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Research Methods

Effectiveness of antitussives, anticholinergics, and honey versus usual care in adults with uncomplicated acute bronchitis: a multiarm randomized clinical trial

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Background: Despite the frequent use of symptomatic therapies in cough, evidence of their benefits is lacking.

Objective: We compared the effectiveness of 3 symptomatic therapies and usual care in acute bronchitis.

Methods: Multicenter, pragmatic, multiarm parallel group, open randomized trial in primary care (ClinicalTrials.gov, Identifier: NCT03738917) was conducted in Catalonia. Patients ≥18 with uncomplicated acute bronchitis, with cough<3 weeks as the main symptom, scoring ≥4 in either daytime or nocturnal cough (7-point Likert scale), were randomized to usual care, dextromethorphan 15 mg t.i.d., ipratropium bromide inhaler 20 µg 2 puffs t.i.d, or 30 mg of honey t.i.d., all taken for up to 14 days. The main outcome measure was the number of days with moderate-to-severe cough. A symptom diary was given. A second visit was scheduled at days 2–3 for assessing evolution, with 2 more visits at days 15 and 29 for clinical assessment, evaluation of adverse effects, re-attendance, and complications.

Results: We failed to achieve the sample size scheduled due to the COVID-19 pandemic. We finally recruited 194 patients. The median number of days with moderate-to-severe cough (score ≥ 3) in the usual care arm was 5 (interquartile range [IQR], 4, 8.75), 5 in the ipratropium bromide arm (IQR, 3, 8), 5 in the dextromethorphan arm (IQR, 4, 9.75), and 6 in the honey arm (IQR, 3.5, 7). The same results were obtained in the Kaplan–Meier survival analysis for the median survival time of each arm with the usual care as the reference group.

Conclusion: The symptomatic treatment evaluated has shown to be ineffective against cough.

Lay summary

Cough is the most frequent symptom reported by patients with lower respiratory tract infections. Despite being a defense mechanism, cough is unpleasant and negatively affects sleep and overall well-being. Accordingly, many patients with acute cough seek medical help to mitigate symptoms and reduce their duration despite the typically self-limiting nature of the condition. In this randomized clinical trial, we explored the benefit of 3 common symptomatic treatments recommended in some guidelines for relieving this symptom during the course of uncomplicated acute bronchitis, a cough suppressant, an inhaler, and honey intake. Although the total number of patients initially expected could not be achieved due to the disruption caused by the COVID-19 pandemic, the results of our study demonstrate a lack of efficacy of these products as the number of days of severe-to-moderate cough was similar in the 3 arms and comparable to the group of patients allocated to usual care.

Key words: antitussive agents, cough, dextromethorphan, honey, ipratropium, randomized controlled trial

Introduction

Acute bronchitis is a prevalent lower respiratory tract infection (RTI) in primary care.[1] Cough constitutes the most prominent manifestation of acute bronchitis and lasts an average of 3 weeks.[2] Since antibacterials are not recommended for routine treatment of bronchitis, general practitioners (GP) are challenged with providing symptom control as the viral syndrome progresses.[3] Home remedies and over-the-counter medicines are the mainstays of treatment including analgesics, nonsteroidal anti-inflammatory drugs, mucolytics, expectorants, decongestants, antihistamines, as well as antitussives, β2-agonists or other bronchodilators, and natural treatment.[4] Across Europe, there are large variations in the recommendations for the treatment of acute cough.[5]

The reviews carried out so far conclude that these symptomatic therapies provide no benefits. In general, the studies

Key Messages

- Many patients with acute cough seek medical help to mitigate symptoms.
- We explored the benefit of 3 usual symptomatic therapies for relieving cough.
- The duration of severe-to-moderate cough was similar in the different arms.

