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Safety and Efficacy of a Fixed-Dose Combination of Paracetamol, Phenylephrine and Chlorpheniramine Syrup in the Symptomatic Treatment of Common Cold in Children: A Post Marketing Surveillance Study in India

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Abstract:

Introduction: *The common cold affects children frequently, with 7-10 episodes annually, imposing significant economic and social burdens. Early management to reduce symptom severity and duration is crucial.*

Objective: *To evaluate the safety and efficacy of a fixed dose combination (FDC) syrup containing paracetamol, phenylephrine, and chlorpheniramine, for treating common cold symptoms in children aged 6-18 years.*

Methods: *The study was conducted in India from March 2021 to December 2022, included 200 children aged 6 to <18 years with cold symptoms lasting 6-72 hours. They received paracetamol 250 mg, phenylephrine hydrochloride 5 mg, and chlorpheniramine maleate 2 mg per 5mL syrup for 5 days. For safety evaluation, the incidence of adverse events and the tolerability of study treatment were assessed, while improvement in common cold symptoms and complete resolution were assessed to evaluate the efficacy of the study treatment.*

Results: *One patient reported mild drowsiness unrelated to the study drugs. Treatment was well-tolerated, with "good to excellent" responses reported by 94% (parents) and 95% (investigators). Symptom severity significantly decreased by day 5 ($p<0.001$), with total symptom scores reducing from 9.12 to 0.13 (mean diff: 8.99, 95%CI: 7.86-10.12; $p<0.001$). 92% of patients showed complete symptom resolution by study end, with no symptom worsening.*

Conclusion: *The FDC of paracetamol, phenylephrine, and chlorpheniramine syrup effectively managed common cold symptoms in children aged 6 years and older, demonstrating good tolerability.*

Keywords: *Children, Chlorpheniramine; Common cold; Paracetamol; Phenylephrine.*

1. INTRODUCTION

Common cold is a widely encountered condition characterized by symptoms such as nasal congestion, runny nose, sneezing, sore throat and cough. Generally, 4 out of every 10 individuals in India experience symptoms of cold or cough at least once in six months.[1]

The frequency of common cold episodes decreases with age.[2] School-age children commonly experience 7-10 episodes annually, compared to adults who typically have 2-5 episodes per year.[3] Although these symptoms usually improve within one to two weeks, the common cold can have a notable impact on focus, productivity, and may require time off from work or school.[4] These ailments can negatively impact mental health and reduce cognitive performance.[5]

In the initial stages of a cold, a sore throat is often one of the first symptoms experienced. As the cold progresses, symptoms like a runny nose, congestion, sneezing, wheezing, and cough can intensify and become more pronounced. Fever is more common, typically in children with colds. Common cold may be also accompanied by weakness, headache and joint pain.[6] Treatment primarily focuses on relieving symptoms and preventing them from worsening. Antihistamines combat sneezing, cough, and nasal discharge, while decongestants address nasal stuffiness, and analgesics target sore throat, discomfort, muscle pain, fever and

headache.[1] According to the Systematic Reviews of clinical studies, analgesics[7,8], decongestants[9], and antihistamines[10] offer better relief from multiple symptoms associated with the common cold.

There is no singular effective treatment for the common cold and mostly medications are prescribed in combinations like analgesics along with decongestants and antihistamines thus providing symptomatic relief. Paracetamol, a widely used Non-Steroidal Anti-Inflammatory Drug (NSAID), is one of the common medications used in the combination therapy for common cold.[11] It is a centrally acting, analgesic and antipyretic agents, effectively addressing to restore symptoms such as fever, headache, ear pain, muscle, and joint pain associated with the cold. However, it doesn't help to relieve cough or congested nose.[12]

Phenylephrine, acting as a selective adrenergic receptor agonist, serves as an efficient nasal decongestant by constricting blood vessels in nasal passages, reducing nasal mucus volume, and relieving congestion.[13] Chlorpheniramine, a first-generation antihistamine, targets nasal H1 receptors to block histamine action, thereby preventing allergic responses and offers anti-allergic and anti-inflammatory effects in the nasal mucosa.[14] Its efficacy extends to alleviating sneezing, nasal congestion, and discharge, making it a preferred option for histamine-mediated allergies.[15]

According to the Cochrane Review, the symptomatic treatment with an analgesic-decongestant-antihistamines combination showed significant improvement in common cold and allergic rhinitis than monotherapy.[16] We conducted this study to evaluate the safety and efficacy of a fixed-dose combination (FDC) of paracetamol, chlorpheniramine, and phenylephrine syrup in the treatment ofthe common cold in children aged 6 years and above.

