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Oral Agomelatine and Ramelteon for Pre-operative Anxiolysis and Sedation: A Prospective, Randomized Comparative Study

Salin Kumar Adusumilli[1], Pradeep Hosagoudar[2], M Venkateswara Pradeep[3]

[1]Assistant Professor, Department of Anesthesiology, Alluri Sitaram Raju Academy of Medical Sciences, Eluru, Andhra Pradesh 534005, India. [2]Professor and Head, Department of Anesthesiology, Kodagu Institute of Medical Sciences, Madikeri, Karnataka 571201, India. [3]Resident, Department of Anesthesiology, P.E.S. Institute of Medical Sciences and Research, Kuppam, Andhra Pradesh 517425, India.

Abstract

Background: Adequate pre-operative anxiolysis and sedation are important in patients undergoing surgery. Agomelatine and Ramelteon are analogues of melatonin and have been used routinely to induce sleep in insomnia patients. *Aims:* To compare the effects of Tab. agomelatine and Tab. ramelteon on pre-operative anxiety, sedation and orientation. *Subjects and Methods:* This was a prospective, randomized, comparative study conducted after institutional ethics committee approval on 60 ASA I adult patients undergoing elective surgeries under general anesthesia. After obtaining written and informed consent, the patients were randomly allocated into two equal groups: Group A (n = 30) received Tab. agomelatine *10 mg* and Group R (n = 30) received Tab. ramelteon *8 mg* orally, *1 hour* before induction of anesthesia. Patient's anxiety, sedation and orientation were assessed at 0, 15, 30, 45, 60 minutes and before induction of anesthesia. *Statistical Analysis:* Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver. 2.11 were used for analysis of data. Data was expressed as mean ± standard deviation or absolute values. Qualitative data were compared with the Chi-square test and fisher's exact test. Quantitative variables were compared with the student 't' test. The level of statistical significance was set at $p < 0.05$. *Results:* Decrease in anxiety levels from baseline in both the groups and greatest reduction was at *15 minutes*. In both the groups, increasing sedation score was noted after *15 minutes* and greatest sedation around *60 minutes*. Orientation score between the two groups was unchanged from baseline and between the two groups as well and hence no p-value. *Conclusion:* Tab. agomelatine *10 mg* and Tab. Ramelteon *8 mg* administered orally, *60 minutes* before induction of anesthesia provided comparable anxiolysis and sedation but did not affect orientation of the patient.

Keywords: Melatonin; Agomelatine; Ramelteon; Sedation; Anxiety.

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Introduction

Pre-operative anxiety is common in patients undergoing surgery and it is described as an unpleasant state of uneasiness or tension that is secondary to a patient being concerned about a disease, hospitalization, anesthesia and surgery, or the unknown.[1,2] High anxiety levels will have all the signs of sympathetic stimulation and stress and may have unfavorable effects on induction and maintenance of anesthesia as well as on the recovery from anesthesia and surgery.[1] It may cause patients

Corresponding Author: Pradeep Hosagoudar, Professor and Head, Department of Anesthesiology, Kodagu Institute of Medical Sciences, Madikeri, Karnataka 571201, India.

E-mail: drpaddy82@gmail.com

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to avoid planned surgery. Anxious patients require higher doses of anesthetic induction agents and post-operative analgesic drugs.[1,3]

Melatonin (N-acetyl-5-methoxy tryptamine), is a naturally occurring neurohormone secreted by pineal gland in humans.[3] Several studies have reported that Melatonin cause pre-operative anxiolysis and increase the level of sedation without impairing orientation.[3] The hypnotic property of melatonin endows this neurohormone with the profile of a novel hypnotic and anesthetic sparing effect.[4] Melatonin has analgesic potential in addition to anxiolytic and sedative effects without disturbances of the cognitive and psychomotor skills and thus improves the quality of recovery.[5] Agomelatine and Ramelteon are analogues of Melatonin and having the above advantages, were used to compare their effects in our study.

Aims and Objectives

To compare the effects of Tab. agomelatine *10 mg* and Tab. ramelteon *8 mg* on pre-operative anxiety and sedation in patients undergoing elective surgeries under general anesthesia and to compare their effects on peri-operative orientation.

