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Original Research Article

Safety and efficacy of a fixed dose combination of oral drops of paracetamol, phenylephrine hydrochloride, and chlorpheniramine maleate in the symptomatic treatment of common cold in children: an active post-marketing surveillance study

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ABSTRACT

Background: Common cold often accompanied by mild fever and systemic symptoms in children, poses a significant social burden. Scientific evidence suggests that the pathogenesis of colds involves the activation of multiple inflammatory pathways, rendering single-molecule treatment ineffective against the symptoms. This active post-marketing surveillance study evaluated the safety and efficacy of a fixed-dose combination containing paracetamol, phenylephrine hydrochloride, and chlorpheniramine malate in treating common cold in children aged 2 to 5 years.
Methods: In this clinical study, 200 children with common cold symptoms were enrolled. Maxtra® P oral drops, a fixed-dose combination containing paracetamol (125 mg), phenylephrine hydrochloride (2.5 mg), and chlorpheniramine maleate (1 mg) per ml drops, were administered as 1 ml every 4 to 6 hours for 5 days. Safety was assessed using the global tolerability assessment based on responses from parents and investigators. Efficacy was evaluated based on symptom severity scores categorised as absent, mild, moderate, severe, or very severe.
Results: Complete remission from common cold symptoms was achieved in 82% (164 patients) of 200 patients. Statistically significant reductions ($p<0.001$) in symptom severity scores were observed for all common cold symptoms from day 1 to day 5. No adverse events were observed. Maxtra® P oral drops were regarded as good to excellent for treating common cold symptoms by 92.5% of parents and 97.5% of investigators.
Conclusions: The observations of study indicate that Maxtra® P oral drops are efficacious and well- tolerated for treating common cold in children aged 2 to 5 years.

Keywords: Paracetamol, Phenylephrine, Chlorpheniramine maleate, Common cold

INTRODUCTION

Common cold is an acute, self-limited upper respiratory infection that may also involve the lower respiratory tract.[1] Children are especially susceptible because they have not yet acquired immunity to many of the viruses, have poor personal hygiene practices, and are frequently in close contact with other children who have viral infections. On an average, young children suffer from 7 to 10 colds each year.[2]

The characteristic symptom complex of the common cold consists of cough, dysphonia, throat discomfort, sore or scratchy throat, nasal congestion, rhinorrhoea, sneezing, headaches, myalgia, and fever.[3] Symptoms usually peak at 2 to 3 days and have a mean duration of 7 to 10 days.[3] The treatment of the common cold in paediatric

populations usually presents unique challenges, necessitating a careful balance between symptom relief and ensuring the safety of therapeutic interventions. The Cochrane review concluded the combination of analgesics, decongestants, and antihistamines yields superior relief for various symptoms of common cold and allergic rhinitis, as also reported by Picon et al and Eccles et al.[3-6] The fixed-dose combination of phenylephrine, chlorpheniramine maleate, and paracetamol can offer better relief from cold symptoms in children. However, considering the unique characteristics of this age group and the potential for safety, a comprehensive and vigilant post-marketing surveillance study is imperative to evaluate the safety and efficacy of the combination in real-world settings.

Phenylephrine, chlorpheniramine malate, and paracetamol are combined to address the multifaceted nature of common cold symptoms. Phenylephrine, a selective adrenergic receptor agonist, aims to alleviate nasal congestion by its dominant and direct vaso-constricting effects on capacitance blood vessels of the nasal mucosa, while chlorpheniramine maleate, a first-generation antihistamine, targets anti-inflammatory and allergic manifestations by competitively binding to H1 receptors in the nasal mucosa to prevent the histamine-induced vaso-reactive responses, thus decreasing nasal discharge. Paracetamol, a widely used antipyretic and analgesic, complements these actions by providing relief from fever and reducing the discomfort associated with cold symptoms.[7,8] Polymorphonuclear leukocytes and kinin concentrations increase during colds. Paracetamol inhibits leukocyte migration and kinin release in nasal epithelium and nasal secretions.[9] Thus, the synergy of these components offers a holistic approach to the management of the various symptoms of common cold in young children.

