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Research Article

Comparison of Effects ofthe Dipyrone, Caffeine and Chlorphenyramine Combination Versus Paracetamol, Phenylephrine, and Chlorphenyramine Combination on Symptomatic Relief of Common Cold and Recovery Time: A Double Blinded Non-Inferiority Study

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Abstract

Objective: To determine whether the effects of combination of sodium dipyrone monohydrate 500mg, caffeine 30mg, and chlorpheniramine maleate 2mg (Benegrip) is not inferior than the combination of sodium dipyrone monohydrate 250mg plus 2mg of chlorpheniramine maleate (Resphenol), in the symptomatic relief for common cold and upper airway infection. Methods: An open, prospective, controlled, randomized, parallel, unicentric, and non-inferiority clinical study, in which 91 participants were randomly assigned to the Benegrip group and 90 patients to the Resphenol group. Patients were submitted to a questionnaire in which scored the symptoms on inclusion and randomization, on the third day, and on the seventh consecutive days. Results: There were no statistically significant differences in the symptom scale scores between the groups. The incidence of adverse events was 4.1% in the Benegrip group and 3.6% in the Resphenol group. Conclusion: The study demonstrated the effectiveness of the Benegrip combination in the treatment of common cold and its non-inferiority when compared to Resphenol.

Keywords: *Upper Respiratory Tract Infections; Common Cold; Treatment Of Common Cold; Questionairre Study; Randomised Controlled Study*

Introduction

Common cold falls within the group of upper respiratory tract infections (URTI). It is a benign, self-limiting condition of viral etiology. It is probably the most common disease in the industrialized world [1-3], wherein, a child may be infected 6 to 8 times per year and an adult, 2 to 4 times per year [4]. URTI has a strong economic impact, being the main reason for absenteeism from work and school in 2013 in Brazil [5] [6]. This incidence is similar in developed and underdeveloped countries, varying from 30 to 40% of all emergency room visits [7]. They can also trigger other pathologies such as asthma [8], exacerbation of chronic obstructive pulmonary disease [9], and bacterial pneumonia [10].

Headache, sneezing, chills, sore throat, malaise, cough, runny nose, and nasal obstruction are the most common symptoms of common cold [11], with a variable clinical course from seven days to ten days [12], and there may be neurological impairment, as a drop in psychomotor capacity [13].

The treatment of this self-limiting acute respiratory viral condition is restricted to symptomatic relief. Smith., *et al.* [14], in their Cochrane review, claimed that over-the-counter drugs are often recommended as the first line of treatment, but there is limited evidence about the effectiveness of these drugs and the type of drug combination that is most suitable as an initial approach. Several drugs can be used, mainly, analgesics, antihistamines, and alpha-adrenergic agonists.

Analgesics such as dipyrone and paracetamol are commonly used to treat common cold, which are suitable for relief of symptoms such as headache, sore throat, and malaise [15]. The use of paracetamol showed a significant response in the relief of headache, febrile discomfort, and pain in patients with URTI [16].

Antihistamines have shown minimal benefits and are associated with adverse sedative effects [17]. Chlorpheniramine maleate is a first-generation antihistamine, that acts competitively antagonistic with histamine for H1 receptors present in the effector cells of the airways, thus reducing edema of the nasal mucosa, and the production of nasal secretion. A systematic review showed better control of URTI symptoms with antihistamines in five days than a placebo [18].

Phenylephrine hydrochloride is an alpha-adrenergic, non-catecholamine, with a nasal decongestant effect [19]. Phenylephrine hydrochloride is a potent vasoconstrictor that has direct and indirect sympathomimetic effects, by inhibiting the cyclic AMP and norepinephrine release, respectively. It acts on nasal receptors causing vasoconstriction and thus reducing edema and congestion. It has minimal effects on the cardiovascular, urinary, central nervous, and endocrine systems, with bioavailability of only 38% [20], but it seems to double when associated with paracetamol [21].

