p=0.0007) in melatonin group as compared to midazolam group two hours after premedication. In postoperative period sedation scores were significantly lower(p<0.0001) and orientation scores were significantly higher (p=0.01)and better in melatonin group. There was significant reduction in the induction dose of propofol for melatonin group (p<0.0001). There was no significant difference in incidence of amnesia in both the groups(p=0.1). Patients in melatonin group performed DSST (p=0.04)and TDT (p=0.04) significantly better than midazolam group after two hours of premedication. All 30 patients in melatonin group performed DSST and TDT correctly in less than 60 seconds, whereas 4 patients out of 30 could not perform DSST and 4 patients could not perform TDT in midazolam group. P value was 0.04, which was statistically significant. Postoperatively there was no difference in the anxiety between both the groups. All the drugs we used were safe in terms of adverse effects encountered. Many authors have found out that melatonin is therapeutically safer even at very high doses .The minor problems that our patients complained were headache and dizziness. We did not come across any cases of serious cognitive dysfunction or any psychomotor impairment.

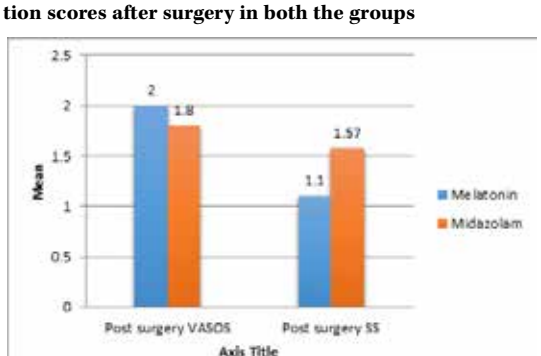
Table 1 : Comparison of VAS(AS),SS , TDT , DSST VAS(OS) between two groups

		GRP						
		Melatonin			Midazolam			
		Mean	SD	Median	Mean	SD	Median	
2hr premedVAS(AS)		1.13	1.22	1.00	2.17	.87	2.00	**<0.0001**
2hr premedSedation scores(SS)		1.10	.31	1.00	1.40	.50	1.00	**0.0007**
Premed dose of propofol administered (mg)		90.67	12.58	100.00	99.33	2.54	100.00	P<0.0001
		Melatonin		Midazolam		p		
		n	Column N %	n	Column N %			
@2hrafterpremedTDT	Done	30	100.0	26	86.7	0.04		
	not done	0	.0	4	13.3			
@2hr afterpremed DSST	done	30	100.0	26	86.7	0.04		
	not done	0	.0	4	13.3			
Postsurgery VAS(os)		2.00	.00	2.00	1.80	.41	2.00	0.01
PostsurgerySedation scores		1.10	.31	1.00	1.57	.57	2.00	<0.0001

Graph 1 :Mean VAS anxiety scores and sedation scores among both groups after two hours of premedication.



Graph 2 : Comparison between VAS anxiety scores and Sedation scores after surgery in both the groups



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CONCLUSION

We would like to conclude that oral melatonin is better than oral midazolam for premedication of adult patients, coming for surgeries under general anaesthesia. 6 mg melatonin may be an adequate dose for premedication. At this dose, melatonin produces anxiolysis with minimal sedation, and a better recovery profile without impairment of cognitive and psychomotor functions. Midazolam has been found to produce postoperative cognitive dysfunction and psychomotor impairment, especially in elderly. However, oral melatonin is known to preserve working memory, memory retrieval, sustained attention, and flexibility of thinking.

Melatonin may be a good choice for patients undergoing ambulatory surgeries and in those situations where the impairment of cognitive functions and amnesia would be detrimental in geriatric age group.

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