Efficacy and Safety for the Fixed-Dose Combination of Paracetamol, Phenylephrine, Chlorpheniramine Maleate, Sodium Citrate, and Menthol in Suspension for Common Cold in Pediatric Patients

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Abstract

Background: Acute upper respiratory tract infection (URTI), frequently referred to as common cold, is a self-limiting disease of the upper respiratory tract (URT). Children are more prone to viral infection because their immune systems are underdeveloped. Studies showed that a combination of analgesics, antihistamines, and decongestants is more effective than monotherapy. This clinical trial evaluated the efficacy and safety of the fixed-dose combination (FDC) of Paracetamol, Phenylephrine, Chlorpheniramine maleate, Sodium citrate, and Menthol in children suffering from common cold.

Methods: This was an open-label, non-randomized, non-comparative active post-marketing surveillance study. Children suffering from common cold between 2 and 12 years of age were included. The duration of the study was five days. The efficacy assessment parameter was the total symptom score (TSS). The patients visited the clinical trial site on the first day (baseline visit), the third day (re-evaluation visit), and the fifth day (conclusion visit).

Results: A total of 311 patients completed this study. The mean TSS on day 1 was 9.06 which was reduced to 4.79 on day 3 and further reduced to 0.19 on day 5. On day 3 and day 5, the percentage reduction in the mean TSS as compared to baseline was 47.33% and 95.56% respectively. The one-way ANOVA test results revealed that there was a statistically significant decrease ($p< 0.0001$) in TSS from the first to the fifth day. Additionally, there were no severe adverse drug reactions reported during the study, and no adverse events led to the premature discontinuation of the study. Only 20 mild adverse events were reported.

Conclusion: FDC of Paracetamol 250 mg, Phenylephrine 5 mg, Chlorpheniramine maleate 2 mg, Sodium citrate 60 mg, and Menthol 1 mg per 5 ml was efficacious and safe for the symptomatic treatment of common cold in children.

Keywords:- Paracetamol, Phenylephrine, Chlorpheniramine Maleate, Common cold, Children

Introduction

Common cold is a mild and acute URTI infection that causes symptoms such as nasal congestion, nasal discharge, sneezing, sore throat, cough, malaise, and fever.[1] Common cold is typically caused by respiratory viruses such as Rhinovirus, Influenza virus, Respiratory syncytial virus (RSV), Parainfluenza viruses (PIVs), and Human Coronaviruses (HCoVs). Among these, Rhinovirus is the most prevalent, causing 50% of common cold

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infections. The repeated occurrence of viral infection in children with weak immune systems is due to the lack of long-lasting immunity provided by these viral infections.[2] The viruses that cause common cold activate the body's innate immune system, which releases bradykinin and prostaglandins. Bradykinin affects blood vessels and nerves, causing pain, sore throat, sneezing, running nose, dilated blood vessels, and congestion. Prostaglandins cause inflammation, resulting in malaise, a low-grade fever, and headaches.[1] In infants, the infection becomes apparent only after the nasal discharge changes color. Fever is more common in preschool children and infants than in adults.[2] Influenza, and RSV, which commonly cause acute URTIs, are the most frequent causes of morbidity and mortality in infants under the age of five. If left untreated, common cold infections can spread to the lower respiratory tract and lead to complications such as bronchiolitis, pneumonia, and the exacerbation of chronic respiratory diseases like asthma, bronchitis, and chronic obstructive pulmonary disease (COPD). These complications are a leading cause of hospitalization in children.[1]

Globally, 85-88% of Acute Respiratory Infections (ARIs) are acute URTI, while the remaining are acute Lower Respiratory Tract Infections (LRTI).[3] In 2018, according to the National Health Portal of India acute URTI affected 4,19,96,260 individuals globally, and 3,740 infant deaths occurred the same year due to acute URTI.[4] Severe acute respiratory infection is a leading cause of death in the pediatric population accounting for 14.3% of infant deaths and 15.9% of deaths in young children aged between one and five years in India in 2018.[5] Persistent and recurrent cases of common cold can lead to a decline in the quality of life. In the USA, according to the ACHOO survey, 44.5% of children did not attend school for 1-2 days due to the symptoms of common cold and 57% of children had sleep disturbances due to coughing and nasal congestion.[6]

