Original Article

Comparative Study of Efficacy and Safety of Ramelteon vs Zolpidem in Patients of Insomnia in Tertiary Care Centre of East India

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ABSTRACT

Introduction: Insomnia can lead to anxiety disorders, major depression, substance use disorders, suicidality, diabetes, and hypertension. Although zolpidem is considered as safe drug, it is associated with some reported adverse effects like drowsiness, headache, and dizziness when it is used for short-term. Because of the risks associated with non-benzodiazepine agonist of benzodiazepine receptor, alternative dugs like supplementation with melatonin and agonists of melatonin receptor have been investigated for insomnia.

Aims/ objective: To compare the efficacy and safety of ramelteon and zolpidem for improvement in sleep in patients of chronic primary insomnia.

Materials and Method: 50 patients were randomized using web generated random numbers into group ramelteon and group zolpidem with 25 patients in each group. Patients of ramelteon group were instructed to take ramelteon 8 mg at bedtime and patients of zolpidem group were instructed to take zolpidem 10 mg at bedtime for 14 days. The primary efficacy outcome measure was to measure the change in sleep latency from baseline to day 14. Secondary efficacy outcome measures were duration of sleep, number of awakenings, quality of sleep based on self-assessment of patients and frequency of rebound insomnia. These measures were evaluated using patient questionnaires.

Results: We observed a significant reduction in subjective sleep latency in patients taking ramelteon (reduced from 63.04 ± 34.51 minutes at baseline to 30.93 ± 21.65 minutes; $p < 0.05$) and also in patients taking zolpidem (reduced from 61.96 ± 44.73 minutes at baseline to 31.24 ± 26.17 minutes; $p < 0.05$) after end of therapy. There was more incidence of headache, dizziness and anxiety in zolpidem group as compared to ramelteon group. Overall, there was no significant difference between ramelteon and zolpidem pharmacotherapy with respect to adverse events ($p<0.05$).

Conclusion: Ramelteon was proved to be as efficacious as zolpidem with respect to sleep latency, duration, and quality. In addition, there is low risk of adverse drug reactions like withdrawal and rebound symptoms, impairment in learning and memory, impairment in motor co-ordination, and it has less abuse potential.

Keywords: Ramelteon, Zolpidem, Insomnia, Sleep Latency, Sleep Duration, Sleep Quality.

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INTRODUCTION

Insomnia is defined as a complaint of difficulty in falling (sleep latency) or staying asleep (sleep maintenance) which is related to significant distress or impaired daytime function and happens in adequate environment and opportunity for sleep. [1, 2] It is a common disorder, with point prevalence of approximate 10% in general population. [3]

In most of the cases, insomnia is associated with other concurrent physical or psychiatric disorders. Because of this co-occurrence, it was hypothesized that insomnia was one of the symptoms of this condition but it has been suggested by current evidences that the association of insomnia and these disorders is usually complex and also bidirectional sometimes. [4]

In fact, Insomnia can lead to anxiety disorders, major depression, substance use disorders, suicidality, diabetes, and hypertension. [5-8] Because of this reason and also because of association of insomnia with deterioration in quality of life and increase in risk of falls and accident, it has been suggested that pharmacotherapy should be targeted to address insomnia specifically if it is present along with other psychiatric or physical disorders. [9, 10]

For the patients meeting the diagnostic criteria for insomnia, many treatments option that is empirically supported are available. There are also non-pharmacological interventions in addition to pharmacotherapies.[10, 11] In addition to improve sleep hygiene through non-pharmacologic approaches, pharmacological agents for sleep are often prescribed for the management of hospital-related insomnia. [12]

One of the most used groups of pharmacological agents for sleep aids in the hospital setting are non-benzodiazepine agonists of GABA receptors because of strong evidence of their efficacy in insomnia particularly in the outpatient setting. [13] Although zolpidem is considered as safe drug, it is associated with some reported adverse effects like drowsiness, headache, and dizziness when it is used for short-term. In addition to this, zolpidem also come with label warnings for abnormal behavioural and thought changes, abuse potential and withdrawal symptoms if stopped suddenly, and central nervous system depressant effects. [14]

For hospitalized patients, Kolla and colleagues reported that zolpidem was found to have significant association with an increase in risk of inpatient accidents and falls leading to hip fractures, which is associated with increase in morbidity and health-care expenses.[15]

Because of the risks associated with non-benzodiazepine agonist of benzodiazepine receptor, alternative dugs like supplementation with melatonin and agonists of melatonin receptor have been investigated for insomnia. Melatonin is an endocrine hormone released by the pineal gland and is known to bind and activate two high-affinity GPCR (G-protein-coupled receptors) namely MT1 and MT2 and this interaction leads to initiation and maintenance of sleep. [16]

Ramelteon is a agonist of melatonin receptor that is currently available in market of the United States for the pharmacotherapy of insomnia. Mechanism of action of ramelteon is related to high selectivity of ramelteon for MT_1 and MT_2 receptors.

