Homeopathic medicine for acute cough in upper respiratory tract infections and acute bronchitis: A randomized, double-blind, placebo-controlled trial

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abstract

Cough is a frequent symptom associated to upper respiratory tract infections (URTIs) and, although being self-limiting, it might deeply affect the quality of life. Homeopathic products are often employed by patients to treat cough, but the evidence on their efficacy is scarce. Thus, we tested the efficacy of a homeopathic syrup in treating cough arising from URTIs with a randomized, double blind, placebo controlled clinical trial.

Patients were treated with either the homeopathic syrup or a placebo for a week, and recorded cough severity in a diary by means of a verbal category-descriptive score for two weeks. Sputum viscosity was assessed with a viscosimeter before and after 4 days of treatment; patients were also asked to provide a subjective evaluation of viscosity.

Eighty patients were randomized to receive placebo (n = 40) or the homeopathic syrup (n = 40). All patients completed the study. In each group cough scores decreased over time, however, after 4 and 7 days of treatment, cough severity was significantly lower in the homeopathic group than in the placebo one (p < 0.001 and p = 0.023, respectively). Sputum viscosity was collected from 53 patients: in both groups its viscosity significantly decreased after 4 days of treatment (p < 0.001); however, viscosity was significantly lower in the homeopathic group (p = 0.018). Instead, the subjective evaluation did not significantly differ between the two groups (p = 0.059). No adverse events related to any treatment were reported.

We concluded that the homeopathic syrup employed in the study was able to effectively reduce cough severity and sputum viscosity, thereby representing a valid remedy for the management of acute cough induced by URTIs.

1. Introduction

Cough is one of the most frequently reported symptoms in medical practice. Its features and duration depend on the etiology and are greatly influenced by environmental factors. Acute cough is diagnosed when it has been present for no more than 3 weeks [1], and its most common causes are upper respiratory tract infections (URTIs) and acute bronchitis [2,3]. These illnesses usually present a viral etiology, are self-limiting, and generally resolve within a couple of weeks [4]. However, cough can persist beyond the resolution of the infection [5]. Cough, along with mucociliary clearance, is the most important defensive mechanism of the airways [6,7]. In healthy subjects, mucus traps inhaled particles while mucociliary clearance continuously drains out the mucus produced, thereby minimizing contact of external agents with the pulmonary epithelium, and thus protecting it [8]. Coughing, on the other hand, promotes the expulsion of excess secretions or foreign materials that might have been accidentally inhaled. Indeed, in the presence of respiratory infections, irrespective of their viral or bacterial
origin, the efficiency of mucociliary clearance is often impaired, although the reasons for this are not yet completely clear. One possible explanation is that the combined actions of pathogens and of released inflammatory mediators strongly impede mucociliary clearance, by both increasing the production of high-viscosity mucus and reducing the efficiency of ciliary beating [9]. As a consequence, the progressive accumulation of secretions and the presence of inflammatory mediators such as tachykinin trigger the cough reflex [10].

Although the current guidelines do not recommend the use of antitussive/protussive agents to manage acute cough, preferring instead a wait-and-see approach, it should be considered that frequent coughing usually causes a reduction in the patient’s quality of life [11,12], and can in many cases also lead to complications. Today, a wide range of antitussive/protussive agents are available on the market, and symptomatic treatment is often prescribed following a consultation for acute cough, even though the effectiveness of many of these treatments is still a matter of debate [13,14].

In the arena of alternative and complementary treatments, homeopathic medicines are the most controversial and disputed category, mainly due to the lack of randomized, placebo-controlled studies [5,15–18] and other methodological flaws in the studies conducted thus far, which often limit the validity of the conclusions drawn. Nevertheless, homeopathic medicines are widely employed in the management of acute cough, and the percentage of patients who resort to homeopathic medicines in Western countries is constantly rising [19–21].

The goal of the present study was to investigate the antitussive properties and safety of a homeopathic syrup for managing acute cough arising from non-complicated URIs in adults, by means of a single-center, randomized, double-blind, placebo-controlled clinical trial aimed at testing the effect of the syrup on cough severity.

