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RANDOMISED DOUBLE BLIND STUDY TO COMPARE EFFECTIVENESS OF HONEY, SALBUTAMOL AND PLACEBO IN TREATMENT OF COUGH IN CHILDREN WITH COMMON COLD

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ABSTRACT

Background: Acute upper respiratory infection is the most common childhood illness and presents with cough, coryza and fever. Available evidence suggests that cough medicines may be no more effective than honey-based cough remedies.

Objective: To compare effectiveness of honey, salbutamol and placebo in the treatment of cough in children with acute onset cough.

Design: Randomised control trial

Setting: Aga Khan University Hospital Paediatric Casualty

Subjects: Children between ages one to twelve years presenting with a common cold between December 2010 and February 2012 were enrolled.

Outcome measures: Frequency, severity and extent to which cough bothered and disturbed child and parental sleep were assessed at baseline and over the subsequent five days through telephone interview using a validated scoring tool.

Results: One hundred and forty five children were enrolled in the study (45- placebo, 57 –honey, 43 –salbutamol). Of the 145 children 51% were male. Honey significantly reduced the total mean symptom score by day three ($p < 0.001$). Total mean difference in scores between day zero to five demonstrated a significant difference of honey's efficacy over placebo ($p < 0.002$) however no difference was noted when compared to salbutamol ($p < 0.478$). Significant differences in both total as well as each individual symptom score was detected with honey consistently scoring the best whilst placebo and salbutamol scored the worst. In paired comparisons honey was superior to placebo but not salbutamol, whilst salbutamol was not superior to placebo.

Conclusion: Honey was most effective in symptomatic relief of symptoms associated with the common cold whilst salbutamol or placebo offered no benefit.

INTRODUCTION

Common cold is a viral infection affecting the upper airways and is defined by the presence of rhinorrhoea and cough for about five days' duration. Other symptoms may include acute nasal congestion, fever, sore throat, myalgia and headache. Common cold contributes to significant childhood morbidity, sleep disturbance in child and family members, loss of school days for the older child, parental anxiety and low productivity. Cough mixtures are among the most commonly prescribed medications for coughs and colds in adults and children (1, 2). Cough mixtures may have one or more of various medicaments; anti-

tussives, anti-histamines, expectorants, decongestants or mucolytics. Recent systematic reviews from the Cochrane database and recommendations from the American College of Chest Physicians and the World Health Organisation (WHO) suggest a lack of efficacy of most cough mixture ingredients whether used singly or in combination.(3, 4).

Recently there have been blinded trials suggesting benefit from use of natural demulcents such as honey, for the treatment of the common cold (5). It has also been recommended as a soothing agent for cough in children by the WHO (3). Additionally, honey has anti-oxidant properties and increases

cytokine release, which may explain its anti-microbial effects and apparent benefit in both common cold and during skin wound healing (4,7,8). Honey is readily available, affordable and culturally acceptable to most parents. However, there has been caution drawn to possible infantile botulism associated with use of honey in infants, especially before the age of one year (10-13). There has not been any such reports from Africa suggesting that African honey may be safe to use in children under 12 months of age and unlike cough mixtures is not associated with any important adverse effects (5). Paul and colleagues (5) note that darker honeys, such as the buckwheat variety, consist of more phenolic compounds than other varieties and that the associated anti-oxidant effect might have contributed to the improvement seen in those children treated with this kind of honey.

Salbutamol is a common ingredient of cough mixtures and is often prescribed singly or in combination mixtures for children with the common cold despite formal evaluation of its efficacy. Justification for its use is based on its ability to induce mucociliary clearance of lower airways by increasing frequency of cilia beat hence faster expectoration (6). It is also a potent bronchodilator which theoretically should allow easy expectoration of mucus and thus a quicker relief of cough symptoms. Some of the side effects of salbutamol include tachycardia, palpitations, headache and tremor.

