COMPARATIVE STUDY ON SAFETY AND EFFICACY OF LORATADINE, PREDNISOLONE & THEIR COMBINATION IN THE TREATMENT OF CHRONIC URTICARIA.

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Summary

Treatment of chronic urticaria is challenging because of the chronicity of the disease and in most of the cases the reason is unknown. Though many modalities of treatment are available newer generation antihistamine, loratidine is proved to be efficacious and safe. Even immunosuppressant glucocorticoid, prednisolone is found to be beneficial.
In view of paucity of studies this is an attempt to do a comparative study of newer generation H_1 antihistamine loratidine with glucocorticoid prednisolone in the treatment of chronic urticaria.

Objectives: To compare the efficacy and safety of loratidine, prednisolone & their combination in the treatment of chronic urticaria.

Methodology: Prospective, randomized, open clinical study conducted on 100 patients were randomly allocated into 3 groups. After initial clinical examination and relevant investigations, group I received Tab. Loratidine 10mg, group II Prednisolone 20mg per day in a tapering dose, Group III combination of both for two weeks. After two weeks patients were assessed for efficacy based on improvement grading and reduction in differential eosinophil count (DEC), absolute eosinophil counts (AEC); safety based on the incidence of adverse events.

Results: There was reduction in AEC and DEC and clinical improvements were almost similar in both loratidine alone group and combination group.
Incidence of adverse events among loratidine group was less compared to other groups.
There was a significant reduction in AEC and DEC ($p<0.05$) and also significant clinical improvement in combination group ($p<0.05$) (85%) than prednisolone (54%) alone.
There was no statistically significant difference in DEC, AEC reduction and clinical improvement between combination and loratidine group.

Conclusion: Analysis of all the parameters shows that combination of loratidine and prednisolone and loratidine alone are almost similar in efficacy in the treatment of chronic urticaria. Side effects are less with loratidine

Key words: Loratidine, Prednisolone, Chronic urticaria, Absolute Eosinophil Count, Improvement grading.

Introduction

Urticaria is a transient vascular reaction pattern characterized by circumscribed, edematous, itchy lesions usually lasting for few hours to 1 or 2 days. Urticaria is referred to as chronic when wheals occur daily or almost daily for a period of at least six weeks with an estimated lifetime prevalence of 0.5% across all populations studied [1]. It is one of the commonest skin conditions and poses the problem not only to the patient's quality of life and performance but also a therapeutic challenge to the treating physician in view of its multiple aetiological factors (like foods, drugs, inhalant allergens, infection, insect and arthropod bites, contactants, internal disease, psychogenic factors, genetic abnormalities and physical agents) and in most of the cases, aetiology cannot be determined inspite of exhaustive and expensive diagnostic approach and is termed as chronic idiopathic urticaria.

The urticarial wheal and flare occur due to severe pathological mechanisms including both immunological and nonimmunological which alternatively converge on mast cells and basophils to release mediators mainly histamine. Histamine acts on H_1 and H_2 receptors on the skin to produce localised vasodilatation and transudation of fluid from capillaries and thus results in wheal, flare and pruritus. So H_1 antihistamines are the main stay of therapy in the treatment of chronic urticaria. Various other modalities of treatment like combination of H_1 and H_2 antihistamines, sodium chromoglycate, calcium channel blockers**,** kallikrein inhibitors, prostaglandins inhibitors etc are tried. A course of systemic glucocorticoids is given alone or in combination with H_1 blockers if above therapies do not adequately control chronic urticaria. Immunosuppressive properties of glucocorticoids are beneficial in the treatment of chronic urticaria, but long term therapy has given rise to serious adverse effects.

Newer non sedative antihistamines are found to be beneficial in chronic urticaria because of their non sedative nature, efficacy and convenience compared to the older generation antihistamines. Loratidine is one of the new non sedative anti histaminics and compared to others has excellent clinical response and better safety profile in the treatment of chronic urticaria [2, 3].

In view of the paucity of the studies, it was an attempt to do a comparative study of loratadine, prednisolone and their combination in the treatment of chronic urticaria.

Objectives

To compare the efficacy and safety of loratidine, prednisolone & their combination in the treatment of chronic urticaria.

Methodology

This was a prospective, randomized, open labeled, comparative clinical study of loratidine, prednisolone and their combination in the treatment of chronic urticaria. The study was conducted for a period of 8 months. Institutional ethical committee approval was obtained before starting the study.

Subjects: Hundred (100) patients in the age group between 12 and 60 years, suffering from urticaria for at least 6 weeks and more were enrolled for this study and were recruited from the dermatology outpatient department of a tertiary care hospital.

Children less than 12 yrs of age, pregnant women, lactating mothers, female on oral contraceptive pills, patients on antihistamines treatment for 72 hrs or steroids for one month and patients with any chronic illness were excluded from the study.

On the basis of detailed proforma, selected cases of chronic urticaria were thoroughly interviewed individually to record the circumstances which precipitated the attack as noticed by the patients. Based on the different causative factors, chronic urticaria in the selected patients was categorized as cold urticaria, dermographic urticaria, cholinergic urticaria, drug induced urticaria, food urticaria, inhalant urticaria and chronic idiopathic urticaria [4].

