SEDATION CHARACTERISTICS OF MELATONIN AND MIDAZOLAM FOR PREMEDICATION OF ADULT PATIENTS UNDERGOING CATARACT SURGERY UNDER LOCAL ANAESTHESIA

RANA ALTAF AHMAD[2], FCPS, ABDULHAMID AL-SAEED, FFARCSI,
SAMIR M. AL-MANSOURI[3], MBBS, KSUF, SALEH A. AL OBEIDAN[3], MD

This prospective, double blind placebo controlled study is designed to compare the effects of sublingual melatonin versus midazolam for premedication of adult patients scheduled to undergo cataract surgery under local anaesthesia. Seventy five patients ASA1&2 ranged from 40-70 yr scheduled for cataract surgery procedure were studied. Patients were classified into 3 groups. Group 1 received midazolam, group 2 received melatonin and group 3 received placebo. Patients in group 1 received sublingual 0.5% midazolam solution 0.1mg/kg body weight. Group 2 received sublingual melatonin0.05mg/kg body weight. The control group received sublingual placebo (saline).All drugs were given 100 min before the local block. Sedation, anxiety and orientation were quantified before and 10, 30, 60 min after premedication and 15, 30, 60 min after admission to the recovery room. One way ANOVA and non-parametric Kurskal-wallis test were for statistical analysis.

Patients who received premedication with either midazolam or melatonin had significant decrease in anxiety levels compared with control group and midazolam group significant increase in level of sedation before operation was noticed compared with melatonin and control groups ($p<0.05$). Midazolam produced highest scores of sedation at 30 and 60 min after administration and significant psychomotor impairment in the preoperative period compared with melatonin and placebo groups($p<0.05$). Postoperative patients who received midazolam, melatonin premedication showed no increase in level of sedation at all intervals. There was no significant difference between the groups for anxiety levels or trigger dot testing performance after operation compared with control ($p>0.05$). Amnesia was not significant in both the groups. In conclusion, melatonin can be used effectively for premedication of adult patients without hangover effect compared to midazolam.

Introduction

MIDAZOLAM BELONGS TO A CLASS of benzodiazepine derivative characterized by rapid onset of action[14]. Following oral administration, peak plasma concentration rises within 30 to 45 min. The onset of sedative effects has been reported within 15 min, with peak effects in 30 to 60 min. Elimination half-life after intravenous administration was reported to be 2.3 h. The bioavailability after the ingestion of 10, 20 and 40 mg midazolam in the form of a tablet ranged from 31 % to 73% due to extensive first pass hepatic extraction of midazolam[15]. The pineal hormone melatonin (n-acetyl-5-methoxytryptamine) has several putative functions including regulation of circadian rhythms, regulation of the reproductive axis, and antioxidant activity[1, 2, 3]. Auto radiographic studies and receptor assays have demonstrated the presence of melatonin receptors in various regions of the central nervous system and in other tissues in humans[4]. Exogenous administration of melatonin has been found by several investigators to facilitate sleep onset and improve quality of sleep [5, 6]. Available data suggest that the sleep inducing properties of melatonin may differ from those of benzodiazepines. Benzodiazepine derivative reduces duration of (REM) sleep after single administration of high dose or long time administration of low dose [7, 8]. Benzodiazepine also reduce slow wave sleep thus negatively influencing sleep quality but in contrast single dose melatonin produce no suppression of REM sleep and there is no hangover effects like

[1]Department of Anesthesia, College of Medicine, King Saud University Hospitals
[2]Department of Anaesthesia and
[3]Department of Ophthalmology, King Abdulaziz University Hospital, College of Medicine, King Saud University, Riyadh.
Address for correspondence: Rana Altaf Ahmad, DA – FCPS, Consultant Anaesthetist, King Abdulaziz University Hospital, P.O. Box 245, Riyadh 11411, Kingdom of Saudi Arabia.
E-mail: drranaaltaff@yahoo.com

benzodiazepine[9,10]. This prospective, randomized, double blind placebo controlled study was conducted to compare the effects of sublingual melatonin versus midazolam as premedication in local anaesthesia for cataract surgery in adult patients. The sedative, anxiolytic and amnesic effects of both drugs in addition to residual effects in the immediate postoperative period were evaluated.