2. MATERIALS AND METHODS

2.1. Study Design and Ethics

It was a post-marketing study conducted during March 2021 to December 2022 at 4 different hospitals in India. The study followed the ethical standards of the Declaration of Helsinki, Good Clinical Practice, and the New Drugs 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/2021/02/031188.

2.2. Patients

Patients were assessed for their eligibility in the study before enrollment. A detailed medical history was obtained from the parents or guardians of each patient. The physical examination of each patient was conducted by the investigators. Patients aged between 6 to 18 years who had experienced common cold symptoms lasting between 6 and 72 hours before participation were enrolled in the study. Adolescent children aged 12 to 18 years provided their assent, with parental or guardian consent. The patients who were hypersensitive to any formulation ingredient, hepatic or renal dysfunction, those who had taken an antihistamine, analgesic, or decongestant within a day before study enrolment and/or patients deemed unsuitable for inclusion in the study by the investigator were excluded from the study.

2.3. Study Treatment

The investigational product was FDC of paracetamol 250 mg, phenylephrine hydrochloride 5 mg and chlorpheniramine maleate 2 mg per 5mL syrup (Maxtra®PDS, Zuventus Healthcare Limited). The prescribed dose was 5 mL (6 to 11 years) and 10 mL (12 to 18 years) every 4-6 hours for 5 days. Patients were provided with a dosing schedule in the 'Patient Daily Diary' and were instructed to record their medication intake after each dose.

2.4. Study Procedure

After eligibility, the two visits (Day 1 & Day 5, respectively) were planned for all the patients. On Day 1, patients were assessed for symptoms and initiated the study treatment. Investigators examined each patient for any occurrence or signs of adverse events and assessed the study treatment tolerability on Day 5. The investigator evaluated the improvement in symptom severity on Day 5 by recording the symptom severity scores during both visits. Complete resolution of

the common cold symptoms by the patient was also evaluated on Day 5. Other investigational drugs and any concomitant medication including multi-vitamins, multi-minerals or antibiotics were not allowed during the study duration.

2.5. Study Assessment

2.5.1. Primary outcome measure

The safety of the study drug was evaluated by monitoring adverse events and assessing the tolerability of the study treatment. Parents were requested to promptly report any adverse events that occurred during the study. The investigator examined and recorded all the reported adverse events to ensure the safety profile of the study drug. Both investigators and parents responded to the treatment and response was rated on a scale of 0 to 3 where 0: poor, 1: satisfactory, 2: good, and 3: excellent.

2.5.2. Secondary outcome measure

The study evaluated the efficacy of treatment by analyzing improvements in 11 common cold symptoms. Each symptom was rated on a 5-point Likert-type scale for intensity (0 = absent/no symptom, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe) by the investigator at baseline and Day 5. The illustration of the scoring system for common cold symptoms is presented in Table 1. The efficacy of the treatment was also assessed by calculating the reduction in individual symptom scores from Day 1 to Day 5. The percentage of patients achieving resolution of the symptoms was also calculated. The severity score of the symptoms was compared between the two visits using the Student's t-test with a statistical significance level set at $p<0.05$.

Table 1. *Scoring system for total symptoms score*

Sr. No.	Common Cold Symptoms	No Symptoms	Mild	Moderate	Severe	Very Severe
1.	Runny Nose	⓪	①	②	③	④
2.	Nasal Congestion	⓪	①	②	③	④
3.	Sneezing	⓪	①	②	③	④
4.	Sore Throat	⓪	①	②	③	④
5.	Hoarseness	⓪	①	②	③	④
6.	Cough	⓪	①	②	③	④
7.	Wheezing	⓪	①	②	③	④
8.	Difficulty in breathing	⓪	①	②	③	④
9.	Headache	⓪	①	②	③	④
10.	Fever	⓪	①	②	③	④
11.	Malaise	⓪	①	②	③	④

3. RESULT

A total of 200 patients who met the eligibility criteria were enrolled and completed the study. The demographic characteristics of all participants are outlined in Table 2.

