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Original Article

Randomized controlled trial of erdosteine for acute cough in children with colds

Yenny, Roni Naning, Amalia Setyati

Abstract

Background The prevalence of the common cold in children is high, with 30% of cases exhibiting an acute cough, the most common complaint by parents. Erdosteine, a recently developed cough medicine, is available for children. Erdosteine has been reported to increase mucociliary clearance, act as an antioxidant and prevent bacterial adhesion.

Objective To assess the clinical improvement in acute cough in children with a common cold taking erdosteine vs. a placebo.

Methods We conducted a double-blind, randomized, controlled trial at the Public Health Center of Gedongtengen, Yogyakarta with 140 children selected by a consecutive sampling method. Research subjects were randomized by computer program into two treatment groups, those receiving erdosteine therapy and those receiving a placebo. Both groups were monitored for 6 days. A scoring system was used to assess the improvement of acute cough symptoms and analyzed by chi-square test.

Results No significant differences in basic characteristics, cough severity, or environment were found among the 140 children with common cold in the two groups. After 6 days of treatment, no significant difference in clinical improvement of acute cough was found between the erdosteine (65 subjects improved out of 70) and placebo groups (62/70), 92.5% and 88.6%, respectively (P =0.382).

Conclusion Erdosteine was not more effective than the placebo for treatment of acute cough in children with common cold. **[Paediatr Indones. 2011;51:111-5]**.

Keywords: *common cold, cough, erdosteine, children*

The common cold is a self-limiting acute, upper respiratory tract infection often with flu-like symptoms including acute cough, and usually caused by viruses (50% by rhinovirus).[1] Acute coughing lasts less than 2 weeks and is usually present in 30% of common cold cases.[2] Children suffer from the common cold an average of 6-8 times per year and coughing is a frequent complaint by parents who take their child to visit the doctor.[3,4] In Indonesia, 40-60% of patients in primary health centers and 15-30% of outpatients visit doctors due to the common cold, which makes it one of the most common health complaints. In Yogyakarta, the prevalence of the common cold in children below 5 years of age is 59.4% a year (Indonesian Health Ministry, 2004).

Both in vitro and in vivo experiments have shown that erdosteine increases mucociliary clearance, acts as an antioxidant and prevents bacterial adhesion. [5-9] One study reported that in 158 children aged 2-12 years old with acute lower respiratory tract infection, acute cough symptoms improved in 46.8%

From the Department of Child Health, Gadjah Mada University Medical School, Yogyakarta, Indonesia.

Reprint request to: Yenny, MD, Department of Child Health, Gadjah Mada University Medical School, Jalan Kesehatan No.1, Yogyakarta 55281, Indonesia. Tel. +62-274-560300, Fax+62-274-583745, E-mail: *hu.yenny@yahoo.com*

of the erdosteine group by the 5th day of therapy, compared to 33.4% in the placebo group.[10] Another study of 100 children aged 2-5 years with acute lower respiratory tract infection showed statistically significant improvement in symptoms in 59.8% in the erdosteine group after 7 days of the therapy compared to 36.6% in the placebo group (P=0.01).[11]

Erdosteine is widely prescribed by physicians. However, there is little data on its effectiveness in acute upper respiratory tract infections, especially common colds in children. Therefore, this study aims to assess the effectiveness of erdosteine on clinical improvement of acute cough symptoms in children <5 years old with the common cold in Indonesia.

Methods

We performed a randomized, double-blind, controlled trial in the Public Health Center (PHC) of Gedongtengen, Yogyakarta from August 1, 2007 until April 30, 2008. We included children aged 12-60 months with common cold ≤5 days, with total cough score ≥2 (**Table 1**), good nutritional state, and who did not receive mucolytics, expectorants, antitussives, antihistamines or corticosteroid therapy before the study enrollment. We excluded those with acute otitis media, heart disease, cough preceded by choking, lower respiratory tract symptoms (tachypnea, dyspnea, rhonchi, wheezing, stridor, crepitation, asymmetric breathing sounds, or chest wall retractions), and family/patient history of asthma, allergic rhinitis, urticaria and food/drug allergies.

Subjects fulfilling the criteria were computer randomized into 2 groups after determining the sample size. Subjects received either erdosteine (8 mg/kg/day) or placebo dry syrup in 2 divided doses daily for 6 days. If the subject vomited within 0.5 hour of taking the syrup, another dose was given. Erdosteine and placebo preparations were stable up to 7 days and similar in package, flavor and color.

Disease duration was measured starting from the first day of cough and/or cold until the first day of therapy at PHC. Mild fever was defined as a temperature of <39°C both before and during the study. Risk factors were defined as a history of common cold exposure at home or school within the past week and subjects' exposure to exogenous stimulants such as cigarette smoke or mosquito repellant during the study. Additional therapy of paracetamol at a dosage of 10mg/kg every 6 hours was given for 3 days if the subject had fever. School was defined as children's enrollment status in kindergarten. Mother's education is shown as the level completed.

