Research Paper

Comparison of efficacy, safety, and cost-effectiveness of rupatadine and olopatadine in patients of allergic rhinitis: A prospective, randomized, double-blind, parallel group study

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ABSTRACT

Objective: To compare the efficacy, safety, and cost-effectiveness of rupatadine and olopatadine in patients of allergic rhinitis (AR). **Materials and Methods:** A 2-week, single-centered, randomized, double-blind, parallel group comparative clinical study was conducted on patients with AR. Following inclusion and exclusion criteria, 67 patients were recruited and randomized to two treatment groups and received the respective drugs for 2 weeks. At follow-up, parameters assessed were total nasal symptom score (TNSS), change in total and differential count of eosinophil. **Results:** In olopatadine group, there was a significantly higher reduction in TNSS ($P < 0.05$) than that of rupatadine. Both the drugs significantly reduced the absolute eosinophil count, but olopatadine ($P < 0.001$) was found to be superior. The incidence of adverse effects was found to be less in olopatadine group when compared with rupatadine group. **Conclusion:** Olopatadine is a better choice in AR in comparison to rupatadine due to its better efficacy and safety profile.

Key words: Absolute eosinophil count, atopic disorders, TNSS

INTRODUCTION

Allergic rhinitis (AR) is one of the most prevalent atopic disorders that affect productivity and quality of life. AR is characterized by sneezing, itching, rhinorrhea, nasal congestion, nasal hypersensitivity, and non-nasal symptoms such as itching and watery eyes or itching ears and palate, and signs of invasion of nasal mucosa by inflammatory cells.[1] The prevalence of AR varies from population to population, but on an average, it can affect 25%–35% of people. AR is associated with sleep disturbances that result in impaired work productivity and interference with cognitive and emotional functioning.[2]

Today's therapy is based on three measures, mainly avoidance or elimination of the causative agent (allergen),

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symptomatic pharmacotherapy, and specific immunotherapy. The new patient should be managed differently according to the duration and severity of the clinical picture, patient's personal preferences, accessibility and the affordability of medications, and the success and effectiveness of a therapeutic option applied in the patient's particular case. The current therapeutic modalities for the management of AR include: H1 receptor antagonists (antihistamines), decongestants, mast cell stabilizers, leukotriene (LT) receptor antagonists, corticosteroids, and anticholinergic agents in oral or topical nasal formulations.[3]

Two new second-generation H1-receptor antagonists, olopatadine and rupatadine, are known as dual blockers since both these drugs block the action of not only the histamine but also of other inflammatory mediators such as platelet-activating factor (PAF), LTs, and chemokines. Olopatadine is a newly approved drug for the treatment of AR. It is a selective histamine H1-receptor antagonist, in addition possessing inhibitory effects on PAF and on the release of inflammatory lipid mediators such as LT and thromboxane (TX) from human polymorphonuclear leukocytes and eosinophils.[2] Olopatadine was shown to be highly useful for the treatment of AR, chronic urticaria, and conjunctivitis in double-blind clinical trials.[4,5] Rupatadine is a selective and long-acting oral histamine H1-receptor antagonist that has also been shown to have PAF antagonist activity.[6] It is indicated for use in AR and chronic idiopathic urticaria in patients aged 12 years or more.[7]

Although individually olopatadine and rupatadine are efficacious in AR, data on the head-to-head study of these drugs in Indian population are scanty. In spite of extensive literature search, we could not find any study comparing the cost-effectiveness of these drugs. Therefore, we aimed to compare the efficacy and safety of olopatadine with that of rupatadine and to determine the cost-effectiveness so that better option will be offered for the treatment of AR.

MATERIALS AND METHODS

Study design

This was a prospective, randomized, double-blind, parallel group, comparative 2 weeks clinical study conducted in eighty patients of AR attending ENT outpatient department (OPD) in a tertiary care teaching hospital. Patients were divided into two groups with forty patients in each group to receive either olopatadine 10 mg or rupatadine 10 mg once daily orally for 2 weeks [Figure 1].[2] Study was conducted during January 2014 to December 2014. The study was approved by the Institutional Ethics Committee (IEC). After the written informed consent was obtained from each patient, patients were enrolled in the study. CTRI acknowledgment number is REF/2014/12/008163.