2. Material and methods

2.1. Study population

The study was conducted at our outpatient clinic specifically devoted to the management of cough, located in Bologna (Italy) from January to December 2012. Eighty consecutive patients who presented at the clinic with productive acute cough caused by non-complicated URIs were enrolled in the study. Inclusion criteria were: at least 18 years of age and cough induced by URIs lasting from 3 to 5 days. Exclusion criteria were: pre-existing respiratory problems; having undergone antibiotic treatment within 7 days prior to enrollment in the study; use of antitussive agents or any other medication that might positively or negatively affect the cough symptom.

2.2. Trial treatment

Once enrolled in the study, patients were randomly assigned with a 1:1 ratio to one of the following groups: homeopathic or placebo. A computer program was used to generate block randomization. The homeopathic group received a homeopathic syrup (Stodal® 200 mL, Boiron SA, 2-avenue de l’Ouest Lyon, 69510 Messimy, France); patients were instructed to take a dose of 15 mL four times a day for 7 days, while follow-up lasted another 7 days. The composition of the homeopathic syrup was as follows: Anemone pulsatilla 6 CH, Rumex crispus 6 CH, Bryonia dioica 3 CH, Ipecacuanha 3 CH, Spongilla tosta 3 CH, Sticta pulmonaria 3 CH, Antimonium tartaricum 6 CH, Myocarce 6 CH, Coccus cacti 3 CH, Drosera MT. It is important to note that concentrations are expressed in the usual format for homeopathic products, where 1 CH stands for a 1:100 dilution, so that a dilution of 3 CH means that three serial 1:100 dilutions were performed from a starting concentration of 1 M (i.e., 1 mol/L), and thus the overall dilution is 1:100^3, which corresponds to a final concentration of 1 µM. Similarly, a 6 CH dilution corresponds to a final concentration of 1 PM. The placebo group received a syrup made with the following excipients (which were the same ones present in the homeopathic syrup): glucose syrup, ethanol 96% (V/V) 0.340 g, benzoic acid 0.085 g, caramel 0.125 g. The two treatments had the same flavor and were stocked in consecutively numbered bottles of 200 mL each, that were identical in the appearance. Each patient received two bottles.

2.3. Primary endpoint

The primary endpoint was the reduction of cough severity, as measured by a validated verbal category-descriptive (VCD) scores which patients reported on diary cards. Score severity was evaluated at fixed time points: before beginning the therapy and after 2, 4, 7 and 14 days. We used the patient-complied VCD scores because these have been shown to have the highest correlation with objectively-measured cough severity [22]. The scale has 6 discrete values: 0 – no cough; 1 – one short period of mild cough without hardship; 2 – some short periods of cough without much hardship; 3 – frequent coughing that does not affect normal daily life or sleep; 4 – serious coughing that is very frequent and interferes with normal daily life or sleep; 5 – distressing continuous coughing that did not stop for 24 h. Cough resolution was considered to be achieved with a VCD score of 0 or 1.

2.4. Secondary endpoints and safety measurements

Laboratory examinations of the viscosity of secretions were performed at baseline and after 4 days, based on analysis of the modifications of the rheological properties of collected mucus samples. The viscosity analysis was carried out using a rotational viscometer (Contraves® LS, Zurich, Switzerland). The rotational viscometer is a device consisting of a cylindrical rotating element inserted into a cylindrical container that holds the fluid whose viscosity is to be measured. When the rotating element is put in motion, the viscosity of the fluid causes a torque to be exerted on the cylindrical container. Measuring the strength of the pair of forces allows the fluid’s viscosity to be precisely determined. The unit of measurement of torque is Newton × meters (N m).

Patients reported their subjective assessments of mucus on the following scale: 0 – no presence of expectorate; 1 – fluid (easy to expectorate); 2 – medium density (no marked difficulty to expectorate); 3 – viscous (distressing and difficult to expectorate).

All the subjects enrolled in the study were carefully monitored for the occurrence of side effects. Everyday, patients had to compile a diary reporting the presence or absence of side effects and describing any problems.

