

SHORT REPORT

Safety and efficacy of cetirizine versus cetirizine plus ranitidine in chronic urticaria: Double-blind randomized placebo-controlled study

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Abstract

Background: First-line treatment for chronic urticaria is H1 non-sedating antihistamines. When these fail, guidelines recommend combination with H2 antihistamines. **Aim:** We conducted a randomized, double-blind, placebo-controlled trial. **Methods:** Thirty-two patients with chronic urticaria were included. Group A (16 subjects) treated with cetirizine plus ranitidine and Group B (16 subjects) with cetirizine plus placebo, both for 30 days. Efficacy measures were Urticaria Activity Score (UAS), Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) and time of symptom remission, safety measures were clinical and laboratory effects. **Results:** Complete remission was obtained in ten patients (62.5%) from Group A and seven patients (44%) from Group B ($p = 0.28$). The UAS in Group A was 1.53 ± 2.09 versus Group B 2.06 ± 1.34 ($p = 0.20$). The CU-Q2oL in Group A was 12.93 ± 19.20 versus Group B 12.68 ± 10.30 ($p = 0.20$). At the end of treatment, 13 patients (81%) from Group A and 14 patients (87.5%) from Group B had some type of adverse effect ($p = 1.0$). **Conclusions:** Combination of cetirizine with ranitidine was not more effective than cetirizine alone in chronic urticaria. Both treatments resulted equally safe; however, our main limitation is the small sample size.

Keywords

Antihistamines, chronic urticaria, clinical trial, efficacy, safety, treatment

History

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Introduction

Clinical guidelines for chronic urticaria recommend drugs that inhibit second-generation H1 receptors (H1 antihistamines) (1), if this fails, a combination of H1 antihistamines and H2 receptor inhibitors (H2 antihistamines) is an alternative, the guidelines emphasize the need for clinical trials to support its efficacy (1–3). We evaluate the safety and efficacy of cetirizine plus ranitidine versus cetirizine plus placebo.

Materials and methods

Double-blind, randomized, placebo-controlled clinical trial in patients with chronic urticaria was conducted. The study was approved by the Ethics Committee and written consent was obtained before study inclusion. A probability sample of 16 patients per group was obtained (95% CI and power of 80%).

Patients of either gender, ≥ 18 years of age, and without H1 and/or H2 antihistamine treatment for 15 days prior to the study were included. Patients with allergies to cetirizine and/or ranitidine, pregnant and breastfeeding were excluded. Elimination criteria included laboratory abnormalities (blood count, blood chemistry and transaminases) twice the upper

normal value at any of the visits, those not attending all follow-up visits and any side effect requiring hospitalization.

Randomization was done by choosing a closed envelope with the study group designation (Figure 1). Group A: cetirizine tablets (10 mg/24 h for 30 days) plus ranitidine tablets (300 mg/24 h for 30 days). Group B: cetirizine tablets (10 mg/24 h for 30 days) plus placebo tablet with the same appearance as ranitidine, one each 24 h for 30 days. The study included four visits: baseline, at 15, 30 and 45 days.

Safety was defined as the presence of any adverse effect unrelated to urticaria. Efficacy was evaluated with the Urticaria Activity Score (UAS) (presence of hives and itching) evaluated on a scale of 0–6 points (0 corresponds to minimal disease activity and 6 to maximal activity) (4,5). Quality of life was investigated using the Spanish version of the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), exploring itching, inflammation, physical activities, sleep, limitations and physical appearance (scale of 0–100 points, where the higher the score, poorer the quality of life (6–8)).

Time of symptoms remission was investigated with respect to the days after treatment initiation. Therapeutic efficacy was evaluated by the patient by a Visual Analog Scale (VAS) with a score from 0–10 with respect to the presence of itching, number of lesions and their duration; the higher the score indicated greater symptomatology.

For data analysis, means and standard deviation were used. For intergroup comparisons, the Mann–Whitney U -test and χ^2 or Fisher's exact test were used. A statistically significant difference was considered when $p < 0.05$ was obtained.

