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Original Research Paper

Efficacy and Safety of the combination of Paracetamol, Phenylephrine, and Chlorpheniramine Maleate for the treatment of common cold in Indian infants.

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ABSTRACT:
Background: On an average, infants in India experience 6 to 8 episodes of the common cold per year. Numerous studies suggest that combination therapy, which includes antihistamines, decongestants, and analgesics, is more effective in treating the common cold compared to single-drug therapy. This study aimed to assess the efficacy and safety of the fixed-dose combination (FDC) of Paracetamol, Phenylephrine, and Chlorpheniramine maleate in Indian infants suffering from common cold. **Methods**: A total of 415 infants were enrolled in this study. They received the investigational product, which was an FDC containing Paracetamol (125 mg), Phenylephrine (2.5 mg), and Chlorpheniramine maleate (1 mg) per 1 ml administered in the form of oral drops. The efficacy parameter was calculated using total symptom score (TSS). The total duration of the study was 5 days with three planned visits (visit 1 on day 1, visit 2 on day 3 and visit 3 on day 5). A change in TSS from day 1 to day 5 was analysed. The safety profile was assessed by monitoring and recording adverse events throughout the study period. **Results**: 338 infants completed the study. The mean TSS on day 1 was 8.95, which was decreased to 4.97 on day 3 and further dropped to 0.21 on day 5. This reflects a remarkable 97.59% reduction in TSS compared to baseline ($P < 0.0001$). Notably, by the end of the five days, 279 out of 338 patients (82.54%) were completely free from common cold symptoms. Also, no serious adverse events were reported during this active post-marketing surveillance study. **Conclusion**: The FDC of Paracetamol, Phenylephrine, and Chlorpheniramine maleate oral drops in infants was effective and safe for alleviating common cold symptoms in Indian infants.

Keywords: Paracetamol, Phenylephrine, Chlorpheniramine maleate, and Common Cold.

INTRODUCTION:

The National Institute for Health and Care Excellence (NICE) defines the common cold as a mild, self-limiting upper respiratory tract infection (URTI) characterized by symptoms such as nasal stuffiness, nasal discharge, sneezing, sore throat, and cough. Rhinovirus is identified as the most prevalent virus responsible for causing the common cold.[1] According to a report by the National Health Portal of India, acute URTI affected a staggering 4,19,96,260 individuals in 2018 alone.[2]

The recent National Family Health Survey-5, conducted between 2019 and 2021, revealed that approximately 2.8% of infants under the age of five were impacted by acute respiratory tract infections.[3] Furthermore, severe acute respiratory infection (SARI) poses a significant threat, contributing to mortality rates in children under five years. In India, it accounts for 14.3% of infant deaths and 15.9% of deaths among young children aged between 1 to 5 years.[4] Infants commonly exhibit symptoms such as fever, sneezing, runny nose, nasal congestion, persistent crying, and coughing when affected by common cold.[5]

The common cold can progress to the lower respiratory tract, and pave the way for secondary bacterial infections, potentially resulting in bronchiolitis, sinusitis, pneumonia, and exacerbation of asthma, especially in infants. Severe cases may require hospitalization, raising the risk of mortality among infants.[5] Thus, early intervention becomes crucial for providing relief from common cold symptoms, particularly in infants and young children.

Given the diverse range of symptoms associated with the condition, a multifaceted approach is often

necessary. This involves combining various medications into a single formulation to address different symptoms of the common cold. Antihistamines, for instance, target symptoms such as sneezing, irritation, and watery rhinorrhoea. Chlorpheniramine maleate is a first-generation, systemic antihistamine that binds to H1 receptors, preventing histamine from attaching to its receptor site and alleviating associated symptoms. Additionally, it has an anti-muscarinic action.[6] Further decongestants work to relieve nasal stuffiness.[7] Sympathomimetic decongestants such as Phenylephrine bind to the alpha-1 adrenergic receptor present on the smooth muscle cells of the blood vessels of the nasal mucosa. The release of norepinephrine causes vasoconstriction, leading to the reduction of nasal mucosal oedema.[8] Additionally, analgesics are employed to mitigate sore throat discomfort. Paracetamol is an antipyretic and non-steroidal anti-inflammatory drug (NSAID) commonly used to reduce mild to moderate fever and sore throat pain.[9] Hence, the combination of antihistamines, decongestants, and analgesics can offer a comprehensive approach and provide relief from the array of symptoms commonly experienced during a common cold. Furthermore, according to De Sutter et al., combination therapy with antihistamines, decongestants, and analgesics is more efficacious in reducing symptoms of common cold than monotherapy with any one of these drugs.[10] However, there remains a dearth of clinical trials evaluating their efficacy and safety, especially in Indian infants. Therefore, this study aimed to evaluate the efficacy and safety of an FDC of Paracetamol, Phenylephrine, and Chlorpheniramine maleate in Indian infants with common cold.

