

"Persistent post-infectious cough" is better treated by which one? Prednisolone, Honey, Coffee, or Honey plus coffee: A meta-analysis

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Cough is a common symptom of upper respiratory tract infection. One of the causes of chronic cough is persistent post-infectious cough (PPC). PPC is a cough that persists longer than three weeks after a "common cold". PPC has poor response to routine treatments. The aim of this study was to evaluate and compare the therapeutic effects of prednisolone, coffee, honey, and "honey plus coffee" in the treatment of PPC. This was a Meta-analysis of three double blind randomized clinical trials conducted on 245 adult participants presenting PPC during an eight-year period from 2005 to 2013. The included participants were assigned into five groups. For each group a special jam-like paste was prepared. Every participant was told to dissolve 25 grams of his/her prescribed product in 200 mL of warm water and drink it every eight hours for one week. All the participants were evaluated before the treatment and two weeks later, to measure the severity of their cough. Comparing the effectiveness of all five regimens, this study found "honey with coffee" as the most effective treatment modality for PPC. Honey plus coffee can successfully treat PPC at a short time. So, it is recommended.

Keywords: Persistent post-infectious cough, Upper respiratory tract infection, Honey, Coffee, Prednisolone

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Cough is a common symptom of upper respiratory tract infections (URTI)¹. According to one theory, cough is mainly because of hypersensitivity and it can be provoked by many factors^{2, 3}. In fact, cough is a reflex of the respiratory tract with a protective and defensive nature. Mechanical or chemical stimulation of sensory nerve receptors in the pharynx, larynx, trachea and bronchi triggers cough reflex⁴.

Common causes of chronic cough are: Lung and tracheal diseases, upper airway cough syndrome resulted from URTI, pharyngitis and allergic rhinitis^{4,6}. Other causes are gastro-esophageal reflux disease, exposure to environmental pollution or cigarette smoke, persistent post-infectious cough (PPC), respiratory tract foreign bodies and psychogenic cough.

PPC is a cough that persists after a common cold or an URTI for longer than three weeks or even sometimes for many months^{5,7, 8}. This cough is reported as 11– 25% of all the chronic coughs⁹. PPC patients suffer from a persistent tickling or irritating sensation in the throat, which often leads to paroxysms of coughing⁹. Since, PPC does not result in severe disability; some people ignore it. But mostly educated people and the ones with special meticulous jobs find this condition troublesome and seek medical helps. Frequently referred to cough clinics, these patients are checked for other causes of chronic cough. Therefore, PPC may be a vexing problem for the patients and the physicians alike^{5, 10}.

The main infectious etiology of PPC is rarely confirmed¹¹. Respiratory viruses, particularly respiratory syncytial virus (RSV), adenoviruses, parainfluenza, influenza, etc. have all been implicated^{5,7}. The pathogenesis of the PPC is probably long-lasting and widespread pharyngeal mucosal

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Abbreviations: URTI = Upper respiratory tract infection;
PPC = Persistent post-infectious cough

"inflammation" and "desquamation of the epithelial cells" with "nerve endings damage", that lead to hyperactivity of the cough reflex^{9,11,12}. These can make the pharynx more sensitive to local irritants and may lead to a vicious cycle and more damage to mucosa^{9,13}. PPC can be stimulated by many factors like cigarette smoke, aerosol sprays, chemical fumes, perfumes, dust, even drinking, eating, talking, laughing, and breathing cold air⁹.

Making an accurate diagnosis is the key to successfully treat PPC. This chronic cough is almost intractable and has poor response to routine treatment modalities. Currently available treatments for PPC are: antihistamines, narcotics and centrally acting antitussive agents such as codeine and dextromethorphan^{7,10}, inhaled or systemic corticosteroid^{5,7,11} inhaled ipratropium bromide, bronchodilators, cromoglycate^{5,7}, and the combination of honey with coffee^{14,15}.

Honey is one of the oldest known drugs and since ancient times, has been regarded as a health giving substance. Its medical use is recorded from around 3000 BC. Onward and is addressed as a curative substance in the holy Bible and other holy Books. Honey has been valued highly in the Middle East and is mentioned as a curative substance for human illnesses in the holy Quran 1400 years ago.

