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Efficacy and Safety of a Combination of Levocetirizine and Phenylephrine in the Treatment of Allergic Rhinitis and Eustachian Tube Dysfunction

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Abstract:

Introduction: *Allergic Rhinitis (AR) and Eustachian Tube Dysfunction (ETD) are commonly seen in adults. Treatment options for AR and ETD is directed towards multiple symptom relief. A FDC of Levocetirizine, an anti-histaminic and Phenylephrine, a nasal decongestant is popular in the treatment of Allergic Rhinitis and Eustachian Tube Dysfunction in adults. This Phase IV study judged the efficacy and safety of a combination of Levocetirizine and Phenylephrine in treatment of Allergic Rhinitis.*

Methodology: *Of 203 registered, 174 patients completed the study. Safety assessment was made by inspecting the adverse events during trial. Efficacy assessment was made by decrease in TSS and extrapolating to four point Likert type scales.*

Results: *Reduction in TSS was from 6.97 (baseline) to 3.90 (day 3) and 1.43 (day 5). One point reduction in Likert-type symptom scale from Moderate to Mild took just 3 days. Nearly all the patients had >50% reduction in symptom score at all visit and majority of patients had complete relief from the symptom. 23 episodes of adverse events occurred and were of mild intensity, sedation and drowsiness being dominantly seen.*

Conclusion: *A combination of Levocetirizine and Phenylephrine is safe and effective in the treatment of Allergic Rhinitis and Eustachian Tube Dysfunction.*

Keywords: ***Levocetirizine, Phenylephrine, Allergic Rhinitis, Eustachian Tube Dysfunction, Total Symptom Score***

INTRODUCTION

Allergic rhinitis (AR) is one of the most common diseases considered by the expression of inflammatory symptoms in the upper respiratory tract. The development of AR is produced by the interaction between genetic predisposition and environmental factors. It affects about one tenth of the world's population and its incidence is increasing[1]. AR was usually categorised into seasonal AR and perennial AR based on the duration of exposure and symptoms[2]. Perennial AR is mainly caused due to indoor allergens while seasonal AR caused due to outdoor allergens[3]. In 2001, the World Health Organization (WHO) proposed a new Allergic Rhinitis and its Impact on Asthma (ARIA) classification, which classifies AR according to severity and symptom duration[4]. Several drug classes are existing for the treatment of AR, like oral and intranasal antihistamines, intranasal corticosteroids, leukotriene receptor antagonists and Cromolyn sodium[5]. AR if not treated, leads to acute asthma, thus resulting in hospitalization of the patients. The signs and symptoms of AR are Sneezing, Rhinorrhoea, Nasal Congestion, and Nasal Itching[6].

Eustachian Tube Dysfunction (ETD) is a result of a predisposing Allergic condition. It includes obstruction and abnormal patency of ETD, which is caused by extrinsic and intrinsic factors due to inflammation. The percentage of ETD in a group of AR patients was higher than in healthy subjects[7]. There is limited data on ETD prevalence and incidence, a UK national study of hearing reported that 0.9% of the 2708 adults assessed were considered to have ETD[8]. The signs and symptoms of ETD are otitis media with effusion, middle ear atelectasis and chronic otitis media[9, 10].

Additionally, adequate postoperative management is an essential part of perioperative care because it affects the results of the surgery and patient discomfort following the surgery[11]. The patency of Eustachian Tube is important post ENT surgeries like Tympanoplasty and Myringotomy. If ETD persists post these surgeries, then it can lead to the failure of the surgery[9].

A combination of Anti-Histamines with Nasal Decongestants and NSAID is quite popular in treatment of common cold and has abundant clinical data. AR, ETD and

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Post ENT surgery would not warrant the use of NSAID as these conditions are essentially afebrile and associated with less pain[12]. Moreover, NSAID can lead to some adverse effects like gastritis, nausea, vomiting and rarely even hepatic failure[13].

Monotherapy has a shortfall to provide relief of all the symptoms of AR, ETD and Post ENT surgery. Hence, multiple drug combinations including Antihistamine and Nasal Decongestants are used to these indications. Levocetirizine, an active enantiomer of cetirizine, is a second generation piperazine derivative and H1 selective antihistaminic agent that was approved by the USFDA in 2008 for the relief of symptoms associated with allergic diseases[14, 15, 16]. Though it has some side effects such as sedation, dizziness and fatigue but it is considered to be effective and safe for treating allergic disease. Surprisingly, Levocetrizine has a more rapid onset and longer duration of action than other antihistamines. Moreover, it exerts anti-inflammatory effects in patients with allergic disorders[17]. Phenylephrine, a selective α1-adrenergic receptor agonist, is a nasal decongestant. Its main and direct effect is vasoconstriction of capacitance blood vessels of the nasal mucosa that reduces blood volume, leading to nasal decongestion[18].

