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Comparison of efficacy and tolerability of oral desloratadine, rupatadine and ketotifen in seasonal allergic rhinitis

Syed Khadeer[1,*], Girish K[2], B Jagannath[3]

[1]*Dept. of Pharmacology, Sri Rajiv Gandhi College of Dental Science & Hospital, Bengaluru, Karnataka, India*
[2]*Dept. of Pharmacology, Kempegowda Institute of Medical Sciences, Bengaluru, Karnataka, India*
[3]*Dept. of ENT, Kempegowda Institute of Medical Sciences, Bengaluru, Karnataka, India*

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ABSTRACT

Background: Rhinitis is inflammation of nasal mucosa which characteristically presents as running nose, blocked nose, itching on nose or sneezing. Allergic rhinitis is more common than non-allergic rhinitis. Antihistamines are the mainstay of SAR treatment. Desloratadine, rupatadine and ketotifen are the commonly prescribed anti histamines in our region. In this study, we have compared efficacy and tolerability of desloratadine, rupatadine and ketotifen in SAR.

Patients and Methods: This was a prospective, randomized, three arm, open label comparative study of desloratadine, rupatadine and ketotifen in SAR, conducted at Department of ENT, Kempegowda Institute of Medical Sciences, Bangalore; between January 2014 and December 2014. Patients' severity of SAR symptoms were assessed by TNSS, QoL was measured using Medical Outcomes Study questionnaire (SF-12). SF-12 was administered at the start of study and then at the end of study. Adverse effects were monitored during clinical examination at each visit. Study subjects were systemically randomized into three groups – desloratadine (DES), rupatadine (RUP) and ketotifen (KET). Based on the assigned group; desloratadine was given orally in dose of 10mg OD, rupatadine orally 10 mg OD and ketotifen orally 1mg BD. All medications were given for 4 weeks. Follow up was done for all patients every week during treatment period of 4 weeks. The primary outcome measure was change in mean TNSS from baseline; secondary outcome measures were changes in the individual nasal symptom scores, change in the quality of life and tolerability to the study medications.

Results: Total 150 patients were recruited for this study, divided into 3 groups. DES and RUP were equally effective but significantly better than KET in improving rhinorrhea, nasal congestion, TNSS and AEC. (p=0.05). All the drugs were equally effective with no statistically significant intergroup difference in improving sneezing, nasal itching and QoL. RUP appeared to have better tolerability as the total number of adverse events were marginally less.

Conclusion: DES and RUP are comparatively more effective and faster acting than KET. All the study medications were well tolerated with few mild, self-limiting, transient adverse events requiring no intervention.

1. Introduction

Rhinitis is inflammation of nasal mucosa. It characteristically presents as at least two of the following symptoms: running nose, blocked nose, itching on nose and sneezing. Around 40% of the world's population gets affected with rhinitis at least once. Rhinitis could be allergic or non-allergic. Causes for non-allergic rhinitis include infection, vasomotor imbalance, drug-induced, etc. Allergic

* *Corresponding author.*
E-mail address: nsyedkhadeer@gmail.com (S. Khadeer).

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rhinitis is more common than non-allergic rhinitis and it contributes to being a major cause of chronic rhinitis.[1,2] Allergic rhinitis is a hypersensitivity disorder in a sensitized person, induced by exposure of nasal mucosa to allergen(s) leading to IgE mediated inflammation. Rhinitis symptoms stated above should be present for more than 1 hour daily for at least 2 weeks to qualify as allergic rhinitis. Associated symptoms like lacrimation, itching of eyes, anosmia or postnasal drip or disturbed sleep might also be seen in some patients.[3,4] It needs to be emphasized that allergic rhinitis can have many associated complications like conjunctivitis, pharyngitis, sinusitis, asthma, nasal polyposis, otitis media, atopic dermatitis, lower respiratory tract infection, dental occlusion, eczema, lymphoid hyperplasia and obstructive sleep apnea.[5–8] All of these worsen the morbidity of the patient.