Materials and Methods

This was a prospective, randomized, comparative study conductedin a 750 bedded tertiary care hospital between *December 2016* and *June 2018* after obtaining Institutional ethics committee approval. After obtaining written and informed consent, a total of 60 ASA I patients scheduled for elective surgeries under general anesthesia, were randomly allocated by envelope method into two equal Groups. Patients in Group A received Tab. agomelatine *10 mg* whereas those in Group R received Tab. ramelteon *8 mg* orally *60 minutes* before induction of anesthesia. Considering the power of study at 80% and α-errorat 95%, the minimal sample size in each group was 20. However, we included 30 patients in each group to make up for possible drop outs and better validation of results.

Patients scheduled for elective surgery under general anesthesia with ASA physical status Class I, aged between *18* and *60 years*, weighing *40–70 kgs* consenting (written and informed consent) to participate in the study were all included. Patient's refusal, age more than *60 years* or less than *18 years*, ASA physical status Class II and above, pregnant and lactating women, patients with sinus bradycardia/heart block/conduction defects, patients with Ischemic Heart Diseases (IHD)/Rheumatic Heart Disease, patients in shock, head injury, psychiatric illness, hepatic disease, renal disease with impaired renal function parameters, patients with COPD, bronchial asthma and any respiratory disease, patients with known allergy to Agomelatine or Ramelteon or Melatonin were all excluded from the study.

Pre-anesthetic assessment was done one day prior to the surgery and examined for airway, general physical and systemic examination. Appropriate blood tests and other tests were performed as needed. Nil per oral for *8 hours* for solids/milk/juice and *2 hours* for water was advised and were pre-medicated using Tab. ranitidine *150 mg* and Tab. ondansetron *4 mg* on the night and *2 hours* prior to induction of anesthesia. After obtaining written and informed consent and meeting inclusion and exclusion criteria, 60 patients were randomly assigned into two equal Groups by envelope method. Patients in Group A (n = 30) received Tab. agomelatine *10 mg* whereas those in Group R (n = 30) received Tab. ramelteon *8 mg* orally with sips of water in the pre-operative room, *60 minutes* prior to induction of general anesthesia by a anesthesiologist not involved in the study. Anesthesiologist recording the observations and all patients participating in the studywere blinded to the drug administered.

Patients were monitored for anxiety levels using VAS score, sedation score and orientation score as explained below. The Visual Analog Score (VAS) score for anxiety was between 0 and 10, where 0 implied no anxiety and 10 worst imaginable anxiety. Sedation score as 1= awake, 2 = drowsy, 3 = asleep but arousable to call, 4 = asleep but not arousable to call, Orientation score as 0 = none, 1 = oriented to either place or time, 2 = oriented to both place and time. Anesthesiologist blinded to the randomization sequence and the study medication, recorded the VAS anxiety score, sedation score and orientation score at 0, 15, 30, 45, an 60 minutes following administration of either Tab. agomelatine or Tab. ramelteon. The duration of anesthesia was noted. In addition, patients were monitored for vital signs heart rate, blood pressure and oxygen saturation using plethysmography and adverse effects of the study medications e.g., headache, nausea, enuresis, depression and dizziness.

Statistical Analysis

All patients enrolled, were involved in the study and there were no dropouts. Sample size of 30 in each group was considered for this study. Data

was expressed as mean ± standard deviation (SD) or absolute values. Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs and tables. Qualitative data were compared with the Chi-square test and fisher's exact test. Quantitative variables were compared with the student '*t*' test. The level of statistical significance was set at $p < 0.05$ and a $p < 0.001$ as strong significance.

Results

All sixty patients included in the study, participated in either groups and there were no dropouts. Patients did not vary significantly with respect to age, sex, weight between the two Groups, shown in **Table 1**. The baseline mean VAS anxiety scores on the day before surgery and on the day of surgery were comparable between the two groups, shows in **Table 2**. After pre-medication at *0 minutes*, the VAS score was comparable between the two Groups. At *15, 30, 45* and *60 minutes* after pre-medication, the VAS score decreased in both the groups, but was statistically insignificant, shown in **Table 2**.

Table 1: Comparison of demographic data of the patients

Patient characteristics	Group A (n = 30)	Group R (n = 30)	p-value
Age (*years*)(Mean ± SD)	37.26 ± 9.74	36.63 ± 9.4	0.281
Sex (Male : Female)	15:15	20:10	0.538
Weight	55.9 ± 8.31	55.7 ± 8.03	0.744

Group A = Agomelatine Group, Group R = Ramelteon Group, $p < 0.05$ as significant, SD = Standard Deviation.

