



EXHALED NITRIC OXIDE AS A BIOMARKER OF ASTHMA INFLAMMATION IN EGYPTIAN CHILDREN

Thesis

**Submitted For the Fulfillment of the
Ph.D. Degree in childhood studies**

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2010**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

" رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ الَّتِي أَنْعَمْتَ عَلَيَّ
وَعَلَىٰ وَالِدَيَّ وَأَنْ أَعْمَلَ صَالِحًا تَرْضَاهُ وَأَدْخِلْنِي
بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ "

صدق الله العظيم

سورة النمل آية (١٩)

I dedicate this Thesis to

The spirits of my Father & Mother

My wife

My Lovely Son & Daughter

Acknowledgment

I wish to express my deep gratitude for **Prof. Dr. Gamal Samy Aly** professor of pediatrics, Vice President of Community & Environment Affairs, Ain Shams University, for his enlightening, supervision, continuous care and kind support throughout this work. I had the honor to proceed with him in this work and for his constant guidance, experienced advice and great encouragement that has been of most importance and to whom I will always be indebted.

I am deeply obliged to **Prof. Dr. Tharwat Ezat Deraz** Professor of Pediatrics, Faculty of Medicine, Ain Shams University for his most valuable advice and cooperation and his constant and unlimited help and encouragement all through this work and his tremendous efforts and outstanding experience which greatly helped this work to appear in this way.

I would like to express my deep appreciation and most gratefulness for **Prof. Dr. Ola Mostafa Ibrahim** Professor of Child Health, Child Health Department, National Research Center for her supervision. I had the honor to precede with her this work, for her constant guidance, experienced advice and great encouragement that has been of most importance and to whom I will always be indebted.

I am greatly thankful to **Dr. Naser Mohamed Mostafa** Assistant Professor of Air Pollution, Air Pollution Research Department,

✍ Acknowledgment ✍

National Research Center for his tremendous efforts and outstanding experience which greatly helped me.

Words are few to speak and do fail to express my deepest gratitude to **Dr. Asmaa Al-Husseiny ahmed** Lecturer of pediatrics Faculty of Medicine, Ain Shams University for her continuous attention, follow up and providence of all facilities possible to complete this work. Without her honest assistance and abundant patience, this work would have never come to light.

I wish to express my deep appreciation to **Dr.Ebtissam Mohamed Salah EL-Din** Assistant Professor researcher of Child Health, Child Health Department, National Research Center for her kind efforts and continuous supervision.

I do appreciate the kind and active participation of **Dr. Alia Abd El-Shakour** Professor of Air Pollution, Air Pollution Research Department, National Research Center in the laboratory part of this work.

I sincerely acknowledge the help and encouragement from every member of pediatrics chest clinic, Children Hospital, Ain Shams University, members of the Child Health Department, National Research Center and members of the Air Pollution Research Department, National Research Center. I truly admire the services they provide to their patients

✍ Acknowledgment ✍

Last but not least, Words are not enough to thank the parents of the children and the children too who shared in this study in order to achieve the best care for them.

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Abstract

Background

Asthma is major public concern in the world. This is more serious in countries with limited resources and lower public awareness, the prevalence of asthma and wheezing has rising during the last four decades among the pre-adolescent children. Also, the prevalence of asthma increased significantly in 6-12 years old school children in the 9-years period from 1995 to 2004 from 9.8% to 17.8%.

The fractional concentration of exhaled nitric oxide (FENO) is associated with the degree of airway inflammation. Measurement of FENO has proven useful in clinical diagnosis and management of asthma and in epidemiologic assessment of asthma and other respiratory diseases in children and adults.

Fraction exhaled nitric oxide has been proposed as a simple and non invasive marker of airway inflammation in asthmatic children. Nitric oxide level in the airways is considered as an index of the airway inflammation and injury

Objectives

In this study, we aim to evaluate the efficacy of measuring fractional exhaled nitric oxide (FENO) as a biochemical marker of

asthma inflammation, and to identify its applicability in judging management and follow-up of the inflammatory process in mild asthma. In addition, our study aimed to compare the effectiveness of oral administration of montelukast, and that of inhaled corticosteroid on children with mild persistence asthma after 8 weeks of treatment.

Patients and Methods

The study included fifty children diagnosed as mild persistent asthma as defined by the GINA guideline. Their age ranged from 5 to 15 years. They were divided into 2 groups; first group (n=25) received oral montelukast (5mg once daily) for 8 weeks, and the second group (n=25) received inhaled corticosteroid (fluticasone propionate 50 mcg twice-daily) for the same period. The study also included 50 healthy children with age and sex matched, served as a control group. All children were subjected to full clinical examination, spirometry, anthropometric measurements and assessment of fractional exhaled nitric oxid (FENO) level and eosinophilic count. Reassessment of these parameters was done to asthmatic children after the treatment period.

