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Efficacy and safety of Pranabb® syrup to reduce cough and improve sleep quality in children compared to usual recommended hydration measures

Abstract

Background: Coughing is crucial for protecting the airways, but associated to unpleasant symptoms that often lead to pediatrician visits. Natural remedies like honey and essentials oils are being increasingly used to effectively relieve symptoms associated with cough.

Objectives: Evaluate the efficacy and safety of Pranabb® cough syrup, an organic honey-based natural formulation tailored for pediatric patients, in relieving cough symptoms.

Methods: One-week multicenter comparative clinical study of 50 children, 28 in the treatment group and 22 in the control group with supportive measures (increased hydration). Pediatrician appointments were scheduled at the baseline and on day 7, with a progress check call on day 3. Parents kept a daily cough diary.

Results: Day 3 results show a significant decrease in daytime cough, night-time cough and global score more pronounced and statistically significant in the study group, although the more severe baseline level in the study group. On day 7, decrease in daytime and overall cough scores was greater in the study group ($p<0.05$). The frequency of awakenings due to coughing decreased on day 3 only in the study group ($p<0.05$) and on day 7 for both groups, although it was higher and more significant in the study group (-1.82 $p<0.01$ vs -1.25 $p<0.05$). In addition, the safety analysis confirms that the syrup is not toxic to children.

Conclusion: Pranabb® Cough Syrup is safe and effective, reducing cough severity and nighttime awakenings in children and improving parents' ability to sleep. More randomized clinical trials will be interesting to get more homogeneity between the two groups at baseline.

Keywords: syrup, cough, upper respiratory tract infection, protective barrier, essential oils, honey

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Introduction

Cough is a physiological response to airway irritation, serving a fundamental role in airway protection and maintenance of airway patency. Cough has two main functions: preventing food and fluids from entering the lower airways and aiding the removal of excess material that exceeds the mucociliary system's transport capacity due to its quantity, size, or characteristics.[1] Cough is probably the most bothersome symptom of upper respiratory tract infections (URTIs) and leads to numerous pediatrician visits.

Mucosal dehydration and mechanical stimuli caused by dripping nasal mucus, along with various pathogens and irritants, are key factors in triggering the urge-to-cough (UTC) and sustaining URTI-associated acute cough. In this regard, up to 85% of the benefit of cough syrups depends on their demulcent action, forming a protective layer on mucous membranes to reduce pain and inflammation.[2]

Although over-the-counter (OTC) cough and cold medications with antihistamines and decongestants or cough suppressants are commonly used, there's limited evidence supporting their efficacy, and they often come with unwanted side effects and potential harm.[3,4] As a result, natural remedies found in traditional medicine have gained popularity in recent years. Honey is one such natural cough treatment. In addition to its humectant properties, the natural sweetness of honey, stimulates salivation and provides a pleasing taste experience for the brain. The sweet taste and its viscous consistency make it an ideal cough remedy, and honey also offers anti-inflammatory, antioxidant, and antibacterial properties.

Recent research highlights the health benefits of honey.[5] A single 2.5 mL evening dose of honey for children aged 2 to 5 years significantly reduces cough frequency compared with supportive care in an unblinded study.[6]

Honey also outperforms dextromethorphan and no treatment for relieving nighttime cough and sleep issues in children with URTIs.[7] Another study comparing two honey types with diphenhydramine finds both types of honey more effective in improving nocturnal cough than diphenhydramine, with no difference between them.[8] A 2018 Cochrane review, concluded that honey is more effective than diphenhydramine, placebo, or no treatment for cough relief.[5]

Honey's benefits can be enhanced when combined with other natural substances. Several clinical trials have shown that honey-based syrups with mixed natural components may help alleviate URTI-associated nocturnal cough.[2]

Pranabb® Cough Syrup (PBB) is a honey and essential oil-based syrup designed for pediatric patients with acute upper respiratory tract conditions. Three key functional elements are components of the syrup:

a. Honey for its ability to form a soothing film over the mucous membrane (a demulcent action), which indirectly reduces pain and inflammation thanks to a protective barrier effect and reduce mucosal dryness thanks to its humectant effect,

b. Manioc and Corn syrups that enhance viscosity and help film formation and

c. Glycerol due to its properties of lubrication, demulcent activity and sweetness, contributes to the benefit of cough syrups. Additionally, the syrup contains the essential oils (*Thymus QT thujanol oil, Citrus limon oil, Mentha spicata oil, Pinus sylvestris oil*). These oils have a history of traditional use as cough remedies and have been the subject of various studies that have highlighted their antimicrobial, antioxidative, and anti-inflammatory properties.[9–12]

This clinical investigation aims to evaluate the efficacy and safety of PBB in the treatment of cough associated with acute upper respiratory tract infections among children.

