Original Article

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Role of Fractional Exhaled Nitric Oxide for Monitoring Bronchial Asthma

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ABSTRACT

Background: Monitoring during treatment of asthma is usually done by various clinical tools, spirometry, sputum eosinophils and fractional exhaled nitric oxide. Fractional exhaled nitric oxide is a simple and noninvasive tool and has a good agreement with asthma control test score. This study aims to correlate fractional exhaled nitric oxide with asthma control test score.

Methods: This cross-sectional study was conducted at National Academy of Medical Sciences, Bir hospital, Chest unit, Department of Medicine, over a duration of six months. Patients aged more than 18 years with bronchial asthma diagnosed at least three months prior were included into the study. Those with recent severe exacerbations, known other chronic respiratory disease and smokers were excluded. Asthma control test score was obtained at baseline. All included patients underwent fractional exhaled nitric oxide measurement followed by measurement of Forced vital capacity(FVC) Forced expiratory volume in one second (FEV1) and FEV1/FVC ratio.

Results: Forty patients with a mean age of 40.5±11.1 years were included in the study. Majority were females (65%) and the median duration of symptoms was 24 months (Interquartile range= 18-60). Mean fractional exhaled nitric oxide level was 27.8 (±16.0) parts per billion (ppb) and asthma control test score was 19.3 (±4.7). Mean fractional exhaled nitric oxide levels were significantly different across different severity (well controlled, partially controlled and poorly controlled) of asthma (p=0.013). The mean fractional exhaled nitric oxide values and total asthma control test score shows statistically significant negative correlation (Pearson correlation coefficient (r) = -0.462, p=0.003). Asthma control test and FeNO values guided the change of inhaled steroid dose in 17 of the 40 patients.

Conclusion: Fractional exhaled nitric oxide can be used when available, along with asthma control test for monitoring control and adjusting the inhaled steroid dose in asthma.

Keywords: Asthma control test (ACT); bronchial asthma; Fractional exhaled nitric oxide (FeNO).

INRODUCTION

Bronchial asthma is a heterogeneous disease with chronic airway inflammation.[1] Treatment monitoring is usually done by various clinical scores like asthma control test (ACT), asthma control questionnaires(ACQ) and Global initiative for asthma (GINA) scores and objective measurements like spirometry, sputum eosinophils and Fractional exhaled nitric oxide (FeNO) test. ACT is the most used clinical score, which is simple and self-administered by the patients.[2] FeNO is biomarker of eosinophilic airway inflammation and is simple and noninvasive.[3] Studies have shown a good agreement between FeNO and ACT score, and both are reliable for assessment of disease severity, response to treatment, and compliance.[4,5]

FeNO test was introduced recently in our country and is available only at few centers. Only a few studies[6,7] have evaluated the utility of this important tool in our population. These studies have compared FeNO levels in healthy volunteers with those in COPD and well controlled asthma. The correlation of FeNO levels with various levels of asthma control is not studied in our population. This study aims to assess the relationship between FeNO levels and level of asthma control as measured by ACT score.

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METHODS

This cross-sectional study was conducted at Chest unit, Department of Medicine, National Academy of Medical Sciences, Bir hospital between June 2023 and November 2023. Ethical clearance was obtained from Institutional Review Board, NAMS (Ref no 584, approved on 2023/5/11 AD). All patients presenting to chest clinic with a diagnosis of bronchial asthma were screened. Those aged more than 18 years and diagnosed with asthma at least 3 months prior and on regular treatment with inhaled corticosteroids were included into the study. Patients hospitalized for asthma exacerbation during prior four weeks, with known other respiratory disorder, not adhering to their treatment for more than 2 weeks within 3 months and current smokers were excluded.The relevant history, examination findings and investigations were recorded. Inhaler technique was assessed in all patients. Appropriateness was assessed by the researcher using standard inhaler device assessment tools.[8] The asthma control level was determined according to ACT score. Sample size calculation was done as follows:[9]

Total sample size=N= $[(Z\alpha + Z\beta)/C]^2+3$

With α (two-tailed) =0.05 (Type I error rate), β =0.10 (Type II error rate), C =0.5*ln [(1+r)/(1−r)] and correlation coefficient of r=-0.68, sample size was calculated. Previous correlation coefficient found in asthmatic patients after inhaled steroid in study done in India was r= − 0.68.[5] A minimum required sample size calculated was 18. We chose to include 40 patients for the study.