Paracetamol and dipyrone are antipyretic and analgesic medications that act on the cyclooxygenase system. The additive effect of phenylephrine hydrochloride as a symptomatic relief and as an adjuvant in the prevention of local complications is uncertain, with doubts about the additive effect of the alpha-adrenergic in the symptomatic control and recovery time of common cold and URTI in adults. Hence, the primary objective of the present study is to compare the efficacy in relieving the signs and symptoms of upper airway infections using two formulations containing, a combination of 500mg sodium dipyrone monohydrate, 30mg caffeine and 2mg chlorpheniramine maleate, called Benegrip®, to the combination of 400mg paracetamol, 4mg phenylephrine hydrochloride and 4mg chlorpheniramine maleate, called Resfenol®. Additionally, its secondary objective is to determine whether Benegrip® combination was non-inferior to the Resfenol® combination in the symptomatic relief related to the common cold, as reported by the patient.

Materials and Methods

An open, prospective, controlled, randomized, parallel, single-centered, non-inferiority study was conducted to compare Benegrip®, the combination of 500 mg sodium dipyrone monohydrate, 30mg caffeine, and 2mg chlorpheniramine maleate and Resfenol®, a combination of 400 mg paracetamol, 4mg phenylephrine hydrochloride, and 4mg maleate chlorpheniramine, when used in the treatment for URTI and common cold.. The study was carried out at the ABC Medical School (FMABC), between April 2015 and April 2017, approved by the local Research Ethics Committee, and consent was obtained from all patients. The volunteers were recruited through posters at the college.

A total of 181 participants were selected and randomized (91 for the Benegrip® group and 90 for the Resfenol® group). Of these, 7 participants were excluded: one over 65 years of age, one with URTI, one for having participated in the clinical study for less than 12 months, and 4 for using prohibited drugs., 18 participants were discontinued; eleven for loss of follow-up and seven due to lack of adherence. The study eventually included 156 participants, 74 in the Benegrip® group and 82 in the Resfenol® group.

The objective was to determine whether the Benegrip® combination was superior to the Resfenol® combination in providing symptomatic relief to the common cold, as reported by patients. Such relief was assessed using a symptom rating scale (Figure 1).

Status	Absent	Sporadic / Little intense / (Mild)	Present in part of the day or night / medium intensity (moderate)	Frequent / intense / interferes with sleep or activities (severe)
Signs / Symptoms / Score	0	1	2	3
Nasal obstruction				
Coryza				
Cough				
Nasal Itching				
Sneeze				

Figure 1: *Score of Signs and Symptoms.*

Inclusion criteria were, ages between 18 and 65 years, of both sexes, and any race, symptoms of viral infection of the upper airways (with runny nose, nasal obstruction and itching, coughing, and sneezing) with a minimum evolution time of 48 hours and a maximum of 72 hours, scores above 7 on the scale table of the signs and symptoms scores (Figure 2), report of two or more signs or symptoms classified as moderate (score 2) on the scale table of the scores of signs and symptoms, able to provide written informed consent, understand and respond to applied questionnaires, and availability to adhere to the treatment and attend scheduled appointments, and respect the withdrawal period for the drugs listed in the prohibited medication item (Annex PROHIBITED MEDICATION). Exclusion criteria included volunteers with a history of hypersensitivity to any of the components of the formulas, participation in any clinical investigation in the past 12 months, presence of upper airway infection (suspected or known) of bacterial origin, chronic mouth breathing report, patients undergoing chronic drug treatment for allergy, presence of grade II and III deviated septum, nasal polyps, or other conditions that determine nasal obstruction on direct visualization or previous history; current treatment with inhaled beta-agonist agents; history of lung disease (asthma, bronchiectasis, neoplasms); concomitant use of other antihistamines, decongestants, mucolytics, or antitussives; patients who are aware of having HIV or immunocompromised; hx of gastroesophageal reflux disease; presence of significant diseases or clinically significant disorder at the investigator's discretion, may interfere with the study or require treatment that may interfere with the assessment of efficacy and/or safety. Patients with pregnancy potential underwent a urinary beta HCG examination; if the result was positive, there were excluded from the study. All included patients were randomized to receive either Resfenol® or Benegrip®.

