Research Article

Clinical Efficacy and Safety of the 1st Non-Medicated, Safe, and Nearly Instant Cough Treatment for Children

Nathalie Maneby[1], Megha Vijay[2], Sandeep Kumar[3], Guillaume Bonnet[1], Remi Shrivastava[4†]

ABSTRACT

Background: Acute and chronic coughs are the most frequent pathologies in children and are closely associated with recurrent epidemics of Covid-19. This is a multi-factorial disease, involving viral infection, broken throat mucosa integrity, secondary bacterial infection, inflammation and excessive mucus production, responsible for triggering cough reflex. When clinical signs appear, the disease has already become multifactorial, only a multitarget treatment can provide quick relief. In the absence of any multitarget treatment, we conceived a new generation of topical, osmotic, throat surface-cleaning polymeric film, capable of cleaning the throat surface and fluidizing mucus, nearly instantly. The clinical efficacy and safety of this medical device compared to saline solution are evaluated in kids.

Methods: The test product contained a glycerol-based, mechanically resistant, osmotic, polymeric film solution for application on the throat surface. An observational, randomized, placebo-controlled study was performed after Ethics Committee approval on 30 children aged 3 to 15, presenting symptoms of acute and/or chronic cough. After randomization, test product (n=20) and saline control (n=10) solutions were applied as 3-4 sprays 4-5 times/day for 15 days. Changes in all the key cough symptoms (cough frequency, throat irritation, sleep disturbances, chest discomfort) as well as effect on the quality of life and need for anti-biotherapy were compared against saline solution treatment.

Results: The test product was highly efficient in significantly suppressing all the cough symptoms vs the comparator product within 3 days of treatment. The need for antibiotics was drastically decreased and no adverse effects were recorded during the study.

Conclusion: Detaching and draining all the free-floating throat surface contaminants with a nearly instant, polymeric osmotic film, without the use of any chemical drug, represents a totally new approach to the treatment of cough in children. This mechanically acting, multitarget, new generation of polymeric drugs can help reduce the problem of antibiotic resistance and long-term side effects of currently used chemical cough treatments in children.

Keywords: Clinical study, Cough treatment, Children, Safe, Instant, Nonmedicated, Polymeric technology.

Abbreviations: TP: Test Product, **CP:** Comparator Product, **NS:** Statistically not Significant, **URT:** Upper Respiratory Tract, **LRT:** Lower Respiratory Tract

Introduction

Coughing is one of the most common diseases in children, occurring 4 to 6 times a year and lasting usually between 1-3 weeks [1]. The most frequent etiology for acute cough is Upper Respiratory Tract (URT) viral and bacterial infections which subside within 1-3 weeks, while subacute and chronic coughs are usually due to recurrent Lower Respiratory Tract (LRT) infection, asthma, and pertussis [2]. Occupational irritants such as fumes, gases, cleaning products, or dust may cause cough, either by triggering cough reflex or by inducing oxidative stress and eosinophilic inflammation [3]. The cough reflex protects the airways and lungs from aspiration of inhaled irritants and pathogens and clears the air spaces of accumulated secretions [4].

According to Jurca et al [5], nearly 60% of children in the age group of 4-8 years are reported to cough, usually with a cold, with only small differences between age groups. Among these children, about 25% of children cough during night- time. It leads to many medical consultations, affecting the quality of life and placing a considerable burden on children, families, and society [6]. Coughing in children does not induce potentially serious illnesses and may have multiple triggering factors, justifying a "wait and see" approach for the treatment of acute cough [7, 8, 9].

Received: 06-February-2023, Manuscript No. ijocs-23-88846;

Editor assigned: 08-February-2023, PreQC No. ijocs-23-88846 (PQ);

Reviewed: 11-February-2023, QC No. ijocs-23-88846 (Q);

Revised: 14-February-2023, Manuscript No. ijocs-23-88846 (R);

Published: 22-February-2023, DOI:10.37532/1753-0431.2022.17(2).282

[1]Research scientists, Vitrobio Research Institute, ZAC de Lavaur, Issoire, France
[2]Clinical trial coordinator, MBBS, Mudra Clincare, Navi Mumbai, India
[3]Medical device research scientist, M Pharma, Polytrap Pharma, 122 Pricanko Colony, 452009, Indore, India
[4]Research scientist, Naturveda Research Institute, ZAC de Lavaur, Issoire, France.
[†]Author for correspondence: Remi Shrivastava, Research scientist, Naturveda Research Institute, ZAC de Lavaur, Issoire, France, Email: remi.s@naturveda.fr

The most common initiating cause is a viral infection, particularly influenza, rhinovirus, or respiratory syncytial virus in the nose and throat [10]. Virus- induced cellular destruction leads to extensive infiltration of immune cells and the release of several pro-inflammatory cytokines, particularly TNF-α, INF-γ, IL-5, and IL-6, which are involved in URT inflammation. In fact, the virus is not the main cause of cough symptoms, but the cellular damage initiated by virus growth creates a favorable ground for the growth of dormant local bacteria such as Streptococcus sp., which leads to further cellular damage and generates particles of dead cell [10, 11]. When these waste particles enter the URT, they trigger a cough reflex to protect URT against infection. Later stages of infection are characterized by throat mucosa inflammation and obstruction of the airways due to the formation of mucus plugs containing mucus, fibrin, cellular debris, and lymphocytes [12]. If the infection continues, more and more mucus is produced which gets thicker and viscous over time. Mucus protects the throat mucosa by forming a barrier to minimize pathogen–host cell interaction but at the same time, it also minimizes the therapeutic potential of any topically applied medication. One more opportunist bacterium, *Bordetella pertussis*, that causes pertussis is found in the nose and throat of infected children. The damaged, inflamed, and broken nasal mucosa offers an excellent opportunity for *B. pertussis* to invade and grow [13, 14]. The first stage of pertussis symptoms begins as a cold with a runny nose, sneezing, mild fever, and cough. Sneezing and coughing spread these bacteria through air droplets. The cough lasts 1-2 weeks and then worsens, if not treated. The second stage includes uncontrolled coughing followed by a whooping noise when the person breathes in the air. DTaP (Diphtheria, Tetanus, and Pertussis) vaccine protects children against severe disease but still, pertussis remains one of the most commonly occurring serious childhood diseases in the world. It is therefore important to curb coughing by eliminating or at least minimizing the causative factors such as viruses, bacteria, dead cells, and other cough reflex- inducing particles from the throat surface during the early phase of infection in children [14, 15].