2.5. Statistical analysis

Sample size was computed based on the observations of Kim et al. [23] for the change in cough scores after three days of treatment, and extrapolated to four days of treatment. Considering a type I error probability of 0.05 and a power of 0.80, in order to detect a difference in the severity score of 0.6, with a within-group standard deviation (SD) of 0.9, requires a sample size of 36 subjects per group. In order to take into account a drop-out rate of about 10%, it was decided to enroll 40 patients per group.

The intention-to-treat population was considered for the statistical analysis. Data are reported as mean ± standard deviation or as frequencies. Non-parametric statistics (Wilcoxon matched-pairs test)
and Mann–Whitney U tests) were chosen for the statistical analysis because these tests are robust and independent from the data distribution and are adequate for both ordinal data (cough severity score and sputum characteristics evaluation) and interval-scale data (age and viscosity). For dichotomous variables (gender and presence of cough) we employed the Fisher’s exact test. The Spearman-rank correlation coefficients were computed together with their standard errors and were used to analyze the relationship between the patients’ subjective evaluations of sputum and the laboratory assessments of mucus viscosity. The Spearman-rank correlation coefficients were compared by means of the z distribution.

Statistical significance was considered to be achieved for two-tailed p values lower than 0.05. The analysis was performed using the SPSS package (Version 19.0 for Windows, IBM Co., Armonk, NY, USA). Sample size was computed using the PS Power and Sample Size Calculations software version 3.0 (Department of Biostatistics at Vanderbilt University, Nashville, TN, USA).

2.6. Ethics

The study was approved by our local Research Ethics Committee and all participants gave their written informed consent. The study protocol was compliant with the ethical guidelines of the World Medical Association (WMA) Declaration of Helsinki and subsequent amendments.

3. Results

3.1. Demographic characteristics

A total of 80 patients were enrolled in the study, of which 40 were randomized to the homeopathic group and 40 to the placebo group. All patients completed the study and all of them were compliant with the scheduled treatment administration. The two groups were comparable for gender (17 males/23 females in the homeopathic group vs. 14 males/26 females in the placebo group; p = 0.647) though the homeopathic group was older on average (55.9 ± 17.2 years for the homeopathic group vs. 43.1 ± 14.0 years for the placebo group; p = 0.001).

3.2. Cough severity and resolution

The time-course of the cough scores for the two groups, indicative of cough severity, is reported in Fig. 1. Cough severity prior to start of treatment was comparable for the two groups (p = 0.882). In both groups, cough improved over time achieving statistical significance vs. the baseline from day 2 (p = 0.003 after 2 days in the placebo group; p = 0.005 after 2 days in the homeopathic group; p < 0.001 after 4, 7, and 14 days in both groups). No significant difference was found between the two groups after 2 days (p = 0.939) while after 4 and 7 days of treatment, cough scores were significantly lower in the homeopathic group vs. the placebo group (p < 0.001 and p = 0.023, respectively), whereas the scores again became comparable at day 14 (p = 0.532). Also if we look at the absolute decrease from baseline for each time point, the above significant differences at days 4 and 7 are likewise maintained (p < 0.001 and p = 0.007, respectively) and no significant differences in the improvement of the cough score were found after 2 and 14 days (p = 0.767 and p = 0.354, respectively). The percentage of patients with a cough score of 2 or more at each time point is reported in Fig. 2. Consistently with the observations for the time-course of cough severity, at days 4 and 7 the homeopathic group had significantly fewer patients presenting cough than the placebo group (p = 0.048 and p = 0.005, respectively), whereas at days 2 and 14 the two groups were similar.

3.3. Sputum viscosity and subjective evaluation

Sputum viscosity measurements were available only for 53 subjects (66.3% of the total population) from whom it had been possible to collect a sufficient amount of mucus: 25 (62.5%) patients in the homeopathic group and 28 (70.0%) patients in the placebo group (p = 0.637). For the other 27 patients, sputum samples could not be collected due to scant secretions or difficulty in expectoration. The two groups were comparable at baseline (p = 0.454), as shown in Fig. 3. Although viscosity was significantly reduced after 4 days of treatment in both groups (p < 0.001), in the homeopathic group (p = 1.000 and p = 0.546, respectively). Note that, although the majority of patients (67/80) were free of cough at the end of the follow-up period, in a small subset (5 patients in the homeopathic group (12.5%) and 8 patients in the placebo group (20.0%)) cough was still present, but to a degree that generally did not interfere with normal daily activities (one patient in the active treatment group and two patients in the placebo group only had a severity score equal to 4).

