Original Article

Comparison of Efficacy and Safety of Ramelteon plus Zolpidem versus Zolpidem in Patients of Insomnia in Tertiary Care Centre of East India

Dr. Sonu Kumar, Dr. Md Atique Ur Rahman, Dr.Rupesh Kumar Roy, Dr. Raushan Kumar Ranjan*

1. Dr. Sonu Kumar, Assistant Professor, Department of Genral Medicine, RDJM Medical College and Hospital, Turki, Bihar, India.
2. Dr. Md Atique Ur Rahman, Senior Resident, Department of Genral Medicine, IQCT Medical College, Durgapur, West Bengal, India.
3. Dr.Rupesh Kumar Roy, Senior Resident, Department of Genral Medicine, Indira Gandhi Institute of Medical College, Bihar, India, India.
4. Dr. Raushan Kumar Ranjan, Senior Resident, Department of Pharmacology, Indira Gandhi Institute of Medical College, Bihar, India.

***Corresponding author's E-mail:** drraushankumar.ranjan@gmail.com

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ABSTRACT

Introduction: Lack of sleep can lead to a variety of conditions, including anxiety disorders, major depression, drug addiction issues, thoughts of committing suicide, type 2 diabetes mellitus, or hypertension. Although zolpidem is generally thought to be a safe drug, there have been a few reported side effects, such as headaches, lightheadedness, and drowsiness when taken short. Because of the risks associated with non-benzodiazepine agonist of the GABA receptor, other therapies for insomnia have been investigated, including melatonin analogues as well as agonists at the melatonin receptor.

Aims/ objective: To compare the efficacy and safety of ramelteon plus zolpidem versus zolpidem for improvements of the depth, duration, and standard of sleep for those with chronic primary insomnia.

Materials and Method: 40 patients in group Z + R were recommended to take zolpidem 5mg + ramelteon 8 mg at bedtime, while 40 patients in group Z were instructed to take zolpidem 10 mg before sleep for 14 days. The primary efficacy outcome measure was the reduction in sleep latency from the start of pharmacotherapy to day 14. Secondary efficacy outcome measures included the duration of sleep, the frequency of awakenings, the quality of sleep as judged by the patient's self-report, and the prevalence of reflex insomnia. These indicators were evaluated using questionnaires given to patients.

Results: Ramelteon + zolpidem combination therapy achieved significantly better improvement in sleep duration and number of awakening ($p<0.05$). There was significantly better improvement in sleep ramelteon + zolpidem group as compared to zolpidem group with respect to modified Clinical Global Impression scale-2 ($p<0.05$). There were more cases of headache, dizziness as well as anxiety in patient receiving zolpidem monotherapy as compared to patients on ramelteon + zolpidem combination therapy. Overall, there was no statistically significant difference between group Z and R with respect to adverse effects ($p>0.05$).

Conclusion: When comparing zolpidem and ramelteon + zolpidem for their efficacy in enhancing sleep latency and maintenance, ramelteon + zolpidem combination therapy showed significantly better results with respect to sleep onset, latency and duration with better safety profile.

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

INTRODUCTION

Insomnia is defined as a complaint of difficulty in falling asleep (sleep latency) or staying sleep (sleep maintenance) which happens in an environment that is conducive to getting enough sleep and is linked to significant distress or diminished functioning during the day. [1, 2] It is a common disorder, with an estimated frequency of approximately ten percent in the general population.[3]

Most of the time, additional psychological or physiological disorders coexist with insomnia. Because of their coexistence, it was thought that insomnia was one of the illness's symptoms; however, more recent studies show that the association between these illnesses and insomnia is usually multifaceted and sometimes bidirectional.[4]

In fact, sleeplessness can cause severe depression, anxiety problems, substance misuse disorders, type 2 diabetes, hypertension, as well as thoughts of committing suicide. [5-8] This is the rationale for the suggestion that, in cases where insomnia coexists with other psychiatric or physical illnesses, medication be specially designed to address insomnia. Insomnia has also been connected to a reduction in life quality and a higher chance of accidents and falls. [9, 10] Patients who meet the diagnostic criteria for insomnia have access to a wide range of empirically supported therapeutic choices. Non-pharmacological methods exist in addition to pharmacotherapies. [10, 11]

For the management of insomnia related to hospital stays, pharmacological sleep aids are often advised in along with non-pharmacologic techniques for improving sleep hygiene. [12]