Due to dearth of clinical data for the combination Levocetirizine and Phenylephrine, the current study was conducted to document the safety and efficacy of this combination in the treatment of AR, ETD and in Post ENT surgery in adults.

METHODOLOGY

This multicentered phase IV clinical trial enrolled 12 ENT centres in various cities in India. This study was conducted from February 2017 to April 2017. A total of 203 patients were enrolled for the study, out of which 174 patients completed and 29 patients were lost to follow-up.

Inclusion and Exclusion Criteria

The study included patients of both gender of the age 18 years and above. Patients involved in the study were diagnosed of Allergic Rhinitis and Eustachian tube dysfunction having 4 out of the 8 symptoms of Sneezing, Rhinorrhoea, Nasal Congestion, Nasal Itching, Sore throat, otitis media with effusion, middle ear atelectasis and chronic otitis media were embodied in the study. Only the patients who would strictly cohere to the protocol were enrolled for the study. Patients with hypersensitivity to the individual study drugs were excluded. Patients having blood pressure of more than 130/90mm were refrained from the study as Phenylephrine which is present in the study drug can result in vasoconstriction causing increase in BP. Patients who cannot adhere to the Protocol (mentally ill and patients with psychological problem) were excluded from the study.

Study Intervention

Study drug – A Tablet with a combination of Levocetirizine 2.5mg + Phenylephrine Hydrochloride 10mg was provided by the sponsor free of cost to the patient enrolled in the study. Study dosage and administration – Patients were instructed to take the one tablet twice a day for a study period of 5 days with a glass of water.

Study Procedure

The study was conducted for 5 days. Patients of AR, ETD and post ENT surgery satisfying the inclusion and exclusion criteria were employed for the study. Medical history was taken and physical examination (including the vital signs, systemic and general examination) was carried out by the investigators. Patients were dispensed 10 tablets in a blister pack of the study drug by the investigator. Patients were asked to maintain a symptoms diary and note any adverse events occurring during the study duration. Three visits were outlined for the patients recruited in this study – V0 (baseline visit) on day 1, V1 (re-evaluation visit) on day 3 and V2 (conclusion visit) on day 5. Total Symptom Score (TSS) and adverse events occurring were noted during each visit along with medical history and physical examination. Investigators were asked to cease the study drug in case of severe adverse event and with discretion, clinical experience contingent upon mild to moderate adverse events.

Concomitant Therapy

No Pharmacological intervention and medication including, topical decongestants (sprays/ drops and aromatic oils), antibiotics, multi-vitamins and multiminerals were allowed during the study duration, other than study drug. Non-Pharmacological interventions like drinking of warm/hot water at regular intervals and steam inhalation were allowed and encouraged during the study.

Efficacy Assessment

The primary assessment was reduction in Total Symptom Score (TSS) which was a score of all the symptoms on an eleven-point scale (0 to 10) where 0 is no symptoms and 10 is maximum tolerated symptoms. The TSS was further extrapolated to the Likert-type symptom severity scale with 4 grades – no symptoms (0 on TSS), mild (1 – 4 on TSS), Moderate (5 – 8 on TSS) and Severe (9 – 10 on TSS). The secondary assessment was number of patients having no symptoms (0 on TSS) on day 5 and number of patients having more than 50% reduction in TSS.

Safety Assessment

Patients were enquired for any adverse event and the same if present was noted in the case record form during each post-dose visit. Patients with any adverse events if present were noted in the case report form after thorough investigation. These adverse events were characterized into non-serious adverse events and serious adverse events. Naranjo's scale

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of probability was used to classify the adverse event as non-drug related or drug related. Adverse events were followed up by the investigators till the symptoms subside.

Regulatory and Ethical Matters

The study drug in combination has been approved for manufacturing and marketing in 2010.The said combination is available under various brands but is classified as schedule H drug in India, i.e. to be sold in presence of prescription of registered medical practitioners only. Patients involved in this study read and signed the informed consent form. The protocol, informed consent form, case record form, investigators CV, investigators undertaking, investigators medical registration certificates (including post-graduation certificates) and ethics committee registration certificates were submitted to the office of Drug Controller General of India (DCGI), Central Drugs Standard Control Organization (CDSCO) and are registered under ref. no. 2510/17.