When symptoms appear, the disease has already become multifactorial, involving growing pathogens, cellular damage, dead and dying cell aggregates, the presence of multiple cough-specific inflammatory cytokines, inflamed cells, and excessive production of viscous and adherent mucus on the throat surface. This physiopathology leads to symptoms such as frequent coughing, fever, throat pain, sleep disturbances, chest discomfort, and poor quality of life in children. An ideal treatment should therefore suppress each of these factors to reduce the cough reflex [16].

Unfortunately, none of the currently available treatments is directed at fulfilling these basic requirements. Commonly used treatments include antitussives that help block the cough reflex, expectorants that make URT secretions easier to expel by coughing, antihistamines to reduce inflammation, or decongestants that constrict URT blood vessels to reduce congestion [17]. Almost all these drugs are chemicals and not suitable for children, they have multiple side effects, they act only symptomatically, and many scientific studies show that they have little benefits regarding cough relief [18]. Other home treatments include analgesics, antibiotics, mucolytics, phytotherapy, or the application of honey on the throat, but their efficacy is limited as they are usually mono-targeted [19].

Saltwater gargling containing as up to 3.4% NaCl may be considered a multitarget treatment as due to its hypertonic nature, it generates slight osmosis that helps clean non-adherent contaminants from the throat surface [20]. The use of salt solution is very limited in children because the solution is not adherent, gets diluted within a few minutes, requires frequent applications which are not practical in children, and increasing salt concentrations are highly irritant to the URT mucosa, generating an excessive secretion of histamine and methacholine [21, 22].

Taking into consideration the physiopathology of cough infection in children and the multitargeted treatment requirements, we envisaged conceiving a highly osmotic but stable and non-irritant solution that can be applied on the throat surface to form a film. It was postulated that topical application of such a solution should form a stable osmotic film to protect the throat mucosa against environmental contaminants and irritation. Secondly, being highly osmotic, the film should generate a strong osmotic liquid flow from the inside towards outside the throat tissue, thereby detaching and draining throat surface contaminants and diluting sticky mucus [22, 23]. Such a mechanically acting treatment can act as a strong throat surface protective barrier,

anti-irritant due to continuous osmotic flow, antimicrobial due to detaching and draining microorganisms, anti- inflammatory due to the removal of surface inflammatory cytokines, mucus fluidizing due to osmotic liquid flow leading to sticky mucus dilution, and cough reflex minimizing due to the elimination of throat surface contaminants.

As glycerol is nearly 18-times more osmotic than salt solution, non-irritant, and cell-friendly, we conceived a glycerol-based throat solution that was rendered filmogen and resistant to mechanical pressures for a period of 4-6h, by incorporating specific glycerol molecule binding natural polymers [24]. The clinical efficacy of this polymeric filmogen osmotic solution (VB-ChSp) for the treatment of acute and chronic cough in children is investigated against saline solution as a Comparator Product (CP).

Materials and Methods

Study type: Comparative, randomized, parallel-group, observational clinical trial in children with polymeric glycerol filmogen solution versus 0.9% NaCl saline solution, for the treatment of cough in children.

Objectives of the study: To assess the efficacy, safety, and tolerability of the test product (TP) compared to saline solution as a Comparator Product (CP) in children.

Clinical trial oversight: The trial was performed by Mudra CLINCARE (Protocol: COU/OBS/2018), located at Awaskar Building 402107 Mumbai, India, certified to conduct clinical investigations on human subjects (N° UQ-2022122821 following ISO-14155 guidelines). The study was coordinated by Dr Megna Vijay and was performed at Malsons Multispeciality Hospital and ICU, Navi Mumbai, MS, India, as per the regulations applicable to studies in children. The protocol was approved by relevant ethics committees (Altezza Institutional Ethics Committee, Shree Ashirwad Hospital, Dombivli, Maharashtra, India and institutional review boards (Reg. No. ECR/247/Inst/MH/2013/RR-16, dated 28/12/2018). The authors vouch for the conduct of the trial, adherence to the protocol, the accuracy and completeness of the data, and reporting of adverse events. The trial complied with the International Conference on Harmonization Guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, and relevant national and local regulations. At the time of screening, the children's parent(s) signed written informed consent forms.