There is strong evidence that non-benzodiazepine agonists of GABA receptors constitute one of the most commonly used groups of pharmacological sleeping aids in hospital settings. This is especially the case when treating insomnia in outpatient settings. [13] Although zolpidem is generally thought to be a safe drug, there have been a few reported side effects, such as headaches, lightheadedness, and

drowsiness when taken short. In addition, the zolpidem label warns about unusual shifts in behavior as well as thought processes, possible abuse, withdrawal signs if stopped suddenly, and depressant impacts on the brain. [14]

Kolla et al. report that research on zolpidem and falls as well as inpatient accidents has demonstrated a substantial association with an increased risk of hip fractures, which is associated with a greater likelihood of morbidity as well as health care expenses for hospitalized patients.[15]

Because of the risks associated with non-benzodiazepine agonists at the GABA receptor, other therapies for insomnia have been investigated, including melatonin analogue or agonists at the melatonin receptor. Melatonin, a hormone secreted by the pineal gland, has been demonstrated to bind to and activate the high-affinity GPCRs MT1 and MT2. Sleep is brought on and sustained by this interaction. [16]

In the US, ramelteon, a melatonin receptor agonist, is currently prescribed as a pharmaceutical treatment for insomnia. Ramelteon's mode of action is associated with its great selectivity for MT1 as well as MT2 receptors.

When it comes to human MT1 as well as MT2 receptors, ramelteon is about 17 times more effective than melatonin. It can also bind these particular receptors having an affinity which can be up to 3–5 times greater. These findings are supported by in vitro studies that evaluated the functional actions of forskolin on the production of cAMP and its affinity for binding to particular melatonin receptor subtypes.[17]

In outpatient settings, melatonin is a useful drug for managing adult primary insomnia as well as other sleep issues linked to the circadian cycle. It has been demonstrated to have a low impact on psychomotor performance and to be well tolerated. [18, 19] Andrade and colleagues performed a short trial on 33 patients who got melatonin or a placebo, despite the fact that there is a dearth of hospital data concerning the efficacy of ramelteon. They discovered that there were no notable side effects and the participants in the melatonin group saw significant benefits in the amount, quality, and commencement of sleep. The patients in that trial benefited greatly from melatonin for the first seven days of treatment. [20]

Taking into account the findings of previous studies and supporting the scant data supporting the use of ramelteon for insomnia, this study was conducted to compare the efficacy and safety of ramelteon plus zolpidem versus zolpidem for improvements of the depth, duration, and standard of sleep for those with chronic primary insomnia.

MATERIALS AND METHODS

In this open-label randomized controlled trial, study participants were randomized 1:1 to two study groups. at accordance with ICH-GCP guidelines and with approval from the institutional ethics committee, the study was conducted at an eastern Indian tertiary care facility. All study participants provided signed informed consent after talking over the participant information document that was provided by the researcher at the time of consent.

A sample size of 37 per group was required for the detection of a difference size of 0.9 and a power of 90% at the 5% level of statistical significance. Assuming a 5% attrition rate, we planned to randomly allocate a total of 60 patients for this trial, with 30 patients in both groups.

Inclusion Criteria:

Patients between the ages of 18 and 65 who are classified as primary insomniacs according to the DSM-IV Diagnostic Criteria, regardless of gender.[3]

Exclusion Criteria:

- Patients with temporary or transitory insomnia
- Patients with anxiety disorders, work shift
- Patients with psychiatric disorders
- Patients with bed sores

Intervention:

During the course of the study, which lasted roughly 21 days, all eligible patients got pharmacotherapy for 14 days then had a 7-day follow-up visit. Group Z and group Z + R, each consisting of 40 patients, were created by randomizing 80 patients using web generated random numbers. It was recommended that patients in the Z group take 10 mg of zolpidem before bed, whereas patients in the Z + R group should take 5mg Zolpidem 8 mg of ramelteon before bed. Tablet counts were performed at each follow-up stage of the trial to evaluate the overall medication compliance.

Outcome Measurement:

The primary efficacy end point was the reduction in sleep latency form the start of therapy to day 14. Secondary outcome measures included the duration of sleep, the frequency of awakenings, the quality of sleep as judged by the patient, and the prevalence of reflex insomnia. These indicators were evaluated using questionnaires given to patients. In the initial phase, at the conclusion of the first and second weeks, a 12-lead ECG, vital signs, physical examination, and a pregnancy test-related laboratory assessment were carried out. The patients were given instructions to update their sleep journals each day once they awoke. The proforma contained information on the length, latency, and frequency of awakenings during sleep.