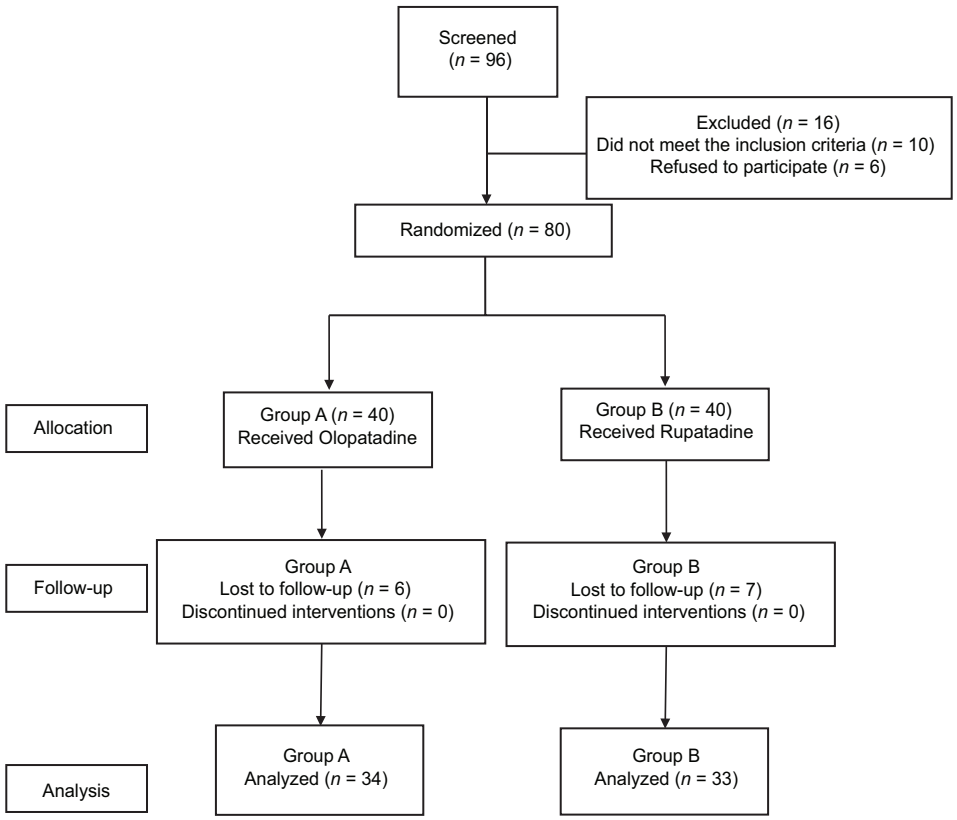

Figure 1: Study flowchart

Selection of patients

Inclusion criteria

- Patients between 18 and 65 years of either gender with history of having intermittent or persistent mild, moderate, to severe AR
- Patients with TNNS of ≥8 not treated with antihistamines in the last 3 days
- Patients who could understand and were able to adhere to the dosing and visit schedules
- Patients who agreed to record the adverse events accurately and consistently.

Exclusion criteria

- Patients with H/O asthma requiring chronic use of inhaled or systemic corticosteroids had been unresponsive to antihistamine treatment in the past
- Patients with history of allergies to study medication or unable to tolerate antihistamines
- Use of study drug in the last 3 days before baseline
- Subjects with significant systemic diseases, allergic conjunctivitis using steroid or antihistaminic eye drops, and pregnant women, nursing mothers.

Study site

The present study was performed at a tertiary care hospital in central India. After clinical diagnosis of AR which was done by ENT surgeon, baseline investigations were carried out and patients were given drugs for 2 weeks. After 2 weeks, again investigations were repeated, and data were analyzed. In total, 10 ml blood of each patient was withdrawn by taking all aseptic precautions at both 0 and 2 weeks. Nonresponders were treated appropriately by the ENT surgeon in ENT OPD.

Enrolment of patients

Patients attending ENT OPD were screened by the ENT surgeon and principal investigator. Diagnosis of AR was made on the basis of patient's chief complaints and history. Those meeting the inclusion criteria were briefed about the study. After the written informed consent was obtained from each patient, patients were enrolled in the study. A patient information sheet was given to all prospective participants.