performed had small sample sizes and methodological flaws, making comparison difficult.[6] The latest Cochrane review on cough medication concluded that cough suppressants provide no clear benefit.[6] Despite this, some guidelines recommend a short course of antitussives to reduce severe cough.[7] A non-negligible percentage of patients with acute bronchitis present exaggerated bronchial responsiveness.[8] Although the latest Cochrane review does not support the routine use of β2-adrenergic inhalers, some guidelines recommend their use in some patients.[9,10] Honey has shown to alleviate cough symptoms compared with no treatment but is not more effective than dextromethorphan.[11] However, in a recent meta-analysis in patients with different RTIs including COVID-19, honey showed no benefit in adults.[12]

The benefits of these treatments in adults with acute bronchitis, with cough as the predominant symptom, are unclear. The main aim of this study was to evaluate the clinical effectiveness of adding 3 symptomatic treatments (dextromethorphan, ipratropium bromide, or honey) to usual care in reducing days with moderate-to-severe cough compared with usual care.

Methods

Study design

This was a multicentre, multiarm, pragmatic, parallel group, open randomized clinical trial (RCT) conducted in different primary care centers in Catalonia. The recruiting GPs started the study in January 2019, and the study was interrupted in March 2020 because of the COVID-19 infection outbreak, as recommended by the authoraties.[13] In December 2020, several measures were taken to resume the patient inclusion, but the different COVID-19 outbreaks made it impossible in the majority of the centers. Finally, the sponsor decided to stop the clinical trial in October 2021. The trial design has been published previously,[14] and the trial protocol is available in Supplementary Material. Written informed consent was obtained from all patients before screening.

Eligible patients were 18 years of age or older, attending the primary care consultation with symptoms of acute bronchitis, defined as an acute lower RTI with cough as the predominant symptom, starting within 3 weeks before study inclusion, and scoring ≥4 in either daytime cough or nocturnal cough on a 7-point Likert scale. The exclusion criteria are described in Supplementary Appendix 1.

Randomization

Patients were assigned sequentially as they entered the study, allocation ratio 1:1:1:1. Randomization of patients was performed by registering the patient in an electronic case report form (eCRF) during the index visit. Once a patient had been included in the trial and randomized, the investigator provided the assigned treatment and recorded the dispensing and medication code in the electronic form. Randomization lists and implementation in the eCRF were performed by personnel not involved in the conduct of the trial.

Intervention

After inclusion of the patients in the trial, they were randomized into one of the 4 treatment groups: (i) usual clinical practice; (ii) usual clinical practice + dextromethorphan, one 15 mg-tablet t.i.d.; (iii) usual clinical practice + ipratropium bromide, two 20-μg puffs t.i.d.; and (iv) usual clinical practice + 30 g of honey (one tablespoon) t.i.d., all drugs up to a maximum of 14 days. More information is provided in Supplementary Appendix 2.

Following usual clinical practice, doctors could prescribe the concomitant therapy they considered appropriate, including analgesics such as nonsteroidal anti-inflammatory drugs or paracetamol, mucolytics, expectorants, antihistamines, and antibiotics. However, they were not allowed to prescribe antitussives, including codeine, anticholinergic inhalers, and the use of honey, including honey candies, tablets, or infusions with honey.

Outcomes

The primary outcome was the duration of moderate-severe cough in days. Each symptom was scored by the patient on a 7-point Likert scale (0 = not affected; 1 = very little problem; 2 = slight problem; 3 = moderately bad; 4 = bad; 5 = very bad; 6 = as bad as it could be). The number of days until the last day the patient scored 3 in either daytime cough or nocturnal cough in the paper-based symptom diary was considered as the main outcome.

Different secondary outcomes were taken into account: (i) duration of symptoms (number of days until the last day the patient scores 0 in all the symptoms); (ii) duration of moderate-severe daytime cough; (iii) duration of moderate-severe nocturnal cough; (iv) clinical evaluation based on clinician's judgment on day 15; and (v) adverse events. The full list of secondary outcomes is described in Supplementary Appendix 3.