As a matter of fact honey is produced from flower nectar by honey bees^{16,17}. It is a delicious remedy¹⁸ and has been reported to contain more than 200 substances such as sugars, proteins, minerals, some vitamins, organic acids and antioxidants (phenolic compounds, enzymes, flavonoids, amino acids, carotenoid like substances, and other phytochemicals)¹⁶⁻²⁰. According to some studies; honey by its antioxidants, can increase cytokine release²¹⁻²³. Moreover, it can prevent cellular oxidative damage which leads to ageing, diseases and death¹⁶. In traditional medicine, honey has been highly valued and used for treatment of URTI and coughing^{1,24-28}.

The World Health Organization (WHO) has cited that honey demulcents may soothe the throat and therefore, it can be a potential treatment for cough and other URTI symptoms^{25,29-31}. Honey is an ancient remedy which has been re-discovered in modern times for the maintenance of health in several diseases^{25,32}, burns, injuries and wounds^{29,33-36}. It has many medicinal properties like wound healing capacity³⁷. Honey by its sweet substances reflexively stimulates saliva secretion and secretion of mucus in

the airways^{1,38,39}. These effects may have been associated with its hyper osmolarity and its anti-inflammatory and antioxidant properties^{25,40,41}. Also, honey reduces inflammation, edema and stimulates epithelialization stages, tissue regeneration and improvement of granulation and debridement^{1,38,39}, which it in turn accelerate tissue repair and lead to wound healing^{1,24,33-35,37,38,42}. Moreover, honey is recommended in dental hygiene. It has therapeutic properties in the treatment of gingivitis and periodontal disorders^{43,44}.

On the other hand, **Caffeine** is a naturally occurring alkaloid found in coffee, tea, cola drinks and cocoa⁴⁵. Methylxanthines (such as theophylline and caffeine) are bronchodilator drugs which are believed to stimulate breathing efforts and have been used to prevent apnea^{45,46}. Also caffeine is hypoalgesic, and it has anti-inflammatory effects^{45,46}. It is the world's most commonly consumed psychoactive substance that stimulates the CNS⁴⁷. Caffeine improves vigilance and psychomotor performance, and increases levels of self-reported alertness and decreases levels of self-reported fatigue and sleepiness.

Moreover, to the best of our knowledge there were only two reports in the Literature that had mentioned the "combination of honey with coffee" as a treatment for PPC^{14,15}. In our previous studies, we have found that honey and/or coffee have some beneficial effects in the treatment of PPC. Considering the great number of people around the world suffering from PPC, the aim of this study was to evaluate and compare the therapeutic effects of honey, coffee, "honey plus coffee", and prednisolone in the treatment of patients with PPC.

Materials and methods

Design and setting

This was a Meta-analysis of the three double blind randomized clinical trials of participants presenting PPC. To increase the power of our two previous studies, we accepted another 64 eligible participants during 2011- 2013. To put in nutshell, these three studies were performed during about an eight-year period at Baqiyatallah University Hospital, Tehran, Iran from 2005 to 2013. All of the 349 participants had the history of several referrals to different physicians and despite a variety of treatments, their cough had persisted. Among them 104 patients with other causes of chronic cough, systemic disease or abnormal routine laboratory tests were excluded from

the study. By and large our three studies were conducted on 245 adult participants who had experienced PPC longer than three weeks (142 men and 103 women).

Ethical considerations

The participants were all volunteers and they were fully informed about the aim of the studies, the benefits of the researches, the prescribed regimens, the follow up sessions and their own duty as participants. Moreover, they were informed about the potential complications such as dyspepsia and insomnia, and how to face them. They were reassured that the data and their files were kept confidential. Then, an informed consent had been taken from them before they were enrolled in the study. The design of these prospective studies was approved by the Ethics Committee of Baqiyatallah University of Medical Sciences according to Helsinki declaration. These trials were registered in Iranian Registry of Clinical Trials (IRCT: 201103034737 N1 and N2).

Participants

In our cough clinic, all the patients were assessed and registered after their check lists had been completed. The check list was about personal data including age, sex, weight, education, occupation, duration of illness and presence or absence of any systemic disease. All the participants underwent a comprehensive history and the physical examination of the respiratory system, ear, nose, and throat. They were thoroughly examined for any abnormality and also underlying causes of cough. In addition routine laboratory tests and chest X-Ray were taken. Other evaluations were carried out as necessary, for example Spirometry, Computed Tomography (CT scan) of paranasal sinuses, and High-Resolution Computed Tomography (HRCT) of thorax.

Patients with PPC for more than three weeks of duration of illness were included in this study. But smokers and ones with systemic disease and/or abnormal routine laboratory tests were excluded. As a matter of fact, a high majority of the patients have more than a single cause at the same time for chronic cough^{5, 48-51}. Therefore, in this study we excluded every patient with other causes of cough, or we first treated those other conditions.

