# Efficacy and safety of Linkus, Aminophylline diphenhydramine and acefyllin piperazine for the treatment of cough in children

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**Abstract**: To evaluate the safety and efficacy of Linkus, Aminophylline with Diphenhydramine group and Acefyllin Piperazine with Diphenhydramine cough syrup on children having cough and sleep difficulty associated with cough. To determine the effects of Linkus polyherbal syrup (group A) and compared with other parallel allopathic groups (Group B and C) for cough on children and associated sleep quality and improvement. 360 children having cough inducted in 3 different groups randomly selected. Three parallel groups were the part of the study. The first study group was the herbal syrup Linkus, second group of children were taking a syrup of multinational pharmaceutical industry having Aminophylline plus Diphenhydramine however the third group received another famous brand having Acefyllin Piperazine with Diphenhydramine. Informed assent and informed consent have taken from the study subjects and their parents. Subjects with acute cough were included in the study however the subjects with chronic cough considered to be excluded. Every group of individual in the study was informed about the investigational drugs provided. Ethnic groups, frequency of cough and diseases illness (<0.05) were determine on every group on the investigational syrup. Cough impact on child and its sleep of three different syrups (every group) were assessed on day1 and day 14($p<0.001$) via a likert scale. For the evaluation of pain assessment Wong baker face scale were used and level of significance in each group ($p<0.001$). Significant results were observed in the Linkus Group as compared to the other parallel groups including Aminophylline plus Diphenhydramine and Acefyllin Piperazine with Diphenhydramine on day 14 ($p<0.001$). Side effects on group B and group C (Aminophylline with Diphenhydramine and Acefyllin Piperazine with Diphenhydramine) were almost similar in number however Linkus syrup has minimum side effects on study duration. Polyherbal syrup Linkus shows better results in treatment of cough including side effects as compare to the other parallel groups B and C (Aminophylline with Diphenhydramine and Acefyllin Piperazine with Diphenhydramine). For nocturnal sleep Linkus providing better results in cough and associated problems. Pain were significantly reduce on day 14 with the herbal Linkus syrup group A (<0.001). Group B and C found less effective with more side effects as compared to Linkus syrup. Poly herbal Linkus syrup could substantially improve the clinical effect and relieves coughs and benefit lung functions and better sleep facilitation.

**Keywords**: Cough, efficacy, Linkus, Aminophylline, Diphenhydramine and Acefyllin Piperazine and Children sleep.

## INTRODUCTION

Cough is the most frequent symptom for children in United States (Herry and Woodwell, 2002). Cough is particularly waxing at night and often effects ill children sleep and their parents sleep. Dextromethorphan (DM), Diphenhydramine (DPH) an Chlorpheniramine maleate are the common medication used as OTC products for upper respiratory tract infection (UTIs). According to census of Pakistan 1998, the population of Karachi is exceeding 10 million and the growth rate is 6%, which is twice the national growth rate. Diphenhydramine, Chlorpheniramine maleate is the effective anti-tussive medication for upper respiratory infection (Gruber *et al* 1961; Clemens *et al* 1997) and didn't find better as compared to placebo for controlling acute cough Korppi *et al* 1991; Schroeder *et al* 2002). However in recent studies on DM and DPH have some conflicting results too Parvez *et al*; Curley *et al* 1988). For complying the reasons, considerable population of children using alternative forms of treatment like herbal medicine.

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Cough is particularly waxing at night and often effects ill children sleep and their parents. Linkus is the polyherbal blend uses for upper respiratory tract infection. The composition of Linkus syrup includes *Adhatoda vasica* contains *vasicinone* and *vasicine* which helps to reduce cough, common cold and serves as an expectorant (Silva *et al* 2000). The root of *Glycyrrhiza glabra* contains active glycyrrhizin helps for URI (Bown,1995; Numazaki, *et al*.,1994). *Piper longum* fruit and root contains active piperlonguminine, piperine, piperlongumine and helps for cough and other respiratory tract infections (Tsukiyama,, 200). The *Hyssopus officinalis, Alpinia galangal, Zingiber officinale, Cordia latifolia*are used to control coughing and respiratory tract infections (Chevalier, 1996; Hernandez *et al* 2007). The objective of the study is to conduct an open label, Phase IV randomized control trial in 3 parallel groups having Linkus syrup, Aminophylline with Diphenhydramine (group 2) and Acefyllin Piperazine with Diphenhydramine (group 3) on children having to 11 years of age. Prior to the study, we postulated that the patient having the interventional treatment at least for 14 days with cough and associated symptoms will be evaluated.