Despite the established individual safety profiles of these components, the fixed-dose combination warrants meticulous evaluation, particularly in the paediatric age group, where subtle variations in drug response and susceptibility to adverse effects are more pronounced.[10-12] This necessitates a surveillance study that transcends the controlled environment of clinical trials, offering insights into the safety and efficacy of the drug in real-world scenarios.

We conducted an active post-marketing surveillance to assess the safety and efficacy of fixed-dose combination (FDC) of phenylephrine, chlorpheniramine maleate and paracetamol in children with the common cold.

The findings of this study were anticipated to contribute significantly to existing knowledge, informing healthcare professionals and policymakers on the optimal management of the common cold in children aged 2 to 5 years.

METHODS

Study design and ethics

It was an open-label, prospective, multi-centric, active post-marketing surveillance study conducted at 4 geographically distributed centers across India from February 2021 to December 2022, with a total enrolment of 200 paediatric patients (aged 2-5 years). The study followed the ethical standards of the Declaration of Helsinki, Good Clinical Practice, and the New Drugs and Clinical Trial Rules, 2019, India. The study was notified to the Central Licensing Authority of India. Ethics committees at each study center approved the study protocol before the commencement of the study. The written informed consent was obtained from the parents. The trial was prospectively registered with the Clinical Trials Registry-India under registration number CTRI/2021/02/031207.

Eligibility criteria

The study enrolled children of both sexes, aged 2 to 5 years, who had common cold symptoms that persisted between 6 and 72 hours. Study participants were excluded based on the following criteria: hypersensitivity to formulation ingredients, hepatocellular insufficiency, active liver disease or hepatic failure, use of antihistamines, analgesics or decongestants within 1 day prior to enrolment, and those deemed inappropriate for inclusion by the investigator.

Investigational product

Maxtra® P oral drops (manufactured by Zuventus Healthcare Limited) was given to the enrolled patients administered as 1 ml every 4 to 6 hours for 5 days. This oral drop formulation (per ml) contains a combination of paracetamol 125 mg, phenylephrine hydrochloride 2.5 mg and chlorpheniramine maleate 1 mg.

Study procedure

Parents/guardians of eligible patients received comprehensive information about the study and patients underwent a thorough medical history assessment and clinical examination. Prior to enrolment in the study, parents were informed of study procedures and the investigational product, allowing time for decision-making. Written and signed consent was obtained from parents/guardians. After eligibility, two visits (visit 1-day 1; visit 2-day 5) were planned for all the patients. Vitals such as body temperature, pulse rate and respiratory rate were assessed on both visits. On day 1, patients were assessed for symptoms and initiated the study treatment. The investigator evaluated the improvement in the severity of common cold symptoms on day 5. Symptom severity score and study treatment accountability were noted during both visits. Other investigational drugs and concomitant medications

including multivitamins, multiminerals, or antibiotics were not allowed during the study duration.

Study assessment

Safety Assessment

Safety of the study medication was assessed on day 5 based on adverse events reported and their relation to the investigational drug ascertained according to the World Health Organization-Uppsala Monitoring Center (WHO-UMC) scale. The investigators and parents responded the global assessment of treatment tolerability on Likert-type scale reading from 0 to 3, indicating 0 (poor), 1 (satisfactory), 2 (good) and 3 (excellent), for each patient, on day 5.

Efficacy Assessment

The severity of ten respiratory tract symptoms including runny nose, nasal congestion, sneezing, sore throat, hoarseness, cough, wheezing, difficulty breathing, fever, and malaise was assessed using a 5-point Likert scale ranging from 0 (absent/no symptoms), 1 (mild), 2 (moderate), 3 (severe) to 4 (very severe). Additionally, the mean of all symptom scores was calculated at the end of study and represented as total symptom score (TSS).