Treatment details

After initial screening, clinical examination, and laboratory investigations, patients were randomly allocated to receive either olopatadine (Group A) or rupatadine (Group B). Block randomization procedure was used for random allocation of study drugs. Block size of four patients was taken and divided in equal proportions in Groups A and B to ensure uniform allocation ratio of 1:1. All patients received one capsule filled with either olopatadine 10 mg or rupatadine 10 mg once a day at 10 p.m. Clinical findings and laboratory investigations were recorded. Drugs were purchased by the principal investigator and distributed to the patients free of cost. There was no financial burden on the patients. Drugs were purchased by principle investigator from the local market and were of the same company and of the same batch.

Calculation of sample size

By considering power = 90%, significance level of 0.05, standard deviation of 2.5, and expected mean difference of 2, the calculated sample size came to be 34 in each group. Hence, after considering dropouts and noncompliance of the patients, the study sample size was rounded to 40 in each group. Statistical tests used were nonparametric Wilcoxon test, Mann–Whitney Rank Sum test, Fisher's exact test, and parametric paired *t*-test and unpaired *t*-test. GraphPad Prism version 5.01 (GraphPad software, Inc. USA) was used for statistical analysis.

Blinding

Double blinding was done by inserting olopatadine or rupatadine tablet in a nontransparent capsule of the same size, shape, and color. These capsules were given to a third person not directly involved in this study for coding. Codes were maintained by this person and revealed at the end of the study after the data analysis.

Clinical assessment of patients was done by the principal investigator and the consultant ENT surgeon. Patients were assessed for total nasal symptom score (TNSS) at each visit by the principal investigator and the ENT surgeon. Symptom severity was determined by the TNSS which consisted of sneezing, rhinorrhea, itching, and nasal congestion scored on a severity scale from 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe), such that the maximum possible TNSS was 12.[2,8]

Investigations

Total and differential leukocyte counts, renal and liver function tests and electrocardiogram were performed at first visit (0 week) and last visit (2nd week).

Concomitant medication restriction

Participants were advised to avoid concomitant medication with other antiallergic therapy (antihistamines, corticosteroids) or with drugs depressing the central nervous system, such as hypnotics or sedatives, in the last 72 h, topical corticosteroids in the last 7 days, oral corticosteroids in the last 8 weeks, or parenteral corticosteroids in the last 3 months.

Assessment of cost-effectiveness

For cost-effectiveness analysis, cost-effectiveness ratio of both treatment groups was calculated based on formula

Cost effectiveness = cost/outcome[9]

Where the cost of the treatment is direct health cost of the drugs only. For that cost of each tablet of olopatadine and rupatadine and the cost of total treatment on both groups was considered and for the outcome, change in TNSS from baseline to 2 weeks in both olopatadine and rupatadine groups was considered.

Safety assessment

Vigilant follow-up of patients for adverse drug reaction, if any, was recorded in case report form and IEC was informed immediately. Necessary medical aid was provided to the volunteers and they were hospitalized in till complete recovery, at no extra cost to the patient.

Statistical analysis

The normally distributed variables were analyzed using unpaired *t*-test and non-parametric tests were used for non-normally distributed variables. $P < 0.05$ was considered significant.

RESULTS

In total, eighty patients were recruited. Sixty-seven patients completed the study (34 in olopatadine group and 33 in rupatadine group). Thirteen patients lost to follow-up by the end of the study, 6 in olopatadine group and 7 in rupatadine group. Patients were randomly assigned to the treatment with olopatadine (Group A) or rupatadine (Group B) [Figure 1]. The percentage of male patients was relatively more than female patients, 61.76% in olopatadine group and 55.88% in rupatadine group. Both groups were comparable, and there were no statistically significant differences between two groups at baseline [Table 1].

There was no statistically significant difference between olopatadine and rupatadine groups in TNSS at baseline [Table 2]. However, TNSS in olopatadine and rupatadine groups at baseline and 2nd week revealed statistically significant difference after 2 weeks of treatment with olopatadine and rupatadine. The difference in TNSS score was more in olopatadine than in rupatadine group after 2 weeks of treatment [Figure 2].