In Comparison to melatonin, ramelteon has up to 3- to 5-fold higher affinity for binding to MT_1 and MT_2 receptors in human and has approximately 17 times more potency at these receptors. These findings have been recorded in vitro studies that evaluated affinity to bind towards individual subtypes of melatonin receptors and the relative functional activities on cAMP production induced by forskolin.[17]

Melatonin has been found to be well tolerated with decreased impact on psychomotor functions and its efficacy has been established for the pharmacotherapy of primary insomnia in the adults and other sleep disorders related to circadian rhythm in the outpatient setting. [18, 19] Inpatient data on efficacy of ramelteon is limited, however Andrade and colleagues had done a small study on 33 patients who were given either melatonin or placebo and reported that there was significant improvement in onset, quality, and depth of sleep in melatonin group and they haven't found any significant adverse events. Benefits to patients were mostly apparent during the first seven days of melatonin treatment in that study. [20]

Keeping findings of previous studies in mind and to strength of limited evidence for use of ramelteon in sleep disorders, this study was done to compare the efficacy and safety of ramelteon and zolpidem for improvement in sleep in patients of chronic primary insomnia.

MATERIALS AND METHODS

This was an open label randomised controlled trial with parallel 1:1 allocation of study participants into two study groups. The study was conducted in tertiary care centre of eastern India after approval of institutional ethics committee under ICH-GCP guidelines. Written informed consent was taken from all study participants after explaining them participant information sheet which was provided to them at the time of consent.

A sample size of 23 per group was required in order to detect an effect size of 0.9 with 80% power at a 5% level of statistical significance. Assuming a 20% drop-out rate, we planned to randomize a total of 50 patients in this study to target a minimum of 40 evaluable patients.

Inclusion Criteria

Male or female patients between 20 and 65 years old; Patients meeting the DSM-IV Diagnostic Criteria for primary insomnia.

Exclusion Criteria

Patients with transient or situational insomnia, e.g., insomnia due to time zone shifts, shift-work schedules, acute stress, drugs, or alcohol; Patients having a history or current manifestations of sleep apnoea, restless leg syndrome, or a history of routine daytime napping; Patients having a current or past history of seizure disorder, clinically significant head injury, or a major psychiatric disorder that could likely affect the study; Patients with concurrent hormonal therapy or a clinically significant, acute, recurrent or chronic unstable illness or disorder that was likely to affect the study, as judged by the investigator; or Patients having clinically significant liver dysfunction and/or renal dysfunction.

Intervention

The study period for all eligible patients was approximately 21 days, during which time the patient underwent treatment period for 14 days and a follow-up period for 7 days. 50 patients were randomized using web generated random numbers into group ramelteon and group zolpidem with 25 patients in each group. Patients of ramelteon group were instructed to take ramelteon 8 mg at bedtime and patients of zolpidem group were instructed to take zolpidem 10 mg at bedtime. The overall compliance to pharmacotherapy was measured by tablet counts at all follow ups during the study.

Outcome Measurement

The primary efficacy outcome measure was to measure the change in sleep latency from baseline to day 14. Secondary efficacy outcome measures were duration of sleep, number of awakenings, quality of sleep based on self-assessment of patients and frequency of rebound insomnia. These measures were evaluated using patient

questionnaires. Physical examination, vital signs, 12-lead ECG, and laboratory evaluation with pregnancy test were done at baseline, end of 1st week and end of 2nd week. Patients were asked to update their sleep diary every day upon awakening. Entries had information about sleep latency, sleep duration, and number of awakenings.

Investigator's rating of global improvement of sleep disorders (modified Clinical Global Impression scale-2) at the end of the treatment period: proportion of patients rated as at least 'moderately improved' in each treatment group was also compared.

Sleep quality was given score based on the following scale: 1: excellent; 2: very good; 3: good; 4: fair; 5: poor; 6: very poor; 7: extremely poor.