Medications for common colds are typically used for symptomatic relief. Commonly used medications include antihistamines, nasal decongestants, antipyretics, and anti-inflammatory drugs, which can be used alone or in combination to reduce common cold symptoms. Chlorpheniramine maleate is a first-generation antihistaminic drug, that acts on the H1 receptors with an anti-muscarinic action and is used in the treatment of common cold and other allergic conditions like hay fever and atopic eczema. Histamine activates the NFkB transcription factor, the main factor causing the symptoms of common cold. Antihistamines deactivate the NFkB transcription factor by an inverse agonist mechanism and exert the opposite action of the NFkB transcription factor, leading to symptomatic relief in patients suffering from common cold. Antihistamines also reduce the effects of inflammatory mediators and counteract vasodilatation, increased vascular permeability, nasal irritation, and bronchial smooth muscle contraction caused by the mediators.[7] Additionally, Paracetamol is a widely recognized nonsteroidal anti-inflammatory drug (NSAID) that is commonly used to alleviate the fever associated with common cold infections. This is achieved by inhibiting the activation of inflammatory mediators. It is a selective COX-1 inhibitor, which reduces the production of prostaglandins in the body thereby reducing the fever, and pain from sore throat.[8] Phenylephrine is a systemic, selective alpha-1 receptor agonist. It acts on the nasal mucosa, paranasal sinuses, blood vessels, and bronchial smooth muscle cells in the URT. This causes vasoconstriction of the capillaries and shrinkage of the mucosal cells, which reduces oedema and the volume of the mucous in the nasal mucosa and alleviates nasal congestion.[9] Sodium citrate is commonly used as a mucolytic agent, where it helps to thin/ loosen mucus (phlegm) and reduce the side effects of dry mouth caused by Chlorpheniramine maleate.[10] Menthol is another substance that is commonly used in medications to provide a cooling effect and is considered a potential anti-tussive agent.[11] This active post-marketing study aims to assess the safety and efficacy of an FDC of Paracetamol, Phenylephrine, Chlorpheniramine maleate, Sodium citrate, and Menthol in a suspension form for Indian children with common cold.

Methodology

The study was a non-randomized, open-label, non-comparative active post-marketing surveillance study. It was conducted at seven paediatric special clinical trial sites across Mumbai, Raipur, Belgaum, and Patna. A total of 420 patients were recruited in this study, 60 children at each site. The duration of the study was 5 days. The inclusion criteria were paediatric patients suffering from common cold symptoms. The age of paediatric patients selected was between 2 to 12 years. These patients weighed between 6-40 kg. The inclusion of both genders was accepted. The guardians of the patients had to adhere to the protocol. Patients who were hypersensitive to a single drug or a combination of Paracetamol, Phenylephrine, Chlorpheniramine maleate, Sodium citrate, and Menthol were excluded

from the clinical trial. The patients who were clinically diagnosed with severe hepatic and renal dysfunction were also excluded from the study. The investigational product used in the trial was the FDC for Paracetamol 250 mg, Phenylephrine 5 mg, Chlorpheniramine maleate 2 mg, Sodium citrate 60 mg, and Menthol 1 mg per 5 ml suspension. The patient's guardians were instructed to provide the investigational product to the patient in the dosage advised by the investigator. The investigator, the clinical trial team, and the patient's guardians were aware of the contents of the investigational product and the study procedure as this was an open-label trial.

The patients were selected as per the inclusion and exclusion criteria and the study procedure was explained to the patients and their guardians and consent of the guardians was taken. The consent was obtained before the enrolment of the patient. On the first visit (day 1) all the patients enrolled underwent a complete clinical examination after providing a comprehensive medical history. Patients were asked to visit the clinical trial site on days 3 and 5 considering day 1 as baseline visit. The patient's guardians were instructed to record daily symptoms in a diary. The investigator was permitted to choose whether to withdraw the patient from the research and treat them on the severity of the symptoms in the event of any safety-related problems, adverse events, or serious adverse events. In this 5-day active post-marketing surveillance study for the treatment of common cold, patients' guardians were asked not to administer any pharmacological medication other than the investigational product to their child for their common cold symptoms. Saltwater gargling, steam inhalation, and other home remedies were allowed during the study.

The efficacy was assessed using the TSS, which was evaluated on an 11-point Likert scale. The symptoms of common cold like fever, rhinorrhea, sneezing, headache, body aches, and a running or blocked nose were recorded on the scale. The patient, with the help of their guardian, was instructed to rate the symptoms they experienced on a scale of 0 to 10. The higher the score the worse the intensity of the symptoms. A score of 0 indicated no symptoms of common cold, 1 to 3 indicated mild intensity, 4 to 6 indicated moderate intensity, and 7 to 10 indicated severe intensity symptoms of common cold. A safety assessment was made based on adverse events reported by the guardian of the patient to the investigator at the 2nd and 3rd visits (post-dose visits). A causality assessment for all the adverse events was made using the World Health Organization Uppsala Monitoring Centre (UMC) scale. The investigators were asked to provide complete medical treatment in the event of any adverse event for the patient. This active post-marketing surveillance study was conducted in compliance with the "New Drugs and Clinical Trial Rules 2019", "National Ethical Guidelines for Biomedical and Health Research involving Human Participants", "Good Clinical Practices Guidelines" and other applicable guidelines.