In patients with chronic cough, there is a positive relationship between cough frequency and cough reflex sensitivity⁵². On the other hand, In PPC, the severity of the coughs is often mild to moderate, but

their repetitions make them annoying and the major factor that shows they are subsiding is that their frequency lessens. Thereby, we can assume that the frequency of cough is equal to severity of cough in PPC.

Intervention

All 245 included participants were randomly distributed into five groups. We prepared five regimens of medical jam-like paste. Each 600 gm. of the product consisted of:

1- 500 gm. of "Honey" given to every member of the first group (H group).

2- 70 gm. "original instant Coffee" given to every member of the second group (C group).

3- 500 gm. of Honey and 70 gm. of original instant Coffee, given to every member of the third group (HC group).

4- 320 mg of Prednisolone given to every member of the fourth group (P group).

5- Placebo by supportive treatment included Guaifenesine given to every member of the fifth group ("Control-Placebo" group or CP group).

It's necessary to mention that all the five products were similar in packaging, color, shape, and taste (by adding enough edible brown color, coffee essence, artificial honey flavor and liquid glucose). The dosages of the ingredients were determined according to usual daily usage. The ingredients of each product were gently mixed and homogenized. These products should be kept at room temperature of about 22-26°C. The natural honeys used in these studies were obtained from the region of the Zagros Mountains in the west of Iran and the original instant coffee produced in Spain by Nestle Spain Ltd. The mentioned samples were produced by our pharmacists. The sample sizes were determined using computerized randomized program and they were encoded confidentially and distributed randomly between the participants. They were told to dissolve one tablespoon (about 25 gm.) of the prescribed jam- like paste in one glass (about 200 mL) of warm water (under 60°C), then drink this solution. They were asked to repeat it every eight hours for one week even if it may initially exaggerate their cough. The participants were told about all five prescriptions, but they were blinded about their own regimen. Also they accepted not to use any additional anti-inflammatory and antitussive agents even honey or coffee.

Study investigators who checked patients' signs and symptoms were also unaware of the prescribed

regimens and none of them participated as patients in this study. The process of these researches is illustrated by a Flow Diagram in the attached additional data file.

Main outcome measures

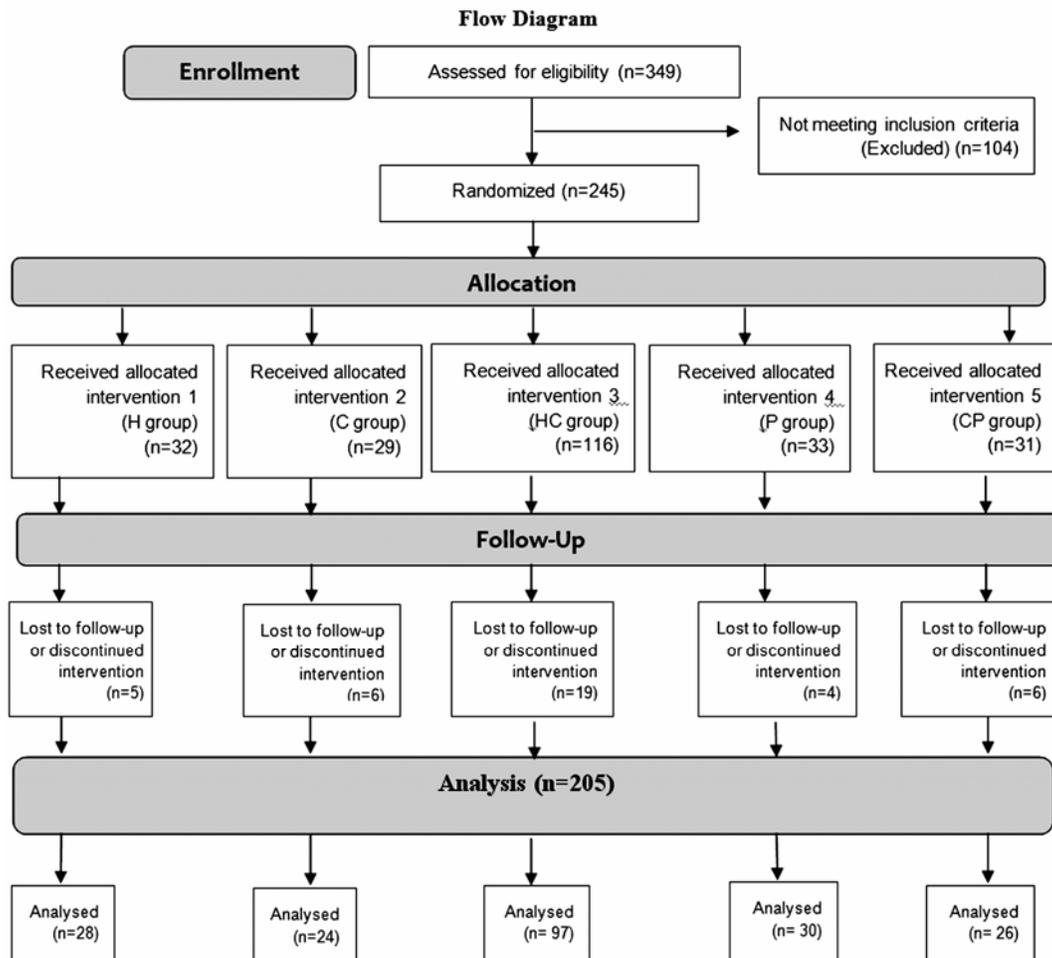
All the participants were evaluated for severity of their cough before their treatment and one week after completion of the treatment to measure the severity of their cough and to complete their check lists. We had chosen the time one week after the completion of the treatment in order to evaluate only the lasting effects of our regimens and to eliminate their sedative effects. A cough questionnaire was designed. The questioners were completed by physicians according to patients' answers using Visual Analog Score. Then, the participants were categorized on the basis of a Likert-type Scale^{1, 53}. It was graded as: Nothing (0), low (1⁺), moderate (2⁺), and high (3⁺).

