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Efficacy of Intravenous Magnesium in Acute severe Bronchial Asthma in adult attending Khartoum Emergency Hospitals

By

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بسم الله الرحمن الرحيم

قال الله تعالى :

(وقل ربِ زدني علماً)

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Dedication

To the soul of my sister "Lyla".

To my mother, father, brothers and sisters

&

to lovely wife and son.

Acknowledgement

Thanks of God

I am deeply grateful to my supervisor Dr. Alaadin Hassan Ahmed, Associate Professor of Medicine, Faculty of Medicine, University of Khartoum, for his careful supervision, generous supply and invaluable advice.

Also great thanks for Medical staff at El Shaab Teaching Hospital and Omdurman Teaching Hospital for their great help, encouragement.

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I wish to express my appreciation and sincere gratitude to the patients who participate in this study.

My gratitude is extended to my families in particular my sister "Amal Obied", for encouragement and support.

List of abbreviations

AA	Acute asthma
ABGs	Arterial blood gases
ED	Emergency Department
IB	Ibratropium
RR	Respiratory rate
HR	Heart rate
BP	Blood pressure
PP	Pulsus paradoxus
PEFR Peak	PEFR Peak expiratory flow rate
SO_2	Saturation of oxygen
pMDIs	Pressurized metered-doses inhalers with spacer

ABSTRACT

Background: studies of IV magnesium sulphate as a treatment for acute asthma have had mixed results with some data suggesting a benefit for acute severe asthma, but not for mild to moderate asthma.

Design: single-blind controlled clinical trial.

Setting: Emergency Departments (ED) of two hospitals (ElShaab and Omdurman Teaching Hospitals).

Patients: patients aged 18 to 60 years presenting with acute severe asthma and PEFR < 50% predicted on arrival to the ED.

Intervention: All patients received nebulized salbutamol at regular intervals, and IV hydrocortisone. Two grams of IV magnesium sulphate were randomly administered to 25 patients (out of 50) using computer randomization program or nothing 30 minute after ED arrival. The primary efficacy end point was PEFR at 240 minute.

Results: Fifty patients were included and mean PEFR at ED arrival was 33.7% predicted. At 240 min, patients receiving magnesium had a mean PEFR of 65.1% predicted compared to

48.2% predicted in those who did not received magnesium (CI 7.97 and 25.89) with P. < 0.005.

In conclusion this study indicated that when 2 g $MgSO_4$ is given as an adjunct to standardized asthma therapy to patients presented with severe acute asthma, there is significant improvement in clinical scenario and pulmonary function. Thus these would support routine use of $MGSO_4$ in patients with severe acute asthma.

So the study recommended for further larger multicenter studies, should support or talk more about the effect of $MgSO_4$ on moderate to severe Sudanese asthmatic patients.

ملخص الأطروحة

إتفق الباحثون على فاعلية سلفات الماغنزيوم الوريدية فى علاج نوبات الربو الشديدة الحدة وليس فى حالة الخفيفة أو المتوسطة.

نوع الدراسة: أحادية الإختيار العشوائي المضبوط.

مكان الدراسة: حوادث مستشفى الشعب التعليمي وام درمان التعليمي فى الفترة من يونيو 2005 إلى يناير 2006م.

مجموعة الدراسة: مرضى الربو الحاد الذين تتفاوت أعمارهم ما بين 18 – 60 سنة الواردين لحوادث مرضى الصدر والربو بالمستشفيات أعلاه.

فى هذه الدراسة تم اعطاء 2 جم من سلفات المغنزيوم بالوريد بعد 30 دقيقة من إعطاء جرعة بخار الفينتولين بالإضافة للهيدروكورتزون (200 ملجم بالوريد) لـ 25 مريضاً من إجمالي 50 مريض تم إختيارهم عن طريق برنامج الإختيار العشوائي بالحاسوب ومن ثم متابعتهم لمدة 240 دقيقة.

أوضحت نتائج الدراسة أن 50 مريضاً ادخلوا فى الدراسة وكان معدل سريان الزفير القصوي عند الوصول للمستشفى 33,7% من المتوقع، وبعد مرور 240 دقيقة من اعطاء سلفات المغنويوم الوريدية (2 جم)، 65.1% من المتوقع مقارنة بـ 48,2% من المتوقع للمرضى الذين لم يعطوا سلفات الماغنسيوم الوريدية (بفارق ثقة يتراوح ما بين 7.97 – 25.89%) بقيمة بـ أقل من 0.005.

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INTRODUCTION AND LITERATURE REVIEW

1.1. Definition of asthma:

Asthma is a chronic, episodic, disease of the airways, and it is best viewed as syndrome. In 1997 the national Heart lung and blood institute (NHLBI) included the following features as integral to the definition of asthma; [1,2] recurrent episodes of respiratory symptoms; variable airflow obstruction that is often reversible, either spontaneously or with treatment; presence of airway hyperreactiviy and, importantly, chronic airway inflammation, which is characterised by oedema, infiltration with inflammatory cells especially, mast cells, eosinophils, T-lymphocytes, macrophages, neutrophils, and epithelial cells, hypertrophy of glands and smooth muscle and damaged epithelium. The inflammation results in the state of hyper-responsiveness where airways narrow easily in response to a wide range of stimuli.[3] This may result in coughing, wheezing chest tightness and shortness of breath, which are often worse at night. The airway narrowing is usually reversible but in some patients with chronic asthma the inflammation may lead to irreversible airways

obstruction.[4] In general the more severe the asthma the more frequent and severe are the attacks.

All patients with asthma are at risk of having exacerbiations characterized by a progressive increase in shortness of breath, cough, wheezing or chest tightness, and by a decrease in expiratory airflow that can be quantified by simple measures of pulmonary function such as the peak expiratory flow rate (PEFR). Terms like acute asthma (AA)/ asthma attack, or status asthmatics have been used to describe this condition. The severity of exacerbations may range form mild to life threatening. Deterioration usually progress over hours, days, or "weeks; however, a few patients have sudden (over minutes) and unexpected increase in airway obstruction.[5]

1.2. Prevalence and etiology:

Asthma is very common; it is estimated that 4 to 5% of the population of the united State is affected. Similar figures have been reported from other countries. Bronchial asthma occurs at all ages but predominantly in early life. About one-half of cases develop asthma before age 10, and another third occur before age 40. In

childhood, there is a 2 : 1 male/female preponderance, but the sex ratio equalizes by age 30.[6]

Acute asthma (A.A) is a common medical emergency faced by Emergency Department (ED) and intensive care specialists. In the United States, asthma represents the 11th most frequent ED diagnosis nationwide, and adolescents and young adults are the most likely age groups to visit the ED for treatment.[7]Women visit the ED and are hospitalized for AA twice as often as men.[8.9]

Previous data suggested that 40% of these hospitalizations occur during the premenstrual phase of the cycle.[10] Men are less likely than women to report severe asthma symptoms and activity limitations in the presence of airway obstruction.[11]

1.3. Pathophysiology:

Different triggers cause asthma exacerbations by inducing airway inflammation or provoking acute bronchospasm or both. Triggers vary from person to person and from time to time. Exposure to indoor and outdoor allergens, air pollutants, respiratory tract infections (primarily viral), exercise, whether changes, foods, additives, drugs, and extreme emotional expressions are me main triggers identified clinically. Other factors

that may cause exacerbations are rhinitis, bacterial sinusitis, poly posts, menstruation, gastroesophageal reflux, and pregnancy. The mechanisms of acute airflow limitation vary according to the stimulus. Allergen-induced bronchoconstriction results from the IgE-dependent release from airway mast cells of mediators, including histamine, prostaglandins, and leukotrienes, that contract the smooth muscle.[12]Acute airflow limitation may also occur because airways in asthma are hyperresponsive to a wide variety of stimuli. In this case, the mechanisms for causing bronchoconstriction consist in combinations of release of mediators from inflammatory cells and stimulation of local and central neural reflexes. Finally, airflow limitation results from edematous swelling of the airway wall with or without smooth-muscle contraction. The increase in microvascular permeability and leakage leads to the mucosal thickening and swelling of the airway outside the smooth muscle. Progressive airway narrowing due to airway inflammation and/or increased bronchiolar smooth-muscle tone is the hallmark of an asthma attack, and leads to increased flow resistance, pulmonary hyperinflation, and ventilation/perfusion (V/Q) mismatching. Without correction of

the airway obstruction, respiratory failure is a consequence of increased work of breathing, gas exchange inefficiency, and respiratory muscle exhaustion.[12]

Gas Exchange:

Mild-to-moderate hypoxemia, along with hypocapnia and respiratory alkalosis, are common arterial blood gas (ABG) findings in severe AA.[13,14] If airflow obstruction is severe and unrelieved, there may be progression to hypercapnia and metabolic acidosis, the former as a result of muscle fatigue and inability to maintain adequate alveolar ventilation, and the latter a result of lactate production by the respiratory muscles exceeding clearance mechanisms.

Asthma Attack Evolution:

There are two different pathogenic scenarios involved in the asthma attack progression.[15] When airway inflammation is predominant, patients show a progressive (over many hours/days, or even weeks) clinical and functional deterioration (type 1 or slow-onset acute asthma). Upper respiratory tract infections were frequent triggers, and these patients exhibited a slow therapeutic response. Also, they may have allergic

inflammation with eosinophils in the airways. In the less common asthma progression scenario, bronchospasm is predominant and patients presenting with a sudden-onset asthma attack (type 2 or asphyxic or hyperacute asthma) characterized by rapid development of airway obstruction (<3 to 6 h after the onset of the attack). Respiratory allergens, exercise, and psychosocial stress are the most frequent triggers. Surprisingly, these patients show a more rapid and complete response to treatment. Finally, they have a predominance of neutrophils in their airways.[16]

Fatal asthma:

In many countries, asthma mortality increased from the 1960s to the second half of the 1980s, but reached a plateau and has subsequently declined.[17,18] This recent downward trend may reflect better management of this condition in primary care. Asthma has a, low mortality rate compared with other lung diseases, but mortality does occur, typically in patients with poorly controlled disease whose condition gradually deteriorates over a period of days or even weeks before the fatal attack.[19,20] Occurrence of this type of asthma progression is between 60% and 90% of adults with AA who have fatal and near-fatal

crises.[19,20,21,22,23] This observation suggests many patients have a window of opportunity for recognition and reversal of this period of deterioration. Infrequently, death occurs suddenly. Accordingly, most deaths are preventable, and a useful practice is to assume that every exacerbation is potentially fatal.[23,24]