Statistical analysis

For the sample size calculation, we considered a mean duration of severe symptoms in uncomplicated acute bronchitis of 5.5 days (SD 4.5) and a reduction of 1.5 days as a clinically relevant outcome.[15] The main outcome was evaluated in the intention-to-treat (ITT) population. Results are presented as percentages, mean and standard deviations, or median and interquartile range (IQR). To analyze the time of moderate-to-severe cough for the main result variable, a survival analysis was carried out using the Kaplan–Meier method. Comparison between the 4 survival curves was undertaken using the log-rank test. Cox proportional hazards regression survival models were used to calculate the hazard ratio (HR) and 95% confidence intervals (CI) for the probability of cough resolution, using the usual group as the reference

group. The Cox proportional hazards regression assumptions were tested using Schoenfeld residuals. All analyses were performed with the R statistical package. The full description is described in Supplementary Appendix 4.

Results

Study participants

The required sample size of 668 patients could not be achieved since although 15 centers were opened, most were not able to include any patient after the beginning of the COVID-19 pandemic. A total of 194 subjects were recruited and randomized and constituted the ITT population (Fig. 1). The demographic and clinical characteristics of the randomized population were well matched among the groups (Table 1). A total of 101 patients were discontinued during the study period and all were excluded from the per-protocol population (Fig. 1).

Primary outcome

No differences were observed in our primary outcome as the median number of days (IQR) with moderate-to-severe cough (score ≥3) in the usual care arm was 5 (IQR = 4, 8.75), 5 (IQR = 3, 8) in the ipratropium bromide arm, 5 (IQR = 4, 9.75) among those taking dextromethorphan, and 6 (IQR = 3.5, 7) in those allocated to honey arm. Similar results were obtained in the Kaplan–Meier survival analysis for the median survival time of each arm with the usual care as the reference group (Table 2).

Figure 2 shows the Kaplan–Meier survival analysis showing the time with cough. Neither ipratropium bromide, dextromethorphan nor honey increased the likelihood of cough resolution compared to usual care (HR = 1, 95% CI = 0.6 to 1.68; HR = 0.91, 95% CI = 0.54 to 1.53; and HR = 1.11, 95% CI = 0.67 to 1.86), respectively.

Secondary outcomes

Regarding complete resolution (score = 0), the median number of days was 13 (IQR = 8.25, 14) in the usual care arm, 13 (IQR = 7, 14) in the ipratropium bromide arm, 10 (IQR = 6.25, 13.75) in the dextromethorphan arm, and 11 (IQR = 7, 14) in the honey arm. The percentage of cure was 79.3% in the usual care arm, 75.8% for ipratropium bromide, 90.6% for dextromethorphan, and 85.3% in the honey arm (Table 2). As shown in Supplementary Fig. 1, the median duration of severe cough was slightly longer among those with a lower peak flow value compared with the rest of individuals (6 days, 95% CI, 5–9, vs. 5 days, 95% CI, 4–6, respectively), and this trend was observed in all the groups except for those taking ipratropium bromide (5 vs. 7 days), albeit significant differences were not observed. The rest of secondary outcome results is described in Supplementary Table 1.

A total of 7 nonserious adverse events were reported during the study period. Only 4 of them were related to the study treatments: 3 events (palpitations, dizziness, headache) among patients treated with ipratropium bromide and 1 (diarrhea) patient assigned to honey.

