Budget impact analysis of Fractional Exhaled Nitric Oxide Monitoring for the Management of Childhood Asthma: The Colombian National Health System perspective

Short running title: Fractional Exhaled Nitric Oxid for Asthma

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Abstract

Background: Fractional exhaled nitric oxide is a simple, non-invasive measurement of airway inflammation with minimal discomfort with results available within a few minutes. For policymakers, the main concerns is the economic impact implicated in adapting this technology, especially in developing countries. This study to evaluate the budget impact of asthma management using fractional exhaled nitric oxide monitoring in patients between 4 and 18 years of age in Colombia.

Methods: A budget impact analysis was performed to evaluate the potential financial impact deriving from Fractional exhaled nitric oxide. The analysis considered a 5-year time horizon and Colombian National Health System perspective. The incremental budget impact was calculated by subtracting the cost of the new treatment, in which FeNO is reimbursed, from the cost of the conventional treatment without FeNO (management based on clinical symptoms (with or without spirometry/peak flow) or asthma guidelines (or both), for asthma-related). Univariate one-way sensitivity analyses were performed.

Results: In the base-case analysis the 5-year costs associated to FeNO and no-FeNO were estimated to be € 469.904.130 and € 480.485.149 respectively, indicating savings for Colombian National Health equal to € 10.581.019, if FeNO is adopted for the routine management of patients with persistent asthma. This result was robust in univariate sensitivity one-way analysis.

Conclusion: Fractional exhaled nitric oxide was cost-saving in emergency settings for infants with persistent asthma. This evidence can be used by decision-makers in our country to improve clinical practice guidelines and should be replicated to validate their results in other middle-income countries.

Key words: Fractional exhaled nitric oxide, Colombia, Persistent asthma.

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Resumen

Antecedentes: El óxido nítrico en aire exhalado es una medición simple y no invasiva de la inflamación de las vías respiratorias cuyos resultados están disponibles en pocos minutos. Para los responsables de la formulación de políticas sanitarias, la principal preocupación es el impacto económico que implica la adaptación de esta tecnología, muy especialmente en los países en desarrollo. Este estudio tiene como objetivo evaluar el impacto presupuestario, en el sistema Nacional de Salud de Colombia, del manejo del asma mediante la monitorización de óxido nítrico exhalado en pacientes entre 4 y 18 años.

Métodos: Se realizó un análisis de impacto presupuestario para evaluar el posible impacto financiero derivado de la implementación de la monitorización óxido nítrico exhalado fraccionado en el asma. El análisis consideró un horizonte temporal de 5 años y la perspectiva del Sistema Nacional de Salud de Colombia. El impacto presupuestario incremental se calculó restando el costo del nuevo tratamiento, en el que se reembolsa el FeNO, del costo del tratamiento convencional sin FeNO (manejo basado en síntomas clínicos (con o sin espirometría / flujo máximo) o guías de asma (o ambos), para los relacionados con el asma). Se realizaron análisis de sensibilidad univariantes de una vía.

Resultados: En el análisis del caso base, los costos a 5 años asociados a FeNO y no FeNO se estimaron en 469.904.130 € y 480.485.149 € respectivamente, lo que indica un ahorro para la Salud Nacional de Colombia igual a 10.581.019 € si se adopta la monitorización de FeNO, en el manejo rutinario de pacientes con asma persistente. La solidez de este resultado fue confirmada en el análisis de sensibilidad univariante, unidireccional.

Conclusión: El óxido nítrico exhalado fraccionado ahorró costos en los entornos de emergencia en población pediátrica con asma persistente. Esta evidencia puede ser utilizada por los tomadores de decisiones en nuestro país para mejorar las guías de práctica clínica y debe ser replicada para validar sus resultados en otros países de ingresos medios.

Palabras clave: Óxido nítrico exhalado, Colombia, asma persistente.

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Background

The periodic assessment and early management of airway inflammation in patients with asthma are the principal strategies to prevent hospitalizations as recommended by international and local clinical guidelines [1]. The frequent measure of airway inflammation during monitoring plays an important role in anticipating exacerbations and optimizing the use of biological and corticosteroid drugs [2,3].

