An interquartile relationship between polyherbal extract based lozenges linkus a phase IV comparative randomised control trial

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Abstract: The aim of the study is to determine the efficacy of polyherbal linkus with the other pharmaceutical marketed syrup having Acefyllin Piperazine, Diphenhydramine group and Aminophylline Diphenhydramine group on the basis of interquartile ranges on children. It was open label multi centric randomize control trial. The study was conducted on different private schools of East and West Malir, Karachi Pakistan with the special approval from the school's honors .Informed consent and assents were taking before the enrollment of the study subjects .The study enrolled participants were 147 who evaluate on cough. Participants were divided into 3 interventional group according to the treatment regimen .One group of participant received Linkus Syrup however the 2nd group received Acefyllin Piperazine and 3rd group received Aminophylline Diphenhydramine group. The frequency of the cough on linkus syrup was considered to be achieved on the basis of interquartile relationship and impact has been observed on child and parent sleep and found significant ($p < 0.01$).Poly herbal Linkus Syrup has the significant impact on cough frequency and associated problem on children and parent's sleep with minimum side effects ($p<0.01$) however the pharmacological treatments are considered to be more unwanted effects on human subjects.

Keywords: Polyherbal linkus, lozenges linkus, syrup, symptom, cough.

INTRODUCTION

Cough is the most common symptom in children and causes discomfort in health care utilization (Goldsobel and Chipps 2010).Over the counter (OTC) cough and cold medicine is very common in children under 2 to 5 years of age (Vernacchio, Kelly *et al.*, 2008). Almost all children experienced cough and associated symptoms (Hay, Heron *et al*. 2005). On a community based survey high prevalence of cough found in children (Clough, Williams *et al*., 1991, Ninan, Macdonald *et al.*, 1995)

The usefulness of anti-cough medications remains debatable in spite its wide spread consumption. Clinical trials are investigating their role are limited, so there are lack of evidence supporting their benefits if any. A systematic review of randomised controlled trials on different kinds of these medications concluded they were not superior to placebo (Schroeder and Fahey 2002). One study favoured dextromethorphan over placebo whereas the other did not find any difference (Kuhn, Hendley *et al*. 1982) Another trial inferred that there was a difference in "cough scores" on the subsequent days but that no significant difference was noted on follow-up, beside that there were no difference between those who used it and those who didn't (Adams, Hosie *et al*., 1993).

Mostly the people who are un-healthy do not necessarily seek any medical advice. A number of sociocultural factors tend to influence that such patient's previous poor experiences with conventional treatments (Lam 2001). Such patients are bound to seek alternatives medication such as natural remedies. Traditional Chinese Medicine has been in vogue in China for the past two millenniums and has been used for various acute and chronic problems (Helman 2007).

Herbal products widely use throughout the globe since 5,000 years (Swerdlow 2000). In the book of history herbal medicine were the only medical therapies used previously. In United States 1 in 5 patients are taking herbal products(Barnes, Powell-Griner *et al*. 2004). In US Pharmacopeia 59% of listing came from Herbal medicinal Products and have been use since half of the century (Barrett, Kiefer *et al.*, 1999, Swerdlow 2000). In this Era of health care, Billions of dollars per year spend on OTC products specifically for cough (Rosendahl 1988, Morice 2002). The only paucity on OTC products is the availability of sound research as unfortunately no clear evidence achieved on alternate medication.

For mentioning the evidences on Herbal medicine Linkus formulation has been developed. Linkus cough syrup contains *Adhatoda vasica* contains vasicinone and vasicine which helps to reduce cough, common cold and serve as an expectorant (Claeson, Malmfors *et al*., 2000). The root of *Glycyrrhiza glabra* contains active glycyrrhizin helps for upper respiratory tract infections (NUMAZAKI, UMETSU *et al*. 1994, Bown 1995, Tsukiyama, Katsura *et al*., 2002). *Piper longum* fruit and root contains active piperlonguminine, piperine, piperlongumine and helps for cough and other respiratory

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tract infections (Scientific, Research *et al*., 1948). *Hyssopus officinalis, Alpinia galangal, Zingiber officinale, Cordia latifolia* are used to control coughing and respiratory tract infections(Rehman, Naveed *et al*., Silva, Pongravoon *et al*., 2000, Altman and Marcussen 2001, Hernandez, Canales *et al*., 2007, Shinwari, Khan *et al*., 2009, Rehman, Shaikh *et al*., 2016).