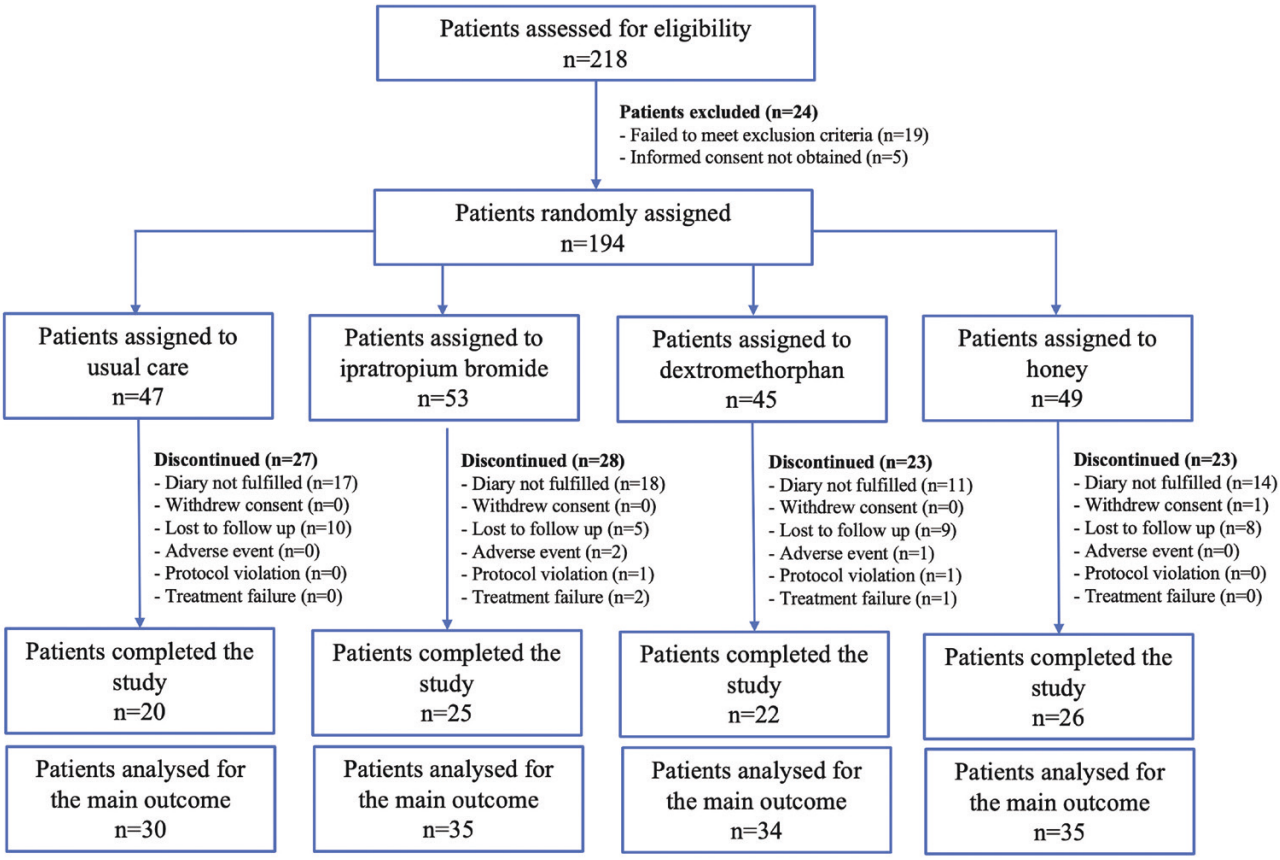

Figure 1. Patient randomization flowchart.

Table 1. Baseline characteristics.