This clinical trial was registered with both the Indian regulatory authority, the Central Drugs Standard Control Organization (CDSCO), and the Clinical Trials Registry of India (CTRI), with the registration number provided CTRI/2021/11/037910. Additionally, ethics committee approval has been obtained from all the local ethics committees which are within a 50 km radius of each trial site.

Results

Out of the 420 patients recruited at 7 clinical trial sites, 311 patients completed the study. 109 patients were lost to follow-up. The efficacy parameter was the TSS obtained on the 11-point scale. The mean score was calculated at each visit. The mean score at baseline (visit 1) was 9.06. At visit 2 and visit 3 the score was 4.79 and 0.19 respectively. The mean TSS score showed a drastic reduction which indicated that the symptoms improved with the investigational product. The percentage reduction in the mean TSS on visit 2 was 47.33% and 95.56% on visit 3 as compared to baseline. The graphical representation of the mean TSS and percentage reduction of the mean TSS as compared to the baseline is given below in Figure 1 (A) and Figure

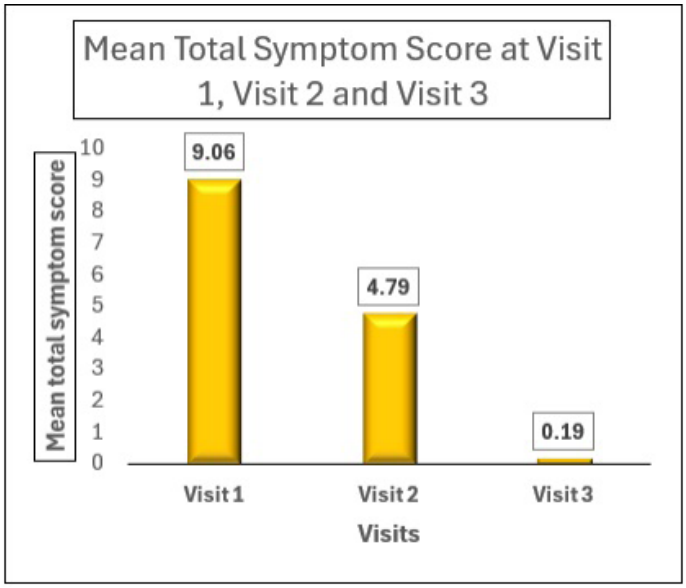

Figure 1 (A): Mean TSS at visit 1 (day 1), 2 (day 3), and 3 (day 5)

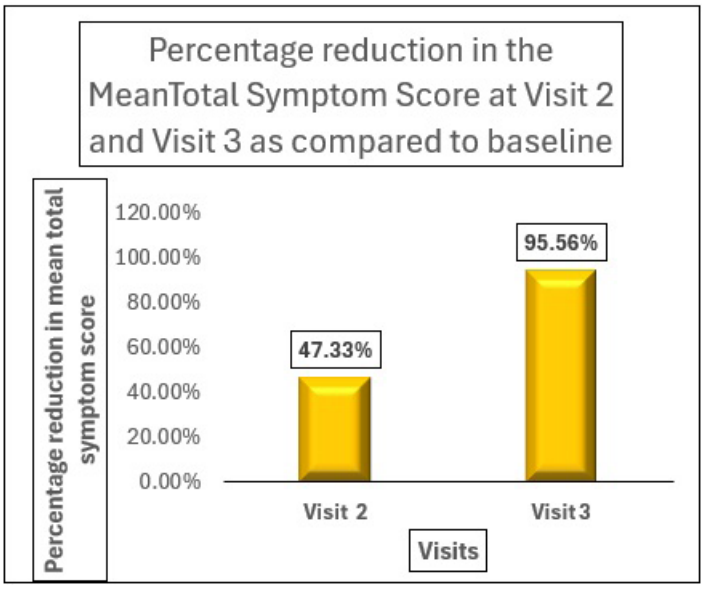

Figure 1 (B): Percentage reduction in mean TSS compared to baseline at visits 2 and 3

1 (B). The outcomes of the one-way ANOVA analysis showed a statistically significant decrease ($p < 0.0001$) in the TSS score from the first to the third visit.

