

## Comparative study of efficacy and safety of Rupatadine with Monteleukast and Levocetirizine with Monteleukast in the treatment of Seasonal Allergic Rhinitis

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**Abstract:** Seasonal allergic rhinitis (SAR) is the most common cause of rhinitis. It is caused by environmental allergies and is characterized by an itching or running of nose, sneezing, and nasal congestion. Rupatadine is a novel drug which exhibits both anti-histaminic and anti-PAF effects through its interaction with specific receptors. Rupatadine is a once daily, selective, non-sedative has a good safety profile and tolerability at the dose of 10mg/day and is devoid of arrhythmogenic effects. Levocetirizine is a selective non-sedative H1 receptor antagonist which causes QT interval prolongation leading to cardiac arrhythmias. Montelukast is an orally active, highly selective leukotriene receptor antagonist (LTRA) that inhibits the cysteinyl leukotriene receptors. It is administered once daily orally in combination with Rupatadine and Levocetirizine to improve efficacy of treatment and quality of life of patient because of its selective action. The present study was undertaken to compare the efficacy and safety of a combination of Rupatadine with Montelukast and Levocetirizine with Montelukast in the treatment of seasonal allergic rhinitis. Efficacy of treatment with Rupatadine and Montelukast combination shows better results than Levocetirizine and Montelukast combination in reducing ARIA (Allergic Rhinitis and its Impact on Asthma) score, TNSS (Total Nasal Symptom Score) value, AEC (Absolute Eosinophil Count) values and TLC (Total Leukocyte Count) values with 2 weeks of treatment. The study concluded that Rupatadine and Montelukast is a better choice in seasonal allergic rhinitis compared with Levocetirizine and Montelukast combination owing to its better efficacy and safety profile.

**Key words:** - Levocetirizine, Montelukast, Rupatadine, Seasonal allergic rhinitis (SAR).

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### I. Introduction

Seasonal allergic rhinitis (SAR) also known as hay fever, is an inflammatory condition of the upper airway that occurs in response to exposure to airborne allergens in sensitized individuals in specific seasons.<sup>1</sup>

Socio-economic impact of SAR is substantial as it relay not only to the cost of management but also to the considerable indirect costs, through reduced productivity and absenteeism from work. It has a significant cause of morbidity and impact on both work and school performance.<sup>2</sup> Seasonal allergic rhinitis afflicts approximately 10% of the U.S population or 30 million individuals. Among this 17.7 million are adults, diagnosed with SAR. SAR has been demonstrated to adversely affect quality of life and sleep, cognition, emotional life and school performance.<sup>3,4</sup>

Allergic rhinitis is broadly divided into seasonal and perennial. SAR is known to be triggered mostly by various types of pollens from grasses, weeds and trees as well as outdoor moulds and spores. SAR presents usually with sneezing, rhinorrhoea, nasal obstruction, pharyngeal obstruction, ocular watering and itching.<sup>5</sup> Symptoms of Perennial allergic rhinitis are similar to that of SAR except that nasal obstruction is more pronounced. Most of the PAR patients exhibit sensitivity to one or more of the non-seasonal allergens eg: spores, moulds, animal dander, dust and mites.<sup>6</sup>

In both SAR and PAR, the underlying process is an allergic response to airborne allergens of different nature. SAR is associated with the epithelial accumulation of effector cells such as mast cells, eosinophils and basophils.

Immunological activation of these effector cells is associated with secretion of pro inflammatory mediators like Leukotrienes, prostaglandins, kinins and preformed mediators like histamine and tryptase. Quantitatively, histamine is the most abundant preformed mediator in the early phase response and has also been associated with many symptoms of this disease such as rhinorrhoea, itching, sneezing and watery eyes mediated

mainly through the histamine H1 receptor<sup>7</sup>.

