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Exercise-induced bronchoconstriction and therapeutic modulation in Iraqi girls intermediate school students

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Abstract
EIB (Exercise-Induced Bronchoconstriction) describes the narrowing that occurs in the airway follow a short period of exercise. EIB is found in 8-10% of normal children population as occult bronchospasm during or after physical activities. The mechanisms of EIB are related to rapid ventilation and mouth breathing which cause heat and water loss during breathing leading to bronchoconstriction. Peak Expiratory Flow Rate (PEFR) measured pre and post-exercise in students aged 12-16 years in girl intermediate school. Any female shows PEFR values reduction $\leq$ 15% after 6 minutes continuous free running considered as asthmatic patient, this give an incidence rate of asthmatic patient of 9% in female students in this age. Treatment of EIB, Zafirlukast treatment gives (85.7%) protection rate. While salbutamol inhalation gives a protection rate 88%.
Only 66.6 % of girls with EIB give an improvement in PEFR values after sodium cromoglycate treatment. A regular measurement of PEFR in school students appears to be a good indicator of EIB, while inhalation of salbutamol 15 minutes before exercise give a good protection against EIB attacks at least for 4 hours.

Keywords: Asthma, bronchoconstriction, salbutamol, sodium cromoglycate, zafirlukast

Introduction
Exercise-Induced bronchoconstriction (EIB) describes the airway narrowing that occurs with exercise. More than 10 percent of the general population and up to 90% of persons previously diagnosed with asthma have EIB [1-4]. The symptoms of EIB include cough, wheeze, chest tightness, shortness of breath, excessive mucus production and feeling out of shape [4].
EIB is one of the most common diseases in children who tend to have high levels of physical activities, EIB are found in 8-10% of healthy school-aged children [5]. Among the estimated pediatric population with EIB up to 40% of them have Allergic Rhinitis and 30% of these patients may develop adult asthma [6].

Pathophysiology: The mechanism of EIB is not entirely understood. The hyperventilation and the rapid breathing through the mouth will cause loss of the water and dryness of the bronchial mucosa which lead to intracellular hyperosmolarity, the osmotic changing will cause stimulants to the mast cell, lead to degranulation of mast cells inflammatory mediators. These mediators will cause oedema, mucus hypersecretion and smooth muscle contraction endpoint, these changes caused by different Triggers in all ages and in all asthma phenotypes ending in airway narrowing which lead to dyspnea [6-10].
Recently, reported that females exhibited more exercise induced dyspnea than males may be due to low physical activity level or due to low fitness [11]. EIB occurs in the presence and absence of bronchial asthma. The prevalence of EIB can be influenced by age, sex, ethnicity/race and environmental conditions [12].
Many therapeutic options are available to prevent E1B attacks, the followings are short notes about the types of E1B treatment:
-Leukotriene Receptor Antagonists (LRA): these agents are generally safe, well tolerated and can be used as a monotherapy or combined with other medicines. LRA such as Montelukast (Singulair,4,5,10mg tablet), Zafirlukast (Accolate,10,20mg tablet) [9], and lipoxygenase inhibitors, such as Zileuton (Zyflo), these agents provide substantial prevention against Exercise-Induced Bronchoconstriction attacks, they are considered as second-line prevention

of EIB [1]. LRA drugs also improve Rhinitis symptoms [2, 13, 14]. Sodium Cromoglycate (mast cell stabilizers) (MCS): They are available as nebulizer solution or powder for inhalation (as a capsule) with spinhaler. MCS such as cromolyn and nedocromil, have been used widely for the prevention of EIB. They block mast cell degranulation and subsequent mediators release [9]. These agents are effective in 70- 85% of EIB patients and have minimal side effects [3], cromolyn nebulizer solution given as 20 mg per 2ml 10-60 minutes before exercise. These drugs less effective than short acting β_2 agonists. Metred dose inhalers have been discontinued [1].

-Short-Acting Beta $_2$ Agonists (SABA**):** EIB and asthma in athletes are common and often require the use of inhaled β_2 agonists. SABA can be used as a prophylactic before exercise to inhibit attacks of EIB [5]. Systemic SABAs are not allowed at all in EIB patients. SABA inhibits Bronchospasm by stimulating β_2 receptors on mast cell so prevent the release of contractile mediators and inducing relaxation of the airway smooth muscle fibers. This drug is taken as 2 puffs 15 minutes before exercise and lasts 4 to 6 hours, these agents like salbutamol and terbutaline [6, 10, 15, 16].

The goals of this study are to determine the incidence rate of EIB among the girl intermediate school students and to manage this occult type of asthma, also to enable patients to exercise at all intensity level without serious respiratory limitation.