On the day of surgery, VAS score decreased from 6.133 ± 1.105 before pre-medication to 0.8 ± 0.76 at *60 minutes* in Group A, greatest reduction observed was at *15 minutes* after pre-medication. In Group R, the VAS score decreased from 5.933 ± 0.994 before pre-medication to 0.366 ± 0.566 at *60 minutes*, and greatest reduction observed was at *15 minutes*, shown in **Table 2**. VAS scores were comparable and statistically insignificant between the two Groups at all time intervals.

Table 2: Comparison of visual analogue score for Anxiety

Visual analog score	Group A	Group R	p-value
Day before surgery	5.833 ± 0.833	5.8 ± 0.846	0.15
On Day of surgery	6.133 ± 1.105	5.933 ± 1.048	0.71
0 minutes	6.066 ± 1.17	5.333 ± 0.994	2.16
15 minutes	4.00 ± 1.017	3.666 ± 0.884	1.35
30 minutes	2.766 ± 0.773	2.466 ± 0.899	1.38
45 minutes	1.66 ± 0.95	1.333 ± 0.958	1.34
60 minutes	0.8 ± 0.7611	0.3666 ± 0.566	2.51

Group A = Agomelatine Group, Group R = Ramelteon Group, $p < 0.05$ as significant.

The mean baseline sedation scores before day of surgery were comparable between the two groups (p = 4.01). Progressive increase in mean sedation score was observed in Group A after *15 minutes* (1.533 ± 0.507) and was highest at *60 minutes* (3.0 ± 0.0). Similar progressive increase in sedation score was observed in Group R after *15 minutes* (1.833 ± 0.530) with highest score observed at *60 minutes* (3.0 ± 0.0), shown in **Table 3**. The sedation score was statistically insignificant between the two Groups after pre-medication at *15*, *30*, and *45 minutes*, and no *p*- value at *0* and *60 minutes*, shown in **Table 3**. None of the patients in either groups had sedation score of 4 *i.e.*, unarousable to call. Data shows no change in orientation score between the two groups and hence no *p*-value, displays in **Fig. 3**.

Table 3: Comparison of sedation scores between the two groups

Time intervals	Group A	Group R	p-value
Day before surgery	1 ± 0	0.5 ± 0.682	4.01
On day of surgery	1 ± 0	1 ± 0	–
0 minutes	1 ± 0	1 ± 0	–
15 minutes	1.533 ± 0.507	1.833 ± 0.530	2.23
30 minutes	2.133 ± 0.507	2.366 ± 0.556	1.69
45 minutes	2.133 ± 0.507	2.366 ± 0.556	1.69
60 minutes	3.0 ± 0	3 ± 0	–

Group A = Agomelatine Group, Group R = Ramelteon Group, $p < 0.05$ as significant.

Discussion

Pre-operative anxiety has unfavorable effects on induction, maintenance and on recovery from anesthesia.[1,2] Hence, use of pre-medication for pre-operative anxiolysis is an important goal in good anesthetic management. Melatonin's hypnotic and sedative properties when taken exogenously led to the postulation that melatonin administered orally could potentially and safely be used for anxiolysis and sedation in treating anxious patients.[6,7] The purpose of this study was to examine the effectiveness of oral melatonin analog namely Agomelatine and Ramelteon as a pre-medication for anxiolysis and sedation in adult patients undergoing different elective surgeries under general anesthesia.The peak effect of Agomelatine and Ramelteon ranges from 60–150 *minutes* and hence, we chose to give the drug *60 minutes* before induction.[8]

Tab. agomelatine in doses *25–50 mg/day* was used in patients with primary diagnosis of generalize anxiety disorder resulted insignificantly reduced

mean Hamilton Anxiety Rating Scale total score.[9] Tab. agomelatine *10 mg* in our study as intention was to produce anxiolysis our patients were not related to anxiety disorder.

In our study, we used the modified VAS to measure anxiety which was used by other authors in previous studies.[3,4] In our study, there was decrease in anxiety scores in both the Groups from baseline, but the decrease in anxiety score were statistically insignificant between the two Groups. The decrease in anxiety score was noted as early as *15 minutes* and maximum decrease in anxiety score was seen at *60 min* in both Group A and Group R. The mechanism of Agomelatine and Ramelteon for anxiolysis has been related to both melatonin receptor activation and an effect on gamma-aminobutyric acid transmission,[9] displays in **Fig. 1**.