Table 2. *Demographic data*

Characteristic	Specification		Data
Age, years	Mean (SD)		11.45, (3.3)
6 to <12 years	Number (%)		107 (53.5)
12 to <18 years	Number (%)		93 (46.5)
Gender	Number (%)	Male	111 (55.5)
		Female	89 (44.5)
Height, cm	Mean (SD)		137.77 (15.4)
Body weight, Kg	Mean (SD)		36.00 (10.87)
BMI, kg/m^2	Mean (SD)		18.52 (3.16)

3.1. Safety Results

3.1.1. Primary Outcome Assessment

The safety results from the study revealed that the Maxtra® PDS syrup was well-tolerated in enrolled patients. A single incidence of mild drowsiness was reported which was unlikely related to the study treatment and resolved without any sequelae. The parents and investigators reported "good to excellent" responses towards treatment tolerability in 94% and 95% of patients, respectively (**Fig. 1 and 2**). There were no any new or unexpected adverse effects reported with the study treatment.

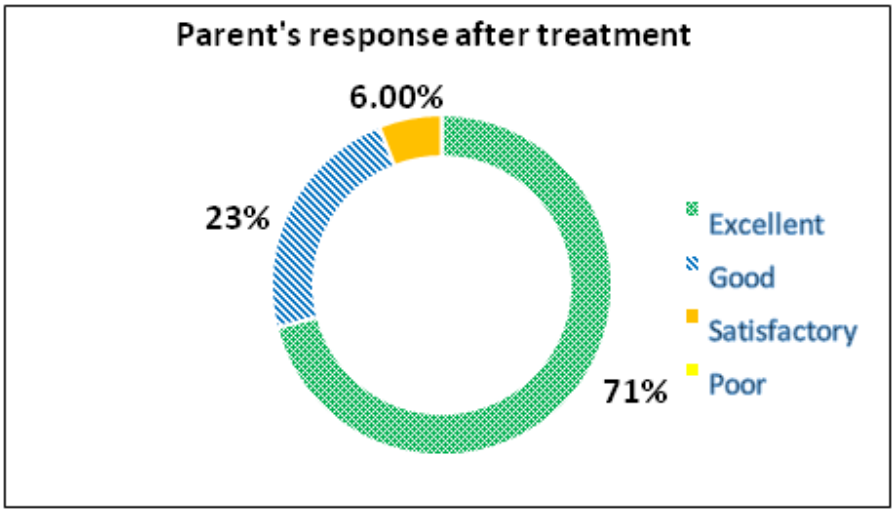

Fig 1. *Assessment of response by the parents (after treatment)*

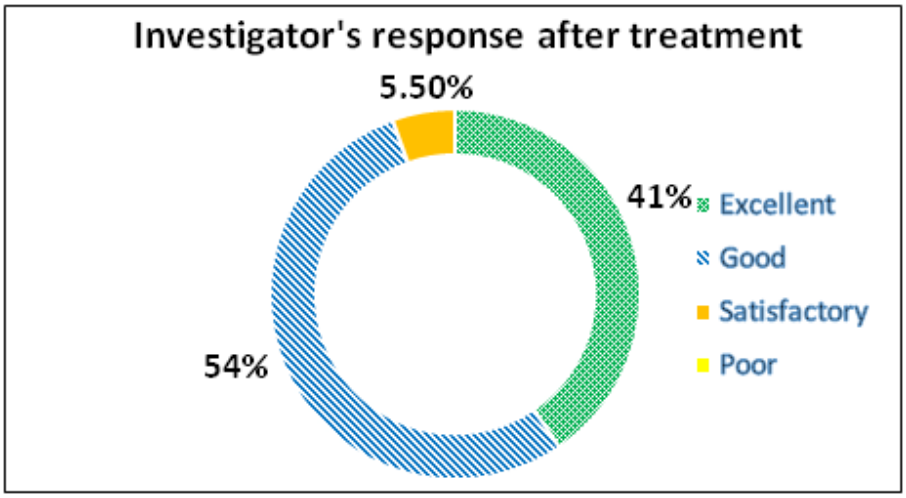

Fig 2. *Assessment of response by the Investigator (after treatment)*

3.2. Efficacy Results

3.2.1. Secondary Outcome Assessment

A statistically significant reduction (p<0.001) from baseline to Day 5was observed in all common cold symptom scores. By Day 5, the mean symptom score of runny nose, sneezing, wheezing, difficulty breathing, and malaise had decreased to zero. The change in mean symptom severity scores are presented in **Fig. 3**. There was a reduction in total symptom score from 9.12 at baseline to 0.13 at Day 5 (mean diff: 8.99, 95%CI: 7.86-10.12; p<0.001).

