Original Article

Efficacy and Safety of Ramelteon versus Zolpidem in Patients of Insomnia in Tertiary Care Centre of Eastern India: A Randomised Controlled Trial

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ABSTRACT

Introduction: Anxiety disorders, severe depression, substance abuse problems, suicidal thoughts, type 2 diabetes, and hypertension can all be brought on by insomnia. Despite being regarded as a safe medication, zolpidem has been linked to a few documented side effects, including headaches, dizziness, and sleepiness when taken briefly. Alternative treatments for insomnia, such as melatonin supplements and agonists of the melatonin receptor, have been studied due to the hazards connected with non-benzodiazepine agonists of the GABA receptor.

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

Materials and Method: Using randomly generated online numbers, 60 patients were divided into two groups: group Z and group R, each with 25 patients. Patients in the group Z were directed to take zolpidem 10 mg at bedtime for 14 days, whereas patients in the group R were advised to take ramelteon 8 mg at bedtime. The improvement in sleep latency from the baseline to day 14 was the main effectiveness outcome measure. The length of sleep, the number of awakening, quality of sleep determined by patient self-assessment, and the incidence of reflex insomnia were secondary efficacy end variables. Patient questionnaires were used to assess these parameters.

Results: There was a significant decrease in subjective sleep latency in the patients receiving ramelteon (reduced from 62.95 ± 33.42 minutes at baseline to 31.02 ± 8.78 minutes; $p < 0.05$) and patient receiving zolpidem (reduced from 62.06 ± 43.64 minutes at baseline to 29.83 ± 7.87 minutes; $p < 0.05$). There was statistically significant improvement in both group R and group Z as per sleep latency, length, and quality ($p<0.05$). Most of the patients in receiving zolpidem or ramelteon had markedly improved sleep as per modified Clinical Global Impression scale-2. There was more incidence of headache, dizziness and anxiety in patient receiving zolpidem therapy as compared to patients on ramelteon.

Conclusion: It has been demonstrated that ramelteon is just as effective as zolpidem in terms of sleep latency, length, and quality. Furthermore, there is less potential for abuse and a minimal chance of negative medication reactions such as rebound insomnia and withdrawal symptoms, learning and memory problems, and motor coordination loss.

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

INTRODUCTION

A complaint of trouble getting asleep (sleep latency) or remaining asleep (sleep maintenance) that occurs in a setting that is conducive to adequate sleep and is associated with severe distress or decreased daytime functioning is known as insomnia. [1, 2] With a point frequency of almost 10% in the general population, it is a prevalent disorder. [3]

The majority of the time, sleeplessness coexists with other medical or psychological conditions. Due to this coexistence, it was assumed that sleeplessness was one of the manifestations of this illness; however, recent research indicates that the relationship between insomnia and these diseases is typically complex and occasionally bidirectional.[4]

Indeed, severe depressive illness, anxiety disorders, substance abuse illnesses, suicidal thoughts type 2 diabetes, and hypertension can all be brought on by insomnia. [5-8] This is the reason why it has been suggested that pharmacotherapy be tailored to specifically address insomnia if it coexists with other psychological or physical disorders. Additionally, insomnia has been linked to a decline in quality of life and an increased risk of falls and accidents. [9, 10] There are numerous empirically supported therapy options available for patients who fit the diagnostic requirements for insomnia. In addition to pharmacotherapies, there are non-pharmacological approaches. [10, 11]

In addition to non-pharmacologic methods for enhancing sleep hygiene, pharmaceutical sleep aids are frequently recommended for the treatment of insomnia associated with hospital stays. [12]

Non-benzodiazepine agonist of the GABA receptors is among the most often utilized classes of pharmaceutical drugs for sleep aids in hospital settings due to compelling data supporting their effectiveness in treating insomnia, especially in the outpatient context. [13] Despite being regarded as a safe medication, zolpidem has been linked to a few documented side effects, including headaches, dizziness, and sleepiness when taken briefly. Furthermore, the label for zolpidem includes cautions about atypical changes in behavior and thought processes, potential for abuse, withdrawal symptoms if abruptly stopped, and effects on the central nervous system that depress. [14]

According to Kolla and colleagues, zolpidem has been shown to have a strong correlation with a higher risk of hip fractures from falls and inpatient accidents, which is linked to higher rates of morbidity and health care costs, for hospitalized patients.[15]