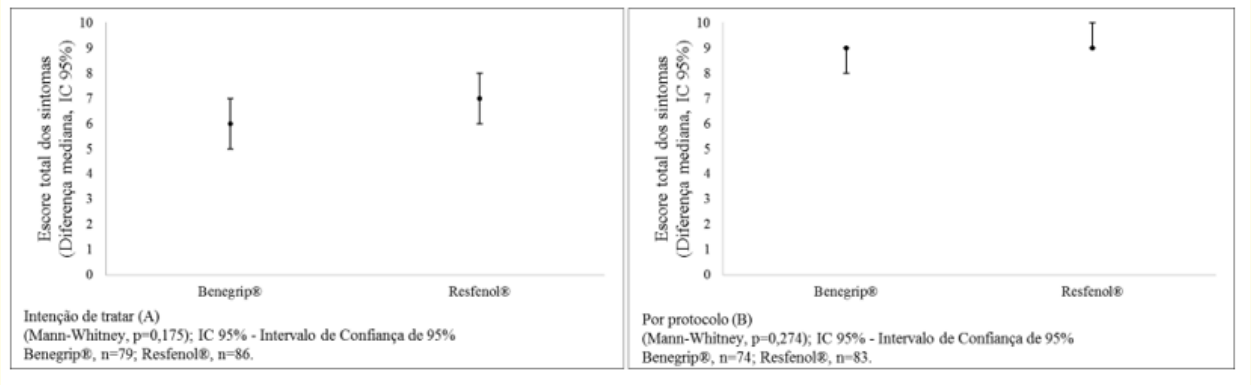

Figure 2: *Primary measure of effectiveness: Difference in total symptom scores between groups in the intention to treat analysis (A) and in the analysis of the population by protocol (B).*

The Benegrip® combination was administered by 2 tablets simultaneously: 1 green coated tablet composed of 250 mg monohydrated sodium dipyrone plus 30 mg of caffeine and 1 yellow-coated tablet composed of 250 mg monohydrate sodium dipyrone plus 2 mg chlorpheniramine maleate, while the Resphenol® combination was administered by a single tablet. Participants were instructed to take the study medication four times a day, following the hours of 8 am, 12 pm, 4 pm and 8 pm, for seven consecutive days. In order to ensure adherence, guidance was provided by a health professional (doctor, nurse, pharmacist), reinforcement techniques, advice, behavioral strategy, and additional supervision.

Patients underwent three visits: inclusion date and randomization, and third and seventh consecutive days.

On the first medical visit, patients were asked about five signs and symptoms of the common cold: runny nose, nasal obstruction, nasal itching, coughing, and sneezing. They were scored on a four-point scale classified by status as, absent - zero points; sporadic or mild or light = 1 point; medium or moderate intensity or present in part of the day or night = 2 points; frequent or intense or severe or interfering with sleep or activities = 3 points. The signs and symptoms were also evaluated by the total sum of the scores presented by them, ranging from 0 to 15. From the set of observations about each symptom, for each patient and their respective scores, the median of observations, and the confidence interval were calculated.

All patients received instructions to fill in a diary at home to record adherence to the medication, use of concomitant medication, adverse events, and records of the same five signs and symptoms (Figure 1). The diary was evaluated on the second and third visits.

On the third day of follow-up, there was a telephone contact, asking about the improvement of symptoms through the score of the table of signs and symptoms. In addition, the participants received general guidance on the treatment and maintenance of filling in the diary. On the third and final visit, on the seventh consecutive day, patients were questioned and scored again using the sign and symptom score table. In the second and third visits, the investigator and the patient assessed the response to therapy and treatment effectiveness using a specific subjective questionnaire on quality of life, signs, and symptoms. To analyze the effectiveness of treatments, differences were obtained between the scores of the table of signs and symptoms collected at the time of the randomization visit and the last visit on the seventh day of treatment.

The diary was assessed for correct completion, administration of prohibited drugs and adherence to treatment. Adherence to treatment was measured in two ways: a) verbal interrogation and b) accounting of the returned drug (pill count).

