

Efficacy and safety of a fixed dose combination of paracetamol, chlorpheniramine maleate and phenylephrine in treatment of common cold: a phase IV, open-labelled, multi-centric study

Mayuresh D. Kiran¹, Monali P. Vakharia^{2*}, Lalit J. Pawaskar³, Shaheen N. Sheikh³

¹Vice President and Head,

²Department of Medical Services, ³Department of Pharmacovigilance, Centaur Pharmaceuticals, Mumbai, Maharashtra, India

Received: 10 December 2018

Accepted: 15 December 2018

***Correspondence to:**

Dr. Monali P. Vakharia,

Email: monali@centaurilab.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Acute coryza or common cold affects the upper airways, sometimes in association with low-grade fever and systemic symptoms, and usually presents with at least two of the following symptoms: cough, dysphonia, throat discomfort, sore throat, nasal congestion, rhinorrhoea, sneezing, headaches, myalgia and fever. A triple combination of analgesics, decongestants and antihistamines provides better relief for multiple symptoms in common cold and allergic rhinitis according to various studies. A combination of Paracetamol as an analgesic, anti-inflammatory and antipyretic, Chlorpheniramine maleate, an anti-histaminic and Phenylephrine as a nasal decongestant is popular in the treatment of common cold. Hence the present study was planned to evaluate efficacy and safety of this combination in treatment of common cold.

Methods: This was a phase IV, open-labelled, multicentric study in 159 patients. Efficacy assessment was done by analyzing the reduction in mean TSS at each follow-up visit and safety assessment was done by analyzing the adverse events during the study.

Results: There was reduction in mean TSS from 6.62 (day 1) to 3.56 (day 3) and 0.69 (day 5). Most of the patients had >50% reduction in total symptom score at visit 3 and 58.49% patients had complete relief from the symptoms at the end of study. Out of 159 patients, 26 i.e. 16.36% experienced adverse events. Sedation and drowsiness (6.29%) were the most common adverse event seen in patients.

Conclusions: A fixed dose combination of Chlorpheniramine maleate, Paracetamol, and Phenylephrine is safe and effective in the treatment of common cold.

Keywords: Chlorpheniramine maleate, Common cold, Paracetamol, Phenylephrine

INTRODUCTION

Common cold is the most frequently encountered disease in medical practice.¹ It is the most frequent human illness and is caused by members of several families of viruses. The most likely offenders are the ± 100 serotypes of rhinoviruses.² It affects most adults, on average two to four times a year, and accounts for up to 40% of work absences among the economically active population in the United States.³ In India, four out of every 10 individuals

experienced symptoms of cold or cough at least once in six months.⁴

Acute coryza or common cold affects the upper airways, sometimes in association with low-grade fever and systemic symptoms, and usually presents with at least two of the following symptoms: cough, dysphonia, throat discomfort, sore throat, nasal congestion, rhinorrhoea, sneezing, headaches, myalgia and fever.⁵ Symptoms usually peak at 2 to 3 days and have a mean duration of 7

to 10 days. When the etiology is presumably bacterial, treatment is antibiotics and medication for symptomatic relief but for common cold and the flu-like syndrome, having a viral etiology, symptomatic treatment remains, in most cases, the standard recommendation.⁶ According to the guidelines of DPHHS, Cochrane review, Picon PD et al, and Eccles R et al, a triple combination of analgesics, decongestants and antihistamines provides better relief for multiple symptoms in common cold and allergic rhinitis.⁶⁻⁹

Paracetamol belongs to a class of Nonsteroidal Anti-inflammatory Drugs (NSAID) and exhibits good central analgesic and antipyretic action. Chlorpheniramine maleate (CPM) is a first generation antihistaminic agent and competitively binds to H1 receptors in the nasal mucosa to prevent the histamine induced vasoreactive responses, exhibiting anti-inflammatory as well as anti-allergic actions. The anti-cholinergic action of CPM is responsible for decrease in the nasal discharge. Phenylephrine is a selective adrenergic receptor agonist, which is an effective nasal decongestant. Its dominant and direct vasoconstricting effects on capacitance blood vessels of the nasal mucosa decreases blood vessel diameter and leads to nasal decongestion. Thus, a triple combination of paracetamol, CPM and phenylephrine helps to take care of constellation of symptoms in common cold.¹⁰

In clinical practice, the treatment for common cold is routinely symptomatic and not directed towards specific etiological agent. Also, such triple combinations of paracetamol, CPM and phenylephrine are available as OTC in developed as well as highly regulated countries like Australia, New Zealand, US, etc and used by patients for symptomatic relief in common cold. There are very few studies evaluating the safety and efficacy of this specific fixed-dose combination in the symptomatic treatment of the common cold in adults and therefore the present study was planned.

