

Efficacy and Safety of the Syrup "KalobaTUSS® " for the Treatment of Cough in Children: a randomized, double blind, placebo-controlled clinical trial

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Abstract

Background: Persistent cough in children often causes discomfort to children and parents reducing their quality of life. In spite of the extensive utilization of over the counter remedies against cough, for most of them efficacy in children has not been demonstrated.

Methods: We conducted a randomized, double blind, placebo-controlled clinical trial recruiting 106 children with persistent cough to evaluate the efficacy and safety of KalobaTUSS[®], a pediatric cough syrup based on acacia honey and on moieties derived from *Malva sylvestris* extract, *Inula helenium*, *Plantago major* extract, *Helichrysum stoechas*.

Results: Children were orally treated with KalobaTUSS[®] or placebo for eight days. Children receiving KalobaTUSS[®] showed an early significant reduction in night-time and day-time cough score measured through a specific scale and a shorter duration of cough in comparison to placebo.

Conclusions: Results show that KalobaTUSS[®] is well tolerated and produces positive effects by reducing severity and shortening the duration of cough in children. (Clinicaltrials.gov n. NCT04073251).

Background

Children cough is a common reason leading parents to seek medical and it is a real dare for pediatricians. Cough is probably the most bothersome symptom associated with upper respiratory tract infections for children and their parents. Frequently cough produces distress and sleep disorders to the whole family [1].

In most cases it is self-restrained, but its perseverance sometimes is exasperating and it can worsen quality of life and common social participation [2].

Influence of persistent children cough on family's life can create growing discomfort. Indeed, children with acute cough may experience transient disability which provokes losing of parents' work and absence of children during school time, so increasing global community cost [3]. Generally, parents' concerns increase when children's cough lasts for more than a week. Consequently, often occurs that parents seek for a medical consult with requirement of drug treatment, though most of antitussive drugs lack of evidence of effectiveness and safety [4].

Despite of the inappropriate prescription of antitussive pharmacological treatment in children has been reduced, pediatrics prescribing attitudes do not still always are reflecting accurate treatment of cough [2]. Furthermore, pediatric approach is always compromised by parental exaggerate perception of symptoms and usual consequent requirement of pharmacological prescription of antibiotics, that they consider the appropriate and effective therapeutic option for cough [5]. Epidemiological data indicate that cough occurring in children produces more anxiety than in adult people, and a lot of people think of this symptom as "a disease". A recent Italian survey confirms this view suggesting that some inclination of pediatricians therapeutic should be modified in favor to realize a better control of cough in children and to

reduce its impact [2]. Moreover, it often happens that attempting to treat cough, children are administered with over-the-counter products having little or no scientific evidence of proven efficacy [6].

The World Health Organization identified honey as a possible demulcent care for cough [7,8]. Demulcent is called a substance which covers the throat and reduces pain when mucous is irritated. Demulcent products are based essentially on sugar and they act as adjuvant to attenuate cough related to dry throat by covering receptors triggering cough or through increase of saliva and swallowing, reducing cough reflex [9].

Administration of honey at time to sleep to relief of cough in child and sleeping difficulty is believed by parents as more desirable than intake of drugs such as diphenhydramine or dextromethorphan or rather than placebo [10,11].

In 2018 the Cochrane Collaboration reviewed six randomized controlled and three not controlled clinical studies carried out in children and boys aging 1-18 years and investigating on use against acute cough of honey, alone or in association with antibiotic drugs in comparison with no treatment, placebo, syrups containing honey or free-honey over the counter antitussive. Authors' conclusions were that honey alleviates cough with a greater size effect with respect to diphenhydramine, placebo or no treatment and with poor or no difference in comparison to dextromethorphan. Moreover, honey reduced time period of coughing in a better way compared to salbutamol or placebo with no adverse effects [12].

Due to above assumptions, it seems interesting to evaluate a different approach to treat cough, instead of pharmacological drugs, for instance a mechanical and non-pharmacological intervention. The safeguarding effect of a mechanical barrier at throat level may be considered a well founded therapeutic perspective acting through an indirect anti-inflammatory activity, able to reduce harm produced by irritant agents or microbes. This protective activity can be acquired with the association of natural substances: honey and plant extracts.

On the light of the above considerations and since number of accessible pediatric antitussive products is reduced because of lack of proof of efficacy, a cough syrup for children (KalobaTUSS®) based on acacia honey in combination with moieties derived from *Malva sylvestris* extract, *Inula helenium*, *Plantago major* extract, *Helichrysum stoechas* to be clinically tested on persisting cough of children, has been developed. This syrup is a Medical Device class IIa, classified in agreement with the Directive 93/42/EC.