Test and comparator products: The TP (Batch CEV18001), designated as Kid Cough spray, was already commercialized in Europe as a medical device and was supplied by Vitrobio Pharma in France (ISO13485 certified). The product solution was presented in 20-ml aluminium containers fitted with a spray for throat application. The solution was prepared by combining osmotically active filmogen glycerol as described by Shrivastava et al. [24], which was rendered filmogen by adding small quantities of CD-cyanidin-E polymeric-premix derived from plants extracts such as Ribes nigrum fruits and Curcuma longa roots. A small quantity of honey was added as a thickener, along with excipients, qsp water. The Comparator Product (CP) was presented identically to the TP and contained only 0.9% NaCl solution. Both TP and CPs were applied as 4-5 sprays to form a thin film on the upper part of the throat. Both products could be applied every 30 min during the first 2h at the start of treatment. Then product was applied 3-4 times per day up to day 15 or until complete recovery.

Trial Participants: The aim was to recruit at least 20 patients in the TP and 10 in the CP group between the age group of 3-15 years. The 1st patient was recruited on 18th September 2018, the last treatment was completed on 27th October 2018, and results were reported on 11th January 2019.

Key inclusion criteria: (1) Children, aged between 3 to 15 years and accompanied by at least 1 parent or caretaker, (2) Participants having clinical manifestations of moderate to severe, acute and/or chronic coughs since less than 72h, with at least one of the complaints of night coughing disturbance, chest discomfort, throat irritation, and fever, (3) Patients/parents ready to abstain from using any drug which may affect the study outcome other than investigational product during the study period, except in cases when physicians judge that the patient's condition needs additional treatment with antibiotics or other medication, (4) Patients with co-operative and understanding skills, (5) Patients/parents accepting not to use any herbal or ayurvedic treatment, throat gargles, honey, propolis containing medications, and tea, or coffee, during study period, and (6) Patients showing overall good health and having vital

signs within the acceptable range.

Exclusion criteria: (1) Children having hypersensitivity or history of allergy to any of the investigational product's components, (2) Children, below the age of 3 or above the age of 15, (3) Parents/patients, unwilling to participate in the clinical trial study, (4) Patients who used any treatment for throat infection or throat pain during the last 72h prior to screening, (5) Patient under any antibacterial or antiviral treatment before recruitment, (6) Patients diagnosed for lower respiratory tract diseases such as laryngitis, tracheitis, bronchitis, pneumonia, asthma, sinusitis, allergic rhinitis, or other chronic life-threatening diseases, (7) Children who participated in another clinical trial within last one year prior to screening.

Withdrawal or removal of patients during the study: Patients/parents were not remunerated and were free to withdraw from the study at any time without giving a reason. Investigators were allowed to withdraw the patient(s) for safety or ethical reasons as well as for non-compliance with the study protocol.

Randomization: Treatments were allocated to patients by carrying out randomization using SAS Version 9.1.3. Biostatisticians generated the randomization schedule. Block Randomization methodology was employed to follow the 2:1 ratio in TP or CP groups.

Primary endpoint: Change in cough frequency score on a 0 (no symptom) to 10 (worst symptom) scoring scale, at 2h after the start of treatment (1st application) on day 1, on day 3, day 6, and day 15, or up to complete recovery compared to placebo.

Secondary Endpoints: Change in (1) chest discomfort, throat irritation, and fever at 2h after the 1st application on day 1 as Baseline Value (BL), as well as on day 3, day 6, and day 15 or up to complete recovery, (2) cough night disturbance scores on day 3, day 6 and day 15, or up to complete recovery, (3) effect on the Quality of Life of the patient with the help of PC-QOL-8 (Parent Cough – Quality of Life) Questionnaire at baseline and at the end of the study, scored on a 0-7 scale, (4) need for antibiotic or other appropriate therapy, in case the patient does not respond to the treatment with records of the number and duration of such treatments, (5) adverse events throughout the conduct of the study, and (6) global treatment assessment by patient/parents and physicians at the end of the study as poor, fair, good or very good, and excellent.

Study chronology and assessments: Four visits were planned for each patient during the study. During the 1st visit to the clinical research center on day 1, the patients were examined for inclusion and exclusion criteria, they signed informed consent, symptoms were noted by the investigator in the patient's diary, patients were randomized and allocated to TP or CP group, were dispensed corresponding treatment, and the treatment process was explained. At the 1st visit, the patient remained with the investigator for 2h to check for any eventual allergic reaction or undesired effect. Visits 2, 3, and 4 were planned on days 3, 6, and 15. At each visit, the investigator checked and completed the patient's diary. In between the visits, the patients completed the diary themselves. The end of study questionnaires were filled out during visit 4 by the patient and the investigator.

Statistical analyses of results: Statistical analysis was performed by unpaired two-tailed Student's test for comparisons between two groups and the two-way ANOVA followed by the post hoc Bonferroni's test for comparisons of multiple groups. $p<0.01$ was considered statistically significant (GraphPad Prism version 8.4.2, La Jolla, USA). NS indicates not significant.

Results

Demographics: As shown in the Consort chart **Figure 1**, a total of 35 patients were recruited, 5 did not meet inclusion criteria, and 30 were enrolled and randomized in 2 groups. 20 patients (12 boys and 8 girls) aged between 4 to 13 years (mean age 8.95 ± 2.74) were included in the TP group while 10 patients (6 boys and 4 girls), also aged between 4 to 13 years (mean age 10.4 ± 2.91) were allocated in the CP group. The demographic distribution of the patients was homogenous. All patients completed the study and fulfilled the study inclusion criteria. About 60% of patients had acute transient cough while 40% had frequent coughing episodes.

