Original Research Article

Indian Journal of Anesthesia and Analgesia
2018;5(1):099-103
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.5118.15

Comparison of Two doses of Melatonin for Pre-Operative Anxiolysis in Adult Patients

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Abstract

Aims: This study was done to determine the efficacy of melatonin as a pre-operative anxiolytic and to compare the effect of two different doses of melatonin for the same. *Settings and Design:* This is a randomised double blinded study. *Methods and Material:* 90 patientsundergoing elective surgery under general anesthesia were enrolled in the study. They were randomised to three groups using a computer generated random number table. They received the study drugs (either placebo, tab. Melatonin 3mg, or tab Melatonin 6mg) placed in identical opaque envelopes. Anxiety was assessed using the VAS anxiety scale and the Amsterdam Preoperative Anxiety and Information Scale (APAIS). Heart rate and blood pressure were measured as the physiological markers of anxiety. Sedation was assessed with the Ramsay Sedation Scale. All these values were recorded before and 60- 90 min after administration of the study drugs. Haemodynamics were also recorded 1 min after intubation. *Statistical Analysis Used:* One-way ANOVA was used for intergroup comparisons of normally distributed data. For comparison of before-after data within a group, students t- test was used. For comparing binomial data like sex and ASA status, the Chi square test was used. *Results:* Anxiety and sedation scores were found to be significantly reduced in patients receiving melatonin 3mg or 6mg, compared to those receiving placebo. Patients receiving melatonin also had lower heart rate and blood pressure after medication and also 1min after intubation. *Conclusions:* We conclude that oralmelatonin is effective for pre-operative anxiolysis in adult patients and a dose of 3mg is adequate for anxiolysis.

Keywords: Melatonin; Pre-Medication; Anxiolysis.

Introduction

Patients scheduled to undergo surgery often experience anxiety. Anxiety arises from apprehension related to the surgical procedure, anaesthesia, and other factors. Preoperative anxiolysis is beneficial as it improves patient satisfaction and reduces postoperative pain and anxiety. Benzodiazepines such as diazepam, alprazolam and midazolam have commonly been used as anti-anxiety drugs in the preoperative setting. Sedation and psychomotor impairment are some of the common side effects of benzodiazepines. Melatonin [1] (N acetyl 5 methoxytryptamine) is an endogenous hormone secreted by the pineal gland. Endogenous melatonin is well recognised for its role in regulation of the circadian rhythm. Pharmacological doses of melatonin have been shown to be effective in treatment of sleep disorders and circadian rhythm disorders. Melatonin has also been used in the treatment of migraine, prevention of cluster headache, jet lag, winter depression, chronic fatigue syndrome, nicotine withdrawal, tardive dyskinesia, adjuctive therapy in cancer, chemotherapy related thrombocytopenia etc [2]. In recent years, many randomized trials [3,4] have investigated the use of melatonin in the perioperative period. Melatonin administered pre-operatively has been found to reduce anxiety in patients undergoing surgery.

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Received on 21.09.2017, **Accepted on** 13.10.2017

We compared two different doses of oral melatonin 3mg, and 6mg, for pre-operative anxiolysis in adult patients undergoing elective surgeries under general anesthesia.

Subjects and Methods

After obtaining institutional ethical committee approval, 90 patients undergoing elective surgery under general anesthesia were enrolled. Informed written consent was taken from all patients. They were randomly allocated to three groups: GROUP C (control group), GROUP M3 (3mg Melatonin group) and GROUP M6 (6mg Melatonin group). Randomization was done with the help of a computer generated random number table. The study drugs were kept in identical opaque envelopes, thus the patient as well as the investigator were blinded to the group allocation of the patient.

Inclusion Criteria

- ASA physical status I and II patients,
- AGE between 18-60 years,
- Patients undergoing elective surgery under general anesthesia.

Exclusion Criteria

- ASA physical status III or more,
- Patients already receiving melatonin for treatment of other conditions,
- Adults with a history of psychiatric disorders, on anti-psychotic drugs, anti-depressants, antiepileptic drugs,
- Obesity and drug allergy,
- Pregnant and lactating women,
- Patients not willing to participate in the study

Preparation and Procedure

Preoperative

The study drug was administered with a few sips of water 60- 90 min before the start of surgery. Anxiety of the patients was assessed by using the VAS anxiety scale [5] and the Amsterdam Preoperative Anxiety and Information Scale (APAIS) [6]. Heart rate and blood pressure were measured as the physiological markers of anxiety. Sedation was assessed with the Ramsay Sedation Scale [7].

