Drug Corner

A Prospective, Interventional, Multicentre, Post-marketing Clinical Study of a fixed-dose combination of Paracetamol (125 mg), Phenylephrine HCL (5 mg), Chlorpheniramine Maleate (1 mg) and Sodium Citrate (60 mg/5 mL) for the Treatment of Common Cold and Flu Syndrome in Children

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Background : Common cold is an acute, self-limiting viral infection of the upper respiratory tract involving the nose, sinuses, pharynx, and larynx. According to various studies, the combination of analgesics, decongestants, and antihistamines provides better relief for multiple symptoms in the common cold. Fixed dose combination of Paracetamol as an analgesic, anti-inflammatory, and antipyretic, Chlorpheniramine maleate, an anti-histaminic, and Phenylephrine as a nasal decongestant is primarily used in the treatment of the common cold. Hence the present post-marketing surveillance study was planned to find any unwanted adverse effects and efficacy of commercially available combination in treating the common cold in children.

Methodology : The prospective, single-arm, multicenter, post-marketing clinical study included 224 children from four different study sites, of which 204 completed the study. Subjects were given this fixed dose combination for three days and then monitored for the next six days. During the study, the efficacy was evaluated using VAS score changes from the beginning to the end of the treatment. Incidence of Adverse Events (AE) and Serious Adverse Events (SAE) was assessed. The product's safety was also evaluated using blood biomarkers such as Hemoglobin, Platelet count, SGOT, SGPT, and creatinine level.

Results : The reduction in symptomatic score of common cold and flu syndrome was observed after 3rd follow-up visit [(0.384±0.168 (visit 1) to 0.001±0.009 (Visit 3), ($p<0.001$)]. No intervention-related or serious adverse events (SAE) were observed in the study or follow-up period. The study found no major changes in the levels of haemoglobin, platelets, SGOT, SGPT, and creatinine.

Conclusions : Fixed-dose combination of Paracetamol (125 mg), Phenylephrine HCL (5 mg), Chlorpheniramine Maleate (1 mg) and Sodium Citrate (60 mg/5 mL) is safe and effective in treating children's common cold and flu syndrome.

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***Key words* : Common cold, Flu syndrome, Children.**

The common cold is one of the highly prevalent illnesses worldwide[1]. It is an acute, self-limiting viral infection of the upper respiratory tract involving the nose, sinuses, pharynx, and larynx[2]. Children experience a high rate of incidence, which creates a significant economic and social burden[1,3]. Around 156 million new cases of respiratory infections occur worldwide every year, and about 1.56 million young children die because of such diseases[4]. Symptoms of the common cold in children typically reach peak intensity shortly after the onset of illness. Regardless of severity, the most prevalent symptoms among children with the common cold are runny nose, stuffed-up nose, dry cough, sore throat, and sneezing[5]. Diagnosis of the common cold can be problematic in young children and infants who cannot communicate their symptoms[6].

The flu syndrome is typical of sudden onset and is characterized by fever, cough, sore throat, myalgia, headache, nasal congestion, weakness, and loss of appetite. Antiviral agents are available for the treatment of flu. Still, they are ineffective against any other causes of upper respiratory infections. Thus, there is considerable interest in the early clinical diagnosis of influenza instead of the common cold[7,8].

Common colds and flu are syndromes of familiar symptoms caused by a viral infection of the upper respiratory tract. It is difficult to define the syndromes precisely because of the significant variation in the severity, duration, and types of symptoms[9].

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Rhinoviruses account for 30-50% of all colds, and coronaviruses are the second most common agent, accounting for 10-15% of cold. Influenza viruses account for 5-15% of cold, and respiratory syncytial viruses are responsible for much flu-like illness, demonstrating much overlap in etiology and symptomatology of common cold and flu syndromes[9,10].

Currently, no antivirals are available to treat the common cold; therefore, symptomatic relief should be the primary focus for treating the common cold. Single drug therapy is not adequate to treat all the symptoms of the common cold, so multiple drug combinations are mainly used for symptomatic relief from the various symptoms of the common cold[11,12].