The objective of the study is to determine an interquartile relationship between Polyherbal Syrup Linkus with Acefyllin Piperazine, Diphenhydramine group and Aminophylline Diphenhydramine group.

MATERIALS AND METHODS

Participants

A randomize control trial was conducted from January to Sept 2016 in the private schools of Pakistan, Including East Malir and West Malir Karachi Pakistan. A special approval has been taken from the schools with the explanation of intent and objective of study. A total 147 patients were included from different private schools, 40 male (13.3±3) and 107 females (35±3.0) with the mean age of 9 ±1.82 and were randomly assigned in 3 groups, 49 in linkus group, 49 in Acefyllin and 49 in Aminophylline Diphenhydramine group.

All participants have given written informed consent from the parents after explaining the nature, objective, intended outcome and assents from the children .They all have complained of acute cough and has been previously episodes of cough (last 3-4 days) or sudden onset consider to be included of the study however Patients considered to be excluded having hypersensitive previously from any herbal drug and not given consents.

Randomization was adopted to assign participants on either group including Linkus, Acefyllin group, and aminophylline diphenhydramine group. The study was un-blinded because all 3 treatments groups have different actives and different dosing regimen. However, for analysis statistician was performed it blinded on codes.

The study was approved on IRB (Institutional review board) of Darul Sehat Hospital, Liaquat Medical and Dental College, Karachi, Pakistan. Study protocol, Case report form, informed consent English and Urdu were presented in front of IRB before start of clinical trial. ICH and GCP godliness (international conference of harmonization and good clinical practices) was adopted.

Procedure

Patient's demographics and basic information including nature of cough, frequency of cough and severity of cough (minor, moderate and severe) asked and filled in Case report form with the help of registered medical practitioner. Frequency was measured on the basis of cough last night before treatment and after treatment on the basis of very much, a lot , somewhat , little occasional and not at all (from number 5 to 1). Child sleep disturbance and effects on parents sleep were rated on the same on all three groups.

The phytochemical based syrup linkus recommended 10 ml given thrice daily for 14 days on acute cough, however in comparison of quadruple therapy the acefyllin group recommended to take 10 ml TDS and same with aminophylline diphenhydramine group.

The dose selection was implemented on the basis of standard practice. All study participants were advised to take not any other medications except the investigational study drug. Linkus syrup's herb were purchased from the Joria market, Karachi and identified on the herbal expert from university of Karachi.

Outcome measure

The outcomes of cough frequency was observed after 14 days treatment of syrups in 3 groups, Children sleep disturbance and child cough impact on parent's sleep was observed from 5 to 1 scale mentioned above on all 3 treatment groups. Medical practitioner filled out case report form regarding demographics data , such as name, gender , severity of cough , frequency of child's cough before and after and its impact of parents sleep before and after . After 14 days of treatment, adverse events and side effects were asked.

RESULTS

Data were stored and analyzed using SPSS version 21.0, mean and standard deviation are reported for age, duration of illness and cough frequency per day before the treatment, count and percentages are given for qualitative data sets like gender, severity of cough and observed side effect of treatment. One way analysis of variance was used to compare the mean across treatment groups and Pearson chi square test was used to see the association of qualitative variables. Wilcoxon sign rank test was applied to see the effect of treatment outcomes at pre and post stages, Median and inter quartile ranges also reported along with p-values. Box plot, bar and pie chart used to display the information in graphical way, all p-values less than 0.05 were considered significant.

Table 1 reports the baseline characteristics of studied sample, it was found that mean age and standard deviation of child on Linkus treatment was 9.96 ± 2.19 years, a significant p-value obtained using ANOVA that showed mean age of children across the group was not same.

On average child cough frequency before the treatment was found more than six times in linkus and Aminophylline, Diphenhydramine and more than five times in Acefyllin Piperazine, Diphenhydramine however there was not any significant changes observed for the mean cough before the treatment.

