Chewable cough tablets with improved palatability: A comparative phase II clinical trial

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Abstract: Cough is the common disease condition which affects patients of every age. Numerous OTC medications available in community pharmacies however no antiviral treatment and even antibiotics has been shown to be effective without pre-existing lung infection. The treatment approach of medicinal herbs has been recognized for many decades and even longer for the treatment and prevention of cough. The aim of this study was to evaluate the safety and efficacy of Mukalbion poly herbal chewable tablets for the treatment of cough with improved palatability against a marketed brand (Poly herbal). For the formulation development of test group, the herbs were supplied by the Procurement department of Herbion Pakistan Pvt. Ltd. *Althea officinalis* (roots), *Hedera helix* (leaves) and *Sisymbrium irio* (seeds) were used for the manufacturing of Mukalbion (poly herbal, test group) chewable tablet. The comparative control clinical trial was carried out during a time frame of 07 months with sample size of 70 patients as per epidemiological software for sample size and each group contained 35 (±5) patients. Chewable tablets were administered and evaluated for effectiveness after 15 days of treatment. The data were collected by the patients through clinical trial questionnaire. The validated quality of life questionnaire (LCQ) was also used for assessment. The results were analyzed by applying paired sample T test by using IBM SPSS version 20.00. The p value was ≤0.005 at 95% confidence interval for cough variables including cough bouts, viscosity of sputum, chest congestion, sore throat and shortness of breath. The LCQ cough scale score was higher in test group as compared to control group. The test group also showed well tolerated in term of palatability. None of the patient claimed any of the side effects and no compliance were observed against the marketed brand.

Keywords: Chewable cough tablets, palatability, polyherbal ingredients, Phase II clinical trial.

INTRODUCTION

Cough is physiological condition or symptoms that causes the respiratory tract to be cleared from foreign material and sputum discharge or secretions. The sensory stimuli that cause coughing also enhance the airway discharge that provides a help full vehicle for expulsion of foreign particulate matter (Alam and Moore, 2017, Shrimanker *et al*., 2017). It was characterized as acute, sub-acute, or chronic cough. Acute cough enduring under 3 weeks and may cause an intense hidden cardiorespiratory issue however generally it caused by a self-restricted viral upper respiratory tract contamination (e.g., Common cold and flu). Sub-acute Cough lasts not more than two months generally due to *Bordetella pertussis* contamination and to be incorporated into the differential diagnosis. Chronic cough keeps going longer than two months. As cough is the frequent symptom for all the seasons with all the ages. Huge amount of drugs is also available in the market specifically for cough but due to lack of safety and efficacy data the confidence of the end user has decreased (Ebell *et al*., 2013, Melvin *et al*., 2014, Kahrilas *et al*., 2014).

Numerous pharmacological cough suppressants available in the market and widely used for the symptomatic relief of cough. However, the uses of herbal anti-tussive agents are now increasing tremendously due to the remarkable effectiveness with less side effects. Mukalbion chewable tablet is a polyherbal formulation for the treatment of dry and wet cough, comprising of *Althea officinalis* (roots), *Hedera helix* (Ivy leaves) and *Sisymbrium irio* (seeds). *A. officinalis* commonly known as marshmallow, their mucilaginous roots are very effective in dry cough, it acts by forming a protective coating on the mucosal lining of the respiratory tract. It also shielding from irritants as it's possess anti-inflammatory activities and provide relief in throat inflammation. It contains polysaccharide in a molar proportion (3:2:3:31) such as L-rhamsose, D-galactose, galacuonnicacid, D-glucuronicacid and p-coumaricacidin which are responsible for its anti tussive activity (Nosalova *et al*., 2013a, Nosalova *et al*., 2013b, Ameri *et*

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al., 2015, Sheikh *et al*., 2014, Sadighara *et al*., 2012). Saponins in Ivy leaves works as an expectorant, anti-spasmodic, anti-inflammatory and respiratory catarrh to provide relief in airway congestion (Yu *et al*., 2014, Zhou *et al*., 2014, Murínová and Dercová, 2014, Song *et al*., 2014, Greunke *et al*., 2015, Yu *et al*., 2016). The seed of *Sisymbrium irio* has expectorant activity which is due to the presence of flavonoids and sitosterols. It is also used as an expectorant provide ease in congestion of chest, asthma and cough (Singh, 2015, Haleem *et al*., 2016).