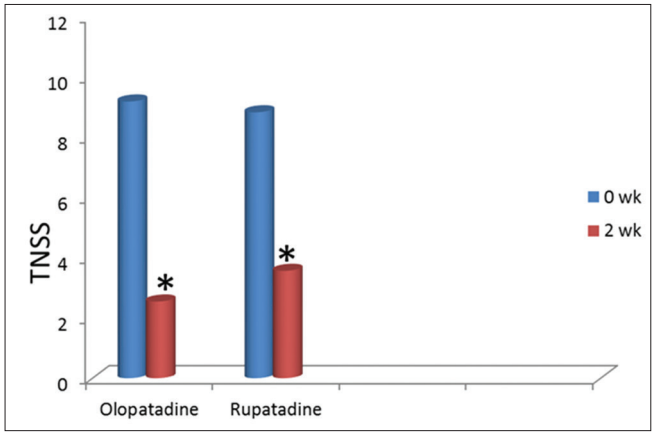

Figure 2: Total nasal symptom score of allergic rhinitis patients in olopatadine and rupatadine groups at baseline (0 week) and after 2 weeks of treatment. Values are expressed as mean (standard deviation); Wilcoxon matched-pair test, TNSS = Total nasal symptoms score

To test whether rupatadine or olopatadine is better at reducing the TNSS, we compared the effects of drugs after 2 weeks of treatment taking into consideration the change from baseline values. Between-group comparison showed that reduction in TNNS at 2 weeks was more ($P < 0.05$) with olopatadine as compared to rupatadine [Figure 3]. There was a significant

Table 1: Baseline demographic data and clinical characteristics of patients of allergic rhinitis

Characteristic	Olopatadine group (*n*=34)	Rupatadine group (*n*=33)	*P*
Number of patients recruited	40	40	
Number of patients at follow-up	34	33	
Age (years)	37.32 (8.65)	36.15 (9.14)	>0.05[$]
TLC	8100 (968.3)	8191 (1104)	0.76[#]
Neutrophils (%)	63.21 (4.82)	62.48 (5.20)	0.48[#]
Lymphocytes (%)	29.47 (5.70)	29.55 (5.57)	0.90[#]
Eosinophils (%)	6.82 (1.50)	6.63 (1.72)	0.76[#]
Monocytes (%)	0.88 (0.97)	0.75 (0.90)	0.64[#]
Basophils (%)	0.58 (0.85)	0.57 (0.70)	0.75[#]
SGOT (IU)	26.06 (9.30)	22.64 (8.05)	0.11[$]
SGPT (IU)	18.95 (5.31)	19.39 (5.17)	0.89[$]
Serum bilirubin (mg%)	0.64 (0.20)	0.62 (0.22)	0.78[$]
Serum creatinine (mg%)	0.76 (0.22)	0.85 (0.23)	0.09[$]
Blood urea (mg%)	20.71 (3.73)	19.90 (4.95)	0.68[$]

Values are expressed as mean (SD); [$]Unpaired *t*-test, [#]Mann-Whitney rank sum test. SGOT=Serum glutamic oxaloacetic transaminase, SGPT=Serum glutamic pyruvic transaminase, TLC=Total leukocyte count, SD=Standard deviation

Table 2: Baseline total nasal symptoms score in olopatadine and rupatadine groups

Parameter	Olopatadine (*n*=34)	Rupatadine (*n*=33)	*P*
TNSS	9.20 (0.76)	8.84 (0.79)	0.08

Values are expressed as mean (SD). TNSS=Total nasal symptoms score, Mann–Whitney rank sum test, SD=Standard deviation