Method

Study design and participants

Prospective, multicenter, open-label, controlled clinical investigation with a CE-marked medical device under normal conditions of use to evaluate the antitussive efficacy of a honey-based syrup in pediatric patients compared to no cough treatment and only supportive measures (recommendation to increase hydration) (control group), with 1 week of follow-up.

The inclusion criteria were children aged 1 to 12 years with a body weight of ≥7 kg, with cough secondary to URTI, and whose parents accepted their participation and signed the informed consent. The exclusion criteria were: history of bronchial asthma, bronchitis, chronic respiratory disease, seizures, epilepsy, or any clinical disorder that, in the physician's opinion, could endanger the patient or interfere with the results; need for antibiotic treatment; use another cough treatment; intolerance or allergy to any components of the syrup; and suspected or confirming SARS-CoV-2 infection in the last 7 days.

All patients were enrolled from March to November 2022. They were divided into two groups based on the treatment received. In the control group, patients were advised to maintain adequate hydration by consuming plenty of fluids throughout the day. In the study group, patients were administered the honey-based syrup, according to the recommended usage instructions: the children between 7 kg and less than 14 kg (1 - 4 years) taking 2.5 ml, twice a day; and the children weighing between 14 kg and up to 28 kg (6-12 years) taking 5 ml, twice a day.

Patients were monitored for duration of one week, during which they had scheduled appointments with the pediatrician at the beginning of the study (baseline) and on day 7 (end of study visit). Additionally, a telephone call was conducted on day 3 to assess the progress of the subjects. Moreover, parents completed a patient diary on cough status every day.

All patients signed a written informed consent at the time of enrollment. The study protocol was approved by an independent ethics committee. This research adhered to the principles outlined in the Helsinki Declaration.

Objectives and variables

The primary outcome was the decrease in cough from the baseline visit to Day 3, assessed as the global score obtained in the Likert cough assessment severity questionnaire based on 6-point Likert scales (0=not at all, 1=not very much, 2=a little, 3=somewhat, 4=quite a bit, 5=a lot, 6=very much/extremely).

The secondary outcomes measured the changes in night-time and daytime cough severity, discomfort caused by cough, the ability of the child and parents to fall asleep and stay asleep. These assessments were conducted between the baseline visit and the visits on Day 3 and Day 7, using Likert scales ranging from 0 to 6. Adverse events (AEs) were monitored throughout the clinical study. The parent and physician satisfaction with the syrup was also measured through a 5-point Likert scale (0=very dissatisfied; 1=dissatisfied; 2=indifferent; 3=satisfied; 4=very satisfied).

Statistical analysis

Continuous variables were presented using measures of central tendency (mean) and dispersion (standard deviation), while categorical or ordinal variables were described using frequencies (n) and percentages (%). For the analysis of primary and secondary efficacy variables, comparisons were conducted using the Wilcoxon signed-rank test and Mann-Whitney U test. The safety analysis was descriptive in nature.

Results

Demographic and clinical characteristics of study patients

Of the 51 pediatric patients initially recruited, one patient in the study group was excluded for not meeting the inclusion criteria. This resulted in a valid population of 50 patients, 28 in the study group and 22 in the control group (of which one had no follow-up data available), 25 men (50%) and 25 women (50%), with a mean (SD) age of 4.5 (3.2) years (range: 1 – 12 years). No significant differences were observed between the groups in terms of sex and age distribution.

Baseline assessment of cough

Before starting the study, patients reported a higher average of days with cough higher in treatment group than control group (3.8 ± 2,2 vs 2.7 ±1,2 days; p<0.05) (Table 1).