The majority of deaths occur at home, work, or during transport to the hospital. The most specific marker associated with an increased risk of dying from asthma is a history of repeated hospital admissions, particularly if patients required ventilatory assistance.[25,26] Nevertheless, a history of recurrent admissions is found in only 36% of fatal cases and ventilatory assistance or admission to an ICU in only 6%.[27] Although the presence of such events is extremely important in a given patient, their absence is of no value in assessing risk.[23] It has been reported that a subgroup of patients with near-fatal asthma have blunted perception of dyspnoea, and show more ED visits, hospitalizations, near-fatal asthma attacks, and deaths.[28,29]Additional epidemiologic fatal-asthma markers include psychiatric illness,[30] illicit drug use,[31,32] and the lack of an asthma self-management plan. Also, anxiety and depression are related to the outcome of ED treatment.[33]

Two hypotheses have been postulated for the cause of asthma-related deaths. Cardiac arrhythmias may contribute to some of the observed mortality, particularly in adults. The risk is theoretically increased by hypokalemia and prolongation of the QTc interval coupled to the use of [beta]-agonists in high doses.[34,35] However, in a series of patients with near-fatal attacks, few arrhythmias other than sinus tachycardias and bradycardias were found[19,36]While some have claimed that this mechanism of death is supported by literature that points to an association between more [beta]-agonist use and mortality, this association could be explained on the basis of more severe asthma requiring more treatment and exhibiting a higher death rate despite treatment, not because of it.[37] A more likely hypothesis is that deaths occur as a result of asphyxia due to severe limitation of airflow and hypoxemia. This hypothesis has received support from the pathologic evidence indicating that patients with fatal asthma almost invariably have extensive airway obstruction, with mucous plugging and dynamic hyperinflation apparent even at autopsy.[38]

1.4. Emergency department management:

1.4.1. Assessment:

AA is a medical emergency that must be diagnosed and treated urgently. The assessment of an asthma exacerbation constitutes a process with two different dimensions: (1) a static assessment to determine the severity of attack, and (2) a dynamic assessment to evaluate the response to treatment. Overall, it requires an analysis of several factors.[39,40]

1.4.2. Medical History:

A brief history pertinent to any exacerbation should be obtained. The objectives are to determine time of onset and severity of symptoms, especially compared with previous exacerbations, all current medications, prior hospitalizations and ED visits, prior episodes of respiratory failure (intubation, mechanical ventilation), and psychiatric or psychological disorder. The existence of such events has been. associated with poor outcomes, but their absence does not ensure'low risk.[25,26,41]

A number of conditions may mimic or complicate the diagnosis of AA. The absence of a history of asthma, particularly in an adult, should alert the ED physician to an alternative diagnosis.[40] Congestive heart failure, particularly predominant

left ventricular failure or mitral stenosis, occasionally may present with episodic shortness of breath accompanied by wheezing. Perhaps the most common and most difficult diagnostic problem in asthma is its differentiation from COPD. In subjects > 40 years of age, a distinction between COPD and asthma is often difficult, if not impossible. Laryngeal, tracheal, bronchial obstruction resulting from any of a number of causes may produce shortness of breath, localized wheezing, inspiratory strider localized over the trachea, or unilateral hyperinflation noted on chest radiography, which often mimics asthma. Recurrent small pulmonary emboli may be manifested by attacks of shortness of breath and, very rarely, wheezing heard oil careful auscultation. Finally, recurrent attacks of shortness of breath at rest may be due to the hyperventilation syndrome.[41]

1.4.3. Physical examination:

Particular attention should he paid to the patient's general appearance. Patients with the most severe conditions will he sitting upright.[42] The use of accessory muscles has received attention as an indicator of severe obstruction, and the presence of sternocleidomastoid retractions or suprasternal retraction

correlated with impairment in lung function.[43]In consequence, accessory muscle use can be considered a useful sign of severe airflow obstruction.

Respiratory rate (RR) > 30 breaths/ min, tachycardia > 120 beats/ min, or PP > 1.9 mm Hg have been described as vital signs of acute severe asthma. However, composite data from large clinical studies [44,45] demonstrated that > 50% of patients with acute severe asthma have heart rates ranging between 90 beats/min and 120 beats/min, with only 15% exceeding this value. In general, successful treatment of airflow obstruction is associated with a decrease in heart rate/ although some improving patients remain tachycardia because of the chronotropic effects of bronchodilators.

While distinguishing between asthma-related tachycardia and treatment-related tachycardia can be difficult, patients who note subjectively improved, breathing hut exhibit a fine tremor are likely receiving excessive [beta]-agonist dosing. Specifically older patients tend towards treatment-related tachycardia.[46] RRs range between 20 breaths/min and 30 breaths/min in > 50% of patients, and are [greater than or equal to] 30 breaths/min in < 20% of

patients. In severe airflow obstruction, Plusus Paradox's is greater titan the normal value of 10 mm Hg and typically > 15 mm Hg; however, only severe PP (> 25 mm Hg) was a reliable indicator of severe asthma.[47] Additionally, PP is not easy to evaluate. It is also extremely important to emphasize that PP is dependent on patient effort, since it reflects the inspiratory and expiratory excursions of thoracic pressure resulting from active respiratory muscle contraction. When patients fail to improve and have fatigue, with decreasing respiratory effort, PP will fall. Interpreting the falling PP in this context as improvement in airflow obstruction is a grave error. Finally, wheeze and dyspnea are present in virtually all patients with AA, and they correlated poorly with the degree of airflow limitation.[48]

1.4.4. Objective Measurement of Airflow Obstruction:

The measurement of lung function provides a more objective assessment of obstruction, but does depend on good technique and adequate patient effort. On presentation, after the initial treatment, and at subsequent frequent intervals, it constitutes an integral part of the assessment of disease severity (static assessment) and the response to therapy (dynamic

assessment) in any patient > 5 years of age.[1,2] Measurement of airflow obstruction should be made using one of following techniques: PEFR measured with a peak flowmeter, or FEV_1 determined by spirometry. Many studies [40,49] have found satisfactory correlations between both measures among healthy and stable patients or patients with acute asthma. PEFR values tended to have more variability when pulmonary function was more impaired, and to underestimate the degree of pulmonary impairment. Even though spirometry is the "gold standard" in most asthma patients, it is easier to measure PEFR than FEV_1; PEFR measurement is common in the ED because it is inexpensive, portable, and safe. The typical asthmatic patient who presents for care to an ED will exhibit a broad range of PEFR and FEV_1 values.[46,50] Approximately 55% of patients will have values < 40% of normal, and one fifth will range between 40% and 60% of normal.

1.4.5. Pulse Oximetry:

Measurement of oxygen saturation by pulse oximetry (SOi is necessary in all patients with AA to exclude hypoxemia; it allows monitoring of SO_2. on a continuous basis. The measure of

SO_2 indicates which patients may be in respiratory failure and therefore in need of more intensive management.[51] The goal of treatment should be to maintain SO_2 at [greater than or equal to] 92%[52,53]; however, it does not help to predict which patients can behospitalized.[54]

1.4.6 Arterial blood gases (ABGs):

ABG determination is rarely necessary before the initiation of treatment. Because of the accuracy and utility of pulse oximetry only patients whose oxygenation is not restored to > 90% with oxygen therapy require ABG determination. When adequate oxygenation remains a problem despite supplemental oxygen, additional complicating conditions such as pneumonia should be considered. Repeated ABG sampling usually is not needed to determine whether a patient is deteriorating or improving.[55]

1.4.7 Chest Radiography:

Chest radiography plays only a small role in the assessment and management of patients with acute asthma (AA) is indicated only in patients who present with signs or symptoms of pneumothorax (pleuritic chest pain, mediastinal crunch, subcutaneous emphysema, cardiovascular instability, or

asymmetric breath sounds), in patients with clinical findings suggestive of pneumonia, or in an asthmatic patient who after 6 to 12 h of intensive treatment does not respond to therapy.

1.4.8. Cardiac Rhythm Monitoring:

ECGs need not be routinely obtained, but continual monitoring is appropriate in older patients/56) and in those with coexisting heart disease.(2)

1.4.9. Response to Therapy:

Measurement of the change in PEFR or FEVi over time may be one of the best ways to assess patients with acute asthma and predict the need for hospital admission. The response to initial treatment in the ED is a better predictor of the need for hospitalization than is the severity of an exacerbation at presentation.(57) Early response to treatment (PEFR or FEV_1) at 30 min) is the most important predictor of outcome.(58) PEFR variation over baseline > 50 L/min and PEF > 40% of normal, both measured at 30 min after beginning of treatment, are predictors of good outcome.(59,60)

1.5. Treatment:

1.5.1. Convensional therapy:

Initial ED treatment of patients with AA should be titrated to the severity of presentation and the response to initial treatment. Supplemental oxygen is recommended for the majority of patients. The goal of treatment should be to maintain SO_2 at greater than or equal to 92%. Inhaled [beta]-agonists and corticosteroids are the core treatments for almost all patients. The addition of IB to [[beta]-agonists seems indicated as first-line therapy in adult patients with severe exacerbations; pMDIs with large-volume valved spacers are preferred to jet nebulizers, particularly in patients with the most severe obstruction. Inhaled corticosteroids could produce early therapeutic effects in patients with prolonged duration of symptoms before ED presentation.

1.5.2. Magnesium:

1.5.2.1. Introductions:

Magnesium is the fourth most abundant mineral in the body and essential to good health approximately 50% of total body magnesium is found in bone. The other half is found predominantly inside of body tissues and organs. Only 1% of

magnesium is found in blood but the body work very hard to keep blood levels of magnesium constant.[61]

Magnesium is needed for more than 300 biochmaical reactions in the body. It helps maintain normal muscle and nerve function, keeps heart rhythm steady, supports a healthy immune system, and keeps bones strong. Magnesium also helps regulate blood sugar levels, promotes normal blood pressure, and is known to be involved in energy metabolism and protein synthesis. [62,63]

Dietary magnesium is absorbed in the small intestines and is excreted through the kidneys.[61,63,64] Green vegetable such as spinach are good sources of magnesium, beans, peas, nuts and seeds and whole, unrefined grains are also good sources of magnesium.[65] Refined grains are generally low in magnesium.[64,65]

The daily recommended Mg requirement is 250 to 350 mg (10.4-14.6 mmol) in adults and an additional 100 to 150 mg in children and pregnant or nursing women.[66]

1.5.2.2. Biological considerations:

Assay of total plasma Mg by spectrophotometry is precise and easy to perform (0.7-1.1 mmol L-1 or 1.4-2.2 mEq L-1, or 16.8-26.4 mg L-l). However, owing to the intracellular nature of this ion, these values are not exactly indicative of the Mg pool in the organism or of a possible state of deficiency.[67] Other concentrations have been studied to allow better assessment of true Mg deficiencies, namely intracellular (8-10 mmol L-1)[68] and ionized plasma Mg (0.65 ± 0.1 mmol L-l) concentrations.