The current post-marketing clinical study evaluated the safety and efficacy of fixed-dose combination of Paracetamol (125 mg), Phenylephrine HCL (5 mg), Chlorpheniramine Maleate (1 mg) and Sodium Citrate (60 mg/5 mL)[Flucold Syrup], in the treatment of common cold and flu syndrome in children.

Material and Methods

Study Design & Participant :

The study was a prospective, interventional, multicenter, post-marketing trial with 224 participants.

The study followed the ICMR guidelines, New Drugs and Clinical Trial Rules 2019 India, & the Declaration of Helsinki (Brazil 2013) & the ICH E6, R2, "Guidance on Good Clinical Practice" (GCP). Besides, the trial was approved by Royal Pune Independence Ethics Committee, HCG NCHRI- Institutional Ethics committee, MAVENS institutional Ethics committee, Basaveshwara Medical College, and Hospital Institutional Ethics Review Committee (ICBio/CR/WPPL/0309/108).

A total of 224 subjects were enrolled with common flu or cold and were treated with fixed-dose combination of Paracetamol (125 mg), Phenylephrine HCL (5 mg), Chlorpheniramine Maleate (1 mg) and Sodium Citrate (60 mg/5 mL) from which 204 subjects completed the study. The total duration of the study for the patient was nine days (three days treatment with six days of follow-up). The study included patients between the age of 2 to 12 years with recent onset of symptoms not less than 72 hours, such as common cold (with symptoms such as sneezing, rhinorrhea, nasal congestion, headache, discomfort in the throat) & flu syndrome (with symptoms such as high-grade fever, headache, chest discomfort, dizziness). Patients with known hypersensitivity, seasonal perennial allergic rhinitis, a recent history of influenza vaccination, severely immune-compromised patients were excluded from the study.

Participant Removal or Withdrawn Criteria :

The patient can be withdrawn from the study by the investigator for any of the following reasons: the occurrence of an adverse event associated with the administration of the IP, necessitating its cancellation; the emergence of any diseases or conditions during the study that worsens the patient's prognosis and makes it difficult for the patient to continue participating in the clinical research; the need for a prohibited concomitant therapy; research protocol violations; improper inclusion of a patient who did not fulfill the inclusion criteria and met the applicable exclusion criteria; other serious protocol violations, according to the investigators; The withdrawal of the assent form by the patient's representative. Twenty patients were removed from the study due to absenteeism during the follow-up.

Recruitment :

Suitable subjects who agreed to participate in the study were recruited from 4 sites (Jyothi Multispecialty Clinic, Abhinav Multispecialty Hospital, MAVEN's Hospital, Basaveshwara Medical College, and Hospital Chitradurga). Each site recruited participants whose parents willingly provided a written assent form for participation in the study.

Intervention :

All subjects were treated with fixed-dose combination of Paracetamol (125 mg), Phenylephrine HCL (5 mg), Chlorpheniramine Maleate (1 mg) and Sodium Citrate (60 mg/5 mL) for three days and follow up performed for the next six days.

Outcome Measures :

Primary outcome measure —

To evaluate the safety of fixed-dose combination

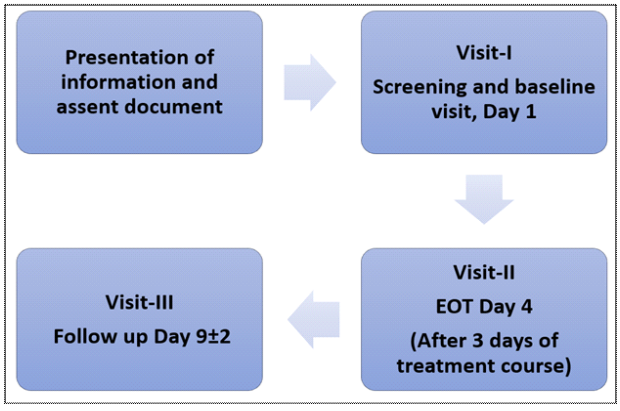

Fig 1 — Schematic flow of study events

(Paracetamol 125 mg + Phenylephrine HCL 5 mg + Chlorpheniramine maleate 1 mg + sodium citrate 60 mg per 5 mL) in the treatment of common cold or flu syndrome in the children. The incidence of adverse events (AEs) and serious adverse events (SAEs) was reviewed during the study.