Patients and Methods

After obtaining institutional approval and informed consent from patients, we studied 75 ASA physical status I,II patients, Age (40 – 70 y) weigh 44-90 kg scheduled for cataract surgery . Patients who were taking centrally acting drugs consuming monoamine oxidase inhibiters, or allergic to study drugs were excluded. The day before study the principal investigator explained the study plan and showed the patients the different scales used in the assessment. Approximately 100 min before surgery patients were shifted to an isolated quite room in the holding area. A pulse oximeter probe was placed on all patients and Spo2, arterial blood pressure and heart rate were monitored continuously. Resuscitative equipment was immediately available at the bed side. Patients were allocated randomly to one of the three groups (n=25 each). First group received sublingual 0.5% midazolam 0.1 mg/kg . The second group received sublingual melatonin 0.05mg/kg body weight. The third group received sublingual placebo (saline). Study drugs and placebo were prepared to a volume of 3ml in a syringe from which needle was removed, marked only with coded label to maintain the double blind nature of study. The content of the syringe was given sublingually approximately 60 min before block of the eye by the anaesthesia technician who was not involved in data collection. At 180 sec the patient will be permitted to swallow the medication. A visual analogue scale (VAS) was used to evaluate sedation and anxiety levels. The scale was a 50 cm long and 10cm high card diagonally divided to a white and bright red triangle. The centimeter scale was on the rear side of the card[16]. The extremes are marked no sedation/anxiety at the white end and sedation/anxiety as bad as ever at the red end. The same interpreter-blinded to group assignment-evaluated VAS for anxiety; orientation score {0=none, 1=orientation in either time or place, 2=orientation in both}; Sedation score {1= awake, 2=drowsy, 3=asleep but arousable, 4=asleep but not arousable} before 10, 30, and 60 min after the administration of premedication and postoperatively at 15, 30, 60 min after admission to post anaesthesia care unit (PACU). Patients were asked to perform the trigger dot test (TDT) at these times. This test was used to quantitatively assess psychomotor activity. All patients positioned with 30 degree head elevation and used the same writing implement (ball point, medium point, black) for all tests. The TDT score represented the total number of dots (42) connected. TDT deviation represented the cumulative shortest distance in mm between the drawn lines and missed dots to account for inter-patient differences in test taking ability. TDT scores and TDT deviations were normalized to baseline scores and deviation for each patient. Changes in scores of different tests and TDT deviation and TDT time relative to baseline values were compared. Amnesia was assessed by showing patients two simple colored figures star and rectangle before premedication. Patients were queried 24 h later as to recall of the figures. In the holding area, an infusion of 5% D/W with ½ NS was started. All the blocks were performed by the ophthalmologists. Peribulbar block was given to all patients using inferior and superior approach by 5ml of Xylocaine 2% and bupivacaine 0.5%. At each block toleration to the procedure was assessed. Standard monitoring were used i.e. pulse oximetry, non invasive blood pressure (NIBP), and Electrocardiography (ECG) (Datex-Ohmeda, Finland).The intraoperative sedation and tolerance to the procedure was done by the concerned anesthetist of the case. In the recovery room the same tests were repeated. Postoperative pain was treated with injection diclofenac sodium 1-2 mg/kg b.w.

One way ANOVA was used to compare the mean values of quantitative variables across the three drug groups. A non-parametric Kurskal-wallis test was used to compare the scores of outcome variables across the three drug groups. A p- value <0.05 was considered significant.

Results

Patients in the three groups were comparable in age, weight, surgery and anaesthesia times (p>0.05) (Table 1). There was no significant difference in VAS for anxiety measurement between the groups after giving premedication at 10, 30, 60 min as well

as postoperativcly at the same interval compared to baseline (p>0.05) (Fig 1).