Malva sylvestris is a biennial–perennial herbaceous medicinal plant domestic in North Africa, Asia and Europe also called with the name “common mallow”. It has been used along in folk medicine for its mucus formed of flavonoids and polysaccharides.

Traditionally, *M. sylvestris* is used for the treatment of various infections or diseases, including cold, cough, tonsillitis, bronchitis. The entire plant exhibits beneficial properties, and it has been used along in folk medicine for its mucus due to the leaves and flowers rich of flavonoids and mucillages. Mucilage is present in the percentage of 6-8% in its leaves containing high molecular weighing acidic polysaccharides

of the rhamnogalacturonan type with, situated in epidermal cells [13]. European Medicinal Agency (EMA) in 2018 assessed its traditional use as a “demulcent preparation for the symptomatic treatment of oral or pharyngeal irritation and associated dry cough” [14,15].

Inula helenium (Elecampane) is a perennial herbaceous plant of the Asteraceae family, native of England and Europe, growing also in North and East of United States, Canada, Asia, India and Siberia. This plant was used for its medicinal properties to treat cough [16].

Inula helenium roots are rich of coumarins, flavonoids, polysaccharides (up to 44% inulin and pectic substances), fatty acids and saponins [17]. The sesquiterpene lactones present in the phytocomplex are responsible for the plant's anti-inflammatory and expectorant properties [18]. Traditionally, extracts of the plant have been used for bronchial/tracheal catarrh and dry irritating cough in children [19].

Plantago major is a plant of Plantaginaceae family native of Asian and European temperate areas. Aerial parts contain iridoids as the main constituents, also are present mucilage (up to 12%), flavonoids, carbohydrates, alkaloids, amino acids, tannins, lipids, steroids, saponins, proteolytic enzymes and vitamins. In traditional medicine the plant was employed against cough related to inflammation of upper respiratory airways [20]. The plant is a quite effective soothing, moistening expectorant remedy for a dry irritable cough because the mucous membranes are lacking in their production of immune rich mucous that coats, soothes and protects the membrane - thus it gets dried out, inflamed and easily irritated [21]. Studies demonstrated that plants belonging to the genus *Plantago* can significantly attenuate cough [22,23].

Helichrysum stoechas is an annual herb belonging to the family of Asteraceae indigenous in the occidental Mediterranean regions [24]. Extract of aerial parts contains mainly isomers of caffeoylquinic and dicaffeoylquinic acids, apigenin glucosides, quercetin and kaempferol. The stems and the flowers of the plant showed to have expectorant, sudorific and laxative properties and they are used for the treatment of common cold [25].

We investigated through a randomized, controlled double blind clinical trial the effects of KalobaTUSS[®], an innovative syrup containing acacia honey and herbal extracts of *Malva silvestris*, *Inula helenium*, *Plantago major* and *Helichrysum stoechas*, on persistent cough in children aging 3-6 years. The extract of *Malva silvestris* is titrated to 80% on mucillages, and the extracts of *Inula*, *Plantago* and *Helichrysum* are titrated to 30% on polysaccharides. The rich composition of the study syrup makes it suitable for use in the treatment of children's cough, acting as a mechanical barrier on the mucosa.

Aim of this trial was to evaluate the efficacy and safety of KalobaTUSS[®] in comparison with placebo on nocturnal and diurnal persistent cough in children.

Methods

Data and recruitment for this randomized, double-blind controlled parallel clinical study were collected performed in the pediatric consulting rooms of the Azienda Ospedaliera Provinciale of Messina in collaboration with the Azienda Ospedaliera Universitaria (AOU) Policlinico “G. Martino” of Messina, Italy. The following inclusion criteria were adopted: children aging 3-6 years, with persistent cough for not less than three consecutive days, leading parents for pediatrician consultation. Exclusion criteria were: children with history of obstructive pulmonary diseases, heart diseases, cystic fibrosis, diabetes, neurological diseases, immunodeficiencies. Children suitable for the study according to the inclusion criteria were allocated in random manner to one of the two groups of treatment (KalobaTUSS® or placebo). Parents, or tutors according children participation to this trial, signed the informed consent form. Random allocation in the two groups of treatment was blinding performed by pediatricians as follows: at admission, subjects were associated with identification numbers randomly assigned to groups of treatment by using block randomization. Both participants (their parents or tutors) and care providers were double-blinded for the interventions. Children belonging to the active group received the syrup KalobaTUSS® and the second group received a placebo as syrup formulation. The double-blind method was adopted and group membership was disclosed after analysis of results. For each of two treatment regimens were administered 4 doses daily, 5 ml each dose, for 8 days of KalobaTUSS® or placebo, respectively. The appearance, consistency, organoleptic characteristics and viscosity of KalobaTUSS® and placebo were very similar. Both the products were supplied by Schwabe Pharma Italia Srl, Egna (BZ), Italy.