SAFETY AND EFFICACY OF CETIRIZINE VS. CETIRIZINE PLUS RANITIDINE IN CHRONIC URTICARIA: DOUBLE-BLIND RANDOMIZED PLACEBO-CONTROLLED STUDY

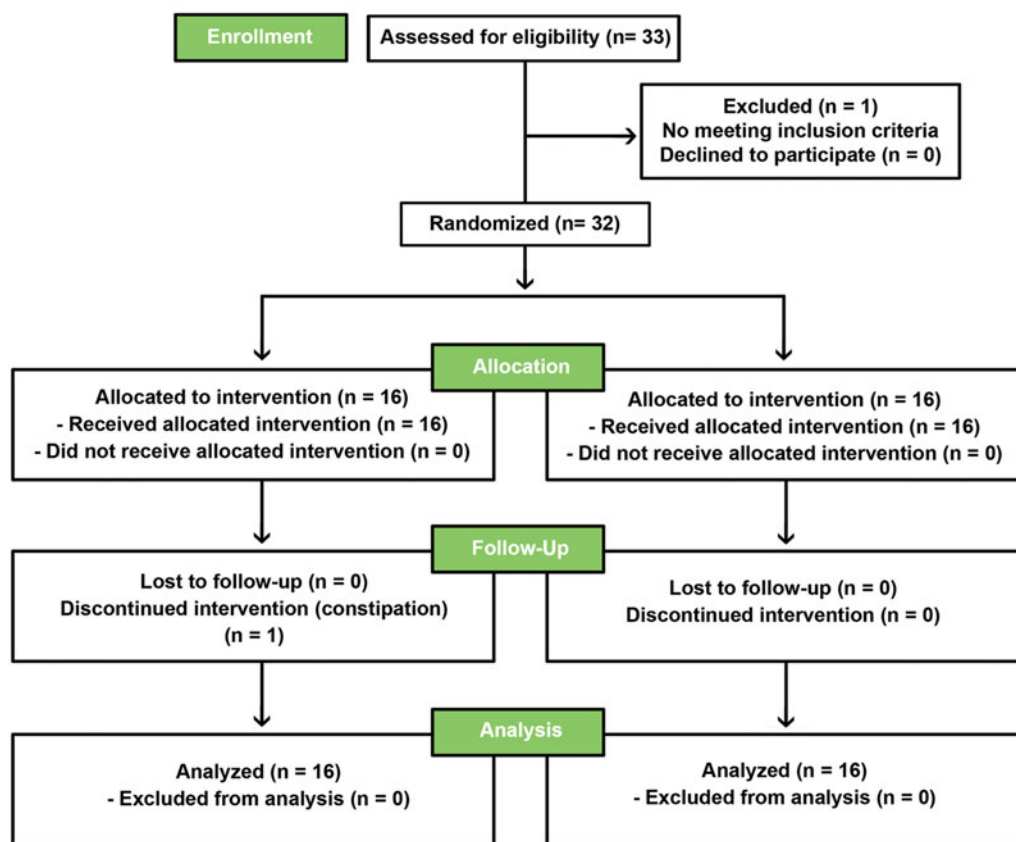


Figure 1. CONSORT flow diagram.

Table 1. Epidemiological variables and clinical manifestations of study groups.

Variable	Group A (cetirizine + ranitidine) n = 16	Group B (cetirizine + placebo) n = 16	p Value
Male, n (%)	2 (12.5)	7 (44)	0.11 ^a
Female, n (%)	14 (87.5)	9 (56)	
Average age (years) ± SD	44 ± 21	38 ± 15	0.36 ^b
Average evolution (months) ± SD	19 ± 18	22 ± 26	0.40 ^b
Clinical manifestations			
Papules, n (%)	16 (100)	15 (94)	0.87 ^c
Erythema, n (%)	15 (94)	16 (100)	0.80 ^c
Pruritus, n (%)	16 (100)	16 (100)	0.96 ^c
Dermographism, n (%)	12 (75)	14 (87)	0.63 ^c
Angioedema, n (%)	9 (56)	6 (37)	0.42 ^c

None of the epidemiological variables or clinical manifestations showed a statistically significant difference. SD, standard deviation.

^aTwo-tailed Fisher's exact test.

^bStudent's *t*-test.

^c χ^2 test.

Results

A total of 32 patients were evaluated. The mean age was 41 ± 19 years (range 19–87), urticaria had a mean duration of 18 ± 23 months (range 1.5–84, Table 1).

Table 2. Adverse treatment effects in both study groups.