The aim of the research is to evaluate the safety and effectiveness of chewable tablets with only 3 herbs as compare to other market herbal brand with multiple herbs. This study is also planned to evaluate out the palatability of tablet as compare to the other marketed brand. No study has formally assessed whether the chewable table is acceptable to children of Pakistan and can adhere to the instructions regarding preparation, dosage, and duration of treatment.

MATERIALS AND METHODS

A control Phase II clinical trial was conducted for the indication of cough at the OPD of local clinic located at Gulshan-e-Hadeed, Karachi. Control drug is a poly herbal marketed brand containing extract *Morus nigra*, dry extract Liquorice, dry extract *Adhatoda vasica*, dry extract *Ocimum basilicum*, *Menthol*, Anisi oil, Eucalyptus Oil, Pine Oil, Cubeb Oil, Cinnamon Oil however the test was only 3 herb ingredient including *Althea officinalis* (Roots), *Hedera helix* (Ivy leaves) and *Sisymbrium Irio* (Seeds).

Patients were diagnosed on the basis of their symptoms. Patients with acute cough cold and flu, Patients with dry and productive cough and Patients between 12-60 years with informed consent were included in the study. However, Patient with invasive respiratory tract instrumentation (e.g. ventilator dependent, tracheostomy, endotracheal intubation) under 12 or above 60 years of age and have Blood stained with cough/sputum were considered to be excluded in this clinical trial. Asthmatics patient presenting with wheeze or patients having clinical significant medical conditions, laboratory abnormality or illness that could put the patient at risk or compromise the quality of the study data as determined by the investigator were also excluded from the trial.

All patients gave verbal or written, informed consent for their participation. The protocol of the study was approved by the Independent Ethics Committee of Jinnah University for women. The sample size of test group was 36 as per inclusion and exclusion criteria. The investigating tablet (Mukalbion chewable tablet) prescribed twice daily 2 tablets for 15 days for 2 weeks. Similarly control group contained sample size of 34 with Marketed herbal brand tablet as prescribed by 2 tablets four times a day for 15days for 2 weeks. ±6 and ±4 patients were loss to follow up in both test and control group.

Assessments were made on the basis of patient case history, on the basis of cough symptoms and Chest X ray (where needed). Validated questionnaire of both the groups were filled before and after treatment and LCQ cough questionnaire were also used for the scoring of cough symptoms as physical, social and Psychological effects. The LCQ known as Leicester cough questionnaire assess cough related QOL questions (quality of life). We assess quality of life by filling the LCQ form before the cough therapy and after 15 days of treatment therapy. It is a 19 item questionnaire which contain 3 domains (physical, psychological and social). The range of total score is 3-21 while 1-7 is the score range in each domain higher score indicates a better quality of life.

After administration of test and control drug the Cough symptoms of the cases were tested after 15 days and analyzed through Paired Sample T-test using IBM SPSS version 20.0. Sample size selection in this clinical study was done based on general physical examination, general appearance of the patients, age, sex and complain of cough symptoms.

The clinical outcome included percentage of reduction of average cough bouts per day, Symptoms of Chest congestion, Sore throat, shortness of breath and reduction of Viscosity of sputum and type of cough. The LCQ questionnaire was used for the evaluation of cough symptoms and the basis of their score the progress of treatment was determined. For determination of palatability of chewable tablets 5 points based hedonic scale was used included the choices 1-5. 5 considered to the very well tolerated and 1 was not tolerated.

RESULTS

The case control Phase II clinical trial has been established to find out the safety and efficacy of polyherbal chewable tablet. Mukalbion for acute cough and compare with marketed herbal chewable tablet.

All selected cases were carefully examined and clinical history was recorded in the clinical trial proforma. The QOL is determined by LCQ cough scale with the determination of efficacy and safety of both drugs. The therapeutic evaluation of drugs was made on the basis of improvement of cough symptoms after the 15 days of drug treatment as shown in fig. 1.