Fractional exhaled nitric oxide (FeNO) may be a surrogate marker for type 2 airway inflammation [2]. FeNO is a simple, non-invasive measurement of airway inflammation with minimal discomfort to the patient and with results available within a few minutes. FeNO correlates with airway eosinophilia in biopsy and bronchoalveolar lavage fluid [3]. In fact, a meta-analysis of eight clinical trials in children found that FeNO-guided treatment reduced asthma exacerbations [4]. However, the routine use of FeNO in asthma and in children has not been uniformly adopted by all countries, especially by developing countries.

For policymakers, the main concerns is the economic impact implicated in adapting this technology, especially in developing countries. Different economic evaluations of the use of FeNO during asthma management in developed countries have demonstrated that FeNO monitoring to guide asthma management was cost-effective [5-8]. However, cost-effectiveness analyses alone do not provide information on the drug's impact on the total healthcare budget, because this is dependent on the number of treated patients .In this paper, we aimed to evaluate the budget impact of asthma management using fractional exhaled nitric oxide monitoring in patients between 4 and 18 years of age in Colombia.

Methods

Analytical framework

A budget impact analysis was performed to evaluate the potential financial impact deriving from FeNO. The analysis considered the perspective of the Colombian National Health System and was conducted over a 5-years' time horizon. A budget impact model (BIM) was developed as a Microsoft Excel® macro-enabled workbook to evaluate the incremental budget impact of asthma management using fractional exhaled nitric oxide monitoring. The incremental budget impact was calculated by subtracting the cost of the new treatment, in which FeNO is reimbursed, from the cost of the conventional treatment without FeNO (management based on clinical symptoms with or without spirometry/peak flow or asthma guidelines (or both), for asthma-related). During the construction of the economic model, 100% adherence to the FeNO strategy was assumed, as well as the absence of differences in market share between the brands, and a stable incidence of asthma in the time horizon studied, details of these assumptions are provided in **Table 1**.

Base case and estimation of target population

A base- case were children (5 to 18 years of age) , without cardiac or neurological or respiratory or another chronic disease, with a diagnosis of persistent asthma and controller treatment, in whom asthma management using fractional exhaled nitric oxide monitoring is performed [1]. To estimate the size of the target population, we estimate the size of the

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population for the first year , applying data about the total population between 4-18 of age in Colombia[9] , the prevalence of asthma in Colombia in children between 4-18 of age in Colombia [10], the frequency of persistent asthma in Colombia [11] , and proportion of patients with persistent asthma with controller treatment in Colombia [12]. An annual population growth of 1.5% was assumed considering the average national growth rate from the period 2015-2019 [9], **Table 2**.

Intervention

Information regarding the effect of FeNO was extracted from a recent systematic review and metanalysis of 8 randomized clincal trials that evaluate the efficacy of tailoring asthma interventions based on fractional exhaled nitric oxide (FeNO), in comparison to not using FeNO (management based on clinical symptoms (with or without spirometry/peak flow) or asthma guidelines or both, for asthma-related). In this study there was a significant lower asthma exacerbations in the FeNO group in comparison to the control group (odds ratio (OR) 0.62, 95% confidence interval (CI) 0.49 to 0.80; 1279 participants; 8 studies)[4]. We assumed to progressively gain market sales from FeNO In the base-case scenario the uptake rate of FeNO was assumed to be 20%, increasing to 20% each year respectively, according to he estimates of the marketing authorization holder.

