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Original Research Article

Efficacy and safety of paracetamol, phenylephrine, chlorpheniramine maleate and sodium citrate in Indian paediatric patients with common cold: an active post-marketing surveillance study

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ABSTRACT

Background: The common cold, mainly caused by viruses, brings discomfort to children with symptoms like sneezing, congestion, runny nose, and sore throat. As no specific antiviral treatments are available to relieve common cold symptoms, it is typically managed using decongestants, antihistamines, and antipyretics. This study aims to assess the safety and efficacy of a fixed-dose combination (FDC) of paracetamol, phenylephrine, chlorpheniramine maleate and sodium citrate in children aged 2 to 12 years with common cold.
Methods: This non-randomized, open-label, non-comparative, active post-marketing surveillance (PMS) study was conducted across multiple centres in India, involving 417 patients. The study assessed efficacy using the total symptom score (TSS) scale over 5 days with visits on days 1, 3, and 5. Safety was evaluated based on adverse events reported by patients on days 3 and 5 of the trial.
Results: Initially, 417 patients were enrolled in the active PMS, of which 309 completed the study. The mean TSS showed a notable decrease from 8.95 at visit 1 to 0.19 at visit 3, depicting a significant reduction i.e., 97.90% as compared to baseline. At visit 1, most patients (95.79%) exhibited severe symptoms, whereas by visit 3, 83.82% were symptom-free, with only 16.18% experiencing mild symptoms.
Conclusions: This active PMS study examined the safety and efficacy of an FDC of paracetamol, phenylephrine, chlorpheniramine maleate and sodium citrate in treating common cold in children in India. The findings indicate a significant reduction in symptoms, with many patients becoming symptom-free by the third visit, demonstrating its efficacy and safety.

Keywords: Paracetamol, Phenylephrine, Chlorpheniramine maleate, Sodium citrate, Common cold

INTRODUCTION

Common cold is an acute, self-limiting viral infection affecting the upper respiratory tract, encompassing the nose, sinuses, pharynx, and larynx.[1] Over 200 viruses can incite a cold, with rhinoviruses being the most prevalent. It is clinically represented by the symptoms of acute respiratory viral infections (ARVI) such as rhinorrhoea, nasal obstruction, nasal congestion, runny nose, and sneezing.[2-4] Adults typically get 2-3 upper respiratory tract infections (URTIs) per year, whereas children have 6-7 episodes per year, thus it is an important problem in paediatric practice.[5] Symptoms of the common cold in children typically reach peak intensity shortly after the onset of illness. Symptom duration is approximately 7-10 days but may range from 2-14 days.[6] The severity and type

of symptoms vary depending on the immune status of the patient and the pathogen causing the infection.[5]

The occurrence of ARVI in children is linked to various factors, including children's demographics, their parents' socioeconomic status, their place of residence, and the household environment in which they are raised. There is a notable increase in acute respiratory infection (ARI) episodes among young children who are anaemic or have low birth weight. Northern Indian states like Jammu and Kashmir (6.4%), Uttarakhand (4.9%), Uttar Pradesh (4.7%), and Punjab (4.6%) have higher rates of ARVI among children, while West Bengal (3.3%) in the east and Meghalaya (5.8%) in the northeast also show elevated prevalence. Southern and western regions, like Tamil Nadu, generally have lower ARI rates.[7]

Although, common cold is generally a mild and self-resolving viral illness, approximately 400,000 children under the age of five lose their lives due to ARI-related illnesses each year in India.[7] Furthermore, common cold are one of the most frequent reasons for missed school and work. Therefore, common cold is a highly prevalent condition, especially among children and may be debilitating, highlighting the importance of effective management strategies.[1]

