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ORIGINAL ARTICLE

Methacholine challenge test by wheezing and oxygen saturation in preschool children with asthma

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Abstract Methacholine challenge test (MCT) performed with spirometry is a commonly used test to evaluate bronchial hyperreactivity (BHR) in children. However, preschoolers do not usually collaborate.

Objectives: To assess the usefulness of MCT through clinical evaluation (wheezing auscultation and decreased pulse arterial oxygen saturation [SpO2]) in recurrent wheezing preschoolers with asthma, in comparison to healthy controls.

Methods: We performed the MCT (modified Cockroft method) on healthy and on asthmatic preschoolers. The end point was determined by the presence of wheezing in the chest and/or tracheal auscultation (PCw) and/or a decrease in SpO2 of $\geq$5 from the baseline value (PCSpO2). Maximal methacholine concentration was 8 mg/ml.

Results: The study population comprised 65 children: 32 healthy and 33 asthmatic children. There were no differences in demographic characteristics between the groups. The median methacholine doses for PCw and for PCSpO2 were significantly lower among asthmatic than healthy children: 0.5 mg/ml (0.25–0.5 mg/ml) vs. 2 mg/ml (1–4 mg/ml), respectively, $p < 0.001$; and 0.25 mg/ml (0.25–0.5 mg/ml) and 2 mg/ml (0.5–4 mg/ml), respectively, $p < 0.001$. The best cut-off point of PCw was observed at a methacholine concentration of 0.5 mg/ml (AUC = 0.72 [95% CI = 0.66–0.77]), its sensitivity was 91%, specificity 43%, PPV 16% and NPV 98%. For PCSpO2 the best cut-off point was a methacholine concentration of 1 mg/ml (AUC = 0.85 [95% CI 0.81–0.89]), with sensitivity of 80%, specificity 74%, PPV 49%, and NPV 92%. There were no adverse reactions.

Conclusion: MCT using clinical parameters such as wheezing auscultation and SpO2 measurement could be a useful and safe test to confirm BHR among preschoolers.

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Introduction

Asthma is the most prevalent chronic disease among children and in the vast majority of cases it starts at preschool age.[1,2] However, it continues to be a difficult disorder to diagnose in preschoolers. This is partly because clinical symptoms of asthma are variable and non-specific, given that other wheezing disorders exist.[3,4] Diagnosis and management of asthma in recurrent wheezing preschoolers are still primarily based on subjective clinical features and findings from medical examinations (atopic manifestations, parental asthma, or response to controller therapy [e.g. inhaled corticosteroids]).[3,4]

On the other hand, bronchial hyperreactivity (BHR) is a traditional hallmark of asthma. Its presence is a good predictor of severity, morbidity, and decline of lung function among asthmatic children.[5,6] Due to its high sensitivity, methacholine challenge test (MCT) performed with spirometry is one of the most common tests for measuring BHR in schoolchildren and adolescents.[7] Nevertheless, since preschoolers usually collaborate poorly in performing acceptable and reproducible serial spirometry manoeuvres, methacholine challenge tests with measurements that require little cooperation, e.g. impulse oscillometry, interrupter technique, and simpler clinical methods such as wheezing auscultation and pulse oximetry saturation [SpO2], have been developed.[8–12]

The aim of this study was to assess the usefulness and safety of a clinical method for measuring methacholine bronchial hyperresponsiveness through wheezing auscultation, decreased pulse arterial oxygen saturation [SpO2] and respiratory rate [RR] in recurrently wheezing preschoolers with asthma and healthy controls. The second aim was to establish methacholine concentration at which a significant airway response occurs.

