USING ISOTONIC MAGNESIUM SULFATE NEBULIZATION AS AN ADJUVANT TREAMENT FOR MODERATE ACUTE EXACERBATION OF BRONCHIAL ASTHMA (AEBA) IN ADULT COMPARING WITH SALBUTAMOL ALONE: A DOUBLE BLINDED, RANDOMISED CONTROL TRIAL

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DR LIEW KET KEONG

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Dr. Liew Ket Keong

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TABLE OF CONTENT

CHAPTER SIX : DISCUSSIONS

List of Tables

List of Figures

LISTS OF ABBREVIATIONS

AEBA	Acute Exacerbation of Bronchial Asthma
ATP	Adenosine Triphosphate
β_2-agonist	Beta 2 – agonist
BP	Blood Pressure
COPD	Chronic Obstructive Pulmonary Disease
DNA	Deoxyribonucleic Acid
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
HRPZ II	Hospital Raja Perempuan Zainab II
HUSM	Hospital Universiti Sains Malaysia
IL	Interleukin
ICU	Intensive Care Unit
MDI	Metered Dose Inhaler
$MgSO_4$	Magnesium Sulfate
NSAID	Nonsteroidal Anti-inflammatory Drug
Pao_2	Partial Pressure of Oxygen
Pco_2	Partial Pressure of Carbon Dioxide
PEFR	Peak Expiratory Flow Rate
SPSS	Statistical Package for Social Science
SD	Standard Deviation
URTI	Upper Respiratory Tract Infection

ABSTRAK

Objektif

Tujuan kajian ini adalah untuk menilai keberkesanan penggunaan satu dos magnesium sulfat nebulisasi bercampur dengan salbutamol untuk merehatkan otot licin saluran nafas, dan seterusnya membuka saluran pernafasan dalam rawatan penyakit lelah berbanding dengan penggunaan salbutamol sahaja. Selepas itu kami juga memerhati sebarang penggurangan yang ketara dalam jumlah tempoh rawatan di antara dua kumpulan kajian.

Kaedah Kajian

Ini adalah satu kajian “double blinded, randomised controlled trial”, yang dijalankan di Jabatan Kecemasan di Hospital Universiti Sains Malaysia, Kelantan bermula dari 1 Oktober 2013 sehingga 1 Oktober 2014. Kami mendaftarkan seramai 120 pesakit yang mengalami serangan lelah pada tahap sederhana, semua pesakit kemudian secara rawak dibahagikan kepada dua kumpulan melalui teknik “block randomization”. Kumpulan A (n = 60) diberi ubat sedut dengan salbutamol sahaja (5mg), Kumpulan B (n = 60) diberi ubat sedut campuran magnesium sulfat isotonik (7.5% w / v) dengan salbutamol (5mg). Tekanan darah, kadar nadi, kadar pernafasan, ketepuan oksigen dan kadar aliran puncak ekspirasi (PEFR) dari setiap pesakit diukur pada permulaan kajian dan pada 20 minit selepas rawatan. Jumlah tempoh rawatan bermula dari waktu pendaftaran sehingga pencapaian PEFR > 80% yang diramalkan telah dicatatkan.

Keputusan

60 pesakit yang telah dibahagikan kepada dua kumpulan kajian mempunyai ciri-ciri asas demografi dan klinik yang setanding. Pada masa 20 minit selepas rawatan diberi, kumpulan A dan kumpulan B menunjukkan peningkatan statistik yang ketara dalam PEFR (100 ± 61 L / min dan 87 ± 42 L / min masing-masing, p <0.001). Kumpulan B menunjukkan pengurangan ketara kadar pernafasan dan peningkatan dalam ketepuan oksigen min (p <0.001). Walau bagaimanapun, tidak terdapat perbezaan statistik yang ketara dalam peningkatan PEFR dan pengurangan jumlah tempoh rawatan di antara dua kumpulan kajian ini. Kami tidak melihat sebarang kesan sampingan dari rawatan yang diberikan dalam sepanjang kajian ini.

Kesimpulan

Kesimpulannya, penggunaan $MgSO_4$ sebagai ubat pembantu kepada salbutamol nebulisasi pesakit lelah tahap sederhana tidak menunjukkan apa-apa kelebihan dalam kesan terapeutiknya jika berbanding dengan salbutamol sahaja. Walau bagaimanapun, paired t-test dilakukan pada pesakit dalam kumpulan B $MgSO_4$ menunjukkan kesan positif dalam membantu pembukaan saluran pernafasan, statistik mempamerkan kemampuan $MgSO_4$ untuk menurunkan kadar pernafasan dan meningkatkan ketepuan oksigen yang ketara. Dalam kajian masa depan, kita mencadangkan terlebih dahulu menjalankan satu kajian perintis untuk menunjukan mengetahui “dose-response relationship magnesium sulfat dalam rawatan penyakit lelah akut, sebelum satu lagi kajian berbagai pusat yang lebih besar dijalankan.