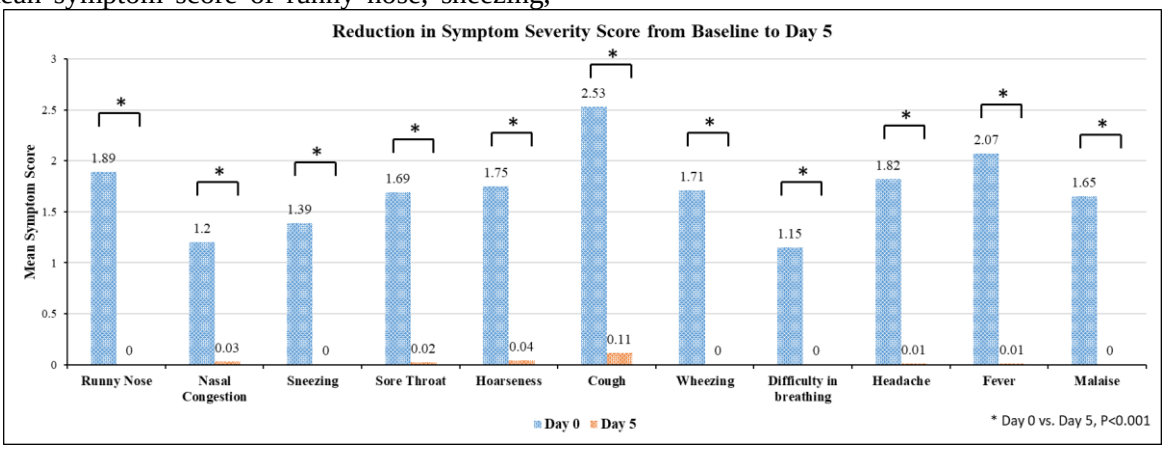

Fig 3. *Assessment of symptom severity score from baseline to day 5*

The complete resolution of symptoms was achieved in 92% of patients, at the end of the study. The nasal, respiratory and generalized symptoms are presented in **Fig.4, 5, 6**. At the end of the study, no patient reported moderate, severe, or very severe symptoms, and there was no indication of any worsening of their condition.