Alternative treatments for insomnia, such as melatonin supplements and agonists of the melatonin receptor, have been studied due to the hazards connected with non-benzodiazepine agonists of the GABA receptor. The pineal gland secretes the hormone melatonin, which is known to bind to and activate the G-protein-coupled receptors (GPCRs) MT1 and MT2, two high-affinity GPCRs. This interaction causes sleep to be initiated and maintained. [16]

The melatonin receptor agonist ramelteon is presently marketed in the US for the pharmacological treatment of insomnia. The strong specificity of ramelteon for MT1 and MT2 receptors is linked to its mechanism of action.

Ramelteon has roughly 17 times more efficacy at human MT1 and MT2 receptors and can bind to these receptors with an affinity that is up to 3–5 times higher than that of melatonin. These results are based on in vitro experiments that assessed the corresponding functional activities on cAMP generation produced by forskolin and the propensity to bind towards specific subtypes of melatonin receptors.[17]

Melatonin is an effective medication for treating adult primary insomnia and other circadian rhythm-related sleep problems in outpatient settings. It has been proven to be well tolerated and to have a minimal affect on psychomotor functioning. [18, 19] Although there is a lack of inpatient data regarding the effectiveness of ramelteon, Andrade and colleagues conducted a small study on 33 patients who received melatonin or a placebo. They found that the melatonin group experienced substantial improvements in the onset, quality, and extent of sleep, and that there were not any significant adverse effects. In that study, the initial 7 days of melatonin administration were largely beneficial to the patients. [20]

Considering the results of earlier research and to strengthen the limited evidence for utilization of ramelteon in insomnia, this study was done to compare the efficacy and safety of ramelteon versus zolpidem for improvement in onset, quality, and depth of sleep in patients of chronic primary insomnia.

STUDY METHODS

The study participants were randomly assigned 1:1 to two study groups in an open-label randomised controlled trial. Following institutional ethics committee permission and adhering to ICH-GCP norms, the study was carried out in a tertiary care center located in eastern India. After discussing the participant information sheet that was given to them at the time of permission, all study participants gave their written informed consent.

For the detection of an effect size of 0.9 with a power of 80% at the five percent level of statistical significance, a sample size of 23 per group was needed. We intended to randomly assign a total of 60 patients—30 patients in each group—for this trial, assuming a 20% attrition rate.

Inclusion Criteria: Patients of either gender of age between 18 to 65 years; Patients diagnosed with primary insomnia as per the DSM-IV Diagnostic Criteria.[3]

Exclusion Criteria: Patients experiencing temporary or transitory insomnia, such as that caused by intense stress, changing time zones, work shift schedules, medications, or alcohol; Individuals who have experienced or currently exhibit symptoms of sleep apnea, restless legs syndrome, or a tendency of frequent midday naps; individuals with a history of seizures or a head injury that meets criteria for clinical significance; or a major psychiatric condition that may have an impact on the study; individuals receiving concurrent hormonal therapy; individuals with a serious acute, recurrent, or chronic unstable disease or disorder that meets criteria for clinical significance, as determined by the investigator; or individuals with serious liver and/or renal dysfunction.

Intervention: All eligible patients participated in the study for about 21 days, during which they received therapy for 14 days and were followed up with a follow-up visit for 7 days. Using randomly generated numbers from the internet, 60 patients were divided into two groups: group Z and group R, each with 30 patients. Participants in the Z group were advised to take zolpidem 10 mg at bedtime, while those in the R group were advised to take ramelteon 8 mg at bedtime. At every follow-up point during the trial, tablet counts were used to assess the overall compliance to medication.

Outcome Measurement: The improvement in sleep latency from the baseline to day 14 was the main effectiveness outcome measure. The length of sleep, the number of awakening, the quality of sleep determined by patient self-assessment, and the incidence of reflex insomnia were secondary efficacy end points. Patient questionnaires were used to assess these parameters. At baseline, the end of the first week, and the end of the second week, a physical checkup, vital signs, a 12-lead ECG, and a laboratory assessment with a pregnancy test were performed. Upon rising each day, the patients were instructed to make updates to their sleep journal. Data on sleep latency, length, and the number of awakening were included in the proforma.