ACT score was calculated using the standard five questions, with four weeks recall, assessing the frequency of shortness of breath, frequency of night-time symptoms, degree of functional limitation, frequency of using rescuers, and patient's self-assessment of their level of asthma control. Each item has five responses scored as 1–5. Asthma control test questionnaires were translated to native Nepali language by a translator, who was an expert in both Nepali and English language. ACT was self-administered by the patients. For those who could not read and write, the researcher facilitated in completing the questionnaires. After obtaining the total ACT scores, patients were categorized as follows: well controlled (scores 20–25), partially controlled (scores 15–19), and poorly controlled (scores <15).[10]

FeNO was measured by a Vivatmo pro© (manufactured in Germany) according to the American Thoracic Society(ATS)/European Respiratory Society (ERS) recommendations. Single-breath online measurement with a flow rate of 50 mL/s was performed and patients were guided by flow indicator during the test.[11] At least two FeNO measurements were done in each patient, with 30 seconds of relaxed tidal breathing in between. Two FeNO values that agreed within 10% of each other (if FeNO > 10ppbor within 1 ppb (if FeNO <10 ppb) were recorded. The mean of these two values were calculated.

Spirometry was performed after the FeNO test using the Easy on PC© (Ndd medical technologies, Switzerland) according to the ATS/ERS recommendation 2019.[12] FVC, FEV1 and FEV1/FVC ratio were measured.

Informed consent was taken from participants fulfilling inclusion criteria prior to enrolment into the study. The data were collected using structured performa and serial code number provided to participants to maintain anonymity of patients. The collected data were tabulated, and statistically analyzed using statistical package for the social sciences (SPSS-25). Descriptive statistics were analysed as frequency, percentage, mean, and median. Independent sample t- test was used to compare means of FeNO across subgroups of asthma patients. One-way anova test was used to compare mean FeNO values across different levels of asthma control. Correlation between FeNO and ACT score was analyzed using Pearson's correlation coefficient. P value < 0.05 was considered statistically significant.

RESULTS

A total of 102 patients were screened during the study period. Sixty-two patients were excluded due to various reasons as shown in figure 1. Non-compliance to inhalers was the most common cause of exclusion. Forty patients eligible for the study underwent ACT test, FeNO and spirometry (Figure 1).

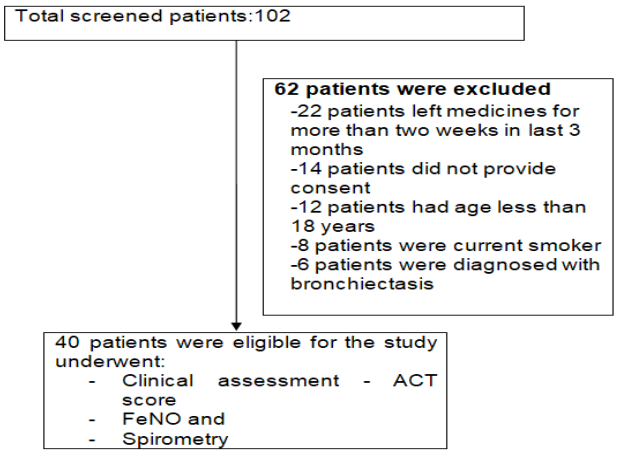

Figure 1. Screening and selection of patients in the study.

The mean age of the study participants was 40.5 (±11.1) years; 26 (65%) were females. The median duration of symptoms was 24 (18-60) months. The mean FeNO level was 27.8 (±16.0) ppb, and the mean ACT score was 19.3 (±4.7). Inhaler technique was appropriate in 25 (62.5%) patients. The baseline characteristics including the demographics, comorbidities and type of inhaler device use in the study population are presented below (Table 1).

