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Original Article

To compare the added effectiveness of ketotifen along with traditional H1 anti histamines for the symptomatic improvement of chronic idiopathic urticaria

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Abstract

Objective To compare the added effectiveness of ketotifen along with traditional H1 anti histamines for the symptomatic improvement of chronic idiopathic urticaria.

Methods The study was conducted in the outpatient department of Dermatology at Punjab Rangers Teaching Hospital over a period of 3 months starting from April 2021 till end of June 2021.
A total of 32 patients with chronic idiopathic urticaria between the age of 15 to 50 years were enrolled. Children below the age of 15 years and patients who were known diabetics and hypertensive were excluded from this study.

Patients were divided in two equal groups A &B, with each given a different regime. Group A was given Ebastine (10mg) in morning and Hydroxyzine (10mg) at night, whereas Group B was given Ebastine (10mg) in morning, Ketotifen (1mg) and Hydroxyzine (10mg) at night.

Two scales were constructed to assess the severity of the disease, one was severity of pruritis and other was frequency of urticarial episodes.
The first variable, which was severity of pruritis was graded into mild, moderate and severe. Mild pruritis requiring only occasional use of antihistamines, moderate requiring these 2-3 times a week and severe disease where antihistamines were taken more than thrice a week

Frequency of the urticarial episodes was similarly graded as mild, moderate and severe with mild disease comprising of episodes of urticaria less than 2 days per week, moderate disease with attacks between 3-4 days per week and severe disease as urticarial attacks for more than 4 days in a week.
Patients were followed after a period of 4 weeks and the response of the treatment was also measured on the same variables, meanwhile results were interpreted to find which drug regime was more efficient to control recurrent episodes of urticaria. .

Results Response in the severity of pruritis was graded as mild (less than 30% improvement), moderate (between 30%-60% improvement) and good response (more than 70% improvement).
Similarly the response in frequency of episodes was also graded into percent improvement of less than 10% (no significant response), 20%-30% (mild), 30%-60% (moderate) and more than 70% (good).

Both the groups showed considerable improvement to a variable extent.
Out of 16 patients of group A, 12 (75%) showed some symptomatic improvement while 4 (25%) reported no improvement at all, whereas among the 16 patients of group B, 14 (87.5%) showed

significant improvement while, 2 (12.5%) had no improvement at all.

Considering pruritis first, out of 12 patients who responded to the treatment, in group A, only 5 (41.6%) showed good response, 6 (50%) showed moderate and 1 (8.3%) had mild response.
Concerning the frequency of urticarial episodes, out of 12 patients of group A, 5 (41.6%) showed good recovery and the remaining 7 (58.33%) showed moderate recovery.

Among the 14 patients of group B who responded to the treatment, 8 (57.14%) showed good response in pruritis, 4 (28.5%) showed moderate response and 2 (14.2%) had mild response.
Regarding the frequency, out of 14 patients of group B, 8 (57.14%) good recovery, 6 (42.85%) showed moderate recovery.

Thus overall, group B (ketotifen group) showed a better response to treatment decreasing the intensity of pruritis and reducing the frequency of episodes to a significant extent as compared to Group A who were taking Ebastine and hydroxyzine alone.

Conclusion Based on the results of the current study, we conclude that Ketotifen, if started as first line therapy, has a better efficacy in reducing the severity of the disease, as compared to traditional H1-antihistamines alone.

Key words
Urticaria, H1 receptor anti histamine, ketotifen.

Introduction

Urticaria (wheals), are transient, erythematous, itchy raised lesions that result from skin reaction which can vary in size from the size of a diem to a hand. The condition is classified as chronic if the disease persists for more than six weeks and recur frequently over months or years.[4]

About 20% of people will develop hives at some point of their life.[5]

Urticaria is classified either acute and chronic urticaria depending upon the eruptions. Acute urticaria last for less than 6 weeks and chronic urticaria last more than 6 weeks.

Young adults and children are more prone to acute idiopathic urticaria, meaning the cause yet not found even after ruling out all the triggers. This type of urticaria last not more than few hours and resolves on its own without any medical intervention.