At the conclusion of the treatment period, the proportion of patients in each therapy group who were judged as at least "moderately improved" by the investigator using the modified Clinical Global Impression scale-2 was also compared.[21]

The following scale was used to score the quality of sleep:

- 1: excellent
- 2: very good
- 3: good
- 4: fair
- 5: poor
- 6: very poor
- 7: extremely poor.

Statistical Analysis: The statistical analysis was carried out using graph-pad, Microsoft Office Excel 365, SPSS ver. 23, and other applications. The acquired data was tabulated and the parameters' means and standard deviations were computed. The t-test was used to compare continuous variables between the two research groups. The categorical variables among the two treatment groups were compared using the chi-square test and Fisher's exact test. A P-value of less than 0.05 was considered to be significant.

RESULTS

60 patients were enrolled in the study with 30 in each group. Thirty-three (64%) of the patients were women, and seventeen (34%) were men. The mean age was 40.23 ± 12.27 years in the zaleplon group and 38.96 ± 11.14 years in the zolpidem group. The baseline characteristics were comparable between the group Z and group R with no statistically significant difference (p<0.05).

Table 1: Comparison of baseline demographic and clinical characteristics between group R and Z

Parameters	Group R (n = 30)	Group Z (n = 30)	P-Value
Age in years (mean ± SD)	40.23 ± 12.27	38.96 ± 11.14	0.68 (Unpaired t test)
Gender			
Male	10	11	>0.99
Female	20	19	(Chi-Square)
Frequency of sleep disorder			
< 3 days/week	3	2	0.78
4-6 days/week	7	9	(Chi-Square)
≤ 7 days/week	20	19	
Duration of sleep disorder			
≤1 month	5	6	0.68
> 1 month – ≤3 months	6	5	(Chi-Square)
> 3 months – ≤6 months	3	6	
> 6 months	16	13	
Sleep latency in minutes (mean ± SD)	62.95 ± 33.42	62.06 ± 43.64	0.93 (Unpaired t test)

SD = Standard Deviation

Table 2: Comparison of mean changes in sleep measure from baseline to day 14 of treatment between group R and Z

Mean Changes in Sleep Measures	Group R (n = 30)	Group Z (n = 30)	P-Value (Unpaired t test)
Sleep latency in minutes (mean ± SD)	31.02 ± 8.78	29.83 ± 7.87	0.58
Sleep duration in minutes (mean ± SD)	66.43 ± 23.72	72.62 ± 17.20	0.25
Number of awakenings (mean ± SD)	0.70 ± 0.23	0.62 ± 0.26	0.21

There was a significant decrease in subjective sleep latency in the patients receiving ramelteon (reduced from 62.95 ± 33.42 minutes at baseline to 31.02 ± 8.78 minutes; p < 0.05) and patient receiving zolpidem (reduced from 62.06 ± 43.64 minutes at baseline to 29.83 ± 7.87 minutes; p < 0.05). There was statistically significant improvement in both group R and group Z as per sleep latency, length, and quality (p<0.05). Number of awakenings was also decreased

significantly in both groups. There was no statistically significant difference between group Z and group R as per sleep latency, length, and quality (p>0.05).

Table 3: Comparison of two groups based on global improvement of sleep disorders between group R and Z

Category of Improvement	Group R (n = 30)	Group Z (n = 30)	P-Value (Chi-Square)
Markedly Improved (%)	6	7	0.93
Moderately Improved (%)	14	12	
Slightly Improved (%)	8	8	
Unchanged (%)	2	3	

Most of the patients in receiving zolpidem or ramelteon had markedly improved sleep as per modified Clinical Global Impression scale-2. However, there was no statistically significant difference between group R and group Z as per modified Clinical Global Impression scale-2 (p>0.05).

Table 4: Comparison of two groups based on treatment-emergent adverse events between group R and Z

Category of Improvement	Group R (n = 30)	Group Z (n = 30)	P-Value (Chi-Square)
Headache	1	3	0.61
Dizziness	2	5	0.42
Anxiety	1	4	0.35

There was more incidence of headache, dizziness and anxiety in patient receiving zolpidem therapy as compared to patients on ramelteon. Overall, there was no statistically significant difference between group Z and R with respect to adverse effects (p>0.05).

