



**Original Research Article**

DOI: <http://dx.doi.org/10.22192/ijcrms.2017.03.01.007>

## Efficacy and Safety of a combination of Paracetamol, Levocetirizine and Phenylephrine in the symptomatic treatment of Common Cold and Allergic Rhinitis: Phase IV Clinical study

**Dr. Mayuresh Kiran<sup>#</sup>, Mr. Lalit Pawaskar\* & Dr. Pramila Yadav<sup>^</sup>**

<sup>#</sup> General Manager, Medical Services, Centaur Pharmaceuticals Pvt. Ltd.\* Research Associate, Pharmacovigilance, Centaur Pharmaceuticals Pvt. Ltd.^ Professor, Dept of Pharmacology, Pad. Dr. D. Y. Patil Medical College, Navi Mumbai.

**Corresponding author:**

Dr. Pramila Yadav<sup>^</sup>. Professor, Dept of Pharmacology, Dr D Y Patil Medical College, Navi Mumbai.

E-mail: [drpramilayadav10@gmail.com](mailto:drpramilayadav10@gmail.com)

---

### Abstract

**Introduction:** Common cold and allergic rhinitis are one of the most frequently encountered diseases in clinical practice. Though self-limiting, it accounts for major loss of work and school days so symptomatic therapy to treat the symptoms is often employed. A combination of Paracetamol, an antipyretic/anti-inflammatory, Phenylephrine, a nasal decongestant and Levocetirizine, an anti-histaminic is popular in the treatment of common cold and allergic rhinitis. This Phase IV study evaluated the efficacy and safety of a combination of Paracetamol, Phenylephrine and Levocetirizine in treatment of common cold and allergic rhinitis. **Methodology** –Of 234 enrolled, 201 patients completed the study. Efficacy assessment was made by reduction in TSS and four point Likert-type scales. Safety assessment was made by analyzing the adverse events during trial. **Results** –Reduction in TSS from 6.82 (baseline) to 3.63 (day 3) and 1.14 (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. 24 episodes of adverse events occurred and were of mild intensity. **Conclusion** – A combination of Paracetamol, Phenylephrine and Levocetirizine is safe and effective in the treatment of common cold and allergic rhinitis.

**Keywords:** Paracetamol, Phenylephrine, Levocetirizine, Common Cold, Allergic Rhinitis, Total Symptom Score (TSS), Likert-type symptom severity scale.

---

### Introduction

Acute Coryza, also known as Common Cold is a major and recurrent cause of morbidity, affecting adults and children. Common cold is also one of the most frequently encountered disease in clinical practice. <sup>1</sup>Although usually benign, it accounts for substantial job absenteeism and

primary care visits. <sup>2</sup>Adults have an average of two to four episodes annually, and young children may have as many as six to eight episodes. Common cold is caused by various respiratory viruses, most commonly a rhinovirus though other viruses may be involved like respiratory syncytial

virus, coronavirus, adenovirus, influenza and parainfluenza viruses. Common Cold is accompanied by the symptoms of Fever, Headache, Bodyache, Blocked Nose, Sneezing and Running Nose.<sup>3</sup>

As per American Academy of Family Physicians, there are no effective antivirals to cure the common cold and few effective measures to prevent it (including vaccines), treatment should focus on symptom relief.<sup>3</sup> As a single drug may be inadequate to relieve all the symptoms of common cold, frequently multiple drug combinations are used to treat these varieties of the symptoms.<sup>4</sup>

Allergic Rhinitis is a symptomatic disorder of the nose induced after exposure to allergens via IgE-mediated hypersensitivity reactions, which are characterized by 4 cardinal symptoms of watery rhinorrhea, nasal obstruction, nasal itching and sneezing. Though it is not frequently encountered in clinical practice as common cold, but it still accounts for a prevalence of 10-30% in adults and nearly 40% in children, in the US. Complications of allergic rhinitis include sinusitis, otitis media (serous type), tonsillitis and pharyngitis, all of which are painful conditions.<sup>5</sup>

