STUDY PROTOCOL

Title

Effect of Oral Azithromycin Three Times Per Week on Reduction of Asthma Exacerbations in Adults with Persistent Asthma

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Introduction

Asthma is a common and potentially serious chronic disease that imposes a substantial burden on patients, their families and the community. It causes respiratory symptoms, limitation of activity, and exacerbation that require urgent health care and may be fatal if not addressed properly. Asthma causes symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time in occurrence, frequency and intensity. These symptoms are associated with variable expiratory airflow,i.e. difficulty in breathing air out of the lungs due to bronchoconstriction, airway wall thickening, and increased mucus (GINA, 2017).

Asthma is one of the important public health problems worldwide with wide differences in prevalence and severity throughout the world. The World Health Organization (WHO) estimates that 235 million people currently suffer from asthma (Fact sheet of asthma, 2011) and by 2025 it has been estimated that a further 100 million will be affected. Asthma accounts for one in every 250 deaths worldwide and 1% of all disability. In overall health terms chronic symptoms of asthma account for 8% of self reported poor health in 18-64 year olds and 3.5% of days of limited activity, putting asthma above diabetes but below arthritis as a chronic health problem. Psychological distress and feelings of decreased control are high in people with asthma and strongly associated with physical health(Rees,2006).

The fundamental causes of asthma are not completely understood, but strongest risk factors for developing asthma are a combination of genetic predisposition with

environmental exposure to inhaled substances and particles that may provoke allergic reactions or irritate the airways (Fact sheet of asthma, 2011).

The prevalence of asthma in childhood is 10-30% (Robinson et al., 2009) . It is the leading cause of hospitalization in children under 15 years of age, and the leading cause of school absence (Singhi et al., 2003). Several cross-sectional studies conducted over last 2-3 decades indicate an increased prevalence(15-20%) of asthma in the United kingdom, Australia, New Zealand , United States of America and other developed countries and low prevalence rates in Asian countries esp. in China and India (ISAAC, 1998; ECRHS, 2001). It has been observed that wide variations exist between countries in prevalence of asthma, its clinical presentation and natural history (Anderson et al,. 1994). In south East Asia region, asthma has become a substantial public health problem (Pal et al., 2009).The prevalence of school children asthma in south east Asia region like China (1-2.4%), Hong Kong (7.2-8%), Indonesia (2.3- 8.2%), Malaysia (13.8%), and India (7.2%) (Pal et al., 2009).

The First National Asthma Prevalence Study (NAPS) in Bangladesh in 1999, showed that about 7 million people (5.2% of the population) are suffering from current asthma and prevalence is more in rural area than in metropolitan area (Hasan et al., 2005).

Moderate persistent asthma is defined as symptoms occur almost every day, night awakening > 1 attack/ week but not nightly and in between attacks FEV1 is > 60% to < 80% of predicted value. Severe persistent asthma is defined as symptoms occur throughout each day, night time awakening is often every night and FEV1 is < 60% of predicted value (GINA, 2017).

Severity of degree of airflow obstruction in acute state may be classified as normal, mild, moderate, severe, life threatening. Moderate asthma is classified when FEV1 is <65 to 50%. Severe asthma is classified when FEV1 is <50 to 30% (National guidelines of Asthma & COPD, 2016).

Well-controlled asthma reduces the burden for patients and health services. Control of asthma may mean minimal symptoms and freedom from exacerbations for patients, normal peak flow or low scores on standard questionnaire for doctors, or composite measures in clinical trials. The long term goal of asthma management are to achieve good control of symptoms, including nocturnal symptoms and exercise-induced asthma, to minimize future risk of exacerbations ,the achievement of best possible pulmonary function to minimize fixed airflow obstruction, with minimal side effects and to maintain normal activity levels (Rees,2006).

The pharmacological options for long term treatment of asthma fall into the three main categories like reliever medications, controller medications and add on therapies for patient with severe asthma. Relievers have a direct bronchodilation effect and relieve the symptoms of asthma. They are the mainstay of drugs for the acute relief of asthma symptoms, symptoms relieve during maintenance treatment of asthma and protection against exercise -induced asthma. (GINA ,2017).