## METHODS

A phase IV randomized, open label clinical trial was conducted on different private schooling systems. External IRB (institutional review board) approval has been taken from Darul Sehat Hospital, Karachi, Pakistan. For conducting a clinical trials multiple certified clinical research associate (CRA) were hired.

Children of 2-11 years age with oral assents were included in the study. Written informed consent was taken by guardians and they were free to quit any point in time. Children having history of bronchopulmonary dysplasia, asthma, chronic bronchitis, cystic fibrosis and allergic rhinitis were excluded. Patients having autoimmune diseases and having allergic reaction /hypersensitivity from any herbal products were also excluded in the study. Children on supplementations including heavy metals, iron, zinc and any other alternative and herbal medication were considered to be excluded. Only one child from each family was incorporate in the study.

Children were inducted through the seasonal camps on private schools. After successful completion of inclusion criteria, patients were recruited in the study. Medical records and history were completely checked and reviewed. Cough impact on children sleep assessed by the guardian. Investigational brochure was distributed in each patient for awareness on each and every active ingredient present in the study drug. After physical examination and details history patients were inducted in the study.

At the time of patient enrolment, demographics, duration of illness, cough frequency score per day were gauged with the help of parents and guardian with the help of 5 level likert scales. After recruitment, patients were randomly divided into 3 groups. First group of study's subject were on Linkus syrup (Herbal medicine), However 2$^{nd}$ group of random picked subjects were on Aminophylline with Diphenhydramine (allopathic medicine) and 3$^{th}$ groups were taking Acefyllin Piperazine with Diphenhydramine (allopathic medication). After 14 days of treatment cough frequency and impact were assessed on subjects and juvenile life.

Enrolment duration was 5 months from private schooling system of East Karachi, Pakistan .In every site with Linkus syrup (group 1) other 2 brands of allopathic syrup (Aminophylline Diphenhydramine (group 2) and Acefyllin Piperazine with Diphenhydramine (group 3)) identical appearance with sweet taste were placed. Randomization was prepared from computerized generated system. After enrolment a subject study code was given to the patients for further follow up and consultation. The guardian/parents were fully aware about the concept of the study and the drug. Due to spillage of investigational drug, two complementary bottles with dosing spoon were given for the proving the adherence contact information of principal investigator and CRAs were shared with the guardian/parents. Third follow-up visits were mandatory for each patient.

Dosing instructions were given by clinical investigator and CRAs recommended by the manufacturing company of all 3 groups (National and multinational Pharma). Children having 2-6 years (Aminophylline, Diphenhydramine) were taking 1.25-2.5 of 5ml teaspoon every 4-6 hours however 6-12 years children were on 0.75-1.5ml teaspoon on every 4-6 hours. Children having 2-3 years (Acefyllin Piperazine with Diphenhydramine) were taking 2.5ml 3 times daily and 3-12 years were taking 5ml 3-4 times daily. The third group of study subjects was taken Linkus syrup 1-2 teaspoon 3-4 times daily. The Investigators and clinical research coordinator contact information shared with every study subject/ guardian/ Parents for 24/7 contact in case of any side effects and ADRs reporting. The parents/guardians were asked to note patients sleep quality and frequency of cough from day 1 to day 14. Frequency was measured on the basis of cough last night before treatment on day 1 and after treatment on day 14 on the basis of Likert Scale (from 5 to 1). Child sleep disturbance and effects on parents sleep were rated on the same on all four groups. For the determination of severity of cough a validated Wong baker pain scale used in the study.