The percentage of patients in each therapy group who were assessed by the investigator to be at least "moderately improved" at the end of the treatment period employing the "modified Clinical Global Impression scale-2" was further 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 data from patients with primary insomnia were presented in tabular form using Microsoft Excel 2019 and then transferred to graph pad version 8.4.3 for further statistical analysis. Continuous data such as age, sleep latency, and sleep duration were presented as mean ± SD and compared using unpaired t-test. Categorical data such as gender, global improvement, and incidence of adverse effect was compared using chi-square or fisher's exact test with a p-value <0.05 as the cut-off for statistical significance.

RESULTS

80 patients were recruited in the study with 40 in each group. 52 (65%) of the patients were women, and 28 (35%) were men. The mean age was 41.35 ± 11.19 years in the zolpidem + ramelteon group and 39.88 ± 10.06 years in the zolpidem group. The baseline characteristics were comparable between the group Z and group R+Z with no statistically significant difference (p<0.05).

There was a significant fall in subjective sleep latency in the patients receiving ramelteon + zolpidem (reduced from 63.07 ± 22.34 minutes at baseline to 31.16 ± 7.64 minutes; p < 0.05) and patient receiving zolpidem (reduced from 62.56 ± 33.52 minutes at baseline to 29.91 ± 6.75 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. Ramelteon + zolpidem combination therapy achieved significantly better improvement in sleep duration and number of awakening (p<0.05).

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

Parameters	Group R + Z (n = 40)	Group Z (n = 40)	P-Value
Age in years (mean ± SD)	41.35 ± 11.19	39.88 ± 10.06	0.54 (Unpaired t test)
Gender			0.81 (Fisher's exact test)
Male	13	15	
Female	27	25	
Frequency of sleep disorder			
< 3 days/week	4	3	0.72 (Chi-Square)
4-6 days/week	9	12	
≤ 7 days/week	27	25	
Duration of sleep disorder			
≤1 month	7	8	0.60 (Chi-Square)
> 1 month – ≤3 months	8	7	
> 3 months – ≤6 months	4	8	
> 6 months	21	17	
Sleep latency in minutes (mean ± SD)	63.07 ± 22.34	62.56 ± 33.52	0.94 (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 + Z (n = 40)	Group Z (n = 40)	P-Value (Unpaired t test)
Sleep latency in minutes (mean ± SD)	31.16 ± 7.64	29.91 ± 6.75	0.44
Sleep duration in minutes (mean ± SD)	65.35 ± 15.86	73.54 ± 12.18	0.01
Number of awakenings (mean ± SD)	0.68 ± 0.15	0.59 ± 0.12	0.004

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

Category of Improvement	Group R + Z (n = 40)	Group Z (n = 40)	P-Value (Chi-Square)
Markedly Improved (%)	20	7	0.007
Moderately Improved (%)	14	16	
Slightly Improved (%)	4	14	
Unchanged (%)	2	3	

There was significantly better improvement in sleep ramelteon + zolpidem group as compared to zolpidem group with respect to modified Clinical Global Impression scale-2 ($p<0.05$).

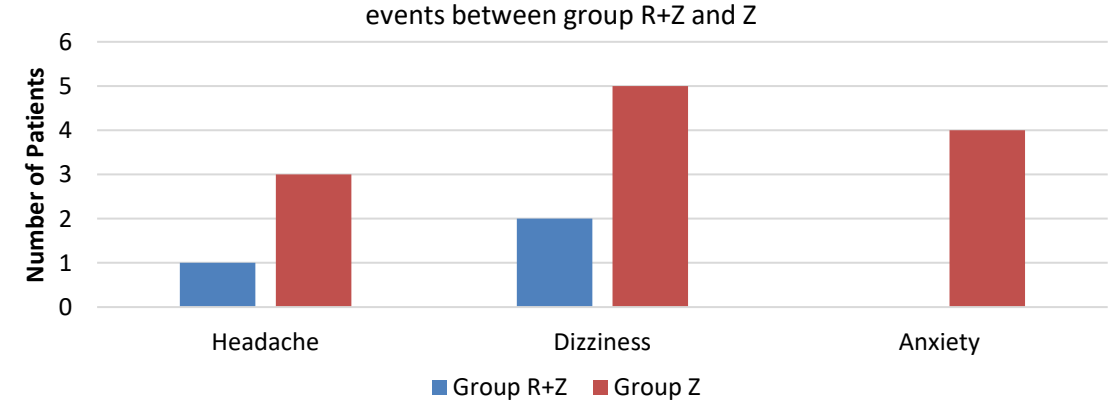
Figure 1: Comparison of two groups based on global improvement of sleep disorders between group R+Z and Z