A written informed consent was taken from all the patients included in the study after explaining the patients about the diagnosis, the nature and purpose of the proposed therapy. The benefits and risks of the proposed therapy i.e. with loratidine or prednisolone or their combination were discussed with the patient.

Participants enrolled in the study were subjected thoroughly to complete general physical examination, systemic examination and local examination of skin and also an ENT check up, dental check up and gynecological checks up to rule out the focus of infection. Certain diagnostic tests were carried out in selected patients as suggested by the history of their illness to diagnose the different types of chronic urticaria like dermographism test, ice cube test, and exercise test.

Of the 100 cases of chronic urticaria, each patient was selected randomly and assigned into 3 groups. Group1, Group 2 and Group 3. Group1 contains 34 patients, group 2 and group 3 contains 33 patients each. These 3 groups received the following treatment.

Group 1: Tab loratidine 10mg daily for 15 days.

Group 2: Tab prednisolone 20mg per day for first 3 days, later dose was gradually tapered by 5mg/ day every 3 days to 5mg/day. Total duration was 12 days.

Group 3: Combination of Tab loratidine and prednisolone. Dose and dosage schedule same as Group 1 and Group 2.

Follow up: Done after 2 weeks of treatment.

Laboratory tests: Routine analysis of blood- Haemoglobin, Total leukocyte count(TLC), differential neutrophil count (DNC), differential lymphocyte count (DLC), differential eosinophil count (DEC), absolute Eosinophil Count(AEC), Erythrocyte sedimentation rate (ESR) and Urine- albumin, sugar, microscopy were estimated in each patient.

Efficacy of the drugs was assessed based on the changes in the TLC, DEC, AEC and also by improvement grading arbitrarily as follows.

Improvement in signs and symptoms of urticaria was graded as follows:

Grade 1- Complete relief from itching and skin lesions.

Grade 2- Skin lesions disappeared completely, itching decreased slightly.

Grade 3- No improvement in both itching and skin lesions.

Safety of the drugs was assessed based on the adverse events reported or changes in the vital signs and physical examination recorded before and at the end of the treatment.

Statistical analysis

Interval data were expressed as mean +/- SD and categorical data in percentage. Since haematological counts showed moderately skewed, a non parametric method, Mann Whitney test was used. Categorical data was analysed by chi-square test. P value of < 0.05 was considered significant.

Results

Among the 100 cases of chronic urticaria, baseline demographic data, including patient's age, sex, severity and types of chronic urticaria is given in Table 1. Majority of the participants were between age group

31-40yrs (37%). 43% were males and 57% were females. Male to female ratio is 1:1.32. Moderately severe urticaria was common (65%), and among different types, physical urticaria was common (46.03%). (Table.1)

In Table 2, it was observed that TLC, DNC and DLC showed alteration in their counts after treatment in each group and were not statistically significant ($p > 0.05$) when compared by Mann Whitney test in between the groups.

In Table 2, mean reduction in differential eosinophil count after treatment in loratidine group alone was 1.7 ± 1.3, prednisolone group was 1.5 ± 1.1 and combination group was 2.2 ± 1.3. By using Mann Whitney test when mean difference in their count were compared among the groups, there was statistically significant reduction ($p<0.05$) in combination group than prednisolone alone group. There was no significant difference between loratidine alone group & prednisolone alone group; and loratidine alone and combination group.

In Table 2, mean reduction in absolute eosinophil count after treatment in loratidine group alone was 43.2 ± 47.6, prednisolone group alone was 25.8 ±36.7 and combination group was 53.3 ± 51.9. Maximum reduction was observed in combination group followed by loratidine group alone and prednisolone group alone.

There was a statistically significant reduction ($p<0.05$) in combination group than prednisolone alone group. There was no significant difference between loratidine alone group & prednisolone alone group; and loratidine group alone and combination group.

In this study improvement grading (Table 3) after treatment in 3 groups were as follows. In loratidine alone group (n=34) maximum number of patients 27 (79%) and 7 (21%) patients showed grade 1 and grade 2 improvement respectively. In prednisolone alone group (n=33), 18 (54%) 13 (40%) and 2 (6%) patients showed grade 1, grade 2 and grade 3 improvement respectively and in combination group (n=33) maximum number of patients 28 (85%) and 5 (15%) showed grade 1 and grade 2 improvement respectively.

When Chi-square test was applied and compared between groups, there was a statistically significant clinical improvement in signs and symptoms in combination group over prednisolone alone group.

In loratidine alone group (n=34) out of 3 patients (8%) who experienced adverse effects 1 had slight drowsiness, 1 had headache and 1 patient had dryness of mouth. In prednisolone alone group (n=33) out of 10 (30%) patients who experienced adverse effects 9 had gastric irritation, 1 had headache and anxiety. In combination group, out of 15 patients (45%) who experienced adverse effects 7 had gastric irritation, 2 complained of headache, 1 patient had drowsiness, 1 had dryness of mouth, 1 had vomiting and 1 showed depression and 2 exhibited anxiety. In the present study, maximum number of patients 15 (45%) in combination group had adverse effects followed by prednisolone alone group - 10 (30%) and loratidine alone group- 3 (8%). The difference in the incidence of adverse effects in between 3 groups was not significant.

