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Original Article

Use of exhaled nitric oxide in children with bronchial asthma

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ABSTRACT

Background: Inflammation is an important aspect of the pathophysiology of bronchial asthma and measurement of inflammatory markers of airways can aid in management. Nitric oxide measurement in exhaled breath is a non-invasive method of determining airway inflammation which can be used in assessing severity and response to treatment in children with bronchial asthma.

Methods: Thirty children in the age group 6–14 years with previously or newly diagnosed bronchial asthma reporting for the first time to a tertiary care hospital constituted the study group. Assessment was done by history, clinical examination, spirometry and measurement of fractional excretion of nitric oxide (FeNO) before commencement of treatment as per standard guidelines and on follow up at 2 to 4 weeks intervals for a minimum of three times. **Results:** There was significant correlation between FeNO values, spirometry parameters and clinical profile in the first visit before the initiation of therapy. Children with higher FeNO in the first visit responded better to Inhaled Corticosteroids (ICS) with good clinical and spirometry responses and fall in FeNO on second visit. However, in subsequent visits no significant correlation was observed between clinical control, FeNO levels and spirometry. **Conclusion:** High FeNO values at first presentation could give us a clue as to whether or not a child would respond to ICS but FeNO monitoring may not be helpful in long term follow up as various other factors can affect its value.

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Introduction

Inflammation plays an important role in the pathophysiology of asthma. Various non-invasive markers of inflammation have been studied in asthma including nitric oxide. Nitric oxide (NO)

was discovered in the exhaled air of humans in 1991 by Gustafsson.¹ It is involved in vascular and bronchial dilatation, ciliary beat frequency, mucus secretion and non-adrenergic, non-cholinergic neurotransmission.^{2–4} Studies conducted on the relation between Fractional excretion of Nitric oxide (FeNO) values and eosinophilic airway inflammation have shown a

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significant association between the two.^{5–7} We conducted a study to determine the relation of Fractional FeNO with level of control of asthma in children.

Materials and methods

An observational follow-up study was conducted on children between the ages of 6–14 years with previously or newly diagnosed bronchial asthma who reported to the Asthma Clinic of the Paediatric Outpatient Department of a tertiary care hospital. Inclusion criteria were the confirmed diagnosis of bronchial asthma. These children were on inhaled bronchodilators but were never exposed to inhaled steroids before commencement of study. Children with poor prospects of follow up, those with any other known acute or chronic inflammatory condition and those who could not perform spirometry and FeNO analysis were excluded. Thirty consecutive children who fulfilled the inclusion criteria were enrolled over a period of two years.

Physical examination included anthropometric measurements and general and systemic examination was performed at first visit. Children were clinically categorized as controlled or uncontrolled depending on symptoms and clinical findings. All children underwent spirometry with Compact Spirometer (MIR – Medical International Research, REF-spirolabII, 125–00155). Forced Expiratory Volume in first second (FEV₁) and Forced Vital Capacity (FVC) were recorded. These parameters were read as normal or abnormal when compared to predicted values for height and age as per the recommendations of the American Thoracic Society. Airway obstruction was diagnosed when FEV₁/VC $\leq$ 0.70 and/or FEV₁ < 80%. FeNO was measured with Niox Mino, a hand-held device of Swedish company Aerocrine AB.

Individual disposable test kits available from the same company were used. A FeNO value above 20 ppb was considered high as per standard guidelines.⁸

Children were categorized and treated as per Global Initiative for Asthma (GINA) guidelines 2009. Depending on the clinical response of the child, they were categorized as controlled and uncontrolled asthma and given inhaled corticosteroid (ICS) treatment accordingly. Inhaled corticosteroid used was Fluticasone and Long Acting Beta Agonist used was Salmeterol in recommended doses. Metered Dose Inhaler containing combination of these two drugs were used. The medication was delivered either through spacer and mask, only spacer or rotahaler depending on the age and comfort of the child. The treatment was continued for three to six months. Inhalation/nebulisation with Salbutamol was done during exacerbations of asthma.

Three follow up visits were scheduled at intervals of two to four weeks. At each visit, children were assessed by clinical response, spirometry and FeNO.

Results

In our study on thirty children with bronchial asthma (21 boys and 9 girls) the mean age was 9.63 years. Table 1 shows the FeNO levels during the study. The FeNO levels were significantly

higher in the children with uncontrolled asthma at onset and first follow up (second visit) but did not achieve statistical significance during the third and fourth visits.

Comparisons between FeNO, FEV₁ and FEV₁/FVC during each visit. Table 2 showed that no significant correlation could be deduced between spirometry and FeNO levels.

Discussion

Bronchial asthma is a chronic inflammatory condition which leads to airway limitation. Exhaled nitric oxide is a non-invasive inflammatory marker. It has been implicated in the pathophysiology of lung diseases, including asthma. The measurement of exhaled NO has recently been made available for clinical use. We measured the FeNO levels in children of age group 6–14 years with asthma before starting inhaled steroids and on follow-up. We observed a wide range of FeNO values from less than 5 ppb–178 ppb. A FeNO value of 20 ppb and above has been considered to be evidence of airway inflammation as per American Thoracic Society guidelines.⁸