Paracetamol is a Non-Steroidal Anti-Inflammatory Drug and is a valuable central analgesic. It exhibits good and prompt antipyretic action also. It does not depress respiration, alter acid base balance or cause gastric irritation. Paracetamol thus may be useful in the treatment of the symptoms of common cold like - Fever, Headache and Bodyache. Phenylephrine is as efficacious and a much safer nasal decongestant. It is a selective alpha 1 -adrenergic receptor agonist. At therapeutic dosage Phenylephrine causes vasoconstriction in the nasal mucosa, relieving the nasal blockage caused due to inflammation. Thus Phenylephrine is useful in the treatment of symptoms of common cold like – BlockedNose or Nasal Congestion.<sup>6</sup> Levocetirizine is one of the most often recommended and used 2<sup>nd</sup> generation antihistaminic agents. The primary action of Levocetirizine is competitive binding to the H1 receptors of the vascular tunica medius in the

nasal mucosa to prevent the histamine vasoreactive response. The anti-histaminic action of Levocetirizine would be translated to its anti-allergic and anti-inflammatory action in the nasal mucosa. Levocetirizine being a 2<sup>nd</sup> generation antihistaminic, has lower potential to cause sedation and drowsiness as adverse effects. Levocetirizine is thus useful to control the symptoms of common cold like - Running Nose and Sneezing.<sup>7</sup>

A combination of Paracetamol, Phenylephrine and Levocetirizine is often used to treat common cold and allergic rhinitis. Such combinations are available in developed countries like US, Australia, New Zealand etc., as OTC. Cochrane has reviewed the of combination of antipyretic, decongestant and antihistaminics<sup>8</sup>, however there is dearth of clinical data available for this combination hence a Phase IV (Post-Marketing Surveillance) study was conducted to document the efficacy and safety of the combination of Paracetamol, Phenylephrine and Levocetirizine in the treatment of common cold and allergic rhinitis.

## Methodology

This Phase IV clinical study was conducted at 13ENT specialty centers in various cities of India, from October 2016 to December 2016. A total of 234 patients were recruited for the study, out of which 201 patients completed the study. 33 patients were lost to follow-up.

## Inclusion and Exclusion Criteria

This study included patients of both the gender having age between ages 18 to 75 years. Patients with confirmed diagnosis of common cold or allergic rhinitis (having 4 out of the 9 symptoms of headache, fever, bodyache, nasal congestion, rhinorrhea, sneezing, sore throat, dysphonia and malaise) present for not more than 48hours were included in the study. Only the patients who would strictly adhere to the protocol were recruited for the study.

Patients with hypersensitivity to the individual study drugs, patients having hepatic and renal impairment were excluded as Paracetamol is

present in the study drug. Hypertensives were refrained from the study as Phenylephrine which is present in the study drug can result in vasoconstriction causing increase in BP. Pregnant, Lactating Women and Psychiatric Patients were excluded from this study.

### **Study Intervention**

Study drug – An uncoated tablet containing a combination of Paracetamol 500mg + Phenylephrine 10mg + Levocetirizine 2.5mg was provided by the sponsor free of cost to the patient. Study dosage and administration – one tablet was taken 3 times in a day at 8 hourly interval after meals (Breakfast, Lunch and Dinner) with a glass of water.

### **Study procedure**

The study duration was decided to be 5 days. Patients of common cold and allergic rhinitis satisfying the inclusion and exclusion criteria were recruited for the study. A detailed medical history was taken and physical examination (including the vital signs, systemic and general examination) was conducted by the investigators. Patients were dispensed 15 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 planned for the patients recruited in this study – V0 (baseline visit) on day 1, V1 (reevaluation visit) on day 3 and V2 (conclusion visit) on day 5. Total symptom score and adverse events occurring were noted during each visit along with medical history and physical examination. Investigators were asked to discontinue the study drug in case of severe adverse event and with discretion, clinical experience in case of mild to moderate adverse events.

### **Concomitant therapy**

No Pharmacological intervention and medication including antibiotics, topical decongestants (sprays/drops and aromatic oils), multi-vitamins

and multi-minerals were allowed during the study duration, other than study drug.

Non-Pharmacological interventions like steam inhalation and drinking of warm/hot water at regular intervals were allowed and encouraged during the study duration.