The parents were asked to note any concomitant medication if case of fever and other upper respiratory tract infection. Primary study outcomes were the duration and severity of upper respiratory infections (URIs) and adverse events. However the efficacy of the investigational products were determined on day 0-14 with the measurement of pain scale, gauging cough frequency and cough impact on child and parent sleep. For measuring the symptoms 4 level scale were used to assess changes from 1-5 (poor-excellent) on irritating cough, bronchitis and respiratory tract diseases with mucus with respect to strength of stimulation, amount and consistency with ease of expectorant (Samue *et al* 2007).

## RESULTS

A total of 360 participants were inducted in the study. Overall rate of patient participation from induction to analysis were 54.1%. The analysis based on 65patients in each groups (total=195(65+65+65)) who were completed the follow up. The patient who moves to the foreign country, switched school, felt discomfort, required other benefits to come again were considered to lose of follow up. The demographics of the completed study population were mentioned in table 1. Duration of illness, cough frequency score before treatment, cough impact on child sleep and parents quality were also mentioned in the same table. On all 3 interventional groups, age, ethnic group were found to be the more significant ($p<0.001$). From randomization, to analysis, all details were mentioned in fig. 1.

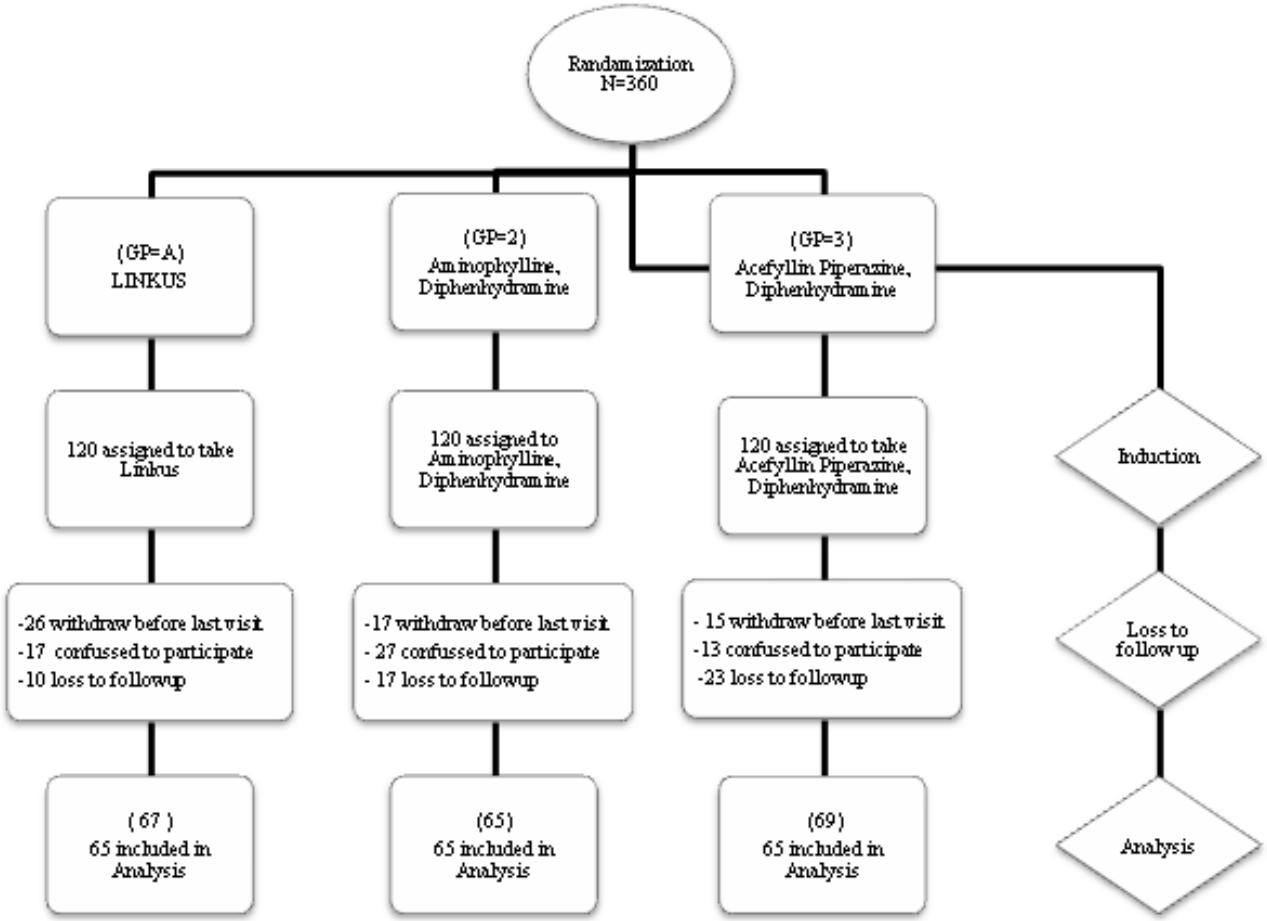


