To evaluate the efficacy and safety of CofNovex plus (EMA) syrup

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Abstract: The cough and cold are very widespread conditions and a common purpose for advice in general practice. Utmost often the sign and symptoms of cough are produced by acute viral airway infection and the course is frequently benign. But it can be converted into bacterial super-infection and can cause acute bronchitis. Herbal medicines are used to treat symptoms of the cough and cold, and among these medicines Ivy leaf is used to treat mucous discharge and irritation in throat due to the cough and cold. In addition to synthetic substances such as acetylcysteine, carbocisteins, ambroxol and bromhexine, herbal medicines contain saponins, which are used in these indications. Not just Ivy, but also the marshmallow and mustard seeds used for these indications. This clinical trial was conducted in 220 patients, in which 110 receive the CofNovex plus European Medicines Agency (EMA) syrup and 110 receive the placebo. The age range of patients was 3 years to above 15 years. The sample paired t-test was applied to evaluate the significant level. CofNovex plus (EMA) syrup was very effective in treating cough and cold symptoms. The new treatment CofNovex plus (EMA) syrup was safe and well tolerated in patient at given specific age group.

Keywords: CofNovex plus (EMA) syrup, cough, herbal treatment, cold.

INTRODUCTION

The preparations of ivy leaf (Hedera helix) are prescribed in pediatric treatment as therapeutic herbs with expectorant action for the management of cough and cold. The usage of diverse types of ivy leaf extract for this illness was legitimately recognized by the herbal medicine committee of the European Medicines Agency (EMA). Cough is a very common illness and a common purpose for advice in general practice (McCormick *et al*., 1995; Hak *et al*., 2006; Charles *et al*., 2004; Chung *et al*., 2008). Most frequently the symptoms of cough are caused by acute viral airway infection (URTI) and the progression is frequently benign and even if bacterial super-infection can take place in acute bronchitis (Gonzales *et al*., 2001; Irwin *et al*., 2000). In long-lasting cough, significant reasons are chronic obstructive pulmonary disease (COPD). Asthma, regarded as obstruction of the airways and hyper-secretion of mucus that additionally cause signs such as wheezing or dyspnea. The improper use of antibiotics in respiratory infections of the respiratory tract is a major problem that causes the pathogen resistance to be an essential issue deprived of disturbing the tenacity of cough on medical care (Fahey *et al*., 1998). Therefore, options non-antibiotic alternative treatments needed. OTC medications which are frequently used to treat cough and cold in children and adults, are mucolytic and antitussive agents, which are also extensively recommended in primary care (Smith *et al*., 2008). In the United Kingdom, cough and cold preparations accounted for turnover of 102 million pounds in 2008 (Proprietary Association of Great Britain 2009), among these anti-cough medicines no antibiotics. Herbal medicines extracts obtained from the Ivy leaf (Hedera helix) are very popular in numerous European countries (Coca *et al*., 2008; Glaeske *et al*., 2008; Guo *et al*., 2006). In 2007, more than 79.9% of herbal cough medicine recommended in Germany understood Ivy extract and amounted to nearly 1.99 million prescriptions countrywide and sales volume of over € 12.9 million (Coca *et al*., 2008). Ivy leaf encloses saponins, which have mucolytic, bronchodilators and antibacterial effects (Sieben *et al*., 2009; Gepdiremen *et al*., 2005). Herbal medicines are used to treat symptoms of the cough and cold (Hanel *et al*., 2004), and these medicines are mucolytic agents often used in cases of irritable cough due to the cold and other respiratory diseases with formation of tough mucus and cause bronchitis. In addition to synthetic substances such as acetylcysteine, carbocisteins, ambroxol and bromhexine, herbal medicines contain saponins, which are used in these indications. Not only Ivy, but also the marshmallow and mustard seeds (Hecker *et al*., 2004) are herbal medicines traditionally used as drops, syrup or infusions administered to treat cough. As for the indication of Ivy dry leaf extract in the treatment of chronic airway obstruction in children (Hofmann *et al*., 2003). There are different systems of medicine for the treatment of Cough and cold, such as Allopathic, Homeopathic, Unani,

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Ayurvedic, Chinese etc. Conventional treatment is more costly so low socioeconomic patients cannot afford it and these therapies also have different hazards or side effects. Herbal system of medicine is a traditional system of medicine having many well-known effective and cost saving treatments for cough and cold without any major side effect. Therefore, this study was conducted to validate the herbal medicine CofNovex plus (EMA) syrup in the treatment of cough and cold.