Management of the common cold primarily involves maintaining personal hygiene and addressing symptoms since there are no antiviral medications available.[8] Symptomatic relief can be achieved through over the counter (OTC) medications. Commonly used OTC cough and cold medications contain a combination of decongestants, cough suppressants, antihistamines, expectorants, and antipyretics. Symptomatic treatment in adults often includes a combination of analgesics, antihistamines, and decongestants.[9] Decongestants work by producing vasoconstriction within the respiratory mucosa, reducing swelling and congestion, while antihistamines block the action of histamine, decreasing congestion and other allergic responses. Some multi-symptom cold formulas contain Paracetamol as an antipyretic and analgesic.[10] Research suggests that a combination of analgesics, decongestants, and antihistamines can provide multi-symptom relief in common cold. Picon et al and Eccles et al demonstrated that a combination of analgesics, decongestants and antihistamines provides benefits for multi-symptom relief in common cold and allergic rhinitis.[11,12] Furthermore, Michael et al suggest a modest yet statistically significant improvement in global symptoms when antihistamines are combined with decongestants or analgesics, or both.[1] Incorporating sodium citrate into a combination of antihistamines, analgesics, and decongestants, serves as an expectorant that enhances the salivary mucous. This addition effectively addresses the dry mouth side effect caused by chlorpheniramine maleate, while simultaneously offering soothing relief to irritated mucous membranes in the pharynx. However, there is a lack of data on the efficacy and safety of this combination specifically in paediatric patients with the common cold. Therefore, this study was conducted to examine the efficacy and safety of the combination of paracetamol, phenylephrine, chlorpheniramine maleate and sodium citrate in treating common cold in Indian paediatric patients.

METHODS

Study design and sample size

This was a multicentre, non-randomized, open-label, non-comparative, active PMS study involving children with common cold symptoms. This study was carried out during the rainy and cold months of June 2022 to August 2022 across four regions in India: The Eastern zone (Bihar), the Central zone (Chhattisgarh), the Southern zone (Karnataka), and the Western zone (Maharashtra). For our study, 417 children were selected from seven paediatric specialist hospitals and outpatient departments located in the specified regions of India.

The central drugs standard control organization (CDSCO) suggests a sample size exceeding 200 patients for clinical trials. Our study referenced a phase III clinical trial conducted by Picon et al which employed a comparable combination treatment and included 146 patients.[11] To achieve a statistical power of 80%, a sample size of 300 patients was determined. Accounting for potential dropouts, we opted to enrol 417 patients to ensure obtaining over 300 evaluable patients.

Study population

The study enrolled children aged 2 to 12 years, weighing between 6 to 40 kg, with a confirmed diagnosis of common cold. Participants were required to be in good physical and mental health, with no significant comorbid medical issues, as determined by thorough assessments of their medical history, physical examination, and nasal health. Only patients and guardians willing to adhere to the study protocol were considered eligible. Children of either gender were eligible for participation. During the screening process, children with allergies to the investigational product and those with severe liver or kidney problems were excluded from the study, ensuring the safety and appropriateness of the study population.

Study intervention and outcome measures

During the study, parents were guided to administer the investigational product comprising of paracetamol 125 mg, phenylephrine hydrochloride 5 mg, chlorpheniramine maleate 1 mg, sodium citrate 60 mg, and mentholated flavoured syrupy base per 5 ml over 5 days. During the baseline visit (day 1), patients and their guardians received detailed information regarding the study procedures and the investigational product. The investigational product was provided to the guardians at no cost, along with explicit instructions for its administration to the patients, as outlined in Table 1. The formulation had been approved

by the Indian regulatory authority i.e., CDSCO for the treatment of the common cold.[13]

Table 1: Dosage for administration of investigational product.

Weight (kg)	Age (in years)	Dose
6-22.9	2-7	5 ml BID
11.9-40	7-12	5 ml TID

Subsequently, the patients' guardians along with the patient were asked to visit the clinical trial site on day 3 (visit 2) and day 5 (visit 3), considering the baseline visit as day 1 (visit 1). During the baseline visit (visit 1, day 1), a thorough medical examination was conducted, encompassing the patient's demographic characteristics and general physical examinations. Baseline efficacy assessments were also performed during this visit. Follow-up assessments on visit 2 and visit 3 included the evaluation of both efficacy and safety. For efficacy assessment, TSS was recorded from the patient at visits 1, 2 and 3. To get the TSS, the patient and their guardian were asked to rate the common cold symptoms experienced by the patient including but not limited to such as fever, rhinorrhoea, sneezing, body aches, headache and nasal issues on a TSS scale ranging from 0 to 10 where 0 means no symptom at all to 10 means highest symptoms of common cold. The TSS was further categorized into four symptom intensity levels with severe intensity symptoms (TSS ranging from 7 to 10), moderate intensity symptoms (TSS ranging from 4 to 6), mild intensity symptoms (TSS ranging from 1 to 3) and no symptoms at all (TSS 0) which was made as per the Likert type symptom severity scale. Safety assessment was made according to the adverse events reported by the patient/patient's guardian to the investigator.