Platelet-activating factor (PAF) is a potent phospholipid activator and inflammatory mediator produced by inflammatory cells such as alveolar macrophages, eosinophils, mast cells, basophils, platelets and neutrophils in response to allergic stimuli. PAF is associated with increased vascular permeability, eosinophil chemoattraction, bronchoconstriction, airway hyper-responsiveness that contribute to the appearance of rhinorrhoea and nasal congestion. From the available experimental evidence, it could be reasonable to infer that the blockade of histamine, PAF and LT receptors will be of superior clinical efficacy than the blockade of anyone of these receptor types in the treatment of allergic rhinitis<sup>8</sup>.

Rupatadine is a novel drug which exhibits both anti-histaminic and anti- PAF effects through its interaction with specific receptors. Rupatadine is a selective, non-sedative has a good safety profile and tolerability at the dose of 10mg/day and is devoid of arrhythmogenic effects<sup>9</sup>.

Levocetirizine is a selective non-sedative, H1 receptor antagonist, which causes QT interval prolongation leading to cardiac arrhythmias.

Montelukast is an orally active, highly selective leukotriene receptor antagonist (LTRA) that inhibits the cysteinyl leukotriene receptors. It is administered once daily orally in combination with Rupatadine and in combination with Levocetirizine to improve efficacy of treatment due to selective action.<sup>10</sup>

Due to these factors the present study was undertaken to compare the efficacy and safety of the combination of Rupatadine with Montelukast and Levocetirizine with Montelukast in the treatment of seasonal allergic rhinitis.

## **II. Aims of The Study**

- 1) To compare the efficacy and safety of Rupatadine and Montelukast with Levocetirizine and Montelukast in the treatment of seasonal allergic rhinitis.
- 2) To study the effect of these two drugs on absolute eosinophil count.

## **III. Methodology**

The cases for this study were taken from the allergy clinic of ENT department in Government General Hospital, Kurnool attached to Kurnool medical college, Kurnool. Patients showing signs and symptoms suggestive of allergic rhinitis were taken for the study, aimed at comparing the efficacy, adverse effects and influence on laboratory parameters of the drugs.

**Data collection:** A Total of 60 patients, divided into 2 groups of 30 patients each. The drugs were studied for each group.

Group I: Rupatadine 10mg + Montelukast sodium 10mg for 2 weeks

Group II: Levocetirizine 5mg + Montelukast sodium 10mg for 2 weeks

### **3.1 SELECTION CRITERIA OF THE PATIENTS**

#### **INCLUSION CRITERIA:**

- A) Age group: Patients in the age group of 12-60 years were included in this study because seasonal allergic rhinitis is mostly seen in this age group.
- B) Sex: Male and female patients were included in the study.
- C) Clinical feature: Patients showing the typical features of allergic rhinitis such as sneezing, running nose, nasal itching, nasal congestion or stuffy nose, and post nasal drip

#### **EXCLUSION CRITERIA:**

- A) Patients unwilling to sign informed consent
- B) Patients with history of hepatic and renal impairment.
- C) Pregnant and lactating mothers.
- D) Children below the age of 12 years

After the selection of the patients, based on the above Criteria, the plan of study comprised of the following:

- 1) Present complaints with duration
- 2) Personal history of exposure to any allergens
- 3) Family history of atopy
- 4) General examination of the patient
- 5) ENT examination
- 6) Investigations: Complete blood picture, absolute eosinophil count
- 7) Treatment

Follow up: This includes, recording of any improvement in symptoms and signs after the treatment, any adverse effects of the treatment and repetition of all the above investigations to see the effects of the given drugs on the investigative parameters.

### **3.2 TREATMENT PRESCRIBED AND FOLLOW UP:**

Patients in group I received tablets of Rupatadine Fumarate 10mg + Montelukast sodium 10mg for 1 week. They were initially given 7 tablets and instructed to take one tablet per day in the evening or before going to bed. The patients were asked to report to the hospital after 1 week and they were followed up with regard to clinical improvement of symptoms and signs and any adverse effects as reported by the patient. Then they were provided with 7 more tablets and instructed to take one tablet per day for another one week. After completion of the total duration of 2 weeks of treatment, the patients again reported at hospital. They were followed up with regard to clinical improvement, any adverse effects reported and also by repetition of all the investigations done before starting the treatment.