Chronic urticaria is the one which lasts more than 6 weeks and usually requires medical treatment. A study conducted in 2013 concluded 70%.

people with chronic urticaria had symptoms that persisted for longer than a year, while 14% had symptoms for 5 or more years. In half of the cases the offending agent was never found.[6]

Most of the people having an episode of urticaria complain of itchy, erythematous, well demarcated, raised lesions all over the body which subside within an hour at one spot but may appear at another spot.

On examination urticaria appears as slightly raised, pink to red swellings that occur alone or in a group or connect over a large area of body.[7]

It is widely known that the cutaneous mast cells have a central role in urticaria. Histamine is released from mast cells on degranulation together with tryptase and some cytokines, the

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receptor for histamines are on post-capillary venules and C-fiber nerve endings. These receptors become permeable to plasma and signals the sensation of itch in the central nervous system. Biopsy of lesion shows an early influx of inflammatory markers of including eosinophils, neutrophils, basophils, and undifferentiated T cells. The stimulus of mast cell degranulation may be immunological or non-immunological. Cross-linking of two or more adjacent allergen-specific immunoglobulin (Ig) E molecules bound to the high affinity IgE receptor (FceRI) on mast cells or basophils will initiate a series of calcium-dependent intracellular signaling events leading to incomplete degranulation in allergic urticaria. Autoantibodies against IgE, FceRI or both on basophils or mast cells cause histamine release in vitro and are thought to underpin autoimmune urticaria. The process maybe complement (C) dependent and C5a itself is a potent degranulating agent in the laboratory.[8]

Management of urticaria starts with classification of type of urticaria. Avoiding substances that trigger episodes of urticaria is the main line treatment. When this is not possible or it is not working, antihistamines come into play. A non-sedating antihistamine is usually preferred but advance cases may require corticosteroids or immunosuppressant drugs.[9]

The most well tolerated initial treatment are the non-sedating anti-histamines like loratadine and cetirizine. If this is not enough, sedating antihistamine is added at night.[10]

There is good evidence that second-generation H_1-antihistamines are helpful in the short- and intermediate-term suppression of urticaria in a dosage of 10 mg daily to completely suppress symptoms of chronic spontaneous urticaria.[11]

Ketotifen was originally developed as a drug to inhibit the release of vasoactive substances from mast cells, initiating its action within minutes of administration and can last up to 12 hours.[12] ketotifen has a chemical structure similar to some first-generation antihistamines, such as cyproheptadine. Oral ketotifen is well tolerated and safe with the most common side effect of sedation. This side effect is observed in 10% to 20% of the patients with a higher dose, but the effect decreases within 1 to 2 weeks. Other less common side effects include dizziness, dry mouth, nausea and headache.

Methods

The study was conducted in Outpatient department of Dermatology at Punjab Rangers Teaching Hospital over a period of 3 months, starting from April 2021 till end of June 2021.

Patients within age group of 15 years to 50 years were divided into two control groups A and B. Group A was prescribed Ebastine (10mg) in morning and Hydroxyzine (10mg) at night, while Group B was given Ebastine (10mg) in morning, hydroxyzine (10mg) and ketotifen (1mg) at night. All patients were asked for a follow up after 30 days in dermatology department.

Children below the age of 15 years and patients who were on active treatment for diabetes and hypertension were excluded from this study.

Inclusion criteria A total of 32 patients with chronic idiopathic urticaria between the age of 15 to 50 years were enrolled. Patients were divided in two equal groups A and B, each given a different regime.