Statistical Analysis

Statistical analysis was performed with the help of SPSS ver-23 & Microsoft Office Excel 365 and graph-pad software. The data obtained was presented in tabular form and calculation of Mean and Standard Deviation of parameters was done. Continuous variables were compared between the two study groups using the t-test. The chi-square test and Fisher's exact test were used to compare categorical variables between the two treatment groups. P-value less than 0.05 was taken as measure of significance.

RESULTS

Forty-eight patients were enrolled in the study with 24 in each group. Thirty-three (64%) of the patients were women, and seventeen (34%) were men. The mean age was 41.31 ± 11.88 years in the zaleplon group and 39.47 ± 10.83 years in the zolpidem group. The baseline characteristics were comparable between the zaleplon and zolpidem group with no statistically significant difference.

Table 1: Comparison of baseline demographic and clinical characteristics

Parameters	Ramelteon Group (n = 25)	Zolpidem Group (n = 25)	P-Value
Age in years (mean ± SD)	41.31 ± 11.88	39.47 ± 10.83	0.57 (Unpaired t test)
Gender			
Male	8	9	0.77
Female	17	16	(Chi-Square)
Frequency of sleep disorder			
< 3 days/week	3	2	0.77
4-6 days/week	6	8	(Chi-Square)
≤ 7 days/week	16	15	
Duration of sleep disorder			
≤1 month	4	5	0.83
> 1 month – ≤3 months	5	4	(Chi-Square)
> 3 months – ≤6 months	3	5	
> 6 months	13	11	
Sleep latency in minutes (mean ± SD)	63.04 ± 34.51	61.96 ± 44.73	0.93 (Unpaired t test)

SD = Standard Deviation

Table 2: Comparison of mean changes in sleep measure from baseline to day 14 of treatment

Mean Changes in Sleep Measures	Ramelteon Group (n = 25)	Zolpidem Group (n = 25)	P-Value (Unpaired t test)
Sleep latency in minutes (mean ± SD)	-32.11 ± 9.67	-30.72 ± 8.98	0.60
Sleep duration in minutes (mean ± SD)	65.54 ± 24.61	71.73 ± 18.09	0.32
Number of awakenings (mean ± SD)	-0.69 ± 0.32	-0.63 ± 0.37	0.54
Sleep quality scale (mean ± SD)	-0.82 ± 0.39	- 0.89 ± 0.41	0.54

There was a significant reduction in subjective sleep latency in the ramelteon group (reduced from 63.04 ± 34.51 minutes at baseline to 30.93 ± 21.65 minutes; $p < 0.05$) and zolpidem group (reduced from 61.96 ± 44.73 minutes at baseline to 31.24 ± 26.17 minutes; $p < 0.05$) after treatment. There was significant improvement in both groups with respect to sleep latency, duration, and quality. Number of awakenings was also reduced significantly in both groups. There was no significant difference between ramelteon and zolpidem pharmacotherapy with respect to sleep latency, duration, and quality ($p<0.05$).

Table 3: Comparison of two groups based on global improvement of sleep disorders

Category of Improvement	Ramelteon Group (n = 25)	Zolpidem Group (n = 25)	P-Value (Chi-Square)
Markedly Improved (%)	5 (20)	6 (24)	0.90
Moderately Improved (%)	12 (48)	10 (40)	
Slightly Improved (%)	7 (28)	7 (28)	
Unchanged (%)	1 (4)	2 (8)	

Most of the patients in either group had markedly improved based on modified Clinical Global Impression scale-2. There was no significant difference between ramelteon and zolpidem pharmacotherapy with respect to modified Clinical Global Impression scale-2 ($p<0.05$).