Outcome measures

The primary endpoint of the present study was the incidences of adverse events reported by parents during the study period and the assessment of study treatment tolerability at the end of the study by the parents and investigator. The secondary endpoint was the proportion of patients experiencing a reduction in the severity of total symptoms score (TSS) and individual symptom score, and the proportion of patients achieving complete symptom remission.

Statistical analysis

Demographic data was expressed as mean (SD) or percentage.

Safety analysis

Safety was assessed by evaluating the total number of parents reporting side effects. Any adverse event that occurred was measured as the percent of side effects reported by the parents. Safety was evaluated with the global tolerability assessment calculated as the percentage of response by the parents and investigators

Efficacy analysis

Data was represented as mean (SD). A comparative evaluation of the data obtained from each visit was conducted. The reduction in TSS was calculated as the difference of the mean of symptom severity scores as recorded during both visits. The reduction in the individual symptom severity score was assessed using Student's t test between two visits. Resolution of common cold symptoms was represented as the percentage of patients achieving complete symptom remission. Statistical significance was set at $p<0.05$.

RESULTS

A total of 200 paediatric patients were enrolled and completed the study. The mean age of patients was 3.74 (±1.00) years. None of patients were dropped out or discontinued the study. The consort flow diagram of the study is represented in Figure 1. The detailed demographic data are presented in Table 1.

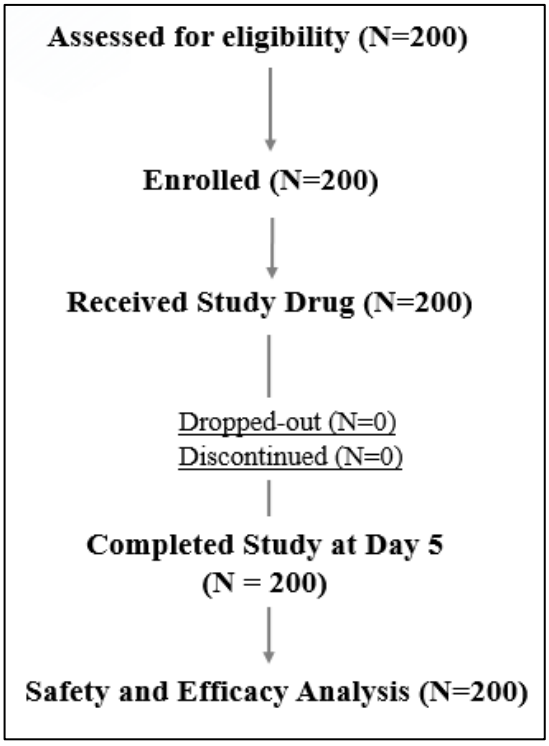

Figure 1: CONSORT flow diagram.

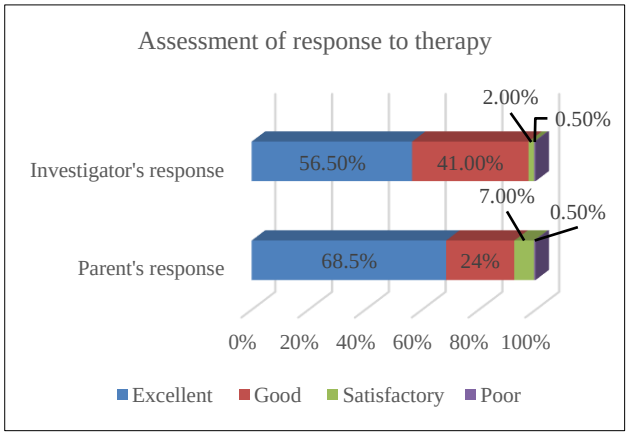

Figure 2: Evaluation of treatment by the parents and the investigator.

