Ain Shams University
Institute of Postgraduate Childhood Studies
Medical Studies Department

EVALUATION OF LOCAL NASAL IMMUNOTHERAPY IN CHILDREN WITH INTRACTABLE ALLERGIC RHINITIS

Thesis
Submitted for fulfillment of PhD in childhood studies
(Child health and nutrition)
Medical Studies Department

By
Magdy Mohamed Abd Al-Rahman Badran
M.B., B.Ch., M. Sc. Pediatrics

Supervised by

Prof. Dr. El-Said Abou Gamrah
Prof. of Allergy and Immunology
Ain Shams University

Prof. Dr. Mostafa El-Nashar
Prof. of ENT
Ain Shams University

Prof. Dr. Suzan Hosny
Prof. of Allergy & Immunology
Ain Shams University

Prof.Dr. Salwa Abd El-Zaher
Prof. of Allergy & Immunology
Ain Shams University

2005

ACKNOWLEDGMENT

I want to express my thankfulness to Prof. Dr.Mostafa El - Nashar Prof. of ENT & Ex Dean of Postgraduate Childhood Studies Institute , Ain Shams University ; who has guided me, created the spirit of this work and made this work achievable through his assistance and supervision.

I would like to forward my sincere appreciation to Prof. Dr. El-Said Abou Gamrah Professor of Allergy & Immunology , Ain Shams University , for giving me the privilege of working under his supervision, and also for dedicating much of his precious time, and wide experience that guided this work to succeed.

I would like to forward my sincere appreciation to Prof. Dr. Suzan Hosny, Professor of Allergy & Immunology ,Ain Shams University , for giving me the privilege of working under her supervision, and also for dedicating much of her precious time, and wide experience that guided this work to succeed.

Also, I am deeply indebted to Prof.Dr. Salwa Abd El-Zaher ,Prof. of Allergy & Immunology ,Ain Shams University ,for her utmost help, kind guidance, valuable instruction and technical support.

I would like to express my deep and sincere gratitude and thanks to the , Ain Shams University Internal Medicine Department Immunology Lab Staff Dr. Mohamed Yosef and Dr Hesham Sand and to the Immunology Vaccine Lab staff Mr. Atef Abd Al Samee and Mr. Ahmad Al abasi .

My thanks and gratitude are also directed to Prof. Dr. Salah Mustafa; Professor of Public Health, Institute Of Postgraduate Childhood Studies, Ain Shams University, for his great statistical support during this study.

At last but not least, my great thanks to my wife "Mrs Badran " and my children, Sherif , and Kawthar , and all my big Family members, for their patience and kindness.

CONTENTS

List of Abbreviations

ACE	**Angiotensin- converting enzyme) inhibitors**
Ags	**Antigens**
APCs	**Antigen Presenting Cells .**
AR	**Allergic rhinitis**
ARIA	**Allergic Rhinitis and its Impact on Asthma**
BALT	**Bronchus Associated Lymphoid Tissue**
CD	**Clusters of Differentiation antigens**
Cfegs	**Clusters Of Free Eosinophil Granules**
CSs	**Corticosteroids**
CSF	**Cerebro Spinal Fluid**
cysLTs	**Cysteinyl Leukotrienes**
ECL	**Eosinophil Cytolysis**
ECP	**Eosinophil Cationic Protein**
EDN	**Eosinophil Derived Neurotoxin**
EM	**Electron Microscope**
Epo	**Eosinophil Peroxidase**
Fab	**Fragments antigen binding sites**
GIT	**Gastro Intestinal tract**
GALT	**Gut Associated Lymphoid Tissue**
GM-CS	**Granulocyte Macophage Colony Stimulating factor**
GATA	**Guanine-Adenine-Thymine-Adenine**
HRQoL	**Health-Related Quality of Life**
ICAM-1	**Intercellular Adhesion Molecules**
LFA-1	**Leukocyte Function-Associated Antigen One**
LNI	**Local Nasal Immunotherapy**
LTC_4	**leukotriene C_4**
LTD_4	**leukotriene D_4**
MALT	**Mucosa Associated Lymphoid Tissue**
Met-Ckb 7	**Met-Chemokine Beta Seven**
Mph	**Meter per hour**
MBP	**Major Basic Protein**
NALT	**Naso-phayngeal Associated Lymphoid Tissue**