No significant changes in vital signs, parameters on physical and general examination were observed during the study in any group.

Table 1: The drugs used:

Drugs	Antibiotics	Zinc suspensions	Anti-emetics	Probiotics	Paracetamol	Others
Percentage	23.86%	23.30%	19.50%	10.60%	7.20%	15.60%

Table 2: Antimicrobial agents used:

Drugs	Cephalosporins	Aminoglycosides	Others
Percentage	45 (38.80%)	58 (50%)	13 (11.20%)

Table 3: Dehydration status and use of IVF, ORS:

	Number of patients	IVF	ORS	IVF+ORS	No IVF+ORS
No dehydration	14	03	04	04	03
Some dehydration	111	39	10	54	08
Severe dehydration	07	03	-	04	-

Table 4: WHO prescribing indicators:

Prescription indicators	Findings
1. Average number of drugs per encounter	4.5
2. Percentage of drugs prescribed by generic name	7.9%
3. Percentage of encounters with an antibiotic prescribed	25.13%
4. Percentage of encounters with an injection prescribed	55.70%
5. Percentage of drugs prescribed from national essential drugs list	37.9%
6. The average cost per admission	Rs. 166.53

Discussion

Even though chronic urticaria has many causative factors, detailed understanding of pathophysiology has given way for the new generation antihistamines as 1st line of treatment which gives symptomatic relief and improves quality of life of these patients. Still in some cases of chronic urticaria ensuring a good quality of life for the patient is challenging to the physician and they combine glucocorticoid with antihistamines as a last measure in the treatment of chronic urticaria.

In the present study, among 100 patients peak occurrence of chronic urticaria was seen in the age group between 31-40 years (37%). Females were more affected than males. The results of age, sex distribution and type of chronic urticaria were supported by the previous studies [5, 6, 7].

DEC and AEC were estimated before and after treatment in all the three groups and were compared between groups. There was a statistically significant reduction in both DEC and AEC in combination group than loratidine alone and prednisolone alone group. And when compared between groups, there was a statistically significant difference between combination treated group (group 3) and prednisolone alone group

(group 2). And the same was not significant between loratidine alone and prednisolone alone group; loratidine alone group and combination group. This suggests that there was a better control of DEC and AEC in patients treated with loratidine and prednisolone combination.

All the patients in each group were evaluated for improvement grading after treatment. There was significant grade 1 improvement (85%) of signs and symptoms in patients treated with combination drugs than prednisolone alone (54%). Whereas grade 1 improvement with loratidine treated group (79%) was almost comparable with combination drugs. Monsoe EW et al [8] study showed loratidine treated patients had significantly ($p<0.01$) greater symptomatic relief than placebo treated group (64% vs 25% improvement). Belaich et al [2] study showed marked or complete relief of symptoms in 64%, 52% and 25% of patients in loratidine, terfenadine and placebo treated group respectively. Thomas et al [3] reported that more number of loratidine treated patients improved compared to cetrizine treated patients (81% vs. 60%). The improvement in signs and symptoms of this study were supported by the above studies.

In the present study, incidence of adverse effects like gastric irritation was more in combination group then followed by prednisolone alone treated group followed by loratidine alone treated group. Incidence of drowsiness was more in loratidine treated group and was supported by the previous study conducted by Haria et al [9].

Cuss et al [10] have been reported that the Ag induced Eosinophilia in nasal and bronchial lavage in guinea pig was decreased by loratidine. Ryosuke et al [11] in their in-vitro study of the effect of loratidine on eosinophil functions have reported that loratidine inhibited eosinophil chemotaxis (i.e. activation) and superoxide anion generation (responsible for allergic reactions) thus suggested that loratidine also has antiallergic properties in addition to H_1 antagonism. Whether loratidine has an effect on in vivo eosinophil migration and chemical mediator release is unclear. The potential action of loratidine on eosinophil may result from either by a direct effect on eosinophils or on indirect effect through other cell population such as mast cells by inhibiting the release of chemotractant and activating factors for eosinophils [10].

Choruses et al [12] stated the mechanism of prednisolone in chronic urticaria is due to its immunosuppressive property i.e. by decreasing eosinophil and basophiles in the circulation as a result of their movement from the vascular bed to lymphoid tissue.

Conclusion

The overall conclusion that can be drawn after making all observations is that loratidine alone is almost as effective as combination of loratidine and prednisolone in the treatment of chronic urticaria considering the effect on differential eosinophil count, absolute eosinophil count and clinical improvement. Considering the adverse effects of prednisolone which can be still more deleterious after long term use, loratidine is found to be a better drug in view of its efficacy and minimum adverse effects. Further studies are needed in large sample size to confirm the findings of the present study.

Acknowledgements

We are very much thankful to Dr. H.S. Siddappa Devaru, Professor and Head, Department of Pharmacology, J.J.M.M.C. Davangere for his kind co-operation and help.

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