Patients in group II received tablets of Levocetirizine 5 mg + Montelukast sodium 10mg for 1 week. They were initially given 7 tablets and instructed to take one tablet per day in the evening or before going to bed. The instructions and procedures are same as first group of patients.

The patients in both groups were instructed not to take any medicine other than the tablets provided to them during the study period. They were also told to stop the medication if they notice any major undesirable effects and to inform the same to the doctors at the allergy clinic. In assessing the improvement of symptoms after the treatment, the patient was told to express his/her improvement as 25%, 50%, 75% or 100% of the initial intensity of those symptoms. If there was no improvement in the patient's opinion, it was recorded as 0%. If the patient was totally relieved of the symptoms, the improvement was recorded as 100%. The doctor's assessment of symptoms and signs based on ARIA score and also TNSS was also recorded.

### **TOTAL NASAL SYMPTOM SCORE**

#### **Assessment:**

	None				unbearablysevere	
Sneezing	1	2	3	45	6	7
Running nose	1	2	3	45	6	7
Congestion	1	2	3	45	6	7
Itching of nose	1	2	3	45	6	7
Post nasal drip	1	2	3	45	6	7

1 – 2 = None - to an occasional limited episode

3 – 4 = Mild - steady symptoms but easily tolerable

5– 6 = Moderately bothersome - symptoms hard totolerate, may interfere with activities of daily living and / or sleep

7 = Unbearablysevere - symptoms are so bad, person do not function all thetime

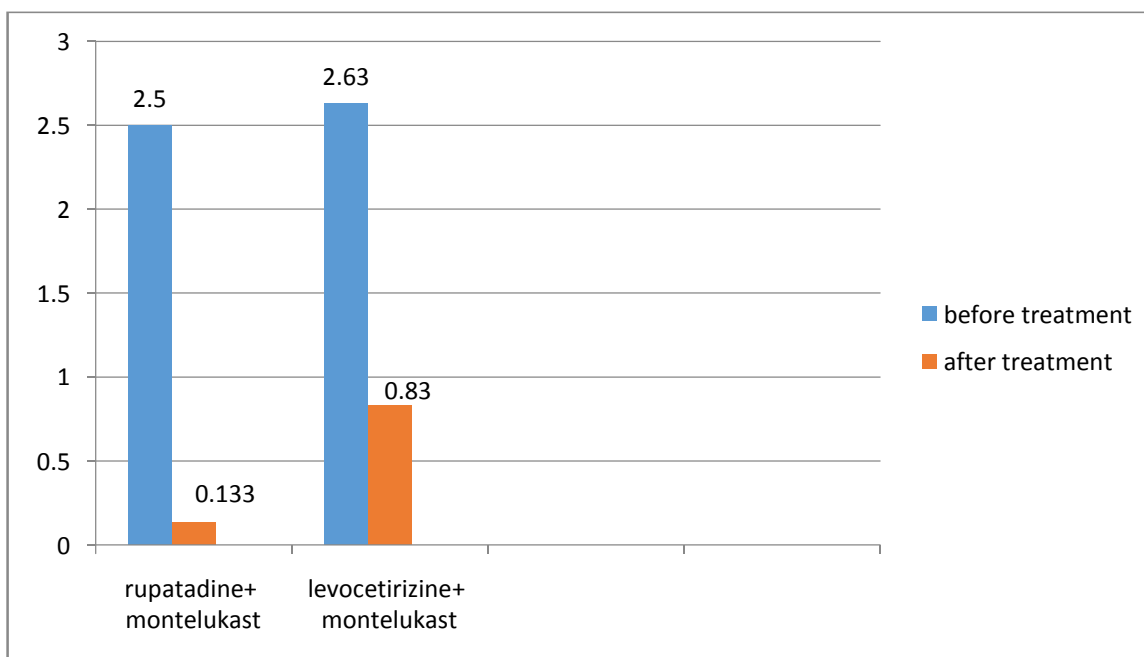
Similarly, the investigation parameters before and after treatment were recorded in a tabular form.