Table 1: Study subjects baseline characteristics

Characteristics	Linkus		Acefyllin Piperazine, Diphenhydramine		Aminophylline, Diphenhydramine		P - value
	Mean	S.D	Mean	S.D	Mean	S.D	
Age(years)	9.96	2.19	8.20	1.19	8.22	2.13	<0.01*
Gender	n	%	n	%	n	%	
Male	16	32.7	10	20.4	14	28.6	0.49
Female	33	67.3	39	79.6	35	71.4	
Severity of cough							
Minor	21	42.9	20	40.8	20	40.8	0.98
Moderate	19	38.8	20	40.8	19	38.8	
Severe	9	18.4	9	18.4	10	20.4	
Side Effects							
Stomach ache	-	-	3	6.1	1	2	<0.01*
Nausea	-	-	3	6.1	-	-	
Nervousness	-	-	1	2	-	-	
Insomnia	-	-	-	-	-	-	
Hyperactivity	-	-	-	-	-	-	
Headache	1	2	4	8.2	2	4.1	
Drowsiness /sleepy	-	-	3	6.1	12	24.5	
Disorientation	-	-	-	-	-	-	
No side effects	48	98	35	71.4	34	69.4	
*p<0.05 considered significant (-) Zero side Effect found.							

Table 2: Impact of Cough on Linkus Group

Linkus	Median	1st Quartile	3rd Quartile	IQR	p-value
Before-Frequency of cough	6	5	7	2	<0.01*
After-Frequency of cough	3	2	4	2	
Before-Child sleep disturbance	4	3	5	2	<0.01*
After-Child sleep disturbance	3	2	4	2	
Before-Impact of cough on parents sleep	3	2	3	1	<0.01*
After-Impact of cough on parents sleep	2	1	2	1	
*p<0.05 considered significant					

Table 3: Impact of Cough on Acefyllin Piperazine Group

Acefyllin Piperazine, Diphenhydramine	Median	1st Quartile	3rd Quartile	IQR	p-value
Before-Frequency of cough	7	6	8	2	<0.01*
After-Frequency of cough	4	3	5	2	
Before-Child sleep disturbance	4	3	4	1	<0.01*
After-Child sleep disturbance	3	3	4	1	
Before-Impact of cough on parents sleep	3	2	3	1	<0.01*
After-Impact of cough on parents sleep	2	1	3	2	
*p<0.05 considered significant					

Table 4: Impact of Cough on Aminophylline Diphenhydramine Group

Aminophylline, Diphenhydramine	Median	1st Quartile	3rd Quartile	IQR	p-value
Before-Frequency of cough	7	4	8	4	<0.01*
After-Frequency of cough	5	4	6	2	
Before-Child sleep disturbance	4	3	5	2	<0.01*
After-Child sleep disturbance	3	2	4	2	
Before-Impact of cough on parents sleep	2	1	4	3	0.08
After-Impact of cough on parents sleep	2	1	3	2	
*p<0.05 considered significant					