Table 1. Baseline characteristics of the study participants.

Characteristics	Data (n=40)
Mean age in years	40.5 (± 11.1)
Gender	
Male	14 (35.0%)
Female	26 (65.0%)
Median duration of symptoms in months	24 (18-60)
Family history of asthma	15 (37.5%)
Co-morbidities	
Rhinosinusitis	15 (37.5%)
Gastroesophageal reflux disease	17 (42.5%)
Obesity	3 (7.5%)
Mean FeNO (ppb) level	27.8 (± 16.0)
Mean ACT score	19.3(± 4.7)
Level of asthma control by ACT	
Well controlled	24(60.0%)
Partially controlled	9(22.5%)
Poorly controlled	7(17.5%)
Mean FeNO values(ppb) across different control level	p=0.013
Well controlled	21.9(±10.1)
Partially controlled	36.5(±15.1)
Poorly controlled	37.0(±24.9)
Type of inhaler device	
Dry powdered inhaler	36 (90.0%)
Metered dose inhaler	3 (7.5%)
Metered dose inhaler with spacer	1 (2.5%)
Inhaler technique	
Appropriate	25(62.5%)
Inappropriate	15(37.5%)

Data are presented as number (percentage), mean (±standard deviation), median (IQR).Abbreviations: ACT=Asthma Control Test, ppb=parts per billion

The mean FeNO values in well controlled, partially controlled and poorly controlled asthma are shown in table 1. The overall between group difference of mean FeNO values were statistically significant (p value= 0.013). While comparing the three groups with each other, statistically significant difference was found between well controlled vs. partially controlled (p=0.046) asthma, but not between partially controlled vs. poorly controlled (p=1.0) and well controlled vs.poorly controlled (p=0.064) asthma as depicted in Figure 2. Subgroup analysis of mean FeNO values was done to assess for various factors which might alter the correlation between ACT score and FeNO values. Mean FeNO values were significantly higher inpatients aged <40 years than aged >40 years (32.8±17.9 ppb versus 22.3±11.8 ppb, p=0.036) FeNO values were not significantly different based on gender, duration of symptoms, presence of GERD, obesity, and inhaler technique.(Table 2)

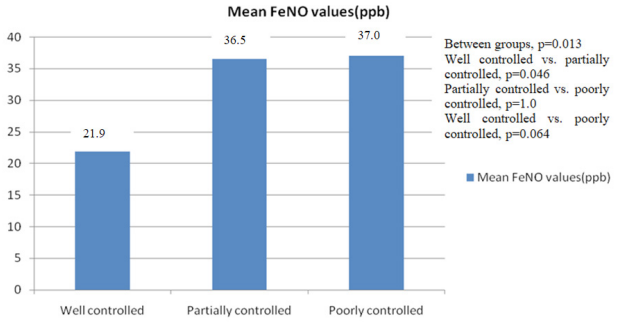

Figure 2. Mean FeNO values vs asthma severity.

Table 2. Mean FeNO values compared in different subgroups of patients.

Characteristics, categories	Mean FeNO(ppb)	p value
Age		
<40 years	32.8(±17.9)	0.036
>40 years	22.3(±11.8)	
Gender		
Male	29.6 (±13.2)	0.606
Female	26.8(±17.5)	
Duration of symptoms		
<3 years	25.2(±13.9)	0.193
>3 years	32.1(±18.7)	
Family history of asthma		

Table 2. Mean FeNO values compared in different subgroups of patients.

Characteristics, categories	Mean FeNO(ppb)	p value
Yes	31.4 (±19.1)	0.286
No	25.7(±13.8)	
Rhinosinusitis		
Yes	35.6(±18.9)	0.016
No	23.2(±12.2)	
GERD		
Yes	26.8(±18.9)	0.655
No	29.2(±11.5)	
Obesity		
Yes	33.6(±15.8)	0.522
No	27.3(±21.5)	
Inhaler technique		
Appropriate	25.3(±13.2)	0.196
Inappropriate	32.1(±19.6)	

Characteristics are presented as mean (± standard deviation).