Time horizon

The time horizon defined was five years. The maximum follow-up time was set to be four years. A longer perspective was not considered relevant for the budget holder. All results are depicted cumulatively from 1 to 5 years

Resource use and cost

A Markov simulation model with Three mutually exclusive non-absorbent states was used to compare the estimated cost associated with asthma management using fractional exhaled nitric oxide monitoring (FeNO) versus asthma management without using fractional exhaled nitric oxide monitoring (standard therapy). According to the natural history, three health states were defined: “no symptoms or asthma controlled”, “suboptimal control without exacerbation”, and “asthma exacerbation” with a cycle length of 1 week. All patients entering the model were children with no symptoms, diagnosed with mild to moderate allergic asthma, and receiving inhaled corticosteroids as maintenance therapy .The probabilities of model and cost of each health state, we extracted from study previously published of asthma in Colombia [13] . In brief, all costs and use of resources were collected directly from medical invoices and electronic medical records. The direct costs considered in the analysis include medical consultation at the emergency room, specialist referrals, chest physiotherapy, diagnosis support (laboratory, electrocardiogram, x-ray, etc.), medication (oxygen, nebulization, antibiotics, corticosteroids, bronchodilators, etc.), medical devices, accommodation services at intensive care units, and accommodation services in general medical wards (Table3).. We use US dollars (currency rate: € 1.00 = COP$ 4,238) to express all costs in the study [14, 15]. For the valuation of the indirect costs associated with parents’ loss of productivity, the human capital method was used, assuming everyone receives an income of at least legal minimum wage for formal or informal work. The cost-opportunity of the productivity loss at the workplace and the caregiver was assessed based on the minimum wage (Colombian minimum wage per month for 2019: € 204). The government-approved

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legal minimum wage was taken as a reference instead of an average or median wage thereof as over 75% of the Colombian population earns minimum wage [9]. Since all the patients with asthma included in this study were children, we assumed that at least one family member accompanied the patient permanently during hospitalization, since pediatric hospitals in the country usually only allows one companion per patient in the hospital. The cost associated with transportation and food (not including an overnight stay) was assumed to correspond to 50% of minimum wage per day.

Sensitivity analyses

The robustness of the base-case was evaluated with one-way sensitivity analyses. The parameters used and their range used in the one-way sensitivity analyses were detailed in **Table 3**. Expert opinion and literature data were used to determine ranges of parameters to be tested in the sensitivity analysis. Results of the sensitivity analysis are presented in tornado diagram showing the impact on base-case of uncertainty in the parameters used in the model. Threshold analysis of FeNO cost to determinate their threshold value. Microsoft Excel® was used in all analyses.

Results

Base-case Results

In the base-case analysis the 5-year costs associated to FeNO and no-FeNO were estimated to be € 469.904.130 and € 480.485.149 respectively, indicating savings for Colombian National Health equal to € 10.581.019, if FeNO is adopted for the routine management of patients with persistent asthma, **Table 4**. The savings by FeNO increased over the years due to the greater number of patients progressively receiving FeNO, with a final percentage of savings of 4.34%.

Univariate sensitivity one-way analysis was performed to assess the robustness of the results from the base-case. The major parameters used in the analysis were varied once as detailed in Table 2 and 3. Results of the sensitivity analysis are presented in a Tornado diagram showing the potential impact on the base-case results of uncertainty about the main parameters used in the model, **figure 1**. In this figure it can be seen that the three variables that have the greatest influence on the expected cost of FeNO were the cost per patient well controlled, the Relative risk of reduction of exacerbations of FeNO and cost per patient of Fractional exhaled nitric oxide .In the threshold analysis of FeNO cost, their threshold value was €49. An increase in the total cost of FeNO per patient higher than this value per patient, resulted in expected cost per patient in FeNO scenario more elevated than no-FeNO scenario, and in a loss of the savings expected in the population consequently, **figure 2.**

Discussion

Our study suggests that FeNO is cost-saving for treatment of infants with persistent asthma. Compared with the current therapy without FeNO, in a five years analysis, the alternative

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with FeNO provided total cost saving € 10.581.019. This study is the first economic analysis, made in our country, showing the real impact if this therapy will be adopt for the current treatment of patients with persistent asthma. We consider this cost saving as relevant, if we compare it with the budget allocated by our country for communicable diseases. The magnitude of cost savings for health system is not negligible , The total health spending for public health in Colombia ranges from € 432 to € 441 million annually [16]. The savings that FeNO at four year, would correspond to almost 1,2% of this budget, which would be achieved with a single intervention, which is not a negligible value in our country.