METHODOLOGY:

This was an active post-marketing surveillance investigation carried out across seven distinguished clinical trial sites throughout India, encompassing paediatric hospitals and outpatient departments (OPDs) specialized in paediatric care in regions including Maharashtra, Karnataka, Chhattisgarh, and Bihar. 415 infants were enrolled in this study, all of whom underwent a five-day treatment regimen. The inclusion criteria for enrolment encompassed infants presenting symptoms commonly associated with the common cold, such as fever, sneezing, rhinorrhoea, nasal obstruction, continuous crying, and coughing. Additionally, infants were required to weigh between 2.5 to 11.8 kg and be aged up to one year. Before the commencement of the study, thorough explanations regarding the treatment and study protocols were provided to the parents or legal guardians of the patients. By ethical standards and recognizing the patients' age, explicit consent was obtained from the parents or guardians, given that the enrolled individuals were under one year of age. The parents or guardians were required to adhere to the study protocol for five days. Patients who were hypersensitive to Paracetamol, Phenylephrine, and Chlorpheniramine maleate, and/or had hepatic or renal dysfunction were excluded from the study.

The investigational product utilized in this study was FDC of Paracetamol (125 mg), Phenylephrine (2.5 mg), and Chlorpheniramine maleate (1 mg) per 1 ml administered in the form of oral drops. This FDC has received approval from the Indian Regulatory Authority (CDSCO) for the symptomatic treatment of the common cold.[11] During the study period, infants received the FDC orally, administered by their parents or guardians. The dosage administered was as prescribed by the investigator or as indicated in Table 1 for five days.

Table 1. Dose as per weight and age of the infant.

Weight in Kg	Age in months	Dose
2.5 – 9.7 kg	1-6 months	0.2 ml tid
6.7 – 11.8 kg	7-12 months	0.2 – 0.4 ml tid

Infants, accompanied by their parents or guardians, were scheduled for visits to the clinical trial site on three specific days: the first day for initial assessment, the third day for a re-evaluation visit, and the fifth day for the conclusion visit. A comprehensive medical history was obtained from the parents or guardians, followed by a thorough clinical examination of all enrolled patients on the first visit (day 1). During subsequent visits, the efficacy and safety of the investigational product were carefully assessed. Parents or guardians were instructed to diligently record the patient's symptoms daily for the analysis of adverse events. The investigator had the authority to adjust treatment based on the severity of symptoms and could withdraw patients from the study in the event of safety concerns or serious adverse events. Throughout the five-day active post-marketing surveillance study for the treatment of common cold, parents or guardians were advised against administering any other pharmacological medications to their children.

The efficacy assessment was done by analysing the reduction in TSS which encompassed the score of all symptoms associated with common cold, rated on an eleven-point scale ranging from 0 to 10, where 0 is no symptom and 10 means maximum tolerated symptoms. The TSS scale was further extrapolated to the Likert-type symptom severity scale consisting of four grades: 0 indicated no symptoms, 1 to 3 represented mild symptoms, 4 to 6 denoted moderate symptoms, and 7 to 10 indicated severe symptoms. Parents or guardians were responsible for scoring the intensity of various common cold symptoms for their infants, including fever, sneezing, runny nose, nasal congestion, persistent crying, and coughing. The mean TSS was calculated for efficacy evaluation at the first, second,

and third visits. Furthermore, at the second and third visits, the percentage reduction in the mean TSS was computed relative to the baseline. In addition to mean TSS calculation, the total number of patients exhibiting no, mild, moderate, and severe symptoms was assessed at each visit.

Following the reports of adverse events by the patient's parent or guardian during the second and third visits, a thorough safety assessment was conducted. The causality of each adverse event was meticulously evaluated utilizing the World Health Organization Uppsala Monitoring Centre (UMC) scale. In instances where patients experienced adverse events, investigators were directed to administer comprehensive medical care to the affected individuals.