Around 09 – 42 % of the world's population are affected at least once with seasonal allergic rhinitis (SAR).[9] Around 20–30 % of the Indian population is estimated to suffer from SAR.[4] The burden of SAR in India is escalating. Patients are now presenting with more severity compared to a decade ago.[10] This should be a reason for concern as many cases are under-recognized and underreported, which often has an impact on productivity at school or work thus affecting the quality of life.[11] Due to the troublesome symptoms and comorbidities of SAR, SAR impacts patients' routine life to great extent.[12–15]

Pharmacotherapy of SAR includes H1 antihistaminics given orally or topically, intranasal steroids, leukotriene receptor antagonists, mast cell stabilizers, anticholinergic agents and nasal decongestants.[16] Anti-histamines are the mainstay of treatment in any case of SAR as histamine plays an essential role in mediating allergic inflammation in the nose via H1 receptors.[17] Histamine via H1 receptors causes vasodilation, increased capillary permeability and stimulation of sensory nerves in nasal mucosa which leads to typical rhinitis symptoms.[18] Among the anti-histamines desloratadine, rupatadine and ketotifen are commonly prescribed in our region. A comparative study needs to be done to evaluate the most suitable antihistamine for SAR. We could not find any relevant study comparing these drugs in India. Hence in this study, we have compared the efficacy and tolerability of desloratadine, rupatadine and ketotifen in SAR.

2. Patients and Methods

This was a prospective, randomized, three-arm, open-label comparative study of desloratadine, rupatadine and ketotifen in SAR. The study was conducted at the Department of Otorhinolaryngology, Kempegowda Institute of Medical Sciences & Research Center, Bangalore, between January 2014 and December 2014. Patients diagnosed with SAR, attending the department of ENT OPD were recruited for this study following our inclusion and exclusion criteria. This study was conducted according to the ICH-GCP guidelines and the revised Declaration of Helsinki. Written informed consent from all participants was obtained after fully explaining the study procedure in a language understood by them. For illiterate patients, informed consent document was read out by individuals not concerned with study or patient.

2.1. Inclusion criteria

1. Subjects between 18 to 65 years of either gender with SAR
2. Total Nasal Symptom Score (TNSS of ≥ 6
3. Willing to give written informed consent and available for regular follow-up

2.2. Exclusion criteria

1. Subjects suffering from non-SAR (i e perennial, vasomotor, infective, drug-induced rhinitis
2. Subjects who have received any of the drugs used in the management of SAR in the past 2 weeks.
3. Subjects receiving glucocorticoids and/or immunotherapy
4. Subjects with known hypersensitivity to any of the study drugs
5. Pregnant, lactating women and those planning to conceive
6. Chronic alcoholism and liver dysfunction

Each patient was asked about their present medical history, past history, drug history, special emphasis on allergy history was given, and its aggravating factors were recorded. Personal history and family history too were noted. The severity of SAR symptoms were assessed by the Total Nasal Symptom Score (TNSS), which is a subjective graded scoring system based on the severity of nasal symptoms.[19,20] Quality of life (QoL) was measured using a 12-item short form of the Medical Outcomes Study questionnaire (SF-12). SF-12 was administered at the start of the study and then at the end of the study.[21,22] Vitals like pulse, BP, respiratory rate, etc. were assessed. Adverse effects were monitored during clinical examination at each visit.

Study subjects were systemically randomized into three groups – desloratadine (DES), rupatadine (RUP) and ketotifen (KET), taking care to maintain similar demographics in all three groups. Based on the assigned group; desloratadine was given orally in a dose of 10mg OD, rupatadine was given orally in a dose of 10 mg OD and ketotifen was given in a dose of 1mg BD. All medications were given for 4 weeks. A wash-out period of 14 days was allowed for those patients previously receiving any prior medication for SAR.

Follow up was done for all patients every week during the treatment period of 4 weeks

The efficacy of the study medications was assessed by mean change in the average TNSS and the individual nasal symptom scores from baseline to the end of the study. Improvement in the QoL was assessed by change in the SF-12 scores at week 4 as compared to that of baseline. Tolerability was evaluated by monitoring for adverse events. Absolute eosinophil count was done at baseline and at end of the study.