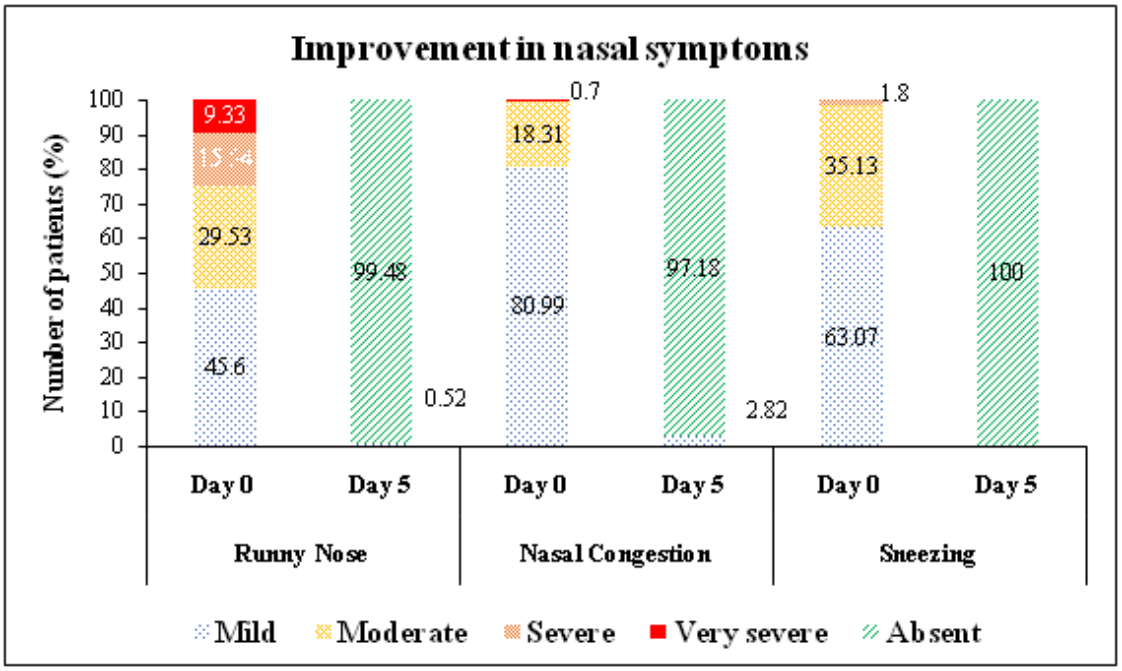

Fig 4. *Assessment of improvement in nasal symptoms*

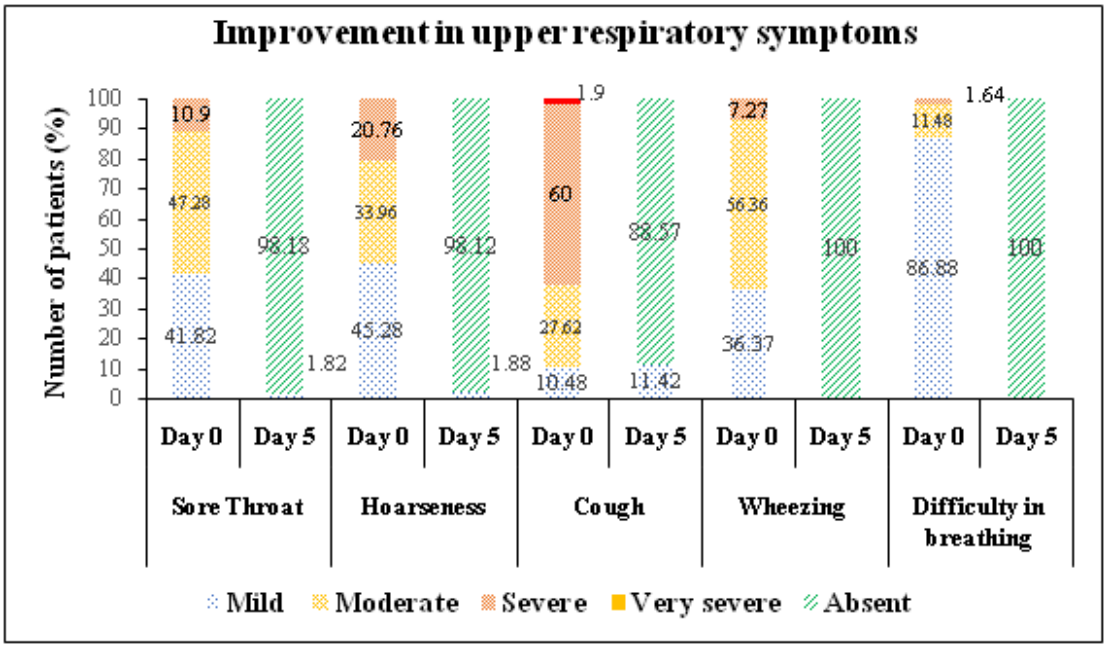

Fig 5. *Assessment of improvement in respiratory symptoms*

It was observed that the symptoms such as sneezing, wheezing, difficulty in breathing and malaise were completely resolved in all enrolled patients after completion of treatment. Less than 2% of patients had mild symptoms such as runny nose, nasal congestion, sore throat, hoarseness, headache and fever. About 62% of patients had a cough in severe intensity which was more pronounced as compared to other symptoms, highlighting its prominence among patients and its impact on their quality of life. On Day 5 after receiving the study treatment, the symptom score for cough decreased by 96%, with approximately 89% of patients achieving complete resolution of this symptom.

