

The use of 4.5% hypertonic saline challenge test in diagnosing asthma in children with chronic recurrent cough

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ABSTRACT

Background The 4.5% hypertonic saline (HS) challenge test has several benefits compared to histamine challenge test as gold standard. Saline is an inexpensive non-pharmacological substance which is relatively safe. Its mechanism in inducing bronchospasm resembles that of asthma. Moreover, it can easily be made in a modest medical laboratory.

Objective To determine the ability of 4.5% HS challenge test compared to histamine challenge test in diagnosing asthma in children with chronic recurrent cough (CRC).

Methods This study was a diagnostic test on children with CRC aged 6 to 14 years, conducted in outpatient clinic of Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta. All subjects underwent lung function tests. Subjects whose FEV₁ was <80% were diagnosed as asthmatic and underwent the 4.5% HS challenge test only. Those whose FEV₁ was 80% underwent the histamine challenge test followed by the 4.5% HS challenge test one or two weeks later. Test results were expressed as positive or negative. Based on the results, we calculated the sensitivity, specificity, predictive values, and likelihood ratios of the 4.5% HS challenge test.

Results Forty-five subjects, consisting of 22 boys and 23 girls, were enrolled. The average age of subjects was 9 years old. Atopic history in the family or in subjects themselves was found in 80% of subjects. Eight subjects had FEV₁ of <80%. Forty-four subjects were diagnosed with asthma based on a baseline FEV₁ of <80% or a positive histamine provocation test. Thirty-seven subjects had a positive 4.5% HS challenge test; all had asthma. Sensitivity and specificity of the 4.5% HS challenge test were 84.1% and 100.0%, respectively; the positive and negative predictive values were 100.0% and 12.5%, respectively. The positive likelihood ratio was infinite and negative likelihood ratio was 0.16.

Conclusion The 4.5% hypertonic saline challenge test can be used as an alternative bronchial provocation test in diagnosing asthma in children with CRC. Further study with larger sample size is needed for widespread usage. [Paediatr Indones 2005;45:93-98].

Keywords: 4.5% hypertonic saline challenge test, bronchial provocation test, asthma, chronic recurrent cough

For the last 15 years, 4.5% hypertonic saline (4.5% HS) has been used for bronchial challenge tests in many countries.¹⁻⁶ This substance is inexpensive, easily formulated, and can be made in a simple medical laboratory.^{2,7} Previous studies showed that 4.5% HS challenge test had a specificity of 92-100% and a sensitivity of 47-67% when used to diagnose asthma.^{3,4,6} Currently, histamine and metacholine are gold standard substances for bronchial challenge tests. However, histamine is difficult to obtain in Indonesia because it is expensive and must be imported.⁷⁻⁹ The sensitivity and specificity of histamine challenge test have been reported to be 92-100% and 92-93%, respectively.^{4,10,11} It has been suggested that 4.5% HS challenge test is a more specific method for diagnosing asthma because its basic mechanism involves initial inflammation followed by contraction of bronchial smooth muscle cells,^{2,12,13} whereas histamine attaches immediately to bronchial smooth muscle receptors.^{1,14-16}

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Furthermore, 4.5% HS is a more natural, non-pharmacologic substance, making it preferable to and possibly safer than histamine.²

The prevalence of asthma in children with chronic recurrent cough (CRC) is quite high; approximately 40 to 60%.¹⁷⁻²⁰ The purpose of bronchial provocation testing on CRC patients is to reconfirm the diagnosis of asthma rather than to screen the patients, since most CRC patients who came to the hospital had already been treated before. Therefore, we need a challenge test which can establish the diagnosis of asthma in these patients. This study aimed to determine the accuracy of 4.5% HS challenge test in diagnosing asthma in children with CRC.

Methods

We reviewed children aged 6 to 14 years with CRC who visited the outpatient clinic of the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta. The study was conducted from October 2003 to March 2004. We included children suffering from CRC who were cooperative and had been drug-free for 3 days before the examination. Children were excluded if they were having asthma attacks (baseline value of FEV₁ <65%), were unable to perform lung function tests, had FEV₁ differing for more than 5-10% in two subsequent measurements, were clinically suspected of cardiovascular disorders/anomalies, or had pulmonary congenital anomaly, chronic pulmonary disease, gastroesophageal reflux, or focal lesions in the lungs. Chronic recurrent cough was defined as cough persisting for more than 3 weeks or recurring more than 3 times in 3 consecutive months. Subjects were recruited on a voluntary basis. Written informed consent was obtained from the subjects' parents. The study protocol had been approved by the Medical Research Ethics Committee of the Medical School, University of Indonesia.

On the first visit, lung function tests were conducted to determine the baseline value of FEV₁. If FEV₁ was <80%, subjects were provoked with 4.5% HS only. If FEV₁ was =80%, histamine provocation test was performed, followed by 4.5% HS challenge test one to two weeks later. Lung function tests and provocation tests were performed by the same examiner.