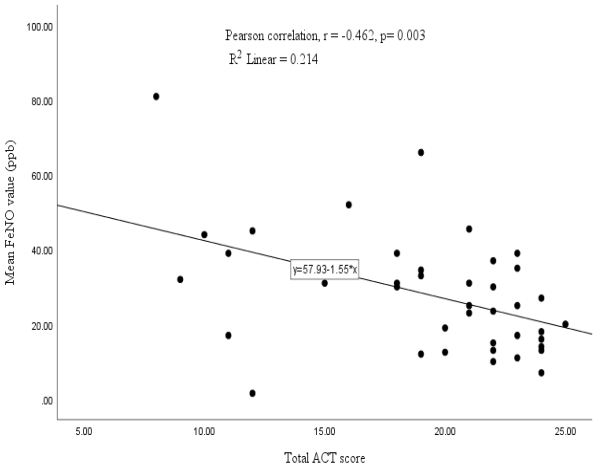

Figure 3.Correlation between mean FeNO values and total ACT score.

The mean FeNO values and total ACT score shows statistically significant negative correlation (Pearson correlation coefficient (r) = -0.462, p=0.003) (Figure 3). FeNO level guided either dose escalation of inhaled steroid or correction of inhaler technique in 29 of the 40 patients. Inhaler technique correction was required in 15 patients and dose of inhaled steroid was increased in 17 patients. FeNO was concordant in nine (52.9%) patients with ACT in whom inhaled steroid dose was increased. FeNO values did not have a significant correlation with percentage predicted FEV_1 (Pearson correlation, r=-0.244, p=0.130) or percentage predicted FVC (Pearson correlation, r=-0.184, p=0.255) which is presented below(Table 3).

Table 3. Correlation of FeNO with percentage predicted FEV1, percentage predicted FVC and ACT.

Parameters	Percentage predicted FEV1	Percentage predicted FVC	ACT
FeNO			
Pearson's r	-0.244	-0.184	-0.462
p value	0.130	0.255	**0.003**
N	40	40	40

DISCUSSION

The burden of asthma is high in low- and middle-income countries like Nepal along with a high mortality rate.[13] The prevalence of asthma is higher in women. Females are more likely to have severe disease and frequent exacerbations.[14] Gastroesophageal reflux was present in 42.5% and recurrent rhinosinusitis in 37.5% patients in our study. Family history of asthma was present in more than a third of our patients. The prevalence of GERD and allergic rhinitis in asthma have been shown to be 59.2% and 33.0% respectively in previous studies.[15,16] Although rhinitis and GERD symptoms might decrease ACT score, they do not enhance eosinophilic airway inflammation and FeNO.[17]Among asthma patients with allergic rhinitis, perennial sensitization has been shown to have higher FeNO levels than seasonal allergens in a cross sectional study by Kalpakliogluz and Kalkan.[18] The FeNO values were similar across subgroups of gender, duration of symptoms, inhaler technique. Comorbid conditions like GERD or obesity also did not affect the FeNO levels. However, the mean FeNO levels were higher in patients aged less than 40 years and those with rhinosinusitis in our study.

The mean FeNO level in well controlled asthma in this study is 21.9±10.1 ppb. According to the ATS-ERS classification, FeNO levels are less than 25 ppb in well controlled asthma.[11] In a study from India by Kavitha et.al. [5], the median FeNO value in well controlled asthma was 25.5 ppb (IQR = 8-131 ppb). The median FeNO values for partly controlled and poorly controlled asthma were 35 ppb and 40 ppb respectively in the same study. The mean FeNO value in clinically controlled asthma was found to be 31.0 ppb in a study by Shrestha et.al[7] from Nepal, which is higher than observed in our study.

This study enrolled only patients with well controlled symptoms irrespective of compliance to treatment. Our patients were different as we included patients with all levels of asthma control and those compliant to inhaler medicines. A good compliance to inhaled corticosteroids tends to lower the eosinophilic airway inflammation and hence the FeNO levels.[19] Inhaler technique might have an effect on asthma control. However, in our study, inhaler technique was not associated with significant difference in mean FeNO values.