Adverse events were recorded and causality assessed using the WHO-UMC causality assessment scale.

The primary outcome measure was change in mean TNSS from baseline; secondary outcome measures were changes in the individual nasal symptom scores, change in the quality of life and tolerability to the study medications.

2.3. Statistical analysis

The collected data was entered into excel spreadsheet and Mean±SD of every parameter was calculated separately for 3 groups. Chi-square test was used for categorical data and one-way ANOVA was used for numerical data for analysis among groups. Kruskal Wallis H test, Friedman's test and Wilcoxon signed-rank test were used when the data was not normally distributed. Tables and graphs were generated using MS Excel and SPSS was used for statistical analysis.

3. Results

Total 150 patients were recruited for this study, which were divided into 3 groups having 50 patients in each group. The mean age was 28.6±7.93 for DES group, 30.7±10.49 for RUP group and 29.64±9.03 for KET group with no significant difference for age among the study groups demonstrating uniform distribution. Gender distribution among groups was uniform, there was no statistically significant difference among groups with regards to gender. [Table 1]

The majority of the subjects had early morning exacerbation of SAR symptoms (n=93, 62%) and 17.33% (n= 26) of the subjects had exacerbation of symptoms in the evening whereas 26.66% (n=40) of the subjects had no diurnal symptom exacerbations. The average duration of symptoms at presentation was about 5.25±2.07 days. The average history of SAR symptoms was about 4.12±1.59 years. The average number of symptoms at presentation were about 4.46±0.59. Average baseline nasal symptom scores and the TNSS score were consistent across the study groups with no statistically significant difference among groups with regards to symptomatology. The eosinophil count and AEC were increased above the normal range in some subjects (n=38, 25.33%). Hemoglobin levels were <10gm% in 3 subjects (n=3, 2%). [Table 1].

3.1. Rhinorrhea

All three study groups showed a gradual and progressive improvement in rhinorrhea. RUP was slightly faster than DES in improving rhinorrhea in the first 2 weeks (p>0.05) but in the subsequent 2 weeks, both RUP and DES showed similar improvements. In comparison, KET showed a slower response than DES and RUP over the 4 week study period which was statistically significant (p=0.05). Overall DES and RUP were equally effective but significantly better than KET in improving rhinorrhea (p=0.05). [Table 2]

3.2. Sneezing

All three study medications were effective in improving sneezing over the 4 week study period. KET showed a slightly slower response in reducing sneezing than RUP and DES during the study period. At week 1, RUP was significantly better than KET in improving sneezing (p=0.015). But at the end of the study, all the drugs were equally effective with no statistically significant intergroup difference in improving sneezing as compared to baseline (p=0.368). [Table 2]

3.3. Nasal itching

All three study medications were equally effective in improving nasal itching with no statistical significance among the study groups (p value=1.00). [Table 2]

3.4. Nasal congestion

Improvement in nasal congestion was gradual and progressive over the study period in all the three groups with desloratadine and rupatadine being equally effective and faster than ketotifen in improving nasal congestion at all visits with a statistically significant difference (p > 0.05). [Table 2]

3.5. Tnss

Mean TNSS improved gradually and progressively over the study period in all the three groups with DES and RUP being equally effective and faster than KET with a statistically significant difference (p > 0.05) [Table 2[Graph 1].

3.6. Absolute eosinophil count

Compared to baseline absolute eosinophil counts (AEC), a decrease was observed and it was statistically significant for DES (p=0.038) and RUP (p=0.001) but it was not statistically significant for KET (p=0.055). RUP was significantly better than DES (p < 0.05). [Table 2].