	Overall	Usual care	Ipratropium bromide	Dextromethorphan	Honey
N	194	47	53	45	49
Sociodemographic and clinical data					
Age, in years, mean (SD[b])	52.8 (16.3)	50.5 (17.8)	56.1 (14.3)	54.0 (17.6)	50.5 (15.40
Female gender, *n* (%)	130 (67.0)	30 (63.8)	37 (69.8)	31 (68.9)	32 (65.3)
Weight, in kg, mean (SD)	71.6 (14.3)	70.8 (14.3)	71.8 (16.5)	70.6 (11.5)	73.0 (14.3)
Height, in cm, mean (SD)	163.5 (9.4)	162.9 (9.5)	163.3 (9.5)	162.2 (9.1)	165.5 (9.4)
Body mass index, in kg/m^2, mean (SD)	26.7 (4.5)	26.6 (4.5)	26.8 (4.8)	26.8 (3.6)	26.6 (4.9)
Smoking status, *n* (%)	33 (17.0)	6 (12.8)	11 (20.8)	9 (20.0)	7 (14.3)
Peak flow, in L/min, mean (SD)	356.4 (149.0)	386.3 (164.5)	321.0 (111.4)	338.7 (164.7)	381.4 (150.2)
Any episode of bronchitis in the previous year, *n* (%)	106 (54.6)	21 (44.7)	33 (62.3)	27 (60.0)	25 (51.0)
Pneumococcal vaccine in the previous 5 years, *n* (%)	28 (14.4)	5 (10.6)	10 (18.9)	7 (15.6)	6 (12.2)
Influenza vaccination in the previous year, *n* (%)	48 (24.7)	7 (14.9)	19 (35.8)	11 (24.4)	11 (22.4)
Current disease					
Daytime cough					
Baseline score, median (IQR[c])	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	4.0 (4.0, 5.0)	4.0 (3.0, 5.0)
Patients scoring ≥4, *n* (%)	154 (79.0)	37 (78.7)	44 (83.0)	38 (84.4)	35 (71.4)
Nocturnal cough					
Baseline score, median (IQR)	5.0 (3.25, 5.75)	4.0 (4.0, 5.5)	4.0 (4.0, 6.0)	5.0 (4.0, 6.0)	4.0 (3.0, 5.0)
Patients scoring ≥4, *n* (%)	145 (74.4)	36 (76.6)	40 (75.5)	36 (80.0)	33 (67.3)
Days with cough, median (IQR)	5 (3, 10)	5 (3, 14)	5 (3, 11)	5 (4, 10)	5 (3, 9)
>1 week of symptoms, *n* (%)	67 (34.5)	18 (38.3)	18 (34.0)	16 (35.6)	15 (30.6)
Medication taken before inclusion					
Number of patients taking any medication, *n* (%)	149 (75.6)	40 (80.0)	40 (75.5)	31 (68.9)	38 (77.6)
Paracetamol, *n* (%)	83 (56.8)	15 (40.5)	27 (67.5)	18 (58.1)	23 (60.5)
Ibuprofen, *n* (%)	40 (27.4)	7 (18.9)	15 (37.5)	8 (25.8)	10 (26.3)
Any antibiotic, *n* (%)	11 (7.5)	2 (5.4)	4 (10.0)	1 (3.2)	4 (10.5)
Antitussive agents, *n* (%)	34 (23.3)	10 (27.0)	7 (17.5)	7 (22.6)	10 (26.3)
Mucolytics or expectorants, *n* (%)	39 (26.7)	11 (29.7)	10 (25.0)	8 (25.8)	10 (26.3)
Anticholinergic inhalers, *n* (%)	4 (2.7)	2 (5.4)	0 (0.0)	2 (6.5)	0 (0.0)
Other inhalers, *n* (%)	11 (7.5)	2 (5.4)	6 (15.0)	2 (6.5)	1 (2.6)
Nasal sprays, *n* (%)	8 (5.5)	1 (2.7)	2 (5.0)	2 (6.5)	3 (7.9)
Homeopathy, *n* (%)	3 (2.1)	0 (0.0)	1 (2.5)	1 (3.2)	1 (2.6)
Herbs or infusions, *n* (%)	29 (19.9)	10 (27.0)	5 (12.5)	4 (12.9)	10 (26.3)
Honey, *n* (%)	37 (25.3)	13 (35.1)	8 (20.0)	6 (19.4)	10 (26.3)
Other natural therapy, *n* (%)	9 (6.2)	3 (8.1)	1 (2.5)	2 (6.5)	3 (7.9)
Other products, *n* (%)	15 (10.3)	4 (10.8)	4 (10.0)	2 (6.5)	5 (13.2)
Recommendations given in the baseline visit					
Paracetamol, *n* (%)	120 (61.9)	31 (66.0)	36 (67.9)	25 (55.6)	28 (57.1)
Ibuprofen, *n* (%)	43 (22.2)	11 (23.4)	10 (18.9)	10 (22.2)	12 (24.5)
Antibiotic, *n* (%)	14 (7.2)	2 (4.3)	6 (11.3)	3 (6.7)	3 (6.1)
Inhalers other than anticholinergics, *n* (%)	26 (13.4)	7 (14.9)	7 (13.2)	7 (15.6)	5 (10.2)
Other drugs, *n* (%)	7 (3.5)	4 (8.4)	0 (-)	2 (4.4)	1 (2.0)

[b]SD, standard deviation;
[c]IQR, interquartile interval.