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/2021/11/037913. 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:

In this study, 415 patients were enrolled, out of which 338 completed the study, while 77 were lost to follow-up. The mean TSS score on day 1 (baseline) was 8.95 which reduced to 4.97 on day 3 and further reduced to 0.21 on day 5. The percentage reduction in mean TSS on day 3 was 44.47%, and 97.59% on day 5 when compared to the baseline. In Figure 1 (A) below, the mean TSS on day 1, day 3, and day 5 is graphically presented whereas, in Figure 1 (B), the percentage reduction in the mean TSS on day 3, and day 5 compared to baseline is graphically presented.

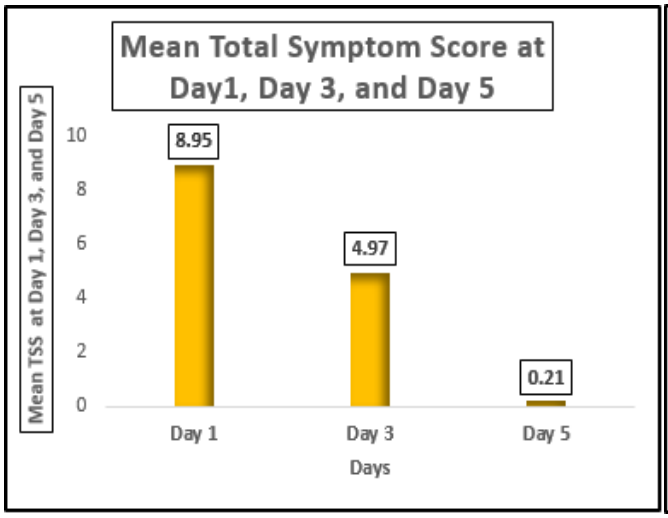

Fig 1 (A)

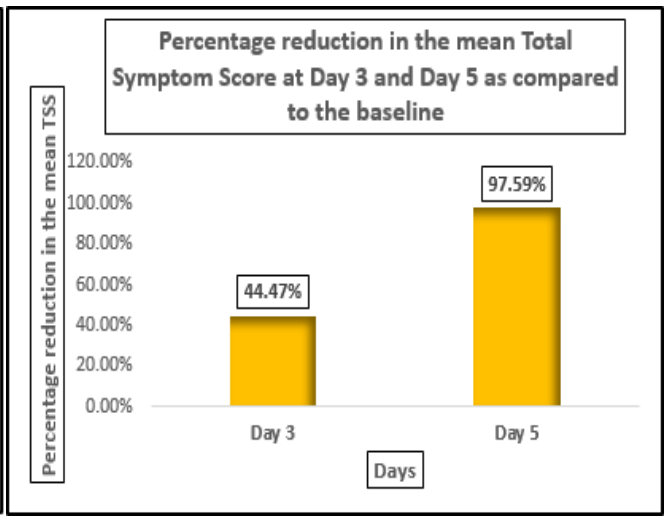

Fig 1 (B)

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

Fig. 1 (B): Percentage reduction in mean total symptom score as compared to baseline at visit 2 (day 3) and 3 (day 5).

On the first day, 329 (97.36 %) patients had severe intensity symptoms, 9 (2.66 %) patients had moderate intensity symptoms, and none of the patients had mild intensity symptoms. On the third day, 11 (3.25 %) patients had severe intensity symptoms, 279 (82.54 %) patients had moderate intensity symptoms, and 48 (14.20%) patients had mild intensity symptoms. On the fifth day, no patients had severe or moderate intensity symptoms, 59 (17.46 %) patients had mild intensity symptoms, and 279 (82.54 %) had no symptoms of common cold.

Five infants experienced mild adverse events, as reported by their parents or guardians. These included drowsiness, sedation, and vomiting. After giving their infants the investigational product, four out of the five parents reported excessive drowsiness and sedation, whereas one parent reported vomiting episodes in their child. Medical management was not required for any of the adverse events.

DISCUSSION:

The current study aimed to assess the efficacy and safety of a FDC of Paracetamol (125 mg), Phenylephrine (2.5 mg), and Chlorpheniramine maleate (1 mg) oral drops in infants suffering from common cold in India. The dosage of FDC administered was as prescribed by the investigator or as indicated in Table 1 for five days. Our findings revealed a significant reduction in TSS from day 1 to day 5 of the treatment ($P<0.0001$). On day 1, the mean TSS was 8.95, which was reduced to 4.97 on day 3 and

further decreased to 0.21 on day 5. The percentage reduction in the mean TSS when compared to the baseline on day 3 was 44.47%, and on day 5, it was 97.59%. Notably, 82.54% of patients achieved TSS score of 0 on the day 5, indicating that 279 infants got complete relief from common cold symptoms. According to the safety outcomes, the FDC oral drops appear to be well-tolerated and safe for use, as only five patients experienced mild-intensity adverse events such as drowsiness, sedation, and vomiting.