Statistical analysis

All the analyses were carried out using SPSS version 15.0 software on 205 final participants. Continuous variables were presented as mean and standard deviation (std). Categorical variables were presented as absolute and relative frequencies. One-way ANOVA, Chi-square test, Wilcoxon Signed Ranks test and Paired t-test were used to compare the groups. All reported P-values were based on two-sided hypotheses. The distribution of mentioned base line data is shown in the Table 1.

Results

In this Meta-analyses of our three clinical trials, the mean (standard deviation, std) of age, weight, duration of illness, were according to appearance: 39.9 (12.6) (yrs.), 76.1 (10.4) (kg), and 2.9 (2.1) (months). Participants' ages ranged from 21 - 65 yrs. and most of cases were in the second and third age groups (78.1% of all patients). Their weight ranged from 50 - 90 kg. Most of them were highly educated



(Table 1). Also, the total mean (std) of the changes of the severity of cough before and after the treatment was degreed as: 2.96 (0.21) and 1.67 (1.01). The differences among variables including age and duration of illness in months before the treatment, in all five groups were similar and according to statistics (ANOVA) were not significant ($p>0.05$), (Table 2).

Chi-square test showed the distribution of variables (including sex, levels of education and occupation) was the same in these five groups ($p>0.05$). According to Wilcoxon Signed Ranks tests, the cough severity was similar in all five groups before the treatment ($p>0.05$). According to paired t test, the changes in severity of cough in the HC group, H group, C group and P group after the treatment proved to be significant ($p<0.05$), but in the "Control-Placebo" group it was not significant ($p>0.05$). Thus, except the "Control-Placebo" modality, all the other these treatment regimens were effective in treating the condition. Analysis of variances showed that the differences among the means of severity of cough after the treatment in five groups were significant ($p<0.001$). In addition, Post Hoc tests (Tukey) showed that the means of severity of cough after the treatment in the (H group - C group) and (P group - CP group) were not significant ($p>0.05$). But the mean of cough severity after the treatment in the HC group was lower than the other four groups, and its difference was statistically significant ($p<0.001$). Therefore, the results of this study demonstrated that "Honey plus Coffee" compared with the other four regimens had a significantly more effective curing impact on cough severity.

Discussion

Each year billions of dollars are spent to control and cure cough while the cough medicines' real effect is not clear^{1, 54}. Even though PPC is reported as only 11– 25% of all the chronic coughs, and it is not associated with disability and mortality; it can cause morbidity and medical costs. Considering the great number of people around the world suffering from PPC, the aim of the present study was to evaluate and compare the therapeutic effects of "honey", "coffee", "honey plus coffee", "prednisolone" and "placebo" in the treatment of patients with PPC.