Out of 30 cases 13 were males and 17were females in the test group and 16 were males and 14 were females in the control group. The age group under study was 10 years to

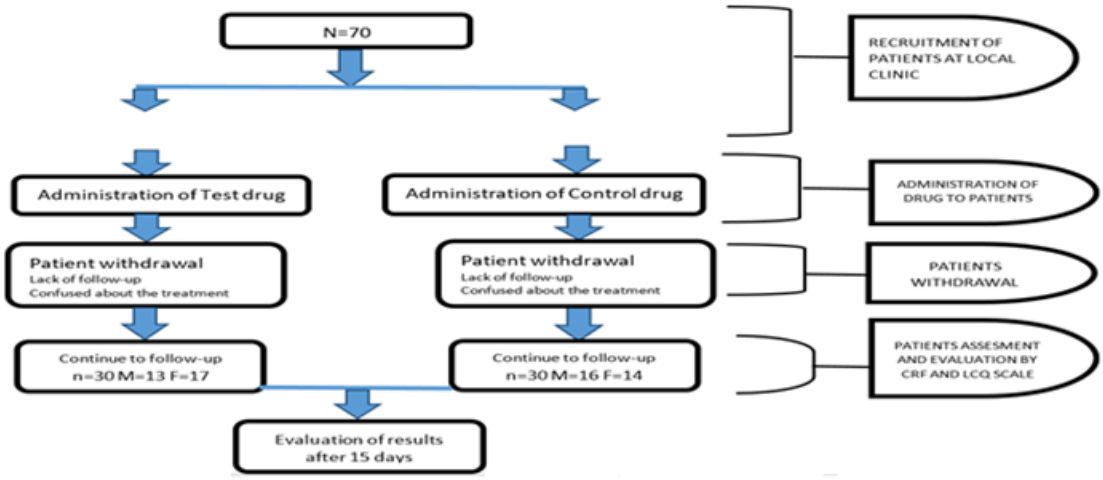

Fig. 1: Schematic View of treatment plan and its assessment strategy

Table 1: Diagnosis and Baseline Symptoms (N=70)

Characteristics		N	%
Age (Years)	12-21	9	13%
	22-32	27	38.5%
	33-43	13	18.6%
	44-54	2	2.85%
	55 and above	9	12.85%
	Mean (SD)	9.273618	0.13211
Gender	Male	29	41.43%
	Female	31	44.28%
		Test group (N)	Control Group (N)
Intensity of cough bouts	Mild	9	8
	Moderate	13	9
	Severe	8	13
Duration of Symptoms	> 7 days	2	2
	≤ 7 days	28	28

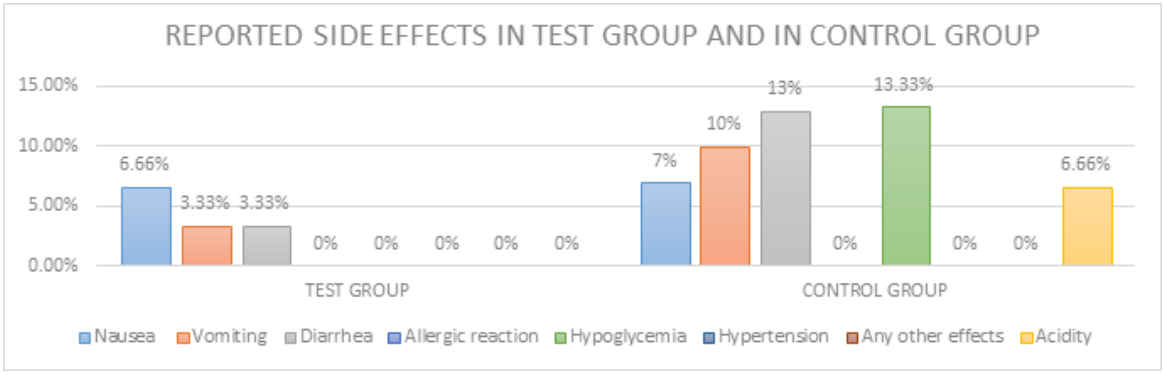

Fig. 2: Reported side effects in both groups

60 years for both treatment arms as shown below. All data was analyzed by applying Paired Sample T-test after 15 days of treatment for evaluation of the efficacy of both treatment drugs of test and control group as Mukalbion chewable tablet and Marketed cough chewable tablet as shown in table 1.

Both groups cough bouts intensity and the status of sores throat are shown in table below. The significant P-value was observed for at 95% confidence interval by applying paired sample t test (α=0.000). The average cough bouts in a day is reduce in Test group as its shows P value less than 0.05% which shows there was significant effect of Mukalbion tablet in reducing cough as compare to the case group as shown in table 2 however less side effects were observed in test group as shown in fig. 2.