The study was approved by the Ethic Committee of AOU Policlinico “G. Martino” with protocol number 95/18 on 17 December 2018. The trial was carried out according to the ethical principles of the Helsinki Declaration and adopting Good Clinical Practice principles (ClinicalTrials.gov identifier: NCT04073251).

Aim of this study was to evaluate the clinical efficacy of KalobaTUSS® by using as primary endpoint the evaluation and analysis of changes in night-time and day-time cough score assessed through a validated questionnaire filled by parents [26]. Secondary objective was to evaluate the safety of the syrup KalobaTUSS® when given in children with persistent cough for 8 days. Cough was clinically diagnosed and evaluated by pediatricians during the first visit and successively monitored by parents by filling a daily diary after receiving instructions by pediatricians. At the end of the administration period, pediatricians visited again children and collected the daily diary filled by parents or tutors for each child.

Size of the sample to enroll for the study was calculated presuming an average baseline cough score of 3 points in both the two groups, and an average change in cough score of 2 points occurring in the arm treated with the study product and 1 point for the placebo arm.

One hundred and ten (110) children with persistent cough were consecutively enrolled and divided in two groups. Enrollment began on 15th february 2019 and was completed on 10th may 2019. Four children, two from each group, left the study before the beginning of treatment. 106 began and completed the treatment (Figure 1). Fifty-four (54) children received the KalobaTUSS® syrup and another group composed of fifty-two (52) children received the placebo syrup. The median age of children completing

the study was $53.02 \pm$ standard deviation (SD) 12.02 months (range, 38-70 months; median age 4.3 months), with no significant age difference between the two treatment groups ($p= 0.8181$). In the total sample of enrolled children, boys and girls were 50.8 % and 49.2 %, respectively. Boys and girls were present in similar percentage both in the KalobaTUSS[®] and placebo arms (Table 1).

The mean period of coughing before recruitment was calculated to be 3.53 ($\pm$ SD 0.57) days for the group of children taking KalobaTUSS[®] syrup arm and 3.52 ($\pm$ SD 0.58) days for the group treated with placebo, with no significant difference between the two groups ($P= 0.93624$). None of the children monitored for the study needed to receive antibiotics or any other pharmacological therapy during the treatment days and for the follow-up period of one week after the end of the study.

Adverse events (AEs) were monitored throughout the whole duration of the clinical study. AEs were described as inappropriate medical events, connected or not, to the procedures or to the product.

Statistical analysis

Statistical analysis of changes in cough score between the groups of treatment was performed by Mann Whitney U test. Demographic data were expressed as means $\pm$ standard deviation (SD), changes produced by treatments were expressed as means $\pm$ standard error (SE). Estimated effect sizes (Cohen d with Hedges bias correction) with 95% CIs are provided for night-time and day-time cough score. Evaluation of events (cough) between the two groups is expressed as Relative Risk and Relative Risk reduction (RR, RRR), 95% confidence intervals (CI) and p -values. A p -value smaller than 0.05 was considered statistically significant.

Results

Night-time cough

Children who received KalobaTUSS[®] syrup showed a significant reduction already on day 1 in night-time score: 1.11 ± 0.01 (mean $\pm$ SE) from N_0 to N_1 vs basal values, compared to a 0.29 ± 0.01 change in score vs basal values for those receiving placebo syrup ($P = 0.00001$), thus indicating a quick improvement of night cough (Table 2, Table 4 and Figure 2). Reduction in scores were observed also either four or eight nights of the treatment period. This effect was observed by comparing the scores obtained after four nights with basal night values or through the comparison of the total sum of nocturnal score after four nights of treatment with KalobaTUSS[®] with the night scores of placebo arm. Application of Hedges's and Cohen's formulas showed a large size effect after the first night and also at the end of treatment in comparison to placebo (Table 2). Differences in reduction of nocturnal cough scores between N_0 (baseline) and N_1 (night 1) or night 4 (N_4) or night 8 (N_8), were greater in children treated with KalobaTUSS[®] compared to placebo group: N_0 vs N_1 was -1.11 ± 0.01 (SE) for KalobaTUSS[®] and -0.29 ± 0.01 (SE) for placebo; N_0 vs N_4 was -2.80 ± 0.02 (SE) for KalobaTUSS[®] and -1.94 ± 0.02 (SE) for placebo; N_0 vs N_8 was -2.80 ± 0.02 (SE) for KalobaTUSS[®] and -1.94 ± 0.02 (SE) for placebo (Table 4 and Figure

3). Nocturnal cough was no longer present in a larger group of children treated with KalobaTUSS[®] compared to placebo arm, either after four days or after eight days of treatment (Table 5).