Ethical approval

This 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" and "good clinical practices guidelines". This clinical trial was registered with both the Indian regulatory authority, the CDSCO, and the clinical trials registry of India (CTRI), with the registration number provided CTRI/2021/11/037912. Three Institutional ethics committees and one independent ethics committee have approved the study protocol and the informed consent documents before the study initiation. The parents (or legal guardians) of all the children participating in active PMS read and signed the IRB-approved informed consent document before participation in the study.

Statistical analysis

A primary database was created in validated 'Microsoft excel spreadsheets while processing case record forms received from the study sites. The data were also analysed using a one-way ANOVA method to examine statistically significant differences between visit 1 and visit 3.

RESULTS

Demographic characteristics

The 309 out of 417 patients finished the study, with 108 lost to follow-up. The proportion of male and female patients was 60.51% and 39.49%, respectively (Table 2). The patients in the study ranged from a minimum age of 2 years to a maximum of 12 years, with an average age of 5 years. Most of the children enrolled in the study were aged between 0 and 5 years. Table 3 illustrates the age-based distribution of the patients in this study.

Table 2: Gender-wise distribution of the study population.

Gender	Percentage (%)
Male	60.51
Female	39.49

Table 3: Distribution of total population according to age, (n=309).

Age (in years)	N	Percentage (%)
0-5	197	63.75
6-10	109	35.28
11-15	3	0.97

Efficacy assessment

The mean TSS at the baseline visit was 8.95 which was reduced to 4.83 at visit 2 and further reduced to 0.19 at visit 3. At visit 2, we observed a 46.03% reduction in the mean TSS compared to the baseline. This improvement became even more pronounced at visit 3, with a remarkable 97.90% reduction in the mean TSS as compared to the baseline. These findings are visually represented in Figure 1.

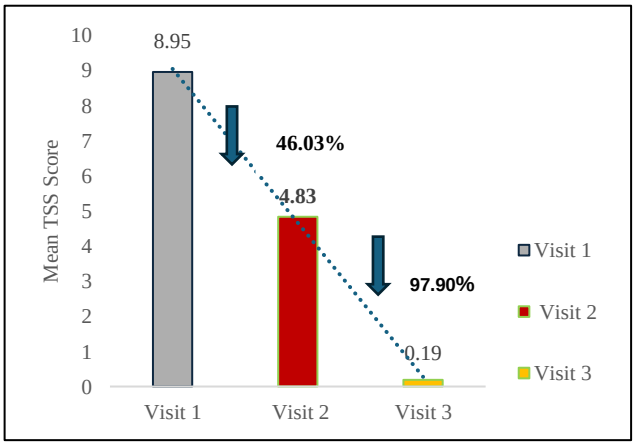

Figure 1: Mean TSS at visit 1, visit 2 and visit 3.
Mean TSS at visit 1, visit 2 and visit 3 and percentage reduction in means TSS on visit 2 and 3 as compared to baseline.

Also, during this study, data from three patient visits was analysed. During the first visit, among the 309 patients who completed the study, it was observed that 95.79% of them exhibited severe intensity symptoms, with TSS ranging between 7 to 10. Additionally, 3.24% of patients had moderate-intensity symptoms and 0.97% experienced mild-intensity symptoms. Moving on to the second visit, 2.91% of patients demonstrated severe intensity symptoms, while a significant portion, accounting for 85.11%, had moderate intensity symptoms. Furthermore, 11.98% of patients displayed mild-intensity symptoms during the 2nd visit. On the third visit, the data revealed that 16.18% of patients had mild-intensity symptoms, whereas the majority, constituting 83.82% of the patients, were free of any symptoms. These findings are visually represented in Figure 2. Also, the outcomes of the one-way ANOVA test demonstrated a statistically significant difference in the TSS value between the first visit and the third visit ($p<0.0001$).