3.7. Quality of life

QoL based on the SF-12 questionnaire was done at the end of the study. Increments observed in the physical component

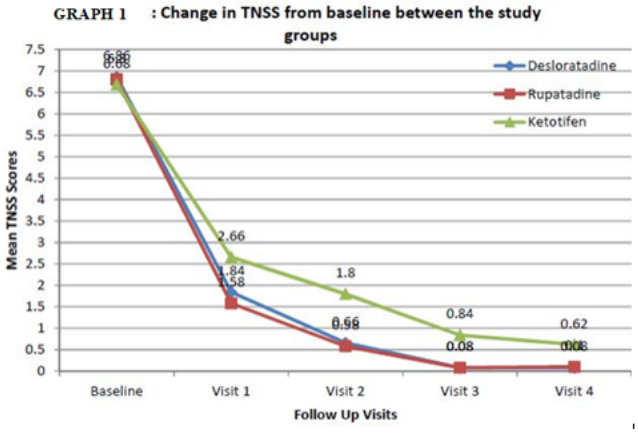
Table 1: Baseline demographics

	Desloaratdine (n=50)	Rupatadine (n=50)	Ketotifen (n=50)
Mean age in years (%)	28.6±7.93	30.7±10.49	29.64±9.03
No. of females	29 (58%)	24 (48%)	23 (46%)
Diurnal symptom variation*			
Early morning	29 (58%)	35 (70%)	29 (58%)
Afternoon	00	00	02 (04%)
Evening	13 (26%)	11 (22%)	02 (04%)
Night	01 (02%)	02 (04%)	00
Nill	11 (22%)	10 (20%)	19 (38%)
Duration Of Symptoms (Days)	5.2±1.95	5.12±2.34	5.44±1.93
No. Of Symptoms At Presentation	4.48±0.61	4.5±0.58	4.42±0.57
Severity of ssymptoms			
Rhinorrhea	1.94+0.31	1.96+0.45	1.90+0.36
Sneezing	1.80+0.45	1.74+0.53	1.72+0.45
Itching	1.24+0.43	1.16+0.37	1.16+0.37
Nasal congestion	1.86+0.50	1.92+0.53	1.90+0.46
TNSS	6.86±0.76	6.80±0.95	6.68±0.71
H/o SAR (years)	4.36±1.54	3.94±1.57	4.08±1.68
Eosinophill Count > 4%	14 (28%)	13 (26%)	11 (22%)
Absolute eosinophil count > 440 cells/mm3	14 (28%)	13 (26%)	11 (22%)
Hb (< 10 gm %)	02 (04%)	00	01 (02%)

*Some subjects had symptom exacerbation at multiple times of the day. 6 subjects in RUP group and 3 subjects in DES group and 1 subject in KET group had symptom exacerbation both in morning and evening. 2 subjects in RUP group and 1 in DES group had symptom exacerbation in morning and night.

Table 2: Change in nasal parameters andtnss from baseline

	Mean ± SD				
	Baseline	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**P value (Kruskal – Wallis test)**
Rhinorrhea						
Desloratadine	1.94±0.31	0.72±0.54	0.16±0.37	0.1±0.22	0.02±0.15	
Rupatadine	1.96±0.45	0.56±0.67	0.16±0.42	0.04±0.2	0.04±0.2	0.05*
Ketotifen	1.9±0.36	0.94±0.37	0.76±0.52	0.22±0.42	0.15±0.30	
Sneezing						
Desloratadine	1.8±0.45	0.26±0.44	0.15±0.19	0.06±0.21	0.03±0.11	
Rupatadine	1.74±0.53	0.16±0.42	0.04±0.2	0.02±0.14	0.02±0.14	0.368
Ketotifen	1.72±0.45	0.36±0.49	0.16±0.24	0.1±0.32	0.04±0.12	
Nasal Itching						
Desloratadine	1.24±0.43	0.18±0.24	0.08±0.14	0.0±0.0	0.0±0.0	
Rupatadine	1.16±0.37	0.1±0.31	0.02±0.1	0.0±0.0	0.0±0.0	1.00
Ketotifen	1.16±0.42	0.14±0.24	0.04±0.11	0.04±0.11	0.0±0.0	
Nasal Congestion						
Desloratadine	1.86±0.5	0.82±0.56	0.42±0.54	0.06±0.24	0.02±0.14	
Rupatadine	1.92±0.53	0.78±0.68	0.34±0.56	0.04±0.2	0.06±0.24	0.0005*
Ketotifen	1.9±0.46	1.32±0.55	0.96±0.49	0.62±0.53	0.32±0.47	
TNSS						
Desloratadine	6.86±0.76	1.98±1.22	0.66±0.92	0.08±0.24	0.08±0.24	
Rupatadine	6.8±0.95	1.58±1.61	0.58±1.18	0.08±0.4	0.1±0.42	0.0005*
Ketotifen	6.68±0.713	2.66±0.92	1.8±0.93	0.84±0.80	0.62±0.67	