Results

Response of the given treatment regarding severity of pruritis included a scale of mild (less

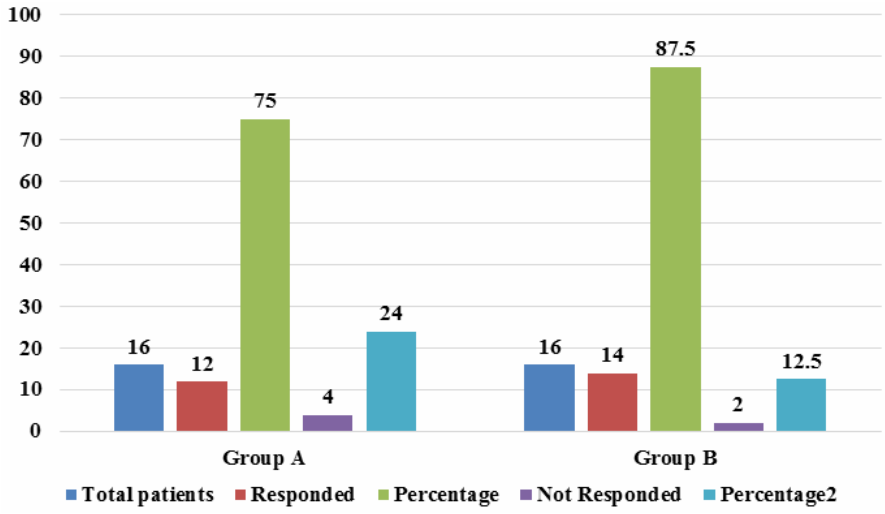

Figure 1 Total number of patients vs. responded patients & non-responded.

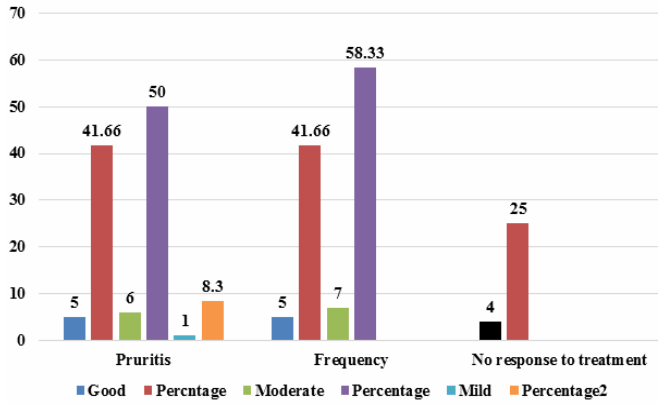

Figure 2 Group A (Ebastine, Hydroxyzine) Evaluation on basis of pruritis and frequency

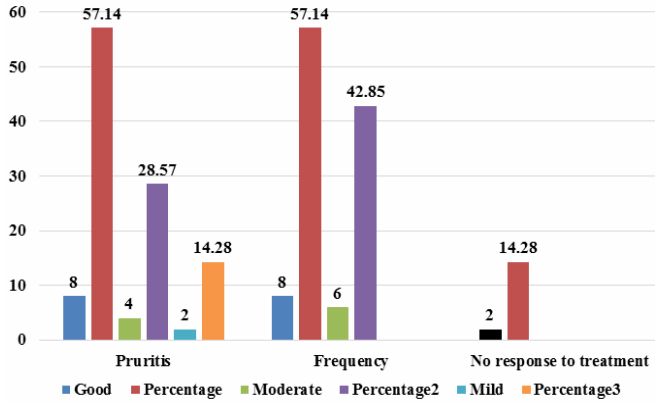

Figure 3 Group B (Ketofetin, Ebastine, Hydroxyzine) Evaluation on basis of pruritis and frequency

than 30% improvement), moderate (between 30%-60% improvement) and good response (more than 70% improvement). Concerning the frequency, response was graded into percent improvement of less than 10% (no significant response), 20%-30% (mild), 30%-60% (moderate) and more than 70% (good).

Both the groups showed considerable improvement to a variable extent.

Out of 16 patients of group A, 12 (75%) subjects showed some symptomatic improvement and 4 (25%) showed no improvement at all, whereas among the 16 patients of group B, 14 (87.5%) showed significant improvement while, 2 (12.5%) showed no improvement at all.

Considering pruritis first, out of 12 patients who responded to the treatment, in group A, only 5 (41.6%) showed good response, 6 (50%) showed moderate and 1 (8.3%) had mild response.