Asthma exacerbations can still occur despite maintenance treatment with inhaled corticosteroids and long-acting bronchodilators, indicating a need for additional treatment options in uncontrolled persistent asthma.(Calhoun et al., 2014, Ivanova et al., 2012). Macrolide antibiotics have combined antibacterial, antiviral, and anti-inflammatory

effects (Gielen 2010, Altenburg 2011, Simpson 2008, Brusselle et al., 2013). Macrolide antibiotics has been reported to be beneficial in both eosinophilic and non-eosinophilic subtypes(Simpson 2008, Brusselle et al., 2013). Though initial systematic reviews of randomised controlled trials reported some benefits of macrolides on asthma symptoms but were unable to draw conclusions about other effects(Kew et al., 2015, Tong et al., 2015, Reiter et al., 2013, Richeldi et al., 2005). A last study reported that adding oral azithromycin 500 mg for 48 weeks to maintenance inhaled corticosteroid–long-acting bronchodilator therapy in patients with symptomatic asthma decreased the frequency of asthma exacerbations and improved quality of life (Gibson et al., 2017).

Considering the implications of asthma exacerbations on patients and the community, and the risk that is caused by these events in patients who remain symptomatic on maintenance therapy, we want to evaluate the effect of oral thrice weekly Azithromycin therapy on reduction of asthma exacerbations in adults with persistent asthma.

Rationale

Exacerbations of asthma cause a significant impact on both patient and society. Adults with uncontrolled persistent asthma despite maintenance treatment require additional therapy. Since macrolide antibiotics can be used to treat persistent asthma, we aimed to assess the efficacy and safety of oral azithromycin as add-on therapy in patients with uncontrolled asthma on standard asthma medications. Though many studies provide clear evidence of benefit of add-on azithromycin in persistent asthma but macrolide antibiotics have been used to treat persistent asthma to reduce asthma exacerbation with contradictory results. One study using low dose azithromycin (200 mg) in a short durationdid not find any significant role in asthma exacerbation prevention whereas another study showed significant role where they used higher dosage (500 mg) for a longer duration.

We wish to conduct a randomised control trial to evaluate the effect of azithromycin (three times weekly administration of 500 mg for 24 weeks) in reducing asthma exacerbation.

Hypothesis :

Null hypothesis:

Oral azithromycin 500 mg, three times weekly on alternate days as an add on therapy for 24 weeks does not lead to reduced asthma exacerbations in patients with persistent asthma.

Alternative hypothesis:

Oral azithromycin 500 mg, three times weekly on alternate day for 24 weeks as an add on therapy in patients with persistent asthma lead to reduced asthma exacerbations.

Aims& Objectives

General Objective:

- To assess the efficacy of oral azithromycin as add-on therapy in reducing exacerbations in persistent asthma patients who are on medium-to-high dose inhaled corticosteroids plus a long-acting bronchodilator.

Specific Objectives:

1. To asses efficacy of azithromycin in reducing frequency of asthma exacerbation
2. To evaluate efficacy of azithromycin in reducing level of exacerbations severity
3. To see efficacy of azithromycin in improving asthma control
4. To assess safety of azithromycin.

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Research Methodology

Study design

Interventional study - Open label randomized controlled trial

Place of study

This study will be carried out at the inpatient and outpatient department of Respiratory Medicine, National Institute of diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka.

Period of study

From June 2018 to June 2019 for one year

Primary outcome variables

Reduction of total number of asthma exacerbations.

Secondary outcome variables

Reduction of total number of types of asthma exacerbation according to severity (moderate vs severe)
Adverse effects occurring in patients treated with azithromycin.
Changes in self reported asthma symptoms

Confounding Variable :

BMI
Serum eosinophil count
Atopy
Pre treatment FEV1

Study population:

Group A : Patients with persistent asthma who will receive azithromycin 500 mg three times weekly in addition to on medium-to-high dose inhaled corticosteroids plus a long-acting bronchodilator

Group B : Patients with persistent asthma who will receive conventional treatment only(on medium-to-high dose inhaled corticosteroids plus a long-acting bronchodilator)

Inclusion criteria :

1. All adult(≥ 12 years) persistent asthma patients of both sexes.
2. Patients who are clinically stable with no recent exacerbations, infections, or changes in maintenance medication for at least 4 weeks before study.

Exclusion criteria:

1. Patients with substantial parenchymal lung disease, such as emphysema
2. Current and ex smokers.
3. Patients with hearing impairment
4. Abnormally prolonged QTc interval were excluded.
5. Known case of asthma with bronchiectasis
6. Known Sensitivity to azithromycin .