![Fig. 1.](image1) Verbal category descriptive (VCD) cough score over time. Average values of cough scores per group (placebo, dashed line; homeopathic syrup, continuous line) are reported for each time point. A score of 5 corresponds to continuous cough at day and night; a score of 0 corresponds to no cough. Data are reported as mean ± standard deviation. p values refer to the comparison of the mean values between the two groups at each time point (Mann–Whitney U test).

![Fig. 2.](image2) Proportion of patients presenting cough. Proportions of patients at each time point presenting a VCD cough score of 2 or more. (Placebo, white bars; homeopathic syrup, black bars); p values refer to the comparison of the frequency values between the two groups at each time point (Fisher’s exact test).
Although the difference did not reach statistical significance after 4 days, the patients themselves assessed it as insignificant and scored it 0 (absence of expectorate). At baseline the two groups had no significant difference in subjective sputum evaluation. The subjective scores for each subject was shown in Fig. 4. Note that in 2 of the patients (1 in the homeopathic group and 1 in the placebo group) from whom mucus was available (a similar score (\(r_s = 0.850 \pm 0.034, p < 0.001\)). Similar results were obtained when considering the absolute improvements of both measurements (\(r_s = 0.855 \pm 0.042, p < 0.001\)).

Additionally, both the objective and subjective mucus assessments correlated well with cough severity, although the correlation was not significantly better (\(p = 0.200\)) for the laboratory determinations of sputum viscosity (\(r_s = 0.778 \pm 0.051, p < 0.001\)) than for the judgments expressed by patients (\(r_s = 0.673 \pm 0.064, p < 0.001\)). Similar results were obtained also when considering the variations from baseline of the two sputum evaluations: \(r_s = 0.720 \pm 0.062 (p < 0.001)\) for the improvement in sputum viscosity and \(r_s = 0.656 \pm 0.072 (p < 0.001)\) for the improvement in patients’ subjective judgment (\(p = 0.501\) between the two correlations).

3.4. Correlations between efficacy variables

Correlations were evaluated by pooling the data for the two study groups at baseline and after 4 days of treatment. Sputum viscosity, as determined by a viscometer, well correlated with (and thus validated) the subjective evaluations reported by patients (\(r_s = 0.850 \pm 0.034, p < 0.001\)). Similar results were obtained when considering the absolute improvements of both measurements (\(r_s = 0.855 \pm 0.042, p < 0.001\)).

The comparison between homeopathic syrup and placebo presents a clear clinical relevance: in fact in the first four days of treatment the mean severity of cough decreased from score 4 (i.e., serious coughing that is very frequent and interferes with normal daily life or sleep) to score 2 (i.e., some short periods of cough without much hardship) in homeopathic group, while in the placebo group the mean cough severity remains greater than score 3 (i.e., frequent coughing).

3.5. Adverse events

Although, none of the patients in either group reported adverse event directly related to the treatment at any time during the study, five side effects unrelated to the treatment were recorded in the diary cards: two cases in the homeopathic syrup group (insomnia and cramps) and three cases in the placebo group (diarrhea, headache, and restlessness).

4. Discussion

The main findings of this study are that treatment of cough with a homeopathic syrup produced a better improvement than that observed in the placebo group after 4 and 7 days of treatment. Moreover, after 4 days of treatment sputum was more fluid in the homeopathic group, although the patients did not appear to significantly perceive this difference. To our knowledge, this is one of the few trials that have addressed the efficacy of a homeopathic medicine by comparing it with a placebo, thus permitting better generalizability of the results.