■ Consort flow chart

■ Effect on cough frequency:

As shown in **Figure 2**, in the CP group, the mean frequency of coughing was not changed up to day 3 but started diminishing from day 6 (-27.12%, $p<0.01$ vs BL) up to day 15 (-44.07% vs BL; $p<0.001$). In the TP group, there were no

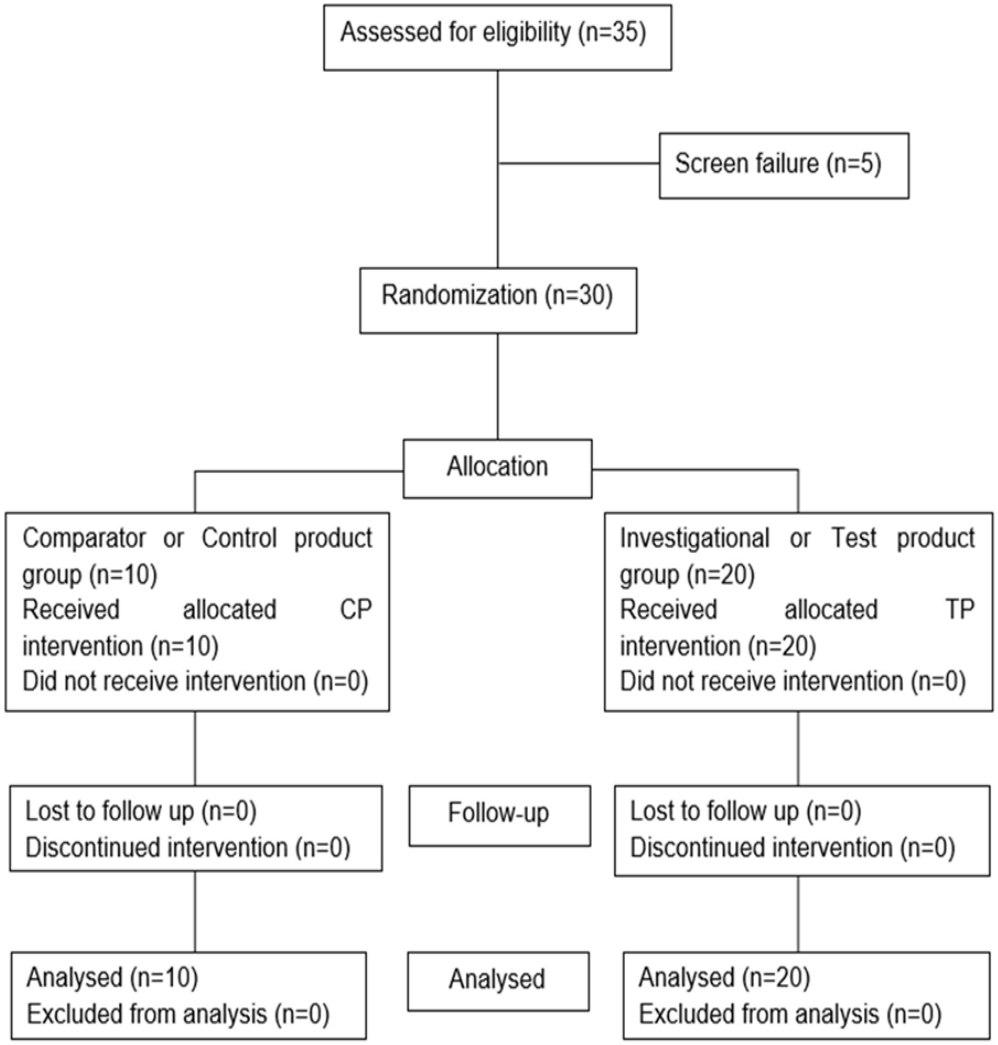

Figure 1: Consort demography diagram: Among 35 patients screened, 30 were randomized into 2 groups comprising 20 in TP and 10 in CP. All patients received allocated treatment and completed the patient diary up to the end of the study.

beneficial effects on cough during the first 2h but a remarkable mean reduction in coughing frequency was noticed from day 3 onwards (-45.79±1.2%) with further decrease on day 6 (-89.71±0.60%) and day 15 (-98.13±0.31%, $p<0.001$ from the day 3 onwards vs BL). On day 3, the difference between the two groups was 47% in favour of treatment ($p<0.001$; 95CI difference [1.5 to 3.7]), this difference continued over time. Most patients in this group had only minor coughs from day 9 with nearly 90% reduction in the cough frequency compared to the start of treatment. However, the use of other medications or antibiotics during this period should be checked. These results indicate that none of the treatments had instant anti-coughing effects as there was no effect on cough frequency at 2h. Among the patients, nearly 60% had an acute cough, the frequency of which reduced automatically within a week or two. In conclusion the results show a significant difference in the evolution of cough frequency in favour of the treatment.

■ Effect on chest discomfort:

The results of chest discomfort are closely identical to the effects observed on cough frequency in both groups **Figure 3**. In the CP, the mean score of chest discomfort was reduced only from day 6 (-34.78±1.25% vs BL, $p<0.01$) which improved further up to day 15 but did not exceed 50±0.82% vs BL ($p<0.001$ vs B) on day 15.