N C	**Numbert of Children In The Family**
NETS	**Nasal Eosinophils Tissue Score**
OME	**Otitis Media with Effusion**
OTC	**Over The- Counter**
PAF	**Platelet Activating Factor**
PAR	**Perennial Allergic rhinitis**
PGD	**Prostaglandin**
PMD	**Piecemeal Degranulation**
PPARγ	**Peroxisome Proliferator-Activated Receptor Gamma**
RH	**Relative Humidity**
RANTES	**Regulated on Activation Normal T Cell Expressed and Secreted**
RAST	**Radioallergosorbent Test**
RLN	**Regional Lymph Nodes**
SAR	**Seasonal Allergic Rhinitis**
SIT	**Subcutaneous Immunotherapy**
SLIT	**Sublingual immunotherapy**
SES	**Socio- Economic Status**
SETS	**Sputum Eosinophils Tissue Score**
SRS-A	**Slow-Reacting Substance Of Anaphylaxis**
TGF	**Tissue growth factor**
TNNSS	**Total Non Nasal Symptoms Severity**
TNSS	**Total Nasal Symptoms Severity**
VLA	**Very Late Antigen**
VOC	**Volatile Organic Compounds**

List of Tables

List of Figures

ABSTRACT

EVALUATION OF LOCAL NASAL IMMUNOTHERAPY IN CHILDREN WITH INTRACTABLE ALLERGIC RHINITIS

Allergic rhinitis is a very common chronic disorder that affects 10% of children and 20% of adolescents and young adults . However, it is frequently underdiagnosed and its importance as a cause of morbidity underestimated . AIM OF THE STUDY: To assess the clinical efficacy and safety of local nasal immunotherapy in children with allergic rhinitis. SUBJECTS & METHODS: This study was conducted on 50 children (5-18 years) from 6 Egyptian governorates in the Allergy Unit in Ain Shams University Hospitals . RESULTS: Skin test results showed significant improvement after LNI , The Number of antigens per patient mean before LNI was 3.44 ± 1.84 and became 0.06 ± 0 .24 after LNI , P< . 001 (Significant) . The mean for Blood Eosinphils before LNI was 3.32 ± 1.30 and it became 2.50 ± 0 .74 after LNI, p < .001 0 (Significant) . The mean for Nasal Eosinphils before LNI was 7.12 ± 1.61 , and it became 2.56 ±0 .88 after LNI , p < .001 (significant) . The mean for Sputum Eosinphils before LNI was 4.68 ± 1.92 and after LNI it became 2.74 ± 0 .94 , p < .001 (significant) . Nasal Eosinophils Tissue Score before LNI Mean was 2.46 ±1.04 and it became 1.06 ±0. 31 after LNI , p < .001 (significant) . Sputum Eosinphils Tissue Score before LNI Mean was 1.49 ±0.55 and it became 1.16 ±0.42 after LNI Mean , p < .001 (significant) . IgE Before LNI Mean was 155.82 ± 101.21 and it became 50.31 ± 32.52 after LNI , P < 0.001 (significant) . Nasal Symptoms Severity Score before and after LNI were (29.60 ± 3.11 and 5.00 respectively) showed a significant improvement , p < 0. 001 . Non Nasal Symptoms Severity Score before and after LNI (21.40 ± 3.90 and 6.00 respectively) showed a significant improvement , p < 0. 001 . CONCLUSION: LNI offers advantages such as good efficacy , safety and a more convenient allergen delivery in children with allergic rhinitis , simplified schedule for self-administration; improved patient compliance; and reduction of local side effects .

KEYWORDS: LNI , IgE , Eosinophils .