Table 1 Baseline assessment of cough

	Control group (n=20)	Study group (n=29)	p-value[a]
Days with cough,* mean (SD)	2.7 (1.2)	3.8 (2.2)	<0.05
Combined cough scores at baseline			
Daytime cough combined score (range: 0-18)	7.86 (3.96)	10.25 (3.24)	<0.05
Night cough combined score (range: 0-30)	12.95 (7.42)	16.64 (7.09)	n.s.
Overall Combined Score (range: 0-48)	20.82 (9.91)	26.89 (9.37)	<0.05
Daytime cough			
How frequent?	2.64 (1.29)	3.46 (1.14)	<0.05
How severe?	2.59 (1.40)	3.36 (1.19)	<0.05
How bothersome?	2.64 (1.47)	3.43 (1.29)	n.s.

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Table 1 Continued...

	Control group (n=20)	Study group (n=29)	p-value[a]
Night cough			
How frequent?	2.82 (1.53)	3.75 (1.62)	<0.05
How severe?	2.82 (1.59)	3.68 (1.61)	n.s.
How bothersome?	2.68 (1.64)	3.75 (1.32)	<0.05
How much did cough affect your child's ability to sleep?	2.23 (1.63)	2.54 (1.79)	n.s.
How much did cough affect your (parent's) ability to sleep?	2.41 (1.74)	2.93 (1.72)	n.s.
Times the child wakes up at night	1.7 (1.5)	2.0 (1.5)	n.s.

*Data is not available for 2 patients

[a]Mann-Whitney U test. n.s. =not significant

At baseline, daytime cough combined score and the overall combined score were significantly higher in the study group than in the control group. The nocturnal cough combined score did not show significant differences compared to the control group but tends to be higher in the study group. The study group reported a significantly higher frequency and severity of daytime coughing than the control group ($p<0.05$). Regarding night cough, the study group reported a significantly higher night cough frequency and bothersome ($p<0.05$) than the control group but did not show significant differences in the affectation both the child's and parent's ability to sleep. The mean number of times the child woke up at night due to coughing at baseline was 1.86±1.5 times (range: from 0 to 6), with no significant difference among groups.

Efficacy

On the third day, all the combined cough scores (daytime cough, nocturnal cough, and combined global score) were reduced more in the study group than in the control group ($p<0.001$ vs $p<0.05$), and unlike baseline the mean combined cough scores did not show significant differences between groups. In addition, the study group experienced a significative decrease in the number of times patients woke up with a cough on the third day while no significant improvement was observed in the control group (Figure 1).

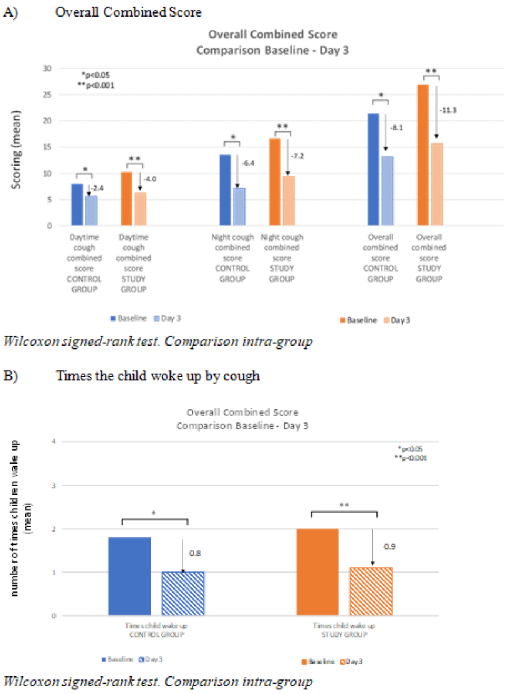

Figure 1 Comparison baseline -day 3.

By the end of day 7, 55% of the subjects in the control group and 50% of the subjects in the study group still had a cough. Both groups exhibited a significant decrease in all combined scores from baseline to day 7 (Figure 2). However, the study group demonstrated higher decreases in all combined scores. Additionally, the number of times patients were awakened by coughing on day 7 significantly decreased in both groups. However, the reduction was more pronounced and statistically significant in the study group.