Interferences with calcium ions at the level of the Mg electrode reduce the relevance of the ionized Mg assay.[67] Because of the long life of Mg and its slow turnover, erythrocytic Mg might be a better indicator of deficiency (values in the literature: 2.10 ± 0.4 mmol-L-l)[65,69] Lymphocytic Mg would appear to be a better indicator of the Mg content of muscle and myocardium and of ionized Mg.[70] However, the relation between these last evaluations and the Mg pool of the organism remains uncertain.[67]

Urinary excretion of Mg is highly variable, ranging from 5 mmol/day-l in the normomagnesimic subject to 0.5 mmol'day-1 in the deficient subject. Measurement of urinary excretion helps separate renal from non-renal causes of hypomagnesemia. In the

presence of hypomagnesemia, high urinary excretion suggests that increased renal loss is the mechanism of Mg depletion, whereas low urinary excretion suggests miscellaneous or gastrointestinal causes. Studies of the urinary excretion of Mg after a loading test can help diagnose Mg deficiency when magnesemia is normal: the subject 'without-deficiency excretes more than 60-70% of Mg input,whereas the subject with a deficiency excretes less than 50%.[70,71]

Various changes in Mg can occur during the perioperative period. Plasma concentrations are decreased after abdominal[72.73] or orthopedic surgery.[74] After heart surgery, mean magnesemia is reduced[75,76] and the frequency of hypomagnesemia increased from 19.2% preoperatively to 71% immediately after surgery before dropping slightly to 65.6% 24 hr later.16 For Zuccala et al., the depletion of intracellular Mg would appear to be closely correlated with reduced serum concentrations. These authors found that both concentrations decreased after orthopedic surgery.[77]

1.5.2.3. Cellular physiological properties of Mg:

1.5.2.3.1. Action on membrane and membrane pumps:

Mg intervenes in the activation of membrane Ca ATPase and Na-K ATPase involved in transmembrane ion exchanges during depolarization and repolarization phases. Mg deficiency impairs the action of ATPase pumps and leads to a reduction of intracellular ATP as well as to increased concentrations of sodium and calcium and decreased concentrations of potassium within the cell.[78] It would thus appear to act as a stabilizer of cell membrane and intracytoplasmic organelles.[79]

1.5.2.3.2. Action on ion channels:

Mg is considered to act as a regulator of different ion channels. A low intracellular Mg concentration allows potassium to leave the cell, thereby altering conduction and cellular metabolism.[78,79] Mg also exerts its effects on calcium channels of potential-dependent L type in membrane and on those of sarcoplasmic reticulum. A competitive antagonist action is directed against calcium inflows. By inhibiting the calcium activation dependent on the sarcoplasmic channel/ Mg limits the outflow of calcium from the sarcoplasmic reticulum, the main site of intracellular calcium storage.[79]Thus, Mg is a calcium channel

blocker and a modulator of calcium channel activity, which means that a rise in intracellular calcium occurs during hypomagnesemia.[66,78]

1.5.2.3.3. Enzymatic activation:

Intracellular free Mg is involved in the energy reactions of phosphorylation and is necessary for the activation of hundreds of enzymatic reactions concerning ATP. Inorganic phosphate and ATP within the cell reduce free Mg, whereas the conversion of ATP to adenosine diphosphate (ADP) increases it.[69]In fact, Mg interacts substrate. Intracellular Mg deficiency is correlated with the impaired function of many enzymes utilizing high-energy phosphate bonds, as in the case of glucose metabolism.[66]

1.5.2.4. Clinical effects of Mg:

- ***Cardiovascular effects:*** The action of Mg on calcium channels and pumps actually serves as a regulator of transmembrane and intracellular flows. In addition, Mg has an indirect effect on cardiac muscle cells by inhibiting calcium uptake on the troponin C of myocytes and thereby influencing myocardial contractility. In a preparation of isolated animal heart, Mg, because of its anticalcium properties, caused a dose-dependent

negative inotropic effect.[80] Rasmussen et al. observed a moderate positive inotropic effect after infusion of Mg into healthy volunteers which could have been related to the vascular effect of Mg in reducing systemic arteriaK81) and pulmonary artery pressures through a decrease of vascular resistance.[79] In vitro studies on isolated aorta, the absence of Mg potentiated the vasoconstrictive effect of angiotensin and acetylcholine, and hypermagnesemia induced the relaxation of smooth muscle.[82] The role of Mg in transmembrane movements of calcium and the activation of the adenylate cyclase involved in the synthesis of cyclic adenosine monophosphate (AMP; a vasodilator) could account in part for this effect. A reduction of cyclic AMP in hypomagnesemia induced an increase of vascular tone.[83] Mg deficiency may also play a role in the pathogenesis of variant angina or coronary spasm[84] and infusion of Mg can produce coronary dilatation and suppress acetylcholine-induced coronary spasm in patients with vasospastic angina.[85]

In anesthetized dogs, a dose-dependent decrease in heart rate and systolic and diastolic arterial pressures was observed after the infusion of Mg.[86] In humans, hemodynamic studies have

shown a peripheral (predominantly arteriolar) vasodilator effect.[87,88] After the rapid infusion of a dose of 3 or 4 g of sulfate ($MgSO_4$), a reduction of systolic arterial pressure occurred, in relation to decreased systemic vascular resistance. Positive inotropic and chronotropic effects compensated for the former by increasing the heart index, whereas pulmonary vascular resistance remained unchanged. In the study by Vigorito et al., coronary vascular resistance decreased as coronary blood flow increased.[89]

Disturbances in cellular ionic movements induced by dysmagnesemia could affect the excitability of the heart cells of nodal tissue responsible for cardiac rhythm disorders.[79]In electrocardiographic studies in anesthetized dogs, a dose dependent lengthening of the PR and RR intervals was noted, as well as a dose-dependent increase of QRS duration, without any modification of the QTc interval. A dose-dependent lengthening of atrioventricular conduction time was also observed.[86]

- ***Muscle and neiiromiiscular transmission:*** Calcium and Mg have opposite effects on muscle. Hypomagnesemia stimulates contraction, whereas hypocalcemia induces relaxation. Hypomagnesemia causes rapid, passive release of calcium by the

sarcoplasmic reticulum as a result of the opening of calcium channels, whereas high concentrations of Mg block this process.[89] Neuromuscular transmission is altered by a preponderant presynaptic effect as well as a postsynaptic effect. Mg acts competitively in blocking the entry of calcium into presynaptic endings. Presynaptic release of acetylcholine is reduced by high Mg concentrations, thereby altering neuromuscular transmission.[67,89] Mg decreases the effects of acetylcholine on postsynaptic muscle receptors and has been shown to increase the threshold of axonal excitation. Hypomagnesemia induces neuromuscular hyperexcitability,[69] while hypermagnesemia causes neuromuscular weakness as well as a reduction or even an abolition of deep tendon reflexes. Excess serum Mg concentrations produce progressive inhibition of catecholamine release from adrenergic nerve endings/ adrenal medulla and adrenergic postganglionic sympathetic fibres[89,90]

- Central nervous system: The property of Mg as an antagonist of N-methyl-D-aspartate (NMDA) receptors is the basis for studies of its adjuvant effect in perioperative analgesia. This calcium inhibitory effect causes central arteriolar vasodilation and acts

against vasospasm. The inhibition of NMDA receptors and the increased production of vasodilator prostaglandins induced by Mg could account for the anticonvulsant action of Mg.

Other clinical effects:

The postulated mechanisms for the bronchodilator effects of Mg includes inhibitory action on smooth muscle contraction, histamine release from mast cells and acetylcholine release from cholinergic nerve terminals.[67,91] The precise mechanism of action for the tocolytic effects[92,93] of Mg sulfate is not clearly defined, but may be related to the action of Mg as a calcium blocker in inhibiting muscle contractions.

1.5.2.5. Dysmagnesemia:

- ***Hypomagnesemia:*** Hypomagnesemia, defined as a plasma concentration below 0.7 mmol L-l, is considered severe when under 0.5 mmol'L-1. This condition is most often associated with a true depletion of Mg in the organism, although a Mg deficit can exist even when magnesemia is normal. Thus, measurement of the urinary excretion of Mg and possibly a loading test can help establish the diagnosis.[94]As the bone and intracellular Mg reserves of the organism cannot be easily mobilized toward the

extracellular sector, a negative Mg balance rapidly leads to hypomagnesemia.[6] A deficit was found in 47% of blood samples obtained from hospitalized patients with increasing Mg thresholds of < 0.6 mmol-L-l, < 0.62 and < 0.74 mmol-L-1 respectively.[72,80,95,96] The incidence of deficit was much higher in patients sampled in surgical and medical intensive care units, reaching 61 and 65% to thresholds of 0.75 and 0.7 mmol"L-l respectively.[97,98] The high rates for these patients were due to an association of several causes of hypomagnesemia. This disorder is often overlooked, although it should probably be searched for systematically because of its significance for the prognosis of patients.[96] In fact, a prospective study of patients hospitalized in wards and intensive care units (ICU) showed that the death rate was twice as high for the group with hypomagnesemia on admission as for the group without a deficit.[177] These data were confirmed by Chernow et al. in a study of postoperative ICU patients, for whom the death rate was 41% vs 13% for patients without hypomagnesemia.[97] Other studies after heart surgery showed that patients with hypomagnesemia experienced more rhythm disorders. Time on

the ventilator was longer[99,100] and morbidity was higher than for patients with normal magnesemia.[100] Another study showed that a greater than 10% reduction of serum and intracellular concentrations was associated with a higher rate of postoperative ventricular arrhythmias.[77] As the regulation of Mg homeostasis is ensured by the digestive tube or the kidney, the main causes of hypomagnesemia are digestive (lack of input or absorption, or excessive elimination) or renal (increased excretion).