Table: 1. *Comparison of patients across the three drug groups in relation to Age ,weight, Surgery time and Anaesthesia time*

Variables	Groups Placebo	zolam	tonin	F-value	p-value
Age (yr.)	58.1	57.1	58.0	58.0	0.92
Weight (kg.)	74.9	74.8	76.6	0.08	0.92
Surgery Time(min.)	57.7	58.8	53.3	0.34	0.71
Anaesthesia Time (min.)	83.5	83.7	76.8	0.40	0.67

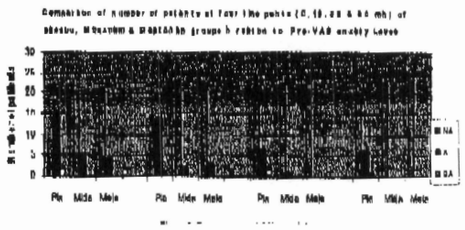

Fig. 1.

There was no significant difference in orientation score between the two groups compared with the baseline in preoperative and postoperative period except in two cases of midazolam group where patients were in deep sleep after pre-medication and surgery has to be cancelled (p>0.05). Furthermore, patients in the midazolam group showed significant (p<0.05) high level of sedation compared with melatonin group at 30 and 60 min (Fig 2). Postoperatively there was no difference in level of sedation of groups 1 and 2 at all intervals compared with the placebo group 3 (Table 2). Orientation score was similar except at 15 and 30 min after premedication in midazolam group. At that time only 20 patients were orientated to time and place compared to melatonin (24%) and placebo (23%) respectively. Regarding psychomotor function, there was significant difference in performing the TDT test for the midazolam group preoperatively at 15, 30, 60 min interval compared to melatonin and placebo (p<0.05) (Figure 3), but there were no difference in the time needed for TDT score or dot missed in the postoperative period between the groups (Fig. 4). Patients who were in deep sleep (asleep but not arousable) were unable to perform the TDT and are not included in the statistical analysis (midazolam group) (Table 2). Two of the patients in the midazolam group were cancelled due to deep sleep (level 4) and inability to give local peribulbar block. In the melatonin group, none of the patients was cancelled. In the midazolam group at 24 hr four patients did not recall the one diagram shown to them. In the melatonin group all patients recalled the two diagrams shown to them. Twenty percent of patients in the midazolam group and 22% of patients in the melatonin group were satisfied with their premedication compared with 15% in the placebo group. Tolerance to the procedure was bad in 4 cases of midazolam group due to hangover effect. The tolerance to the procedure was good in 24 patients in melatonin group compared to placebo. Pain was not experienced by any patient in melatonin and midazolam group. Only one patient in placebo group complained of pain and was treated with diclofenac injection.

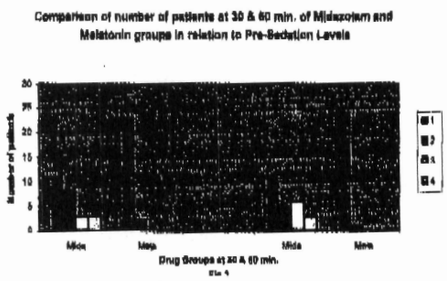

Fig. 2.

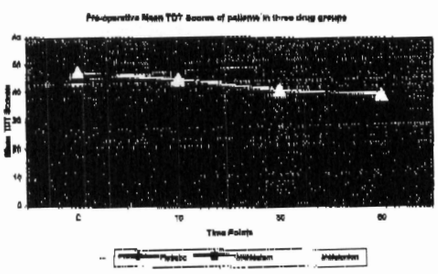

Fig. 3.

Table:2 . *Comparison of Number of Patients at Pre and Post operative stages in relation to VAS-anxiety of three drug groups*

Variables	Groups			p-value
	Placebo	Midazolam	Melatonin	
Pre-anx-C				
Not anxious	19	20	21	<0.0001
Anxious	14	5	4	
Extremely Anx.	2	-	-	
Pre-anx-10				
Not anxious	10	23	22	0.003
Anxious	14	2	3	
Extremely Anx.	1	-	-	
Pre-anx-30				
Not anxious	17	22	25	0.001
Anxious	6	1	-	
Extremely Anx.	2	-	-	
Pre-anx-60				
Not anxious	18	23	25	0.001
Anxious	6	-	-	
Extremely Anx.	1	-	-	
Post-anx-15				
Not anxious	23	24	24	0.37
Anxious	2	-	1	
Post-anx-30				
Not anxious	23	24	25	0.14
Anxious	2	-	-	
Post-anx-60				
Not anxious	23	24	25	0.14
Anxious	2	-	-	