RESULTS

A total of 203 patients were enrolled at 12 centers across India, 174 patients completed the study and were analyzed. Other demographic characteristics are in Table 1.

Table 1: Demographic Characteristics of the patients recruited for the study.

Mean age of patients	35.87
Males	97 (55.74%)
Females	77 (44.25%)
Patients with AR/ETD	145/29

Efficacy Analysis

TSS was recorded at all the visits (V0, V1 & V2) and thus the reduction on TSS was calculated. The mean TSS at V0 or the baseline visit was 6.97, which was reduced to 3.90 at V1 or day 3 and further reduced to 1.43 on V2 or day 5 (Figure1). The reduction in TSS corresponds with the improvement in general and physical examination of the patients.

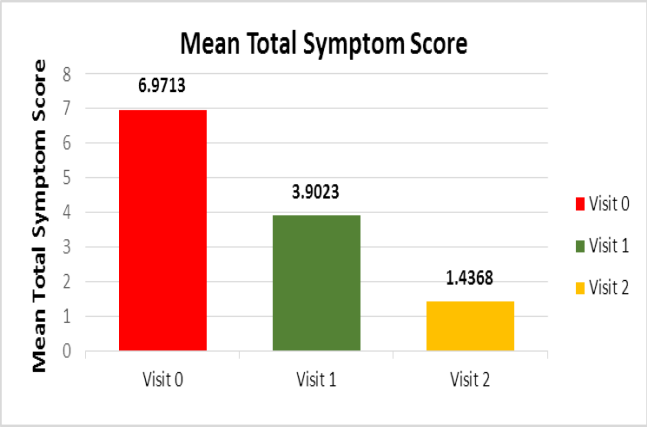

Figure 1: Reduction in TSS at each visit.

At V1 44.02% reduction was seen as in V2 63.18% reduction was seen. Overall reduction in symptoms over 5 days was 79.38%. The percent reduction in TSS is shown below in figure 3.

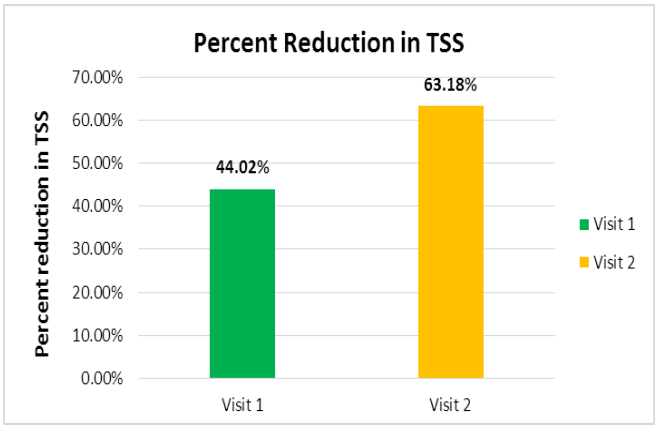

Figure 2: Percent reduction in TSS

Extrapolating the data to the Likert-type symptom scale, at V0 or baseline the mean TSS corresponds to Moderate symptoms which was reduced to Mild in V2 or Day 5.

Out of 174 patients, 86 patients had a TSS of 0 i.e.no symptoms on Likert-type symptom scale and another 24 had the TSS of 1(Figure 3) at the end of 5 days.

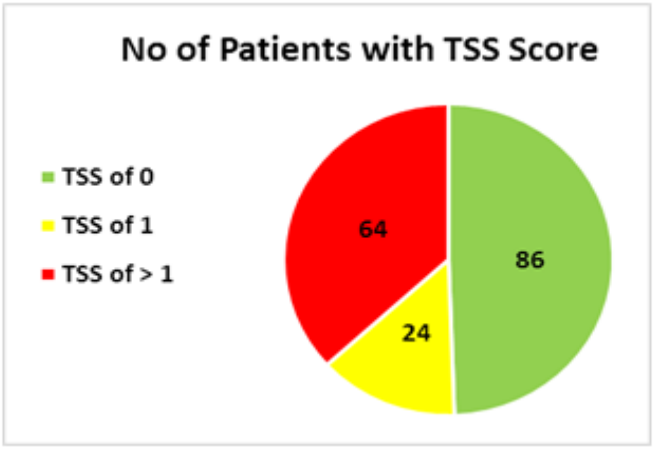

Figure 3: No. of Patients with TSS Score of 0, 1 and > 1 at V2 on day 5.