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

Category of Improvement	Group R +Z (n = 40)	Group Z (n = 40)	P-Value (Fisher's exact test)
Headache	1	3	0.62
Dizziness	2	5	0.43
Anxiety	0	4	0.11

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

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



DISCUSSION

With a small sample size, this study examined the safety and efficacy of ramelteon and zolpidem + ramelteon. A few limitations should be taken into account when assessing the findings, such as the small sample size and absence of blinding. Moreover, we excluded actigraphy and polysomnography, two objective sleep testing methods, from our list of outcome measures. The results of the trial indicate that ramelteon + zolpidem had better efficacy in patients with primary insomnia.

The results also indicated that zolpidem, a frequently prescribed non-benzodiazepine agonist at GABA receptors, and ramelteon had similar efficacy in enhancing quality of sleep in a hospital setting, based on the patients' self-evaluation Ramelteon has been shown to be equally efficacious as zolpidem with respect to of the length, quality, and latency of sleep. Most patients in both groups exhibited considerable improvement, as measured by "the modified Clinical Global Impression scale-2".

When patients discontinued taking ramelteon + zolpidem after six months of treatment, there were not any reports of rebound insomnia or withdrawal symptoms at routine follow-up. These results are consistent with previous clinical trials using ramelteon.[22–24] There was no sign of abuse liability in patients who got ramelteon in a study on drug addicts treated with benzodiazepines, although there was for triazolam. [25] Similar risks are seen with the abuse of various benzodiazepine receptor agonists.[26–28] For example, in a 4-week trial on elderly people suffering from chronic insomnia who received either zolpidem or zaleplon, there were complaints of significant withdrawal and rebound symptoms, particularly in the zolpidem group.[29]

When ramelteon was compared to zolpidem, it was shown to be safe along with a low risk of side events, in line with previous clinical research. For example, two extensive studies that assessed the safety of ramelteon in relation to a variety of safety factors did not find any statistically significant changes in a number of variables, such as electrocardiogram readings, biochemical parameters, haematological assessment, vital signs, or physical examination findings. [30, 31] Remarkably, the study's dropout rate was almost nonexistent, indicating that ramelteon therapy for insomnia might be more bearable. Prior studies evaluating the efficacy and safety of ramelteon found that the ramelteon group's dropout rate was strikingly similar the rate observed in he placebo group. [23]

A number of studies have demonstrated the superiority of ramelteon over conventional GABAergic hypnotics; of particular note are the low incidence of signs of withdrawal and the effects that persisted into the next morning in the ramelteon group. Prior research has repeatedly shown that ramelteon users have better results with regard to mood, a number of cognitive and psychomotor tests, and morning alertness. [32, 33] When the patients awakened up in the morning, they reported feeling rested. [34] Elderly individuals who received 8 mg of ramelteon showed no decline in memory as well as motor function; in addition, their movement and balance during the middle of the night enhanced more than whenever zolpidem was added.[35]

Although the degree of significance varies due to the small number of subjects and some study design limitations, the results with their compatibility with previous studies strongly suggest that ramelteon is useful in helping sleep onset. Four large trials evaluated collectively lend more weight to this outcome. [36]

CONCLUSION

When comparing zolpidem and ramelteon + zolpidem for their efficacy in enhancing sleep latency and maintenance, ramelteon + zolpidem combination therapy showed significantly better results with respect to sleep onsent, latency and duration with better safety profile. Furthermore, there is a lower chance of addiction and side effects, like withdrawal and rebound symptoms, learning and memory problems, and impaired motor coordination. Ramelteon has been shown to be equally effective as zolpidem with respect to of the length, quality, and latency of sleep. The evidence demonstrating ramelteon's effectiveness in a hospital setting has to be strengthened by randomized controlled trials with larger sample sizes.

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