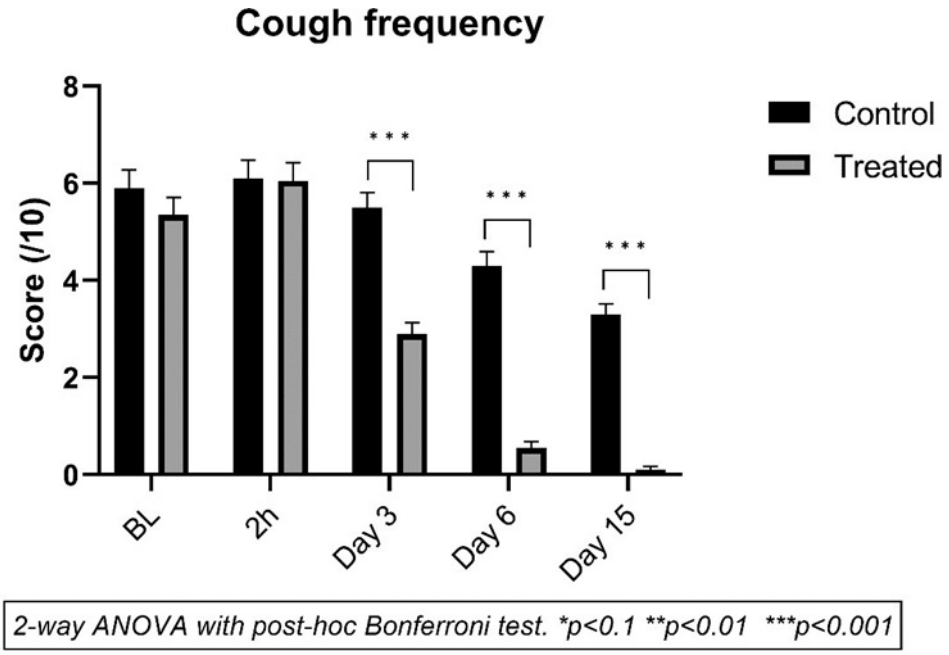

Figure 2: Mean scores of cough frequency in TP (gray bars, n=20) vs CP (black bars, n=10) groups on a 0-10 scale (0 = no symptom). Cough frequency was not changed during the 1st 2h but a strong reduction was observed in TP compared to CP from day 3 onwards. ***P<0.001, 2-way ANOVA with post hoc Bonferroni test.

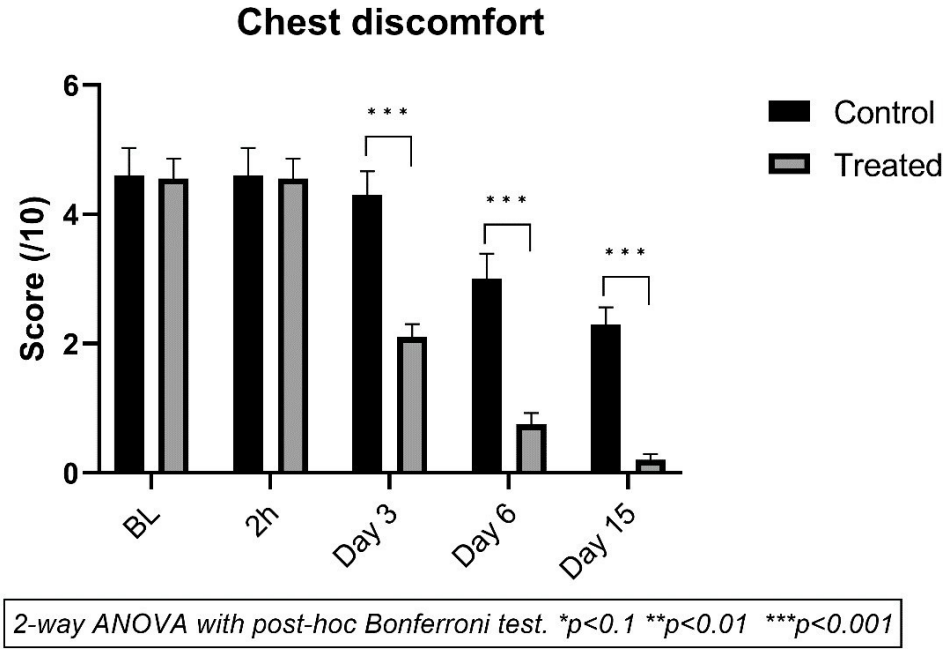

Figure 3: Chest discomfort mean scores in TP (gray bars) vs CP (black bars) groups on a 0-10 scale (0 = no symptom) at BL±, 2h after 1st treatment and on the days 3, 6, and 15. TP significantly reduced chest discomfort vs CP from day 3 onwards (p<0.001 vs CP from day 3 onwards).

■ Chest discomfort score

In the TP group, there was no effect on the chest discomfort parameter during the first 2h but a sharp decline compared to BL was seen from day 3 (-51.06±1.11%) with notable improvement from day 6 (-83.82±0.79%) and day 15 (- 95.74±0.41%; p<0.001). On day 3, the difference between the two groups was 55% in