#### IV. Results

**Table 1:** Comparative % Reduction Of Aria(Allergic Rhinitis And Its Impact On Asthma) Score Values With The Treatment By Two Drugs

	% reduction with Rupatadine + Montelukast	% reduction with Levocetirizine + Monteluksat
<b>Mean</b>	<b>94.99</b>	<b>69.44</b>
<b>±SD</b>	<b>13.24</b>	<b>23.19</b>
<b>±SE</b>	<b>2.42</b>	<b>4.23</b>
<b>P value</b>	<b>&lt;0.0001</b>	

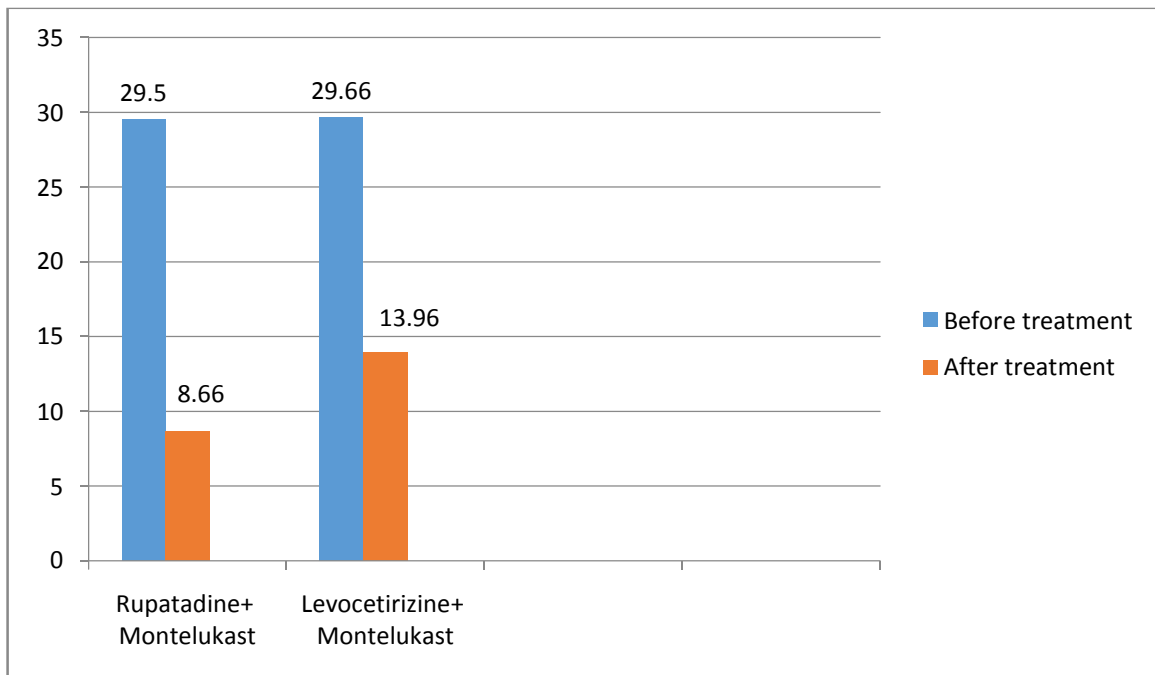
Test is Statistically Significant



Graph 1: changes in Mean ARIA Score values with two drugs  
(Group I – Rupertadine + Montelukast ; Group II – Levocetirizine + Montelukast)

**Table 2:** Comparative % Reduction Of Total Nasal Symptom Score Values With The Treatment By Two Drugs

	% reduction with Rupatadine + Montelukast	% reduction with Levocetirizine +Monteluksat
<b>Mean</b>	<b>69.43</b>	<b>51.13</b>
<b>±SD</b>	<b>14.55</b>	<b>21.49</b>
<b>±SE</b>	<b>2.65</b>	<b>3.92</b>
<b>P value</b>	<b>&lt;0.0003</b>	