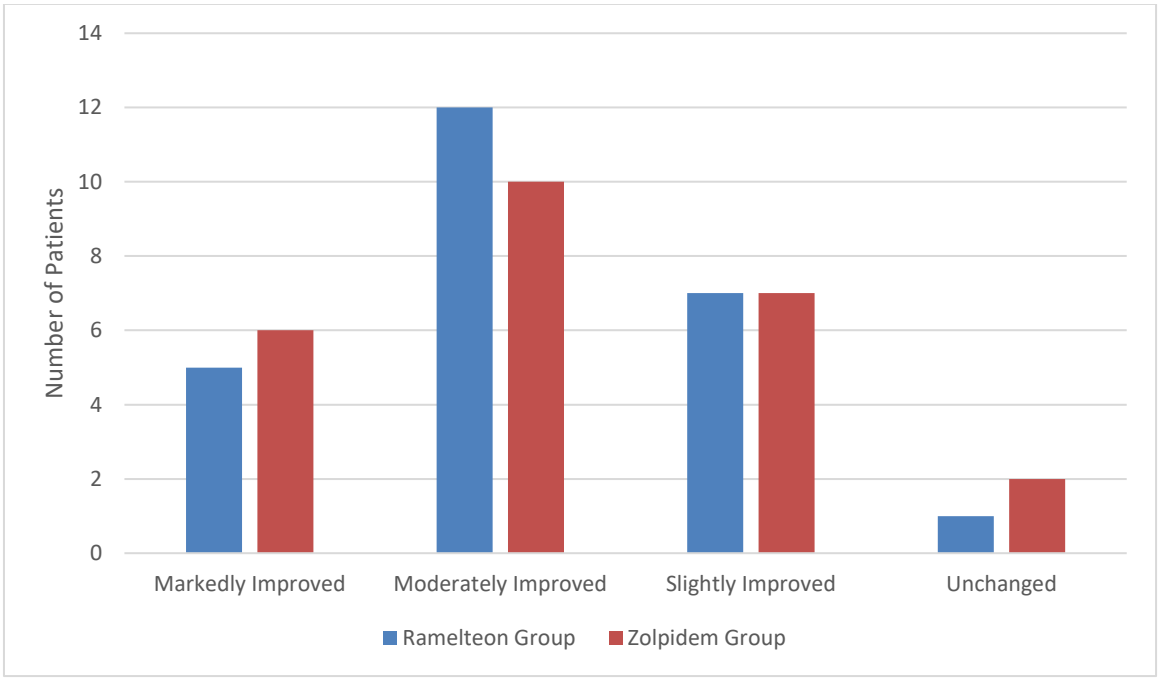

Figure 1: Comparison of two groups based on global improvement of sleep disorders

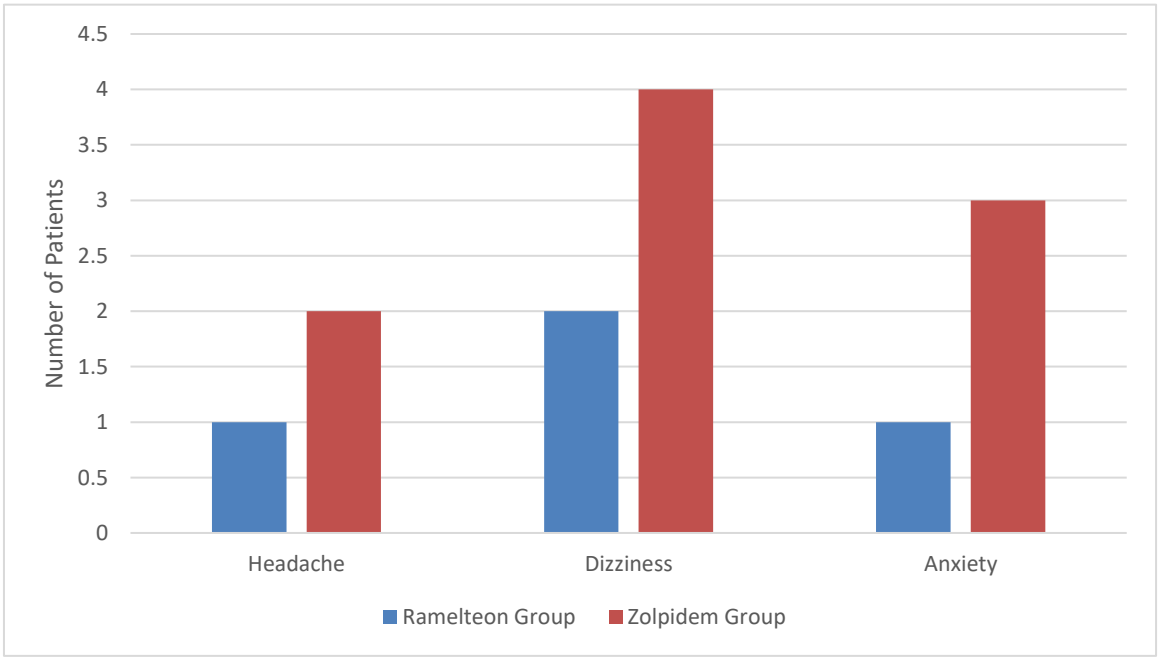

Figure 2: Comparison of two groups based on treatment-emergent adverse events

Table 4: Comparison of two groups based on treatment-emergent adverse events

Category of Improvement	Ramelteon Group (n = 25)	Zolpidem Group (n = 25)	P-Value (Chi-Square)
Headache (%)	1 (4)	2 (8)	0.96
Dizziness (%)	2 (8)	4 (16)	
Anxiety (%)	1 (4)	3 (12)	

There was more incidence of headache, dizziness and anxiety in zolpidem group as compared to ramelteon group. Overall, there was no significant difference between ramelteon and zolpidem pharmacotherapy with respect to adverse events ($p<0.05$).