Subjects and Methods

About 15 visits to the girl Intermediate School in Baghdad the total population of girl students was 300, the difference of PEFR was recorded before and after exercise in all students, the age of participants between 12 to 16 years, the exercise was a part of their routine physical education classes, all these students are participated in the test for EIB. The activities were in the form of continuous free running for 6 minutes at their own speed [17, 18]. The exercise was started after a short period of warming up activity started with stretching and Jogging activities. The Peak Expiratory Flow Rate (PEFR) was measured by using standard Wright Peak Flowmeter. (Peak Flowmeter, Clement Clarke International Ltd Harlow England) and the best of two readings was taken. The first readings before exercise at rest and the other readings were measured after finishing exercise at 3, 6 and 9 minutes. PEFR is the highest flow rate reached shortly after the beginning of a forced expiration, it reflects the expiratory obstruction. For the ethical reasons asthmatic persons, anyone that electively took any anti-asthmatic medication or anyone suffering from recent respiratory infection or allergies were excluded.

PEF Meter is a suitable, portable, inexpensive and it is as sensitive as FEV_1 (forced expiratory volume at first second). It has been stated previously that sport specific field exercise test is much more sensitive in athletes like this study.

All information measurements were taken in a period extended from 10th November 2018 to 17th march 2019.

The reduction in PEFR post-exercise was recorded as follow:

$$\text{PEFR reduction\%} = \frac{\text{Preexercise PEFR} - \text{Postexercise PEFR}}{\text{Preexercise PEFR}} \times 100$$

Any girl students who show a fall in PEFR≥15 from the base line were regarded as asthmatic.

The female patients with EIB were treated with Zafirlukast (Accolate), Sodium Cromoglycat SCG (Intal) and Salbutamol (Ventolin Inhaler). Zafirlukast treatment, 21 girls enrolled in this test, 20 mg tablet Accolate twice a day for the last four days. The last tablet was given 2 hours before exercise on empty stomach, PEFR values recorded pre-exercise at rest and post-exercise at 3, 6 and 9 min, after treatment.

Cromolyn inhalation given to 21 students as 2 puffs one hour before exercise. PEFR values recorded pre-exercise at rest and post-exercise at 3, 6 and 9 min after treatment with Cromolyn inhalation.

Salbutamol treatment (Ventolin inhaler), 21 asthmatic girls were participated in this study, 2 puffs given 15 min before exercise. PEFR readings taken pre-exercise at rest and post-exercise after treatment as in Zafirlukast and SCG treatment.

Results

Results of incidence rate

Three hundred girl students were involved in this study for testing the presence of occult Exercise-Induced Bronchoconstriction (EIB) in seems to be normal female adolescents aged between 12-16 years. PEFR values recorded before exercise at rest and after exercise at 3, 6 and 9 min.

Only 27 girls were found to have a reduction in PEFR readings post-exercise greater or equal to 15%. This give a prevalence rate of EIB was 9% in Iraqi female population in this age. However, when EIB regarded as a reduction in PEFR values equal or more than 10% the incidence rate will be 12.9% (Table 1) (Fig. 1).

Table 1: the total number of girls, normal and EIB students.

Subjects	Girls
Normal subjects	273
EIB subjects	27
Total	300

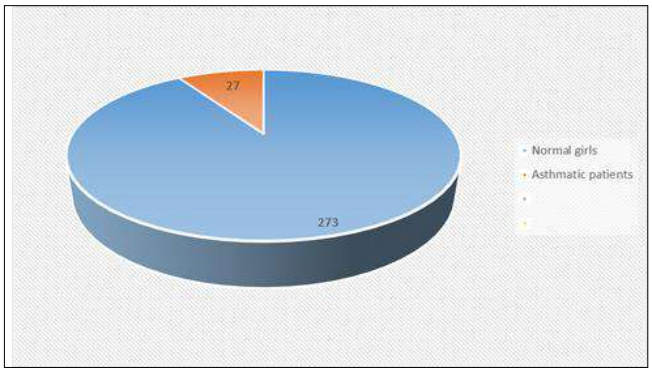

Fig 1: Incidence of EIB among female students aged 12-16 years.

Results of EIB treatment

The mean standard deviation and the range of age, body weight, height and resting PEFR were summarized in table (2).

Table 2: the mean, slandered deviation and the range of age, body weight, height and resting peak expiratory flow rate of exercise induced asthmatic girls.

Parameter	Gils
	21 Students
1. Age (year)	
Mean	13.55
S.D.	1.55
Range	12-16
2. Body weight (kg)	
Mean	39
S.D.	3.5
Range	34-45
3. Height (cm)	
Mean	158.86
S.D.	7.6
Range	143-167
4. Resting PEFR (liter/min)	
Mean	358
S.D.	50
range	260-446

Result of Zafirlukast treatment

Twenty-one female subject suffer from EIB were participated in the study of EIB treatment, Zafirlukast (Accolate) 20 mg tablet were given twice daily for the last four days before exercise, the last tablet given 2 hours before exercise on empty stomach to 21 asthmatic girls (with EIB) aged 12-16 y. Only 18 girls responded to Zafirlukast treatment 85.7%. The changes in PEFR readings after exercise at 3, 6 and 9 min. post-treatment compared with the values pre-exercise at rest were found of significance (Fig. 2).