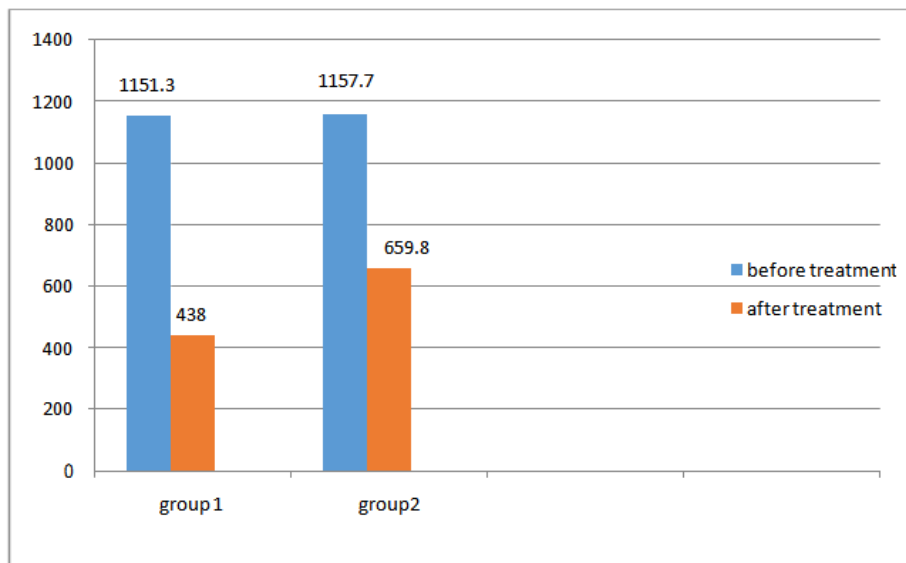


**Graph 2:** changes in Mean TNSScore values with two drugs (Group I – Rupatadine + Montelukast ; Group II – levocetirizine + Montelukast)

**Table 3:** Comparative % Reduction Of Absolute Eosinophil Count (Per Mm3) Values With The Treatment By Two Drugs

	% reduction with Rupatadine+Montelukast	% reduction with Levocetirizine+Montelukast
Mean	60.55	40.62
± SD	18.01	22.44
± SE	3.29	4.10
P value	<0.0004	