In our study, the FeNO levels were significantly lower in well controlled compared to partially controlled asthma. However, the difference was less marked when well controlled and poorly controlled asthma were compared. This might have occurred due to a small sample size leading to under-representation of the poorly controlled patients.This study found a negative correlation of the ACT score with FeNO levels. The results are similar to a cross sectional study done by Nguyen and Chavannes from Vietnam.[4] In a study from India by Katoch et.al.[20], although a negative correlation between the two was evident, the level of statistical significance was not reached. The variable results may be due to inclusion of multiple phenotypes of asthma in these studies. A study on FeNO levels and ACT based on asthma phenotype may provide further insights into the relationship between the two. FeNO levels did not correlate on FEV1 or FVC in our study.

FeNO levels can be used to monitor treatment of asthma and identify refractory disease and non compliance to inhaled corticosteroid. In our study, 17 patients required steroid dose adjustments when both FeNO and ACT score were used. Hence we can conclude that measurement of FeNO is valuable to assess control. In combination with ACT score, FeNO test can identify patients with uncontrolled asthma who require treatment escalation. Similar findings were evident in an observational, single-centre study by LaForce et.al.[21],which showed that the physician's assessment of airway inflammation was incorrect in 50% of patients without FeNO measurement and FeNO measurement substantially altered the treatment decisions in 36% of patients. There is also a good negative agreement between the ACT and FeNO levels in our study akin to other studies. [22]

In Nepal, only a few studies[6,7] have evaluated FeNO levels in asthma patients. Our study compared the two most important determinants of asthma control - FeNO levels and ACT score. The strength of this study is that we have included patients with known asthma, compliant to treatment and excluded those with other respiratory disorders. In patients who are non-compliant or have an inappropriate inhaler technique, ensuring the compliance and correction of inhaler technique is desired first. Only after ensuring this, escalation of inhaled corticosteroids should be done. Combined use of ACT score and FeNO values can be used for this purpose. We have used a plain Nepali language translation of the standard ACT questionnaire in our study, which has not been validated in a prospective cohort. This is one of the limitations of our study. Other limitations include interviewer bias in patients who could not read or write and uneven distribution of patients in well controlled, partially controlled and poorly controlled asthma categories based on ACT score due to small sample size. To determine the role of FeNO in these subgroups of Nepalese patients with asthma, future studies need to evaluate FeNO levels in partially and poorly controlled patients with a larger sample size.

CONCLUSION

In patients with asthma having good compliance to treatment, there is a significant negative correlation between FeNO levels and ACT score. FeNO can be used when available, along with ACT for monitoring control and adjusting the inhaled corticosteroid dose in asthma.

CONFLICT OF INTEREST

None

REFERENCES

1. Bochner BS, Undem BJ, Lichtenstein LM. Immunological aspects of allergic asthma. Annu Rev Immunol. 1994;12:295-335.[PubMed]

2. Alzahrani YA, Becker EA. Asthma Control Assessment Tools. Respir Care. 2016 Jan;61(1):106-16.[PubMed]

3. Ricciardolo FLM, Sorbello V, Ciprandi G. A pathophysiological approach for FeNO: A biomarker for asthma. Allergol Immunopathol (Madr). 2015;43(6):609-16. [PubMed]

4. Nguyen VN, Chavannes NH. Correlation between fractional exhaled nitric oxide and Asthma Control Test score and spirometry parameters in on-treatment- asthmatics in Ho Chi Minh City. J Thorac Dis. 2020 May;12(5):2197-209. [PubMed]

5. Kavitha V, Mohan A, Madan K, Hadda V, Khilnani GC, Guleria R. Fractional exhaled nitric oxide is a useful adjunctive modality for monitoring bronchial

asthma. Lung India Off Organ Indian Chest Soc. 2017;34(2):132–7. doi: 10.4103/0970-2113.201322. [PMC5351354]