Our findings are in-line with previous studies [8]. Adding FeNO to standard asthma care saved € 62.53 per patient-year and improved QALYs by 0.026 per patient-year. The budget impact analysis revealed a potential net yearly saving of €129 million if FeNO monitoring had been used in primary care settings in Spain. Similarly, Harnan et al. assessed the cost-effectiveness of the hand-held electrochemical devices NIOX MINO® (Aerocrine, Solna, Sweden), NIOX VERO® (Aerocrine) and NO breath® (Bedfont Scientific, Maidstone, UK) for the diagnosis and management of asthma [8]. The novo management model indicated that the ICER of guidelines plus FeNO monitoring using NO breath compared with guidelines alone in children is expected to be approximately £45,200 per QALY gained, concluding that FeNO-guided management has the potential to be cost-effective, although this is largely dependent on the duration of the effect.

The latest version of the Global Initiative for Asthma refers to children: “FeNO-guided treatment significantly reduces exacerbation rates compared with guidelines-based treatment (Evidence A). However, further studies are needed to identify the populations most likely to benefit from FeNO-guided treatment and to determine the optimal frequency of FeNO monitoring” [1]. References that support this statement only include RCTs, with no economic evaluations corroborating it. The dynamic between clinical research on effectiveness and the research of efficiency must be coordinated and synchronous in order to make recommendations from the individual to the public health level. The transferability of economic evaluations is clearly complex, but this situation highlights the need to assess health technologies in the clinical guidelines that do not only evaluate effectiveness or safety, but that also review economical topics to increase the level of recommendations in clinical guidelines.

A very important aspect of our model is that it was robust to changing the values of the model's utilities, probabilities, and costs using one-way sensitivity analysis. FeNO was always the cost-effectiveness strategy. A relevant result was to find a drug cost of the FeNO per patient at which this therapy does not cost-saving. This threshold (€49) can be used as a reference for the control and regulation of prices in the country. Show evidence related to the economic impact this drug is essential to policy makers and physician [17] especially in developing countries where economic evaluation of drugs and medical devices in pediatric patients are increasing [18-22].

Our study has some limitations. We used retrospective data reported in a previously cost-effectiveness study, and this information does not exclude the possibility that medical

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invoices were incomplete or missing data. We do not include cost associated with scholar absenteeism and this influences indirect costs in chronic diseases. This study reported that several measures were employed to ensure data accuracy, including software with automatic calculation functions and error alerts and a review of outliers by the research team. Another limitation in the design was to the assumption of complete adherence of this therapy, which can reduce the budget impact of FeNO.

In conclusion, FeNO was cost-saving in emergency settings for infants with persistent asthma. This evidence can be used by decision-makers in our country to improve clinical practice guidelines and should be replicated to validate their results in other middle-income countries.

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of University of Antioquia (2015-4690)

Consent for publication: Not Applicable

Availability of Data and Materials: Jefferson. (2021). BIA FeNO [Data set]. Zenodo. http://doi.org/10.5281/zenodo.4603799

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Conflict of interest:

No conflicts of interest to declare.