Graph 1: Change in TNSS from baseline between the study

scores (PCS) of the SF-12 questionnaire were statistically significant in all three study groups (p= 0.001). However, there was no statistically significant intergroup difference in the improvement observed in the physical QoL (p = 0.894). [Table 2]

Increments observed in the mental component scores (MCS) of the SF-12 questionnaire were also statistically significant in all the three study groups (p= 0.001). However, there was no statistically significant intergroup difference in the improvement observed in the mental QoL (p = 0.154). [Table 2]

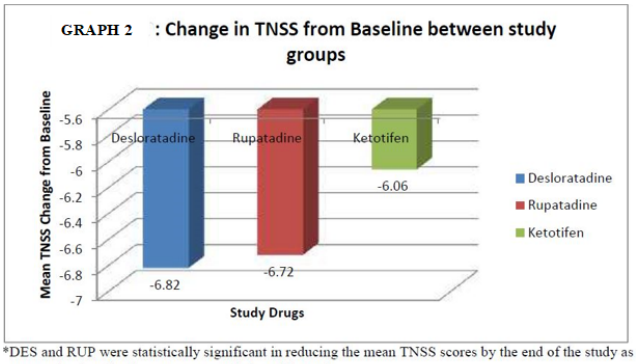
Safety

The majority of the subjects in all groups (n=101, 67.33%) reported no serious ADRs [Table 7]. RUP appeared to have better tolerability as the total number of adverse events were marginally less. The commonly reported ADRs were somnolence, headache, fatigue and dry mouth. The reported ADRs were probable in causality, mild in intensity, transient, self-limiting and resolved over time without any intervention/sequelae. [Table 7]

4. Discussion

In this study, comparative efficacy, tolerability and change in the quality of life to oral desloratadine, rupatadine and ketotifen were assessed in subjects with seasonal allergic rhinitis. Age distribution in our study was similar to the findings from other studies which have supported that occurrence of SAR is common during the 2^{nd} – 4^{th} decade.[20–25]

In the Desloratadine group (DES), a progressive decrease was observed in the mean individual nasal symptom scores and mean TNSS. Nasal itching and sneezing showed a relatively quicker response to DES than rhinorrhea or nasal congestion which responded relatively slowly. At week 1, a good response to DES was observed resulting in the reduction of mean nasal symptom scores of rhinorrhea (62.8%), sneezing (85.55%), nasal itching (85.48%), nasal congestion (55.91%) and the mean TNSS (71.14%) which was statistically significant (p=0.0005). Beyond week 1 until the end of the study, the response to DES was gradual, progressive and sustained for the nasal symptoms: rhinorrhea (98.96%), sneezing (98.33%), nasal itching (100%), nasal congestion (98.92%) and TNSS (98.83%) as compared to baseline which was statistically significant (p=0.0005). [Tables 2 and 3]. Our results are similar to comparative studies and meta-analysis done on DES, which have demonstrated a significant reduction in the nasal symptom severity ranging from 91% to 95% by the end of 3 or 4 weeks of therapy (26,27). In a comparative study between DES 5mg and RUP 10mg, DES 5mg had a slower onset of action over RUP 10mg and hence DES 10mg OD was considered in our study.[24]



*DES and RUP were statistically significant in reducing the mean TNSS scores by the end of the study as compared to baseline(p = 0.0005, Kruskal-Wallis Test)