As far as the placebo effect we have found in our study, it might be due to a natural self-limiting acute cough but it might be also ascribed to a conceivable antitussive effect of the glucose syrup itself [24]. At present there are no studies that have directly tested the hypothesis that a sweet stimulus influences cough. In a study on patients with cough associated with URTI [25], comparing the antitussive effects of no treatment group vs. placebo treatment, the no treatment group had a 7% decrease in cough frequency as compared to 50% decrease in the placebo treatment. In this study, the placebo medicine was a capsule, rather than sweet syrup, thus not supporting this hypothesis. In general the true placebo effect of cough medicine may be explained in terms of psychoneuopharmacology and related to generation of endogenous opioids [24].

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![Fig. 3. Changes in sputum viscosity. The values for each subject able to collect a sufficient amount of sputum for the analysis of mucus viscosity are reported as filled circles, before and after 4 days since the beginning of the treatment. The lines connect the circles belonging to the same subject. Dashes with whiskers at the side of the circles groups represent the mean values with the respective standard deviation. p values refer to the modifications observed within each treatment group (Wilcoxon matched-pairs test).](image)

![Fig. 4. Changes in subjective sputum evaluation. The subjective scores for each subject able to expectorate before treatment start are reported as filled circles. A score of 3 corresponds to viscous (distressing and difficult to expectorate); a score of 0 corresponds to no presence of expectorate. The lines connect the circles belonging to the same subject. Dashes with whiskers at the side of the circles groups represent the mean values with the respective standard deviation. p values refer to the modifications observed within each treatment group (Wilcoxon matched-pairs test).](image)
placebo, improved over time, and in the majority of them cough had disappeared after 14 days, in complete agreement with what other authors have observed [26]. However, severe cough can have a deep impact on quality of life [11,12], so that most of patients seek a remedy for it, either by consulting a physician or by resorting to self-medication.

There are many homeopathic medicines available on the market for the management of cough; however, clinical characterizations of their efficacy are often lacking. This study shows that a homeopathic syrup was able to promote faster resolution of cough than a placebo.

The exact mechanism responsible for these observed effects is not yet clear. However, based on literature available to date, several speculations can be made. Natural compounds such as the extracts contained in the homeopathic syrup used in this study are reported to be associated with various actions (i.e., antioxidant, anti-inflammatory and antimicrobial) [27–34] that may favorably influence the mechanisms involved in pathophysiology of cough, improving the symptomatology [35]. Indeed, in the presence of URTIs, inflammation occurs as a consequence of the immune system’s efforts to counteract the viral infection. In this situation, the innate immune cells produce free radicals to combat the spread of the virus in the body. Although inflammation and the attendant oxidative stress are a defensive mechanism against pathogens, their action is non-specific and also results in tissue damage, increased mucus production and impaired mucociliary clearance, which in turn lead to the symptoms associated with URTIs. In particular, cough is a result of the direct action of free radicals and pro-inflammatory cytokines on cough receptors, combined with the consequences of mucus stagnation [8–10].

Numerous plant extracts exert an antioxidant activity, and the dietary intake of antioxidants is known to help counterbalance the oxidative stress and damage to which aerobic organisms are exposed, also by supporting the regeneration of endogenous antioxidants [36]. Many fruits, including the ones of the Coccus species, are rich in phenols, flavonoids, tocopherols, ascorbic acid and other antioxidant molecules [30, 37, 38]. In vitro antioxidant activity has also been characterized in R. crispus seed and leaf extracts [29, 39], and such extracts have furthermore been shown in vivo to induce the synthesis of glutathione, a well known endogenous antioxidant [39]. In vitro free-radical scavenging activity and reducing activity has also been characterized for several lichens of the genus Sticta [40, 41], as well as for many carnivorous plants of the Droseraceae family, which are rich in flavonoids and elagic acid and frequently present in phytotherapy products used for the management of respiratory disorders [28, 42].

Anti-inflammatory properties have been attributed to extracts from the Bryonia species, which contain terpenes and glycosides [43–45] capable of increasing cortisol and eicosanoid levels and reducing oxidative stress through the regulation of inflammatory response [46, 47]. The triterpenes and their derivatives contained in the extracts of Bryonia and Spongia species [48, 49] are probably responsible for their anti-inflammatory activity reported in animal models [31, 50, 51]. Extracts from A. pulsatilla and from several Ramunculaceae species are used to treat common respiratory disorders [52, 53] and have demonstrated in vitro effects on cyclooxygenase (COX) activity and on pro-inflammatory cytokine expression [54–57].