The mechanism of action of honey has not been definitely known. By the way, though acidity, osmolality, and hydrogen peroxide production have been proposed as important factors²⁴. Honey lowers plasma prostaglandin concentrations due to reducing

Table 1—Characteristics of participants in the study

Factors	H (n=28)	C (n=24)	HC (n=97)	P (n=30)	CP (n=26)
Age groups:					
≤ 30	8	10	19	12	5
31-40	6	8	28	8	6
41-50	4	4	32	6	9
51-60	8	2	16	4	6
≥ 61	2	0	2	0	0
Sex:					
Male	18	12	53	20	13
Female	10	12	44	10	13
Level of schooling:					
Primary & Diploma	8	10	39	12	6
Technical & higher education	10	14	58	13	20
Occupation:					
House worker	8	6	20	5	7
Student & Employee	14	14	59	13	9
Physician	4	4	18	9	9
H = Honey group C = Coffee group HC = Honey plus Coffee group					
P = Prednisolone group CP = Control-Placebo group					

prostaglandin synthesis at the site of application²³. Honey also elevates nitric oxide (NO) in the lesions and has antioxidant and anti-inflammatory activities²³. On the other hand, it seems that the effect of honey in treatment of PPC may be about that sweet substances naturally due to their hyper osmolality, cause reflex salivation and hyper secretion of airway mucus. These can improve mucociliary clearance in the airway, and lead to a demulcent effect in the pharynx^{1, 25, 35, 38, 48}. Moreover, honey by its anti-inflammatory and antioxidant properties, can expedite repairing and healing of the pharyngeal mucosal irritation thereby reduces cough^{1, 25, 31, 32, 35, 37, 38, 48}.

Although it has been mentioned that honey or coffee separately have treatment effects on some respiratory diseases and they cause mucosal tissue healing; to the best of our knowledge there is no report regarding these two together in the Literature, except our previous studies for efficacy of honey plus coffee in the treatment of PPC^{14, 15}. Those studies demonstrated that, "honey plus coffee" was the most effective treatment modality for PPC and also the effect of that combination was more than the effect of each one of the materials separately^{14, 15}.

Table 2—Mean differences between treatments and some explanatory variables

Variables	H (n=28)	C (n=24)	HC (n=97)	P (n=30)	CP (n=26)	P-value
Age (year) (std):	41.9(14.5)	36.8(9.9)	42.3(13.2)	36.1 (11.9)	42.0(11.8)	NS*
Weight (Kg) (std):	74.6(11.1)	78.4(8.6)	76.1(12.9)	77.1(8.8)	73.9(9.9)	NS
Duration of illness (Month) (std):	3.3(1.3)	2.3(1.4)	3.0 (2.9)	2.9(1.5)	2.9(2.7)	NS
Cough severity (Before) (std):	3.0 (0.0)	3.0 (0.0)	2.9 (0.3)	3.0 (0.0)	2.8(0.4)	NS
Cough severity (After) (std):	1.4(0.5)	1.8(1.3)	0.2 (0.5)	2.4 (0.6)	2.7(0.5)	<0.001 S*
H = Honey group	C = Coffee group		HC = Honey plus Coffee group		P = Prednisolone group	
CP = Control-Placebo group			* NS = Not Significant		* S = Significant	

This combination can bring about notable improvements in mucosal tissue healing by repairing the "nerve ending damage" due to mucosal desquamation and mucosal irritability. These can provide possible explanation for the role of "combined coffee and honey" in the successful treatment of PPC. Moreover, honey and coffee are natural edible substances which are safe, agreeable, less expensive, easily available and they have proved to be effective in a short period of time.

Despite the fact that the exact mechanism of action of the combination of honey and coffee is almost unveiled and is not yet fully investigated; the efficacy can be due to the synergistic effects of these two components. Comparing the effectiveness of all four regimens, this new promoted study proved that the "combination of honey and coffee" is the most effective treatment modality for PPC. It can treat PPC and also eliminate unpleasant consequences of illness for the patients and the physicians alike.

Considering the great number of people around the world suffering from PPC, this is wise enough to seek an effective remedy for that. This new treatment modality can bring about considerable improvements in curing patients with PPC and helps both the patients and physicians. Further studies with larger sample sizes and in other settings may improve the power of this results.

Conclusion

PPC may be successfully treated by "combination of honey and coffee" at a short time. This treatment modality can play the role of an alternative medicine in the treatment of PPC. We therefore, recommend the use of this effective treatment modality for the treatment of PPC. However, further investigations are warranted.

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