Graph 2: Change in TNSS from baseline between study groups

In the Rupatadine group (RUP), a progressive decrease was observed in the mean individual nasal symptom scores and mean TNSS. Similar to that of DES group, in RUP group, nasal itching and sneezing showed a relatively quicker response than other nasal parameters. At week 1, a good response to RUP was observed resulting in the reduction of mean nasal symptom scores: rhinorrhea (71.4%), sneezing (90.8%), nasal itching (91.3%), nasal congestion (59.3%) and mean TNSS (76.7%) which was statistically significant (p=0.0005). Beyond week 1, until the end of the study, the response to RUP was gradual, progressive and sustained for the symptoms: rhinorrhea (97.96%), sneezing (98.85%), nasal itching (100%), nasal congestion (96.88%) and TNSS (98.53%) as compared to baseline which was statistically significant (p = 0.0005). [Tables 2 and 3]. Our results are consistent with previous studies - Comparative studies and meta-analysis of RUP 10mg OD versus loratadine 10mg, cetirizine 10mg, levocetirizine 10mg, ebastine 10mg and desloratadine 5mg OD documented a good efficacy profile of RUP 10mg over cetirizine, levocetirizine and ebastine. However, RUP 10mg demonstrated improvement in nasal symptom scores similar to that of loratadine and DES (24,28–31).

Table 3: Summaryof the Treatment outcome at the end of the study period

Symptoms	Desloratadine		Rupatadine		Ketotifen		P value (Lruskal Walls test)
	Change in score from badeline mean + SD	% change from baseline	Change in score from baseline Mean + SD	% change from baseline Mean + SD	Change in score from baseline Mean + SD	% change from baseline	
Rhinorrhea*	-1.92 + 0.31	98.96	-1.92 + 0.45	97.96	-1.75 +0.36	92.10	0.05
Sneezing	-1.77+0.22	98.33	-1.72 + 0.53	98.85	-1.72 + 0.49	97.10	0.368
Itching	-1.24 +0.41	100	-1.16 +0.25	100	-1.16 + 0.37	100	1.000
Nasal congestion+	-1.84+0.5	98.92	-1.88 + 0.53	96.88	-1.5+0.58	83.16	0.0005
TNSS*	-6.82+0.77	98.83	-6.72+0.97	98.53	-6.06 + 0.94	90.71	0.0005

*DES and RUP were better in improving rhinorrhea then KET as compared to baseline (p=0.05)

Table 4: Effect of study drugs on absolute eosinophil Count

Symptoms	Desloratadine		Rupatadine		Ketotifen		P value (Lruskal Walls test)
	Change in score from badeline mean + SD	% change from baseline	Change in score from baseline Mean + SD	% change from baseline Mean + SD	Change in score from baseline Mean + SD	% change from baseline	
Rhinorrhea*	-1.92 + 0.31	98.96	-1.92 + 0.45	97.96	-1.75 +0.36	92.10	0.05
Sneezing	-1.77+0.22	98.33	-1.72 + 0.53	98.85	-1.72 + 0.49	97.10	0.368
Itching	-1.24 +0.41	100	-1.16 +0.25	100	-1.16 + 0.37	100	1.000
Nasal congestion+	-1.84+0.5	98.92	-1.88 + 0.53	96.88	-1.5+0.58	83.16	0.0005
TNSS*	-6.82+0.77	98.83	-6.72+0.97	98.53	-6.06 + 0.94	90.71	0.0005

*DES significantly reduced AEC by visit 4 (week 4) as con1pared to baseline (p=0.038) tRUP significantly reduced AEC by visit 4 (week 4) as compared to baseline (p=0.001) and RUP was significantly better than DES (RUPvs DES, $p < 0.05$, Mann Whitney U

Table 5: Effect of study drugs on absolute eosinophil Count

Study Drugs	Baseline (Mean± SD)	Visit 4(Mean± SD)	P value (Wilcoxon Signed Rank Test)
Desloratadine*	431.2 ±305	411±280	0.038
Rupatadinet	383.2 ±277	324 .4±266	0.001
Ketotifen	400.6±313	385.8±296	0.055

+DES and RUP were better in improving nasal congestion than KET as compared to baseline (p=0.0005)