The clinical safety of using the combination Benegrip® and Resphenol was assessed by monitoring clinical evidence of serious and non-serious adverse events. All events were spontaneously observed or reported, as well as the frequency, intensity, and causal relationship with the product under investigation, were recorded in the medical record and in the clinical record of the study.

Statistical analysis

Qualitative variables were described by absolute and relative frequencies. Quantitative variables were described by measures of central tendency and 95% confidence interval, by means of adherence to normal distribution. Data distribution was assessed using the Shapiro–Wilk test.

To analyze the association between qualitative variables, the chi-square test was used, and Yattes correction was performed according to the expected frequency of the variables. To analyze the differences in quantitative variables between groups, we used the Student's t-test for variables with normal distribution (Shapiro-Wilk, $p \geq 0.05$) and the Mann-Whitney test for variables without normal distribution (Shapiro–Wilk, $p < 0.05$). The level of significance was set at 5%. The analyses were performed using Stata® 11.0 Software.

Results

The flowchart of patient selection for the study and its respective distribution in the groups is shown in figure 3, where there was no selection bias.

SUBJECTIVE EFFECTIVENESS EVALUATION SCORE		
Resolved	Absent signs / symptoms. Not needing additional therapy	Score 3
Much better	Signs and symptoms noticeably better, without impairing quality of life	Score 2
Small improvement	Better signs and symptoms, but with no change in quality of life	Score 1
Unchanged	There is no difference between before and after treatment	Score 0
Worse	here was a worsening comparing the state before and after treatment	Score -1

Figure 3: *Score of subjective effectiveness assessment.*

Table 1 shows the demographic and clinical characteristics of the patients, observing the homogeneity of the sample. The patients were young (mean age, 35 years), with a slight predominance of females (57% in the Benegrip® group and 65% in the Resfenol® group), with no other comorbidities. The clinical presentation measured by the signs and symptoms score table was similar.

Characteristics	Benegrip® N=90 (50,6%)	Resfenol ® N=88 (49,4%)	P
Gender, n (%)			
Female	51 (56,7)	57 (64,8)	0,268*
Male	39 (43,3)	31 (35,2)	
Age (years), median (IC 95%)	35,0 (31,0; 39,0)	35,0 (31,0; 38,0)	0,968**
IMC (kg/m^2), median (IC 95%)	25,8 (24,6; 27,2)	25,1 (24,3; 26,3)	0,629**
Age (years), (°C), median (IC 95%)	36,1 (36,1; 36,2)	36,1 (36,1; 36,2)	0,619**
Heart Rate (bpm), median (IC 95%)	78,0 (73,0; 80,0)	78,0 (74,0; 80,0)	0,342**
Heart Rate (mmHg), median (IC 95%)	120,0 (120,0; 120,0)	120,0 (120,0; 120,0)	0,817**
Diastolic Blood Pressure (mmHg), median (IC 95%)	80,0 (80,0; 80,0)	80,0 (75,7; 80,0)	0,305**
Clínical Characteristics			
Nasal obstruction, n (%)			0,683***
Absent	1 (1,1)	0 (0,0)	
Sporadic / Light Intensity	4 (4,4)	6 (6,8)	
Eventually / Medium Intensity	39 (43,4)	36 (40,9)	
Often / Intense Intensity	46 (51,1)	46 (52,3)	
Runny nose, n (%)			0,518***
Absent	3 (3,3)	1 (1,1)	
Sporadic / Light Intensity	11 (12,2)	8 (9,1)	
Eventually / Medium Intensity	39 (43,4)	35 (39,8)	
Often / Intense Intensity	37 (41,1)	44 (50,0)	
Cough, n (%)			0,055 ***
Absent	11 (12,2)	2 (2,3)	
Sporadic / Light Intensity	28 (31,1)	34 (38,6)	
Eventually / Medium Intensity	29 (32,2)	34 (38,6)	
Often / Intense Intensity	22 (24,5)	18 (28,5)	