6. Shrestha SK, Drews A, Sharma L, Pant S, Shrestha S, Neopane A. Relationship between total serum immunoglobulin E levels, fractional exhaled breath nitric oxide levels and absolute blood eosinophil counts in atopic and non-atopic asthma: a controlled comparative study. J Breath Res. 2018 Feb 20;12(2):026009. doi: 10.1088/1752-7163/aa95da. [PubMed]

7. Shrestha SK, Shrestha S, Sharma L, Pant S, Neopane A. Comparison of fractional exhaled nitric oxide levels in chronic obstructive pulmonary disease, bronchial asthma and healthy subjects of Nepal. J Breath Res. 2017 Sep 13;11(4):047101.[PubMed]

8. 5378_1852_IDAT_PedAsthma_User_Guide_FINAL_Nov2006.pdf.[Web Link]

9. Hulley SB, editor. Designing clinical research. 4th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2013. [WebLink]

10. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test:A survey for assessing asthma control. J Allergy Clin Immunol. 2004 Jan;113(1):59–65.[PubMed]

11. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. American Thoracic Society Documents. 2011;184. [PubMed]

12. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019 Oct 15;200(8):e70–88.[PubMed]

13. Ekezie W, Jenkins AR, Hall IP, Evans C, Koju R, Kurmi OP, et al. The burden of chronic respiratory diseases in adults in Nepal: A systematic review. Chron Respir Dis. 2021 Jan 1;18:147997312199457. [PubMed]

14. Pate CA, Zahran HS, Qin X, Johnson C, Hummelman E, Malilay J. Asthma Surveillance - United States, 2006-2018. Morb Mortal Wkly Rep Surveill Summ Wash DC 2002. 2021 Sep 17;70(5):1–32. doi: 10.15585/mmwr.ss7005a1

15. Grandes XA, Talanki Manjunatha R, Habib S, Sangaraju SL, Yepez D. Gastroesophageal Reflux Disease and Asthma: A Narrative Review. Cureus. 2022 May;14(5):e24917. [PubMed]

16. Alrasheedi SM, Alkhalifah KM, Alnasyan S, Alwattban RR, Alsubhi RA, Alsamani RI, et al. The Prevalence and Impact of Allergic Rhinitis on Asthma Exacerbations in Asthmatic Adult Patients in the Qassim Region of Saudi Arabia: A Cross-Sectional Study. Cureus. 2023 Sep;15(9):e44997.[PMC10565072]

17. Ishizuka T, Hisada T, Kamide Y, Aoki H, Seki K, Honjo C, et al. The effects of concomitant GERD, dyspepsia, and rhinosinusitis on asthma symptoms and FeNO in asthmatic patients taking controller medications. J Asthma Allergy. 2014 Sep;131. doi: 10.2147/JAA.S67062

18. Kalpakliogluz AF, Kalkan IK. Comparison of Orally Exhaled Nitric Oxide in Allergic versus Nonallergic Rhinitis. Am J Rhinol Allergy. 2012 Mar;26(2):e50–4. [PubMed]

19. Donohue JF, Jain N. Exhaled nitric oxide to predict corticosteroid responsiveness and reduce asthma exacerbation rates. Respir Med. 2013 Jul;107(7):943–52. [PubMed]

20. Katoch CDS, Vasan AS, Pathak K. Correlation of fraction of exhaled nitric oxide with asthma control test and asthma severity in diagnosed cases of asthma. Med J Armed Forces India. 2022 Oct;78(4):443–7. [PMC9577272]

21. LaForce C, Brooks E, Herje N, Dorinsky P, Rickard K. Impact of exhaled nitric oxide measurements on treatment decisions in an asthma specialty clinic. Ann Allergy Asthma Immunol. 2014 Dec;113(6):619–23.[PubMed]

22. Hanania NA, Massanari M, Jain N. Measurement of fractional exhaled nitric oxide in real-world clinical practice alters asthma treatment decisions. Ann Allergy Asthma Immunol. 2018 Apr;120(4):414-418.e1.[PubMed]