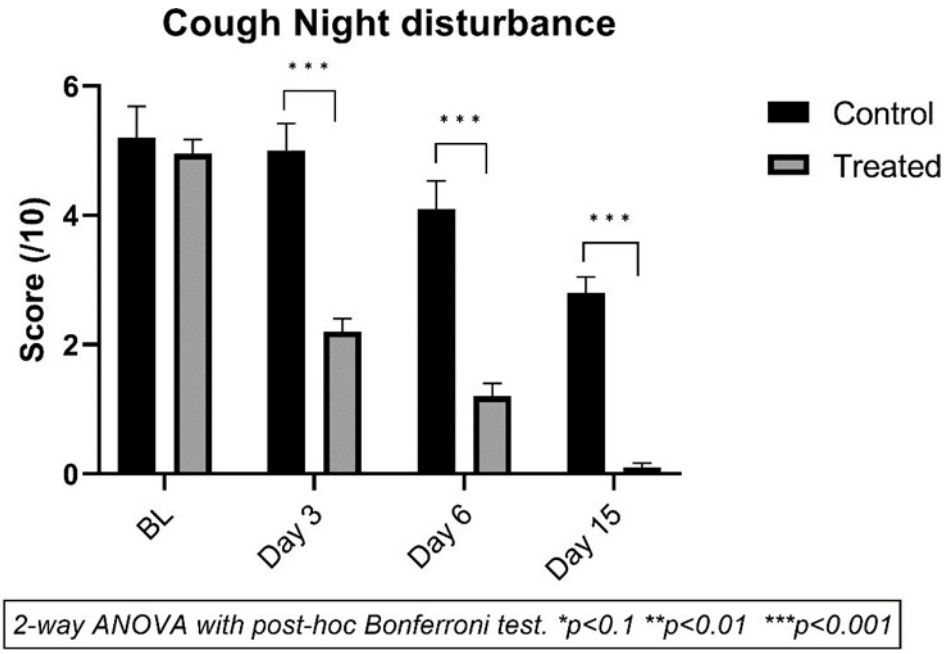

Figure 4: Comparison of the effects of TP (gray bars) vs CP (black bars) on sleep due to night cough, evaluated on days 3, 6, and 15 of treatment. Graphs represent mean ± SD. ***P < 0.001 compared with the control saline-treated CP group.

favour of treatment (p<0.001; 95CI difference [0.1 to 3.4]), this difference continued over time.

Nearly 88% of children and 70% of parents observe sleep disturbances when children cough (6). As shown in **Figure 4**, in the CP group, a slight reduction in cough-induced sleep disturbance was observed only from day 6 onwards (-21.15±1.37% on day 3 and -46.15±0.79% on day 15) but this improvement was moderate. In the TP-treated group, the mean scores of night disturbance were strongly reduced vs BL from day 3 (-55.56±0.89%). Further improvement was observed on day 6 (-75.76±0.88%) and day 15 (-97.98±0.31%). On day 3, the difference between the two groups was 56% in favour of treatment (p<0.001; 95CI difference [1.5 to 4.2]), this difference continued over time. These results correspond to the reduction in cough frequency and chest discomfort observed in the patients of this group.

■ Effect on sleep & night rest

The mean score of throat irritation was not affected in the CP group during the first 2h but showed a progressive and moderate reduction from day 3 onwards. On days 3, 6, and 15, the mean reduction compared to BL was 16.67±0.97%, 31.48±0.95%, and 48.15±0.30%, respectively **(Figure 5).**

■ Effect on throat irritation

In the TP group, a slight reduction in throat irritation was observed as early as 2h after the first product administration (8.0±1.14%) with a statistically significant and strong reduction from day 3 (-66.00±0.92%), day 6 (-88.0±0.68%) and day 15 (-98.0±0.31%), compared to BL. The irritation symptoms disappeared almost entirely at the end of the test product administration period which gives a real indication concerning the effectiveness of the test product.

The effects on irritation we re significantly different from the placebo group as early as 2 hours. This difference was 20% in favour of the treatment (p=0.0135; 95CI difference (0.2 to 2.0). On day 3, the difference between the two groups was 62% in favour of treatment (p<0.001; 95CI difference (1.7 to 3.9), and this difference continued over time.

Effect on general quality of life parameters: The mean score of PC-QL, indicating an effect on the Quality of Life (QOL) parameters was nearly equal in both groups (19.10/70 in CP and 19.77/70 in TP) at the start of the study. After 14 days of treatment, the QOL was highly improved in the test product group (mean score 41.60/70) compared to the comparator group (23.30/70). These results clearly show that the reduction in coughing, chest discomfort, throat irritation, and better sleep, improve drastically the QOL in TP vs CP group (Figure 6) <0.01 and P < 0.001 compared with

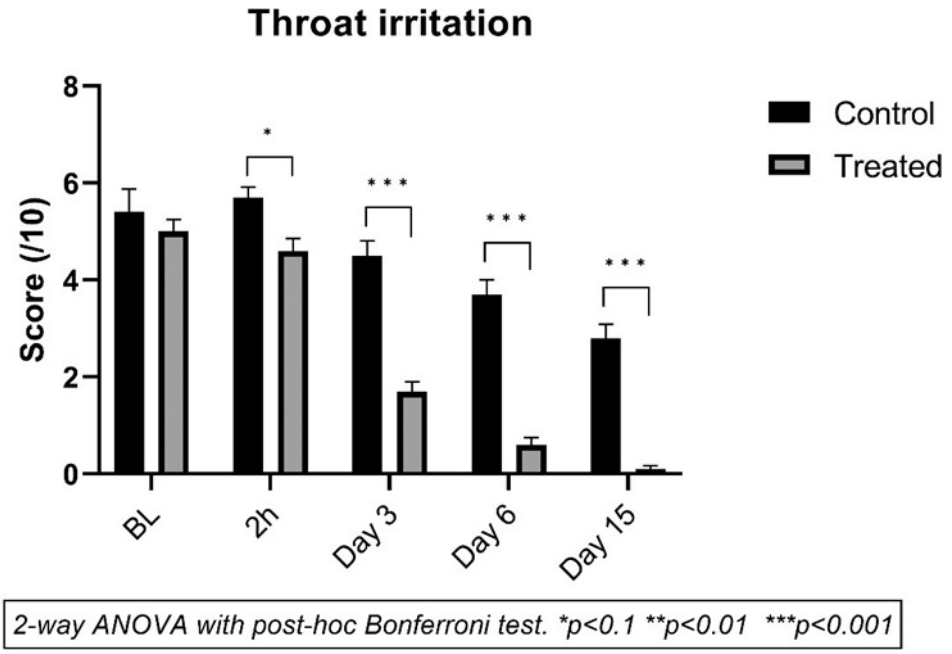

Figure 5: Effect of TP (gray bars) vs CP (black bars) on throat irritation, evaluated 2h after 1st product administration and on days 3, 6, and 15 of treatment. Graphs represent mean ± SD. *p