- ***Hypermagnesemia:*** Hypermagnesemia, which is less frequent than hypomagnesemia/ was found in 9.3, 5.7 and 3.5% of blood samples obtained from hospitalized patients with increasing Mg thresholds of > 0.95 mmorL-1, > 0.99 and > 1.07 mmol-L-l respectively.[95,96] Moderate hypermagnesemia is frequent in patients with chronic renal insufficiency, during rhabdomyolysis (due to release of Mg from disintegrating muscle) and after excessive use of antacids or laxatives containing Mg salts.[101] Severe hypermagnesemia is most often observed during the therapeutic administration of Mg sulfate in

patients with chronic renal insufficiency or during treatment of eclampsia.[102]

Neuromuscular and cardiovascular manifestations are predominant in the clinical symptomatology of hypermagnesemia. However, clinical severity is not always correlated with the degree of hypermagnesemia.[102] Flushing, nausea and/or vomiting can be early signs. Central neurological signs range from somnolence to deep coma. Deep tendon reflexes may be reduced or totally lost. Breathing may be decreased or even stopped because of paralysis of the respiratory muscles. Cardiovascular abnormalities may include hypotension because of peripheral vasodilatation, conduction disorders (lengthening of the PR and/or QT intervals or the QRS complex, and atrioventricular block), bradycardia and even cardiac arrest.[71]

Treatment is based on stopping Mg inputs. An infusion of calcium salts, which momentarily antagonizes some Mg effects, can be initiated in emergency conditions (2.5-5 mmol in a slow iv infusion until disappearance of conduction disorders) when neurological and cardiovascular complications are life-threatening.(70'71'89'90) Loop diuretics inhibit renal reabsorption

of Mg and induce an increased urinary excretion of Mg, but also of calcium, which can cause hypocalcemia and thereby intensify the clinical signs of hypermagnesemia. Calcemia needs to be monitored, and some authors recommend preventive administration 'of calcium salts when diuretics are used. For patients with renal insufficiency, recourse to dialysis involving a Mg-poor fluid is frequent.

Interactions:

Potassium supplements, manganese, loop and thiazide diuretics, oral contraceptives, estrogen-replacement therapy, Cisplatin, cyclosporine, digoxin, or medications that reduce stomach acid: You may need extra magnesium. [103,104]

Antibiotics in the tetracycline family or nitrofurantion (Macrodantin): You should separate your magnesium dose from doses of these medications by at least 2 hours to avoid absorption problems.

Oral diabetes medications in the sulfonylurea family: Work closely with your physician when taking magnesium to avoid hypoglycemia.

What Is the Scientific Evidence for Magnesium?

Migraine Headaches:

A double-blind study found that regular use of magnesium helps prevent migraine headaches. In this 12-week trial/105) people with recurrent migraines were given either 600 mg of magnesium daily or placebo.[106] By the last 3 weeks of the study, the treated group's migraines had been reduced by 41.6%, compared to a reduction of 15.8% in the placebo group. The only side effects observed were diarrhea (in about one-fifth of the participants) and, less often, digestive irritation.

Similar results have been seen in other smaller double-blind studies.[107,108] One study found no benefit,[109] but it has been criticized on many significant points, including using an excessively strict definition of what constituted benefit. [110]

Noise-related hearing loss:

One double-blind, placebo-controlled study on 300 military recruits suggests that 167 mg of magnesium daily can prevent hearing loss due to exposure to high-volume noise.[111]

Kidney stones:

Magnesium inhibits the growth of calcium oxalate stones in the test tube 60 and decreases stone formation in rats.[112] However,

human studies have had mixed results. In one 2-year open study, 56 people taking magnesium hydroxide had fewer recurrences of kidney stones than 34 people not given magnesium, in contrast, a double-blind (and, hence, more reliable) study of 124 people found that magnesium hydroxide was essentially no more effective than placebo.[113]

Hypertension:

Magnesium works with calcium and potassium to regulate blood pressure. Several studies suggest that magnesium supplements can reduce blood pressure in people with hypertension.[114,115] although some have not.

Angina:

In a double-blind, placebo-controlled trial of 187 people with angina, 6 months' treatment with magnesium at a dose of 730mg daily improved exercise tolerance and enhanced overall quality of life.[97] Benefits were also seen in a similar, smaller double-blind trial.[116]

Dysmenorrhea:

A 6-month, double-blind, placebo-controlled study of 50 women with menstrual pain found that treatment with magnesium significantly improved symptoms.[117] The researchers reported evidence of reduced levels of prostaglandin F2 alpha, a hormone-like substance involved in pain and inflammation.

Similarly positive results were seen in a double-blind, placebo-controlled study of 21 women.[118]

Premenstrual symptoms:

A double-blind/ placebo-controlled study of 32 women found that magnesium taken from day 15 of the menstrual cycle to the onset of menstrual flow could significantly improve premenstrual mood changes.[119]

In addition, one small double-blind study (20 participants) found that magnesium supplementation can help prevent menstrual migraines.[120]

Preliminary evidence suggests that the combination of magnesium and vitamin B6 might be more effective than either treatment alone.[121]

Pregnancy-induced leg cramps:

Pregnant women frequently experience painful leg cramping. One double-blind trial of 73 pregnant women found that 3 weeks of magnesium supplements significantly reduced leg cramps as compared to placebo.[122]

One study found that magnesium supplements might be helpful for people with mitral valve prolapse who also have low levels of magnesium in the blood.[123]

There is some evidence that magnesium may decrease the atherosclerosis risk caused by hydrogenated oils, margarine-like fats found in many "junk" foods.[124]

Studies on magnesium supplements for improving sports performance have returned contradictory results.[125,126]

Magnesium supplements do not appear to be very helpful, if at all, for preventing preeclampsia.[127,128,129,130] (Magnesium, taken by injection rather than orally, however, is probably helpful for treating preeclampsia.[131,111,112]

Magnesium is sometimes said to decrease symptoms of restless legs syndrome, but the evidence that its work consists solely of open trials without a placebo group, and such studies are not trustworthy[132,133] Magnesium has also been suggested as a

treatment for Alzheimer's disease, attention deficit disorder, fatigue, fibromyalgia, low HDL-cholesterol, osteoporosis, periodontal disease, rheumatoid arthritis, and stroke. However, no reliable evidence exists that it is effective for any of these conditions.

Magnesium is sometimes suggested for stabilizing the heart after a heart attack, but one study actually found that use of magnesium slightly increased risk of sudden death, repeat heart attack, or need for bypass surgery in the year following the initial heart attack.[134]

Despite some early enthusiasm, combination therapy with vitamin B6 and magnesium has not been found helpful in autism.[105,135,136]

Although magnesium is sometimes mentioned as a treatment to help keep the heart beating normally, a 6-month, double-blind trial of 170 people did not find it effective for preventing atrial fibrillation.[137] However, a small double-blind, placebo-controlled trial found that magnesium supplements reduced episodes of arrythmia in individuals with congestive heart failure.[138] One possible explanation: people with congestive

heart failure often take drugs (loop diuretics) that deplete magnesium. The combination of magnesium deficiency with digoxin may cause arrhythmias.[139,140,141] Thus, it is possible that the benefits seen here were caused by correction of that depletion.

One double-blind, placebo-controlled study failed to find magnesium helpful in glaucoma.[142]

There is no real evidence that oral magnesium helps asthma, and even some evidence that it does not help.[143]

Who may need extra magnesium?

Magnesium supplementation may be indicated when a specific health problem or condition causes an excessive loss of magnesium or limits magnesium absorption.[63,144,145,146]

Some medicines may result in magnesium deficiency, including certain diuretics, antibiotics, and medications used to treat cancer (anti-neoplastic medication).[147,148,149] Examples of these medications are:

- ***Diuretics:*** Lasix, Bumex, Edecrin, and hydrochlorothiazide.
- ***Antibiotics:*** Gentamicin, Amphotericin, and Cyclosporin.
- ***Anti-neoplastic medication:*** Cisplatin.

Individuals with poorly-controlled diabetes may benefit from magnesium supplements because of increased magnesium loss in urine associated with hyperglycemia.[150]

Magnesium supplementation may be indicated for persons with alcoholism. Low blood levels of magnesium occur in 30% to 60% of alcoholics, and in nearly 90% of patients experiencing alcohol withdrawal.[103,104] Anyone who substitutes alcohol for food will usually have significantly lower magnesium intakes.

Individuals with chronic malabsorptive problems such as Crohn's disease, gluten sensitive enteropathy, regional enteritis, and intestinal surgery may lose magnesium through diarrhea and fat malabsorption.[151]Individuals with these conditions may need supplemental magnesium. Individuals with chronically low blood levels of potassium and calcium may have an underlying problem with magnesium deficiency. Magnesium supplements may help correct the potassium and calcium deficiencies.[148] Older adults are at increased risk for magnesium deficiency. The 1999-2000 and 1998-94. National Health and Nutrition Examination Surveys suggest that older adults have lower dietary intakes of magnesium than younger adults.[152,153] In addition, magnesium absorption

decreases and renal excretion of magnesium increases in older adults.[141] Seniors are also more likely to be taking drugs that interact with magnesium. This combination of factors places older adults at risk for magnesium deficiency.[64] It is very important for older adults to consume recommended amounts of dietary magnesium.

Magnesium and asthma:

Several mechanisms have been proposed to explain the potential beneficial effect of magnesium in asthma, in vitro magnesium causes relaxation of bronchial smooth muscle.[154] This may occur by the modulation of the movement of calcium ion, both within the cells and through transmembrane calcium channels.[155]In addition, magnesium decreases the amount of neurotransmitter release of motor nerve terminals, diminishes the depolarizing actions of acetylcholine at the neuromuscular end plate, and depresses excitability of smooth muscle membranes[156] decrease of acetylcholine at nerve terminals, and of sedative action, in addition to inhibition of release of histamine and to

direct in inhibition of musculature contraction.[154] By this action it decrease the airway resistance, increases forced expiratory volume and forced vital capacity and decrease dysnea. The use of magnesium for treatment of A. A was first reported in 1936 by Uruguayan physicians[155] also in 1983, Haury demonstrated that magnesium relaxes smooth muscle and reduces histamine-induced broncho-constriction in Quinea pigs.[156] The study by Silverman et all suggested that in patients with very severe acute asthma, IV magnesium administration improves pulmonary function, but it does not prove that IV magnesium should be added to the conventional treatment.[157]

Rowe BH, Camargo CA Jr; Multicenter Airway Research Collaboration (MARC) Investigators. Carried out a systemic of review of medical literature dealing with the IV magnesium sulfate asthma. Most ED physicians accept the efficacy of MgS04 in acute asthma. Despite this belief and the ready availability of MgS04/ its ED use remains uncommon (2.5% of cases). In both practice and theory, emergency physicians appear to appropriately restrict its use to patients with severe acute asthma.[158]

Bloch et al carried out a randomizes double-blind placebo-controlled study, patients with acute asthma were treated with inhaled beta-agonists at regular intervals and intravenous (IV) steroids. At 30 min after entry, patients received either 2 g IV $MgSO_4$ or IV placebo, and found that Intravenous $MgSO_4$ decreased admission rate and improved FEV1 in patients with acute severe asthma but did not cause significant improvement in patients with moderate asthma.[159]

OBJECTIVES

To evaluate the efficacy of early administration of intravenous magnesium sulphate ($MgSO_4$) in adult with acute severe asthma not responding to conventional therapy.