**Fig. 1**: Scheme of randomization and clinical analysis of patient enrolled as per inclusion critera.

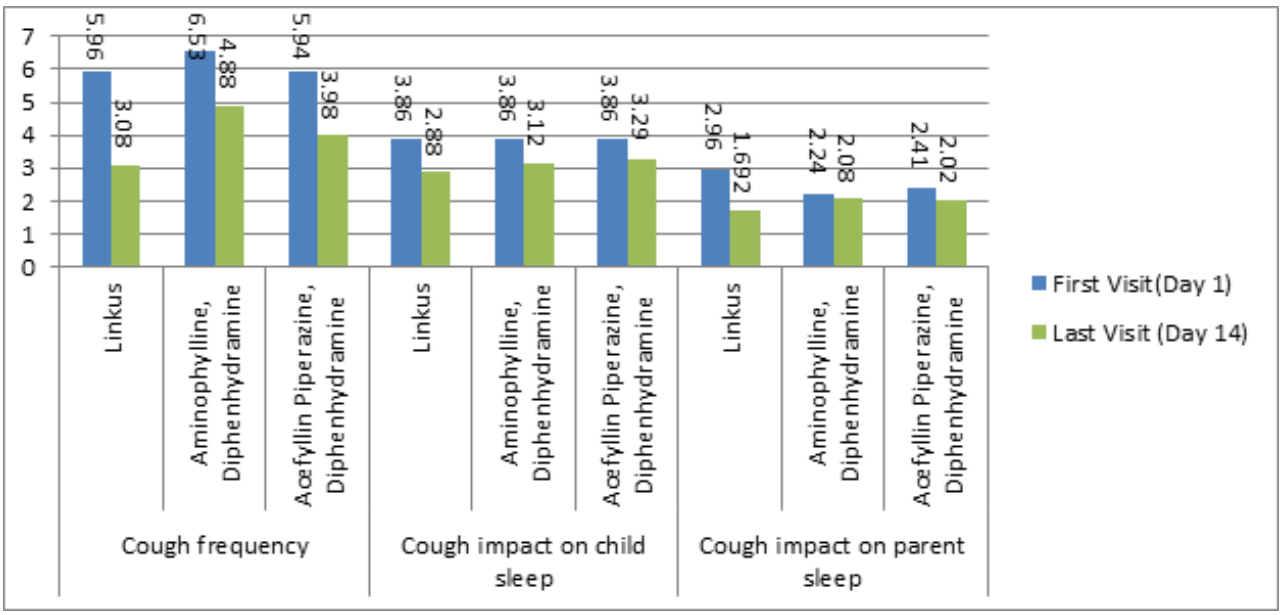


**Fig. 2**: Comparison between interventional syrup with visits on day 14.

**Table 1**: Demographics and baseline characteristics

| Description | | Linkus mean | Linkus ±SD | Aminophylline, Diphenhydrami mean | Aminophylline, Diphenhydrami ±SD | Acefyllin Piperazine, Diphenhydramin mean | Acefyllin Piperazine, Diphenhydramin ±SD | P value |
|---|---|---|---|---|---|---|---|---|
| Age | | 9.96 | ±2.198 | 9.61 | ±1.801 | 8.2 | ±1.190 | 0.0010 |
| Sindhi | | 36 | 55.38 | 33 | 50.77 | 42 | 64.62 | 0.5826 |
| Panjabi | | 5 | 7.69 | 4 | 6.15 | 4 | 6.15 | 0.1529 |
| Balochi | | 5 | 7.69 | 3 | 4.62 | 3 | 4.62 | 0.0017* |
| Urdu Speaking | | 16 | 24.62 | 17 | 26.15 | 8 | 12.31 | 0.0001* |
| Miscellaneous | | 3 | 4.62 | 8 | 12.31 | 8 | 12.31 | 0.0001* |
| Total | | 65 | 100.00 | 65 | 100.00 | 65 | 100.00 | |
| Gender n (%) | Male | 20 | 30.77 | 21 | 32.31 | 13 | 20.00 | 0.0036* |
| | Female | 45 | 69.23 | 44 | 67.69 | 52 | 80.00 | 0.0111* |
| Duration of illness in (days; mean ±SD) | | 4.9 | ±2.034 | 5.27 | ±1.578 | 4.39 | ±2.216 | 0.0449* |
| Cough frequency score per day before treatment, | | 6.63 | ±2.421 | 6.29 | ±1.458 | 6.24 | ±1.407 | 0.0899 |
| Cough impact on child sleep quality, mean ([%]) | | 35 | 71.4 | 31 | 63.0 | 30 | 61.0 | 0.4565 |
| Cough impact on parent sleep quality, mean ([%]) | | 38 | 77.5 | 34 | 69.0 | 31 | 63.0 | 0.3010 |

**Table 2**: Comparison between first and last visit on 3 parallel group (group A, B & C)

| Description | First Visit (Day 1) Unit:Number of cough Mean (n) | Std.Dev | Last Visit ( Day 14) Unit:Number of cough Mean (n) | Std.Dev | P value |