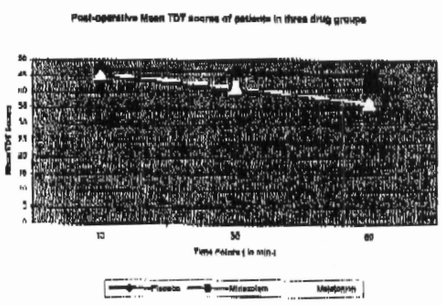

Fig. 4.

Discussion

We have demonstrated that patients who received premedication with either sublingual 0.5% midazolam (0.1mg/Kg) or melatonin (0.05 mg/Kg) had significant decrease in anxiety levels .We also noted that there was significant increase in sedation level with midazolam versus melatonin preoperatively. Previously we studied the effect of melatonin as premedication compared to midazolam in patients receiving general anaesthesia[17].

For a long period of time oral benzodiazepine are used as premedication for their anxiolytic effects in performing local blocks for cataract surgery[18]. Ophthalmologists are concerned because of its sedative and hangover effects. It is documented in other studies that premedication with midazolam was associated with preoperative anxiolysis, sedation and impairment of psychomotor skills[19,20, 21] that combination effects were not good for a patient who underwent local block for ophthalmic surgery and in whom the ophthalmologist needs full cooperation of the patient while performing surgery.

In this study the dose of melatonin 0.05mg/Kg showed no sedative effect compared with midazolam[22]. When compared in the preoperative period only patients in the midazolam group experienced significant impairment of psychomotor skills and significant sedation compared to melatonin and control groups. There was significant reduction in the anxiety in the melatonin and midazolam group when compared with control preoperatively. However, there was no significant difference between all the groups regarding anxiety, sedation scores and TDT performance postoperatively. Amnesia was notable only in the midazolam group for one preoperative event. The amnesic properties of benzodiazepines are already well documented[23]. Our results showed that melatonin had no amnesic effects. The TDT deviation and score impairment relative to the baseline was noted in the midazolam group in the preoperative period and sedative effect was at grade 4 (asleep not arousable). Our results are in accordance with the other studies on psychomotor functions produced by midazolam premedication[19, 20]. On the other hand, with melatonin the dose used in our study, there was no impairment in TDT scoring relative to baseline at peak effect time of 30, 60 min[24]. The peak sedation effects of midazolam were noted at 30 and 60 min respectively after sublingual administration[25]. No patient was asleep in the melatonin group at all

levels. The use of melatonin in anaesthesia was started by the author as a premedication drug and found to be good when compared with the sublingual midazolam and even now onward melatonin is being tried as intravenous induction agent in rats (17,26).

Table: 3 Comparison *of Number of Patients at Pre and Post operative stages in relation to Sedation of three drug groups*

Variables	Groups			p-value
	Placebo	Midazolam	Melatonin	
Pre-sed-C				
Awake	25	25	25	1.0
Pre-sed-10				
Awake	25	23	25	0.13
Drowsy	-	1	-	
Asleep	1	-	1	
Pre-sed-30				
Awake	25	11	23	<0.0001
Drowsy	-	8	2	
Asleep	-	3	-	
Asleep & not arousable	-	3	-	
Pre-sed-60				
Awake	25	11	24	<0.0001
Drowsy	-	5	1	
Asleep	-	6	-	
Asleep & not arousable	-	3	-	
Post-sed-15				
Awake	25	23	25	0.35
Drowsy	-	1	-	
Post-sed-30				
Awake	24	23	24	0.99
Drowsy	1	1	-	
Asleep	-	-	1	
Post-sed-60				
Awake	25	23	25	0.35
Drowsy	-	1	-	

We concluded that sublingual melatonin is better than sublingual midazolam for premedication of adult patients undergoing cataract surgery under local anaesthesia. Furthermore, unlike benzodiazepines, melatonin does not induce hangover effects.

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