Agomelatine administered over *6 weeks* in depressed patients, produced clinically significant improvements of reducing wake time after sleep onset, increases in total slow-wave sleep and favorable quality of sleep and lack of daytime sleepiness.[10] In non-rapid-eye-movement sleep, the cyclic alternating pattern improved significantly after *7 days* treatment with agomelatine compared with placebo.[11] These studies show their effects on sedation and sleepiness. Similar efficacy of ramelteon resulting in reduced latency to sleep and increased total sleep time have been demonstrated in a study in chronic insomnia patients.[12–14]

There was progressive increase in sedation score in both the groups following administration of the study medication. Comparison of sedation scores between the two Groups in our study showed statistically insignificant difference at *15, 30* and *45 minutes*. At *60th minute* both Groups had same sedation scores and hence, *p*-value cannot be derived, displays in **Fig. 2**.

Orientation score was assessed in previous studies following administration of melatonin.[2,13] Hence, we adopted orientation score in our study and observed to be unchanged at all intervals of time in both the groups. For the same reason, *p*-value could not be derived at all intervals of time between the two Groups, displays in **Fig. 3**.

Oral Tab. ramelteon *8 mg* or Tab. agomelatine *10 mg* resulted in predictable sedation and anxiolysis from baseline, approximately *15 minutes* after their administration. They were comparable at all intervals of time resulting in statistically insignificant relationship among the two Groups at these doses. Orientation scores remained unchanged from the baseline in both the Groups implying the advantages of both medications.

The main advantage of this study was that sedation and anxiolysis were predictable without change in orientation scores. At these doses, we did not come across any adverse effects associated with the study medication. The drawback of the study was that we did not have control group to further compare the effects of study medication. Future prospective of this study would be to compare these medications with melatonin for further validation of the results in larger group of patients.

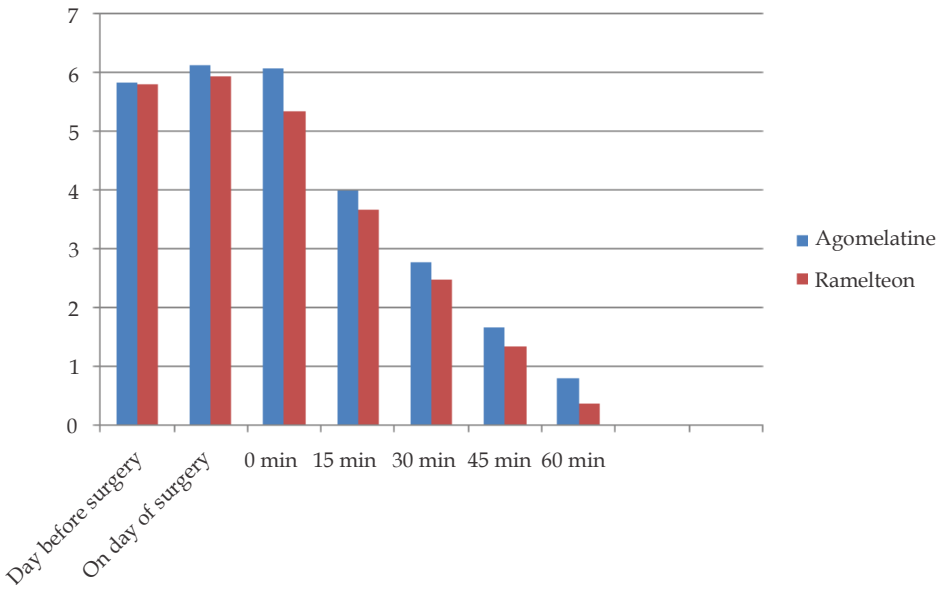

Fig. 1: Comparison of VAS score of anxiety between the groups

Notes: X-axis = Various time intervals, Y-axis = VAS score for sedation.