### **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 asked for any adverse event and the same if present was noted in the case record form during each post-dose visit. These adverse events were classified into serious adverse events and non-serious adverse events. Naranjo's scale of probability was used to classify the adverse event as drug related or non-drug related. Adverse events were followed up by the investigators till their resolution.

### **Regulatory matters**

The study drug in combination has been approved for manufacturing and marketing in 2005 (with minor change in composition). 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.

All the patients participating in this study read and signed the informed consent form, voluntarily. The protocol, case record form,

informed consent form, investigators undertaking, investigators CV, 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. 29394.

## Results

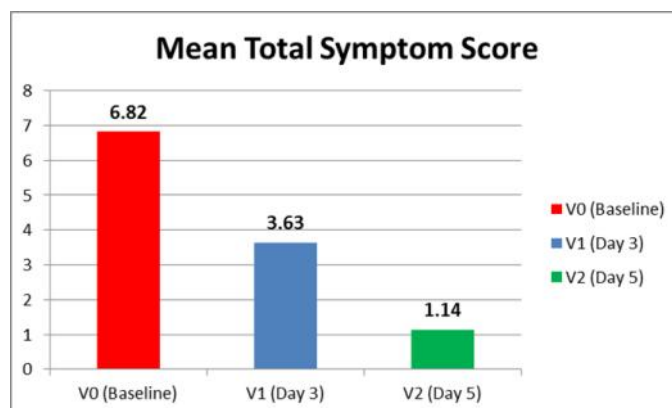
A total of 234 patients were recruited at 13 centers across India, 201 patients completed the study and were analyzed. Other demographic characteristics are in Table 1.

Mean Age of Patients (years)	39.6
Males	102 (50.75%)
Females	99 (49.25%)
Mean BMI (kg/m <sup>2</sup> )	23.71
Patients with Common Cold / Allergic Rhinitis	180/21

## Efficacy analysis

Mean of Total Symptom Score (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 6.82, which

was reduced to 3.63 at V1 or day 3 and further reduced to 1.14 on V2 or day 5 (Figure 1). The reduction in TSS corresponded with the improvement in general and physical examination of the patients.



*Figure 1 : Reduction in TSS at each visit*

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 201 patients, 86 patients had a TSS of 0 i.e. no symptoms on Likert-type symptom scale and another 39 had the TSS of 1 (Figure 2) at the end of 5 days.

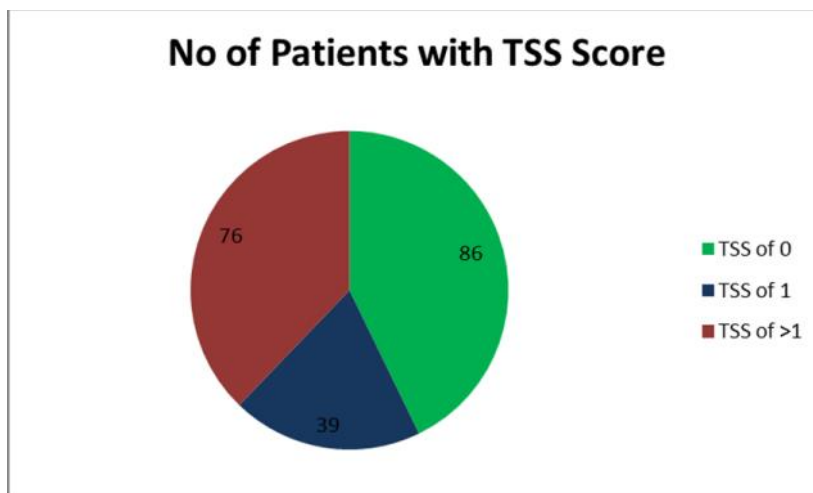


Figure 2 : No. of Patients with TSS Score

More than 50% reduction in TSS was seen in 187 patients from V0 to V1 and in 194 patients from V1 to V2.

### Safety analysis

The overall incidence of reported study drug related adverse effects was 24 seen in 21 patients. The list of adverse events with the number of episodes is mentioned in Table 2.