Day-time cough

KalobaTUSS[®] significantly reduced day-time score after the first day of treatment in the interval from D0 to D1. Point score reduction of day-time was 0.67 ± 0.01 (mean $\pm$ SE) vs basal values in the KalobaTUSS[®] group compared to point score reduction of 0.11 ± 0.01 vs basal values in the placebo group ($P < 0.00001$), thus indicating a quick improvement also of day-time cough. Improvement of cough was furtherly revealed by the difference of day-time cough score reduction (-1.11 ± 0.01) in the group of children treated with KalobaTUSS[®] and by the difference (-0.29 ± 0.01) observed in the placebo arm ($P = 0.00001$). Significant difference in reduction of cough scores was also shown after four days of treatment. This effect was observed by comparing the score of the fourth day with basal values or through the comparison of the sum of daily cough score after four days of treatment with KalobaTUSS[®] with the scores of placebo arm (Table 3, Table 4, Figure 2). Size effect of KalobaTUSS[®] on daytime cough was larger with respect to effects of the study syrup on night time cough either after the first night and at the end of treatment (Table 3). Differences in diurnal cough scores between D₀ (baseline) and D₁ (day 1), or D₄ (day 4) or D₈ (day 8), were greater in children treated with KalobaTUSS[®] compared to placebo group (Figure 2). D₀ vs D₁ was -0.67 ± 0.01 (SE) for KalobaTUSS[®] and -0.11 ± 0.01 (SE) for placebo; D₀ vs D₄ was -1.04 ± 0.02 (SE) for KalobaTUSS[®] and -0.36 ± 0.02 (SE) for placebo; D₀ vs D₈ was -1.91 ± 0.02 (SE) for KalobaTUSS[®] and -1.27 ± 0.03 (SE) for placebo (Table 4 and Figure 3). Diurnal cough was no longer present in a larger percentage of children treated with KalobaTUSS[®] in comparison to the placebo group, either after four days or after eight days of treatment (Table 5). No AEs were observed throughout the whole duration of the clinical study in the two groups of treatment.

Discussion

Cough is frequent in children and its presence is responsible of numerous visits to pediatricians. Cough represents a separate clinical entity when is in absence of organic origin. Such a persistent unintentional cough is generally considered to be a functional disorder [27]. Occurrence of cough in children is attractive for medical research due to recognition that often adult respiratory pathologies (for example chronic obstructive pulmonary disease or asthma) are linked and have their origin with the presence, in the same person, of respiratory disorders of childhood [28].

Dextromethorphan and diphenhydramine are frequently prescribed as antitussive drugs, principally for children [29]. However, a recent Cochrane Collaboration review observed that no evidence supporting or contrary the effectiveness of them used for symptomatic relief of cough [30]. Furthermore, a clinical study in which dextromethorphan and diphenhydramine were each one compared with honey (2.5 mL) administered before bedtime showed that the latter produced a better relief in the control of night-time cough and sleep quality in children with irritative cough [31]. Consequently, an optimal therapeutic

approach has not been identified. On this basis we carried out a clinical investigation with the aim to evaluate the potential beneficial effects of the syrup KalobaTUSS® containing extracts of *Malva silvestris*, *Inula helenium*, *Plantago major* and *Helichrysum stoechas*, and acacia honey on persistent cough in children. The study product could treat cough by a mechanical mode of action: its active substances, honey and herbal extracts, were specifically chosen for capacity to form a barrier over the irritated mucosa in order to indirectly reduce the throat inflammation that triggers the cough reflex.

Preclinical data by in vitro experimental assays (not yet published) showed that the study syrup possesses very good mucoadhesive properties on human oral mucosa cells (static mucoadhesiveness), and it is also able to form a sufficiently resistant mucoadhesive layer (dynamic mucoadhesiveness) to the action of the mucosal liquids with which it comes into contact. This peculiarity, that is the formation of a compact mucosal layer and, in particular more resistant, results in a greater permanence of the product on the mucous membranes and therefore in a greater and prolonged protective action.

The results of the present clinical trial show that in children receiving KalobaTUSS® syrup a significant reduction in night-time (N) and day-time (D) cough was measured through a specific evaluation scale. Reduction in both night and day-time scores appears quickly, already after 24 hours, as it is shown by the evaluation between basal night (N_0 score) and day (D_0 score) and the ones reached during the next night (N_1 score) and day (D_1 score). Moreover, the antitussive effects are maintained after four days of treatment by comparing the scores reached by children treated with KalobaTUSS or placebo with basal values or by comparison of the total sum of daily score obtained by collecting the score of each child after four days of treatment with KalobaTUSS® with the scores of placebo arm.