METHODS

This was a phase IV, multicentric, open labelled, non-comparative, user-initiated study conducted in 12 Centers across India, 3 centers at each region (North, South, East, West or Central) from November 2017- March 2018. A total of 180 patients were enrolled in the study with 21 patients lost to follow up. Hence data of 159 patients was analyzed.

Inclusion and exclusion criteria

Patients with confirmed diagnosis of common cold (having 4 out of 9 symptoms of headache, fever, body ache, nasal congestion, rhinorrhea, sneezing, sore throat, dysphonia and malaise) and willing to participate in the study were enrolled. Patients of both the gender between 18-75 years of age were recruited for this study.

Patients having hypersensitivity to any of the drugs in combination or to any of the ingredient present in the dosage form and patients suffering from hepatic or renal dysfunction were excluded from the study.

Study procedure

All eligible patients were informed about the nature of the study and written consent was taken to participate in the study. A detailed medical history was obtained from all enrolled patients, followed by thorough clinical examination. Patients were given free physician samples of Sinarest New Tablet (FDC of Paracetamol 500mg, Phenylephrine hydrochloride 10mg and Chlorpheniramine maleate 2mg per tablet) and asked to take 1 tablet thrice a day for a total of 5 days. Follow up visits were scheduled at day 3 and day 5 for efficacy and safety assessment after initial assessment and sample distribution at day 1. TSS scale was used by the physician during each visit for symptoms evaluation. Patients were instructed to keep a diary to record daily symptoms and adverse events if any. In case of any safety-related issues and adverse events or serious adverse events, the investigator withdrew the patient from the trial and treated accordingly. No other medications including nasal decongestants (sprays or drops or any aromatic oils), multi-vitamins, multimineral or antibiotics other than study drug combination were allowed during study duration of 5 days. Non-Pharmacological interventions like steam inhalation or drinking of hot water at regular intervals were allowed and encouraged during the study period.

Efficacy and safety assessment

The efficacy assessment was done by analysing the reduction in Total Symptom Score (TSS) which was a score of all the symptoms related to common cold on an eleven-point scale (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 with 4 grades where 0 on TSS scale means no symptoms, 1 to 3 on TSS scale means mild symptoms, 4-6 on TSS scale means moderate symptoms and 7-10 on TSS means severe symptoms. The average TSS of all the patients at each visit, percent reduction in average TSS at all the follow up visits and the number of patients having no symptoms i.e. 0 on TSS on day 5 and having more than 50% reduction in average TSS were analyzed. At each follow up visit, patients were asked for any adverse events and their diaries were assessed. Adverse events were noted and classified into two categories as serious or non-serious. Adverse events observed were followed up at each visit and treated if necessary, by the investigators till their resolution.

Ethical and regulatory matters

The said combination is available in India and classified as schedule H drug which means it should be sold only in the presence of prescription of a registered medical

practitioner. All the patients participated in the study have read and signed the ICF. The protocol, ICF, CRF, investigators undertaking form, investigators CV, ethics committee registration certificates and investigators medical registration certificates (including post-graduation certificates and certificate of registration of additional qualification) were submitted to DCGI office (Drug Controller General of India), Central Drugs Standard Control Organization (CDSCO) and are registered under ref. no. 29393.

Statistical analysis

The data collected was entered into Microsoft excel 2016 and analyzed using mean and percentages.

RESULTS

Data of 159 patients was analyzed out of 180 patients enrolled as 21 patients were lost to follow up.

Efficacy analysis

The mean age of patients in this study was 34.5 years. Out of all patients, 107 (67.3%) were male and 52 (32.7%) were female.

Mean of TSS was calculated at all the visits and at the same time percent reduction in TSS at visit 2 and 3 was recorded. Mean TSS at visit 1 was 6.62 which was reduced to 3.56 at visit 2 and further reduced to 0.69 at visit 3 as shown in Figure 1. There was a reduction of 46.2% in mean TSS at visit 2 compared to baseline visit 1. Reduction in TSS means improvement of symptoms. Similarly, there was reduction of 89.58 % in mean TSS at visit 3 as compared to baseline. This is shown in Figure 2.