MATERIALS AND METHODS

We conducted a hospital based randomised double-blinded clinical trial evaluating effectiveness of honey and salbutamol against that of placebo at the paediatric casualty of the Aga Khan University Hospital Nairobi. This is a national tertiary referral and teaching hospital serving the middle/upper-income society in Nairobi and its environs. The study was approved by the Aga Khan University hospital ethics and research committee. Study patients were recruited from December 2010 through to February 2012. The study population included children aged between one and twelve years with an uncomplicated acute upper respiratory infection. Exclusion criteria included prior use (48 hours) of any cough mixture, study agents, oral anti-histamines, nasal decongestants, steroids or anti-biotics. Other exclusions were any past history of atopy, asthma or any chronic lung disease as well as hospitalisation for lower respiratory tract infection in the past six months.

Cough is a difficult symptom to quantify and investigators have struggled with identification of an appropriate outcome measurement for trials on cough treatment, therefore the Likert scale was used as its one amongst a few validated tools of assessing severity of cough in children and has the benefit of incorporating both child and parental

sleep disturbance as a surrogate for severity of cough intensity (9).

The Likert scale comprised of five questions, each having a score from 0 – 6 ranging from “not at all” to “extremely”. The five questions inquired about the frequency, severity, how bothersome the cough was, how it affected the child’s and the parents’ sleep. Likert scale used is shown in Figure 1 below.

Figure 1

Likert cough assessment severity score

- | |
|--|
| <ol style="list-style-type: none"> 1. How frequent was your child’s coughing yesterday? 2. How severe was your child’s cough yesterday? 3. How bothersome was last night’s cough to your child? 4. How much did last night’s cough affect your child’s ability to sleep? 5. How much did last night’s cough affect your PARENTS ability to sleep? |
|--|

6 Extremely _ 5 Very much _ 4 A lot _ 3 Somewhat _ 2 A little _ 1 Not Much _ 0 Not at all

Informed written consent from the parent/ guardian was taken at the casualty where for those who answered at least somewhat (3 points) for a minimum of two of the three questions related to nocturnal cough frequency, effect on the child’s sleep, and effect on parental sleep based on the previous night’s symptoms at initial assessment. Dispensing of the study drugs was undertaken following a random order previously generated by a statistician not involved in care of study patients. All three study drugs were prepared, bottled, packaged and labeled as Study Drug A, B and C by Universal Corporation Ltd (P.O Box: 1748-00902), based in Kikuyu who also held the code until after statistical analysis was completed. The dose prescribed for all the three study agents was 2.5 ml (age one to two years), 5 ml (age 2-6 years) and 7.5 ml (age six to twelve years) and all were administered thrice daily for five days. Syrup salbutamol has 2 mg of active ingredient per 5ml. The darkest locally available honey was used. Placebo was a brown colored sugar and alcohol free syrup with an inert thickening agent whose ingredients included sodium citrate, citric acid monohydrate, hypromellose, sodium benzoate, saccharin sodium, sodium chloride, caramel colour and water. Parents were then contacted by telephone daily for five days and the Likert scale questionnaire administered repeatedly.

Adherence to medications was confirmed at each telephonic interview as well as any possible side effects. Patients requiring further evaluations by doctors and those for whom anti-biotics were prescribed were excluded from final analysis.

Sample size: To compare that average response for three groups over six days with repeated measurements across the three groups made from baseline to day five, the following formula for sample size per group is used (17).

$$n = \frac{2\sigma^2(1 + (m - 1)p)(z_{\alpha/2} + z_{\beta})^2}{d^2}$$

Sample size was calculated with the aim to detect a 1-point difference between any two treatment groups using 0.05 significance with 90% power, giving 37 subjects per group.

Two main outcome variables were considered in this study; the duration in days from initiation of treatment till the scores reduced to zero and the difference in scores between day- 5 and day -0. In statistical analyses, a generalised linear model was used to compare the mean treatment group scores given the repeated measurements on the cough scores.

Tukey's Honestly Significant Difference was used in post-hoc test to carry out pair-wise comparisons of the groups.