Sampling technique

Each case will be included in this study by consecutive sampling method from patients attending in the outdoor and indoor of NIDCH.

Enrollment:

Then enrollment of the patients after inclusion and exclusion criteria.

Allocation:

Then Patients will be **randomized** into two groups: **Group- A (Azithromycin recipient**) and **Group –B (Standard asthma treatment recipient**)

Sample size:

The Sample size will be determined by using the following formula **(Rathore et al., 2012):**

$$n = \frac{(\sigma_1^2 + \sigma_2^2)(Z\alpha + Z\beta)^2}{(\mu_1 - \mu_2)^2}$$

n = sample size

σ1 = SD1 of placebo group = 0.9

σ2 = SD2 of Azythromycin group = 1.0

μ_1 = mean of ACQ in Placebo group = 1.4

μ_2 = mean of ACQ in Azythromycin group= 1.7

$\mu_1 - \mu_2 = 0.3$

α = 1.96 at a significance level of 5%

β = 0.85 at a power of 80%

So, $n = [(1.0)^2 + (0.9)^2] \times [(1.96+0.85)^2] / (0.3)^2$

$=(1.81) \times 7.9 / 0.09$

$= 160$

But, as there is time constraint, all patients who will meet the inclusion criteria will be selected during the estimated time frame and patients will be allocated to each group.

Operational Definition :

Asthma – Patients fulfilling the GINA 2018 diagnostic criteria for asthma in adults -

"Patients who had asthma defined as a compatible history and documented objective evidence of variable airflow obstruction from bronchodilator response (with post-bronchodilator reversibility of at least 12% and at least 200 mL forced expiratory volume in 1 s [FEV1]), airway hyperresponsiveness, or increased peak flow variability (>12% of amplitude above the lowest peak expiratory flow [PEF] over at least 1 week of monitoring)"

Stable asthma – Patients with no exacerbation at the time of presentation(GINA 2018)

Exacerbation of asthma – Progressive increase in shortness of breath, cough, wheezing or chest tightness over a short period of time that is sufficient to require a change in treatment(GINA 2018)

a. Severe exacerbations were defined as worsening of asthma symptoms that led to one of the following: at least 3 days of systemic corticosteroid treatment of at least 10 mg/day or a temporary increase in a stable oral corticosteroid maintenance dosage of at least 10 mg/day for at least 3 days; an asthma-specific hospitalization; or emergency department visit requiring systemic corticosteroids(Gibson et al. 2017)

b. Moderate exacerbations were defined as any temporary increase in inhaled corticosteroids or antibiotics in conjunction with a deterioration in asthma symptoms or both, or any increase in β2 agonist use for at least 2 days, or an emergency department visit not requiring systemic corticosteroids (Gibson et al. 2017).

Persistent Asthma - Patients fulfilling the criteria as per National guidelines for Asthma & COPD 2016.

Types	**Day time asthma symptoms**	**Night time asthma symptoms**	**Exacerbations**	**Spirometry and PEF meter records**
Intermittent	≤ 2days per week	≤ 2 attack per month	Infrequent Brief, normal activity	FEV1≥80% predicted, PEF variability less than 20%
Mild persistent	More than 2 days per week but not daily	More than 3-4 attacks per month but not weekly	Occasional, minor affect activity or sleep	FEV1≥80% predicted, PEF variability less than 20-30%
Moderate persistent	Daily	≥1 attack per week but not nightly	Occasional, some limitation of activity or sleep	FEV1 >60% to <80% predicted, PEF variability more than 30%
Severe persistent	Throughout the day	Often every night	Frequent, physical activities are extremely limited	FEV1≤60% predicted, PEF variability mor than 30%

3.11 Study Procedure

This study will be a hospital based clinical trial which comprised of:

Run-in phase-

- For confirmation of diagnosis and evaluation of eligibility, each subject will be evaluated with history and symptoms regarding the presentation. Patients age, occupation, working environment, smoking history, past medical history, current medications will be asked. Patients will also asked about the dyspnoea, wheezing, chest tightness, cough, sputum production, daytime symptoms, night time symptoms, triggering factor, activity level, associated diseases. They were examined and necessary baseline investigation (including CBC with ESR, Serum electrolytes, Chest X-ray P/A view, RBS, ECG, Sputum for AFB, etc.) will be done.
- Baseline pulse rate, spirometry with reversibility, serum electrolytes level and ECG will be obtained before giving treatment.
- Drugs will be supplied by " Opsonin pharmaceuticals", a GMP certified company.
- Drugs will packaged as per standardized protocol with specific batch number.