PATIENTS AND METHODS

Nature of study:

Interventional single-blind-controlled clinical trial.

Patients selection:

Patients selected by using computer randomized program. Patients age 18- to 60 years presenting with acute asthma to the Emergency Department (ED of two teaching hospital (Elshaab and Oumdrman) between June 2005 and January 2006.

Exclusion criteria:

- History of congestive heart failure.

- Diabetes Mellitus.

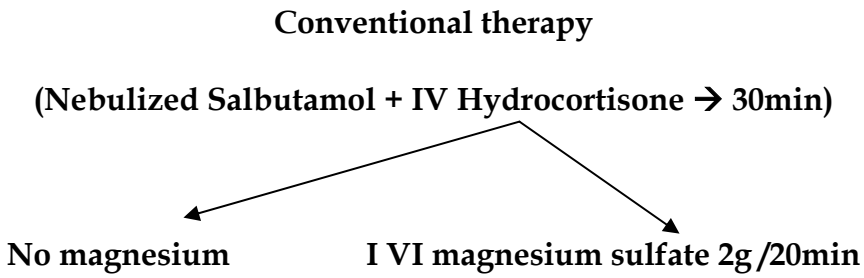
- Angina.

- Chronic renal insufficiency.

- Pregnant women.

- Hypertension.

Intervention:



Eligible patient receive either magnesium sulfate infusion of 2g or not. The vital signs, PEFR, oxygen saturation were measured before, 30mm, 60min, 90min,120min and 240 minutes after the intervention.

Tools:

1- Questionnaire: contains the following;

- History.

- Full physical examination.

- Investigations: include:

  - PEFR using Wright peak meter.

  - Oxygen saturation using Pulse Oximeter,

Statistics:

Data was analyzed using SPSS computer program.

Researching Team:

- The author

Ethical consideration:

- Informed consent from all patients.

- Informed consent from hospital administration.

3. RESULTS

Fifty patients were originally enrolled into the study, all were included into the statistical analysis and all were classified as severe asthmatics based on their initial PEFR/ clinical scenario.

The study included 50 individuals 55% were female. Number of patients who did not receive magnesium were 25. Age ranged (18-60 years). Males were 11 and females were 14.

Number of cases = 25. Age ranged (18 - 60 yr)/ with the same male

:

female distribution.

1. Conclusion of descriptive statistics in asthmatics under study (Table 1).

Cough: present in all asthmatics under study (50/50) (100%).

2. Shortness of breath: present in all asthmatics under study 50/50%).

3. Wheeze: present in most asthmatics under study 47/50(94%) (3 patients in magnesium group presented with silent chest with progression to mild wheezes following magnesium therapy and remained static until 240 min.
4. No one is in exclusion criteria (Fever, Cyanosis, Cardiovascular disease, DM, renal insufficiency, pneumonia (Currently), pregnancy, chronic liver disease, unconscious) 0/50 (0%).
5. All asthmatics admitted to hospital use accessory muscles 100%).
6. Respiratory rate breath >25 is founded in all asthmatics under study who came to hospital.
7. Most patients and those not receiving magnesium their heart beats are above 110 bpm (98%).
8. Pulsus paradoxus found in 24% of asthmatic under study.
9. Only 2% of asthmatics under study came to hospital, presented with chest deformity.
10. The commonest type of wheeze was expiratory type (68%) of all asthmatics admitted to hospital, followed biphasic 28% and then silent 6%.
11. All asthmatics presented with PEFR < 300 L/min.

12. SaO_2 % predominantly ranged between (85-90) in 94% of all asthmatics, followed by SaO_2 >90 in 4%, and followed by SaO_2% <85 in 2%.

Testing Differences between Magnesium group and Control for different signs:

1. Respiratory rate breath:

From Graph 1: we can see that significant difference begins after 30 minutes (p. value 0.02) and continue up to 240 minutes with significant difference (p. value 0.000).

2. Heart rate:

From Graph 2: we can see significant difference begins 30 minutes with p value 0.002,continue significant till 240 minutes/Mg may be having effect on that, but not less 90 beats/minute.

3. Blood pressure:

All asthmatics came to hospital are in normal blood pressure and as seen in graph Mg may has some effect of irregularity for Systolic BP but within normal range .the Diastolic BP showed the same normality in all asthmatics (Graphs 3 & 4).

4. Pulsus Paradoxus:

The difference begins on 90 minutes P value 0.009, with complete absence of pulsus paradoxus eases in patient group, which may mean the Mg may have effect reducing this group (Table 2).

5. Use of accessory muscles:

The difference begins on 90 minutes P value < 0.005, with complete absence of using accessory muscles in patient group have effect in this group (Table 3).

6. Wheeze regression:

The difference begins on 30 minutes P value 0.003, but clear significant difference appears in 90 minutes with p value 0.000, with dramatic regression at through time in this group compared to Control (Table 4) .

7. PEFR in males:

The difference begins on 60 minutes P value 0.032 in Mg intervened group compared to Control (Table 5).

8. PEFR in Females:

As we see in graph the development going gradually but significant difference is in 240 minutes P value 0.005 in Mg intervened group compared to control (Graph 6).

9. SaO_2:

The difference is clear varied and it is significant at 240 minutes with P. value 0.04 that means Mg intervention has improve Oz saturation status (Graph 7).

PEFR % predicted in Patients and those not received magnesium:

Mean PEFR in arrivals is 33.7% predicted, after 240 minutes the predicted PEFR is 65.1% predicted for patients given magnesium and 48.2% predicted for those not received magnesium (95% CI 7.97 and 25.89) with P. value 0.005 (Graph 8, Table 5).

Possible side effect of the drug:

Throughout the study period there was no any side effects of the use of intravenous magnesium sulphate among the study population. Also no death and no one intubated among those who received magnesium sulphate.

Table 1: Distribution of clinical symptoms in the study group

Symptom	**%**
Cough	50/50 (100%)
Shortness of breath	50/50 (100%)
Wheeze	47/50 (94%)
Fever	0 (0%)
Cyanosis	0 (0%)
Cardiovascular disease	0 (0%)
Diabetes mellitus	0 (0%)
Renal insufficiency	0 (0%)
Pneumonia	0 (0%)
Pregnancy	0 (0%)
Chronic liver disease	0 (0%)
Unconscious	0 (0%)
Use of accessory muscles	50/50 (100%)
Respiratory rate breath 16-18	0 (0%)
Respiratory rate breath 18-25	0 (0%)
Respiratory rate breath > 25	50/50 (100%)
Heart rate (pbm) up to 90	0 (0.0%)
Heart rate (pbm) 90-110	1/50 (2%)
Heart rate (pbm) > 110	49/50 (98%)
Pulsus paradoxus	12/50 (24%)
Chest deformity	1/50 (2%)
Wheeze type (expiratory)	34/50 (68%)
Wheeze type (Biphasic)	14/50 (28%)
Wheeze type (silent)	3/50 (6%)
Cardiovascular examination (normal)	50/50 (100%)
Cardiovascular examination (abnormal)	0/50 (0%)
PEFR L/min (1/600 - 400)	0/48 (0%)
PEFR L/min (400 - 300)	0/48 (0%)

PEFR L/min (<300)	50/50 (100%)
SaO_2 % (>90)	2/50 (4%)
SaO_2 % (90 - 85)	47/50 (94%)
SaO_2 % (<85)	1/50 (2%)

Table 2: Difference in pulsus paradoxus in patients received magnesium and those not received magnesium from zero time through 30, 60, 90, 120 and 240 min.

	Pulsus paradoxus time 00		Pulsus paradoxus time 30		Pulsus paradoxus time 60		Pulsus paradoxus time 90		Pulsus paradoxus time 120		Pulsus paradoxus time 240	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Patients received MgSO4	7	18	6	19	3	22	0	25	0	25	0	25
Patients not received $MgSO_4$	6	19	6	19	6	19	6	19	5	20	5	20

Table 3: Difference in use of accessory muscles in patients received magnesium and those not received magnesium from zero time through 30, 60, 90, 120 and 240 min.

	Use of accessory muscles time 00		Use of accessory muscles time 30		Use of accessory muscles time 60		Use of accessory muscles time 90		Use of accessory muscles time 120		Use of accessory muscles time 240	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Patients received MgSO4	25	0	25	0	24	1	7	18	4	21	2	23
Patients not received $MgSO_4$	25	0	24	1	23	2	22	3	21	4	21	4

Table 4: Wheezes regression in patients received $MgSO_4$ and those not received $MgSO_4$ from zero time (arrival) through 30, 60, 90 120, and 240 min.