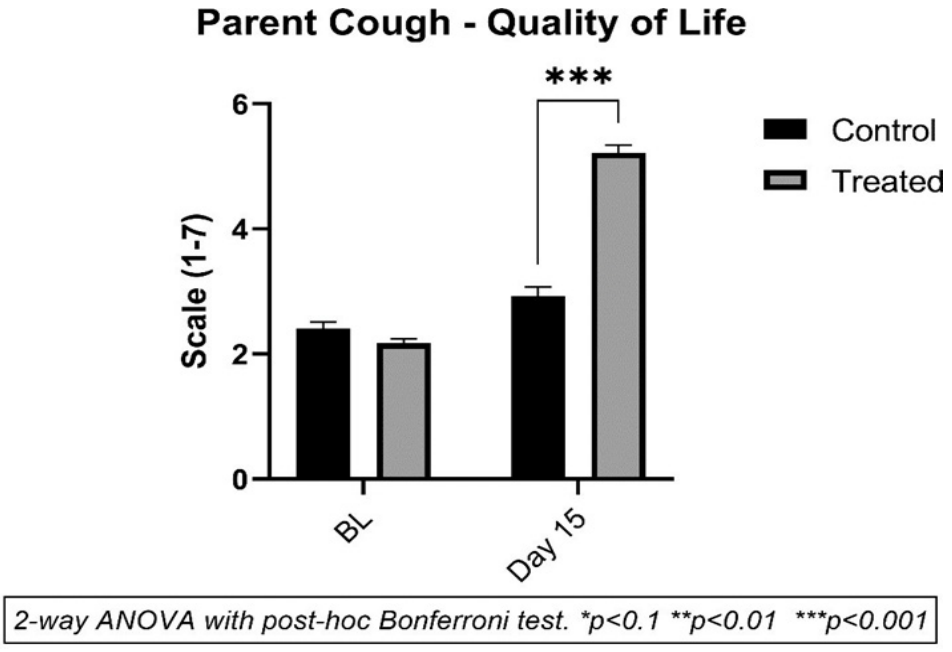

Figure 6: Mean change in scores of QOL parameters in the TP (gray bars) vs CP (black bars) groups based on the PC-QL Quality of Life Questionnaire at baseline vs at the end of the study period. Graphs represent mean ± SD. ***P <0.001 compared with the control saline-treated CP group.

the control saline-treated CP group.

Requirement for anti-biotherapy: Antibiotics were prescribed by the investigators only when they were considered necessary to minimize the risk of further infection to the lower respiratory tract. In this study, no investigator prescribed antibiotics in the TP group (0/20) while in the CP group, 4 out of 10 patients (40%) required antibiotic treatment during the study (2 continued after the end of the study).

Product Assessment: The comparator product was rated excellent by one patient (1/10) good by 6/10, and fair by 3/10 patients. The investigational product was noted good by 1/20 patients and excellent by 19/20. Among

investigators, the CP was rated as fair or very good with beneficial effects on cough, and TP as excellent with high efficacy on cough.

Side effects: No undesired effects which may be attributable to any of the treatments were recorded during the study in any of the two groups.

Discussion

Coughing due to a cold and/or infection is the most common reason for pediatric outpatient visits all over the world [25]. Between 30 to 45% of children in the age group of 1-17 years get a cough without a cold and above 70% with a cold, at least once a year [5, 26]. Shields et al [9, 27] have classified the non-specific isolated cough of children into 3 categories as acute cough with delayed recovery where symptoms reach peak level within a week after the onset and reduce progressively during the next 4-week period; the recurrent acute cough which reaches high intensity within 3-4 days and subsides within the next 3-4 days before restarting as frequent cycles; and persistent non-remitting cough which continues increasing in intensity up to 3-4 weeks, reduces and restarts again [3, 28].

Cough in children is usually caused by an initial viral infection that enters the body during respiration. The virus starts growing in the URT mucosa cells, initiating a moderate cellular destruction process. This phase continues during 2- 3 days with nearly no clinical symptoms except for slight throat irritation and increased mucus production. Throat mucosa cellular destruction offers an excellent opportunity for microbial growth, bacteria attach to the mucosa, cellular damage triggers an inflammatory cascade, huge amounts of inflammatory and pro-inflammatory cytokines are liberated on the throat surface, and the resulting waste products pass from the URT toward the LRT [29, 30]. Coughing starts at this stage as a natural defense mechanism that protects the respiratory tract from inhaling foreign bodies along with bronchial secretions. As a spontaneous reflex arc, it involves throat and respiratory tract mucosa receptors, an afferent pathway, central processing information, and an efferent pathway as cough reflex [31]. This physiopathology of coughing in children proves that when the symptoms appear, the disease has already become multifactorial, and only a multi-target treatment, acting simultaneously on each of these factors, can effectively stop the cough reflex. An ideal non-irritant and totally safe treatment approach should therefore not only stop viral infection but should simultaneously act as an antiseptic, antibacterial, cleaning, hydrating, mucus fluidizing and consequently epithelial cell-regenerating therapy to suppress coughing. Any drug having only one or two of these properties will provide only symptomatic relief but will not eradicate the disease rapidly. As it is practically impossible to incorporate all these essential cough treatment requirements in a single molecule or drug, currently there are only monotargeted symptomatic treatments available in the market [32].