Safety Analysis

The overall incidence of reported study drug related adverse effects was 2 seen in 17 patients. The list of adverse events with the number of episodes is mentioned in Table 2.

Table 2: Adverse event episodes occurred in the study

Adverse events	No of episodes	No of patients	% of total population
Sedation and Drowsiness	18	13	7.47%
Dizziness	5	4	2.29%
Total	23	17	9.77%

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Majority of adverse effects were study drug related with Sedation and Drowsiness dominating.

DISCUSSION

Allergic Rhinitis has a greater impact on productivity, absenteeism, and daily life and since it is treated symptomatically, the treatment is fixated towards symptom control. Similarly, ETD also requires symptom control. In author's knowledge, this was the first clinical trial conducted to study the efficacy and safety of a fixed-dose combination Phenylephrine and Levocetirizine in reducing the symptoms of Allergic Rhinitis and Eustachian Tube Dysfunction.

Strong point of this clinical study is that Total Symptom Score (TSS) is used as a criterion for efficacy reckoning and that this data of TSS is extrapolated to Likert-type symptom scale which is the internationally acknowledged scale for AR and ETD symptom assessment. What makes TSS more impressionable is that it has 11 grades for symptom assessment compared to Likert-type symptom scale which has 4 grades, thus increasing the sensitivity of the study.

There was a reduction in (TSS) in all the patients in the phase IV post market surveillance study. The TSS reduced from 6.97 to 3.90 in first 3 days which is a reduction of 44.03% and from 3.90 to 1.43 in the next 2 days which is reduction of 63.18%. The overall reduction in TSS in the 5 days was 79.38%. One point reduction in Likert-type symptom scale from Moderate to Mild took just 3 days with the study drug. In all the patients, there was a reduction in the TSS. Majority of patients had no (TSS score of 0) to very less (TSS score of 1) at the end of 5 study days. A total of 23 adverse events were related to study drug. Sedation/Drowsiness was the most documented adverse event affecting 9.77% of study population which is due to Levocetrizine.

A Cochrane review analysed 32 studies or metaanalysis of 8930 patients for the treatment of Common Cold, construing that antihistamine analgesic decongestant combinations have some general advantage in adults and older children in treatment of Common Cold 20. Paracetamol, Phenylephrine and Levocetirizine are specified in the list provided for antihistamine-analgesic decongestant.

Eccles et al.[19], proposes the rationale for combining multiple drugs in treatment of common cold to provide relief from multiple symptoms. Additional it suggests, there is no evidence that multi-symptom relief medicines are less safe than single-active ingredient medicines. Multi-symptom relief combination products containing several active ingredients provide an effective, safe, economic and convenient option of treating the multiple symptoms of common cold.

Kiran M et al.[20] conducted a phase IV clinical study of a combination of Paracetamol, Levocetrizine and Phenylephrine essentially in the treatment of common cold and Allergic Rhinitis in children. Safety and efficacy of the combination were evaluated in 156 patients. Efficacy assessment was made by reduction in Total Symptom Score and four point Likert-type scales with reduction in TSS from 5.05(baseline) to 2.58(day 3) and 0.61(day 5) showing >50% reduction in symptom score at all visit. The study concluded that the combination of Paracetamol, Levocetrizine and Phenylephrine is safe and effective in the treatment of Common Cold and Allergic Rhinitis in children.

Kiran M et al.[21] conducted a phase IV clinical study of a combination of Paracetamol, Levocetrizine and phenylephrine in the treatment of common cold and Allergic Rhinitis in adults. Safety and efficacy of the combination were evaluated in 201 patients. Efficacy assessment was made by reduction in Total Symptom Score and four point Likert-type scales with reduction in TSS from 6.82(baseline) to 3.63(day 3) and 1.14(day 5) showing >50% reduction in symptom score at all visit. The study finished that the combination of Paracetamol, Levocetrizine and Phenylephrine is safe and effective in the treatment of Common Cold and Allergic Rhinitis in adults.

CONCLUSION

A combination of Levocetirizine 2.5mg and Phenylephrine Hydrochloride 10 mg provides symptomatic relief and is safe for the treatment of Allergic Rhinitis and Eustachian Tube Dysfunction.

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