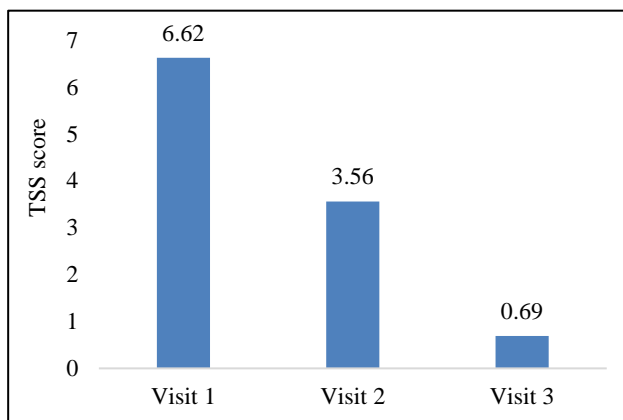


Figure 1: Mean TSS score at each visit.

TSS 0 means patient has no symptoms of common cold or is completely cured. At visit 1, no patient had TSS of 0. At visit 2, 5 (3.14%) patients had TSS of 0 whereas at visit 3, 93 i.e. 58.49% patients were having TSS of 0. This is shown in Figure 3. This shows that at each follow-up visit, number of patients getting completely cured of symptoms

i.e. TSS 0 went on increasing as compared to visit 1 where no patient had TSS 0.

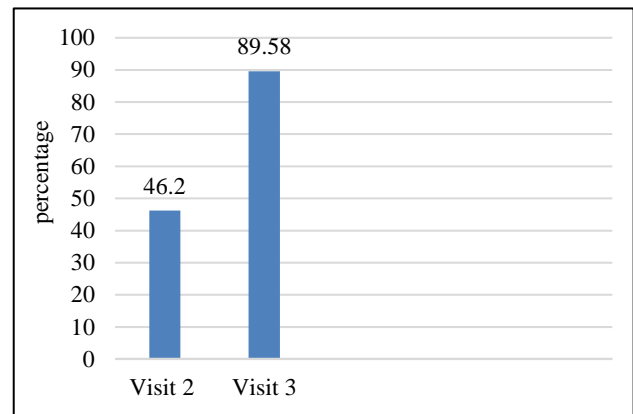


Figure 2: Percent reduction in mean TSS score at follow-up visits from visit 1.

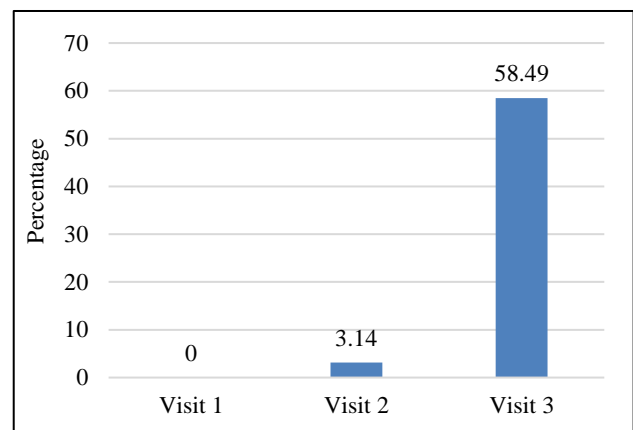


Figure 3: Percentage of patients with TSS 0 at each visit.

Further the data was extrapolated to Likert-type symptom scale in which TSS 0 = no symptoms, TSS 1-3= mild symptoms, TSS 4-6= moderate symptoms and TSS 7-10= severe symptoms.

Figure 4 shows that at follow-up visit 2, percentage of patients with mild and moderate symptoms increases whereas there is no patient with severe symptoms and 3.14% of patients are completely cured as compared to initial visit 1. At follow-up visit 3, total no. of patients getting completely cured increases drastically with no patient having severe symptoms and few patients with mild to moderate symptoms as compared to visit 1. Thus we can say that with the combination drug treatment, severity of symptoms decreases at each visit and patients getting cured increases.

Safety analysis

Among all the patients, 16.36% of patients experienced adverse event. Sedation and drowsiness were the most common adverse event seen in 6.29% of patients followed

by dizziness (4.4%), hyperacidity (2.52%), dryness of mouth and nausea (1.26%), and palpitation (0.63%) (Table 1).

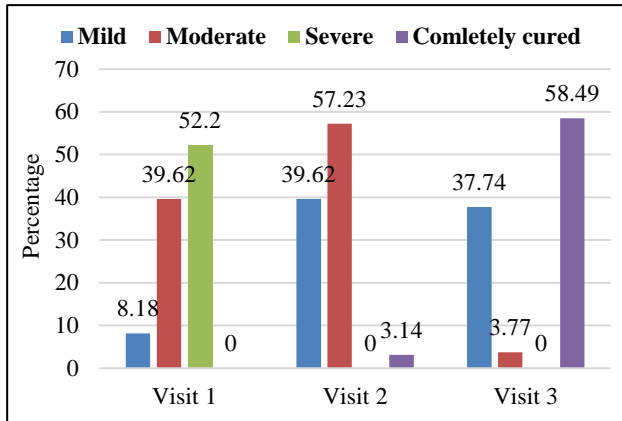


Figure 4: Percentage of patients with symptom severity at each visit.