Apart from a few antiseptics, antibiotics, phytotherapy drugs, saline gargling, or honey which can be applied directly on the throat surface, all other supposedly effective treatments are administered orally. Most of these systemic drugs have central-acting, cough reflex-suppressing properties but they eventually produce a multitude of side effects such as dizziness and nausea, without any effect on multifactorial cough parameters, which is however essential for an efficient treatment. Clinical trials proved that central-acting drugs like codeine and dextromethorphan are not significantly more active than a placebo [33], over-the- counter antitussives, antihistamines, and decongestants medications are as effective as a placebo for acute cough in children and may cause side-effects [34], bronchodilators are not effective for acute cough in non-asthmatic children, antibiotics are generally not effective and not recommended for treating acute coughs caused by a simple viral infection or cold [18, 35], macrolide antibiotics should be given early (first 1–2 weeks) to children with pertussis while antihistamines and intranasal steroids are beneficial only for children with an allergic cough in the pollen season [9]. Saltwater gargling, containing up to 3.4% NaCl, is found to be even more effective than antibiotics or analgesics, sore throat, and wound healing, compared to chlorhexidine but their efficacy on cough suppression is only short-lasting and incomplete [36].

This is the reason why we concentrated our efforts on finding a new generation of topical multi-target cough treatment for children which acts like salt water gargling, but which is non-irritant and much more osmotic compared to 3.4% salt solutions. The formation of filmogen, osmotic, polymeric film on the throat surface creates a strong outward flow of hypotonic liquid from the throat tissue, thereby instantly detaching and draining all the contaminants present on the URT.

A small quantity of natural, unheated honey is also added to the glycerol polymeric film because honey contains Glucose Oxidase (GOx) which oxidizes glucose to gluconolactone and reduces molecular oxygen to hydrogen peroxide [37]. The H_2O_2 bubbles attach to surface contaminants present on the throat mucosa which are then removed along with the air bubbles [38]. The glucose oxidase enzyme is inactivated by heating honey, explaining why heated honey, such as Manuka honey, loses almost all antibacterial activity. Heating honey to remove bacterial contaminants also changes its chemical composition called the Maillard reaction, as well as increases the production of a toxic chemical called 5-hydroxymethylfurfural [39]. VB-ChSp, being a mechanically acting filmogen bandage, acts only on the throat surface, cannot interact with the underlying cellular components, cannot be absorbed, cannot affect systemic parameters, and therefore remains totally safe.

The non-toxicity of glycerol is proven as it is used to preserve canned food, to deep-freeze live cells and tissues, and as an antibacterial agent. Even if glycerol is diluted to 50%, it still remains 9 times more osmotic compared to seawater, which is highly sufficient to attract hypotonic liquid from a live biological surface and to detach contaminants. Although glycerol has higher filmogen properties than seawater, it too gets easily diluted (within 5-10 minutes) due to its higher osmotic properties, and the remaining activity is not strong enough to keep the URT clean over a longer period of time. This inconvenience was resolved by selecting a few natural or synthetic polymers having an affinity for glycerol molecules. The polymers (<1.0%) were added to the glycerol solution to make it more filmogen and flexible as described by Shrivastava *et al* [40].

Results of this clinical study clearly show that the VB-ChSp throat film is much more active compared to saline solution in reducing cough frequency, throat irritation, chest discomfort, and improving sleep as well as the QOL. Continuously removing throat surface contaminants minimizes possibility of their entry into the LRT and reduces the cough reflex. This treatment also dramatically reduces the need for antibiotic therapy as no child in the TP group needed to be prescribed antibiotherapy compared to 40% in the CP group. It is postulated that cleaning the throat surface of microbial and other contaminants accelerates the natural healing process and thus strongly reduces all cough-associated symptoms very fast. The results of the LCQ demonstrate a significant improvement in the quality of life of the patients and the total safety of the TP. Such a therapy in children is particularly useful to avoid side effects of centrally-acting antitussive drugs such as codeine, morphine, or antihistamines, peripherally-acting bronchodilators or anesthetics, systemic antivirals such as amantadine or acyclovir, anti-inflammatory or antibiotics [41, 42]. One should not forget that almost all systemic drugs induce side effects and often cause more harm than good [18, 43], whereas topical application of any chemical on the LRT would block the healing of damaged URT mucosa. Taking into consideration the absence of future research on mono-target anti-cough drugs, multiple side effects, development of bacterial resistance, and inefficacy of antibiotics for the treatment of dry cough [44-46], VB-ChSp opens a totally new horizon for the treatment of cough in children.

Conclusion

Pediatric cough is a very common infection involving viruses, bacteria, cellular damage, inflammation, and excessive mucus production on the throat surface. Being a multi-factorial disease, usually multiple chemical treatments are administered simultaneously, which assist in reducing the disease duration and provide symptomatic relief, but they are slow-acting and may have serious side effects, particularly in children. We developed a totally new and multi-target, filmogen, osmotic throat cleaning device, which acts nearly instantly as a mechanical antibacterial, anti-inflammatory, throat contaminant cleaning, mucus fluidizing, and totally safe cough treatment for children. This treatment is now available in many countries and is registered as a medical device in Europe.

Conflict of interest

The authors have no conflicts of interest to disclose.

Funding

This work was funded by VITROBIO SAS and Naturveda SAS research institutes in France in collaboration with different private pharmaceutical industries engaged in the R&D of future polymeric drugs.

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