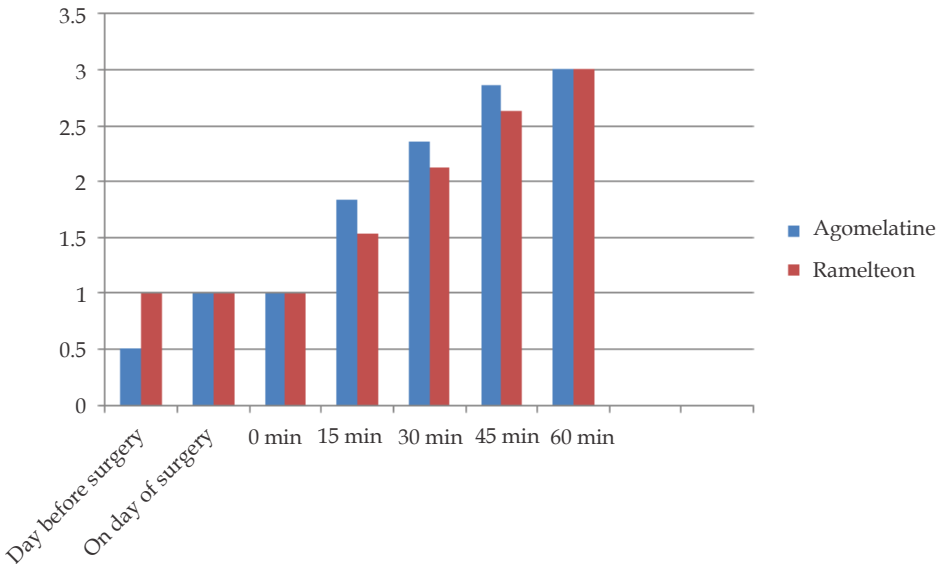

Fig.2: Comparison of sedation score between the two groups

Notes: X-axis = Various time intervals, Y-axis = Sedation score.

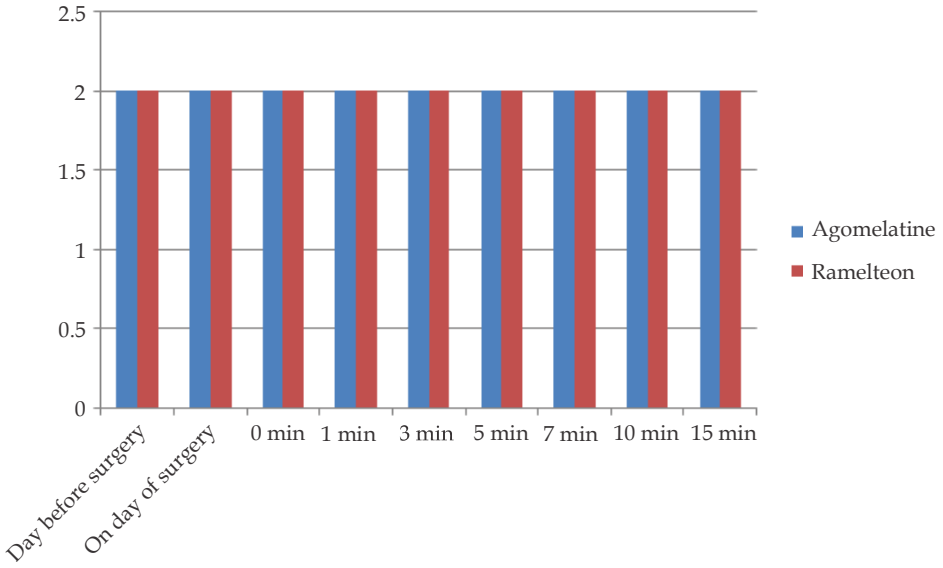

Fig. 3: Comparison of orientation score between the two groups

Notes: X-axis = Various time intervals, Y-axis = Orientation score.

Our study involves only ASA Class I patients and hence, further studies are needed to substantiate their use in higher ASA class of patients.

Conclusion

Tab. agomelatine *10 mg* and Tab. ramelteon *8 mg* administered orally *60 minutes* before induction of anesthesia provides adequate anxiolysis and sedation from baseline. At this dosage, both medications and were comparable with respect to anxiolysis and sedation without affecting the orientation to time and place.

Key Messages

Agomelatine and Ramelteon are melatonin agonists and their tablet formulations are very beneficial in producing anxiolysis and sedation which are very necessary in pre-operative period. They are safe without adverse effects when used at the mentioned doses without affecting their orientation.

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