The total number of patients with no symptoms, mild, moderate, and severe intensity symptoms according to the Likert-type symptom severity scale at each visit was calculated and is given in the Table 1

Table 1: Total Patients with their TSS at each visit.

Visit	Total symptom score	Total patients
Visit 1	0 (no symptoms)	0 (0%)
	1 to 3 (mild symptom)	0 (0%)
	4 to 6 (moderate symptoms)	6 (1.93%)
	7 to 10 (severe symptoms)	305 (98.07%)
Visit 2	0 (no symptom)	1 (0.33%)
	1 to 3 (mild symptoms)	34 (10.93%)
	4 to 6 (moderate symptoms)	269 (86.49%)
	7 to 10 (severe symptoms)	7 (2.25%)
Visit 3	0 (no symptom)	261 (83.92%)
	1 to 3 (mild symptoms)	48 (15.43%)
	4 to 6 (moderate symptoms)	2 (0.65%)
	7 to 10 (severe symptoms)	0 (0%)

305 patients out of the 311 had a score of 7 to 10 (severe intensity) on the symptom scale and only 6 patients had a score of 4 to 6 indicating moderate intensity. Over 5 days the intensity of the symptoms reduced. On visit 2 the number of patients having severe intensity reduced to 7 and the 269 patients had moderate intensity symptoms. 34 patients had mild intensity symptoms on visit 2 and one patient was completely symptom free. On visit 3, no patients had severe symptoms. Only 2 patients had moderate-intensity symptoms, 48 had mild-intensity symptoms and 261 were completely cured of the symptoms of common cold.

12 out of 20 guardians reported that their children were excessively drowsy while taking the investigational product, and one guardian mentioned that their child's sleep duration had increased. In addition, six guardians reported that their child experienced vomiting as a side effect. Furthermore, one guardian stated that their child had difficulty concentrating on their studies while taking the investigational product. The list of adverse events is mentioned in Table no 2.

Table 2: Summary of reported Adverse events:

All Adverse events (AEs)	No. of cases	Percentage of patients	Intensity of adverse events
Drowsiness	12	60%	Mild
Sedation	1	5%	Mild
Vomiting	6	30%	Mild
Difficulty in concentration	1	5%	Mild
Serious AEs	0	0	-
AEs leading to discontinuation	0	0	-
AEs leading to Death	0	0	-

Discussion

Common cold, caused by respiratory viruses, can lead to secondary bacterial infections, especially in children with weakened immunity.[12] Prolonged symptoms can increase the risk of serious conditions like bacterial pneumonia, sinusitis, and otitis media, contributing significantly to infant mortality.[2] Based on a systematic analysis conducted by Li Liu et al.,

bacterial pneumonia, which is a type of LRTI that can arise from a secondary bacterial infection of URT, has emerged as a major contributor to infant mortality. This condition is responsible for 18.7% of fatalities among children under the age of five, placing it second only to preterm birth complications.[13] Therefore, rapid symptomatic treatment of common cold symptoms in infants and young children is essential to prevent secondary bacterial infection. Although research on treating common colds in children is relatively limited, it is an important area of focus for improving pediatric health outcomes.

This study was done in pediatric patients between the age of 2-12 years to evaluate the efficacy of FDC of Paracetamol, Phenylephrine, Chlorpheniramine maleate, Sodium citrate, and Menthol suspension. The study measured the TSS on an 11-point scale across three visits. The mean TSS score at baseline (visit 1) was 9.06 and it reduced to 4.79 and 0.19 at visit 2 and visit 3 respectively. The percentage reduction in the TSS score as compared to baseline was 47.33% on visit 2 and 95.56% on visit 3. Symptom intensity also decreased over visits, with no patients experiencing severe symptoms by visit 3. Results of the one-way-ANOVA method showed that there was a statistically significant reduction in the TSS at visit 3 as compared to visit 1. Some patients reported non-serious adverse events like drowsiness and vomiting, possibly due to Chlorpheniramine maleate and Paracetamol. These findings align with similar studies, suggesting the efficacy of the investigated product in managing common cold symptoms in children. Below we have discussed a few studies that were similar to the study we have conducted.