Methods

This study was carried out at the Pontificia Universidad Catolica de Chile, Santiago, Chile. We prospectively enrolled preschool children related to university employees, outpatients of the paediatric clinic, and children recruited from kindergartens in Santiago. The children were classified as asthmatics or healthy (control group). Asthmatics were included in the study if they had had three or more wheezing episodes in the last 12 months and if they had shown a clinical response to bronchodilator and to controller drugs (e.g. inhaled corticosteroids [ICS] or leukotriene inhibitors).[13] They were classified by their severity, according to guidelines, as having intermittent, mild or moderate persistent asthma.[14] None of the children had a personal history of prematurity, neonatal lung disease, pneumonia, lung resection, central airway obstructive disease or other cardiopulmonary chronic diseases.

The MCT was performed in our paediatric lung function laboratory during the summer of 2008–2010. Neither asthmatic nor healthy children had had any upper or lower respiratory symptoms for at least three weeks prior to the study, nor active rhinitis symptoms. Asthmatics had been free of controller drugs ICS and leukotriene inhibitors for at least one month prior to the study, anti-histamines for at least one week, and short acting bronchodilators for at least 8 h. Children were seated with one parent in a non-stressful environment. The MCT was performed using the 2-min tidal breathing method developed by Cockroft et al.[12,15] with doubling doses of methacholine solutions from 0.06 to 8 mg/ml dissolved in saline. The children were previously nebulised with saline to establish control values. We used a nebuliser and a facemask (Pari Star®, Midlothian, USA). Sixty seconds after the end of each nebulisation, two independent observers (SC and RB or RR) simultaneously determined the respiratory rate for 1 min, observed SpO2 in the monitor, and auscultated the presence of wheezing (over the trachea, and upper front and lower back of the thorax), asking the child to breathe deeper than tidal volume. SpO2 was monitored with a pulse oximeter (Masimo Rad 9®, Masimo Corporation, Irvine, CA, USA). Nebulisations were carried out every 5 min until a maximum of 8 mg/ml of methacholine; nebulisers were calibrated following ATS recommendations,[15] with an output of 0.13 ml/min ±10%.

The endpoint of MCT was set with the concentration of methacholine that determined one or more of the following events: presence of wheezing at auscultation (PC_w), and/or decrease of ≥5 from control SpO2 for at least 10 s (PC_{SpO2}) and/or increase in RR ≥50% from control RR (PC_{RR}). If more than one event was present, i.e. presence of PC_w and PC_{SpO2}, we called it $PC_{w\text{-}SpO2}$. Once the test was completed, children were nebulised with 0.25 mg of ipratropium bromide + 0.5 mg fenoterol bromide (Berodual®, Boehringer Ingelheim, Rhein, Germany) with oxygen flow of 6 l/min for 10 min. The MCT was stopped and considered a failure if the child was uncooperative (cried, hyperventilated, spoke during nebulisation or removed the facemask) or if adverse effects appeared (tearing, nasal symptoms, headache) or if parents requested the test to be stopped.

All parents signed informed consent forms to authorise the participation of their children in the study. The Ethics Committee of the Medical Research Center of the School of Medicine of the Pontificia Universidad Catolica de Chile approved the study (CE #0016/08).

Statistical analysis

To calculate the sample size, we used a previous study[16] in which we found a median of PC_w among asthmatic preschoolers of 0.25 mg/ml (0.06–4 mg/ml) and 1 mg/ml (0.5–8 mg/ml) among healthy children. Therefore, to find significant differences between the two groups we needed at least 10 children in each group (with 80% power and 95% of significance level). We used the Student *t*-test for comparative analysis of the general characteristics of the groups. PC_w and PC_{SpO2} were not normally distributed. Their results were expressed as median and interquartile range. We also obtained their logarithmic values (not shown). Mann–Whitney and/or Kruskal–Wallis test was used to compare the median of methacholine concentrations between the groups. A ROC curve analysis was performed to determine the cut-off points of wheezing auscultation and SpO2 fall. We calculated the AUC (area under curve). Sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) with their 95% CI for PC_w and PC_{SpO2} were additionally calculated. Two-tailed p values of ≤0.05 were considered significant.