RESULTS

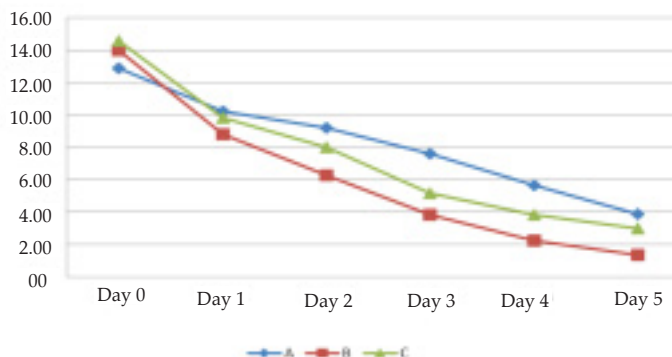
The study enrolled 145 children with acute onset cough but complete data were available for 133 (91.7%). Forty five children received placebo, 57 received honey whilst 43 received salbutamol. Of those randomised to receive placebo, honey and salbutamol, those who were lost to follow up or refused to adhere with medications were six, four and two study participants respectively for the three groups. Fifty-one percent of all participants were male. Table 1 below shows the baseline characteristics of the components of the Likert scale across the three groups.

Table 1
Baseline characteristics of the three study groups

Baseline characteristics	Receiving Placebo (N = 45)	Receiving Honey (N = 57)	Receiving Salbutamol (N = 43)	P-Value
Female No. (%)	21 (50.0%)	24 (44.4%)	22 (53.7%)	0.663
Male No. (%)	21 (50.0%)	30 (55.6%)	19 (46.3%)	
Cough frequency score, mean \pm SD	3.05 \pm 0.76	3.27 \pm 0.75	3.09 \pm 0.84	0.32
Cough severity score, mean \pm SD	2.81 \pm 1.06	3.04 \pm 1.07	2.91 \pm 1.04	0.57
Cough bothersome score, mean \pm SD	2.52 \pm 1.19	2.91 \pm 1.07	2.93 \pm 1.20	0.18
Cough effect on child sleep score, mean \pm SD	2.31 \pm 1.63	2.40 \pm 1.21	2.86 \pm 1.45	0.15
Cough effect on parent sleep score, mean \pm SD	2.19 \pm 1.02	2.36 \pm 1.00	2.77 \pm 1.08	0.19
Combined symptom score, mean \pm SD	12.88 \pm 5.31	13.98 \pm 4.51	14.56 \pm 5.09	0.29

There were no significant differences between both total and individual measures of symptom severity at baseline. The total mean score for children on first day of enrollment was 12.88, 13.98 and 14.56 for placebo, honey and salbutamol respectively ($p = 0.29$).

Figure 1
Total mean Likert scores (A – placebo, B – honey, C – salbutamol)



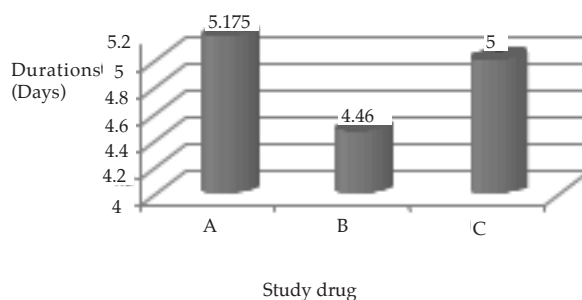
By day three honey had significantly reduced the total mean symptom score ($p = 0.001$) and this significance over both salbutamol and placebo was again noted on days four and five.

The total mean difference in scores between day 5 and day 0 were 8.69, 12.68 and 11.37 for placebo, honey and salbutamol respectively. Honey again demonstrated superior effectiveness in reducing overall symptom score ($p = 0.003$).

A general linear model with cough scores

measured over the six day period indicated a statistically significant difference between honey, salbutamol and placebo ($p = 0.000$). Paired analysis of the total mean difference in scores between day 5 and day 0 demonstrated efficacy of honey over placebo ($p = 0.002$) but when compared to salbutamol, there was no statistically significant difference noted ($p = 0.478$). Effect of salbutamol was not different from that of placebo ($p = 0.075$).