Nasal itching, n (%)			0,443***
Absent	16 (17,8)	13 (14,8)	
Sporadic / Light Intensity	20 (22,2)	21 (23,8)	
Eventually / Medium Intensity	32 (35,6)	24 (27,3)	
Often / Intense Intensity	22 (24,4)	30 (34,1)	
Sneezing, n (%)			0,698***
Absent	4 (4,4)	3 (3,4)	
Sporadic / Light Intensity	18 (20,0)	22 (25,0)	
Eventually / Medium Intensity	36 (40,0)	38 (43,2)	
Often / Intense Intensity	32 (35,6)	25 (28,4)	
Total symptom score	10,0 (9,0; 11,0)	10,0 (10,0; 11,0)	0,294**
*Chi-square; ** Mann-Whitney test; *** Chi-square with Yattes correction 95% CI: Confidence interval per pm			

Table 1: *Baseline and demographic characteristics (Variables of sample homogeneity).*

Tables 2 and 3, respectively, refer to the results of the analysis by protocol regarding the reduction in the score of signs and symptoms and time in days for remission of signs and symptoms, where no statistical difference was observed between the groups, resulting in no difference between Benegrip® and Resfenol®, for the points described in patients with common cold. Such results were consolidated when analyzed by protocol, among individuals who did not violate the study or were discontinued (Figure 4).

Follow-up	Intention to Treat			Population by Protocol		
	N	Total symptom score	p*	N	Total symptom score	p*
Day 1		Median (IC 95%)			Median (IC 95%)	
Benegrip®	74	10,0 (8,5; 10,0)	0,376	73	9,0 (8,0; 10,0)	0,452
Resfenol ®	82	9,0 (8,0; 9,4)		80	9,0 (8,0; 10,0)	
Day 2						
Benegrip®	74	8,0 (7,0; 10,0)	0,514	73	8,0 (6,6; 10,0)	0,530
Resfenol ®	82	7,5 (7,0; 8,0)		80	7,5 (7,0; 8,0)	
Day3						
Benegrip®	74	5,5 (4,0; 6,9)	0,678	72	5,5 (4,0; 6,8)	0,669
Resfenol ®	82	6,0 (5,0; 7,0)		78	6,0 (5,0; 7,0)	
Day 4						
Benegrip®	74	4,0 (3,0; 5,0)	0,377	60	4,0 (3,0; 5,0)	0,423
Resfenol ®	82	4,0 (3,0; 5,0)		64	4,0 (3,0; 5,0)	
Day 5						
Benegrip®	74	3,0 (2,0; 3,0)	0,594	72	3,0 (1,2; 3,0)	0,670
Resfenol ®	82	2,0 (1,0; 3,0)		80	2,0 (1,0; 3,0)	
Day 6						
Benegrip®	71	1,0 (0,0; 2,0)	0,814	69	1,0 (0,0; 2,0)	0,723
Resfenol ®	76	1,5 (0,9; 2,0)		74	1,5 (1,0; 2,0)	
Day7						
Benegrip®	61	1,0 (0,0; 1,0)	0,918	59	1,0 (0,0; 1,0)	0,733
Resfenol ®	69	1,0 (0,0; 1,0)		67	1,0 (0,0; 1,0)	

Table 2: *Score of signs and symptoms score during seven days of follow-up between the Benegrip® and Resfenol® groups.*

Symptoms	Intend to Treat			Population by Protocol		
	N	Days (IC 95%)	p*	N	Days (IC 95%)	p*
Nasal obstruction						
Benegrip®	57	5,0 (5,0; 6,0)	0,038	57	5,0 (5,0; 6,0)	0,048
Resfenol ®	66	5,0 (5,0; 6,0)		65	5,0 (5,0; 6,0)	
Coryza						
Benegrip®	57	5,0 (5,0; 5,0)	0,878	55	5,0 (5,0; 5,3)	0,801
Resfenol ®	66	5,0 (5,0; 5,0)		65	5,0 (5,0; 5,0)	
Cough						
Benegrip®	53	4,0 (3,0; 5,0)	0,507	43	4,0 (3,0; 5,0)	0,539
Resfenol ®	65	4,0 (4,0; 5,0)		47	4,0 (4,0; 5,0)	
Itching Cough						
Benegrip®	56	4,0 (3,1; 5,0)	0,883	56	4,0 (3,1; 5,0)	0,908
Resfenol ®	64	4,0 (4,0; 5,0)		62	4,0 (4,0; 5,0)	
Sneeze						
Benegrip®	65	4,0 (4,0; 5,0)	0,638	63	4,0 (4,0; 5,0)	0,594
Resfenol ®	75	4,0 (4,0; 5,0)		73	4,0 (4,0; 5,0)	