Table 1: Adverse event seen in patients.

Adverse events	No. of episodes	No. of patients	Percentage of patients
Sedation and drowsiness	29	10	6.29
Hyperacidity	9	4	2.52
Dryness of mouth	5	2	1.26
Nausea	4	2	1.26
Dizziness	20	7	4.4
Palpitation	1	1	0.63
Total	68	26	16.36

DISCUSSION

Common cold is the most frequently encountered disease in medical practice. Symptoms usually peak at 2 to 3 days and have a mean duration of 7 to 10 days. It resolves by itself and only symptomatic treatment is required.⁶ According to the guidelines of DPHHS, Cochrane review, Picon PD et al, and Eccles R et al, a triple combination of analgesics, decongestants and antihistamines provides better relief for multiple symptoms in common cold and allergic rhinitis.⁶⁻⁹ This is one of the very few studies conducted to find out efficacy and safety of a fixed dose combination of paracetamol, chlorpheniramine maleate and phenylephrine in treatment of common cold.

Mean TSS at visit 1 was 6.62 which was reduced to 3.56 at visit 2 and further reduced to 0.69 at visit 3. From visit 1 to visit 2 there was a reduction of 46.2% in mean TSS and from visit 1 to visit 3 there was reduction of 89.58% in mean TSS. At visit 1, no patient had TSS of 0. At visit 2, 5 (3.14%) patients had TSS of 0 whereas at visit 3, 93 i.e. 58.49% patients were having TSS of 0. At follow-up visit 2, percentage of patients with mild and moderate

symptoms increases whereas there is no patient with severe symptoms and 3.14% of patients are completely cured as compared to initial visit 1. At follow-up visit 3, total no. of patients getting completely cured increases drastically with no patient having severe symptoms and few patients with mild to moderate symptoms as compared to visit 1.

Out of 159 patients, 26 i.e. 16.36% experienced adverse event. Sedation and drowsiness (6.29%) were the most common adverse event seen in patients which may be due to Chlorpheniramine maleate present in the combination. Hyperacidity and nausea can be contributed to Paracetamol. Dryness of oral/nasal cavity and dizziness may be due to the anticholinergic property of 1st generation antihistaminic like Chlorpheniramine maleate. The vital signs (Blood Pressure, Respiratory rate and Pulse rate) showed no significant change from the baseline readings at follow up visits which are particularly important as Phenylephrine, a vasoconstrictor is a component of the study drug combination.

Picon et al, conducted a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of a fixed-dose combination of paracetamol, chlorpheniramine maleate and phenylephrine in 146 individuals aged 18 to 60 years who had moderate to severe flu-like syndrome or common cold.⁶ The reduction of total symptom score in the fixed drug combination was from score of 14.09 at baseline to 3.54 at the end of 10 days of study period whereas the reduction in case of placebo it was from 14.23 at baseline to 4.64 at the end of 10 days. Comparison of overall symptom scores in the two groups revealed a significantly greater reduction in the treatment group than in the placebo group (p = 0.015). The number, distribution and type of adverse events observed were similar in both the groups. The study concluded that the combination of Chlorpheniramine maleate, Paracetamol and Phenylephrine was safe and more effective than placebo in the treatment of common cold as well as flulike syndrome in adults.

Eccles et al, recommended the combination of products for symptomatic treatment of common cold and flu.⁹ Multi ingredient combination products for multi-symptom relief are formulated to safely, simply, and simultaneously treat multiple symptoms when used as directed. The rationale for the formulation for common cold and flu is therefore practical, logical and reasonable. No evidence has been found that multi-symptom relief medicines are inherently less safe than single-active ingredient medicines. Multi symptom relief combination products containing several active ingredients provide a safe, effective, cost-effective, and convenient way of treating the multiple symptoms of common cold and flu, when used as directed.⁹

Kiran M et al, conducted various studies with different fixed drug combinations- Levocetirizine, Paracetamol and Phenylephrine, Fexofenadine, Paracetamol and Phenylephrine, Chlorpheniramine maleate, Paracetamol

and Phenylephrine to evaluate the safety as well as efficacy of the combination in symptomatic relief in common cold.¹⁰⁻¹² Symptoms related to common cold were measured using Total Symptom Score (TSS) scale on baseline, day 3 and day 5. All of the studies reported reduction in TSS score at day 3 and day 5. More than 50% reduction in TSS score was seen at day 5 compared to baseline in all of the studies. Study conducted using Chlorpheniramine maleate, Paracetamol and Phenylephrine had total of 16.57% patients of study population with adverse events in which majority were sedation and drowsiness which could be because of Chlorpheniramine maleate. Similar results were obtained in this study.