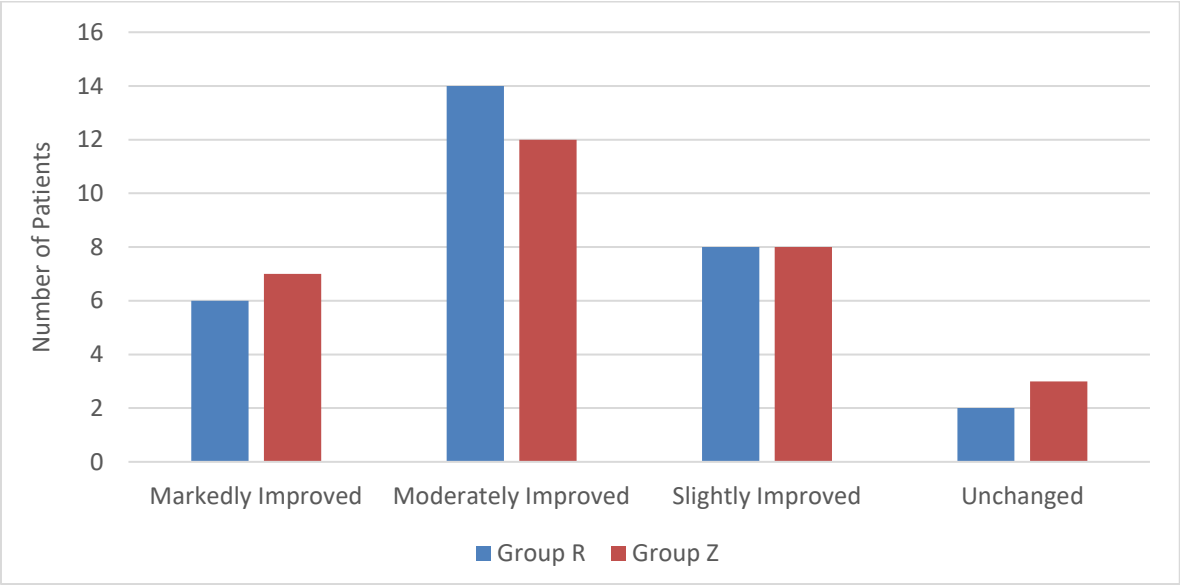

Figure 1: Comparison of two groups based on global improvement of sleep disorders between group R and Z

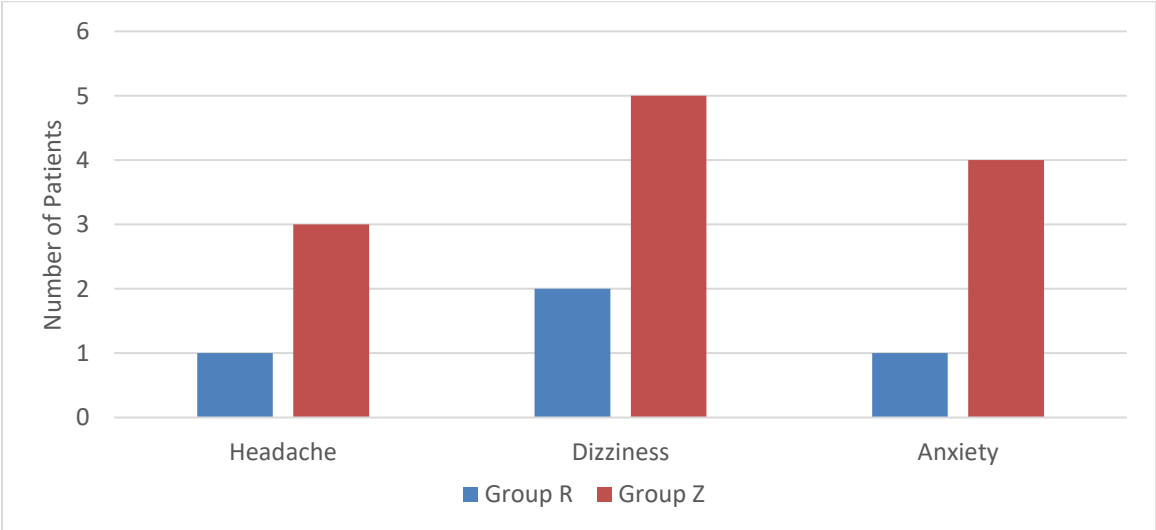

Figure 2: Comparison of two groups based on treatment-emergent adverse events between group R and Z