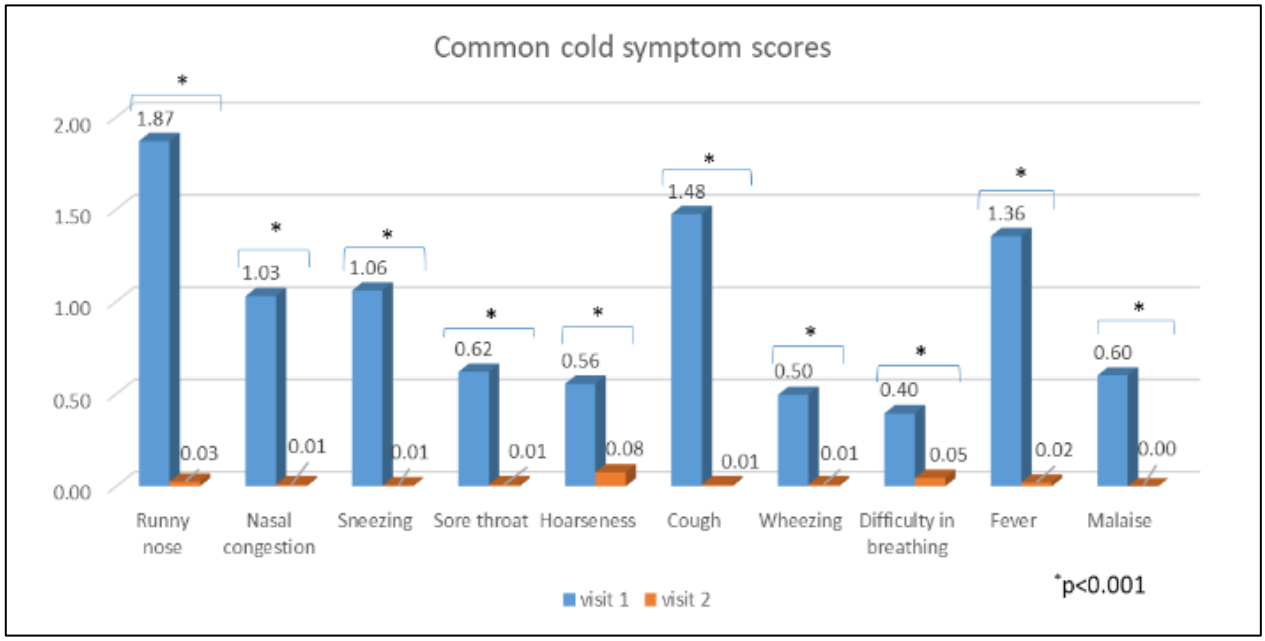

Figure 3: Common cold symptom scores reduction with investigational drugs: visit 1 vs. visit 2 comparison.

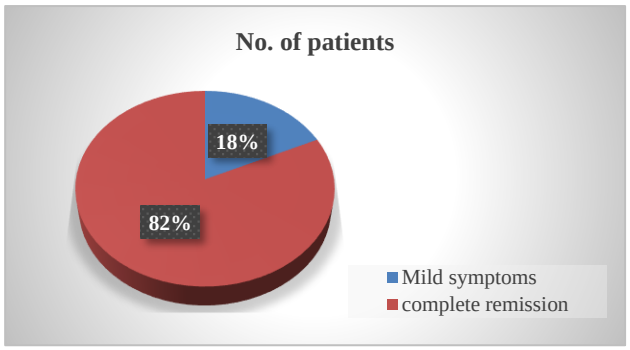

Figure 4: Evaluation of patients achieving complete remission from common cold following the administration of study drugs.

Table 1: Demographic characteristics of the patients enrolled in the study.

Parameters		Demographic data
Age in years, mean (SD)		3.74 (1.00)
Gender	Male, N (%)	118 (59)
	Female, N (%)	82 (41)
Height in cm, mean (SD)		89.17 (14.62)
Body weight in kg, mean (SD)		14.91 (3.51)
BMI in kg/m^2, mean (SD)		20.61 (10.65)

Primary outcome: safety analysis

Incidences of adverse events reported

There were no clinically significant changes observed in vital signs of the patients, between the two visits. No adverse events were observed during the study. Furthermore, no severe and treatment-related adverse events were experienced by the patients.