Adverse effect	Group A (cetirizine + ranitidine) n = 16	Group B (cetirizine + placebo) n = 16	P Value
Somnolence, n (%)	10 (62.5)	11 (69)	0.51 ^a
Fatigue, n (%)	5 (31)	8 (50)	0.82 ^a
Headache, n (%)	3 (19)	6 (37.5)	0.73 ^b
Blurred vision, n (%)	1 (6)	4 (25)	0.40 ^b
Vertigo, n (%)	1 (6)	2 (12.5)	1.0 ^b
Insomnia, n (%)	0 (0)	6 (37.5)	0.04^b
Poor concentration, n (%)	4 (25)	6 (37.5)	1.0 ^b
Dizziness, n (%)	3 (19)	4 (25)	1.0 ^b
Nausea, n (%)	2 (12)	3 (19)	1.0 ^b
Abdominal pain, n (%)	6 (37.5)	3 (19)	0.15 ^b
Loss of appetite, n (%)	1 (6)	2 (12.5)	1.0 ^b
Diarrhea, n (%)	2 (12)	0 (0)	0.16 ^b
Constipation n (%)	1 (6)	4 (25)	0.40 ^b
Xerophthalmia, n (%)	4 (25)	5 (31)	1.0 ^b
Others, n (%) ^c	2 (12)	0 (0)	0.16 ^b

Except for insomnia, none of the adverse effects shown had significant differences between groups. Only one patient from Group A had to be eliminated from the study due to severe constipation, from the remaining cases, none were eliminated due to adverse effects.

^a χ^2 test.

^bFisher's exact test.

^cOne patient presented nocturia during treatment and another reported paresthesia in the plantar foot region.

Bold value indicates that difference is statistically significant.

Table 3. Therapeutic efficacy of both study groups.

Variable	Visit 1 (Day 0)			Visit 3 (Day 30)		
	Group A (cetirizine + ranitidine)	Group B (cetirizine + placebo)	<i>p</i> Value	Group A (cetirizine + ranitidine)	Group B (cetirizine + placebo)	<i>p</i> Value
UAS	4.37 ± 0.88	4.06 ± 0.99	0.421 ^a	1.53 ± 2.09	2.06 ± 1.34	0.200 ^a
CU-Q2oL	26.6 ± 17.2	24.2 ± 11	0.955 ^a	12.9 ± 19.2	12.6 ± 10.3	0.205 ^a
Patient evaluation VAS pruritus	8.5 ± 2.58	7 ± 2.30	0.481 ^a	2.8 ± 3	3 ± 2.63	0.713 ^a
Patient evaluation VAS number of lesions	6.75 ± 1.91	7.12 ± 1.92	0.513 ^a	2.8 ± 3.36	3.25 ± 2.40	0.358 ^a
Patient evaluation VAS lesion duration	6.6 ± 2.02	6.5 ± 2.36	0.845 ^a	2.8 ± 4.33	3.25 ± 2.51	0.369 ^a

According to the UAS, the higher the score, the higher activity. According to the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL), the higher the score, the poorer the quality of life. Patient evaluation with regard to pruritus and presence and duration of lesions was done with the VAS where zero is asymptomatic and 10 represents maximum symptomatology.

*Mann–Whitney *U*-test.

Adverse clinical effects

During Visit 2 (15 days treatment), 11 patients (69%) from Group A and 12 from Group B (75%, $p = 1.0$) had at least one adverse effect. During Visit 3 (30 days treatment), 13 patients (81%) from Group A and 14 (87.5%) from Group B ($p = 1.0$) presented some adverse effect. Insomnia was the only with a statistically significant difference between groups (Table 2).

Adverse laboratory effects

No changes were found in blood count, blood chemistry or transaminases that could be attributed to the use of cetirizine or ranitidine.

Therapeutic efficacy

The therapeutic efficacy did not show statistical differences between groups (Table 3). Complete remission was observed in Group A, in 10 (62.5%), and in Group B in 7 (44%, $p = 0.287$). In Group A, the remission occurred at 5 ± 4.8 days of treatment and in Group B at 4 ± 3.51 days ($p = 0.346$).

During follow-up after treatment suspension on Visit 4 (Day 45), all patients had symptom recurrence (Group A at 3.66 ± 1.55 days versus Group B at 2.75 ± 1.69 days, $p = 0.109$).

Conclusion

Frequency of side effects between study groups did not show statistical difference. The combination of cetirizine plus ranitidine was no more effective than cetirizine alone in the treatment of chronic urticaria. A review of urticaria guidelines (9) mention, that H2 antihistamines should not be considered as part of the treatment “due to new evidence”, but they do not support this using reference. Our main limitation is the small sample size, which places a large limit on what can be concluded. It must be noted that clinical guidelines are based on studies performed in acute urticaria (3) and those studies conducted for chronic urticaria are dated and included first-generation H1 antihistamines (10,11).

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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