Original Article

Comparative study of Rupatadine alone and Levocetirizine with Ranitidine combined therapy in chronic idiopathic urticaria

Kaniz Rahman[1], M A Wahab[2], Lubna Khondker[3], Sharif Mushfaqur Rahman[4], Khadija Begum[5]

Abstract

Objective: Treatment ofchronic idiopathic urticaria (CIU) with combined therapy comprising H_1 and H_2 antihistamine is effective however, associated with high relapse rate. Rupatadine alone is found to be equally effective with less relapse rate and convenient dosage schedule. It was aimed to compare levocetirizine and ranitidine with rupatadine for the management of CIU.

Materials and methods: This single blind randomized controlled trial was conducted at Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University, from April toSeptember, 2013. A total of 40 patients of CIU were randomly enrolled into two equal groups (group A and B). Patients of group-A was treated with 5 mg of levocetirizine once daily plus 150 mg of ranitidine twice daily and group-B was treated with rupatadine 10 mg once daily for one month. The efficacy was assessed 1st and 4th week during treatment and 4 weeks after completion of treatment by observing reduction of itching, regression of the size and shape of lesions and appearance of new lesions. Adverse effects and patient satisfaction were also searched and noted.

Results: Among the respondents, 75% in group A and 80% in group B responded to treatment. About 80% in group A and 85% in group B showed improvement in itching in the first week.Appearance of new lesions in first week was 10% and 5% and at 4th week, 5% and 0% respectively. About 75% in group A and 80% in group B had regression in their lesions at the end of first week and at the end of 4th week, it was 85% and 90%.

Conclusion: The result of the present study showed that levocetirizine and ranitidine combination and newer agent rupatadine alone has similar efficacy in reducing clinical sign and symptoms of CIU, however rupatadine has significantly reduced the relapse rate.

Key words: Chronic idiopathic urticaria; Randomized controlled trial, Rupatadine, Levocetirizine with Ranitidine.

Introduction

Chronic idiopathic urticaria (CIU) is a relatively common skin condition which affects about 0.5% people across the globe;varying between 0.1% and 3% people in Europe and Asia[1]. Studies investigating the natural history of CIU in adults have indicated that about 30–55% of patients go into remission within 12 months, although the disease may persist in some patients for several years[2-4]. Besides being severely debilitating and disfiguring, CIU may also be potentially stigmatizing, worsening the quality of life, following a chronic course with spontaneous remission and relapses for several years[5-7]. The symptoms of CIU, including edema, erythema and pruritus, are primarily associated with histamine release from dermal mast cells, oral H_1-receptor antagonist (H_1 blockers) are the treatment of choice [6,7]. There is evidence that PAF and histamine have mutually complementary activities in vivo. Each mediator is able to promote the release of the other by different tissues and cells[8,9]. Dual blockades of these mediators is likely to be a more effective treatment strategy for CIU.In chronic urticaria there are clinical trials

1. Assistant Professor, Department of Dermatology & Venereology, Ad-din Women's Medical College, Dhaka.
2. Professor, Department of Dermatology & Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
3. Associate Professor, Department of Dermatology & Venereology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
4. Resident, Department of Burn & Plastic Surgery Dhaka Medical College, Dhaka.
5. Associate Professor, Department of Medicine Ad-din Women's Medical College, Dhaka.

Correspondence: Dr. Kaniz Rahman, E-mail: drkaniz19@gmail.com

and isolated observations with multiple treatments either as monotherapy or in combination, involving first and second-generation antihistamines, H_2blockers, corticosteroids and many other drugs. Within this potential range of treatments, the non-sedating (2nd generation) H_1 antihistamines are the only drugs with class one evidence and grade one recommendation[10,11]. Rupatadine is a novel selective long-acting H_1-receptor inverse agonist, which is currently approved as once daily dose of 10 mg, for the treatment of allergic rhinitis[12]. It has shown both antihistamine and anti-PAF effects through its interaction with specific receptors and not due to physiological antagonism[12]. A previous dose-ranging study demonstrated that rupatadine 10 mg once daily for 4 weeks significantly decreased the severity of pruritus, the number of wheals and the total symptom score in patients with CIU, compared with placebo[13]. The aim of the present study was to compare levocetirizine and ranitidine with rupatadine for CIU.

Materials and methods

The study was conducted complying the declaration of Helsinki 1964. Before starting this study, the research protocol was approved by the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. Informed written consent was obtained from the patients without any influences. Data were collected anonymously; confidentiality of data was ensured adequately and any unauthorized access to data was not possible.