Secondary outcome measures —

Evaluation of the efficacy fixed-dose combination of (Paracetamol 125 mg + Phenylephrine HCL 5 mg + Chlorpheniramine maleate 1 mg + sodium citrate 60 mg per 5 mL), in the treatment of common cold and flu syndrome in children.

Statistical Analysis:

Data analysis was performed using ANOVA & χ^2 test & SAS version 9.1 Inc, CARY; the USA used during the study. Efficacy analysis was performed for the per-protocol (PP) population. Primary efficacy was based on PP patients' samples.

Results

A total of 224 patients was enrolled in the study from 4 sites, out of which 20 patients withdrew from the study.

The mean age of the subjects enrolled in the study was 5.877±2.820 years, whereas average weight & height was 19.130±7.978 kg & 101.839±26.169 cm, respectively. The average BMI calculated during the study was found to be at 17.965±6.480 kg/m^2.

Table 1 — *Demographic data of the patient*

Demographics of patient	Values
Age	5.877 ± 2.820 years
Weight	19.130 ± 7.978 kg
Height	101.839 ± 26.169 cm
BMI	17.965 ± 6.480 kg/m^2

During the study, no intervention-related adverse events were observed. Moreover, no Severe & treatment-related Adverse Events (SAE) were observed during the investigation and follow-up period.

Reduction in total symptom score from day 1 to day 4 and during follow-up was assessed using a 4-point scale (0- no symptom, 1-Mild, 2-Moderate, 3-severe). Study results indicated that use of this SYRUP in children significantly reduced total symptom score from 0.384±0.168 (visit 1) to 0.001±0.009 (Visit 3), ($p<0.001$)(Fig 3).

The severity of the flu was assessed using visual analog score (VAS) changes in children. Treatment in children leads to significantly ($p<0.05$) change in VAS score from 4.172±1.668 (Visit 1) to 0.015±0.156 (Visit 3).(Fig 4).

Tolerability was analysed during the study in each subject & a tolerability scale was used during the analysis. It was well tolerated in children, as no side effects were observed (Table 2).