Follow-up phase-

Eligible patients were subjected to randomization into ‘Azithromycin Group (Group A)’ and Standard asthma treatment group (Group-B).

Group-A : After patients are randomized, patients in group A will be treated with oral azithromycin 500 mg three times every alternate day weekly along with other asthma medications (like ICS, ICS/LABA, LTRA, Anticholinergics, SR theophylline or Doxophylline) for 24 weeks.

Group-B : Patient who will be treated with conventional asthma medication for same duration.

- Patients were advised to maintain a dairy if possible in which they record their symptoms and use of medications.
- Adherence to the medication will be checked by interviewing the study subjects and also by return of the empty case of medicine containing same serial number of marked package.

    - Patients will be monitored for 24 weeks and assessment will be done at weeks 4, 12, 24. At each visits assessment of symptoms (ACQ6), medication use, asthma exacerbations, adherence, adverse events (including self-reported respiratory infections), Telephone assessments will be done if a patient was unable to attend/ missed a follow up.
    - Finally results will be analyzed.
    - Per protocol analysis will be done.

Forced spirometry variables will be obtained with a computerized system (MEDGRAPHICS spirometry machine, Model: CPFS/D USB) as recommended by the American Thoracic Society (Miller et al. 2005).

Research Instruments

A semi-structural questionnaire will be followed by face to face interview on the basis of objective of study.

Data collection techniques

Appropriate data will be collected by using a preformed data sheet.

Data processing

After collection, data will be thoroughly checked for completeness and then cleaned. Data will be processed by careful editing.

Data analysis and interpretation

Data will be processed manually and analyzed with the help of SPSS (Statistical package for social sciences) for windows version 22.

Quantitative data will be expressed as mean and standard deviation; and comparison done by paired and unpaired t-test. Qualitative data will be expressed as frequency and percentage and association was carried by Chi-square (χ^2) Test. 95% confidence limit

was taken. A probability value (p) of less than 0.05 was considered to indicate statistical significance.

Quality control and quality assurance

The standard guidelines will be followed like GINA and National Guidelines for ASTHMA & COPD and many other international publications for report writing and better quality of research work.

Ethical consideration

There will be minimum physical, psychological, social and legal risk during taking history, physical examination and investigations. Proper safety measures will be taken in every step of the study. Only researcher will be allowed to access the collected data.

Ethical clearance will be obtained from Institutional Review Board (IRB) of NIDCH to undertake the current study. According to Helsinki Declaration for Medical Research involving Human Subjects 1964, all the patients will be informed about the study design, the underlying hypothesis and the right of the participants to withdraw themselves from the research at any time, for any reason. Informed written consent will be obtained from each subject who voluntarily provide consent to participate in this study.

The following ethical issues will be addressed accordingly:

- Strict confidentiality and security of data related to patient was maintained. The presentation of data and information related to patient was documented anonymously. The data analysis will be completed on the subjects who completed the study according to protocol after recruitment of subjects with valid informed consent.

- There was no additional risk or safety concern due to the research process to either patient or researcher.

There was no potential conflict of interest in this study and an entirely an academic research project.

Time table

Topic selection	: 1 month (February, March 2018)
Literature search	: All through the study period.
Protocol writing	: 2 months (April, May 2018)
Approval of protocol	: 1 month (June, 2018)
Data collection	: 7 months (June, 2018 to January, 2019)
Data Analysis	: 1 month(July, 2019)
Thesis writing	: 1 month (August, 2019)
Binding and submission	: 1 month (September, 2019)

Budget estimation for thesis work

Total Budget = 350,000/- taka only.

Summary of Budget

Sl. No.	Particulars	Amount (Tk)
1	Drug cost	200,000.00
	Investigation cost	100,000.00
2	Statistician	30,000.00
3	Internet cost	3,000.00
4	Composing and printing	4,000.00
5	Stationeries	2,000.00
6	Telephone	5,000.00
7	Transport	3,000.00
8	Miscellaneous cost	3,000.00
	Total	3,00,000.00

Grand total: (Three hundred and fifty Thousand Taka Only) 2,80,000/-

Source of Fund:

Self

Reference :

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