This randomized controlled trial was conducted in the Department of Dermatology and Venereology, BSMMU, from April toSeptember, 2013. A total of 40 patients of CIU were randomly enrolled in a single blind fashion into two equal groups comprising of 20 patients (group A and B) from the patient attending at the out- patient department of Dermatology and Venereology, BSMMU. Patients whose age was between 18 to 60 with CIU (i.e. episodes of hives of characteristic wheal and flare appearance, occurring regularly, at least three times a week) for a period of at least 6 weeks during the last 3 months without an identifiable were included in the study. Patients with physical urticaria (e.g. solar, heat, cold, aquagenic, cholinergic, contact, pressure, etc.), drug-induced urticaria, urticarial vasculitis, senile pruritus or hereditary angioedema, with any dermatological or any other clinically significant disease, with pregnancy and breast feeding and who had received systemic and topical corticosteroids within 4 weeks, desloratadine, loratadine, levocetirizine or cetirizine within 10 days, astemizole within 12 weeks, ketotifen within 2 weeks and patients who had received CNS acting agents (including tranquilizers, antidepressants, sedatives, hypnotics or antiepileptic) at any time were excluded. Patients of group-A was treated with 5 mg of levocetirizine once daily plus 150 mg of ranitidine twice daily and group-B was treated with rupatadine 10 mg once daily for one month. The efficacy was assessed 1st and 4th week during treatment and 4 weeks after completion of treatment by observing reduction of itching, regression of the size and shape of lesions and appearance of new lesions. Reduction of pruritus, regression of the size and shape of lesions,appearance of new lesions were considered as outcome variables. Adverse effects (any skin rash, skin atrophy, anemia, jaundice and other) and patient satisfaction were also searched and noted. Data were recorded in a semi structured data sheet which was prepared keeping in minds the study objectives. After collecting and editing data, frequency distribution table of different variables such as age, sex, were prepared. The chi-square test was done to draw inferance about the efficacy of combined levocitirizine and ranitidine over rupatadine alone. The result was considered significant if p value was ≤ 0.05.

Results

A total of forty patients were included, twenty of them were given oral levocetirizine 5 mg once daily and oral ranitidine 150 mg twice daily. This group was designated as Group-A. Twenty of them was given oral rupatadine 10 mg once daily. This group was designated as Group-B. Both groups were treated for one month. Among the respondents, most of the patients (60%) in group A and (50%) in group B) were in the < 30 years age group, 35.5% patients were in the 30 – 39 years age group, (12.5%) patients were in the > 40 years age group (Table I). The mean age of the patients was 28.5 years and 30.85 years for group A and group B respectively. Lowest and highest ages were 18 and 55 years respectively. It appears from the study that 70% in group A and 60% in group B were male and 30% in group A and 40 % in group B were female (Table I). Current study revealed that 75% patients in group A and 80% patients in group B responded to treatment initially (Figure 1). In the first follow up visit, doctors examined each patient. The enrolled patient who had no itching, whales was considered cured. Patients whose itching was reduced and size and number of the lesions decreased, was considered responding to treatment. The patients who

had new or persistent lesions were considered not cured. At first week of intervention uncured patients were prescribed repeat interventions. There was no significant difference in response to treatment between the two groups.Current study showed 80% patients in group A and 85% patients in group B showed improvement in itching in the first week. At the end of 4 weeks 95% patients showed improvement and it was equal in each group (Table II). At 1st week, 2 patients in group A and 1 patient in group B had new lesions i.e. lesions at sites different from the primary lesions. After 4 week, 1 patient in group - A still had new lesion whereas, there was no new lesion appearing in the group - B patients (Table 3). Result was slightly better for group B, but not statistically significant.Current study revealed 75% of the patients in group A and 80% patients in group B had regression in their lesions in terms of disappearance, decrease in size, shape and distribution of the lesion at the end of first week. At the end of 4th week, 85% patients in group A and 90% patients in group B showed clinical improvement (Figure 2). The difference is again statistically insignificant. All the three drugs included in this study were safe and was associated with very few side effects. Only one patient among 40 complained of mild sedation with rupatidine 10 mg after 1 week of treatment. Two patients in group A (levocetirizine plus ranitidine) complained of headache which is known side effect of levocetirizine. Another patient complained of somnolence which was again in the group A and was due to livocetirizine. Other common side effects of drugs like anaemia, jaundice, skin rashes were not seen among any group of patients. Overall occurrence of side effects (3 compared to 1) was more in group A and although clinically mild, difference was statistically significant (Table IV). Post treatment follow up of patients was done 4 weeks after completion of treatment. It showed that 40% patients in group A and 25% patients in group B had relapse of itching in the previous site which was statistically significant. 20% patients in group A and 15% patients in group B had new lesions at sites different from the primary lesion. 35% patients in group A and 20% patients in group B had relapse of their previous lesions (Table V). The differences were statistically significant. Thus, rupatadine showed significant improvement in relapse rate of CIU lesion over conventional treatment which is the main concern of CIU treatment at present. It was quite evident that patient preferred single daily dosing (rupatadine) then taking 3 drugs daily at two different times. Patient's satisfaction about treatment regime was randomly categorized as A (excellent), B (moderate) and C (not satisfied). 95% of Group–B patients were highly satisfied regarding treatment regime and described dose schedule as easy and convenient. On the other hand, 65% of the patients in group–A were moderately satisfied (B), 5% not satisfied at all (C) complaining of cumbersome dosing schedule (Table VI). Difference was statistically significant.