METHOD

Study design

This clinical trial was a placebo controlled, randomized and single blind study. This clinical trial was conducted at different hospitals in Karachi. Patients were unaware of the treatment assigned to them.

Sample size

The sample size was approximately 220 patients. 110 patients was were required for each group.

Randomization

The patients were randomized into two groups. Each group contains 110 patients. Randomization was carried out by sequential opening of sealed opaque envelopes containing the random group allocations.

Inclusion criteria

- Patients with acute and chronic cough
- Patients with dry and productive cough
- Both genders
- Children 's and adults
- Parent/legally acceptable representative and subject agreed, the subject will not use any other cough or cold treatments during the study.
- Having given written informed consent
- Subjects who are able to understand and are willing to comply to trial instructions
- Satisfactory health except for the cough and cold as determined by the investigator based on medical history and physical examination

Exclusion criteria

- Patients which are on ventilator, which have tracheostomy and endotracheal intubation.
- Blood stained cough/sputum.
- Patients who's not giving informed consent
- Asthmatics presenting with wheeze.
- Current or recent history of clinically significant medical condition, laboratory abnormality or illness that could place the patient at danger or conciliation the value of the study data as determined by the investigator
- Use of prednisone, narcotic antitussives, inhaled corticosteroids within 2 weeks of Screening
- History of hypersensitivity to any excipient of the applied drugs
- History of chronic gastritis or peptic ulcers
- Diabetes or hypoglycemic disorders.
- Patient who are pregnant or breast-feeding.
- Patients recognized as necessitating conditional or rapid referral.

Study procedure

At the first visit of randomization, a detailed clinical history with particular emphasis on the history of cough and cold symptoms was were obtained from all patients. The severity of cough and cold symptoms was were evaluated by a questionnaire. All patients were randomized and assign to either CofNovex plus (EMA) syrup groups (n=110) or placebo group (n=110). Each patient received either CofNovex plus (EMA) syrup or placebo. The result of each group was measured by associating the cough and cold symptoms before treatment and after treatment.

Adverse events

All adverse events that have been individualized or determined by patients were documented with information on the severity, onset, duration and measures related to the study drug. It was permissible the patient to willingly withdraw from the study, regardless of the reason. For patients who withdrew from the study, struggles have been done to determine the intention for desertion. Noncompliance (defined as no ingestion of less than 80.1% of medications) has not been established as a treatment failure and the reason for noncompliance.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS version 21 program. The analysis included all subjects randomized in the groups to which they were assigned. The change in the various parameters for the statistical analysis between groups analysis at the entry and at the end of the study was evaluated. The paired t-test was used to assess the extent of significant proportions. The minimum significance was set at 95% confidence and the p value <0.05 was considered significant.

Composition of CofNovex plus EMA syrup

CofNovex plus EMA syrup contains the powerd extract of Althea officinalis, Sisymbrium irio and Hedera helix.

Ethical committee approval

This study is approved by the Ethical board of Herbion Pharmaceutical (Pvt.) Limited, Karachi, Pakistan.

RESULTS

A total of 220 male and female outpatients (N=110 CofNovex plus (EMA) syrup group; N=110 placebo

group) were included into the study. None of patient stated any adverse or side effect of the study drug. Cough and cold was considered by positive clinical sign and symptoms of fever, cough, sore throat, wheezing, post nasal drip, and body ache. Cough and cold is utmost common respiratory illness in children. Patient's age distribution; sex distribution and frequency distribution of CofNovex plus (EMA) syrup group and Placebo group are shown in fig. 1 and fig. 2 respectively.