Additionally, the product's safety was evaluated by

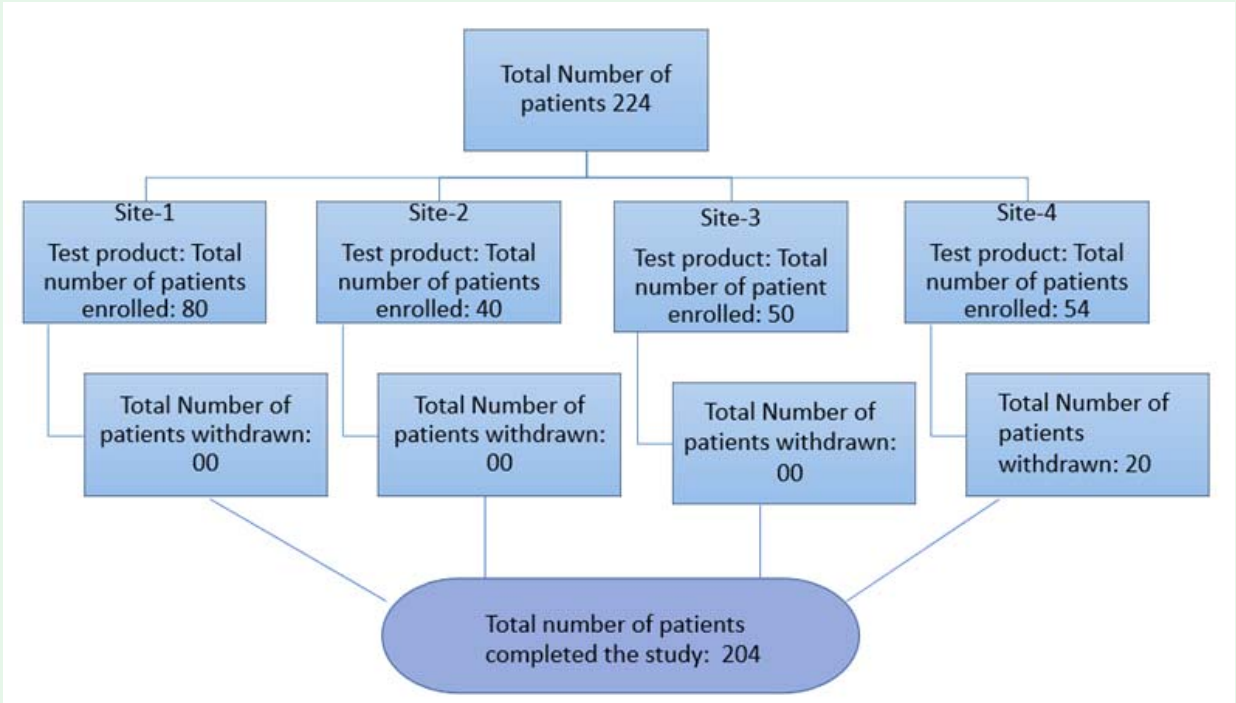

Fig 2 — Disposition of patients

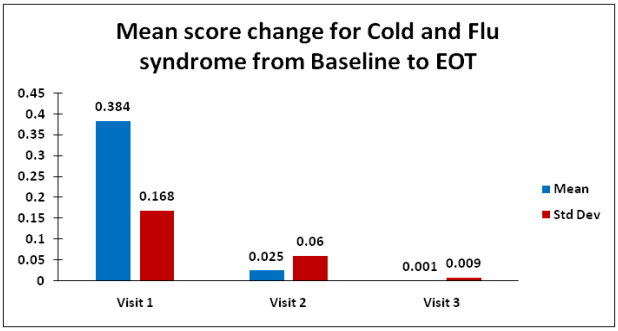

Fig 3 — Mean score change for Cold and Flu syndrome

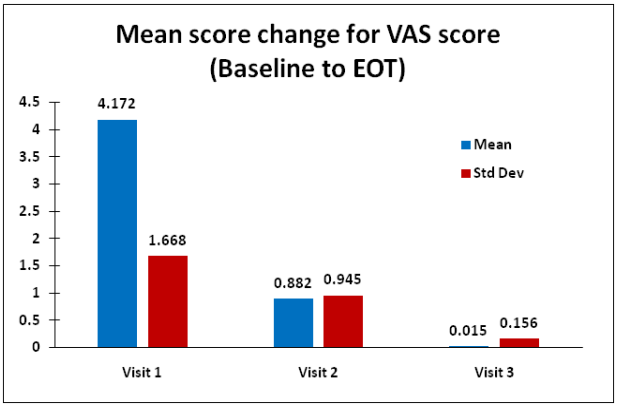

Fig 4 — Significant changes in VAS scores from baseline to EOT

analysing biomarker levels such as haemoglobin, platelet, liver, and kidney function test at the end of the study. fixed-dose combination of Paracetamol (125 mg), Phenylephrine HCL (5 mg), Chlorpheniramine Maleate (1 mg) and Sodium Citrate (60 mg/5 mL) did not significantly affect haemoglobin (11.841±0.976) and platelet (261.613±60.773) count during the study. Liver biomarkers such as SGOT (23.496±14.138) and SGPT (26.957±19.729) levels were found to be normal, indicating the safety in children. Similarly, no elevation was observed in serum creatinine levels (0.665±0.194) at the end of the study (Table 3).