Table 2. Data on cough resolution.

	Overall	Usual care	Ipratropium bromide	Dextromethorphan	Honey
n[a]	134	30	35	34	35
Resolution of moderate to severe cough (score < 3), *n* (%)	123 (91.8)	28 (93.3)	31 (88.6)	32 (94.1)	32 (91.4)
Days to moderate to severe cough resolution (score ≥3), mean (SD)	6.3 (4.2)	6.4 (4.0)	6.1 (4.3)	7.1 (5.1)	5.9 (3.2)
Median (IQR[b])	5.0 (3.0, 9.0)	5.0 (4.0, 8.75)	5.0 (3.0, 8.0)	5.0 (4.0, 9.75)	6.0 (3.5, 7.0)
Moderate to severe daytime cough, in days, mean (SD[c])	6.7 (4.6)	7.2 (4.5)	6.9 (5.0)	6.9 (5.1)	5.7 (4.0)
Median (IQR)	6.0 (3.0, 9.0)	6.0 (4.0, 11.75)	6.0 (3.0, 11.0)	5.0 (3.25, 9.0)	5.0 (3.5, 7.0)
Moderate to severe nocturnal cough, in days, mean (SD)	5.3 (4.5)	7.0 (4.8)	4.7 (4.5)	4.7 (4.0)	5.1 (4.5)
Median (IQR)	4.0 (2.0, 7.0)	6.0 (4.0, 9.75)	3.0 (1.0, 7.0)	4.0 (2.0, 6.75)	5.0 (1.5, 6.5)
Complete resolution of cough (score = 0), *n* (%)	73 (54.5)	19 (63.3)	19 (54.3)	15 (44.1)	20 (57.1)
Days to complete resolution, mean (SD)	11.2 (5.1)	11.5 (4.5)	11.6 (6.2)	10.5 (5.1)	11.0 (4.32)
Median (IQR)	11.5 (7.0, 14.0)	13.0 (8.25, 14.0)	13.0 (7.0, 14.0)	10.0 (6.25, 13.75)	11.0 (7.0, 14.0)
Patient status at day 15 according to doctor's judgment					
Cure, *n* (%)	106 (82.8)	23 (79.3)	25 (75.8)	29 (90.6)	29 (85.3)
Improvement, *n* (%)	19 (14.8)	6 (20.7)	6 (18.2)	2 (6.2)	5 (14.7)
Failure, *n* (%)	3 (2.3)	0 (—)	2 (6.1)	1 (3.1)	0 (—)

[a]Patients with >1 record in the symptom diary.
[b]IQR, interquartile ratio.
[c]SD, standard deviation.