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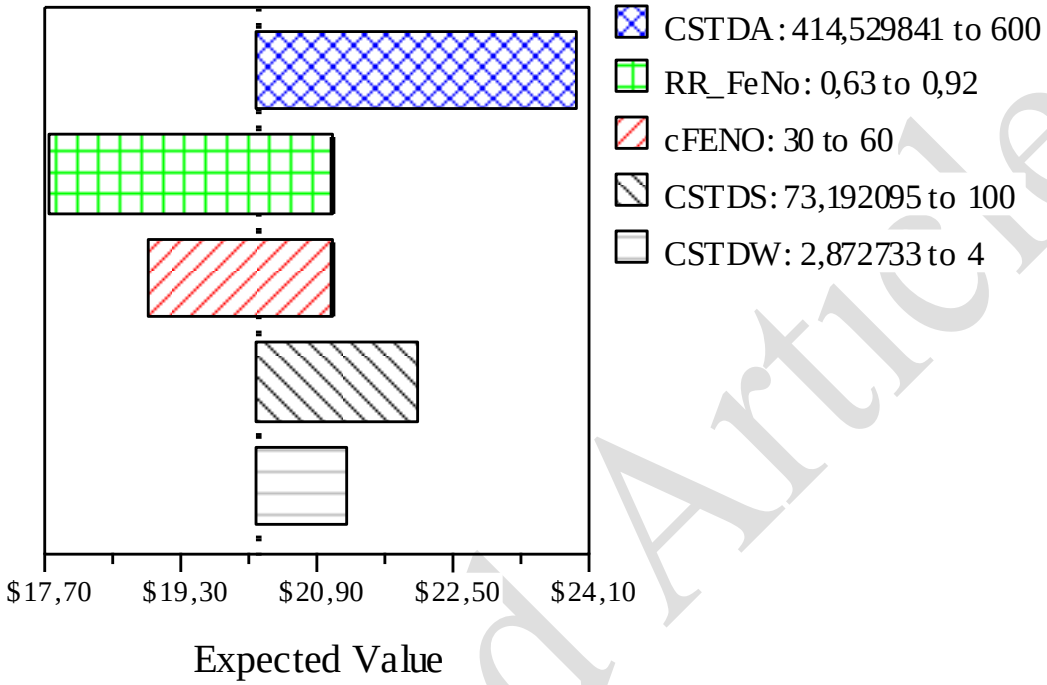
Figure 1. Tornado diagram



CSTDA : Cost per patient well controled

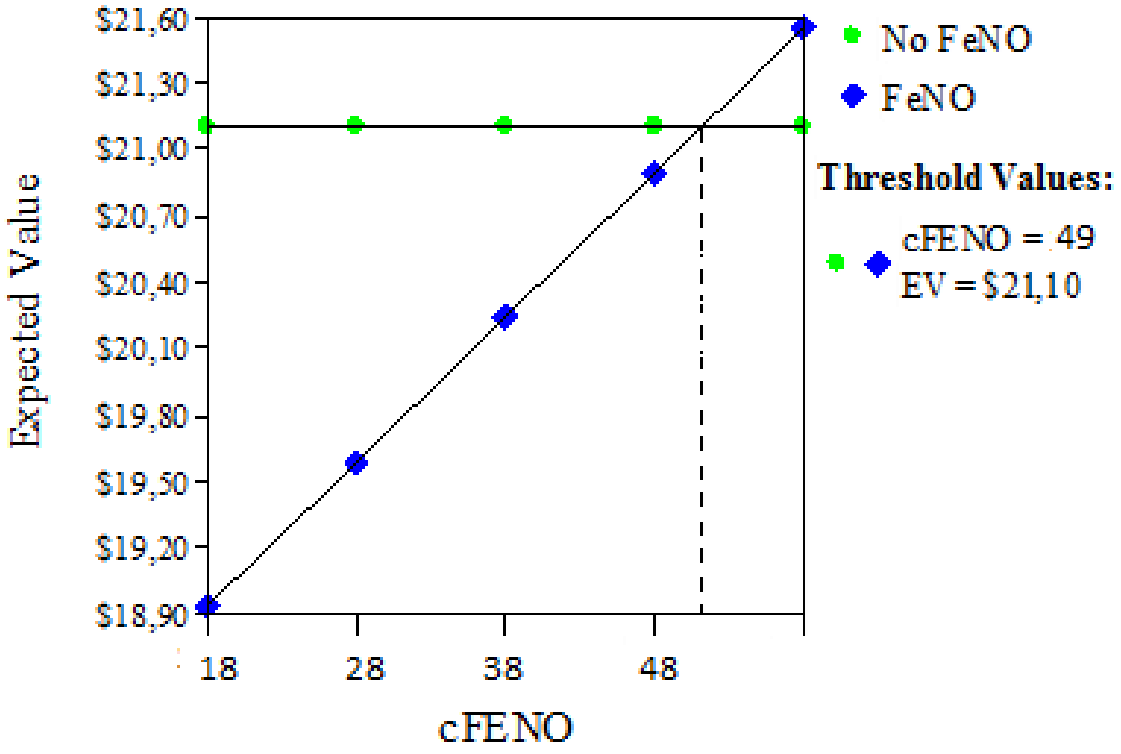
RR_FeNO: Relative risk of reduction of exacerbations of FeNO