|---|---|---|---|---|---|
| **Cough frequency** | | | | | |
| Linkus | 5.96 | ±1.870 | 3.08 | ±1.115 | 0.001* |
| Aminophylline, Diphenhydramine | 6.53 | ±1.401 | 4.88 | ±1.379 | 0.001* |
| Acefyllin Piperazine, Diphenhydramine | 5.94 | ±2.313 | 3.98 | ±1.377 | 0.001* |
| **Cough impact on child sleep** | | | | | |
| Linkus | 3.86 | ±0.957 | 2.88 | ±8.57 | 0.001* |
| Aminophylline, Diphenhydramine | 3.86 | ±0.957 | 3.12 | ±1.11 | 0.001* |
| Acefyllin Piperazine, Diphenhydramine | 3.86 | ±.816 | 3.29 | ±0.764 | 0.001* |
| **Cough impact on parent sleep** | | | | | |
| Linkus | 2.96 | ±0.889 | 1.69 | ±0.812 | 0.001* |
| Aminophylline, Diphenhydramine | 2.24 | ±1.677 | 2.08 | ±1.426 | 0.001* |
| Acefyllin Piperazine, Diphenhydramine | 2.41 | ±1.171 | 2.02 | ±1.127 | 0.088* |
| **Wong Baker Face scale n (%)** | | | | | |
| Linkus | No Pain | Worst Pain ever | No Pain | Worst Pain ever | 0.001 |
| | 33 50.77 | 32 49.23 | 55 84.62 | 10 15.38 | |
| Aminophylline, Diphenhydramine | No pain | Worst Pain ever | No pain | Worst Pain ever | 0.250 |
| | 37 56.92 | 28 43.08 | 39 60.00 | 26 40.00 | |
| Acefyllin Piperazine, Diphenhydramine | No pain | Worst Pain ever | No pain | Worst Pain ever | 0.016 |
| | 24 36.93 | 41 63.08 | 33 51.77 | 32 49.23 | |

Frequency of cough on day 1 and day 14 found highly significant (P<0.001) on applying paired t-test as shown in table 2. The cough impact on child sleep in all 3 parallel groups found to be highly significant (P<0.001).