Table I: Sociodemographic variables of the respondents (n=40)

	Group Group – A (levocetirizine plus ranitidine)	**p Group - B (rupatadine)**	**value**
Age in years			
<30	12 (60.0)	10 (50.0)	>0.05
30 - 39	7 (35.0)	6 (30.0)	
≥40	1 (5.0)	4 (20.0)	
Sex			
Male	(70.0)	12 (60.0)	>0.05
Female	6 (30.0)	8 (40.0)	
Total	**20 (100.0)**	**20 (100.0)**	

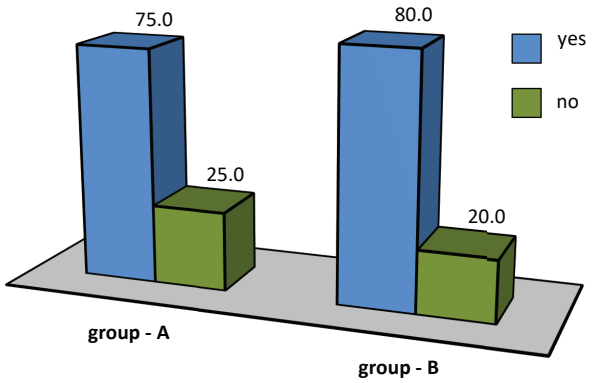

Figure 1: Treatment response (%)

Table II: Distribution of patient according to improvement of itching (n=40)

Improvement of itching	**Group**	
	Group – A (levocetirizine plus ranitidine)	**Group – B (rupatadine)**
1 week	16 (80.0)	17 (85.0)
4 week	19 (95.0)	19 (95.0)

Table III: Distribution of patient according to appearance of new lesion (n=40)

Appearance of new lesion	Group	
	Group – A (levocetirizine plus ranitidine)	Group – B (rupatadine)
1 week	2 (10.0)	1 (5.0)
4 week	1 (5.0)	0 (0.0)

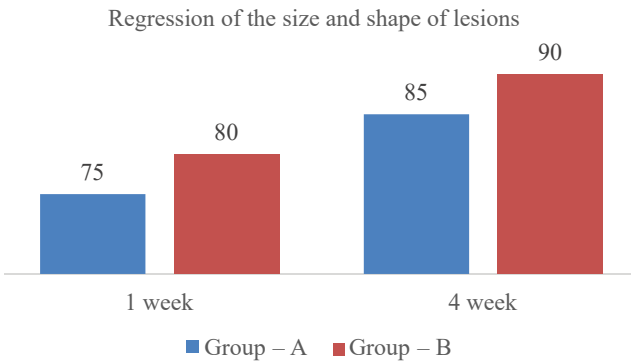

Figure 2: Regression of size and shape of the lesions (%)

Table IV: Distribution of patient according to side effects (n=40)

Clinical observation	Group		p value
	Group – A (levocetirizine plus ranitidine)	Group – B (rupatadine)	
Headache			<0.05
Present	2 (10.0)	20 (100.0)	
Absent	18 (90.0)	0 (0.0)	
Somnolence			
Present	1 (10.0)	20 (100.0)	
Absent	19 (95.0)	20 (100.0)	
Sedation			
Absent	20 (100.0)	1 (5.0)	
Present	0 (0.0)	19 (95.0)	

*Chi-square test was done to measure the level of significance.

Table V: Distribution of patients according to clinical observation after 4 weeks after completion of treatment (n=40)

Clinical observation	Group Group – A (levocetirizine plus ranitidine)	Group – B (rupatadine)	p value
Relapse of itching			
Yes	8 (40.0)	5 (25.0)	<0.05
No	12 (60.0)	15 (75.0)	
Appearance of new lesion			
Yes	4 (20.0)	3 (15.0)	>0.05
No	16 (80.0)	17 (85.0)	
Relapse of the lesions			
Yes	7 (35.0)	4 (20.0)	<0.05
No	13 (65.0)	16 (80.0)	

*Chi-square test was done to measure the level of significance.