The 4.5% HS provocation test was conducted

according to the method set by Riedler.⁵ Provocation time was increased gradually from 0.5 minutes to 1, 2, 4, and 8 minutes. The cut-off point for a positive provocation test was 8 minutes.⁵ The 4.5% HS challenge test was considered positive if FEV₁ decreased 15% from the baseline (PD₁₅) after the dose had been given for up to 8 minutes. The test was considered negative if after 8 minutes of provocation FEV₁ decreased <15% from the baseline.

Histamine provocation test was conducted based on the Cockcroft method.¹⁰ Histamine was given with increasing concentrations, starting from 0.125 and increased to 0.25, 0.5, 1, 2, 4, up to 8 mg/dl. The cut-off point for a positive test was 8 mg/dl. The test was considered positive if FEV₁ decreased 15% from the baseline (PC₁₅) at a concentration of up to 8 mg/dl and negative if the decrease in FEV₁ was <15% at a concentration of >8mg/dl. The FEV₁ measurement was repeated each time the dosage or provocation time of histamine or 4.5% HS was increased. Provocation was stopped when FEV₁ dropped below 15% of the baseline value. When this happened, the patient was given a β₂-agonist. After β₂-agonist inhalation, FEV₁ measurement was repeated. The subject was released when FEV₁ had returned to normal.

The results of hypertonic saline challenge test were compared to the presence or absence of asthma according to baseline FEV₁ value (if baseline FEV₁ was <80%) or histamine provocation test (if baseline FEV₁ was 80%). The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of the 4.5% HS challenge test were calculated using a 2x2 table. Data were processed using SPSS 11.0 for Windows.

Results

Forty-five subjects were enrolled in the study, consisting of 22 boys and 23 girls. The subjects' age ranged from 6 to 14 years, with an average of 9 years. Thirty-seven subjects (82%) had baseline FEV₁ of ≥80% (**Table 1**). FEV₁ varied from 67.4% to 137% with an average of 93.2%. Eight subjects were not provoked with histamine because baseline value of FEV₁ was <80%. Fifty-one percent of subjects had atopic history themselves and 76% had atopic history in the family. In 80% of subjects, atopic history was

TABLE 1. SUBJECT CHARACTERISTICS

Characteristic	Number	%
Sex		
Male	22	49
Female	23	51
Age		
6 to 12 years	42	93
13 to 14 years	3	7
Baseline value of FEV1		
<80%	8	18
≥80%	37	82
Atopic history		
In subject	23	51
In family	34	76
In subject and/or family	36	80
None	9	20

found both in the family and in subjects themselves.

Based on operational terms, 44 subjects had asthma, comprising of 8 patients with FEV₁ of <80% and 36 patients with positive histamine provocation test. Some had accompanying diseases such as sinusitis and pulmonary tuberculosis (Table 2).

Out of 37 subjects on whom the histamine provo-

TABLE 2. DISTRIBUTION OF SUBJECTS BASED ON DIAGNOSIS

Diagnosis	Number	%
Asthma	44	98
Non-asthma	1	3
Other		
Sinusitis	20	44
Pulmonary tuberculosis	2	4

cation test was conducted, 36 were positive and 1 was negative. Twenty-nine subjects (81%) had PC₁₅ of <0.5 mg/ml, 4 (11%) had PC₁₅ of 0.5-2 mg/ml, and 3 (8%) had PC₁₅ of 2-8 mg/ml. The 2x2 table constructed from the test results is shown in Table 3.

Based on these results, the sensitivity and specificity of the 4.5% HS challenge test were 84% and 100%, respectively. For the prevalence obtained among our subjects, the positive and negative predictive values were 100% and 13%, respectively. The

positive likelihood ratio was infinite and the negative likelihood ratio was 0.16.

Discussion

The ratio between male and female children with CRC was nearly equal, while the prevalence of asthma in pre-pubertal males tends to be higher than in females. In this study, the ratio between males and females were close to equal (1:1.1), with the number of females slightly higher than males. This outcome was compatible with a study by Wright, which reported that CRC was equally prevalent in males as in females.^{17,21}

The mean age of subjects was 9 years old (range 6 to 14 years). In our study, subjects aged 6 to 12 years (93%) largely outnumbered those aged 13 to 14 years (7%). This finding showed that the closer a subject gets to puberty, the less CRC and asthma occur, in line with the increase of FEV₁ which reaches its peak at the age of 14 years.²² Wright also stated that CRC prevalence increases until the age of 6 years and decreases at the age of 11 years.¹⁷

The majority of subjects in this study (78%) had a baseline FEV₁ value of ≥80%. Baseline FEV₁ above 80% indicates good lung function, and in asthmatic patients it is considered as infrequent episodic asthma. Most of the subjects (80%) had atopic history in the family and/or in themselves. This result highlights the importance of atopic history in asthma. A study by Clough found that the presence of atopic history was closely related to low FEV₁ values, increased bronchial hyperresponsiveness, FEV₁ variability, and severity of respiratory symptoms.²³

Forty-four (98%) patients with CRC in this study were diagnosed with asthma. This proportion was higher than that obtained by studies of Gunadi¹⁹ and Rahajoe,²⁰ which found the asthma prevalence among CRC patients ranging between 62.5% and 64.5%. In

TABLE 3. COMPARISON OF 4.5% HS CHALLENGE TEST RESULTS TO THE DIAGNOSIS OF ASTHMA.