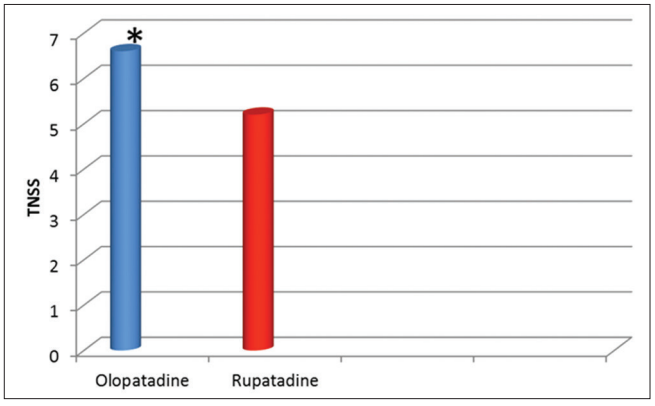

Figure 3: Comparison of effects of olopatadine and rupatadine on total nasal symptom score at 2 weeks of treatment in allergic rhinitis patients considering the change from baseline. Values are expressed as mean (standard deviation); *$P < 0.05$, TNSS = Total nasal symptoms score, Mann–Whitney rank sum test

decrease in neutrophil count, eosinophil count, and increase in lymphocyte count after 2 weeks of treatment in olopatadine group. While in rupatadine group, only eosinophil count decreased significantly after 2 weeks of treatment. Reduction in eosinophil count was more in olopatadine group as compared to rupatadine group at 2 weeks of treatment ($P < 0.05$). There was no significant change in liver and kidney function after 2 weeks of treatment in both groups as compared to baseline.

Adverse events were noted in 10 patients of olopatadine and 8 patients taking rupatadine. Sedation was the most common adverse event in both groups (olopatadine-6, rupatadine group - 5). Headache and dryness of mouth were noted in both groups while gastric irritation was noted in olopatadine group. Adverse event rate was more in olopatadine group as compared to rupatadine group. Adverse events were tolerable, and there was no need to withdraw the patients from treatment group.

For cost-effectiveness analysis, only direct health cost of drug treatment was taken into consideration. The cost of each tablet of olopatadine was Rs. 12.4, and for rupatadine, it was Rs. 5.25. Thus, calculating the total cost of treatment at the end 2nd week gave us the idea of difference of total cost in the treatment which is more in olopatadine group. The cost of treatment was calculated per patient. The cost-effectiveness ratio was calculated as described elsewhere.[9] In our study, effectiveness parameter is TNSS, i.e., the difference in TNSS score after 2 weeks from baseline values in both groups. The treatment modality having less cost-effectiveness ratio is considered as superior. In our study, the cost-effectiveness ratio is less in rupatadine group at the 2nd week stating that the rupatadine is more cost-effective.

DISCUSSION

It remains a challenge to the physicians to treat the symptoms of AR and ensure a good quality of life to the patients. An increase in the understanding of the pathomechanisms of AR in the last few decades has revealed the potential of the new-generation antihistamines with dual-blocking property in the treatment of AR. Rupatadine and olopatadine are known to be effective in AR in several clinical trials, but this study was performed to compare their efficacy and safety and thus to choose the better agent. Inspite of extensive literature search, we could not find any double-blind study comparing the efficacy, safety, and cost-effectiveness of olopatadine and rupatadine in AR. Moreover, data on such types of studies from Indian setup are very scanty. Hence, we considered it worthwhile to conduct this study in Indian setup where patients have less affordability for costly medicines.

The TNSS is a widely accepted and reliable tool to assess the efficacy of a drug in the treatment of AR, and a decrease in the score suggests that there is an overall clinical improvement in the condition. We observed a significant difference in TNSS after completion of the treatment in olopatadine as well as rupatadine groups. Rescue medication was not required in any of the subjects. In the present study, a significant and progressive decrease in the TNSS was observed at the end of 2 weeks of treatment with olopatadine and rupatadine.

In a study conducted to test the efficacy of rupatadine in treating patients with AR, rupatadine was found to be effective in reducing nasal symptoms, improving signs secondary to mucosal inflammation with sustained and even improving results after 2 weeks of treatment.[6] Another comparative dose ranging trial of rupatadine showed improvement in nasal and ocular symptoms of AR.[10] Our study supports this finding of a significant reduction in symptom score and improvement in nasal symptoms.

In a randomized, double-blind, placebo-controlled study, oral olopatadine significantly suppressed sneezing ($P < 0.001$), rhinorrhea ($P < 0.001$), and nasal congestion ($P < 0.05$).[4] In another comparative open-labeled study, olopatadine and rupatadine have decreased the TNSS, but olopatadine was found to be superior to rupatadine in reducing the TNSS.[2] Our study supports this finding of significant reduction in TNSS with rupatadine and olopatadine both. Change in TNSS was significant and more pronounced in olopatadine than in rupatadine group.