Results

Results revealed that asthmatic children had significant lower levels of all spirometric function tests (RFTs), and significant higher levels of both FENO and eosinophil count when compared to controls. After 8

weeks of treatment, both groups of asthmatic children had significant improvement of all RFTs, and significant reduction in both FENO levels and eosinophil count. The levels of both exhaled nitric oxide and eosinophilic count percentage are significantly lower in asthmatic children who treated with inhaled corticosteroids when compared with those who treated with montelukast. Results revealed a significant positive correlation between FENO level and eosinophil count ($r=0.282$, $p= 0.04$).

Conclusions

It concluded that, measurement of exhaled nitric oxide is a useful biomarker for assessment of airway inflammation, and it is beneficial in the monitoring of asthma and follow up responsiveness to treatment. However, the threshold or cut-off levels, and the upper limits of normal EFNO levels is not yet settled, so the optimum use of FENO in clinical practice remains to be established. We also concluded that Inhaled corticosteroids (ICS) are the preferable primary long-term treatment for asthmatic children, and montelukast can be considered an alternative treatment when safety profile, oral administration route and possibly, better adherence to treatment are needed.

LIST OF ABBREVIATION

AHR	Airway hyper-responsiveness
AMP	Adenosine monophosphate
ANOVA	Analysis of variance
ARDS	Acute respiratory distress syndrome
ASM	Airway smooth muscle
ATS/ERS	American Thoracic Society/ European Respiratory Society
BAL	Bronco alveolar lavage
B-blockers	Beta blockers
BMZ	Body Mass index Z score
CAA	Child asthma admissions
cAMP	Cyclic adenosine monophosphate
CBC	Complete blood picture
CD14	Cluster of differentiation
CF	Cystic fibrosis
cGMP	Cyclic guanosine monophosphate
cGTP	Cyclic guanosine triphosphate
CLD	Chronic lung disease of prematurely
CTLA-4	Cytotoxic T-lymphocyte- associated protein 4
cNOS	Cells expressing Nitric oxide synthases
cNOS	Constitutive NOS
CTLA-4	Cytotoxic T-lymphocyte- associated protein 4
Cys-LTs	Cysteinyl-leukotrienes
EBC	Exhaled breath condensate
ECP	Eosinophil cationic protein
ENO	Exhaled nitric oxide
ENOa	Exhaled nitric oxide after treatment

✍ List of Abbreviations ✍

ENOb	Exhaled nitric oxide before treatment
eNOS	Endothelial Nitric oxide synthases
Eosa	Eosinophilic Count after treatment
Eosb	Eosinophilic Count before treatment
EPX	Eosinophil protein X
FENO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GERD	Gastro esophageal reflux
GINA	Global Initiative for asthma
GM-CSF	Granulocyte macrophage colony stimulating factor
HIV	Human immuno-deficiency virus
HAZ	Height for Age Z score
ICS	Inhaled corticosteroids
IFN-γ	Interferon-gamma
IgA	Immunoglobulin-A
IgE	Immunoglobulin-E
IL	Interleukin
IL-1β	Interleukine-1 β
IM	Inflammatory marker
i-NANC	Inhibitory nonadrenergic noncholinergic
iNOS	Inducible nitric oxide synthases
ISAAC	International study of asthma and allergies in childhood
LABA	Long-acting β_2 agonist
L-NAME	L-arginine analogues
LNMA	L-arginine analogues
LRI	Lower respiratory illnesses
LT	Leukotrienes
LTC4	Leukotriene C4

✍ List of Abbreviations ✍

LTD4	Leukotriene D4
LTE4	Leukotriene E4
LTRAs	Leukotriene receptor antagonists
MBP	Major basic protein
MHC	Major histocompatibility complex
NANC	Nonadrenergic noncholinergic
nNO	Nasal nitric oxide
nNOS	Neuronal nitric oxide synthases
NO	Nitric oxide
NOS	Nitric oxide synthases
NSAIDS	Non steroidal anti- inflammatory drugs
O3	Ozone
P.P.b	Part per bilion
PCD	Primary Celiac Dyskinasia
PEF	Peak expiratory flow
PIV	Para-influenza virus
PUFA	Polyunsaturated fatty acid
RANTES	Growth factor Regulated on Activation, Normal T cell-Expressed and Secreted
RFTs	Respiratory Function Test
RSV	Respiratory syncytial virus
sGC	Soluble guanylate cyclase
SNOs	S-nitrosothiols
STAT-6	Signal transducer and activator of transcription 6
TH1	T-helper -1 cell
TH2	T-helper -2 cell
TNF-α	Tumor necrotizing factor- α
VIP	Vasoactive intestinal peptide
WLRI	Wheezy lower respiratory illness
WAZ	Weight for Age Z score

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