Table 2 — *Frequency count for IP Tolerability*

Scale	No. of Subjects
Very good (No Side effects)	202
Good (insignificant side effects which do not cause serious problems to the patient)	02
Satisfactory (side effects which affect the patient's condition but do not necessitate discontinuation of the formulation)	0
Unsatisfactory (an adverse side effect that significantly affects the patient's condition and necessitates discontinuation of the formulation)	0
Highly unsatisfactory (an adverse side effect which necessitates discontinuation of the formulation and use of additional clinical measures)	0

Table 3 — *Mean score for a biomarker of systemic safety*

Serum biomarker	Values (EOT)
Haemoglobin	11.841 ± 0.976
Platelet count	261.613 ± 60.773
SGOT/ AST	23.496 ± 14.138
SGPT/ALT	26.957 ± 19.729
Serum Creatinine	0.665 ± 0.194

Discussion

The study was the first prospective, interventional, multi-centred, post-marketing clinical trial to demonstrate the safety and efficacy of fixed-dose combination of Paracetamol (125 mg), Phenylephrine HCL (5 mg), Chlorpheniramine Maleate (1 mg) and Sodium Citrate (60 mg/5 mL) in treating common cold and flu syndrome in children. However, various clinical studies conducted on adults showed that this combination treats the common cold and flu syndrome.

The findings showed a reduction in the symptomatic score of common cold and flu syndrome from baseline (0.384±0.168) to the end of the treatment (0.001±0.009). A similar study conducted by Picon et al. also revealed that after treatment with a fixed-dose combination of chlorpheniramine maleate, Paracetamol and Phenylephrine for ten days reduced symptom score from 14.09 to 3.54[12].

Similarly, a phase IV open-labelled multicentre study conducted in 159 patients found that mean TSS reduced from 6.62 (Day 1) to 0.69 (Day 5). Most patients included in the study had more than 50% reduction in total symptom score at visit 3, and 58.49% of patients had complete relief from the symptoms[13]. The results of both the study were in line with the current study[12,13].

Visual Analogue Scale (VAS) score analysed symptomatic relief of common cold and flu syndrome. A significant change was observed in VAS scores from baseline (4.172±1.668) to EOT (0.0015±0.156).

Biomarker evaluation showed no effect on liver and kidney function (Sr Cr = 0.665±0.194 parameters) at the end of the study. No major changes were observed in haemoglobin (11.841±0.976) and platelet count (261.613±60.773) after administration of this SYRUP. These outcomes support that combining multiple common cold or flu relief active ingredients in a single dose formula provides the patient the convenience of

treating multiple symptoms with a single product and may promote improved compliance to the treatment. It may also help in both patient safety and the optimal efficacy of the medicines[14,15].

IP Tolerability (ie, is, are there any side effects observed or any changes in treatment) data reported and analysed to check the tolerance of the investigational report. There were no side effects reported during the study. The efficacy analysis was performed to check incidence rates of Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs). Based on reported results, no treatment-emergent or serious adverse event was observed during the study. Five subjects reported mild AE, which is unlikely related to the Other all subjects found no Treatment-emergent adverse events. In contrast to this, a study conducted by Kiran M, *et al* reported six non-serious adverse drug reactions in the study duration of 5 days[16].

Studies conducted by Janin, *et al* and Picon, *et al* with a fixed-combination formulation to treat common cold reported a good safety profile and an excellent tolerance. The rationale for the treatment is that multiple symptoms commonly co-occur and that a combination medicine provides a simplification of therapy compared to the use of monotherapies[12,17].

Conclusion

This study was performed to evaluate the efficacy and safety of combinations (analgesics, decongestants, and antihistamines) in treating common cold and flu syndrome.

After four days of treatment with a fixed-dose combination of Paracetamol (125 mg), Phenylephrine HCL (5 mg), Chlorpheniramine Maleate (1 mg) and Sodium Citrate (60 mg/5 mL)[Flucold Syrup], there was a significant improvement in symptomatic relief of common cold and flu syndrome. The safety results revealed that the Flucold Syrup is safe and well-tolerated in children when administered orally.

Considering the results and outcomes, it is evident Paracetamol 125 mg + Phenylephrine HCL 5 mg + Chlorpheniramine maleate 1 mg + sodium citrate 60 mg per 5 mL was effective for treating cold and flu syndrome in children.

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