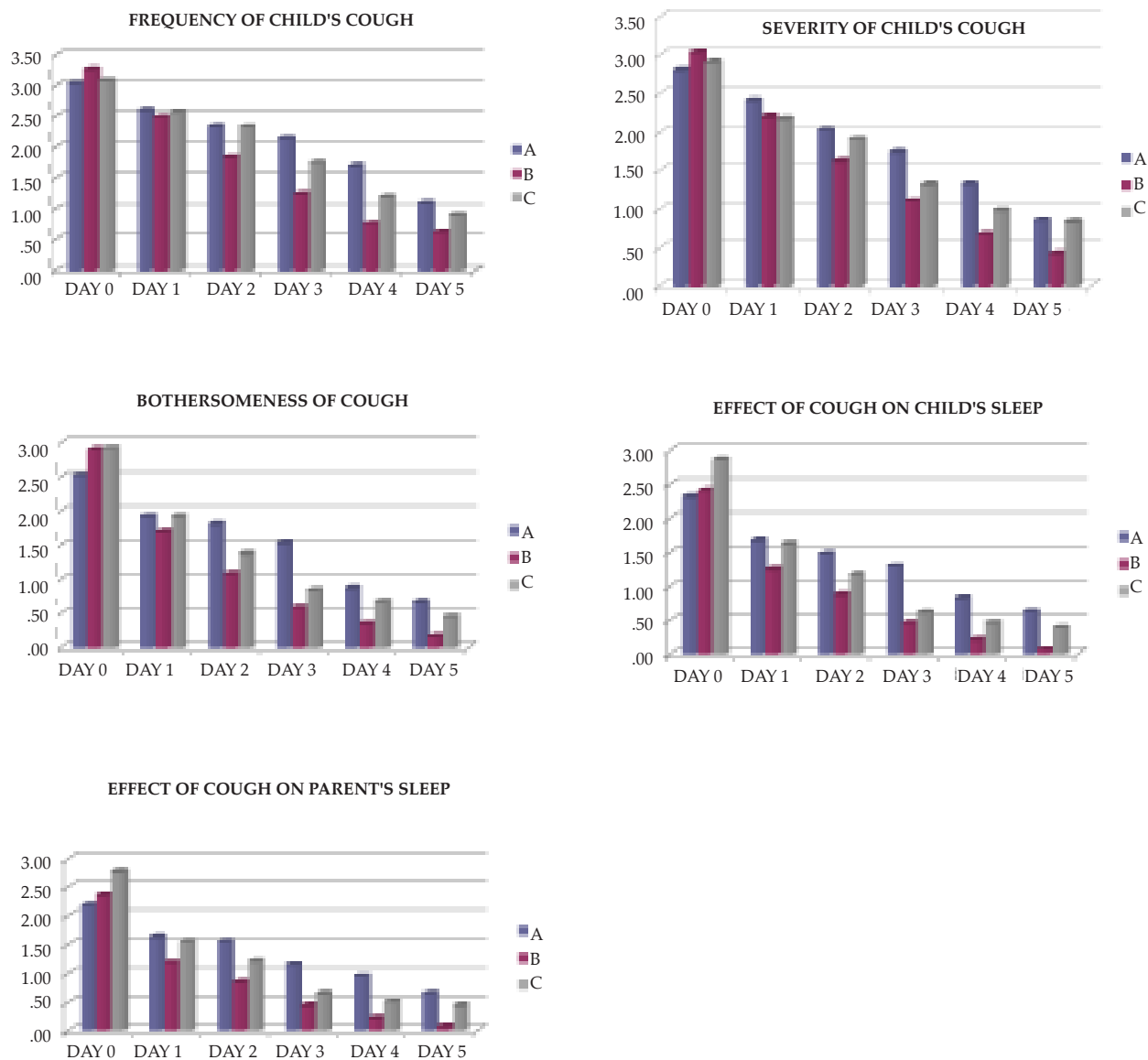
Figure 2
Time interval to clearance of the cough (A – placebo, B – honey, C – salbutamol)



The mean time interval to clearance of cough in days was 5.18, 4.46, 5.0 for placebo, honey and salbutamol respectively using ANOVA ($p = 0.019$), indicating that those on honey were first to get complete relief of their symptoms. This was reconfirmed in paired analysis of mean time interval to clearance of cough score showing honey superiority over placebo ($p = 0.023$). However difference in response between honey and salbutamol was not statistically different ($p = 0.11$). Effect of salbutamol was comparable to that of placebo ($p = 0.81$).