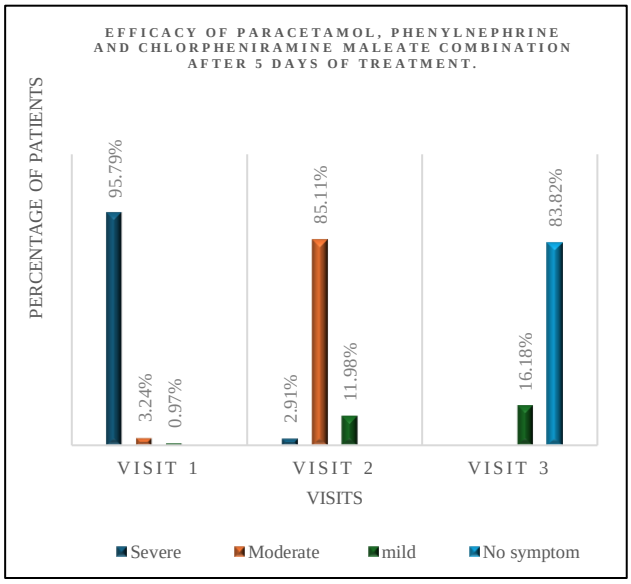

Figure 2: Quantitative data for mild, moderate, and severe intensity symptoms or no symptoms at visits 1, 2 and 3.

Safety assessment

A total of 20 cases of non-serious adverse drug reactions were reported, none of these patients were withdrawn from the study as the reported adverse reactions were expected and no medical management was required for the same. All 20 patients who experienced non-serious adverse reactions completed the study. The most prevalent non-serious adverse reaction was drowsiness, accounting for 80% of cases, followed by nausea at 15% and vomiting was reported in only 5% of cases. These findings collectively suggested that the investigational product has a generally well-tolerated safety profile among the study participants, with all the reported adverse reactions being non-serious and expected in nature. The list of adverse events is mentioned below in Table 4.

Table 4: Summary of reported adverse events.

All Adverse events (AEs)	N	Percentage (%)	Intensity of adverse events
Drowsiness	16	80	Mild
Nausea	3	15	Mild
Vomiting	1	5	Mild
Serious AEs	0	0	-
AEs leading to discontinuation	0	0	-
AEs leading to death	0	0	-

DISCUSSION

The findings of this active PMS study provided valuable insight into the efficacy and safety of FDC of, paracetamol, phenylephrine, chlorpheniramine maleate and sodium citrate in paediatric patients with common cold in India. The study demonstrated a significant reduction in common cold symptoms over 5 days, with most patients experiencing relief by the third visit. The results indicate a notable decrease in the TSS from baseline to visit 3, reflecting a substantial improvement in symptom severity. Initially, 95.79% of patients experienced severe symptoms, which decreased to 2.91% by visit 2 and only 16.18% showed mild symptoms by visit 3, with 83.82% becoming symptom-free. Despite non-serious adverse reactions in 20 patients, all completed the study without requiring medical intervention. Drowsiness (80%) was the most common adverse event. Statistical analysis using one-way ANOVA confirmed a significant reduction in TSS at visit 3 compared to baseline ($p<0.0001$). This reduction was particularly pronounced, with a 97.90% decrease in the mean TSS, highlighting the effectiveness of the investigational product in alleviating common cold symptoms. Moreover, most patients transitioned from severe symptoms at baseline to either mild symptoms or complete symptom resolution by visit 3, indicating a significant therapeutic response.

Picon et al conducted a phase III, comparative study to evaluate and compare the efficacy and safety of the combination of chlorpheniramine maleate, paracetamol and phenylephrine vs placebo for treating the common cold and flu-like symptoms in adults. They found that the treatment group had significantly reduced symptom scores compared to the placebo group. Importantly, the safety profile of the investigational product was favourable, with the majority of reported adverse reactions being non-serious and expected, such as drowsiness, nausea, and vomiting. None of the reported adverse reactions necessitated withdrawal from the study, indicating good tolerability of the medication among patients with common cold. Given the high prevalence of common cold among children in India and its associated morbidity, effective management strategies are essential to reduce the burden of illness and improve quality of life. The results of this study support the use of chlorpheniramine maleate,

paracetamol, and phenylephrine combination therapy as a safe and effective option for managing common cold symptoms in paediatric patients.[11]