Test is Significant

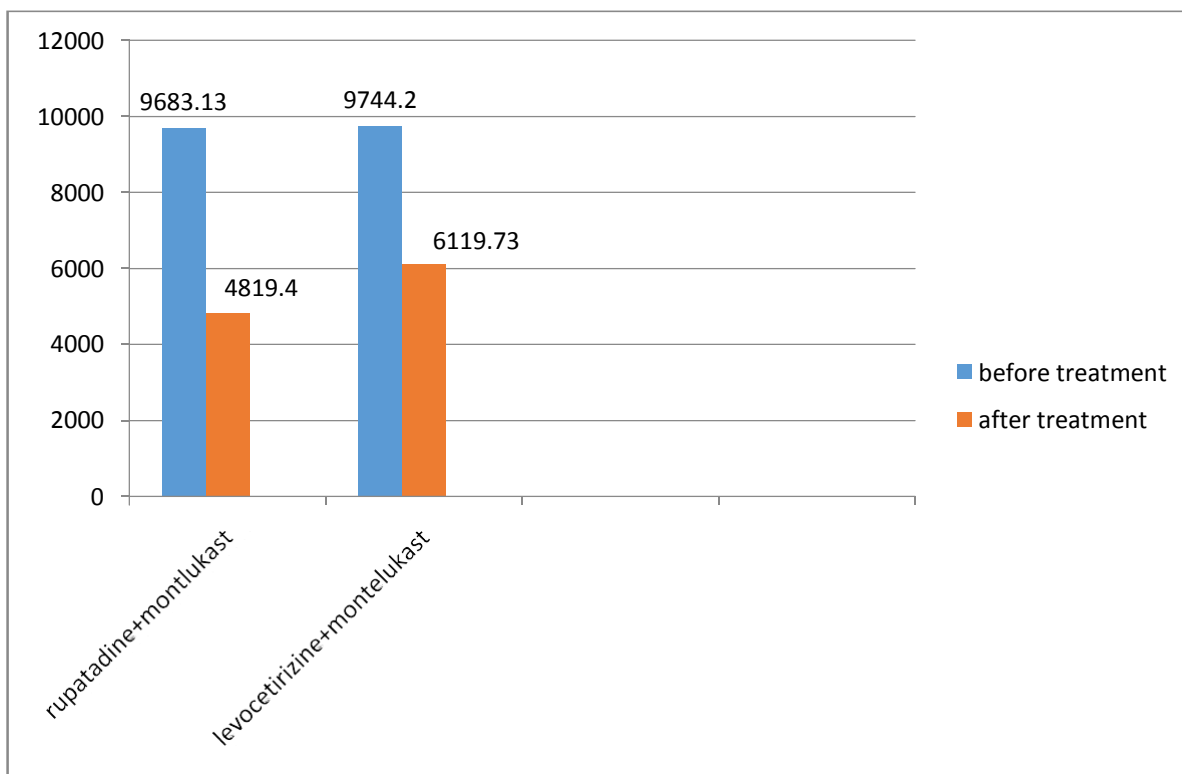


**Graph 3:** Changes in Mean Absolute Eosinophil count values with the two drugs (Group I – Rupatadine + Montelukast ; Group II – Levocetirizine + Montelukast)

**Table 4:** Comparative % Reduction Of Total Leukocyte Count Value With The Treatment By Two Drugs

	%reduction with rupatadine +montelukast	% reduction with levocetirizine+montelukast
<b>Mean</b>	48.33	37.23
<b>±SD</b>	12.48	13.07
<b>±SE</b>	2.28	2.38
<b>P value</b>	<0.001	

Two samples are significant different



Graph 4: changes in mean total leukocyte count values with two drugs (Group I – Rupatadine + Montelukast ; Group II – Levocetirizine +Montelukast)

**Table 5: ADVERSE EFFECTS REPORTED DURING TREATMENT BY BOTH DRUGS**

Group I: Rupatadine 10mg + Montelukast 10mg for 2 weeks (n=30)

Group II: Levocetirizine 5mg + Montelukast 10mg for 2 weeks (n=30)

Drug	No .of patients reported with adverse effects	Somnolence	Headache	Fatigue	Dry mouth	Asthenia
<b>Group I</b>	<b>4</b>	<b>2</b>	<b>0</b>	<b>1</b>	<b>1</b>	<b>0</b>
<b>Group II</b>	<b>9</b>	<b>1</b>	<b>4</b>	<b>1</b>	<b>1</b>	<b>2</b>
<b>Total</b>	<b>13</b>	<b>3</b>	<b>4</b>	<b>2</b>	<b>2</b>	<b>2</b>

**P value: 0.269718**

Result is not significant.

Statistically there is equal rate of adverse drug reactions with 2 drug combinations

## V. Discussion

Allergic rhinitis is one of the most common diseases, representing approximately 20 % of the general population. Seasonal allergic rhinitis accounts for 20 % of cases of allergic rhinitis, and evidence suggests that, the prevalence of the disorder is increasing.

The percentage of reduction of ARIA score values were compared in combination of drugs, statistically significant values ( $p$  value =  $<0.0001$ ) were obtained. The present study shows that there is significant reduction in ARIA scores with Rupatadine with Montelukast combination than Levocetirizine with Montelukast combination in seasonal AR patients.

The second scoring system for assessing efficacy of treatment is-total nasal symptoms score (TNSS). In this we calculated total nasal symptoms alone. The present study shows that the percentage reduction of total nasal symptom score values with two drug combinations are also statistically significant ( $p = <0.0003$ ).

For the reduction of TNSS values, Rupatadine with Montelukast combination is little more effective than Levocetirizine with Montelukast combination in patient with seasonal AR.