DISCUSSION

This study was done on a small sample size while comparing the efficacy and safety of ramelteon with zolpidem. While assessing the results, there are also some limitations that should be kept in mind, like the no blinding and small sample size. In addition to that, our outcome measures did not include any objective sleep tests like actigraphy and polysomnography. From the result of this study, we can say that both ramelteon 8 mg and zolpidem 10 mg were effective in reducing the time to fall asleep in patients who were diagnosed with primary insomnia.

From the results, it was also demonstrated that similar effectiveness in quality of sleep based on patients self-assessment in both ramelteon and zolpidem which is a commonly used non-benzodiazepine agonist of benzodiazepine receptor used in the hospital setting. There was also no difference between ramelteon and zolpidem with respect to disturbance in sleep or any supplementation. There was a significant decrease in subjective sleep latency in the patients taking ramelteon (reduced from 63.04 ± 34.51 minutes at baseline to 30.93 ± 21.65 minutes; $p < 0.05$) and zolpidem group (reduced from 61.96 ± 44.73 minutes at baseline to 31.24 ± 26.17 minutes; $p < 0.05$) after treatment. Ramelteon was proved to be as efficacious as zolpidem with respect to sleep latency, duration, and quality. Most of the patients in either group had marked improvement with respect to modified Clinical Global Impression scale-2.

After discontinuation of ramelteon by patients after 6 months of pharmacotherapy, there was no reports of rebound insomnia or withdrawal symptoms on regular follow-up. These results are consistent with previous clinical trials of ramelteon. [22-24] In a study done on substance abusers who were prescribed ramelteon or the benzodiazepine triazolam, there was no report of any potential for abuse liability in patients given ramelteon but there was abuse potential with triazolam. [25] Similarly, other benzodiazepine receptor agonists are also associated the potential for abuse. [26-28] For example, in a 4-week research done on elderly patients of chronic insomnia who were given zaleplon or zolpidem, there were reports of significant rebound and withdrawal symptoms particularly in the zolpidem group. [29]

Ramelteon was found safe with low incidence of adverse events as compared to zolpidem which is similar to earlier clinical researches. For example, two long-term studies which was designed to assess the safety of ramelteon with respect to various safety variables and reported no clinically significant changes with respect to many variables, like vital signs, findings of physical examination, clinical biochemistry, haematological analysis, urinalysis, and ECG findings. [30,31] It is worth noting that this study also had a relatively lower dropout rate, which indicate towards better tolerability with the utilization of ramelteon in insomnia. Earlier study which evaluated efficacy and safety of ramelteon have found that dropout rate in ramelteon group was very similar to rate observed in placebo group. [23]

Low incidence of next-morning effects and withdrawal symptoms in ramelteon group is important findings in many studies that established ramelteon superior to classic GABAergic hypnotics. The better results in patients taking ramelteon with respect to morning alertness, numerous cognitive and psychomotor parameters as well as mood parameters has been repeatedly reported in earlier studies. [32, 33] Patients reported feeling of refreshment in morning after waking up. [34] There was no impairment in memory and motor functions in elderly patients prescribed ramelteon at a dose of 8 mg and also there was better result with respect to mobility and middle-of-the-night balance as compared to zolpidem. [35]

Despite some variation in level of significance due to the small sample size and some limitation in study design, the results and its correlation with other studies strongly suggest effectiveness of ramelteon in facilitating sleep onset. This evidence is also strengthened by a pooled analysis of four large trials. [36]

CONCLUSION

No differences were found between ramelteon and zolpidem with respect to their effectiveness in improving sleep latency and sleep maintenance. Incidence of sleep disturbance or need of supplementation was similar between ramelteon and zolpidem. Moreover, there is low risk of adverse drug reactions like withdrawal and rebound symptoms, impairment in learning and memory, impairment in motor co-ordination, and it has less abuse potential. Ramelteon was proved to be as efficacious as zolpidem with respect to sleep latency, duration, and

quality. Prospective, randomized clinical trials are required to further strengthen the evidence for the effectiveness of ramelteon in the hospital setting.

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