INTRODUCTION

Allergic Rhinitis is defined as a symptomatic disorder of the nose resulting from an IgE-mediated immunological reaction following exposure to allergen. Allergic rhinitis is the most prevalent chronic allergic disease in children. Although it is not life- threatening, it can have a significantly detrimental effect on a the quality of life, and it may exacerbate a number of common comorbidities, including asthma and sinusitis (Gelfand , 2005) .

Allergic rhinitis (AR) is the most common chronic atopic disease, and it is associated with considerable costs and comorbidities. (Sanico , 2004) . Hay fever is a modern disease. It was virtually unknown before 1800 and has become common only during the last hundred years. The first case to be described medically was in 1819 but the causes of the disease were not identified until 1873. Medical statistics show that the incidence of hay fever rose steadily during the nineteenth century in many countries including France, Germany and the United States. The numbers of people affected by hay fever have continued to increase since 1900 and it has become prevalent in countries, such as Japan ,where it was unknown 40 years ago.

AR usually is thought to be a minor annoying disease, it can be quite significant. Quality-of-life studies have demonstrated that patients find AR to be just as debilitating and intrusive as severe asthma. AR is an immunoglobulin E (IgE)–mediated reaction to a variety of allergen triggers. The most common allergens are dust mites, pets, cockroaches, molds, and pollens. These triggers cause a release of mediators that lead to a variety of symptoms, including sneezing; nasal congestion; stuffiness; rhinorrhea; cough; itching of the nose, eyes, and throat; sinus pressure; headache; and epistaxis (Becker , 2004) .

Allergic rhinitis is a very common chronic disorder that affects approximately 20% the population in USA, Europe and Asia . Its prevalence in children is 10% and in adolescents and young adults is 20% (Sly, 2000). However, it is frequently underdiagnosed and its importance as a cause of morbidity underestimated. It has a serious toll on the children's health, well being, school performance and quality of life. Common complications include sinusitis and rhinitis medicamentosa. The median age of presentation is 10 years (Becker, 2004). Allergic rhinitis is present in 75% of children with bronchial asthma (Warner, 1989).

Sensitization to outdoor allergens e.g. Pollen occurs when the child is 3-5 years and to indoor allergens e.g. House dust mites at an earlier age. The antigen will cross–link to IgE molecule on the surface of mast cells causing their degranulation releasing a variety of mediators such as histamine, prostaglandin D_2 , platelet activating factors, leukotrienes and other mediators. Two reactions follow this, the first involves immediate symptoms as nasal itching, nasal discharge, sneezing and congestion. The second reaction occurs hours later and is due to recruitment of inflammatory cells with the release of eosinophils and basophils mediators (Sly , 2002).

Symptoms of allergic rhinitis include, rhinorrhea, nasal congestion, postnasal discharge, repetitive sneezing and itching of the nose or eyes. Often associated with snoring, frequent sore throat, and headache (Becker, 2004) .

On examination, children often show nose wrinkling and twitching. Repeated rubbing of the nose tip with the dorsum of the hands is characteristic. The nasal mucosa is usually edematous and congested. Watery mucoid secretions may be noted in the nasal cavities and posterior pharyngeal wall. Conjunctivitis may be associated with allergic rhinitis. Signs of atopic dermatitis may be evident (Warner, 1989) .

No studies are needed if the clinical history is evident. When the history is confusing the followings are helpful:

1. **Nasal smears for eosinophils.**
2. **CBC for eosinophilia.**
3. **Ig E: May be elevated.**
4. **Skin testing to identify the triggering agent (Becker, 2004).**

The prognosis of allergic rhinitis is not good (Sly, 2000). Only patients who receive allergen-specific immunotherapy are cured (Becker, 2004) .

The Aim of the study is to assess the clinical efficacy and safety of local nasal immunotherapy in children with intractable allergic rhinitis.

CHAPTER 1:

EPIDEMIOLOGY OF ALLERGIC RHINITIS

Allergic rhinitis is the most common allergic disease,it is the most common chronic disease in United States affecting 20–40 million people in the US alone, including 10-30% of adults and up to 40% of children . Allergic rhinitis significantly affects quality of life accounting for two million missed school days and three million missed work days (Skoner ,2001) & (Matricardi & Rosmini , 2002) .