The cause for reduction in total symptoms score of common cold may be due to study drug combination or self-resolving nature of the disease itself. Several papers have suggested that common cold mostly resolves in average 7 days.¹⁰ So to minimize this limitation in this study, duration was decided to be kept 5 days, so the benefit observed on day 5 would be mostly due to the study drug combination.

CONCLUSION

Common cold is the most frequently encountered disease in medical practice. It is also a self-limiting disease, resolves by itself and only symptomatic treatment is required. Our study showed that fixed dose combination of Paracetamol 500mg, Phenylephrine 10mg, Chlorpheniramine maleate 2mg, provides optimum symptomatic relief and is safe for use in the symptomatic management of common cold.

Funding: Funding sources by Centaur Pharmaceuticals, Mumbai, Maharashtra, India

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Mossad SB. Fortnightly review: treatment of the common cold. *BMJ: British Medical Journal*. 1998 Jul 4;317(7150):33.
2. Van Schoor J. Colds, flu and coughing: a review of over-the-counter cold and flu medicines. *South African Family Practice*. 2013;55(4):334-9.
3. Kirkpatrick GL. The common cold. *Primary Care: Clinics in Office Practice*. 1996 Dec 1;23(4):657-75.
4. Health in India and the over the counter opportunity. Nielsen newswire. 2013. Available at:

<https://www.nielsen.com/qa/en/insights/news/2013/health-in-india-and-the-over-the-counter-opportunity.html> as accessed on 20/11/2018 at 10:13 hrs.

5. Jackson GG, Dowling HF, Spiesman IG, Boand AV. Transmission of the common cold to volunteers under controlled conditions. I. The common cold as a clinical entity. *AMA Arch Intern Med*. 1958;101:267-78.
6. Picon PD, Costa MB, da Veiga Picon R, Fendt LC, Suksteris ML, Saccilotto IC, et al. Symptomatic treatment of the common cold with a fixed-dose combination of paracetamol, chlorphenamine and phenylephrine: a randomized, placebo-controlled trial. *BMC infectious diseases*. 2013 Dec;13(1):556.
7. Health guidelines. The common cold. 2013;10-17. Available at: <https://dphhs.mt.gov/Portals/85/dsd/documents/DDP/MedicalDirector/CommonCold101713.pdf> as accessed on 20/11/2018 at 12:08 hrs.
8. De Sutter AI, van Driel ML, Kumar AA, Lesslar O, Skrt A. Oral antihistamine-decongestant-analgesic combinations for the common cold. *Cochrane Database of Systematic Reviews*. 2012(2).
9. Eccles R, Fietze I, Rose UB. Rationale for Treatment of Common Cold and Flu with MultiIngredient Combination Products for Multi-Symptom Relief in Adults. *Open J Resp Dise*. 2014;4:73-82.
10. Kiran M, Pawaskar L, Yadav P. Efficacy and safety of a combination of paracetamol, levocetirizine and phenylephrine in the symptomatic treatment of common cold and allergic rhinitis. *Int J Curr Res Med Scien*. 2017;3(1):53-9.
11. Kiran M, Pawaskar L. Safety and Efficacy of a combination of Paracetamol, Phenylephrine and Fexofenadine in adult patients of Common Cold and Allergic Rhinitis: Phase IV Study. *World J Pharmaceut Resea*. 2017;6(4):1624-34.
12. Kiran M, Pawaskar L, Yadav P. Efficacy and Safety of a combination of Paracetamol, Chlorpheniramine maleate and Phenylephrine in the symptomatic treatment of Common Cold: Phase IV Clinical study. *The Indian Practitioner*. 2017;70(2).

Cite this article as: Kiran MD, Vakharia MP, Pawaskar LJ, Sheikh SN. Efficacy and safety of a fixed dose combination of paracetamol, chlorpheniramine maleate and phenylephrine in treatment of common cold: a phase IV, open-labelled, multi-centric study. *Int J Basic Clin Pharmacol* 2019;8:34-8.