Table VI: Distribution of patient according to patient satisfaction (n=40)

Patient satisfaction	Group		p value
	Group – A (levocetirizine plus ranitidine)	Group – B (rupatadine)	
A (excellent)	6 (30.0)	19 (95.0)	<0.05
B (moderate)	13 (65.0)	1 (10.0)	
C (not satisfied)	1 (5.0)	0 (0.0)	
Total	20 (100.0)	20 (100.0)	

*Chi-square test was done to measure the level of significance.

Discussion

CIU is a highly prevalent in the general population which affects the quality of life[7, 14,15]. It is defined as the presence of wheals on a recurrent basis, more than twice a week,and during over six consecutive weeks.[14,15] Clinical trials revealed multiple treatment options such as first- and/or second generation antihistamines, H_2 antihistamines, leukotriene antagonists, corticoids, cyclosporine and other immunosuppressors, calcineurin

inhibitors, sulfasalazine, intravenous immunoglobulins, plasmapheresis or phototherapy[14]. Consequently, non-sedating (or second-generation) H1 antihistamines are considered as the first line symptomatic treatment[14,15]. Rupatadine is a new potent nonsedative reverse H1 agonist and 10 mg of rupatadine is a fast, long-acting, efficacious and safe treatment option for the management of CIU.[15] There have been fewer studies with head to head comparison of individual antihismines and combination of multiple options with a single antihistamine[7,13-15].

The study was conducted in the department of Dermatology and Venereology, BSMMU, Dhaka. The study was intended to compare the safety and efficacy and adverse effect between oral levocetirizine plus ranitidine combination and oral rupatadine alone therapy in the management of CIU. A total of forty patients were included, twenty of them were given oral levocetirizine 5 mg once daily and oral ranitidine 150 mg twice daily. This group was designated as Group-A. Twenty of them was given oral rupatadine 10 mg once daily. This group was designated as Group-B. Both groups were treated for one month. In this study, 26 patients were male and 14 patients were female, male-female ratio was 1.86:1.

In this study, 75% patients in group A and 80% patients in group B responded to treatment, however, the difference was not statistically significant. The study revealed that, 80% patients in group A and 85% patients in group B showed improvement in itching in the first week. In this study, at 1st week, 2 patients in group A and 1 patient in group B had new lesions and after 4 week, 1 patient in group - A still had new lesion whereas, there was no new lesion appearing in the group - B patients. Again, the difference was not statistically significant.In this study, 75% of the patients in group A and 80% patients in group B had regression in their lesions in terms of disappearance, decrease in size, shape and distribution of the lesion at the end of first week and at the end of 4th week, 85% patients in group A and 90% patients in group B showed clinical improvement. Current study revealed 40% patients in group A and 25% patients in group B had relapse of itching in the previous site; 20% patients in group A and 15% patients in group B had new lesions at sites different from the primary lesion; 35% patients in group A and 20% patients in group B had relapse of their previous lesions. The differences were statistically significant. This finding is also supported by other studies[6,7,13-15]. Thus rupatadine showed significant improvement in relapse rate of CIU lesion over conventional treatment which is the main concern of CIU treatment at present which is supported by other placebo control studies[15]. Though, head to head studies is yet to compared. It was quite evident that patient preferred single daily dosing (rupatadine) then taking 3 drugs daily at two different times. Patient's satisfaction in found more in rupatadine group than the other group and the difference was statistically significant. This finding is supported by other repeated studies[6,7,12-15].

The present study had the following limitations. Factors should be kept in mind while deciding on the implications of the findings of the study such as the small sample size, lack of objective assessment tools, single center-based study. Additional rigorously conducted prospective randomized trials with large sample sizes, full reporting of outcomes and double blinding of assessors are required. Increase transparency is needed if the sample cohort of patients is reported on in different studies and avoidance of multiple publications is strongly recommended.

Conclusion

The result of the present study showed that both conventional treatment with levocetirizine and ranitidine combination and newer agent rupatadine alone has similar efficacy in reducing clinical sign and symptoms of CIU. However, rupatadine has significantly reduced the relapse rate and so it is a more efficacious and safer option with less adverse effects for the treatment of CIU in comparison to conventional treatment. Rupatadine is also more convenient option for patients in term of dosage schedule.

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