The stress on the immune system induced by URTIs may in some cases favor bacterial superinfection that can worsen symptoms and require additional therapies — i.e., antibiotic treatment — to eradicate the infection. Note that antimicrobial activity has been shown in vitro for R. crispus and Drosera extracts [29, 32, 42] against both Gram-positive and Gram-negative bacteria. Similarly, members of the Spongia genus produce antimicrobial molecules able to inhibit bacterial macromolecular synthesis and aggregation in biofilms [58, 59], suggesting that the homeopathic syrup employed in the present study might help to prevent the occurrence of bacterial superinfections.

In our study, the homeopathic medicine considered was able to decrease sputum viscosity to some extent, although this was not directly perceived by the patients. We can suppose that this improved hydration of secretions was probably due to the synergic activity of the syrup ingredients. Additionally, Antimonium salts and Ipecacuanha extracts are thought to favor expectoration through the activation of vagal reflexes [60, 61], further promoting mucus expectoration.

Although saliva admixture could be a notorious problem (by presenting sometimes some difficulties in collecting an adequate amount of expectorate and making this secondary variable less helpful for the assessment of efficacy) on the fourth day of our study the reduction in sputum viscosity correlated well with the improvement in coughing and the judgments expressed by patients (though the correlation was more pronounced for the objectively measured sputum viscosity than for its subjective assessment by patients). Thus, it appears likely that the syrup exerts a modulating action on the inflammation arising from URTIs, which is able to restore mucociliary clearance and promote mucus hydration, whereas a direct mucolytic action seems less probable.

Finally, it should be pointed out that age of our active treatment group was higher than that of the placebo group even if the mean age of our population was in a range which did not show a noteworthy relationship with caught. The effect of age on cough is still controversial. In fact, although some authors reported that the cough reflex is declining with older age [62], suggesting that the natural course of cough could be shorter in these patients, some other authors (both in previous and more recent studies) did not found significant difference in the cough reflex threshold to citric acid between young and elderly subjects [63–65]. For this reason we have made an additional analysis of the cough scores made by adjusting the results for the age difference between the two groups. Such an analysis has shown that the age difference did not affect the results of the efficacy assessment of the present study (data not shown), thus ruling out age as a possible confounding factor.

5. Conclusions

Although viral URTIs and acute bronchitis are, in the majority of cases, self-limiting diseases, the high incidence of associated distressing cough is a common symptom that frequently requires treatment.

The antitussive drugs available to date are not always effective, and sometimes have significant side effects, especially in children [14]. For this reason, many people autonomously seek remedies in the field of alternative medicine. However, in many cases phytotherapeutic and homeopathic medicines lack a clear demonstration of clinical efficacy, as is instead required for standard drugs. This double-blind, randomized, placebo-controlled study shows that the tested homeopathic medicine was more effective and faster than a placebo in alleviating cough caused by uncomplicated URTIs. Probably, the efficacy of the homeopathic medicine observed in this setting would not have been achieved with a single extract, but is rather a result of synergistic actions of the active ingredients contained in the plants that make up the syrup. Although our study does not elucidate the exact mechanisms of action of the tested homeopathic treatment, which have yet to be fully understood, our data does add to the growing body of evidence indicating that homeopathy can be a safe and beneficial strategy for treating acute productive cough. These results suggest that the tested homeopathic syrup could be a therapeutic option for subjects with...
diseases of the upper and lower airways where cough and mucus overproduction are the principal symptoms, as the treatment proved to be well tolerated and effective in reducing the viscosity of secretions and improving cough. The currently available studies on homeopathy are as yet insufficient, so that new, well-designed, controlled trials are needed to clarify the role that homeopathy can have in everyday clinical practice.

Competing interests

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Author contribution

AZ designed and conducted the study; AMML and AP performed the statistical analysis; AZ, MM, FT, AMML and ML wrote the manuscript. All the authors approved the final version of the manuscript.

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