The Cochrane database of systematic reviews conducted an extensive assessment to evaluate the effectiveness of antihistamine-decongestant-analgesic combinations in mitigating the duration and severity of common cold symptoms in both adults and children. Their analysis encompassed 27 clinical trials involving 5117 participants with the common cold. Among these, fourteen trials investigated antihistamine-decongestant combinations, two explored antihistamine-analgesic combinations, six examined analgesic-decongestant combinations, and five evaluated antihistamine analgesic decongestant combinations. Notably, in trials involving antihistamine-analgesic-decongestant combinations, four trials reported global effectiveness with only a 2% incidence of adverse effects, indicating a favourable safety profile compared to other combinations. This Cochrane review highlighted the antihistamine-analgesic-decongestant combination as the most effective for symptomatic treatment of the common cold.[14]

Kiran et al conducted a study to assess the safety and efficacy of a FDC in managing common cold symptoms in children. The FDC comprised paracetamol (250 mg), phenylephrine hydrochloride (5 mg), chlorpheniramine maleate (2 mg), sodium citrate (60 mg), and menthol (1 mg) per 5 ml suspension. The study involved 216 children aged 2 to 12 years who had at least four out of nine common cold symptoms, such as headache, fever, body ache, nasal congestion, rhinorrhoea, sneezing, sore throat, dysphonia, and malaise. Participants visited the clinical trial site three times over five days, attending appointments at the baseline (V1), re-evaluation (V2), and conclusion (V3) visits. The TSS was used as the efficacy parameter, and the mean TSS and percentage reduction in TSS were computed at each visit. The mean TSS decreased from 6.10 at V1 to 2.87 at V2 and further to 0.48 at V3, with percentage reductions of 52.88% and 92.01%, respectively. By the end of the study, 108 patients (67% of the total) were symptom-free. Mild adverse events were reported by 35 patients, mostly excessive sedation, and drowsiness. These events were non-serious and did not require medical intervention. The study concluded that the FDC was effective and safe for managing common cold symptoms in children.[15]

The observed reduction in symptom severity aligns with previous research highlighting the efficacy of FDC therapies containing analgesics, decongestants, and antihistamines in providing multi-symptom relief for common cold in paediatrics. A study conducted by Kiran et al investigated the benefits of a syrup formulation containing chlorpheniramine maleate, paracetamol, and phenylephrine in 200 paediatric patients afflicted with the common cold. The results of the study showcased the effectiveness of this combination, revealing a 41.5% reduction in symptoms by day 3 and 85.9% by day 5 of the treatment. The adverse events associated with this combination were minimal, with only 6 non-serious cases reported during the study. These findings not only underscore the therapeutic efficacy of the triple combination but also emphasize its safety, making it a promising and well-tolerated option for managing common cold symptoms in the paediatric population.[16]

However, it's important to acknowledge the limitations of this study, including its non-randomized, open-label design and the absence of a comparator group. Future research incorporating randomized controlled trials and comparative effectiveness studies could provide further insights into the relative efficacy and safety of combination therapies for common cold in paediatric populations. However, as this was not a phase III or phase IV clinical trial, a comparator arm was not necessitated. This was a planned active PMS.

CONCLUSION

This active PMS study evaluating the efficacy and safety of, paracetamol, phenylephrine, chlorpheniramine maleate and sodium citrate FDC therapy in Indian paediatric patients with common cold demonstrated significant symptom reduction and favourable safety outcomes over 5 days. These findings support the effectiveness of the investigated combination therapy in alleviating common cold symptoms and highlight its potential as a safe and valuable treatment option for paediatric patients in India.

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 FDC of paracetamol 125 mg, phenylephrine hydrochloride 5 mg, chlorpheniramine maleate 1 mg, sodium citrate 60 mg and mentholated flavoured syrupy base per 5 ml which is the investigational product used for the conduct of the study is available in the Indian market under the brand name of Sinarest Syrup.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee, registration number provided CTRI/2021/11/037912.

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