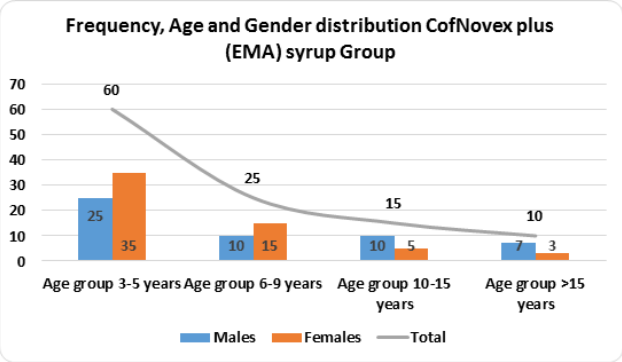

Fig. 1: Frequency, Age and Gender Distribution CofNovex plus (EMA) syrup Group

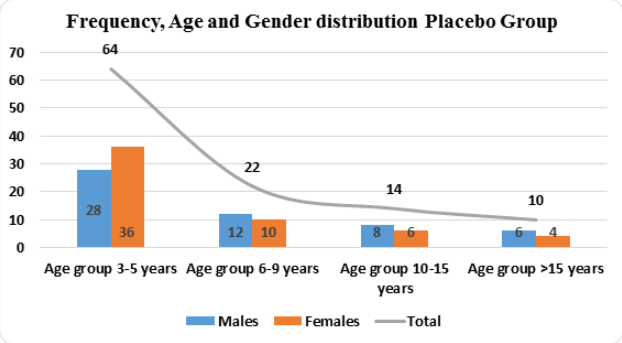

Fig. 2: Frequency, Age and Gender Distribution Placebo Group

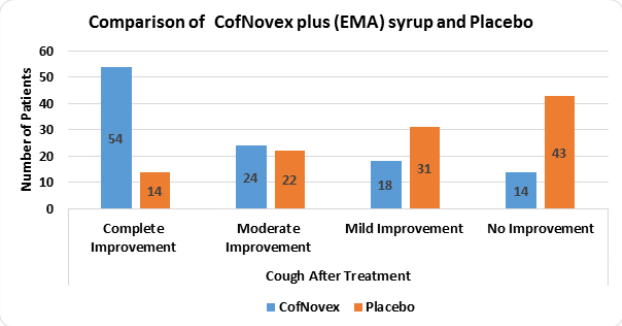

Fig. 3: Comparison of Cough after treatment in CofNovex plus (EMA) syrup and Placebo Groups

Clinical response

The therapeutic evaluation of the drug was made on the basis of improvement in the subjective signs and symptoms i.e. [Complete improvement (4), moderate improvement (3), mild improvement (2) and no improvement (1)].

Cough

Cough symptom has been recorded in patients. Patients presenting with symptom of cough observed after treatment in both groups. In CofNovex plus (EMA) syrup group 49% patients show complete improvement, 22% show moderate improvement, 16% show mild improvement and 13% show no improvement. In Placebo group 13% patients show complete improvement, 20% show moderate improvement, 28% show mild improvement and 39% show no improvement. The overall effects of CofNovex plus (EMA) syrup and Placebo on cough after treatment is shown in table 1 and fig. 3.

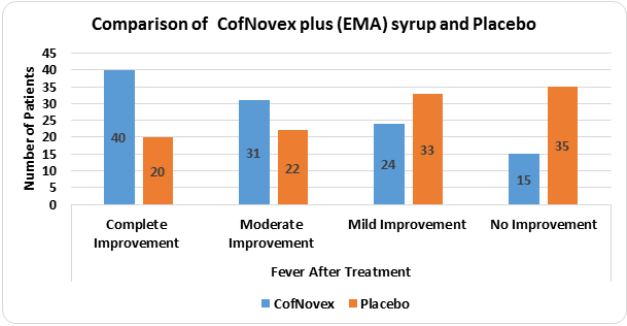

Fig. 4: Comparison of Fever after treatment in CofNovex plus (EMA) syrup and Placebo Groups

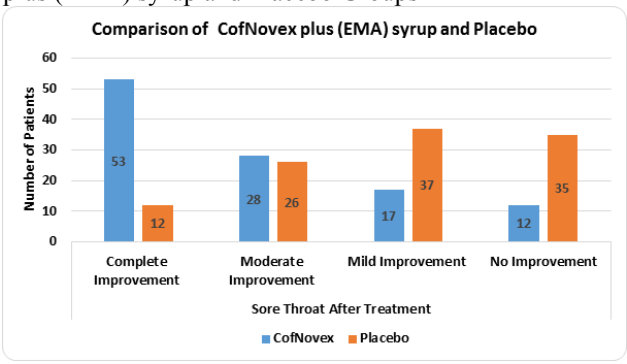

Fig. 5: Comparison of Sore Throat after treatment in CofNovex plus (EMA) syrup and Placebo Groups