Evidence from 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. In this study, the FDC comprised Paracetamol (400mg), Chlorpheniramine maleate (4mg), and Phenylephrine (4mg). 138 adults with moderate to severe flu-like symptoms or a common cold were enrolled, and the duration of treatment was 10 days. The mean TSS in the treatment group decreased from 14.09 at baseline to 3.54 by the end of the study, whereas in the placebo group, it decreased from 14.23 to 4.64 over the same period. Importantly, the treatment group exhibited a significantly greater reduction in overall symptom scores compared to the placebo group ($p=0.015$). Notably, both groups were provided with rescue medication (500 mg Paracetamol), and it was observed that the usage of rescue medication was notably higher in the placebo group (50.7%) compared to the treatment group (25%). This indicates that the FDC therapy effectively relieved symptoms without the need for additional rescue medication, further supporting its efficacy in managing common cold and flu-like symptoms in adults.[12]

A phase IV clinical trial was conducted by Kiran et al., assessing the efficacy and safety of a combination medication containing Chlorpheniramine maleate (1 mg) and Phenylephrine hydrochloride (2.5 mg) for treating infants with the common cold in India. This trial involved infants aged 1 to 12 months, with a similar weight range, and took place across various paediatric hospitals and outpatient departments in India. Out of 215 patients enrolled, 177 completed the trial. Over the five-day duration of the trial, there was a significant reduction in TSS from the baseline, with 82.54% of patients achieving complete relief from symptoms by the conclusion of the trial. Adverse events were reported in 27 patients, primarily consisting of mild symptoms such as sedation and dry mouth. The findings from this study align closely with our own, suggesting that the combination of Chlorpheniramine maleate and Phenylephrine Hydrochloride is effective in treating common cold symptoms in Indian paediatric patients.[13]

In another study conducted by Kiran et al., a comparable investigational product was evaluated, focusing on the efficacy and safety of FDC in syrup form. This combination consisted of Paracetamol 125 mg, Phenylephrine 5 mg, Chlorpheniramine maleate 1 mg, and Sodium Citrate 60 mg per 5 ml. The study enrolled children aged between 2-12-years exhibiting symptoms of the common cold. Out of the 400 patients recruited, 336 completed the study. Efficacy was assessed using the TSS, an 11-point scale indicating symptom severity. The mean TSS at baseline was 6.41, which decreased to 2.65 on day 3 and further to 0.47 on day 5. Percentage reductions from baseline on day 3 and day 5 were 58.56% and 92.66%, respectively. Adverse events were reported in 12 patients during the study, all of which were non-serious and did not require any medical intervention. The study concluded that the FDC of Paracetamol, Phenylephrine, and Chlorpheniramine maleate is both effective and safe for treating the common cold in patients aged 2 to 12 years.[14]

Our study provides robust evidence supporting the efficacy and safety of the FDC of Paracetamol, Phenylephrine, and Chlorpheniramine maleate oral drops for the management of common cold symptoms in infants. Moreover, our findings align with previous studies, reinforcing the effectiveness of FDC therapy in paediatric and adult populations. However, more research is warranted to explore its efficacy and potential side effects in the larger cohort of Indian infants with common cold.

CONCLUSION:

Common cold is typically a self-resolving illness that typically subsides within a week, and only symptomatic treatment is generally necessary. This active post-marketing surveillance study demonstrates that the FDC of Paracetamol, Phenylephrine, and Chlorpheniramine maleate oral drops is highly effective in alleviating common cold symptoms in Indian infants. With a significant reduction in TSS and a high percentage of patients achieving complete relief, the FDC proves to be a valuable therapeutic option. Importantly, the safety profile of the FDC remains favourable, with few mild adverse events reported. These findings highlight the importance of FDC of Paracetamol, Phenylephrine, and Chlorpheniramine maleate oral drops in addressing the burden of common cold among infants in India.

DISCLOSURE:

The investigational product used in the study is available in the Indian market under the brand name of ‘Sinarest Oral Drops’ which is the FDC of Paracetamol (125 mg), Phenylephrine (2.5 mg), and Chlorpheniramine maleate (1 mg) per 1 ml. This study was conducted in compliance with the “New Drugs and Clinical Trial Rules 2019” and other applicable regulatory guidelines. 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.

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