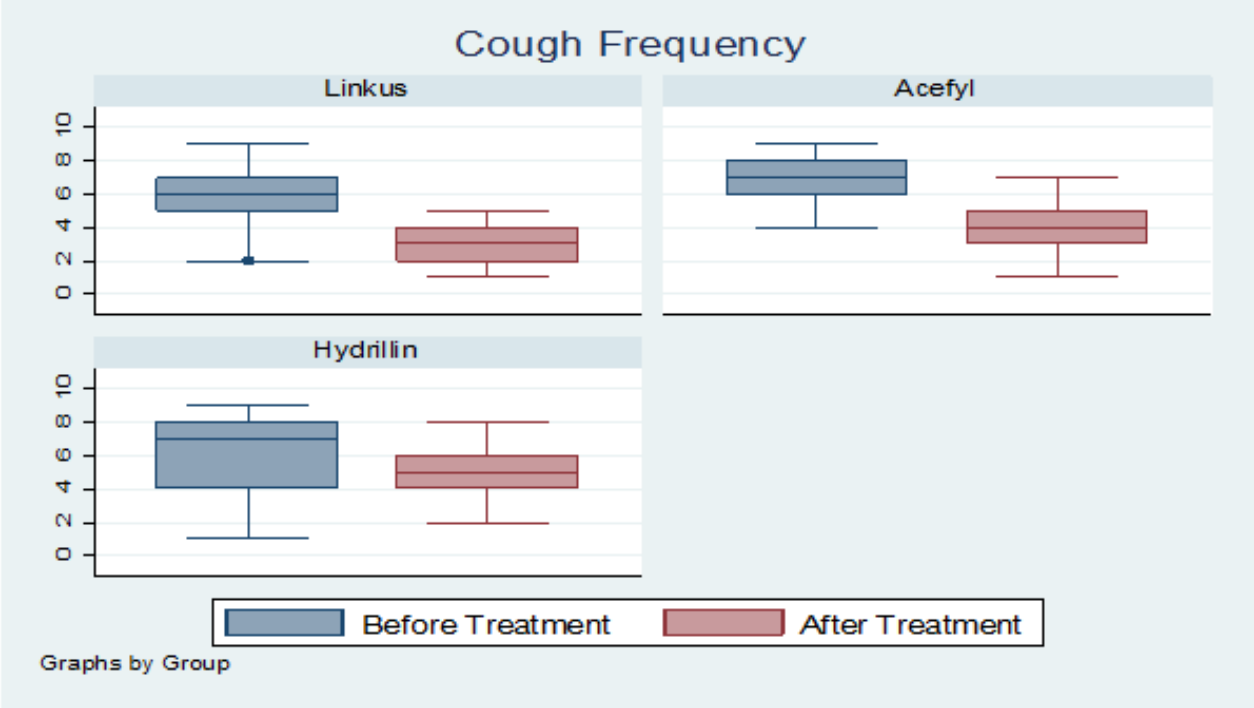

Fig. 1: Box Plot for different variables.

More samples on the treatment were found with female gender, minor severity of cough and without impact on child sleep; however Gender, severity of cough and impact on child sleep did not give any association with the treatment group.

Most of the side effects were observed from Aminophylline, Diphenhydramine treatment, 24.5% samples found with complain of sleepy, 6.1% samples on Acefyllin Piperazine, Diphenhydramine treatment were found with the same complain.

Table 2 gives the results of four level symptoms median scores and their Inter quartile range before and after the treatment of linkus using Wilcoxon rank test, it was found that cough frequency significantly got down after the treatment of linkus, it also gives significant impact on child sleep and their parents sleep.

Table 3 gives the results of four level symptoms median scores and their Inter quartile range before and after the treatment of Acefyllin Piperazine, Diphenhydramine using Wilcoxon rank test, it was found that cough frequency significantly got down after the treatment of Acefyllin Piperazine Diphenhydramine, it also gives significant impact on child sleep and their parents sleep.

Table 4 gives the results of four level symptoms median scores and their Inter quartile range before and after the treatment of Aminophylline, Diphenhydramine using Wilcoxon rank test, it was found that cough frequency significantly got down after the treatment of Aminophylline, Diphenhydramine, it also gives significant impact on child sleep but their parents sleep did not received the impact of treatment and it was found in significant.

Above Box plots give the distribution of Cough Frequency in three treatments at pre and post stage. It was observed that before treatment cough frequency was not normally distributed, however after the treatment median line found closed to the center which gives the evidence that distribution of cough after the treatment approximately normal.

DISCUSSION

The current study intended to look the interquartile relationship between Linkus and other marketed allopathic brands for acute cough and its impact on child and parents sleep. The results of the study showed that the medication on different interquartile ranges have significant reduction on cough and its impact on sleep .However on Linkus therapy the side effects were less as compare to other allopathic medication include Acefyllin Piperazine and Aminophylline Diphenhydramine.

Herbal medicine data base explains that the consumption of traditional medicine reached in 2.1 to 2.3 billion(De Smet 1997). Conversely the knowledge about side effects of pharmacological medications has been increased which convert a consumer more towards traditional and herbal

medicine (Ventegodt, Omar *et al*. 2011). The biggest challenges of alternate and comprehensive medicine are to convert into complete sciences. This study aimed to prove the effects of herbal medicine interquartile ranges and its impact on cough with the comparison of other successful marketed multinational pharmaceutical brands. Significant relationship found on all treatment groups on indication of cough and other associated problems. Linkus syrup have possess the therapeutic value for the treatment of Cough and its related problems with other standard conventional therapies .The side effects as compare to the conventional therapy found less.

CONCLUSION

Findings of the current therapy demonstrate that that the herbal syrup Linkus possesses equal therapeutic ranges on cough on different interquartile ranges as compare to other market best sale conventional pharmaceutical medication. Linkus will be the best herbal medication with no or less side effects on children under 2 to 11 years of age. Safety and efficacy of the targeted syrup has been proven previously and maintaining the practitioner confidence on traditional herbal medicines.

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