cFeNO: Cost of Fractional exhaled nitric oxide

CSTDS: Cost per patient in sub-optimal control

CSTDW: Cost per patient in asthma exacerbation

Figure 2. Threshold analysis of FeNO cost



cFeNO: Cost of Fractional exhaled nitric oxide

Table 1. Assumption used to develop the base case analysis

Assumption	References
The compliance is considered to be 100%	Assumption based on the opinion of clinical experts
All tradebrands during the time horizon have the same market share without price differences between them	Assumption based on the opinion of clinical experts , since this technology is not yet approved in local clinical practice guidelines and no trademark has entered the local market.
The incidence of persistent asthma is stable over the time horizon	Assumption based on the opinion of clinical experts

Table 2. Parameter used in the case base

Type of parameter	Base Case value	Range for one-way sensitivity analyses	Reference
Demographics			
Population between 5-18 years	9.541.341		(9)
Annual population growth	1.5%		(9)
Epidemiology			
Prevalence of asthma	9.2%	5 -12%	(10)
% persistent asthma	53%	20-60%	(11)
% infants with controller treatment	20%	10-30%	(12)
FeNO effectiveness			
Relative risk of reduction of exacerbations	0,76	0,49-0,80	(4)
Market Share			
1 year	20%		
2 year	40%		
3 year	60%		
4 year	80%		
5 year	100%		

Table 3. Cost used in base case and sensitivity analyses

Model input	Base case value	SA range for one-way sensitivity analyses	Distribution
Intervention cost			
FeNO per patient	39.6	4.2-45	γ(SD:1.08)
Hospitalization cost			
Daily cost in pediatric ward	84.5	71.4-90.7	γ(SD:8.53)
Hospital length of stay (days)	5.50	4.00-8.00	γ(SD:1.04)
PICU related cost			
Daily cost in PICU	361	382-311	γ(SD:18,89)
PICU lenght of stay (days)	10.9	7,75-15,05	γ(SD:3,26)
Emergency visit prior hospitalization cost			
Daily cost of emergency ward	59	45.5-63.5	γ(SD:19.27)
Direct medical cost per patient-day			
Specialist referrals	9,5	9,2-9,8	γ(SD:1,72)
Chest physiotherapy	4,6	4,4-4,8	γ(SD:1,23)
Chest radiography	2,5	2,4-2,7	γ(SD:0,73)
Others diagnostic imaging	0,01	0-0,2	γ(SD:0,08)
Complete blood cell counts	1,0	0,96-1,0	γ(SD:0,28)
Other laboratory tests	3,9	3,7-3,9	γ(SD:0,37)
Oxygen	1,2	1,1-1,3	γ(SD:0,41)
Nebulization	14,4	1,1-1,3	γ(SD:4,52)
LEV	1,0	0,9-1,1	γ(SD:0,16)
Antibiotics systemics	1,1	0,9-1,1	γ(SD:0,49)
Systemic o Inhaled Corticosteroids	0,1	0-0,8	γ(SD:4,18)
Bronchodilators	0,03	0,03-0,04	γ(SD:0,02)
Other drugs	0,6	0,6-0,7	γ(SD:0,04)
Medical devices	9,1	8,6-10	γ(SD:2,66)
Indirect cost patient-day	15,3	14-17	γ(SD:4,30)

Table 4. Base case

	Overall num patients	Num patients treated with FeNO	Cost FeNO (€)	Cost No FeNO (€)	Savings (€)	% Savings
Year 1	86979	9220	111.455.654	112.430.562	974.909	0,87%
year 2	93502	19822	118.766.801	120.862.855	2.096.054	1,73%
Year 3	94905	30180	119.484.556	122.675.797	3.191.242	2,60%
Year 4	96328	40843	120.197.120	124.515.934	4.318.814	3,47%
Year 5	97773	51820	120.904.178	126.383.673	5.479.495	4,34%
Total	371714	100065	469.904.130	480.485.149	10.581.018	2,20%