Table 3: *Time in days of remission of signs and symptoms between the groups treated with Benegrip® and Resfenol®.*

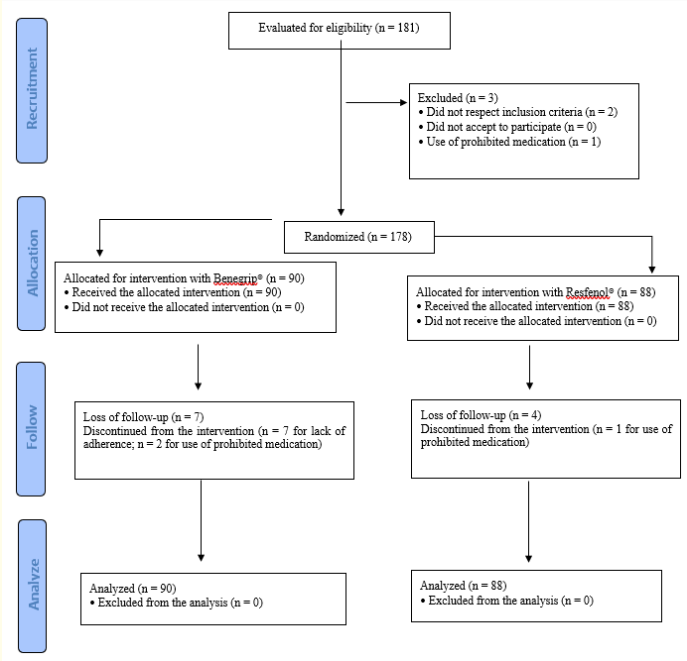

Figure 4: *Flowchart of the stages of conducting the clinical study.*

The incidence of adverse effects was low, corresponding to 4.1% in the Benegrip® group and 3.6% in the Resfenol® group (Table 4).

Group	id	Event	Initial	Resolved	Intensity	Relation	Action Take	Adverse event serious
Benegrip®	25	Urticarial reaction on the face	15/10/2015	21/10/2015	Mild		Interruption medication	No
Resfenol®	26	Headache	22/10/2015	22/10/2015	Moderate	No	Mudança de medicamento concomitante	No
Benegrip®	37	Headache	22/01/2015	22/10/2015	Moderate	No	Mudança de medicamento concomitante	No
Resfenol®	118	Somnolence	22/08/2016	25/08/2016	Mild	Yes	Nenhuma ação tomada	No
Resfenol®	140	Somnolence	21/02/2017	24/02/2017	Mild	Yes	Nenhuma ação tomada	No
Benegrip®	157	Migraine	11/03/2017	12/03/2017	Mild	No	Nenhuma ação tomada	No

Table 4: *Adverse effects that occurred between the Benegrip* ***® and*** *Resfenol* ***® groups.***

Discussion

This is the first study to compare the combination of dipyrone, caffeine, and chlorpheniramine with paracetamol, phenylephrine, and chlorpheniramine, which are frequently used for symptomatic relief of URTI. The compositions differ in their analgesic, vasoconstrictor, and nasal decongestant effect.

Dipyrone [22] and paracetamol effects were compared in isolation, with superiority over placebo and similar potency, despite different adverse effects [23]. Paracetamol can relieve symptoms of nasal obstruction and rhinorrhea, but it does not seem to affect cough, malaise, wheezing, and sore throat [24]. We believe that the effects of paracetamol or dipyrone were indifferent in the studied population.