Scores obtained with the questionnaire filled by parents showed that night-time cough severity is reduced to a greater extent by treatment with the study syrup with respect to the day-time cough. This aspect could be not further investigated due to the known additional limitations in the study of night-time cough in children. It may not be considered like cough during the day because to diurnal changes in respiratory physiology and difference in environmental cough triggers as it has been recognized that the analysis of factors in determining night cough may be confounded by environmental exposures [32]. The reduction of night-time cough scores is a very important topic in cough management as contrast of night-time cough is difficult to obtain, it causes considerable discomfort and produces loss of sleep both in children and parents.

Even though it was not still complete, the relief of symptoms due to the study syrup action was already significant after the first 24 hours, thus suggesting an early response to treatment. The early effect was also associated to a quick relief of cough. The fastest relief was shown by the larger percentage of children without nocturnal and diurnal cough in the group treated with the study syrup in comparison to the group of children treated with placebo, both after four and eight days of treatment when compared to the placebo group. The safety of the product for antitussive use has been assessed with no report of adverse events. Palatability, color, odor and density was also well accepted for both the study syrup and the placebo syrup.

Despite of limitation due to the collecting data undirectly through children's parents, this clinical trial suggests that there are beneficial effects of acacia honey together with specific fractions derived from *Malva sylvestris*, *Inula helenium*, *Plantago major*, and *Helichrysum stoechas* extracts tested on persistent cough in children. The significant improvement observed in cough score can be attributed to the demulcent and mucolytic characteristics of the study product. While antitussive drugs act either on the cough center of central nervous system which controls coughing, or on the peripheral cough receptors located into the trachea, pharynx and branching points of large airways and distal smaller airways, effect against cough of many natural substances is due to the protecting and demulcent activities of mucilage results from the content of mucilage, which exerts protective and demulcent activity [33].

Mucilages are a complex of polisaccharidic molecules and they are part of different organs of the plant, mainly the aerial parts. When in contact with water, mucilages tend to swell and to create a jelly film on the contact surface. When mucilages come in contact with respiratory mucosa, they adsorb humidity present in the mucus, jellyfy and form bonds with the structure of the mucosa [34]. In the case of inflammatory states, this film has a smoothing and emollient action on irritated mucosa: this action is defined "demulcent". With this term it is meant a soothing and protective action on the irritated or inflamed tissue of mucosa [9].

Ingredients of KalobaTUSS® create a protective film on the mucosa, calming cough and protecting the upper respiratory tract. Active principles contain a high amount of polysaccharides and mucilages which create a filming barrier on the oropharyngeal and larynx mucosa through a bioadhesion mechanism of action. The adhesion on the upper respiratory tract mucosa limits the contact with external irritating agents, promotes hydration and limits irritative processes [35].

Apart from the known protective effects of mucilage it has been also suggested that the palatableness of honey itself promoting salivation and discharge in the airways could lead to liquefaction of mucus and attenuation of cough cause by lower irritation in the larynx and pharynx [36]. In conclusion, the results of this study show that KalobaTUSS® is well tolerated and produces positive effects by reducing cough severity and shortening the duration of persistent cough in children.

Abbreviation

AOU: Azienda Ospedaliera Universitaria; AEs: adverse events; SD: standard deviation; SE: Standard error; RR: relative srisk; RRR: relative risk reduction; CI: confidence intervals; N: night-time; D: day-time.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethic Committee of Azienda Ospedaliera Universitaria (AOU) Policlinico "G. Martino" with protocol number 95/18 on 17 December 2018.

The signed informed consent to participate in the study was obtained from all children parents or tutors.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

Authors Ilaria Carnevali, Lara Pauletto, Floriana Raso, Marco Testa, are employed by the company Schwabe Pharma Italia, Egna (BZ), Italy. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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The name of the product (KalobaTUSS®) was included in the manuscript with the appropriate permissions obtained from the copyright holders of this product.

Authors' contribution

LPR, contributed to conception and design, acquisition and interpretation and critically revised the manuscript; CI, Contributed to analysis and interpretation and drafted the manuscript; PL, Contributed to analysis and interpretation; RF Contributed to conception and design and contributed to analysis and interpretation; TM, contributed to analysis and interpretation and critically revised the manuscript; CF, contributed to conception and design, acquisition and interpretation and drafted the manuscript; MC, contributed to analysis and interpretation, drafted the manuscript and critically revised the manuscript; SEE, contributed to analysis and interpretation; CG, contributed to conception and design, contributed to acquisition, analysis and interpretation, drafted the manuscript. All authors have read and approved the manuscript.