Adverse Events	No. of Episodes
Sedation and Drowsiness	11
Hyperacidity	8
Nausea	3
Dizziness	1
Palpitation	1
<b>Total</b>	<b>24</b>

Majority of adverse effects were study drug related with Sedation and Drowsiness dominating, 1 non-study drug related adverse event was also documented which was shoe bite (ulcer above the heel).

### Discussion

Common cold is a self-limiting disease but is responsible for significant absenteeism in schools and job. Providing symptom control would reduce the number of days missed due to common cold, hence the treatment is directed towards symptom control only.<sup>9</sup>

In author's knowledge, this is the first clinical study of the combination of Paracetamol, Phenylephrine and Levocetirizine in treatment of common cold and allergic rhinitis. Strength of this clinical study is that Total Symptom Score (TSS) is used as the parameter for efficacy assessment

and extrapolated to Likert-type symptom scale. TSS has 11 grades for symptom assessment compared to 4 with Likert-type symptom scale, making TSS more sensitive. The data of TSS is extrapolated to Likert-type symptom scale which is internationally accepted scale for common cold symptom assessment.

There was a reduction in Total Symptom Score (TSS) in all the patients in this Phase IV Post Marketing Surveillance Study. The TSS reduced from 6.82 to 3.63 in 3 first days which is a reduction of 46.77% and from 3.63 to 1.14 in the next 2 days which is a reduction of 68.59%. The overall reduction in TSS in 5 days was 83.28%. One point reduction in Likert-type symptom scale from Moderate to Mild took just 3 days with the study drug.



Majority of patients had no (TSS score of 0) to very less (TSS score of 1) at the end of 5 study days. Nearly all the patient had more than 50% reductions in symptoms at every visit.

A total of 24 (11.94%) adverse events were related to study drug. Sedation and drowsiness was a major adverse effect which can be contributed to the antihistaminic Levocetirizine present in the combination. Levocetirizine being a 2<sup>nd</sup> generation antihistaminic, it still produces sedation and drowsiness in some patients. Hyperacidity and nausea can be contributed to Paracetamol. The vital signs (Blood Pressure, Respiratory rate and Pulse rate) showed no significant change from the baseline readings which are particularly important as Phenylephrine, a vasoconstrictor is a component of the study drug.

Picon et al.<sup>10</sup>, conducted a Phase III clinical study of a combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate (different antihistaminic than the study drug in this trial) in treatment of common cold, in Brazilian population.<sup>8</sup> Efficacy and Safety of the combination were evaluated in 146 patients and were compared with placebo. The reduction of symptom score in the combination (test) arm was from baseline score of 14.09 to 3.54 at the end of 10 days study period. The reduction in placebo arm was from a baseline score of 14.23 to 4.64 at the end of 10 days. The number, type and distribution of adverse events were similar in both the groups. The study concluded that the combination of Paracetamol, Phenylephrine and Chlorpheniramine maleate is better than placebo in the treatment of common cold and flu-like syndrome in adults.

A Cochrane review<sup>8</sup> analysed 32 studies or meta-analysis of 8930 patients for the treatment of common cold, inferring that antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children in treatment of common cold. Paracetamol, Phenylephrine and Levocetirizine are mentioned in the list provided for antihistamine-analgesic-decongestant.

Eccles et al.<sup>11</sup>, suggests the rationale for combining multiple drugs in treatment of

common cold to provide relief from multiple symptoms. Further it suggests, there is no evidence that multi-symptom relief medicines are inherently 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.

The limitation of the study was common cold being a self-limiting disease, may resolve spontaneously. The cause for reduction in symptoms may not be solely attributed to the study drug. We have tried to minimize this limitation by keeping the study duration for 5 days as opposed to earlier study (with Chlorpheniramine as antihistaminic) where it was 10 days. Several papers suggest common cold resolves in about 7 days<sup>9</sup>, so the benefit offered on day 5 would be majorly due to the study drug.