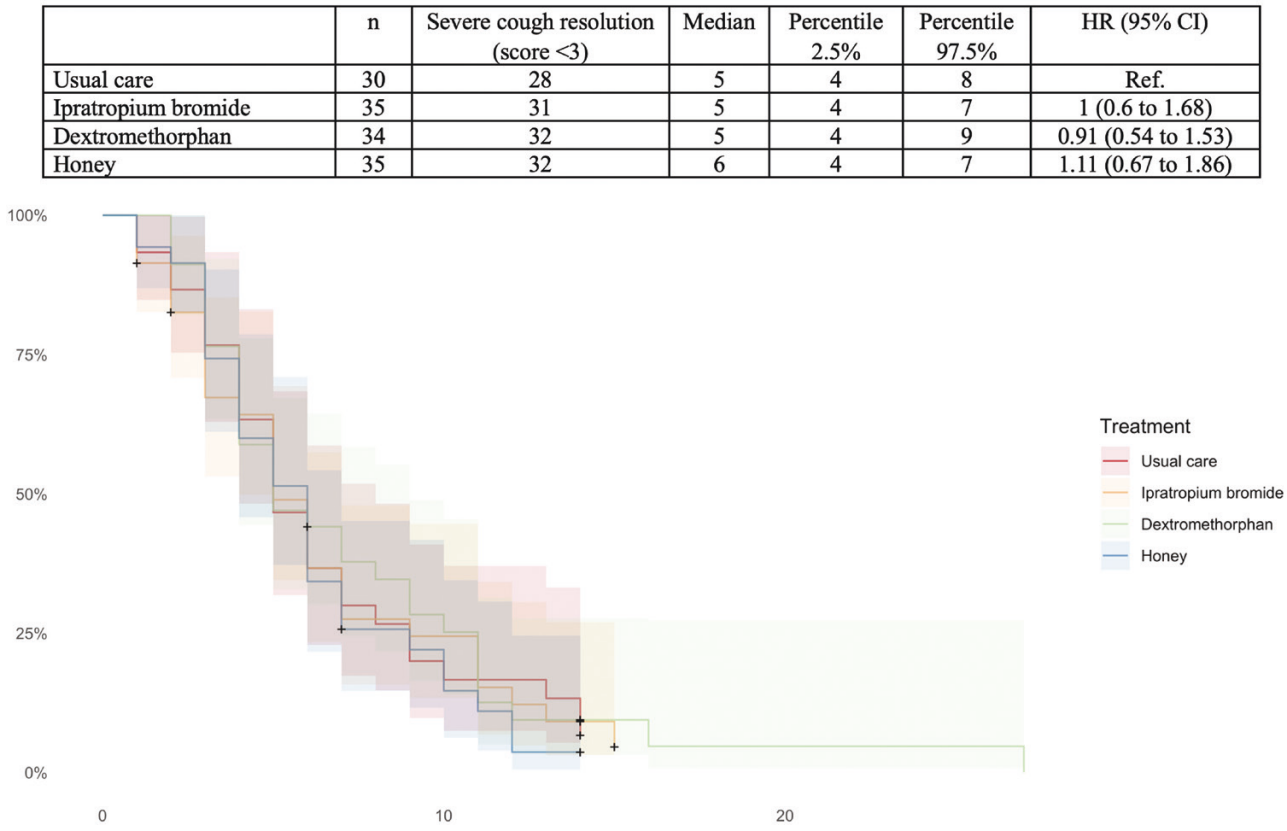

Figure 2. Kaplan–Meier survival analysis of days with moderate-to-severe cough, that is, time (days) from baseline visit until patient last scored ≥3 in either daytime or nocturnal cough in the symptom diary.

Discussion

Our results show that 3 different symptomatic treatments commonly used in acute bronchitis for relieving cough had no influence on the clinical outcomes of the patients. On the basis of the results obtained, we cannot demonstrate that any symptomatic treatment analyzed in this RCT in adults with acute cough is best, but because of the limited number of patients, the study was underpowered. This study involved the use of drugs which have been in the pharmaceutical market for a long time and a natural product that is frequently used for the relief of symptoms due to RTIs.

Strengths and weaknesses of the study

The major limitation of this study was the limited number of patients included which could lead to false negative results. The outbreak of the COVID-19 pandemic in March 2020, and the successive waves of the disease during the following 2 years made it impossible to resume the study in only 3 of the centers, considering that patients with RTIs, resembling COVID-19 infection, clearly interfered with the normal development of the trial. Moreover, the differences observed for the primary outcome suggest that even with a largest sample size we would not find significant differences between treatments. With the actual results, none of the experimental treatments are showing a clinically relevant improvement and the initially planned sample size would have not been enough to guarantee statistical power. We estimate that we would need up to 700 samples per arm (a total of 2,800 samples) to reach a power of 80%.

This was an open study, in which neither physicians nor patients were blind to the patient's assignment to the study group. Notwithstanding, the open nature of the clinical trial ensured that the results obtained are very close to the reality of primary care. However, the main outcome considered in our study was assessed by the patients themselves and not subject to the doctors' judgment. The use of nonreturned symptom diaries can also be considered as a limitation, as the main objective as well as some of the secondary objectives of the study were based on information provided by the patients themselves in these symptom diaries. However, participant clinicians encouraged patients to fill them out appropriately and return them at the different follow-up visits scheduled, and in fact about 70% of these diaries were returned. Only patients with acute cough were taken into account in this trial, thereby making the generalizability of these results only valid for patients with uncomplicated acute bronchitis.