All these values were recorded before and 60- 90 min after administration of the study drugs.

Intraoperative

Standard monitoring was done using 5 lead ECG, pulse oximetry and non-invasive blood pressure. Anaesthesia was induced with intravenous injection fentanyl and propofol. Muscle relaxation was achieved with injection atracurium. Airway was secured with endotracheal tube, size 8mm ID in male patients and 7 mm ID in female patients.

The heart rate, systolic and diastolic blood pressures were recorded 1 minute after intubation

Results

One-way ANOVA was used for intergroup comparisons of normally distributed data. For comparison of before- after data within a group, students t- test was used. For comparing binomial data like sex and ASA status, the Chi square test was used. Data are expressed as mean ± SD.

The three groups were comparable with respect to age, sex and ASA status.

Anxiety and sedation scores were compared before and 60-90 min after study drug administration. VAS and APAIS anxiety scores were comparable between the three groups before study drug administration.

There was a significant decrease in APAIS anxiety scores in the study groups after study drug administration (p value- 0.000). Before-after comparisons within the groups showed a decrease in scores in all three groups. The decrease in group C was not significant (p value 0.32), whereas it was significant in Groups M3 and M6 (p values- 0.000 and 0.000 respectively).

There was a significant decrease in VAS anxiety scores in the study groups after study drug administration (p value- 0.002). Before- after comparisons within the groups showed a significant reduction in all three groups (p values of 0.0315, 0.000 and 0.000 respectively for groups C, M3 and M6).

Before study drug administration, all patients were awake with a RAMSAY sedation score of 2. There was an increase in the sedation scores in the study groups after drug administration (p values of 0.001 and 0.000 respectively for groups M3 and M6).

Table 1: Demographic features

	Group C	Group M3	Group M6	p- value
Age (mean ± SD)	35.0 ± 9.4	38.2 ± 10.5	36.1 ± 11.0	0.478
Sex (M:F)	14: 16	17: 13	15: 15	0.733
ASA status (I: II)	20: 10	16: 14	19: 11	0.545

Table 2: Anxiety and sedation scores

Parameter (Mean ± SD)	Group C	Group M3	Group M6	P value intergroup
APAIS anxiety before medication	15.1 ± 4.8	15.8 ± 3.4	14.8 ± 4.1	0.632
APAIS anxiety after medication	14.0 ± 3.6	11.3 ± 3.0	10.1 ± 2.1	0.000
P value (before- after)	0.320	0.000	0.000	----
VAS anxiety score before medication	4.9 ±2.0	5.5 ± 1	5.0 ± 1	0.218
VAS anxiety score after medication	4.0 ± 1.0	3.5 ± 1.5	2.8 ± 1.2	0.002
P value (before- after)	0.0315	0.000	0.000	----
RAMSAY score before medication	2 ± 0	2 ± 0	2 ± 0	----
RAMSAY score after medication	2 ± 0	2.4 ± 0.6	2.5 ± 0.6	0.000
P value (before- after)	---	0.001	0.000	-----

Table 3: Hemodynamic parameters

Parameter (mean ± SD)	Group C	Group M3	Group M6	P value for intergroup
HR before medication	80.4 ± 7.6	78.0 ± 10.2	81.3 ± 8.4	0.329
HR after medication	78.0 ± 6.0	72.4 ± 9.0	71.1 ± 6.0	0.001
P value (before- after)	0.180	0.028	0.000	----
HR 1min after intubation	101.0 ± 10.7	96.1 ± 11.2	84.0 ± 12.4	0.000
Systolic BP before medication	122.0 ± 8.0	126.0 ± 10.1	120.4 ± 8.2	0.096
Systolic BP after medication	120.0 ± 8.4	124.0 ± 7.8	116.0 ± 7.6	0.001
P value (before- after)	0.349	0.394	0.035	----
Systolic BP 1 min after intub.	146.4 ± 10.0	135.4 ± 11.1	128.4 ± 5.3	0.000
Diastolic BP before medication	82.2 ± 6.8	84.0 ± 7.0	80.4 ± 7.2	0.144
Diastolic BP after medication	80.0 ± 4.8	80.1 ± 5.1	76.4 ± 4.8	0.005
P value (before- after)	0.153	0.017	0.014	----
Diastolic BP 1min after intub.	96.1 ± 10.2	90.0 ± 8.5	84.0 ± 7.7	0.000

Heart rate and blood pressures were compared between the three groups before and after administration of study drug. Heart rate, systolic and diastolic blood pressures were comparable between the three groups before study drug administration. After study drug administration, there was a significant difference in the heart rates between the three groups (p value- 0.001). Before- after comparisons within the groups showed no significant decrease in Group C and a significant decrease in heart rate in Groups M3 and M6 (p- values of 0.028 and 0.000 respectively). Heart rates compared one minute after intubation also showed significantly lower heart rates in the study groups (p- value 0.000).