Table 6: Quality of life (qol) ssseement by standard form 12(SF-12) physical component scores

Physical component Scores(PCS)	Treatment Groups				
	Baseline	Visit 4	95%CI		P Value (t-test)
	Mean + SD	Mean+ SD	Lower bound	Upper Bound	
Desloratadine	41-37+2.22	55-91-0.84	-15194	-13881	0.001
Rupatadine	40.76+2.14	55-79+0.82	-15.624	-14.435	0.001
Ketotifen	41.14+1.87	55.86+1.86	-15446	-13921	0.001
Between groups	95% confidence interval				
	Lower bound		Upper bound		0.894+
	55.649		56.062		

Table 7: Quality of life (Qol) Assessment by standard form -12(SF-12) mental componenet score(n=150

Mental Component Score (MCS)	Treatment groups				P Value (t-test)
	Baseline	Visit 4	95% CI		
	Mean + SD	Mean + SD	Lower bound	Upper bound	
Desloratadine	44.62	61.95 + 0.91	-18.13	-16-52	0.001
Rupatadine	47.39 +2.70	62.02 + 0.99	-15.38	-13-89	0.001
Ketotifen	43.30 + 1.93	61.42 + 2.57	-18.98	-17-26	0.001
		95% confidence interval			
Between groups (One Way ANOVA)	Lower bound 61.5284		Upper bound 62.074		0.154+

+DES and RUP were better in improving TNSS than KET as compared to baseline (p=0.0005)

Table 8: Adverse events

ADR	Desloratadinen(%)	Rupatadine n(%)	Ketotif n n(%)
No Adverse Effects	34(68)	38(76)	29(58)
Somnolence	9(18)	7(14)	11(22)
Headache	5(10)	3(6)	4(8)
Fatigue	5(10)	4(8)	6(12)
Dry mouth	2(4)	-	5(10)
Nausea	-	1(2)	-
Dizziness	-	-	1(2)

In the Ketotifen group (KET), a progressive decrease was observed in the mean individual nasal symptom scores and mean TNSS. Nasal itching and sneezing showed a relatively faster response to KET than rhinorrhea or nasal congestion. At week 1 a good response was observed resulting in the reduction of mean nasal symptom scores: rhinorrhea (50.52%), sneezing (79.06%), nasal itching (87.93%), nasal congestion (30.5%) and mean TNSS (60.17%) which was statistically significant (p=0.0005). Beyond week 1 until the end of the study (week 4), the response to KET was gradual, progressive and sustained for the symptoms: rhinorrhea (92.10%), sneezing (97.67%), nasal itching (100%), nasal congestion (83.16%) and TNSS (90.71%) as compared to baseline which was statistically significant (p = 0.0005). [Tables 2 and 3].

All three study groups demonstrated a gradual and progressive improvement in rhinorrhea. RUP was slightly faster than DES in improving rhinorrhea in the first 2 weeks (p>0.05) but in the subsequent 2 weeks, both RUP and DES showed similar improvements. In comparison, KET showed a slower response than DES and RUP over the 4 week study period which was statistically significant (p=0.05). Overall DES and RUP were equally effective but significantly better than KET in improving rhinorrhea (p=0.05). [Table 3][Graph 2]. All three study medications were effective in improving sneezing over the 4 week study period. KET showed a slightly slower response in reducing sneezing than RUP and DES during the study period. At week 1, RUP was significantly better than KET in improving sneezing (p=0.015). But at the end of the study (week 4), all the drugs were equally effective with no statistically significant intergroup difference in improving sneezing as compared to baseline (p=0.368). [Table 3][Graph 2]. All three study medications were equally effective in improving nasal itching with no statistical significance among the study groups. [Table3][Graph 2]. Improvement in nasal congestion was gradual and progressive over the study period in all the three groups with desloratadine and rupatadine being equally effective and faster than ketotifen in improving nasal congestion at all visits with a statistically significant difference (p= 0.0005). [Table 3][Graph 2]. Mean TNSS improved gradually and progressively over the study period in all the three groups with DES and RUP being equally effective and faster than KET with a statistically significant difference (p= 0.0005). [Table 3][Graph 2].