Allergic rhinitis is a major chronic respiratory disease due to its prevalence , impact on quality of life , impact on work /school , performance and productivity , economic burden , and its links with asthma. Allergic rhinitis is defined as being a "major" disease based upon the epidemiologic parameter; prevalence. Its prevalence however, is dependent upon the definition of the disease itself. It can be high if the definition is fuzzy, e.g. "signs and symptoms," or it can be low (therefore a rare or "minor" disease) when strict definitions are applied .

Frequency:

In the US: Prevalence in the United States is 10-20%. Rates as high as 38.2% were demonstrated when patients were asked if they experienced fewer than 7 days of symptoms. When AR was defined as symptoms lasting more than 31 days, prevalence dropped to 17% . Internationally: In temperate areas of Europe and Asia, frequency is similar to that in the United States (Becker , 2004).

Sex: No sex predilection exists.

Age:

Onset of allergic rhinitis is usually under age 30 and its peak incidence is in childhood and adolescence . Allergic rhinitis is more common in children than adults and is one of the major chronic conditions in children < 18 years old (Skoner , 2001) .

In 80% of cases, it develops before the age of 20 years . Symptoms develop by 2–3 years of age in 20% of cases, and 40% of cases have symptoms by 6 years . Symptoms tend to improve with age, particularly in those who have an early onset of the disease.(Kalliomaki et al , 2001) .

AR usually presents in early childhood. AR caused by sensitization to outdoor allergens usually occurs when a child is older than 2 years; however, sensitization in children aged 4-6 years is more common. Clinically significant sensitization to indoor allergens may occur in younger children if the children have significant exposures to allergens such as molds, furry animals, cockroaches, or dust mites. Some children may be sensitized to outdoor allergens at this young age if they have significant exposure, as is seen if a parent works in the landscaping field. Incidence continues to increase until the fourth decade of life, when symptoms begin to fade; however, individuals can develop symptoms at any age (Becker , 2004).

Race:

No race predilection exists; however, individuals from various racial backgrounds seek out medical attentions often than whites. Becker , 2004).

Prevalence

Prevalence is greater in boys than girls, but there is little difference between the sexes in adulthood (Skoner , 2001) .

The prevalence of allergic diseases varies worldwide. The International Study of Asthma and Allergies in Childhood (ISAAC) found that 12-month prevalences of allergic rhinoconjunctivitis in 13–14 year olds varied between 1.4% and 39.7%: low prevalences were found in

Albania, Georgia, Estonia, Lativia, Romania, and Indonesia, and high prevalences were found in Nigeria, Paraguay, Malta, Hong Kong, and Australia (Clayton , 1998) .

In 1999, the reported prevalence of allergic rhinitis in young adults approximately 16-18 years of age was 23% in Great Britain, 26% in the USA , and 36% in Japan.In the United States, allergic rhinitis ranks as the fifth most common chronic disease (Schoenwetter et al ,2004) .

The prevalence of allergic rhinitis is increasing in both adults and children, particularly in populations with a Western lifestyle : the number of children affected has doubled in the last 20 years (Ceuppens , 2000) .

The cause of this increase is uncertain, but possible factors include

1. **Higher levels of airborne pollution,**
2. **Rising dust mite populations,**
3. **Less ventilation in houses and offices,**
4. **Dietary factors, and the trend towards sedentary lifestyles. (Kalliomaki et al , 2001) .**

Other more controversial theories that attempt to explain the increased prevalence of allergic rhinitis over the last 40 years include the following :

1. **Changes in diet ,antibiotic use, immunizations, and patterns of infection in childhood, leading to changes in the numbers of people with T-helper (Th) 2, rather than Th1 immune responses .**
2. **The 'hygiene hypothesis' associated with the greatly improved sanitation typical of a Western lifestyle, which is gaining credence (Schoenwetter et al ,2004) .**