There was significant difference in the FeNO levels with the clinical severity of asthma before initiating ICS therapy. Children with uncontrolled asthma had higher FeNO values in the first and second visits. Similar observation was made by Smith et al.⁹ This suggests that high FeNO at first visit predicts the need for ICS. However on follow up during subsequent visits, there were no significant relation between FeNO, clinical improvement and spirometry. The reason for this could be the heterogeneity of the children. It could also be due to undetected noncompliance or faulty inhaler technique. Other factors like airway viral infection, allergic rhinitis and nitrate rich food can influence FeNO levels. Our study suggests that FeNO level cannot be used to measure response to treatment as well as to titrate the dose of ICS and other antiasthma medications in children on long term follow up. Similar observations were made by Szefer et al who observed in 780 children that the addition of fraction of exhaled NO as an indicator of control of asthma resulted in higher doses of inhaled corticosteroids (ICS), without clinically important improvements in symptomatic asthma control.¹⁰ A meta-analysis performed by Jartti et al on the controlled studies of childhood asthma management guided by repeated FeNO

Table 1 – Control of asthma and FeNO levels at first follow-up visit.

	Number	Normal FeNO	High FeNO	P value
1 st visit				
Controlled	4	4	0	<0.05
Uncontrolled	26	8	18	
2 nd visit				
Controlled	10	8	2	<0.05
Uncontrolled	20	8	12	
3 rd visit				
Controlled	5	4	1	NS
Uncontrolled	25	11	14	
4 th visit				
Controlled	7	5	2	NS
Uncontrolled	23	11	12	

Table 2 – Correlation between FeNO, FEV1 and FEV1/FVC during study.

Parameter	N	Mean	SD	CI	Pearson correlation	P value
FENO 1 (ppb)	30	31.50	24.84	15.96–33.74	1	NS
FEV1%	30	81.73	12.04	7.74–16.36	0.054	
FEV1/FVC	30	87.06	8.90	5.72–12.10	–0.175	
FENO 2	30	23.40	17.20	11.05–23.36	1	NS
FEV1%	30	82.98	13.17	8.46–17.90	0.077	
FEV1/FVC	30	88.88	8.10	5.21–11.01	–0.259	
FENO 3	30	28.23	22.43	14.41–30.46	1	NS
FEV1%	30	82.13	12.75	8.19–17.31	0.139	
FEV1/FVC	30	87.40	8.90	5.72–12.10	–0.159	
FENO 4	30	25.17	21.05	13.52–28.58	1	NS
FEV1%	30	82.47	12.26	7.88–16.66	–0.011	
FEV1/FVC	30	88.80	7.20	4.63–9.79	–0.167	

measurements suggest that utilising FeNO to tailor the dose of ICS in children cannot be recommended for routine clinical practice since there is a danger of excessive inhaled corticosteroid doses in children without meaningful changes in clinical outcomes.¹¹ In a study by Malby et al on one hundred ninety-six, 6-year-old children with no asthma symptoms, intermittent asthma symptoms, and persistent asthma there was significant correlation between FeNO values and bronchial hyperresponsiveness whether the child had symptoms of asthma or not.¹² These findings suggest that caution should be exercised while using surrogate markers for the diagnosis of asthma.

In conclusion, our study suggests that in a child with clinical features suggestive of chronic persistent asthma, a high FeNO in the first visit will confirm the diagnosis and may be useful as an indicator for ICS. However it cannot be used effectively for follow-up decisions.

Conflicts of interest

All authors have none to declare.

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REFERENCES

- Gustafsson LE, Leone AM, Persson MG, et al. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. *Biochem Biophys Res Commun.* 1991;181:852–857.
- Jain B, Rubinstein I, Robbins RA, et al. Modulation of airway epithelial cell ciliary beat frequency by nitric oxide. *Biochem Biophys Res Commun.* 1993;191:83–88.
- Ialenti A, Iannaro A, Monaco S, et al. Modulation of acute inflammation by endogenous nitric oxide. *Eur J Pharmacol.* 1992;211:177–182.
- Belvisi MG, Stretton CD, Yacoub M, et al. Nitric oxide is the endogenous neurotransmitter of bronchodilator nerves in humans. *Eur J Pharmacol.* 1992;210:221–222.
- Gratziau C, Lignos M, Dassiou M, et al. Influence of atopy on exhaled nitric oxide in patients with stable asthma and rhinitis. *Eur Respir J.* 1999;14:897–901.
- Berlyne GS, Parameswaran K, Kamada D, et al. A comparison of exhaled nitric oxide and induced sputum as markers of airway inflammation. *J Allergy Clin Immunol.* 2000; 106:638–644.
- Payne DN, Adcock IM, Wilson NM, et al. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. *Am J Respir Crit Care Med.* 2001;164:1376–1381.
- Dweik RA, Boggs PB, Erzurum SC, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med.* 2011;184:602–615.
- Smith AD, Cowan JO, Brassett KP, et al. Exhaled nitric oxide: a predictor of steroid response. *Am J Respir Crit Care Med.* 2005;172:453–459.
- Szeffler SJ, Mitchell H, Sorkness CA, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults: a randomised controlled trial. *Lancet.* 2008 Sep 20;372:1065–1072.
- Jartti T, Wendelin-Saarenhovi M, Heinonen I, et al. Childhood asthma management guided by repeated FeNO measurements: a meta-analysis. *Paediatr Respir Rev.* 2012 Sep;13:178–183.
- Malby Schoos AM, Chawens BL, Bonnelykke K, et al. Fraction of exhaled nitric oxide and bronchial responsiveness are associated and continuous traits in young children independent of asthma. *Chest.* 2012 Dec;142:1562–1568.