DISCUSSION

This study compared the safety and effectiveness of zolpidem and ramelteon using a limited sample size. Some limitations, such as the limited sample size and lack of blinding, should be considered when evaluating the results. Furthermore, we did not include objective sleep testing like actigraphy or polysomnography as part of our outcome measures. Based on the study's findings, we can conclude that patients with primary insomnia were able to fall asleep faster when using ramelteon (8 mg) or zolpidem (10 mg).

Based on patients' self-assessment, the results also showed that zolpidem, a frequently used non-benzodiazepine agonist of the GABA receptor, and ramelteon had comparable efficacy in improving sleep quality in a hospital context. Additionally, there was no distinction between zolpidem and ramelteon in terms of supplementing or sleep disturbance. After therapy, the patients using ramelteon (reduced from 62.95 ± 33.42 minutes at baseline to 31.02 ± 8.78 minutes; $p < 0.05$) and zolpidem (reduced from 62.06 ± 43.64 minutes at baseline to 29.83 ± 7.87 minutes; $p < 0.05$) showed a significant decrease in subjective sleep latency. It has been demonstrated that ramelteon is just as effective as zolpidem in terms of sleep latency, length, and quality. Based on the modified Clinical Global Impression scale-2, the majority of patients in both groups showed significant improvement.

Following six months of medication, when patients stopped using ramelteon, there were no reports of rebound sleeplessness or withdrawal symptoms during routine follow-up. These outcomes are in line with earlier ramelteon clinical trials. [22–24] In research on drug addicts who were given the benzodiazepine triazolam or ramelteon, there was no evidence of abuse liability for patients who received ramelteon, but there was for triazolam. [25] In a comparable way, there is a risk of abuse linked with other benzodiazepine receptor agonists. [26–28] For instance, there have been reports of severe rebound and withdrawal symptoms, especially in the zolpidem group, in a 4-week study conducted on older patients with chronic insomnia who were administered zaleplon or zolpidem. [29]

Similar to past clinical studies, ramelteon was determined to be safe with a low rate of adverse events when compared to zolpidem. For instance, two lengthy studies that evaluated the safety of ramelteon in relation to a range of safety factors found no statistically significant alterations in a number of variables, including vital signs, physical examination results, clinical biochemistry, haematological evaluation, urinalysis, and electrocardiogram readings. [30, 31] It is noteworthy that the study's dropout rate was comparatively negligible, suggesting that ramelteon treatment for insomnia may be more tolerable. Previous research assessing the safety and effectiveness of ramelteon discovered that the dropout rate in the ramelteon group was remarkably comparable to that of the placebo group. [23]

Important findings from numerous studies that showed ramelteon's superiority over traditional GABAergic hypnotics include the low prevalence of withdrawal symptoms and next-morning effects in the ramelteon group. Previous studies have consistently demonstrated improved outcomes for individuals taking ramelteon in terms of mood, several cognitive and psychomotor measures, and morning alertness. [32, 33] Patients stated feeling refreshed when they woke up in the morning. [34] When 8 mg of ramelteon was provided to older patients, there was no reduction in memory or motor function; additionally, the patients' movement and middle-of-the-night balance improved more than when zolpidem was used. [35]

The results and their agreement with other research strongly imply that ramelteon is beneficial in aiding sleep onset, even though there is some variance in the degree of significance because of the small number of participants and some limitations in the study design. A combined evaluation of four sizable trials adds credence to this evidence. [36]

CONCLUSION

When comparing zolpidem and ramelteon for their ability to enhance sleep latency and maintenance, no differences were observed. The likelihood of experiencing sleep disturbances or requiring supplements was comparable for both zolpidem and ramelteon. Additionally, there is less potential for addiction and a minimal risk of negative drug effects, such as rebound and withdrawal symptoms, memory and learning impairments, and motor coordination impairments. It has been demonstrated that ramelteon is just as effective as zolpidem in terms of sleep latency, length, and quality. Randomized, prospective clinical trials with greater sample size are needed to bolster the data supporting ramelteon's efficacy in a hospital context.

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