Comparison with other studies

To the best of our knowledge, this is the first trial to demonstrate the effectiveness and safety of different common treatments for mitigating cough due to acute bronchitis. Studies evaluating the role of different symptomatic therapies carried out so far considered low sample sizes, included patients with different uncomplicated RTIs and many times only infections of the upper airways and used doses different from those recommended in clinical practice.

The results obtained in this novel RCT are in agreement with most of the studies carried out so far. We prioritized the use of dextromethorphan, as this antitussive is recommended by clinical guidelines, and ipratropium bromide inhalers, since the majority of studies carried out so far have considered β2-agonists, with very poor results on effectiveness, and the fact that anticholinergics are frequently used in primary care in our country. In our study, we wanted to evaluate the effectiveness of honey in the adult population since its benefits have only been explored in pediatric cases. Unlike most published studies, these treatments were recommended for a maximum of 14 days because the average duration of symptoms with cough due to acute bronchitis is 3 weeks.

The benefit of antitussives in unconclusive so far. A meta-analysis of 6 studies in adults with upper airway infections found that codeine is not effective. One report on a series of 3 successive studies on a total of 451 adults favored dextromethorphan given in a single dose to placebo in terms of cough counts and subjective visual analogue scale, but no data about impact on cough intensity were provided.[6,16] We observed some beneficial results with dextromethorphan regarding some secondary variables compared with the other arms, mainly in the median duration of moderate-to-severe nocturnal cough, days to complete symptom resolution and percentage of cure at day 15, although the clinical relevance of this observation is unclear.

Similar results have been shown with inhalers. Only in one of the clinical trials included in the review by Becker et al.[9] showed a significant improvement in symptom scores in adults receiving fenoterol when there was bronchial hyper-reactiveness, wheezing or a decrease in forced expiratory volume in the first second compared to placebo. This effect, however, was not observed among patients not presenting airflow obstruction.[17] This same effect has been described with inhaled anticholinergics, such as ipratropium and tiotropium alone or associated with β2-agonists, but these studies were primarily conducted in patients with cough due to upper airway infections.[18,19] The release of acetylcholine in the airways by parasympathetic stimulation could trigger hyper-reactiveness and increase mucosal secretion in the walls of the airways, and this might explain the possible antitussive properties of inhaled anticholinergic drugs..[20] We observed a slightly shorter duration of severe cough among those with lower peak flow measurements treated with the anticholinergic inhaler. Another RCT on the effects of inhaled fluticasone in patients with acute cough showed a small effect on symptom severity in the second week of disease.[21] Notwithstanding, this beneficial effect shown in those patients with bronchial hyper-reactiveness must be weighed up against their side effects.

In the update Cochrane review on benefit of honey, including 6 clinical trials and nearly 900 children, honey alleviated cough symptoms compared with no treatment or diphenhydramine, but was not found to be more effective than dextromethorphan or salbutamol regarding cough severity. Apart from the limitations of the small sample sizes of these studies, most children received active treatment (different types of honey depending on the studies) for only one night, and studies evaluating their use in adult populations are lacking.[11] In adults, honey was only shown to be effective in reducing the severity of cough in patients with cough due to an upper RTI.[12] In our study, honey was not effective in relieving cough severity but presented a clinical resolution comparable to dextromethorphan, results that are comparable to those observed among children.

Conclusions

The present RCT is the first study to demonstrate that symptomatic treatment is not effective for relieving cough in patients with uncomplicated acute bronchitis. However, the low sample size of the current study might lead to bias and compromise the results obtained. These results have important implications for the daily clinical practice of clinicians who have to face this common cause of medical consultation.

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Supplementary material

Supplementary material is available at *Family Practice* online.

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Ethics approval

The study was approved by the Primary Care Research and Ethics Committee of the Research Institute IDIAP Jordi Gol, Barcelona, Spain (reference number, AC18/002) and by the Spanish Agency of Medicines and Medical Devices.

Conflict of interest

C.L. reports receiving research grants from Abbott Diagnostics. The other authors declare no competing interests.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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