The other parameters assessed in this study for testing efficacy of drug combinations are Absolute Eosinophil Count and Total leukocyte count. The comparative percentage reduction of AEC (per  $\text{mm}^3$ ) values with the treatment by two combinations shows statistically significant values ( $p = < 0.0004$ ). The results show that Rupatadine with Montelukast combination is superior in reducing cell/ $\text{mm}^3$  of AEC than Levocetirizine with Montelukast combination in 2 weeks after treatment.

Individually the two drug combinations effectively reduced the total leukocyte count values in patient with seasonal allergic rhinitis in 2 weeks of treatment. Comparative percentage reduction of total leukocyte count value with the treatment by two drug combinations was statistically significant ( $p = <0.001$ ). The results show that Rupatadine with Montelukast combination was superior in reducing TLC than Levocetirizine with Montelukast combination.

Efficacy of treatment with Rupatadine and Montelukast combination shows better results than Levocetirizine and Montelukast combination in reducing ARIA score, TNSS value, AEC values and TLC values with 2 weeks of treatment.

Safety of the two drug combinations was evaluated by assessing adverse reactions during the treatment. The common side effects with antihistamines are somnolence, headache, dry mouth, fatigue, dizziness, and asthenia.

A total of 30 patients have been given Rupatadine-10mg with Montelukast-10mg combination for 2 weeks. Among 30 patients with moderate to severe seasonal AR, 4 patients had adverse drug events during treatment process. The most frequent treatment related adverse effects during this period are somnolence and headache. Among 4 patients, 2 patients had somnolence, 1 patient had fatigue and 1 patient complained dry mouth. The second group of 30 patients were given Levocetirizine 5mg and Montelukast 10mg combination for 2 weeks. Among the total 30 patients, 9 patients had adverse events during the treatment process. The most frequent treatment related adverse effects with Levocetirizine and Montelukast combination are headache in 4 patients, fatigue in 1 patient, weakness in 2 patients and dry mouth in 1 patient.

By analyzing and comparing the adverse effect profile of both the drug combinations, it can be concluded that there is no statistically significant difference in the ADR profile.

Studies related to this study shows that Rupatadine was more efficacious in relieving symptoms of seasonal allergic rhinitis. It also reduced ARIA scores, absolute eosinophil count values and total leukocyte count. It is also cost effective.

Rituparna Maiti, MD et al in their study titled "Rupatadine and Levocetirizine for Seasonal Allergic Rhinitis" came to conclusion that Rupatadine is a better choice in seasonal allergic rhinitis compared with Levocetirizine owing to its better efficacy and safety profile.

E. M. Guadano et al in their study titled "Rupatadine 10mg and Ebastine 10mg in seasonal allergic rhinitis: a comparative study" came to conclusion that Rupatadine, a new non-sedating, once daily antihistamine, relieved common nasal and non-nasal symptoms of SAR over 14-days after treatment.

In the light of above discussion Rupatadine with Montelukast combination is superior in relief of symptomatology of SAR. It is also superior in reduction of absolute eosinophil count and total leukocyte count values in SAR. The safety is far superior when compared to the Levocetirizine with Montelukast combination. So Rupatadine with Montelukast combination is more efficacious and safer than Levocetirizine with Montelukast combination.

## VI. Conclusions

The two drug combinations, Rupatadine with Montelukast and Levocetirizine with Montelukast were found to have good efficacy in controlling the symptoms of the seasonal allergic rhinitis, but the results show that Rupatadine with Montelukast is slightly more effective than Levocetirizine with Montelukast combination. Rupatadine with Montelukast has a good safety profile and other adverse effects are minimal in comparison

with Levocetirizine and Montelukast therapy. From the results of the present comparative clinical analysis of Rupatadine with Montelukast and Levocetirizine with Montelukast, cost of treatment for both groups is almost same. The study concluded that Rupatadine and Montelukast is a better choice in seasonal allergic rhinitis compared with Levocetirizine and Montelukast combination owing to its better efficacy and safety profile.

Because non-blinding was a limitation and no specific allergen tests and IgE assay could be done in our hospital due to non-availability and cost factor involved. Further studies are required to confirm the superior efficacy on a more scientific platform. The findings of this study need to be confirmed by multicentric, randomized, double blind large population studies.

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