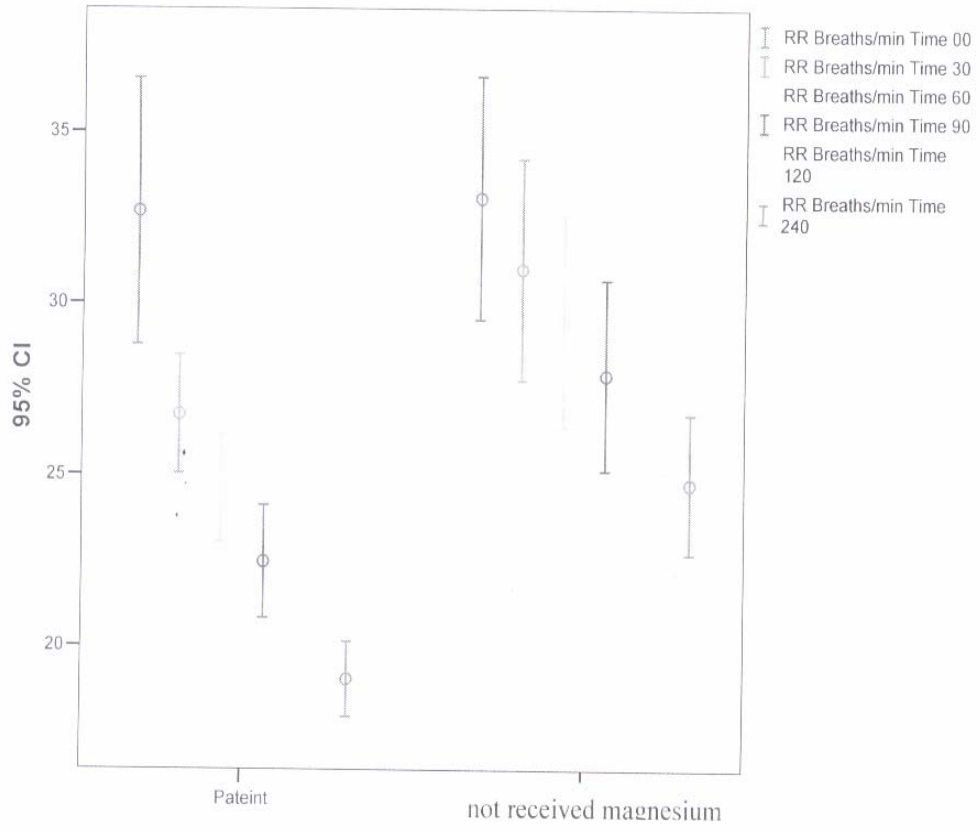
	Patient received $MgSO_4$	**Patient not received $MgSO_4$**
Wheezes time 00:		
- Severe	20	24
- Moderate	2	1
- Mild	0	0
Wheezes time 30:		
- Severe	9	22
- Moderate	12	3
- Mild	1	0
Wheezes time 60:		
- Severe	1	18
- Moderate	20	7
- Mild	1	0
Wheezes time 90:		
- Severe	0	8
- Moderate	21	16
- Mild	1	1
Wheezes time 120:		
- Severe	0	2
- Moderate	7	22
- Mild	15	1
Wheezes time 240:		
- Severe	0	1
- Moderate	0	21
- Mild	22	3

Table 5: Mean of peak expiratory flow rate (% predicted) and respiratory rate (RR) in $MgSO_4$ and non-magnesium groups

	Baseline (the time of zero)		**240 min after infusion**	
	$MgSO_4$	**No $MgSO_4$**	**$MgSO_4$**	**No $MgSO_4$**
PEFR	33.7	33.5	65.1	48.2
Respiratory rate	35.23	36.1	24.25	31.32

Graph 1:

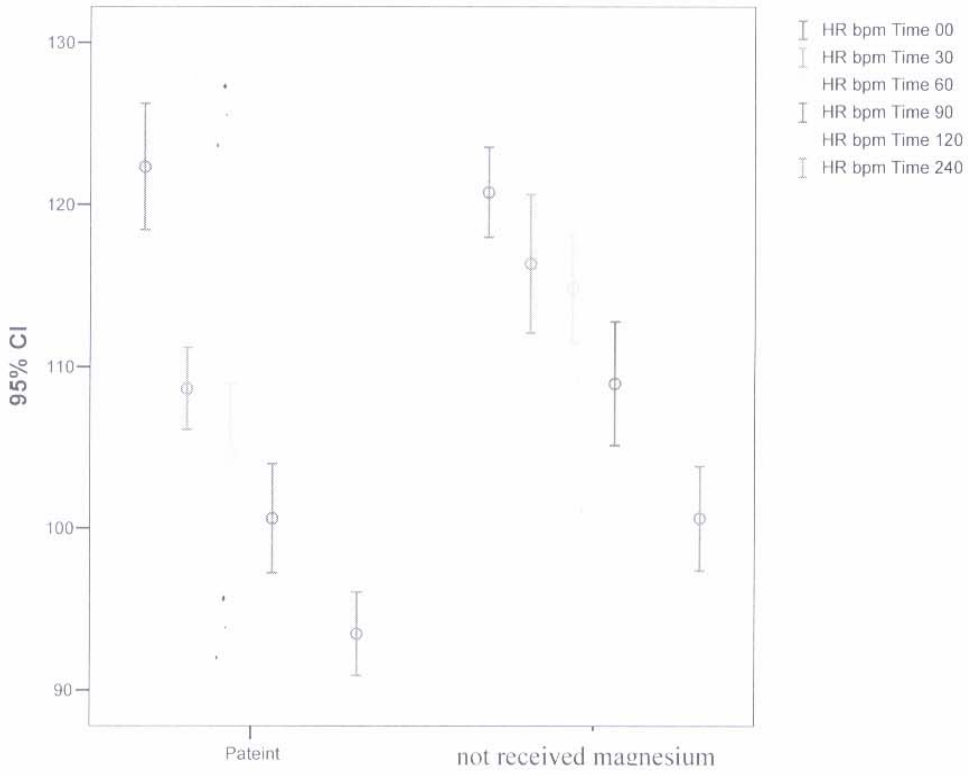
Respiratory rate in patients who received magnesium and those who not received magnesium from zero time throughout 30,60,90,120 and 240 minute



Patients and those not received Magnesium

Graph 2:

Heart rate in patients who received magnesium and those not received magnesium from zero time throughout 30,60,90,120 and 240 minute

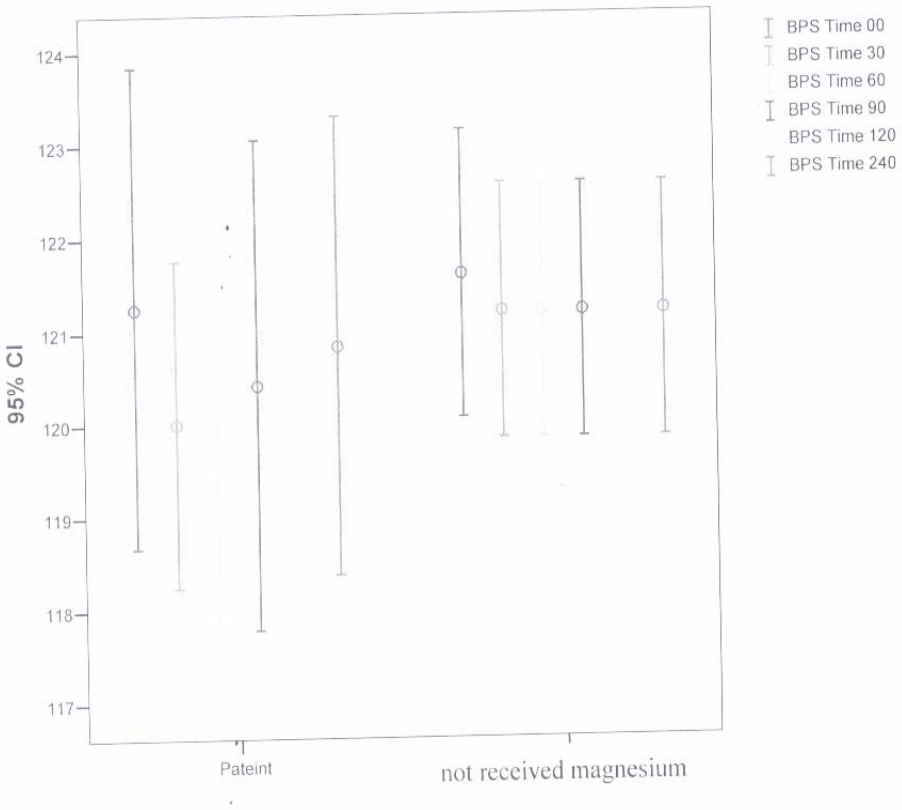


Patients and those not received Magnesium

Graph 3:

Blood pressure (systolic) in patients who received magnesium and those not received magnesium from zero time throughout 30, 60, 90, 120 and 240 minute

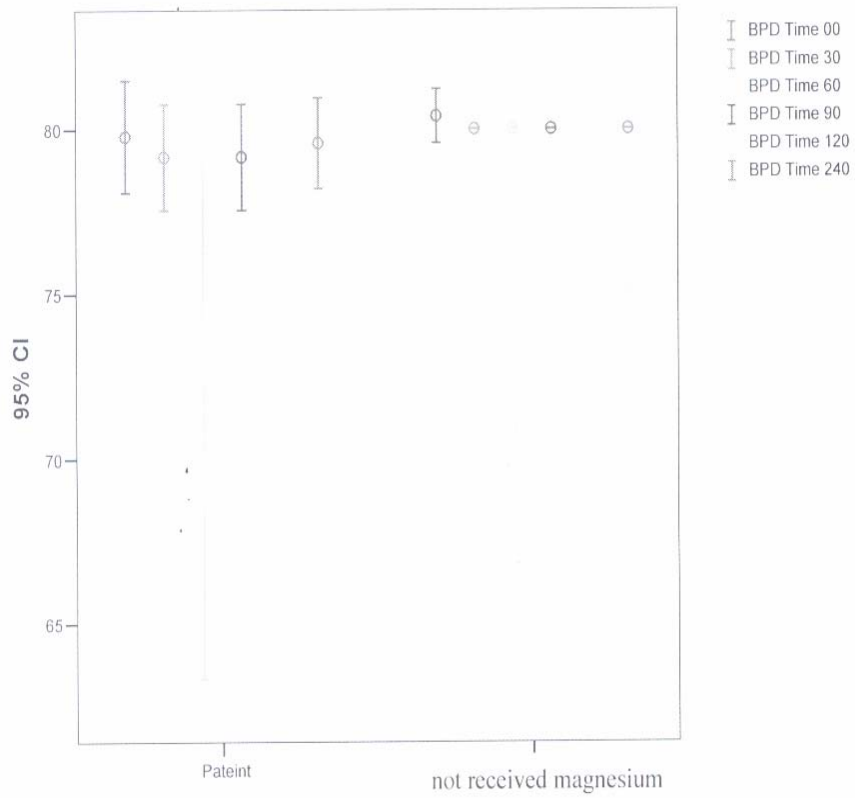
Graph 4:



Patients and those not received magnesium

Graph 4:

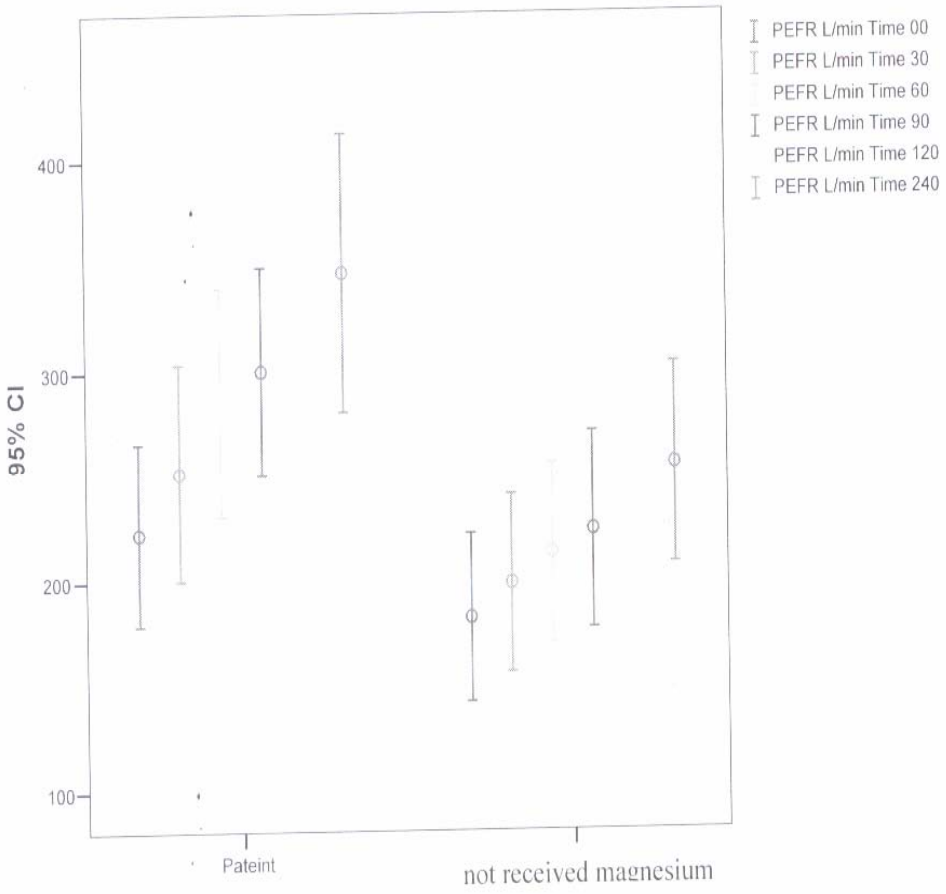
Blood pressure (diastolic) in patients who received magnesium and those not received magnesium from zero time throughout 30, 60, 90, 120 and 240 minute



Patients and those not received Magnesium

Graph 5:

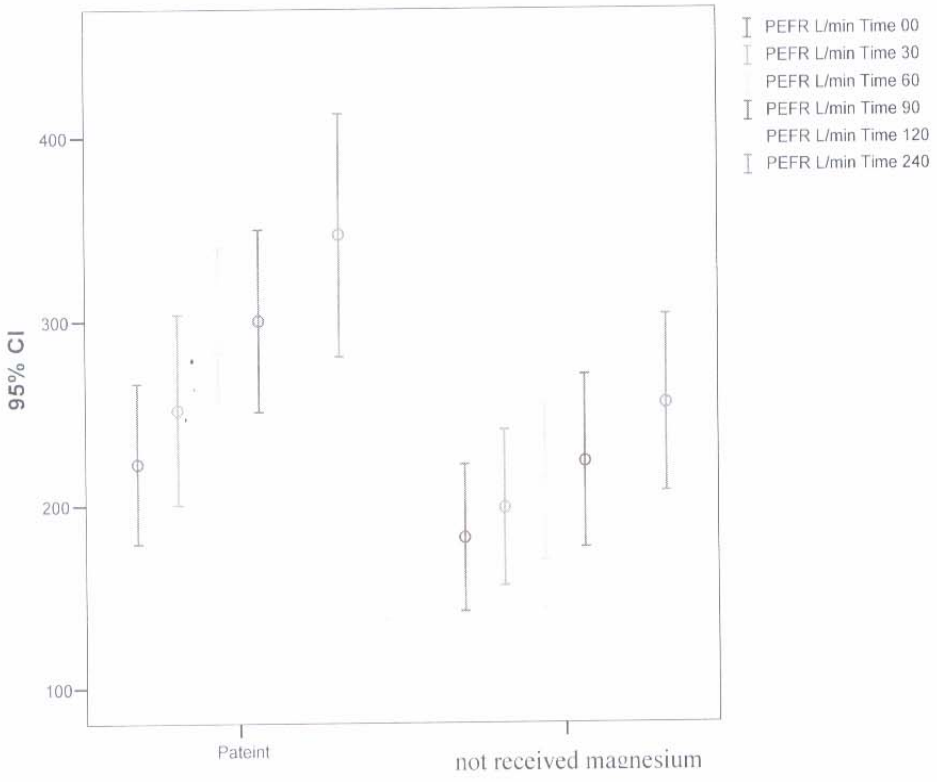
Peak expiratory flow (PEFR) rate in patients who received magnesium and those not received magnesium from zero time throughout 30,60,90, 120 and 240 minute (Males)



Patients and those not received Magnesium

Graph 6:

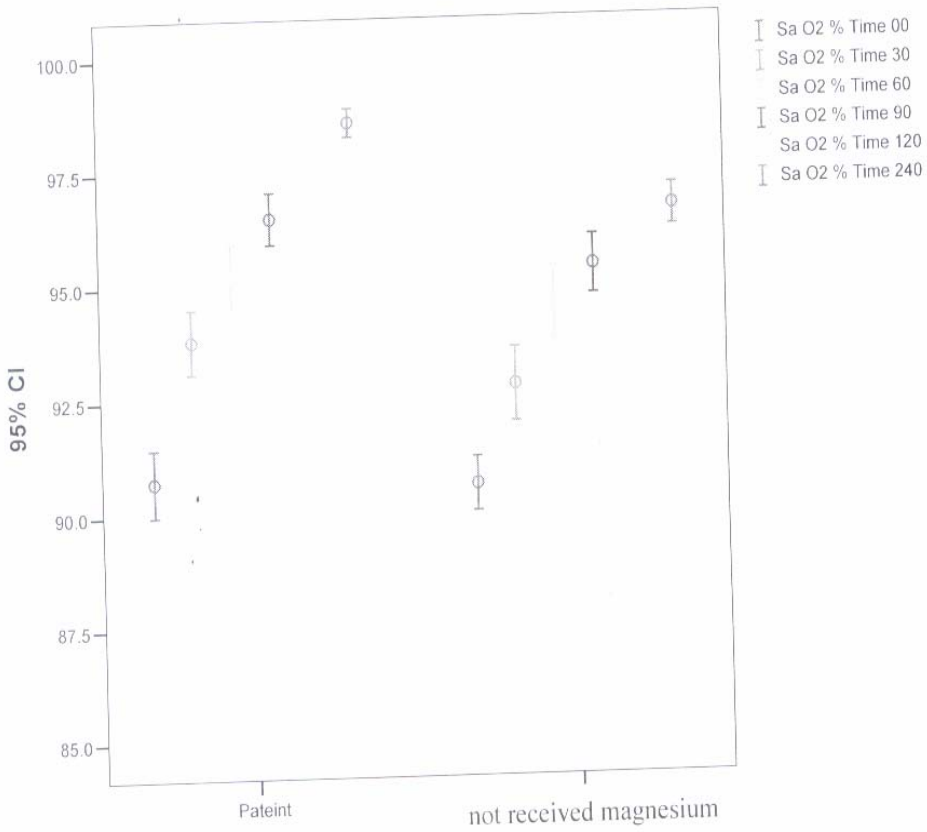
Peak expiratory flow (PEFR) in patients who received magnesium and those not received magnesium from zero time throughout 30,60, 90, 120 and 240 minute (Females)



Patients and those not received Magnesium

Graph 7:

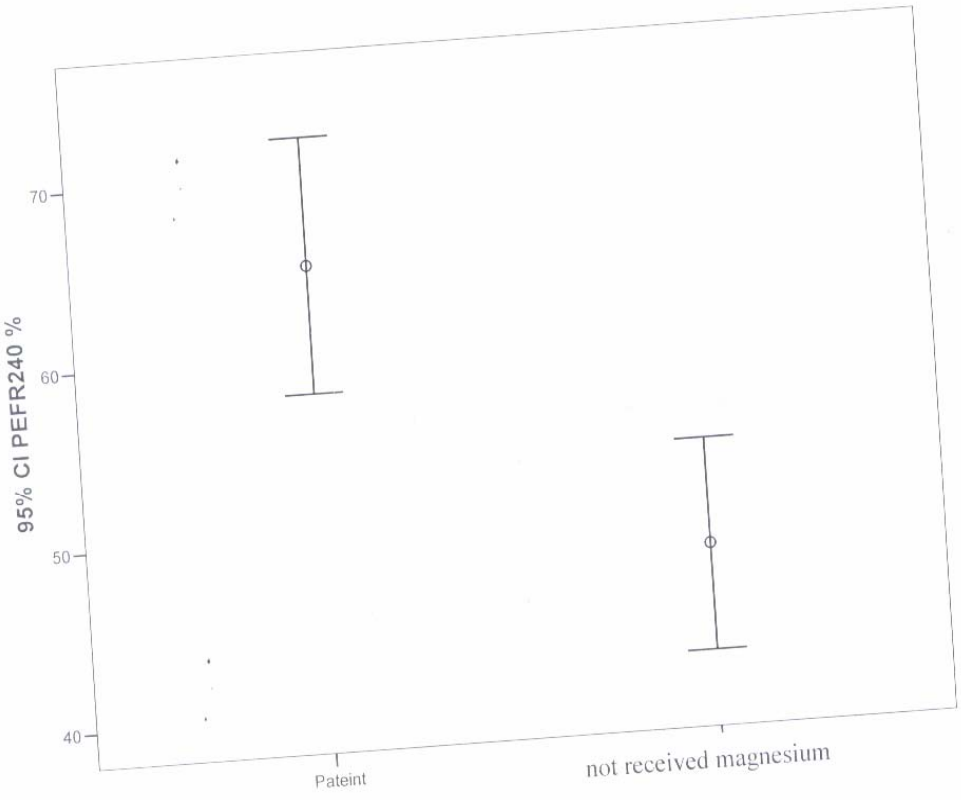
Oxygen saturation (SO_2) in patients who received magnesium and those not received magnesium from zero time throughout 30, 60, 90, 120 and 240 minute



Patients and those not received Magnesium

Graph 8:

Mean expiratory flow rate in patients who received magnesium and those not received magnesium from zero time arrival and after 240 minute



Patients and those not received Magnesium

4. DISCUSSION

This interventional single-blind controlled clinical trial demonstrates that 2 g of IV magnesium sulphate ($MgSO_4$) when administered as an adjuvant to standard therapy improves pulmonary function in patients presented to Emergency Department (ED) with severe asthma. Also from the study there is dramatic improvement in clinical scenario (such as respiratory rate, heart rate, wheezes, pulsus paradoxus, use of a accessory muscles and oxygen saturation status (P. value < 0.005 in all).