The trend of cough impact on parent sleep was also seemed significant in Linkus syrup group and Aminophylline Diphenhydramine (P<0.001) however in Acefyllin Piperazine with Diphenhydramine group (P<0.088). The pain assessment on Wong baker scale before (day 1) and on day 14 were only significantly high in Linkus cough syrup (p<0.001) however on group B and C (Aminophylline, Diphenhydramine) (p<0.250), Acefyllin Piperazine, Diphenhydramine (p<0.016) were not found significant on pain assessment.

The 5 level symptoms criteria were observed with the help of Likert Scale (5 =Excellent, v.good-4, good-3, fair -2, Poor=1) on Strength of stimulus towards cough, Amount of expectorant, consistency of the expectoration, Ease of expectoration, Bronchitis and respiratory tract diseases with the formation of Mucus on Linkus syrup.

**Table 3**: Data of the 5 level symptoms score of the sub groups on Linkus cough syrup.

| Description | Irritating cough (with or without common cold) n=29 | | | | | | | | Bronchitis (Acute or chronic) N=11 | | | | | | | | Respiratory tract disease with formation of mucus n=09 | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Strength of stimulus towards cough** | **5** | **4** | **3** | **2** | **1** | **Mean** | **±S.D** | **p-value** | **5** | **4** | **3** | **2** | **1** | **Mean** | **±S.D** | **p-value** | **5** | **4** | **3** | **2** | **1** | **Mean** | **±S.D** | **p-value** |
| Day 1 | 0 | 9 | 10 | 10 | 0 | 3 | ±0.81 | 0.001 | 0 | 9 | 1 | 1 | 0 | 2.18 | ±0.41 | 0.001 | 0 | 7 | 1 | 1 | 0 | 2.3 | ±0.71 | 0.008 |
| Day 14 | 19 | 2 | 4 | 3 | 1 | 1.6 | ±1.06 | | 9 | 1 | 0 | 0 | 1 | 1.09 | ±0.30 | | 6 | 1 | 1 | 0 | 1 | 1.3 | ±0.71 | |
| **Amount of expectorant** | **5** | **4** | **3** | **2** | **1** | **Mean** | **±S.D** | **p-value** | **5** | **4** | **3** | **2** | **1** | **Mean** | **±S.D** | **p-value** | **5** | **4** | **3** | **2** | **1** | **Mean** | **±S.D** | **p-value** |
| Day 1 | 6 | 17 | 5 | 1 | 0 | 2.03 | ±0.73 | 0.001 | 0 | 5 | 4 | 2 | 0 | 2.7 | ±0.78 | 0.002 | 0 | 4 | 3 | 4 | 0 | 3 | ±0.89 | **0.001** |
| Day 14 | 21 | 5 | 1 | 0 | 2 | 1.24 | ±0.51 | | 5 | 2 | 2 | 0 | 2 | 1.54 | ±0.82 | | 5 | 1 | 1 | 0 | 2 | 1.3 | ±0.70 | |
| **Consistency of the expectoration** | **5** | **4** | **3** | **2** | **1** | **Mean** | **±S.D** | **p-value** | **5** | **4** | **3** | **2** | **1** | **Mean** | **±S.D** | **p-value** | **5** | **4** | **3** | **2** | **1** | **Mean** | **±S.D** | **p-value** |
| Day 1 | 4 | 10 | 8 | 7 | 0 | 2.6 | ±1.0 | 0.002 | 0 | 4 | 4 | 1 | 0 | 2.5 | ±0.53 | 0.001 | 0 | 5 | 2 | 1 | 0 | 2.5 | ±0.75 | 0.002 |
| Day 14 | 15 | 4 | 6 | 1 | 3 | 1.6 | ±0.93 | | 6 | 1 | 0 | 0 | 2 | 1.11 | ±0.33 | | 5 | 1 | 1 | 0 | 2 | 1.3 | ±0.70 | |
| **Ease of expectoration** | **5** | **4** | **3** | **2** | **1** | **Mean** | **±S.D** | **p-value** | **5** | **4** | **3** | **2** | **1** | **Mean** | **±S.D** | **p-value** | **5** | **4** | **3** | **2** | **1** | **Mean** | **±S.D** | **p-value** |
| Day 1 | 5 | 10 | 8 | 6 | 0 | 2.5 | ±1.5 | 0.009 | 2 | 5 | 4 | 0 | 0 | 2.18 | ±0.75 | 0.014 | 0 | 5 | 3 | 1 | 0 | 2.5 | ±0.72 | 0.001 |
| Day 14 | 19 | 5 | 2 | 1 | 2 | 1.4 | ±0.77 | | 6 | 2 | 1 | 0 | 2 | 1.36 | ±0.67 | | 6 | 1 | 0 | 0 | 2 | 1.1 | ±0.33 | |