		Asthma		Totals
		Present	Absent	
4.5% HS challenge test	Positive	37	0	37
	Negative	7	1	8
	Totals	44	1	45

both studies, the diagnosis of asthma was based on clinical examination only, which may account for this difference.

The prevalence of sinusitis in asthmatic children was quite high. Several theories have attempted to clarify this occurrence. One postulated that the bronchus becomes more reactive due to the existence of postnasal drip or due to the effect of inflammatory mediator stimulation reaching the nasal passageway, causing the bronchus to tighten. Erwin *et al*²⁴ found that obstruction of the upper nasal passageway occurred when sinusitis was left untreated. After medication, obstruction of the upper nasal passageways will disappear. In this study, it turned out that 20 (63%) of 32 asthma patients had sinusitis based on sinus X-ray. This prevalence was possibly higher if the sinus photo was taken for all patients.

We found the sensitivity and specificity of the 4.5% HS challenge test to be 84.8% and 100%, respectively. This is in accordance with results found in previous studies; the specificity of the test has always been found to be higher than the sensitivity. Araki⁴ found that the test's specificity was 100%, while its sensitivity was 58%. The lower sensitivity value in Araki's study was due to the use of control subjects, which resulted in less positive test results. Moreover, the majority of subjects in Araki's study were mildly asthmatic patients with FEV₁ values only slightly below 80%.⁴ In our study, there were 8 patients with FEV₁ values below 70%, with a range of 67.4 to 79.8%.

In both Araki's and our study the specificity was 100%. All control subjects in Araki's study had a negative result.⁴ In our study, patients with CRC who had negative results in both the histamine provocation test and 4.5% HS challenge test were finally diagnosed with lung tuberculosis and sinusitis. Another study by Supriyatno⁷ found the sensitivity and specificity of 4.5% HS challenge test to be 86.7% and 85.7%, respectively.

Epidemiological studies to evaluate the reliability of the 4.5% HS challenge test in diagnosing asthma had been carried out by Riedler⁵ and Liz.⁶ Both studies were conducted in children of 13 to 15 years old with wheezing in the past 12 months and compared them with control subjects. Riedler's study reported sensitivity and specificity values of 47% and 92%, respectively, while Liz's reported these to be 44% and

90%, respectively.^{5,6} Liz also found that when the test was performed on subjects who had been clinically diagnosed with asthma by doctors, the sensitivity increased to 67%, while the specificity remained constant.⁶

The higher specificity of the 4.5% HS challenge test when compared to sensitivity may be caused by the work mechanism of the 4.5% HS solution, which activates inflammatory mediators first and creates bronchial contractions later. This is in line with the basis of asthma pathophysiology, which is inflammation.^{12,13} In normal subjects inflammation does not occur, thus producing a negative challenge test. A study by Smith concluded that, being a more specific than sensitive test, the 4.5% HS provocation test may result in a high number of false negatives.²⁵

In our study, out of 44 patients with positive histamine provocation test, 7 had negative 4.5% HS challenge test. Five out of seven patients with histamine PC₁₅ values of 0.25 to 2 mg/dl (bronchial hyperresponsiveness) had atopic history in the family; some had a history of wheezing. These five patients were clinically categorized as having mild asthma, with asthma attacks occurring less than once a month and FEV₁ of >80%. This was in accordance with findings by Smith, which showed that patients with mild asthma may have negative 4.5% HS challenge test results.²⁵ Of the subjects with histamine PC₁₅ close to the cut-off point of 8 mg/dl, 2 were ultimately diagnosed with pulmonary tuberculosis.

Positive and negative predictive values are heavily affected by the prevalence of the disease. A hospital-based study would result in higher positive and negative predictive values compared to an epidemiological, population-based study.^{4,7} In our study, the positive predictive value was 100%, compatible with findings by Araki.⁴ In contrast, in his epidemiological study Liz⁶ found a positive predictive value of only 28%. The negative predictive value in our study was only 12.5%.

The positive likelihood ratio found in this study was infinite, indicating that a positive 4.5% HS provocation test was found far more frequently in those with asthma than in those without. The negative likelihood ratio of 0.16 indicated that false negatives do occur, albeit at a low rate.

We conclude that the 4.5% hypertonic saline

challenge test is a sufficient method for diagnosing asthma in children with CRC. This test can be used as an alternative to the histamine provocation. However, further study with large sample size will be needed for widespread usage of this test.

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