## Conclusion

A combination of Paracetamol 500mg, Phenylephrine 10mg and Levocetirizine 2.5mg provides optimum symptomatic relief and is safe for the treatment of common cold. Importantly these drugs should be present at optimum dose as many combinations available in the market with Paracetamol 325mg, misleading the clinicians that the regulators have reduced the dose of Paracetamol to 325 mg in combinations. This information is incomplete, as the suggestions for dose reduction of Paracetamol to 325 mg is with respect to the combinations with other analgesic/anti-inflammatory and not for Anti-Cold combinations.<sup>12</sup>

## Acknowledgements

We would like to acknowledge Dr. T. S Choudhary (Ujjain), Dr. Bharat Soni (Khandwa), Dr. Jalil Mujawar (Solapur), Dr. Deepak Bhisegaonkar (Aurangabad), Dr. Vilas Kirdak (Aurangabad), Dr. N. Ramesh (Nanded), Dr. ReetChander Jain (Panipat), Dr. Vikas Khanna (Fatehabad), Dr. Sanjay Kumar (Patna),

Dr. Rakesh Nayan (Patna), Dr. Syed Himayatullah(Aurangabad), Dr. Preeti Sharma (Patna) and Dr. C.D. Tathe (Aurangabad) who were the co-investigators in this study.

**Disclosure:**

Dr. Mayuresh Kiran, principal investigator of this study is an employee of Centaur Pharmaceuticals Pvt. Ltd. This study was conducted as a part of Pharmacovigilance activity for Sinarest LP Tablets manufactured and marketed by Centaur Pharmaceuticals Pvt. Ltd. in accordance with Pharmacovigilance Program of India (PvPI).

**References**

1. Mossad SB, Treatment of the common cold, BMJ 1998, 317:33–36.
2. Ruth Martin Misener. Commentary on Review: a single dose of nasal decongestant reduces congestion in the short term in adults with the common cold; insufficient evidence exists on the effectiveness of repeated doses. Evidence-Based Nursing 2005; 8:12.
3. Madeline Simasek e al., Treatment of the Common Cold, American Family Physician, Volume 75, Number 4, February 15, 2007.
4. De Sutter et al., Antihistamines for the common cold, The Cochrane Library 2003, Issue 3.
5. Yang-Gi Min, The Pathophysiology, Diagnosis and Treatment of Allergic Rhinitis, Allergy Asthma Immunol Res. 2010 April;2(2):65-76.
6. Knollmann, Björn C., ed. Goodman & Gilman's the pharmacological basis of therapeutics. Vol. 12. New York: McGraw-Hill Medical, 2011.
7. Sheen-Yie Fanget al.,An Open-Label, Multicentre Study of Levocetirizine for the Treatment of Allergic Rhinitis and Urticaria in Taiwanese Patients,Chinese Journal of Physiology, 2010, 53(4): 199-207.
8. De Sutter et al., Oral antihistamine-decongestant-analgesic combinations for the common cold (Review), The Cochrane Library 2012, Issue 2.
9. Julia Fashner et al., Treatment of the Common Cold in Children and Adults American Family Physician, Volume 86, Number 2, July 2012.
10. Picon et al., Symptomatic treatment of the common cold with a fixed-dose combination of paracetamol, chlorphenamine and phenylephrine: a randomized, placebo-controlled trial BMC Infectious Diseases 2013, 13:556.
11. Eccles, R., Fietze, I. and Rose, U.-B. (2014) Rationale for Treatment of Common Cold and Flu with Multi-Ingredient Combination Products for Multi-Symptom Relief in Adults. Open Journal of Respiratory Diseases, 4, 73-82.
12. DCGI Letter 4-012012-DC, CDSCO FDC Division dated 13-09-2013.

<b>Access this Article in Online</b>	
	Website: <a href="http://www.ijcrims.com">www.ijcrims.com</a>
	Subject: Pharmaceutical Sciences
<b>Quick Response Code</b>	

[How to cite this article:](#)

Mayuresh Kiran, Lalit Pawaskar & Pramila Yadav. (2017). Efficacy and Safety of a combination of Paracetamol, Levocetirizine and Phenylephrine in the symptomatic treatment of Common Cold and Allergic Rhinitis: Phase IV Clinical study. Int. J. Curr. Res. Med. Sci. 3(1): 53-59.  
DOI: <http://dx.doi.org/10.22192/ijcrms.2017.03.01.007>