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Tables

Table 1. Baseline characteristics of children enrolled for the study.

	KalobaTUSS®	Placebo	Whole sample	Statistics
Children n.	54	52	106	
Mean age (months)	53.2 ± 11.8	52.9 ± 12.3	53.0 ± 12.0	NS
Median age (months)	52	51.5	52	—
Sex (male/female)	28/26	26/26	54/52	NS
Consecutive days of cough before recruitment	3.53 ± 0.57	3.52 ± 0.58	3.59 ± 0.65	NS

Data are expressed as means ± standard deviation. NS = not significant.

Table 2. Night-time cough score before and after treatment with KalobaTUSS® or placebo.

Score	KalobaTUSS®	Placebo	Effect size (Hedges' g)	Effect size (Cohen's d)	P
N ₀ score (baseline)	3.78 ± 0.01	3.75 ± 0.02	0.036806	0.036776	0.8493
N ₁ score	2.65 ± 0.02	3.48 ± 0.02	0.760777	0.76118	0.0006
N ₄ score	0.98 ± 0.02	1.81 ± 0.02	0.737756	0.736129	0.0008
N ₈ score	0.20 ± 0.01	0.73 ± 0.02	0.605444	0.602798	0.0075
Total score of first 4 nights	6.46 ± 0.07	9.36 ± 0.08	0.734184	0.733648	0.0003
Total score of all 8 nights	8.20 ± 0.11	13.40 ± 0.11	0.838006	0.83697	0.00001

Data are expressed as means ± standard error. N = night. P was considered significant when < 0.05.

Table 3. Day-time cough score before and after treatment with KalobaTUSS® or placebo.

Score	KalobaTUSS®	Placebo	Effect size (Hedges' g)	Effect size (Cohen's d)	P
D ₀ score (baseline)	2.07 ± 0.01	2.08 ± 0.01	0.013795	0.013793	0.9442
D ₁ score	1.41 ± 0.01	1.96 ± 0.01	0.794567	0.793031	0.0004
D ₄ score	1.15 ± 0.02	1.75 ± 0.02	0.543784	0.542748	0.0139
D ₈ score	0.28 ± 0.01	0.85 ± 0.02	0.682739	0.676823	0.0063
Total score of first 4 nights	5.09 ± 0.05	7.58 ± 0.06	1.041877	1.031956	0.0002
Total score of all 8 nights	7.33 ± 0.11	11.83 ± 0.12	0.766493	0.764947	0.0002

Data are expressed as means ± standard error. D = day. P was considered significant when < 0.05.

Table 4. Differences in cough scores of the night (N_0 score; baseline) and the day (D_0 score; baseline) before enrollment compared with night 1 (N_1), night 4 (N_4), night 8 (N_8), and day 1 (D_1), day 4 (D_4), day 8 (D_8), respectively.

	KalobaTUSS®	Placebo	P
N_0 vs N_1	- 1.11 ± 0.01	- 0.29 ± 0.01	0.00001
N_0 vs N_4	- 2.80 ± 0.02	-1.94 ± 0.02	0.00014
N_0 vs N_8	- 3.57 ± 0.02	- 3.06 ± 0.02	0.00758
D_0 vs D_1	- 0.67 ± 0.01	- 0.11 ± 0.01	0.00036
D_0 vs D_4	- 1.04 ± 0.02	- 0.36 ± 0.02	0.00804
D_0 vs D_8	- 1.91 ± 0.02	- 1.27 ± 0.03	0.03940

Data are expressed as means ± standard error. P was considered significant when < 0.05.

Table 5. Evaluation of events (cough) between the two groups is expressed as Relative Risk and Relative Risk reduction (RR, RRR), 95% confidence intervals (CI) and p -values. A p -value smaller than 0.05 was considered statistically significant.