After study drug administration, systolic BP was significantly lower in Group M6 (p value- 0.001). Before- after comparisons within the groups showed no significant change in Groups C and M3, and a significant decrease in Group M6 (p value- 0.035). There was also a significant reduction in the systolic blood pressure in the study groups 1 min after intubation (p value- 0.000). After study drug administration, diastolic BP was significantly lower in Group M6 (p value- 0.005). Before- after comparisons within the groups showed no significant change in Group C, and a significant decrease in Groups M3 and M6 (p values- 0.017 and 0.014 respectively). There was also a significant reduction in the diastolic blood pressure in the study groups 1 min after intubation (p value-0.000).

Discussion

T Patel [8] et al did a comparative study between oral melatonin and oral midazolam on preoperative anxiety, cognitive, and psychomotor functions. Oral melatonin 0.4 mg/kg was found to provide adequate anxiolysis comparable to that of oral midazolam. Also, unlike midazolam, melatonin did not impair the general cognitive and psychomotor functions. These results are consistent with our study. However, a higher dose of melatonin has been used in this study (0.4 mg/kg).

D Ionescu [9] et al studied the effect of melatonin as premedication for laparoscopic cholecystectomy

in a double- blind, placebo-controlled study. Oral melatonin 3mg administered the night before and on the morning of surgery was compared with oral midazolam (3.75mg) and placebo. Melatonin and midazolam both provided anxiolysis but melatonin was found to produce better perioperative anxiolysis, and a better recovery profile as assessed by sedation and memory. In our study, melatonin in the dose of 3 or 6mg has been shown to produce adequate pre-operative anxiolysis.

M Acil [10] et al studied the perioperative effects of melatonin and midazolam premedication on sedation, orientation, anxiety scores and psychomotor performance. In this study, melatonin was given sublingually in the dose of 5mg. Melatonin premedication was associated with preoperative anxiolysis and sedation without postoperative impairment of psychomotor performance. The results are consistent with our study.

M Naguib [11] et al compared melatonin and midazolam for pre-medication in a double- blind, placebo controlled study. Patients were given sublingual midazolam 15 mg, melatonin 5 mg or placebo, approximately 100 min before a standard anaesthetic. Patients receiving the study drugs had a significant decrease in anxiety levels and increase in levels of sedation preoperatively. Pre-operatively, midazolam was found to produce more sedation and psychomotor impairment.

The same authors (M Naguib [12] et al) studied the comparative dose-response effects of melatonin and midazolam for premedication of adult patients in a double-blinded, placebo-controlled study. Doses of 0.05, 0.1, or 0.2 mg/kg sublingual midazolam or melatonin or placebo were given to 84 women, approximately 100 min before a standard anesthetic. Patients who received the study drugs had a significant decrease in anxiety levels and increase in levels of sedation preoperatively. Midazolam was found to produce significant psychomotor impairment. Patients receiving higher dose of midazolam had higher post-operative sedation levels. The authors concluded that melatonin was a good choice for ambulatory surgery patients, and a dose of 0.05 mg/kg melatonin was an adequate dose for premedication.

These results are consistent with our study, since we have shown adequate anxiolysis with 3 mg of oral melatonin.

In our study, we compared the hemodynamic parameters of heart rate and systolic and diastolic blood pressure, as markers of anxiety. Patients receiving the study drugs had a significant decrease in heart rate and blood pressures, which was consistent with decrease in anxiety. We also compared the hemodynamic parameters 1 min after intubation. Patients receiving melatonin had lower heart rates and blood pressures 1 min after intubation, compared to controls. Two recent studies by AA Mohamed [13] et al and P Gupta [14] et al have shown melatonin to be effective in attenuation of haemodynamic response to laryngoscopy and intubation. These results are consistent with our study.

Conclusion

We conclude that oral melatonin is effective for pre-operative anxiolysis in adult patients and a dose of 3mg is adequate for anxiolysis.

Key Messages

Melatonin, an endogenous hormone, has been shown in clinical studies, to have anxiolytic effects. We compared two doses of oral melatonin, 3mg and 6mg for pre-operative anxiolysis in adult patients. We found that oral melatonin is effective for pre-operative anxiolysis in adult patients and a dose of 3mg is adequate for anxiolysis.

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