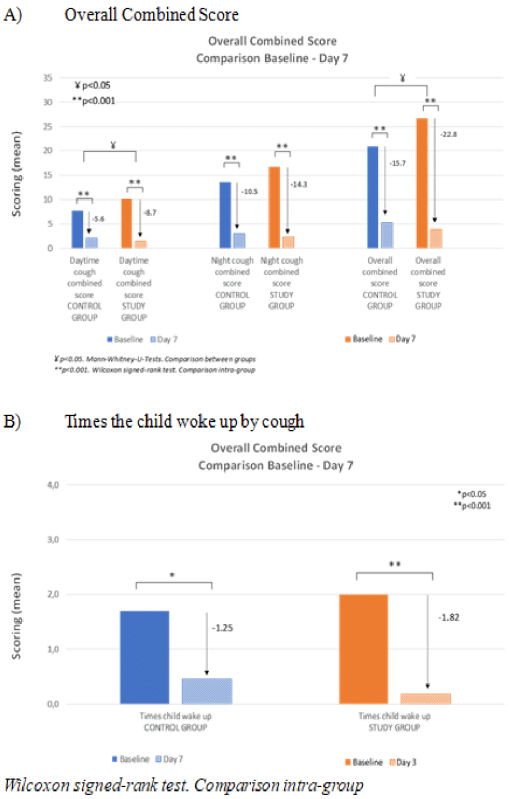

Figure 2 Comparison Baseline -Day 7.

Patient's diary data shown that both groups experienced a gradual decrease in nocturnal cough over time (Figure 3). The study group exhibited a quicker decrease of each symptom until Day 7 for all except affectation of the parent's ability to sleep until day 5 (Figure 3).

At the end of the study, 25 of the 28 parents of cases treated with syrup reported being satisfied with the investigational device (89.3%), of which 14.3% were very satisfied. As for the doctors, also 25 of the 28 cases treated with syrup (89.3%) reported being satisfied with the investigational device, with 21.4% of the doctors reporting that they were very satisfied (Table 2).

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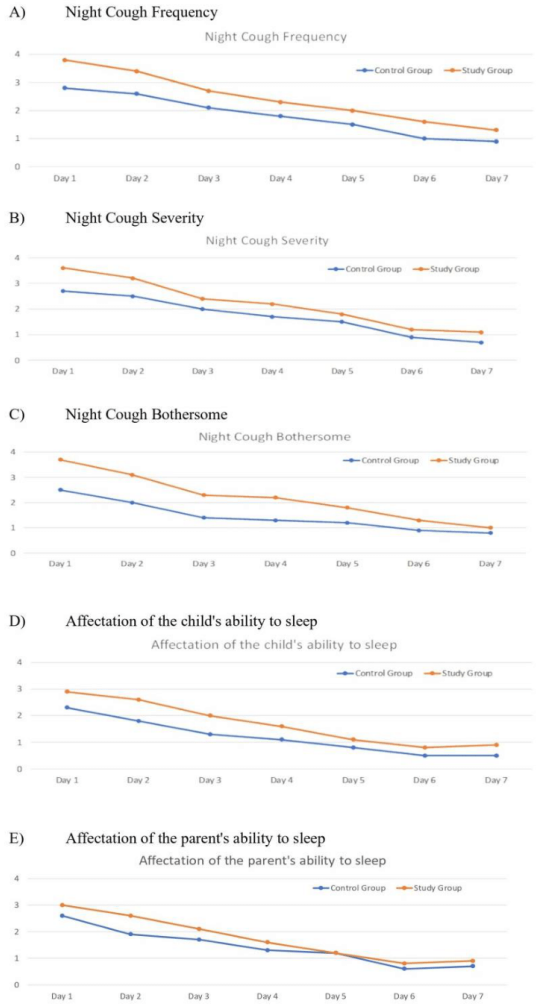

Figure 3 Day 1 – Day 7 (n=48).

Table 2 Degree of satisfaction with investigational device

Satisfaction with the investigational device	Physicians*		Parents	
	N	%	N	%
Very unsatisfied	1	3.57	1	3.57
Dissatisfied	0	0	1	3.57
Moderately dissatisfied	0	0	0	0
Neither satisfied nor dissatisfied	2	7.14	2	7.14
Moderately satisfied	5	17.86	10	35.71
Satisfied	14	50	11	39.29
Very satisfied	6	21.43	4	14.29
All	28	100	28	100

Safety

No serious adverse events were reported during the study. Five individuals experienced mild adverse events (AE): nausea, abdominal pain, diarrhea and cough for 1 minute after taking the syrup due to the texture. All AEs were resolved on their own without the need to stop treatment.