Olopatadine and rupatadine are known as dual blockers since both these drugs block the action of not only the histamine but also of other inflammatory mediators such as PAF, LTs, and chemokines. The probable superiority of olopatadine over rupatadine may be attributed to the following findings. Olopatadine can reduce the amount of cell-associated PAF by 52.8%, which is more than rupatadine.[11] PAF known to increase vascular permeability and is increasingly recognized as an important mediator in inflammation. It also suppresses LTs and TxA2 release, and PAF formation by reducing arachidonic acid release from membrane phospholipids, probably through interference with phospholipase A2.[12] Olopatadine has been shown to suppress the activity of S100A12, which is a member of the S100 family of calcium-binding proteins, and exerts multiple pro-inflammatory activities including chemotaxis for monocytes and neutrophils.[13] All these actions inhibit the inflammatory mediators which are the main contributors for vasodilation, vascular leakage, and eosinophil chemotaxis, thus decreasing the symptoms of AR by reducing number of sneezing, itching, rhinorrhea, and nasal blockade more significantly as compared to rupatadine.

Allergic conditions are usually associated with the changes in the percentage of eosinophil and its absolute count and probably that's why the effects of the drugs have not been directly reflected on total leukocyte count and neutrophil count. The increase in eosinophil count is the hallmark of the late phase of AR. The scrupulous control of this parameter is an important therapeutic

aim in the treatment of AR.[2] Our study showed a significant decrease in differential eosinophil count in both groups. The comparative change in the differential count of eosinophil in olopatadine group was found to be significantly more as compared to the rupatadine group. This observation supports the previous study of analysis of rupatadine and olopatadine.[2,6] There was no significant difference in differential monocyte count and differential basophil count in both groups. In our study, we did not find any significant change in biochemical parameters. This observation supports the previous study on safety analysis of rupatadine and olopatadine.[2,6]

Most frequently occurring adverse event with rupatadine was sedation, which supports the previous studies conducted on rupatadine for its safety profile. Other adverse events noted were headache, gastric irritation, and dryness of mouth.[9,14] Similarly, with olopatadine, the most commonly occurring adverse event was sedation, which supports the finding of the previous study. Other adverse events noted were headache and dryness of mouth which were also found in the previous study.[2,14] Our study did not reveal any change in electrocardiogram (ECG), supporting the previous studies which also showed no change in ECG findings.[10,14,15]

To compare the cost-effectiveness of two drugs, only the direct health cost of the drug treatment was taken into consideration. When we compared the cost-effectiveness ratio of the treatment, i.e., rupatadine and olopatadine, we found that cost-effectiveness ratio was less in rupatadine. For pharmacoeconomic analysis, treatment modality having less cost-effectiveness ratio is considered as superior. Thus, it suggests that rupatadine is more cost-effective than olopatadine for the treatment of AR. However, after an in-depth search, we could not find any study related to our finding. This information can help physicians in selecting a drug for treating the patients of AR. Patients, who can afford costly treatment, can be prescribed more effective olopatadine, while for patients who cannot afford, it can be prescribed rupatadine as it is more cost-effective.

Although the present study was double-blind with small sample size and of short duration, the results of the study cannot be ignored. However, studies with larger sample size and longer follow-up periods, along with measurements of absolute eosinophils counts, may yield more meaningful data to compare rupatadine and olopatadine. Furthermore, to determine the cost-effectiveness, studies considering direct cost, indirect and incremental cost can provide more meaningful data to compare rupatadine and olopatadine.

CONCLUSION

Both rupatadine and olopatadine provide effective relief of the symptoms of AR. However, clinical benefit occurs significantly more with olopatadine. It may be due to additional PAF antagonistic property and anti-inflammatory effects of olopatadine that act directly on the H_1 receptor. However, rupatadine was more cost-effective than olopatadine in treating the patients of AR in term of effectiveness.

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Conflicts of interest

There are no conflicts of interest.

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