Figure 3

Assessment of individual parameters of the Likert score versus the three study drugs (A – Placebo, B – honey, C – salbutamol)



When each individual parameter was evaluated honey scored consistently better than either placebo or salbutamol with significant differences noted again on day three for each individual variable which included frequency of cough ($p = 0.003$), severity of cough ($p = 0.03$), how bothersome was last night's cough to your child ($p = 0.038$), effect of last night's cough on child's ability to sleep ($p = 0.001$) and how much did last night's cough affect the parents ability to sleep ($p = 0.006$).

Table 2
Side effects profile of the study drugs

Side Effects Reported	Placebo Count (percent)	Honey Count (Percent)	Salbutamol Count (percent)
Nausea	3 (1.4)	8 (2.9)	0 (0)
Abdominal pain	1 (0.5)	7 (2.5)	3 (1.4)
Diarrhea	6 (2.9)	7 (2.5)	9 (4.3)
Vomiting	8 (3.8)	15 (5.4)	10 (4.8)
Hand tremor	0 (0)	0 (0)	0 (0)
Rash	0 (0)	1 (0.4)	4 (1.9)
Tachycardia	1 (0.5)	2 (0.7)	1 (0.5)
Others	5 (2.4)	4 (1.4)	3 (1.4)

Children administered honey had more reports of gastrointestinal complaints but none were significantly more than that of either placebo or salbutamol group.

The rest of the side effect profile was minimal with none of the study drugs showing significant differences over that of placebo.

DISCUSSION

In this study, honey performed better in clearance of cough symptoms over either placebo or salbutamol using the Likert score as a tool of validation. Studies by both Paul in 2007 and Cohen in 2012 comparing just honey to placebo over single day duration showed similar results (5, 16).

This study we believe is the first fully blinded randomised placebo controlled trial evaluating effectiveness of honey over a five day duration of the common cold during which honey continued to show significant difference over placebo.

The putative mechanism of action of honey as a soother of cough ranges from its possible antioxidant activity, demulcent and or natural antiseptic/antibiotic properties (4,7,8). Substitution of cough mixtures with honey will translate into major cost savings, a 300 ml bottle of honey costs US\$ 4- 6 locally and would be enough to treat four children thus reducing the real cost per child to approximately one US dollar whereas a standard cough mixture or syrup salbutamol will retail at five dollars per bottle hence five times the cost. Its benefit over salbutamol continues to emphasise the need to curtail the widespread abuse of cough mixture prescriptions worldwide. It positively lends weight to the WHO directive on the role of demulcents for the common cold (3).

Although not significant there were more gastrointestinal side effects with honey over either placebo or salbutamol.

This study showed no benefit of salbutamol over either placebo or honey. It was hypothesised that it may have helped with nocturnal cough and thus effect of sleep but this was not significant when analysed. Salbutamol and other short acting bronchodilators are used as a common ingredient for many cough mixtures both in Kenya and worldwide which led us to justify its inclusion as one of our study agents. Placebo controlled randomised trials comparing the effectiveness of antihistamines and dextromethorphan have been conducted by Paul *et al* (5) confirming that these individual agents have no effect on cough symptoms of the common cold but we have as yet to find similar trials using salbutamol in the same manner. There was no noted increase of hand tremor and tachycardia in the study group using salbutamol as against placebo in this study.

One drawback encountered during this study was the large number of patients who could not be initially recruited as they had taken one of the study drugs, cough mixture or antihistamines prior to presentation to seek further treatment.

In conclusion, honey has consistently showed benefit for the cough symptom during the common cold and this study offers reason to continue to advocate for its use as a cheaper, safer and easily available cough mixture. Salbutamol for the common cold symptoms has not been shown to be useful and hence its prescription should be avoided.

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