Discussion

The results of this study show that honey-based syrup is effective in achieving a faster and more significant reduction in cough related to acute upper respiratory tract infections than supportive measures alone in children.

As a control group, no treatment and only supportive measures (increased hydration) were chosen after confirming that this is currently the most common practice by primary care pediatricians given the lack of evidence on the ability of the different drugs to alleviate the cough,[3] their associated risks,[4,13] and the recommendation by professional organizations.[14] However, in some cases, the parents' request for an effective and rapid intervention leads the pediatrician to prescribe some treatment.[15] Because the use of OTC cough medicines can be potentially dangerous,[16] pediatricians are increasingly turning to natural, non-drug products when prescribing cough and cold treatment.

In this study, the results on the third day show a further decrease in daytime cough, night-time cough, and overall combined score with the honey-based syrup than hydrating measures and unlike baseline scores (significantly higher in the study group), all combined cough scores did not show significant differences between groups. Likewise, all score improvements were more significant in the study group than in the control group. On the seventh day, an inversion of the initial situation was observed. All cough assessment scores, and all combined scores were lower in the study group than in the control group, whereas at baseline they were higher than in the control group, which is relevant if we take into account that, in line with the published epidemiological data on cough due to URTI,[2] half of the subjects were still coughing after one week.

The greater and more rapid improvement observed in the child's cough may be attributed to the demulcent characteristics of the study product. Although a certain demulcent effect can be achieved with moisturizing measures,[17] the use of a specific formulation containing complex natural substance with bio adhesive and demulcent activity can exert a softening and mechanical barrier effect. According to current evidence, honey may relieve cough and cold symptoms by increasing saliva production and swallowing (thanks to its viscosity) coating peripheral sensory receptors that send irritative stimuli thus interfering with the impulse to cough.[2] It is a mechanism like the demulcent effect observed with mucilage-based syrups (such as Aromaforce® Junior Cough Syrup) whose bio adhesive properties on the mucosa protect it from irritation and reduce the impulse to cough, significantly reducing the severity of cough.[18]

Additionally, the study demonstrated a greater effect of the syrup compared to hydration measures in reducing the number of nocturnal awakenings of the child, like other studies that evaluated the effect of honey or honey products on the improvement of sleep quality.[7,19,20] Cough can affect the quality of sleep in almost 90% of children with cough due to URTI and their parents[21] and are probably one of the main reasons why parents request pediatrician treatment. Therefore, maintaining sleep rhythm should be considered a priority objective in cough management and the honey-based syrup studied has been found to be preferable to hydration measures to improve children's sleep.

Regarding the safety results, analysis conducted also supports the good product's safety profile, with no observed toxicity in children. In addition, the satisfaction questionnaire reinforces the effectiveness and safety of the tested product but also highlights the importance of patient compliance in the overall efficacy of cough treatment.[22,23]

The main limitation of the study was the variance in baseline characteristics that could be attributed to the allocation method employed, which relied on the clinician's discretion. One possible explanation for this outcome is that pediatricians may have opted to

administer honey-based syrup to patients with more severe or frequent cough symptoms. Taking this factor into account when interpreting the results is crucial since it introduces a baseline bias that hinders a direct comparison of the progression of cough symptoms between the two groups. On the other hand, there is an inherent limitation associated with the indirect collection of data by parents' subjective perception of cough children. The reliability of this method in assessing the effectiveness of cough treatments has been previously validated and widely utilized in the scientific literature.[19] Furthermore, to obtain a comprehensive understanding of the treatment's effect, a cough diary and satisfaction questionnaire were administered to both pediatricians and parents.[24] This allowed a comprehensive assessment of the treatment's impact.

Conclusion

The results show that PBB syrup has a good safety profile and is effective in achieving faster and more significant cough reduction, especially in the first three days, even reversing the severity of cough at the end of the process and reducing the number of times the child wakes up compared to measures of hydration. However, new randomized clinical trials will be interesting to confirm the efficacy of the medical device, that yet evident but not so much significant.

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Conflicts of interest

The author declares that there are no conflicts of interest.

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