	KalobaTUSS® (children with cough)	Placebo (children with cough)	<i>RR</i> (95% <i>CI</i>)	<i>RRR</i> (95% <i>CI</i>)	<i>p</i>
Night time cough after four days of treatment	34/54	43/52	0.76 (0.6-0.9)	0.24 (0.032-0.40)	0.0256
Night time cough after eight days of treatment	7/54	22/52	0.306 (0.143-0.65)	0.69 (0.34-0.85)	0.0023
Day time cough after four days of treatment	38/54	45/52	0.81 (0.66-0.99)	0.18 (0.0032-0.33)	0.046
Day time cough after eight days of treatment	8/54	24/52	0.32 (0.16-0.65)	0.68 (0.35-0.84)	0.0016

Figures

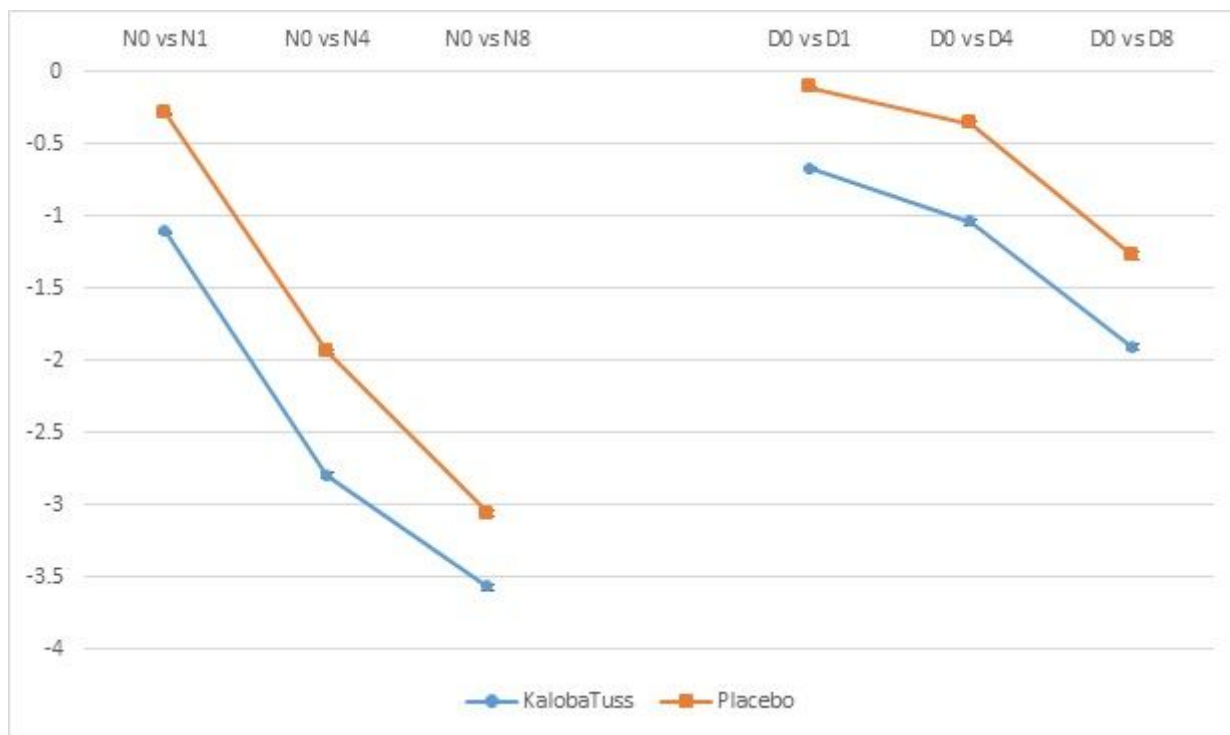


Figure 1

Reduction in night-time and day-time cough scores in children treated with KalobaTUSS® or Placebo. * = $P < 0.01$ vs Placebo.

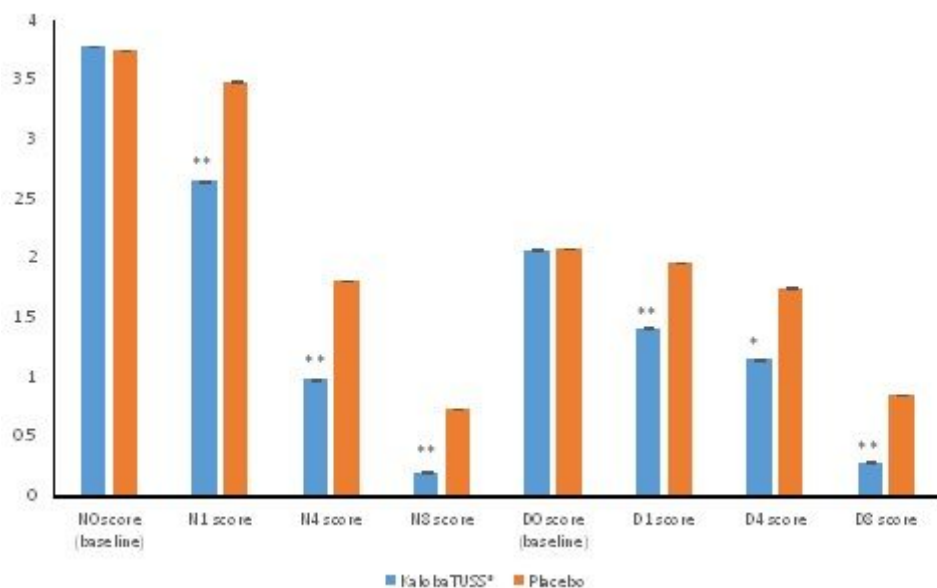


Figure 2

Night-time or Day-time cough score before and after treatment with KalobaTUSS® or placebo. * = $P < 0.05$ vs placebo; * = $P < 0.01$ vs placebo.