Table 2: Characteristics of cough in both groups (before & after)

Characteristics		Test Group		P-Value	Control Group		P value
		Befoe N (%)	After N (%)		Before N(%)	After N(%)	
Intensity of cough bouts	Mild	30%	20	0.000	26.7	16.7	0.098
	Moderate	43.3	0		30	13.3	
	Severe	26.7	10		43.4	40	
Sore throat		86.7	36.7	0.000	90	60	≤0.005
Chest congestion		70	20	0.000	76.7	56.7	0.056
Viscosity of sputum	Slightly Thick	16.7	30	≤0.005	43.3	33.3	0.339
	Moderate thick	56.7	3.3		30	20	
	Very thick	16.7	3		10	13.3	
	No Sputum	10	63.3		17	33.3	
Shortness of breath		86.7	50	≤0.005	90	73.3	0.057

Table 3: LCQ score before and after treatment in both groups

Items	Mean (S.D)	Average score at Day 1	Average score at Day 15	P value
		Test group (Mukalbion Poly-herbal tablet)		
Physical	3.5265(1.453)	3.7345	7.594	0.000
Psychological	4.11 (0.528)	3.103	6.708	0.000
Social	2.507(0.242)	2.234	4.116	0.000
Total score		9.072	18.418	0.000
		Control Group (Marketed Poly-herbal group)		
Physical	7.594(0.522)	3.12	5.204	0.000
Psychological	6.708(0.4116)	4.11	5.461	0.000
Social	4.1162(1.002)	2.24	3.45	0.000
Total score		9.47	14.115	0.000

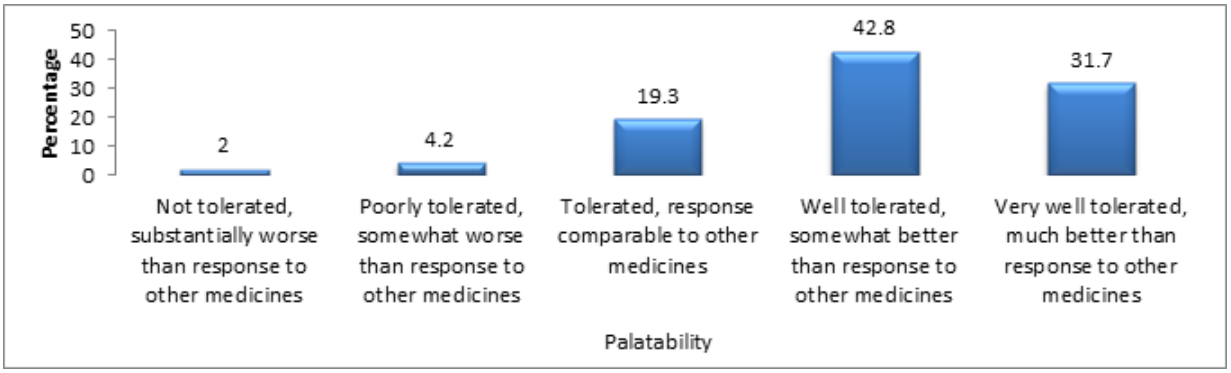

Fig. 3: Palatability of test group

The LCQ questionnaire was also applied on both group for the assessment. The LCQ is a 19 item questionnaire that assesses cough-related QOL. It has 3 domains (physical, psychological and social). The total score range is 3-21 and domain scores range from 1-7; a higher score indicates a better quality of life. The questionnaire was revised so that each item related to the patient's experience within a 24-hour time frame.

According to LCQ scoring the average score at Day 15 after Mukalbion treatment was greater than the average score at Day 15 of after control-drug. The following table represents the LCQ score between before and after mukalbion treatment and significant results were obtained. We have applied Paired Sample T- test for the assessment of LCQ cough scale (α=0.000) as shown in table 3.

No serious adverse effects and toxicity reported with this dose during the treatment course of 15 days in Mukalbion polyherbal chewable tablets.6.66% patients experience, nausea and 3.33% patients were experience vomiting. No allergic and harmful effect is reported.

The 5 points hedonic scale shows the palatability of test group chewable as shown in fig. 3 and most of the results showed well tolerated in term of palatability.

DISCUSSION

MUKALBION is effective and safe for the treatment of cough with palatability. The average cough bouts were reduced after 15 days of treatment. It also shows remarkable effects on the sputum of cough. It reduces viscosity of sputum which shows their effectiveness in productive cough. It relief sores throat as compared to marketed brand (<0.005). It is effective in bronchitis, common cold and flu. The cough quality of life is more improve in Mukalbion chewable tablet which is evaluated by LCQ scale score. None of the patient claims any of the side effects and shows more compliance against the marketed brand with good palatability.

CONCLUSION

The phase II clinical trial established the safety and efficacy of chewable cough table as compare to competitive market brand with improved palatability.

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