Common cold was diagnosed in children using the 2006 AAP Guidelines that define the condition as having cough and cold with fluid and clear secretions or mucopurulent discharge for less than 10 days, with or without mild fever (<39°C), good general condition and no abnormalities on chest examination.[12] Acute cough was defined as a cough lasting for 14 days with total clinical cough score ≥2. Cough score improvement was defined as a decrease in the total clinical cough score, while no improvement was a persistence or increase in the total cough score (**Table 1**).

Patient compliance to treatment and adverse drug effects were taken as secondary outcomes. Adverse drug effects were defined as the unexpected effects related to the drug during the treatment. Drug compliance was defined as fulfilling the drug administration schedule and no missed dosages during the entire treatment course. Compliance was checked at PHC when patients returned for control visits with the bottles to see if >85% of the drugs had been taken by the patients. Dropout was defined as the parents' refusal to continue the study, inability to reestablish contact with parents, or the child's condition worsening and requiring hospitalization.

A physician at PHC was trained to select subjects diagnosed with the common cold who met the inclusion criteria through history taking and physical examination. The kappa value was 0.78 for agreement between researcher and PHC physician. A trained nurse at PHC filled research forms, explained to parents how to fill the drug compliance forms, and set the follow-up appointment. A trained pharmacy assis-

Table 1. Cough clinical score

Secretions	Sleep at night
0. Cough without mucous	0. Good
1. Cough with mucous	1. Awaken once due to cough
2. Cough till vomit	2. Awaken > once due to cough
	3. Child cannot sleep due to cough

tant gave either erdosteine or placebo according to the randomized list along with other drugs prescribed by the doctor. All participants, parents, physician, nurse, and pharmacy assistant were blinded to the content of the research drugs.

Patients were examined on the day of enrollment and the 6th day of treatment, using the same clinical cough scoring scale. Secondary outcomes were also evaluated, including drug side effects and dropping out of the therapy regimen.

The Ethics Committee of Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia approved this study. Informed consent was obatained from parents.

Effectiveness of the erdosteine compared to placebo was predicted to be 25%, based on data obtained from previous studies on acute cough.[10,11] By taking an alpha=0.05 and estimating a 10% patient loss, sample size was calculated as 140 with 80% power. Data was presented in tabulation form with means and standard deviations. Numerical data was then grouped into categories and converted to percentages. Chi square test was used to assess differences between erdosteine and placebo in acute cough improvement. Multivariate logistic regression was used to assess and identify other factors influencing cough improvement. Subjects who dropped out or were lost on follow up were included, since this was an intention to treat analysis. We used a confidence interval of 95% and performed doubled data entry and statistical analysis with Stata 9.0.

Results

Out of 808 patients who visited PHC, 140 subjects were enrolled our study. All subjects divided into two groups of 70 each, the treatment group and the placebo group. One participant in the placebo group dropped out because they were unable to be contacted (**Figure 1**). We did an intention to treat analysis and therefore included subject who dropped out.

Demographic characteristics of participants are shown in **Table 2**. There were no significant differences in subjects' age, weight, gender, duration of the disease, initial cough score, mothers' education, history of smoke exposure, history of common cold exposure, fever, or drug compliance between the treatment and placebo groups. Before treatment, cough severity of total score 2-3 was not significantly different between the treatment (94.3%) and placebo (95.7%) groups (P=0.713).

On the 6th day of follow-up, no significant difference in clinical improvement of cough symptoms between the two groups was observed. In the erdosteine group, 92.9% improved and in the placebo group, 88.6% improved (P=0.382) (**Table 3**). During the course of treatment, no side effects were reported except by one participant in the erdosteine group who suffered from vomiting but did not require hospitalization.

Table 2. Characteristics of subjects.

Characteristic	Erdosteine n=70	Placebo n=70
Age (months)		
12 – 35, n (%)	36 (51.4)	36 (52.2)
36 - 60	34 (48.6)	34 (47.8)
Weight (kg)		
10-12, n (%)	33 (47.1)	36 (52.2)
13-15	20 (28.6)	18 (26.1)
16-19	17 (24.3)	16 (21.7)
Illness duration, days, n (%)		
1-3	57 (81.4)	57 (82.6)
4-5	13 (18.6)	13 (17.4)
Gender, n (%)		
Boys	37 (52.9)	38 (55.1)
Girls	33 (47.1)	32 (44.9)
Initial cough score, n (%)		
2-3	66 (94.3)	66 (95.7)
4-5	4 (5.7)	4 (4.3)
Mother's education, n (%)		
Primary school	10 (14.3)	7 (10.1)
Junior high school	27 (38.6)	38 (55.1)
Senior high school	28 (40.0)	22 (31.9)
College	5 (7.1)	3 (2.9)
School, n(%)		
Yes	40 (57.1)	53 (76.8)
No	30 (42.9)	17 (23.2)
Smoke exposure, n (%)		
Yes	48 (68.6)	54 (78.3)
No	22 (31.4)	16 (21.7)
Common cold exposure, n (%)		
Yes	37 (52.9)	39 (56.5)
No	33 (47.1)	31 (43.5)
Fever, n (%)		
Yes	25 (35.7)	31 (44.9)
No	45 (64.3)	39 (55.1)
Compliance, n (%)		
Yes	59 (84.3)	57 (82.6)
No	11 (15.7)	13 (17.4)