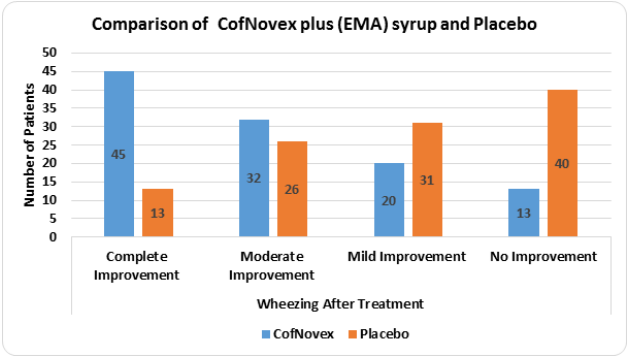

Fig. 6: Comparison of Wheezing after treatment in CofNovex plus (EMA) syrup and Placebo Groups

Fever

Fever symptom has been recorded in patients. Patients presenting with symptom of fever observed after treatment in both groups. In CofNovex plus (EMA) syrup group 36% patients show complete improvement, 28% show moderate improvement, 22% show mild improvement and 14% show no improvement. In Placebo group 18% patients show complete improvement, 20% show moderate improvement, 30% show mild improvement and 32% show no improvement. The overall effects of CofNovex plus (EMA) syrup and Placebo on fever after treatment is shown in table 2 and fig. 4.

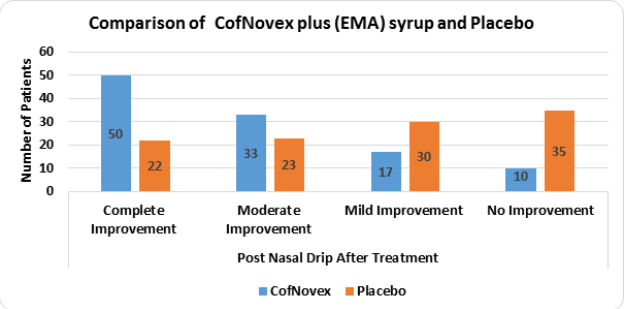

Fig. 7: Comparison of Post Nasal Drip after treatment in CofNovex plus (EMA) syrup and Placebo Groups

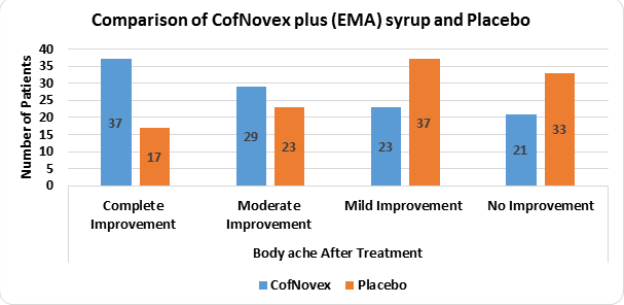

Fig. 8: Comparison of Body ache after treatment in CofNovex plus (EMA) syrup and Placebo Groups

Sore throat

Sore throat symptom has been recorded in patients. Patients presenting with symptom of sore throat observed after treatment in both groups. In CofNovex plus (EMA) syrup group 48% patients show complete improvement, 25.5% show moderate improvement, 15.5% show mild improvement and 11% show no improvement. In Placebo group 11% patients show complete improvement, 24% show moderate improvement, 34% show mild improvement and 32% show no improvement. The overall effects of CofNovex plus (EMA) syrup and Placebo on sore throat after treatment is shown in table 3 and fig. 5.

Wheezing

Wheezing symptom has been recorded in patients. Patients presenting with symptom of wheeze observed after treatment in both groups. In CofNovex plus (EMA) syrup group 41% patients show complete improvement, 29% show moderate improvement, 18% show mild improvement and 12% show no improvement. In Placebo group 12% patients show complete improvement, 24% show moderate improvement, 28% show mild improvement and 36% show no improvement. The overall effects of CofNovex plus (EMA) syrup and Placebo on wheeze after treatment is shown in table 4 and fig. 6.

Post nasal drip

Post nasal drip symptom has been recorded in patients. Patients presenting with symptom of post nasal drip observed after treatment in both groups. In CofNovex plus (EMA) syrup group 45% patients show complete improvement, 30% show moderate improvement, 15% show mild improvement and 10% show no improvement. In Placebo group 20% patients show complete improvement, 21% show moderate improvement, 27% show mild improvement and 32% show no improvement. The overall effects of CofNovex plus (EMA) syrup and Placebo on post nasal drip after treatment is shown in table 5 and fig. 7.

Body ache

Body ache symptom has been recorded in patients. Patients presenting with symptom of body ache observed after treatment in both groups. In CofNovex plus (EMA) syrup group 34% patients show complete improvement, 26% show moderate improvement, 21% show mild improvement and 19% show no improvement. In Placebo group 15% patients show complete improvement, 21% show moderate improvement, 34% show mild improvement and 30% show no improvement. The overall effects of CofNovex plus (EMA) syrup and Placebo on body ache after treatment is shown in table 6 and fig. 8.