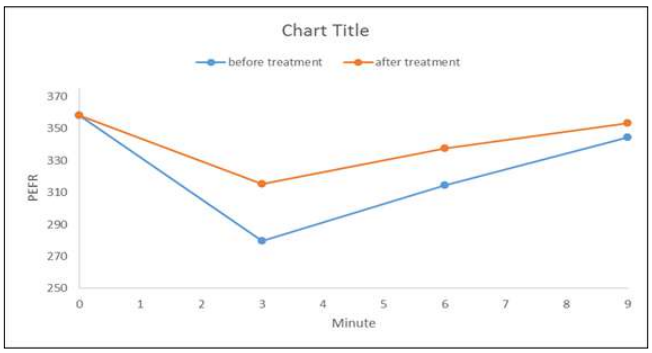

Fig 2: The PEFR before and after zafirlukast treatment in girls.

Results of Sodium Cromoglycate treatment SCG

Fourteen female students out of 21 responded to SCG Inhalation (intal). SCG was given as 2 puffs one hour before exercise to 21 girl students with EIB. This gives a response rate of (66.6%). There is a significant difference in PEFR readings after SCG treatment at 3, 6 and 9 minutes post-exercise compared with prexercise PEFR readings at rest (Figure 3).

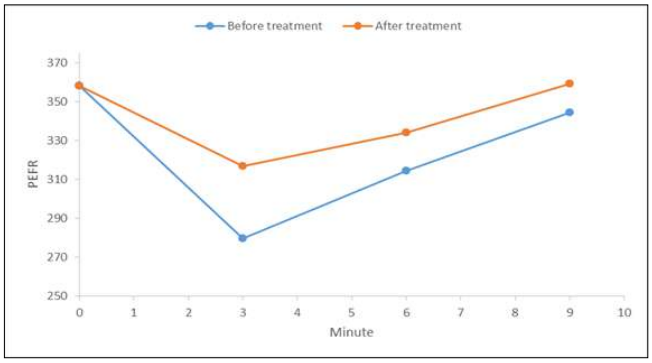

Fig 3: The PEFR readings before and after SCG treatment in girls.

Results of Salbutamol Inhalations (Ventolin inhaler)

Salbutamol inhalation was used as 2 puffs 15 minutes before exercise to 21 asthmatic students (with EIB). Seventeen out of 21 asthmatic girls responded to salbutamol treatment 88%. All responded girl students showed a reduction in PEFR values post-exercise less than 5% after salbutamol inhalation compared with the pre-exercise values. Salbutamol is the drug of first choice in prevention EIB attacks. (Fig.4).

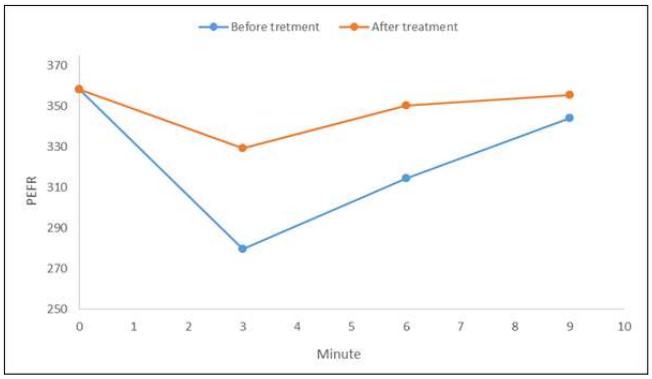

Fig 4: The PEFR readings before and after salbutamol treatment in girls.

The result of the EIB treatment with Zafirlukast, SCG, and Salbutamol were summarized in table (3). This table shows the mean and S.D, of PEFR before exercise and after cessation of exercise at 3, 6and, 9 minutes after treatment, Salbutamol has a higher protection rate in girl students while SCG has the lowest protection rate.

Table 3: there are significant differences between (a) and (b), (a) and (c), (a) and (d) under P≤ 0.01.