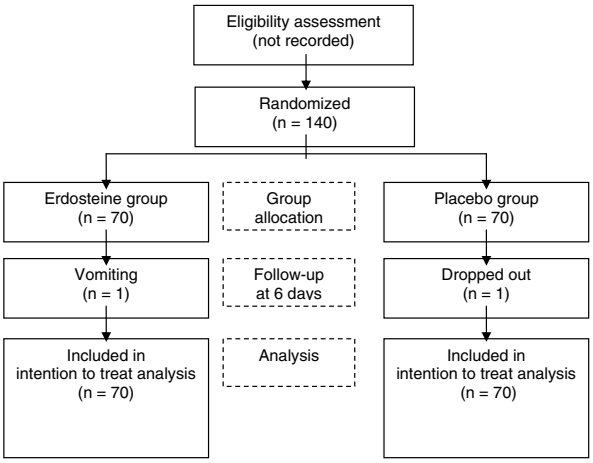

Figure 1. Consort diagram

Table 3. Improvement of acute cough symptoms.

	Erdosteine n = 70	Placebo n = 70	P
Cough score improvement			
Yes, n (%)	65 (92.9)	62 (88.6)	0.382*
No, n (%)	5 (7.1)	8 (11.4)	
Side effects			
Yes, n (%)	1(1.4)	-	0.319*
No, n (%)	69(98.6)	69 (100)	

* X2 = significant if P value < 0.05

Table 4. Multivariate logistic regression analysis for other factors that may influence the improvement of the acute cough symptoms.

Factors	P	RR	95% CI
Good drug compliance	0.790	1.020	0.880-1.183
Illness duration (1-3 days)	0.856	0.986	0.844-1.152
Initial cough score (2-3)	0.713	0.986	0.913-1.064
School (Yes)[19]	0.013	0.744	0.585-1.946
Smoke exposure (Yes)	0.196	0.876	0.716-1.072

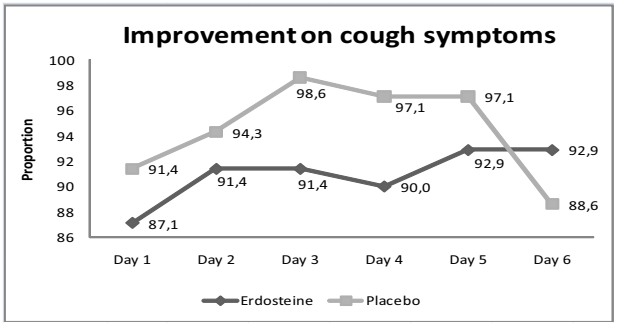

Figure 2. Improvement of cough over 6 days with no significant difference (P = 0,382) in percentage of subjects between erdosteine and placebo group.

In our study, there was a significant difference among children that attended kindergarten between the two groups (P=0.013). However, after multivariate regression analysis, we found that children attending kindergarten did not strongly correlate to treatment between the groups (**Table 4**).

By the 3rd day of treatment, there was improvement in symptoms in the erdosteine group (91.4%) and in the placebo group (98.6%), however they were not significantly different. (**Figure 2**)

Discussion

Our findings differed from those of two previous studies by Titti et al.[10], and Balli et al.[11] One explanation could be that their studies were on subjects with acute lower respiratory tract infections, which are more likely to be caused by bacteria. For their purposes, erdosteine was prescribed along with antibiotics. The anti-adhesive effect of erdosteine prevents bacterial adhesion to the respiratory tract and synergizes with the antibiotic effects, influencing outcomes.[13] Another difference is in the nature of cough receptors in the upper and lower respiratory tracts. The upper tract is mechanosensitive, while lower tract is chemosensitive.[14] In vitro studies showed no correlation between concentrations of nitrite oxide and IL-8 and nasal secretions of common cold patients, while IL-8 levels significantly increased in symptomatic patients.[15,16] Erdosteine significantly reduced the production of tumor necrosis factor-α (TNF-α) and interleukin-1β,6 (IL-1β,6) in alveolar macrophages.[17,18]

Children under five years of age who attended school or kindergarten have been shown to have a 50% higher chance of having a common cold compared to those staying at home.[19] We found a significant difference among children attending kindergarten between the erdosteine and placebo groups.

Systematic review studies show that cough medicine is not recommended as first-line therapy for acute cough in children.[20-22] When used, patients require routine monitoring and the drug must be discontinued if no improvement occurs within the expected time period.[23] Clinicians need to explain the appropriate use of cough medicines to parents and encourage them to bring their children back if coughing does not subside to look for possible alternative causes.

A limitation of this study was that there was some subjectivity to the quantitative scoring of cough severity. Total cough scores were measured at home by parents and there was no kappa test for agreement between parents and doctors in assessing coughs.

In conclusion, we observed that erdosteine had no effect on clinical improvement of cough symptoms in upper respiratory tract illnesses compared to the placebo. This study may form the basis for future research.

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