Previous studies of Meta-analysis on DES and RUP demonstrated significant efficacy of DES and RUP over placebo (28). A direct comparative study between RUP 10mg and DES 5mg by Lukat et al. demonstrated no significant difference between DES and RUP in nasal symptom improvement in SAR and our study also showed similar results where we found no statistically significant difference between DES and RUP (24). A meta-analysis of DES showed that DES was as equally effective as the newer 2nd generation antihistamines like levocetirizine and fexofenadine in AR/SAR and this can be correlated to the observation of our study where DES and RUP were equally effective (32). A meta-analysis of RUP demonstrated a significant efficacy over ebastine, cetirizine and levocetirizine (28). Very few studies have used oral KET in AR/SAR and there are no studies that have compared oral KET with either oral DES or RUP in AR/SAR. Oral KET 1mg BID was compared against cetirizine 10mg OD by Lai

et al in children with perennial allergic rhinitis and they demonstrated significant efficacy of cetirizine over KET in improving nasal symptoms. This data could support the observations of our study where DES and RUP were better than KET (33).

Absolute Eosinophil Count decreased from baseline and it was statistically significant for DES (p=0.038) and RUP (p=0.001) but it was not statistically significant for KET (p=0.055). RUP was significantly better than DES ($p < 0.05$). [Table 4]. previous studies have assessed the effect of RUP and DES on AEC reduction and have shown statistically significant reduction in AEC by RUP and also showed that RUP was better than DES. Similar results were observed in our study (28,29,34).

Quality of Life (QoL) assessment based on the SF-12 questionnaire at the end of the study revealed that increments in the physical component scores (PCS) were statistically significant in all the three study groups (p= 0.001). However, there was no statistically significant intergroup difference in the improvement observed in the physical QoL. [Table 5]. Increments observed in the mental component scores (MCS) of the SF-12 questionnaire were also statistically significant in all the three study groups (p= 0.001). However, there was no statistically significant intergroup difference in the improvement observed in the mental QoL. [Table 6]. Previous studies have demonstrated a significant improvement in QoL for DES and RUP. However, no comparative data is available to demonstrate a significant change in QoL for antihistamines like DES or RUP (28,29,35–37).

RUP appeared to have better tolerability as the total number of adverse events were marginally less. [Table 7]. The commonly reported ADRs were somnolence, headache, fatigue and dry mouth. The reported ADRs were probable in causality, mild in intensity, transient, self-limiting and resolved over time without any intervention/sequelae. Similar adverse events were observed in other studies as well[26–37] .

Thus in the present study, the newer second-generation non-sedative antihistamines like desloratadine which is an inhibitor of IgE and non-IgE mediated release of IL-4 and IL-13 and rupatadine which is a PAF antagonist were compared with ketotifen which is a mast cell stabilizer with antihistaminic property for their efficacy, tolerability and QoL in SAR. Desloratadine is an active metabolite of loratadine.

4.1. Our study has certain limitations

The main limitation of the present study was small sample size, involvement of a single center and we didn't perform a skin prick test (SPT) for identifying the allergen. Additionally, in our study, the efficacy of DES 10mg was not compared with the usual recommended adult dose of 5mg or with a much larger dose of 7.5mg and 20mg.

Elaborate multi-centric studies involving a larger number of subjects from different geographical regions may be required to generate more useful data regarding the relative efficacy and tolerability of these medications.

5. Conclusion

DES, RUP and KET produced a significant reduction in TNSS and individual nasal symptom scores. DES and RUP are comparatively more effective and faster acting than KET in reducing the primary outcome measure, TNSS. DES and RUP are comparatively more effective and faster acting than KET in reducing rhinorrhea and nasal congestion scores.

RUP is comparatively more effective in reducing AEC than DES and KET.

All the study medications were well tolerated with few mild, self-limiting, transient adverse events requiring no intervention. QoL showed a significant improvement for the study drugs.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Author biography

Syed Khadeer, Assistant Professor

Girish K, Professor and HOD

B Jagannath, Professor

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