Concerning the frequency of urticarial episodes, out of 12 patients of group A, 5 (41.6%) showed good recovery and the remaining 7 (58.33%) showed moderate recovery.

Among the 14 patients of group B who responded to the treatment, 8 (57.14%) showed

Table 2 Response to treatment in both Group A and Group B

		Group A *n (%)*	*Group B* *n (%)*
Responses	Respondent	12 (75 %)	14 (87.5 %)
	Non-respondent	4 (25 %)	2 (12.5 %)
Pruritis recovery	Good Recovery (>70%)	5 (41.6 %)	8 (57.14 %)
	Moderate Recovery (30-60%)	6 (50 %)	4 (28.5 %)
	Mild Recovery (<30%)	1 (8.3 %)	2 (14.2 %)
Frequency	Good Recovery (>70%)	5 (41.6%)	8 (57.14 %)
	Moderate Recovery (30-60%)	7 (58.33 %)	6 (42.85 %)
P value		P = 0.7	P = 0.2

good response in pruritis, 4 (28.5%) showed moderate response and 2 (14.2%) had mild response. Regarding the frequency, out of 14 patients of group B, 8 (57.14%) good recovery, 6 (42.85%) showed moderate recovery. Thus overall, group B (ketotifen group) showed a better response to treatment decreasing the intensity of pruritis and reducing the frequency of episodes to a significant extent as compared to Group A who were taking Ebastine and hydroxyzine alone.

Discussion

Quality of life has been an important subject in modern medicine especially for health professionals. It can be defined as an individual satisfaction with life in domains that the individual considers important.

Chronic urticaria is a debilitating allergic skin disease that considerably affects health related quality of life. A study was conducted to evaluate the effects of urticaria on quality of life, showed that the highest mean scores were nervousness and shame over lesions presented by patients.[13]

A study conducted at Hinduja Hospital, India from July to October in which 48 patients were enrolled reveled that in majority of the case urticaria had a serious impact of life activities of a patient including sleep disturbances and physical appearances.[14]

Taking nonsedating antihistamine drugs daily helps block the symptom- producing release of histamine.[15] In 2011, doctors started prescribing ketotifen more frequently for severe urticaria because of its availability in the market. A retrospective study was conducted on 51 patients in which, modified Urticaria Activity score of 18 out of 24 patients significantly improved, and rest of the 22 patients reported some improvement in their symptoms. The need for additional routine medicines decreased in 14 patients and 4 to 6 patients stopped taking steroids after starting ketotifen.[16]

A case report was published during 1997, in United States, reporting that a 43 years old lady used ketotifen for refractory chronic urticaria and her symptoms which included severe pruritis resolved within days.[16]

In 1998, two Turkish physicians wrote a letter to editor of Dermatology journal, claiming that Ketotifen was widely used in Turkey in patients with urticaria and it should be considered as first line treatment for chronic urticaria.[16]

A study lasted for 56 months compromising of 26 male and female patients with chronic urticaria which were prescribed Ketotifen. There

was positive improvement in hive breakouts in more than 80 percent of the participants.[17]

The objective of current study was to compare the added effectiveness of ketotifen along with traditional H1 anti histamines for the symptomatic improvement of chronic idiopathic urticaria. The observation that was made based on results showed greater & earlier improvement of symptoms in patients who were prescribed ketotifen along with other antihistamines upon first visit. Emphasis must be placed on prescribing ketotifen as a first line therapy along with other traditional antihistamines to alleviate the distress associated with severity of this disease as the drugs causing early relief of symptoms impart a better compliance to the treatment, as compared to delayed onset of relief, which creates a sense of dissatisfaction and non-compliance to therapy.

Conclusion

The current study concluded that ketotifen, a drug that belongs to class of second-generation noncompetitive H1-antihistamine and mast cell stabilizer, has proven to be a great therapy for patients with chronic urticaria as a first line treatment and therefore it should be regularly prescribed along with other H1-blockers to patients with chronic idiopathic urticaria..

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