These results supported the use of $MgSO_4$ to improve pulmonary function in severe ill asthmatics patients and also helped define its limitations. These results also suggested that illnesses severity as represented by pulmonary function can be important determinant of response to therapeutic interventions and this factor should be considered when evaluating new treatment regimen.

Previous controlled studies using adjunct therapy with $MgSO_4$ have yielded conflicting conclusions. Skobeloff, et al.[160] found that giving 1.2 g of IV $MgSO_4$ to patients in the ED significantly improved peak flow and decreased admission rates, compared to patients receiving placebo, which is similar to that of

our study results. Green and Rothrock[161] using 2 g of $MgSO_4$ failed to find any difference. However, patients studied by Green and Rothrock likely represented a group with less severe disease. Also Robert A. Silverman, et al in Multi-center trial demonstrates that 2 g of IV $MgSO_4$ administered as an adjuvant to standard therapy improves pulmonary function in patients presenting to ED with severe asthma which came similar to our results.

Similarly in a large multicenter study of 248 subjects with acute severe asthma, treatment with $MgSO_4$ 2 g IV was beneficial in the subset of patients who presented with severe airway obstruction (forced expiratory volume in 1 second [FEV_1] < 25% predicted), but not in subjects with less severe airway obstruction. [162]However, not all investigators have found benefits in severely affected individuals. Porter and colleagues[162] conducted a double-blinded placebo-controlled trial involving 42 subjects who presented to an emergency department with a peak expiratory flow rate < 100 L/min (or < 25% predicted). Treatment with MgS04 2 g IV in addition to standard therapy was not helpful, and in fact, the treated subjects had significantly lower peak expiratory flow rate (PEFR) 1 hour after receiving the medication.

A number of case reports also indicates $MgSO_4$ is beneficial for treating acute severe asthma.[163,164,165,166,167] While results of controlled clinical trials evaluating the effect of MgS04 in acutely ill ED patients widely differ. When 1.2 g of $MgSO_4$ or placebo was administered to 38 patients with moderate to severe airway compromise significant improvement occurred in peak flow an hospital admission rates.[168] In another study, 2 g of $MgSO_4$ was administered to 120 patients with wide range of asthma severity and there was no improvement in hospital admission rates or peak flow.[169] Again in 48 patients with moderate to severe asthma, no significant benefit was noted from 2 g of $MgSO_4$. Also subsequent research control trial (33 evaluable people) found no significant difference in hospital admissions between intravenous magnesium sulphate and placebo. Another subsequent RCT (42 people with acute asthma receiving inhaled bronchodilators and IV corticosteroids) found that intravenous magnesium sulphate did not improve PEFR at 60 minutes compared with placebo (P = 0.04).

It found no significant difference between treatments in the proportion of people admitted to hospital.[7]

Different smaller studies use magnesium sulphate as an adjuvant to standardized asthma therapy do not demonstrate a significant improvement in either PEFR or reduction of hospital admission rates' in moderate to severe asthmatics. However, if a distinction is made, it is demonstrated that intravenous magnesium sulphate does improve both PEFR and reduce hospital admission rates in the severe subgroup.[170,171,172]

Prespecified subgroup analysis of adults with more severe airflow obstruction (5 RCTs, sample size not reported; forced expiratory volume in 1 second [FEV_1] < 30% at presentation, failure to respond to initial treatment, or failure to improve beyond 60% in FEV_1 after 1 hour) found magnesium sulphate significantly improved peak expiratory flow rate (PEFR) and reduced rates of hospital admission compared with placebo (hospital admission rates: OR 0.10, 95% CI 0.04 to 0.27, no significant heterogeneity (P > 0.1).[139]

Taking into consideration potential differences in a response to treatment based on illness severity. Block, et al.[173] tested 145 patients with varying degrees of air flow obstruction

was found that only 35 patients with FEV1 <25% predicted had an improvement in pulmonary function.

This randomized, double- blind, controlled study was conducted on patient to determine the effect of IV $MgSO_4$ for improvement of pulmonary function in patients with acute asthma non - responding to routine therapy presenting to the pulmonary department. Peak expiratory flow rate (PEFR) was done before $MgSO_4$ (25 mg/kg) and normal saline (100 ml) as a baseline criteria and after infusion of drugs at 30 min and 3 hr. All patients were also given bronchodilators. The main outcome was PEFR. Data were analyzed by X^2 and t-test and differences between each point was considered significant at $p< 0.05$. The Peak expiratory flow rate 3 hrs after baseline increased in MgS04 group in comparison with saline group (82.60 5.8 versus 47.8 8.7 P=0.002). Respiratory rate of breathing in $MgSO_4$ was also decreased at 30 min and 3 hr after baseline. Cyanosis, diaphoresis and using of respiratory accessory muscles by patients were decreased in $MgSO_4$ in comparison with saline group. According to the results, it is suggested that $MgSO_4$ can be as an adjuvant agent for the treatment of patients with acute non- responding asthma.[174]

Many reports has shown that magnesium sulphate has certainly a role as an adjuvant to traditional therapy in asthma and asthma-like conditions and has been helpful in the treatment of acute exacerbation of asthma.[175]

This support previous observations that the response to $MgSO_4$ is related to initial FEV_1, PEFR.

The mechanism for a beneficial effect of magnesium on pulmonary function is not clear. Magnesium is required for a wide variety of cellular activities and biological processes, and therefore, can potentially exert an effect on any number of pathways, based on the present literature, a number of mechanisms can possibly explain the immediate improvement noted after administration of magnesium in this study points to an acute bronchodilator effect; magnesium causes relaxation of bronchial smooth muscle. This may occur by modulation of calcium ion movement both within the cell and through transmembrane calcium channels.[176] Magnesium is also known to decrease the amount of neurotrausmitter released at motor nerve terminals, diminishes depolarizing action of acetylcholine at neuromuscular end plate and depress excitability of smooth-muscle membranes.

There is evidence that prostaglandin mediated vascular smooth-muscle relaxation is magnesium dependent. Magnesium is necessary for steps involving the interaction of Beta-agonist receptor complex- G-protein and guanosine triphosphate, leading to activation of adenyl cyclase. It has also been reported in vitro that magnesium decreases super-oxide production in neutrophilis obtained from adult asthmatics; therefore, providing some evidence that magnesium has an anti-inflammatory effect. This is a possible explanation for the sustained improvement in pulmonary function even several hours after magnesium was administered.[177] It is not known whether the effect of magnesium is primarily due to replacement of an underlying deficiency or through a direct pharmacologic effect. Although response to magnesium in previous study was independent of baseline serum magnesium levels.

The serum measures may not reflect intracellular concentrations or total body stores. Therefore, some patients with normal serum levels may have had a deficiency of magnesium.

Also, frequent -Beta-agonist therapy, causes acute decreases in serum magnesium levels, although the influence on biological availability of magnesium is not known.

Magnesium is relatively inexpensive- readily available and easy to administer. Minor side effects can include transient flushing, light-headedness, lethargy, nausea, or burning at the IV site and transient urticaria. Neither of them occurred in this study.

Considering the different rout of administrations of magnesium sulphate, we found the conclusion of two research control trials of nebulised isotonic magnesium sulphate compared salbutamol plus 0.9% saline with salbutamol plus isotonic magnesium sulphate through a nebuliser and found that magnesium sulphate significantly increased PEFR compared with 0.9% saline (increase in PEFR after 10 minutes: 61% with magnesium sulphate 31% with saline; difference 30%, 95% CI 3% to 56%; P = 0.03).

Overall this study results were similar to above studies results considering the effects of MgS04 on pulmonary function, and if there were differences may be in most studied moderate to

severe asthmatic patients, but this study targeted only severely ill asthmatic patients. Additional studies are needed to better define which patients are most likely to benefit from this treatment.

CONCLUSION AND RECOMMENDATIONS

- In summary our data indicated that when 2 g of $MgSO_4$ is given as an adjuvant to standardized asthma therapy to patients presented 'with severe acute asthma, there is significant improvement in clinical scenario and pulmonary function. Thus these would support routine use of $MgSO_4$ in patients with severe acute asthma.
- Further larger multicenter studies should support or talk more about the effect of $MgSO_4$ on moderate to severe Sudanese asthmatic patients.
- Also should address optimal dose and infusion rates of I.V $MgSO_4$.
- Finally a large multicenter controlled study should be done comparing the effect of nebulised magnesium sulphate versus IV magnesium sulphate (nebulised Vs IV MgS04) as an adjunct to conventional asthma therapy in patients with severe acute asthma in Sudan.

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University of Khartoum
Graduate Colleague
Efficacy of l.V Magnesium Sulfate in Acute Severe asthma

In Khartoum Teaching Hospitals

1. Name: ..... **2. Age:** .....

2. Sex: 1 -Male 2- Female ☐

C/O:

1. Cough 1- Yes 2-No ☐
2. SOB 1-Yes 2-No ☐

☐

3. Wheeze 1-Yes 2-No

4. Fever 1- Yes 2-No ☐

5. Cyanosis 1-Yes 2-No ☐

History of:

1. Cardiovascular Dis. 1-Yes 2-No ☐

2. DM 1-Yes 2-No ☐

3. Renal insufficiency 1- Yes 2-No ☐

4. Pneumonia (currently) 1-Yes 2-No ☐

5. Pregnancy 1- Yes 2-No ☐

6. Chronic liver Dis. 1- Yes 2-No ☐

O/E:

1. Conscious 1-Yes 2-No ☐

2. Use of accessory respiratory muscles 1-Yes 2- No ☐

3. Respiratory Rate Breaths/min

1- 16-18 2- 18-25 3- > 25 ☐

4. Heart Rate (b pm)

1- Up, 90 2- 90-110 3- >110 ☐

5. Pulsus Paradoxus 1- Yes 2-No ☐

Chest Deformity 1- Yes 2-No ☐

Wheeze 1- Expiratory 2- Biphasic 3- Silent chest ☐

CVS/E 1- Normal 2-Abnormal ☐

Investigations

1. PEFR/min.

1. 1/600 – 400 2. 400 – 300 3. < 300 ☐

2. SO_2 1. >90 2. 90 – 85 3. < 85% ☐

Intervention:

All patients received nebulized salbuamol initially every 20 min, hydrocortisone 200 mg I.V + 2 g of magnesium sulfate 2g in 100 ml (N.S 0.9), I.V over 20 min.

Time/min	RR breath/ min	HR bpm	BP mmHg	PP	Use of accessory muscles	Wheezes	PEFR L/min	SO2%	Silen ches
0	19	6	19	6	19	6	19	5	20
30									
60									
90									
120									
240									