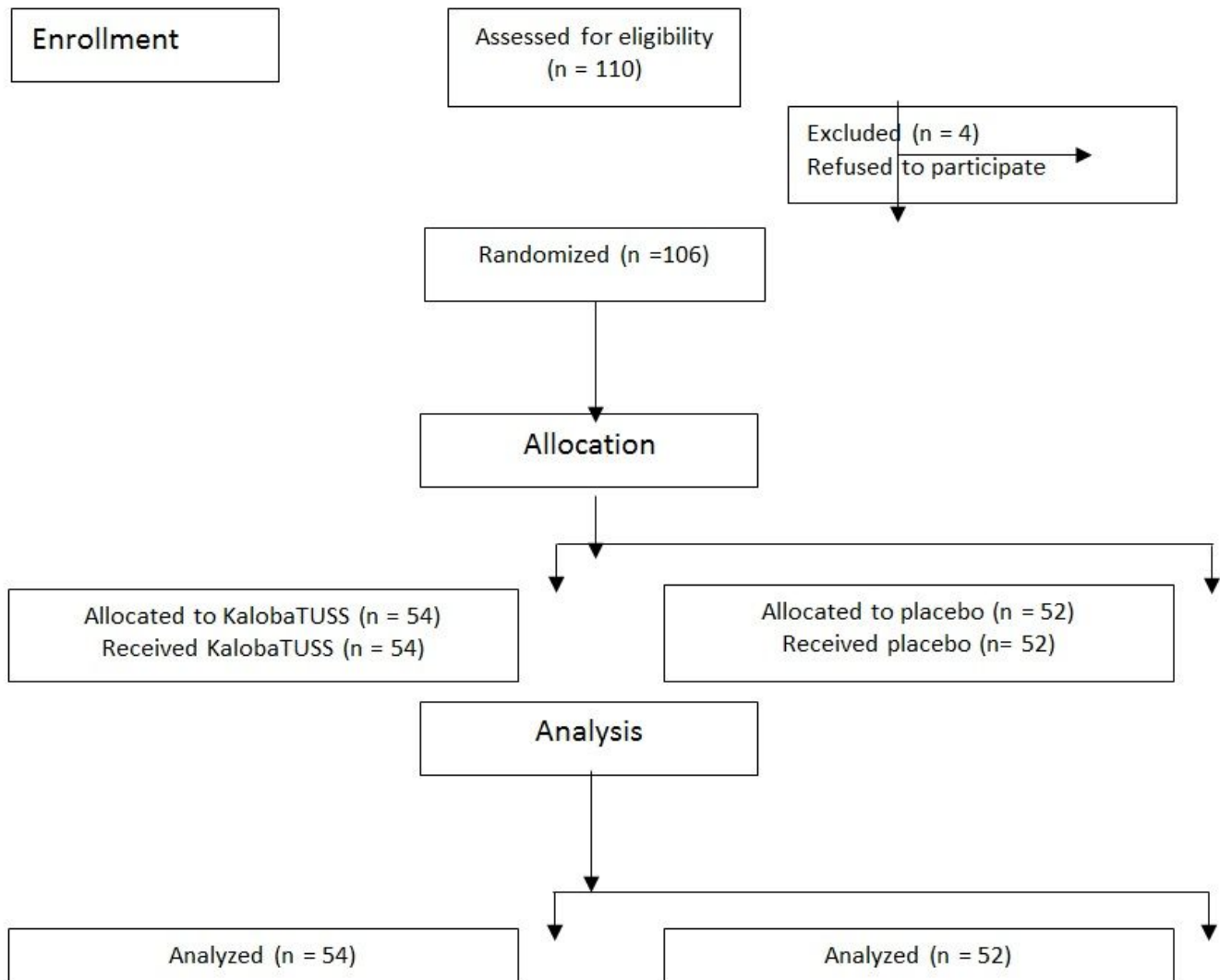


Figure 3

Study Flowchart

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CONSORTChecklistforBMCPediatrics23620.doc](#)