DISCUSSION

Although many studies conclude that Ivy leaf extracts are effective in diminishing the symptoms of acute cough and cold, its efficacy is not established beyond reasonable doubt. For a combination of Ivy leaf, marshmallow and mustard seeds, effectiveness has been demonstrated in this clinical trial. Ivy leaf efficacy in previous studies vs. active controls and placebo (Mansfeld *et al*., 1998) establish an enhancement of pulmonary function tests (PFT) matched to placebo in children with bronchial asthma. PFT in children who were hospitalized due to chronic obstructive pulmonary disease presented an inclination towards dominance of the Ivy leaves extract over acetylcysteine, a chemically distinct conventional drug in this condition (Gulyas *et al.,* 2006). In fully-fledged patients with chronic bronchitis, the Ivy leaves extract was matched to ambroxol, another conventional drug used for the study condition (Meyer-Wegener *et al*. 1993). The positive results of this study for the CofNovex plus (EMA) syrup correspond with the pharmacological actions of Ivy leaf, marshmallow and mustard seeds. The results of this multi center study proved the advantage of the treatment with the fixed fluid extract combination of Ivy leaf, marshmallow and mustard seeds in cough and

Table 1: Comparison of Cough after treatment in CofNovex plus (EMA) syrup and Placebo Groups

Level of Improvement	Complete improved	Moderate improved	Mild improved	No improved	P value
CofNovex plus (EMA) syrup	54(49%)	24(22%)	18(16%)	14(13%)	.0001
Placebo	14(13%)	22(20%)	31(28%)	43(39%)	

Table 2: Comparison of Fever after treatment in CofNovex plus (EMA) syrup and Placebo Groups

Level of Improvement	Complete improved	Moderate improved	Mild improved	No improved	*P value*
CofNovex plus (EMA) syrup	40(36%)	31(28%)	24(22%)	15(14%)	.0001
Placebo	20(18%)	22(20%)	33(30%)	35(32%)	

Table 3: Comparison of Sore Throat after treatment in CofNovex plus (EMA) syrup and Placebo Groups

Level of Improvement	Complete improved	Moderate improved	Mild improved	No improved	*P value*
CofNovex plus (EMA) syrup	53(48%)	28(25.5%)	17(15.5%)	12(11%)	.0001
Placebo	12(11%)	26(24%)	37(34%)	35(32%)	

Table 4: Comparison of Wheezing after treatment in CofNovex plus (EMA) syrup and Placebo Groups

Level of Improvement	Complete improved	Moderate improved	Mild improved	No improved	*P value*
CofNovex plus (EMA) syrup	45(41%)	32(29%)	20(18%)	13(12%)	.0001
Placebo	13(12%)	26(24%)	31(28%)	40(36%)	

Table 5: Comparison of Post Nasal Drip after treatment in CofNovex plus (EMA) syrup and Placebo Groups

Level of Improvement	Complete improved	Moderate improved	Mild improved	No improved	*P value*
CofNovex plus (EMA) syrup	50(45%)	33(30%)	17(15%)	10(9%)	.0001
Placebo	22(20%)	23(21%)	30(27%)	35(32%)	

Table 6: Comparison of Body ache after treatment in CofNovex plus (EMA) syrup and Placebo Groups

Level of Improvement	Complete improved	Moderate improved	Mild improved	No improved	*P value*
CofNovex plus (EMA) syrup	37(34%)	29(26%)	23(21%)	21(19%)	.0001
Placebo	17(15%)	23(21%)	37(34%)	33(30%)	

cold that was evidently superior to placebo. The tolerability of the herbal medication was very good and comparable to placebo; no adverse events were reported. Our results show that CofNovex plus (EMA) syrup was very effective in the treatment of cough and cold. The overall efficacy was excellent. It is recommended to conduct large scale clinical trial in future to use this product to large number of patients in terms to prove its efficacy in more authentic way.

CONCLUSION

This clinical trial was conducted to evaluate the efficacy and safety of poly herbal formulation CofNovex plus (EMA) syrup. This was placebo controlled, randomize and single blind clinical trial. The present study clearly stated the effectiveness of CofNovex plus (EMA) syrup in treatment of Cough and Cold among children as well as in adults. The beneficial efficacy could be due to synergistic action of potentially evaluated herb by European Medicines Agency (EMA).

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