**Table 4**: Side effects of study interventional drugs (A, B and C)

| Side Effects | Linkus | | Aminophylline, Diphenhydramine | | Acefyllin Piperazine, Diphenhydramine | |
|---|---|---|---|---|---|---|
| | (n) | % | (n) | % | (n) | % |
| Stomache | 0 | 0.00 | 3 | 4.62 | 0 | 0.00 |
| Headache | 1 | 1.54 | 4 | 6.15 | 7 | 10.77 |
| Drowsiness/Sleepiness | 4 | 6.15 | 7 | 10.77 | 11 | 16.92 |
| Rashes | 1 | 1.54 | 0 | 0.00 | 1 | 1.54 |
| Other | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 |
| No side effects | 59 | 90.77 | 51 | 78.46 | 46 | 70.77 |
| | 65 | 100.00 | 65 | 100.00 | 65 | 100.00 |

Strength of stimulus towards cough with irritating cough, with bronchitis and respiratory tract diseases with formation of mucus were found highly significant (<0.01). The symptoms score were previously used and validated. Comparison of interventional group with the visits of day 1 to day 14 were mentioned in fig. 2. The children in the Linkus treatment group improved as compare to other interventional drug (<0.001).

Children were asked about the adverse effects on day 14. Through the telephonic conversation with the parents, day to day report collected during the study period. In the interventional group (all 3 parallel groups), Linkus has less side effects as compare to other groups as shown in fig. 2.

## DISCUSSION

Herbal and allopathic products as an OTC medication have widely distributed. This investigation sought that the herbal treatment Linkus were more superior as compare to the other investigational market drug (A & B). The sleep quality of children and parents were relatively high in poly herbal Linkus cough syrup and the disturbance due to cough has reduced. Disappointment was with Group A & B which were used extensively throughout the globe.

Published research on asthma, chronic cough or cystic fibrosis (Archer *et al*., 1985; Hamutcu *et al* ,2002) but its first on its kind of research on school going children in Pakistan .In addition children's quality of sleep in every interventional group were evaluated. However, the limitation of the study is the co-operation and understanding of the parents/guardians. Phone calls and patient's home visit was the only tool to minimize loss to follow up.

Cough is the most frustrating symptoms and lead absentees affects due to sleep disturbance of parents and children. The diphenhydramine was used in both allopathic medication causes restlessness, insomnia, acute dystonia, increased risk of severe injury and nervousness with in therapeutic doses Michelson *et al.,* 1958; Finkle *et al*., 2002.

## CONCLUSION

The Polyherbal syrup Linkus has shown better results in treatment of cough inclusive side effects as compare to Aminophylline with Diphenhydramine and Acefyllin Piperazine with Diphenhydramine. In addition Linkus was beneficial for nocturnal sleep and pain were significantly reduced.

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