Type of treatment	PEFR readings Pre-exercise at rest	PEFR readings post exercise		
		3	6	9
Before treatment	358.0±50.5	379.7±42.1 (a)	314.6±70.0	344.3±61.3
1-zafirlust	356.1±35.7	315.3±66.2 (b)	337.6±45.8	353.3±44.0
2-SCG	360.0±42.8	316.9±50.7 (c)	334.1±52.2	359.2±46.2
3- salbutamol	359.8±45.5	329.1±53.5 (d)	350.4±41.8	355.5±45.2

Discussion

To determine the incidence rate of exercise induced asthma in Iraqi girls aged between 12-16 years. A fall in PEFR readings greater than or equal to 15% regarded as asthmatic [19—24]. The severity of EIB cannot be predicated from the resting level of lung function, for this reason the exercise was chose as the indirect challenge to produce Bronchospasm. So the exercise was in the form of 6 minutes

of continues free running on their own speed to induce bronchospasm [17, 18, 19, 23, 24].

Field exercise test the advantage of this test is that, it is similar to the environment where the athletes experience most of their respiratory symptoms [20, 23, 24]. The most common trigger factors seen in asthmatic patients are exercise [19].

Katten *et al.* [25] found that an exercise challenge test demonstrated EIB in 105 asthmatic children 99%, for this reason asthmatic subjects were excluded from this study. PEF meter was found to be a simple, portable, inexpensive, suitable for mass readings in the field work [17, 19, 24].

Three hundred girls were participated in this study, only 27 girls were found to have EIB and a reduction in PEFR readings more than or equal to 15% with an incidence rate (9%). A previous study was done in Iraqi football players aged between 18-25 years give a 5.7% incidence rate of EIB among players. This study has been done in a similar condition but different ages.

Marbut *et al.* [26] found an incidence rate of 12.5% in primary school pupils aged 8 to 13 year. The women had a significant larger reduction of forced expiratory values in the first second (FEV_1) than did the men, it indicated that women may have a lower tolerance to EIB or could be a symptoms of low fitness [15], the prevalence is within the order of 6% to 12% in the general community [24] which nearly similar to the results of this study.

Zafirlukast treatment (Accolate). It is Leukotrience receptors antagonist (LRAs) is used to prevent asthma attacks Zafirlukast is usually taken twice a day as tablet (20mg) only. It works by blocking the action of certain natural substances that cause swelling and tightening of the airways. Zafirlukast is used orally twice daily, before or after meals it is better to be taken at the same times every day.

Zafirlukast is also be used to treat Allergic Rhinitis and to prevent EIB [3, 27]. Zafirlukast have shown to improve pulmonary function and symptoms in patients with mild to severe asthma in 5 years of age and older. LIRAs provide significant protection against exercise and Antigens Induced Allergy [27, 28]. This medicine is given10mg twice daily to patient aged between 5-11years while given 20mg twice a day from 12years old and above 1hour before or 2h after meals [1].

SCG in an anti-inflammatory agents work in as a monotherapy or in cooperation with $Beta_2$- agonists, preventing the early bronchospastic phase and the late inflammatory phase of EIB, these medicines inhibit the degranulation of mast cell mediators. They are effective in 70-85 % of patient with EIB and have minimal side effect [3] this agent should be taken shortly before exercise [7]. Cromolyn used widely for the prevention of EIB, should be administered 15-30 min before exercise [7, 10]. This agent is generally second line because of the duration of effect and the efficacy is less than $beta_2$ agonists [7, 12, 13]. Most investigators reported that SCG was effective in 60-70% of patient with EIB [29], in this study SCG gave a response rate 66.5% and there are a significant difference in PEFR values after using SCG at 3, 6 and 9 minutes post-exercise.

Treatment with $Beta_2$ agonist, salbutamol is considered to be a first choice for treatment young athletes with EIB, inhaled $Beta_2$ agonists are first line medication of EIB both as treatment and prophylaxis of EIB, because of its rapid onset of action a short acting $beta_2$ agonists should be taken 15 min pre-exercise [3, 22] the most common therapeutic recommendation to decrease or inhibit symptoms of EIB is the prophylactic use of short acting bronchodilators ($beta_2$ agonists) such as Salbutamol (Ventolin inhaler) shortly pre-exercise, these agent work by simulating $Beta_2$-receptors on the bronchial smooth muscle causing muscle fibers relaxation and bronchodilation as well as possibly inhibit mast cell degranulation. SABAs given by mouth inhalation 5-20 min pre-exercise are usually effective for 2-4 hours in protecting against or attenuating EIB [16, 19, 20, 22]. Pervious study showed that SABA are most effective drugs to reduce EIB providing complete protection against EIB (90%) of subject when given immediately before exercise, this results agreed with thin study the protection is 88.2% of EIB in female patients [30].

Conclusion

1. The prevalence rate of EIB in Iraqi Girls Intermediate School is 9%
2. Salbutamol is the drug of choice if given 15 minutes before the exercise; the protection rate is 88%.
3. Zafirlukast treatment showed a protection rate 85.7% in female students aged between 12-16 years
4. SCG treatment showed a protection rate 66.6%.

Ethical clearance: Was taken from the scientific committee of the Iraqi Ministry of health

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