The antihistamine chlorpheniramine was present in both compared formulations at doses of 4mg and 2mg. Its effectiveness was analyzed in IVAS with 10mg dosage, four times a day for seven days, with improvement in symptoms of nasal obstruction, cough, sore throat, and runny nose [25]. When compared to placebo in 227 patients undergoing IVAS, there was an improvement in the symptoms reported by both the patient and the physician [26].

Both compositions have a stimulant such as caffeine (Benegrip®) and phenylephrine (Resphenol®), capable of causing vasoconstriction and being a decongestant [27]. Caffeine reduced the symptoms of malaise, improving results in warning tests of an English population with URTI [28]. A randomized study tested adults with URTI for psychomotor performance one hour after caffeine 100mg, observing faster tests compared to ibuprofen and placebo alone [14].

The efficacy of phenylephrine 10mg single dose was greater than a placebo in a meta-analysis that grouped 113 patients with URTI, showing a 20% reduction in nasal resistance symptoms [29]. Systematic review and meta-analysis showed no difference in nasal symptoms in the dose of phenylephrine used, wherein a concentration of 25mg showed a significant reduction in nasal resistance in 27.6% (95% CI 17.5% to 37.7%), a factor that was not observed when only symptoms were evaluated [30]. In the present study, only symptoms

reported by the patients were evaluated, wherein the objective measurement of nasal resistance by rhinomanometry could have added a better distinction [31].

The effects of the antihistamine-decongestant combination were assessed in a meta-analysis and systematic review (OR 0.27, 95% CI 0.15 to 0.50) [32], with the necessary number to treat (NNT) of five adult patients. The present study corroborates the results of this review, but the combination of drugs and dosages evaluated were not the same.The objective of this study was not to evaluate a specific symptom, such as rhinorrhea or nasal obstruction, wherein, antihistamines, and phenylephrine could have had a better response [18]. This factor should be better evaluated in further studies designed to identify specific improvement of a type of symptom.

Another factor to be considered is the ability of the symptom scales to be sensitive enough to detect differences between medications that may exist. The symptom score is subjective and depends largely on the patient's motivation and collaboration in completing it. The measure of resistance to nasal airflow is certainly more sensitive to assess the effect of drugs on the nasal obstructive component and would be a potential tool to identify patients who could benefit from the addition of alpha adrenergics to the symptomatic treatment of viral infections of the upper airways.

This study evaluated predominantly young patients without associated pathologies, a factor that substantially reduces the risk of developing adverse effects associated with the combinations [33]. Different formulations were found to be similar, including adverse events, incidence, and intensity, as well as symptomatic relief and non-interruption of daily activities. In the literature, drowsiness was the most common adverse effect of chlorpheniramine reported in patients with URTI [26]. Phenylephrine at a dose of 25mg did not show an increase in the heart rate or blood pressure in a meta-analysis and a systematic review that aimed at that purpose [30], suggesting that the association with other drugs may have an adrenergic potentiating effect. The association of phenylephrine plus paracetamol showed a greater potential to increase blood pressure than phenylephrine alone, as observed in those with previous cardiovascular involvement [33], a group that was absent in our sample. Regarding the association of antihistamine-decongestant, there was no significant difference in adverse effects, with an increase in reports of dry mouth (OR 3.77, 95% CI 1.75 to 8.14) and insomnia (OR 3.02, 95% CI 1.08 to 8.47) in the major review and meta-analysis treatment group [32].

Our study had several limiting factors. We can mention the number of patients studied, where the analysis is complex because it is a disease of rapid clinical course, self-limited, and variable symptoms. Finally, employing objective measures such as nasal resistance [31] could increase the quality of the data beyond the use of a questionnaire.

Conclusion

The present study concludes that the use of the combination dipyrone sodium monohydrate 500mg, caffeine 30mg, and chlorpheniramine maleate 2mg, entitled BENEGRIP® is effective for symptomatic relief of the common cold, showing itself to be non-inferior to 400mg paracetamol, hydrochloride phenylephrine 4mg, and chlorpheniramine maleate 4mg, entitled RESFENOL®®.

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Conflict of Interest

Declare if any financial interest or any conflict of interest exists.

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