Assessment of study treatment tolerability

The safety evaluation also included the global tolerability assessment based on the response of the parents and investigators, wherein 68.5% of the parents and 56.5 % of the investigators reported excellent response with Maxtra® P oral drops, in treating symptoms of the common cold, as shown in Figure 2. Overall, Maxtra® P oral drops were well tolerated in the children aged 2 to 5 years.

Secondary outcome: efficacy analysis

Reduction in the severity of symptoms

There was a significant reduction ($p<0.001$) in TSS observed in all patients at the end of study. TSS represented as mean (SD) reduced from 0.95 (1.00) to 0.02 (0.52), indicating that the patients experienced significant relief from common cold symptoms by the end of the study. Less than 10.0% of patients reported mild symptom scores for individual symptoms, at the end of study. The reduction in individual symptom scores between the two visits is represented in Figure 3.

Patients achieving complete remission

A total of 82% of the patients experienced complete remission of common cold symptoms as indicated in

Figure 4. None of the patients had severe or very severe symptoms at the end of study treatment.

DISCUSSION

Common cold is one of the most prevalent illnesses in the world, particularly among pre-school children with compromised immune systems or allergic conditions. The social impact of this seemingly benign disease is widespread, not only affecting individual health outcomes, but also economic burden.[13] Simplifying the overall treatment regimen with fixed dose combination therapy can be cost-effective, with improved patient compliance.[3] Therefore, to ensure the safety and efficacy of the fixed dose combination, a robust post-marketing surveillance study for Maxtra® P oral drops in children aged 2 to 5 years was conducted.

In this post-marketing surveillance study, no adverse events were observed. Furthermore, none of the patients required additional rescue medication, corroborating the findings of previous research conducted by Pankaj et al.[14] Maxtra® P oral drops were regarded as excellent for treating common cold symptoms by 68.5% of parents and 56.5% of investigators.

During the study period, the efficacy was assessed using the symptom severity scale, demonstrating significant decrease ($p<0.001$) in TSS scores on day 5 compared to the baseline score. Another study conducted by Picon et al observed a significant reduction ($p=0.015$) of TSS, in the paracetamol, phenylephrine, and chlorpheniramine combination group compared to the placebo group.[3] In a phase IV, open-label, multi-centre study involving 159 patients, a significant reduction [6.62 to 0.69 ($p<0.001$)] in the TSS was observed, on day 5. At the end of the study, most of the participants experienced more than 50% reduction in TSS, and 58.49% of patients achieved complete relief from symptoms.[15]

About 94% of patients in the present study reported no rhinorrhoea by day 5. A similar study conducted by Montijo-Barrios et al demonstrated that rhinorrhoea reduced by 70% on the first day, 43% on the third day, 11% for the fifth and practically disappearing by the seventh day of treatment with similar fixed dose combination.[16]

In our study, 82% of the participants achieved complete symptom remission with Maxtra® P oral drops. In another PMS study involving 415 infants, 82.54% of the infants achieved complete resolution of common cold symptoms.[17]

There is scarce evidence regarding the concerns associated with prescribing medications that combine paracetamol with decongestants and/or antihistamines to manage cold symptoms in young children as reported in different studies.[18-20] To lessen these concerns and provide assurance to paediatricians, our research has shown that Maxtra® P drops, a paracetamol-based medication, is well-tolerated and efficacious for use in children in actual clinical settings. Healthcare professionals should keep in mind these science- backed data while prescribing paracetamol-based medications to alleviate cold symptoms in children aged 2 to 5 years.

CONCLUSION

Common cold is the most frequently encountered disease in paediatric practice. Our study showed that Maxtra® P oral drops provides optimum symptomatic relief and is well- tolerated for use in the symptomatic management of common cold in young paediatric patients.

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