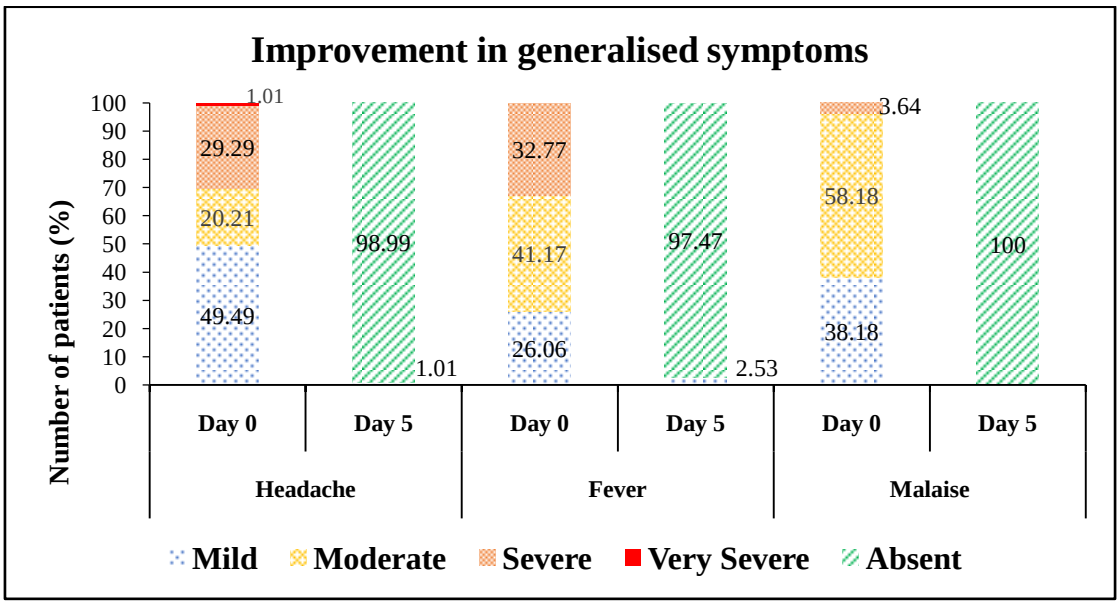

Fig 6. *Assessment of improvement in generalized symptoms*

4. DISCUSSION

Common cold symptoms are mainly associated with infected mucosa, peak within 1-3 days and resolve within 7-10 days, but in some cases, they may persist up to 3 weeks.[17] Typically patients present with nasal (runny nose, nasal congestion), acute upper respiratory (sore throat, cough, rhinorrhea) and generalized symptoms (malaise and fever).[18] Therefore, the symptomatic treatment is necessary.

The Cochrane Review on combination treatments for the common cold noted that a combination of analgesic-decongestant-antihistamine in children improved nasal congestion in 5 days as compared to any of these medications given alone.[4] A NSAID-decongestant combination reduced the duration of nasal congestion as compared with pseudoephedrine or placebo.[4] The combination of phenylephrine and chlorpheniramine has been used for a long time as an effective treatment for the common cold.[19,20,21] The fever is common in children[17] during the first 3 days of the common cold.[22] Every 4th patient needed additional paracetamol in the common cold.[20] Therefore, paracetamol can be added in combination with phenylephrine and chlorpheniramine. However, healthcare professionals express concern about the paucity of clinical evidence showing the safety of combination of paracetamol with antihistamines and decongestants for treating the common cold. Hence, to provide reassurance to healthcare professionals regarding the safety of formulation containing paracetamol with decongestant and antihistaminic, we conducted a clinical study of Maxtra® PDS syrup (a paracetamol-containing syrup) and evaluated its safety, efficacy and tolerance in real-time clinical practice.

In this study, Maxtra® PDS syrup was found to be well-tolerated by the patients. The response to treatment was found to be positive and satisfactory, based on the treatment tolerability and improvement in the common cold symptoms, as reported by the parents and the investigator. In this study, the total symptom score was reduced by 99% after 5 days of treatment. Kiran et al., reported a 92% reduction in total symptom score after five days of treatment.[23] Another study by Kiran et al reported an 88% reduction in total symptom score after five days of treatment.[24] The clinical trials conducted across different age groups showed that the combination treatment of paracetamol, phenylephrine, and chlorpheniramine led to a reduction of more than 90% in the total symptom score after 5 days.[1,25,26] In a placebo-controlled study, the overall symptom scores showed a significantly greater reduction in the paracetamol, phenylephrine, and chlorpheniramine combination group as compared to the placebo group ($p = 0.015$).[20]

In the common cold, early symptoms such as sore throat, headache, sneezing, chills, and malaise develop rapidly. Fever occurs early but is of short duration. The early onset of nasal congestion and sneezing, preceding the

development of cough, initially affects the upper airways and can progress to the lower airways.[27] So the complete resolution of common colds typically occurs within 7-10 days. Healthcare professionals often prefer a multi-faceted approach for multi-symptom relief, with 2-3 drugs combined into a single formulation. The study demonstrated the Maxtra® PDS syrup, a combination containing paracetamol, phenylephrine, and chlorpheniramine, effectively reduces the nasal, acute respiratory and generalized symptoms of common cold within 5 days of treatment.

5. Conclusion

This study indicates that the combination of these medications effectively alleviates common cold symptoms without compromising safety. The study findings provide reassurance to healthcare professionals and caregivers, supporting the use of paracetamol with phenylephrine, and chlorpheniramine in pediatric patients aged 6-18 years. This approach offers a convenient and reliable option for managing cold symptoms in children, contributing to their overall well-being and comfort during illness.

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Competing Interest

The authors declare that they have no conflict of interest.

Consent

Informed consent was obtained for all patients from their parents.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional ethics committee, the Indian Council of Medical Research (ICMR), and the Declaration of Helsinki. Approval was obtained from the Institutional Ethics Committee of each study center.

Source Of Funding

None

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