De Sutter et al., from the Cochrane Acute Respiratory Infections Group, published a review article that evaluated the effects of antihistamines, decongestants, and pain relievers on patients with common cold. This was updated in the year 2021. They evaluated 30 studies from 2012 to 2021, involving 6304 participants. These studies tested four combinations of treatments which are, antihistamines and decongestants, antihistamines and pain relievers, pain relievers and decongestants, and a combination of all three. The trials included different antihistamines like Chlorpheniramine and decongestants like Phenylephrine. Adults and older children experienced relief from common cold symptoms with these treatments, but there wasn't enough evidence for their effectiveness in younger children. Common side effects included dizziness and dry mouth, which may be due to the first-generation antihistamines. Overall, these combinations could help alleviate common cold symptoms in adults and children. According to the results, they concluded that these combinations may be beneficial in reducing the symptoms of common cold, but there was no significant evidence for the effectiveness of the following combinations in younger children.[14]

A randomized, double-blind, placebo-controlled clinical trial conducted by Picon et al. supports the efficacy of FDC therapy in treating common cold and flu-like syndrome in adults aged 18-60 years. They enrolled 146 patients, dividing them randomly into two groups: one receiving the treatment and the other receiving a placebo. The patients rated their symptoms on a scale from mild to severe. Both groups were allowed to use additional medication if needed. Results showed that the treatment group had a significant decrease in symptoms compared to the placebo group. It was also observed that the usage of rescue medication was notably higher in the placebo group compared to the treatment group. This indicates that the FDC therapy effectively relieved symptoms without the need for any additional rescue medication. The study concluded that this combination was safe and effective for treating cold and flu symptoms in adults.[15]

Kiran M et al, conducted a clinical trial to evaluate the efficacy and safety of an FDC of Phenylephrine hydrochloride, Paracetamol, Chlorpheniramine maleate, Sodium Citrate, and Menthol in children with common cold. This non-randomized, non-comparative clinical trial took place at 12 pediatric specialty sites across India. Children aged 2 to 12 years, weighing between 6 to 39.9 kg, with at least 4 out of 9 common cold symptoms were included. Patients with certain allergies or medical conditions were excluded. 200 patients participated, receiving treatment for 5 days with evaluations on day 3 and day 5. The TSS assessed efficacy, with 174 patients completing the study. Results showed a reduction in TSS from baseline at both visits, indicating symptom improvement. The authors concluded that the combination was beneficial for treating common cold symptoms. While no serious adverse events were reported, some patients experienced mild side effects such as drowsiness and vomiting.[16]

Kiran M et al. conducted a post-marketing surveillance (PMS) study to assess the efficacy and safety of the combination of Paracetamol, Phenylephrine, Chlorpheniramine maleate, Sodium

Citrate, and Menthol for the treatment of common cold. Out of 200 enrolled patients, 182 completed the study. Efficacy was evaluated by measuring TSS and then it was further extrapolated to a four-point Likert-type symptom severity scale. Initially, at baseline, the mean TSS was 5.703 which decreased to 3.335 on day 3 and further reduced to 0.802 on day 5. Reductions in mean TSS compared to baseline were 41.522% on day 3 and 85.934% on day 5. Only 6 non-serious adverse drug reactions were reported during the study. The trial concluded that the FDC Of Paracetamol 250 mg, Phenylephrine 2 mg, Chlorpheniramine Maleate 2 mg, Sodium Citrate 60 mg, and Menthol 1 mg per 5ml was effective and safe for symptomatic treatment of the common cold in Indian patients aged 2 to 12 years.[17]

The study design may have a potential limitation. Notably, the investigational product utilized in this study was not evaluated in comparison to a control group comprised of a placebo or another medication. Therefore, future research may be required to include randomized, placebo-controlled studies to assess the efficacy of the FDC of Paracetamol, Phenylephrine, Chlorpheniramine Maleate, Sodium Citrate, and Menthol for the treatment of common cold symptoms.

Conclusion

Pharmacological treatment is mostly given for relief from the symptoms of common cold as the disease itself is self-limiting. Accordingly, this study has shown that the investigational product, which was an FDC of Paracetamol 250 mg, Phenylephrine 5 mg, Chlorpheniramine maleate 2 mg, Sodium citrate 60 mg, and Menthol 1 mg per 5 ml suspension, was found to be both efficacious and safe for the symptomatic treatment of the common cold in paediatric patients.

Disclosure

Dr. Manoj Patil (Karnataka), Dr. Hemraj Ingale (Maharashtra), Dr. Avinash Gawali (Maharashtra), Dr. Vikas More (Maharashtra), Dr. Navindra Kumar (Bihar), Dr. K. P. Sarabhai (Chhattisgarh) and Dr. Sadanand Shetye (Maharashtra) were investigators for the conduct of the study. The study was conducted in compliance with all the applicable regulatory guidelines. The investigational product used in the study is available in the Indian market under the brand name Sinarest Plus Suspension, which is the FDC of Paracetamol 250 mg, Phenylephrine 5 mg, Chlorpheniramine maleate 2 mg, Sodium citrate 60 mg, and Menthol 1 mg.

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