ABSTRACT

Objective

The aim of this study is to evaluate the efficacy of single dose nebulized magnesium sulfate in augmenting bronchodilatory effect of salbutamol in acute asthma as compare to salbutamol alone. In addition, we also observe for any significant reduction in total treatment duration in this two study groups.

Methodology

This was a double blinded, randomized controlled trial, conducted in Emergency Department of Hospital Universiti Sains Malaysia, Kelantan between 1st October 2013 and 1st October 2014. We enrolled a total of 120 patients with moderate acute exacerbation of bronchial asthma, all the patients were then randomized into two groups via block randomization technique. Group A (n=60) nebulized with salbutamol only (5mg), Group B (n=60) nebulized with isotonic magnesium sulfate (7.5% w/v) plus salbutamol (5mg). Blood pressure, pulse rate, respiratory rate, oxygen saturation and peak expiratory flow rate (PEFR) of each patient were measured at baseline and at 20 minutes post-treatment. Total duration of treatment started from time of enrollment until achievement of predicted PEFR > 80% was recorded.

Results

The 60 patients enrolled in each treatment arm had comparable baseline demographic and clinical characteristics. At 20 minutes post-treatment, Group A and Group B

showed statistically significant improvement in PEFR (100±61 L/min and 87±42 L/min respectively, p value <0.001). Group B showed significant reduction of mean respiratory rate and improvement in mean oxygen saturation (p value <0.001). However, there were no statistically significant differences in means improvement of PEFR and reduction of total duration of treatment between two groups. We did not observe any adverse effect from treatment at all time.

Conclusion

In conclusion, the use of $MgSO_4$ as an adjuvant to salbutamol nebulization in moderate AEBA patient does not show any superiority in their therapeutic effect in comparing to salbutamol alone. However, paired t-test done on group B population has shown the feasible bronchodilatory property of $MgSO_4$, it is able to bring about a statistically significant decrease in respiratory rate and improvement in oxygen saturation. In future study, we suggest a pilot study to be conducted to establish the dose-response relationship of magnesium sulphate in the treatment of acute asthma before a larger, multicentre trial is proposed.

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Dr Liew Ket Keong

Mmed Emergency Medicine

Department of Emergency Medicine

School of Medical Sciences, University Sains Malaysia

Health Campus, 16150 Kelantan Malaysia

Introduction: Bronchial asthma is a major respiratory disease worldwide. An estimated of 300 million individuals all over the world of all different ages have bronchial asthma. Exacerbation of bronchial asthma frequently presented with progressive worsening of shortness of breath associated with wheezing, cough or chest tightness. Magnesium sulfate ($MgSO_4$) is a new agent that has been recommended as an additional treatment for AEBA since early of 21^{st} century. Its intravenous use in severe and life threatening AEBA has been proven to reduce hospital admission rates. However its use as a nebulizer in the treatment of AEBA is still lack of strong evidence for recommendation.

Objectives: The aim of this study is to evaluate the efficacy of single dose nebulized magnesium sulfate in augmenting bronchodilatory effect of salbutamol in acute asthma as compare to salbutamol alone. In addition, we also observe for any significant reduction in total treatment duration in this two study groups.

Patients and Methods: This was a double blinded, randomized controlled trial, conducted in Emergency Department of Hospital Universiti Sains Malaysia, Kelantan between 1st October 2013 and 1st October 2014. We enrolled a total of 120 patients with moderate acute exacerbation of bronchial asthma, all the patients were then randomized into two groups via block randomization technique. Group A (n=60) nebulized with salbutamol only (5mg), Group B (n=60) nebulized with isotonic magnesium sulfate (7.5% w/v) plus salbutamol (5mg). Blood pressure, pulse rate, respiratory rate, oxygen saturation and peak expiratory flow rate (PEFR) of each patient were measured at baseline and at 20 minutes post-treatment. Total duration of treatment started from time of enrollment until achievement of predicted PEFR > 80% was recorded.

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Dr Shaik Farid Abdul Wahab: Supervisor

1.0 INTRODUCTION

1.1 Background of the study

Bronchial asthma is a major respiratory disease worldwide. An estimated of 300 million individuals all over the world of all different ages have bronchial asthma. The global prevalence of bronchial asthma is ranging from 1% to 18% of total disease burden (Masoli et al, 2004). In Malaysia, asthma is one of the commonest problems treated in the emergency department. The prevalence of bronchial asthma in adult in Malaysia was estimated to be 4.5% (Ministry of Health, 2006).

Patients who suffer from bronchial asthma, their symptoms can be well controlled with medications or it also can deteriorate at any time if any process of airway inflammation causing bronchoconstriction, which is referred to as acute exacerbation of bronchial asthma (AEBA). AEBA range in severity from mild to life threatening, where most of the time warrant visit to clinics or emergency departments for acute treatment via nebulization.

Exacerbation of bronchial asthma frequently presented with progressive worsening of shortness of breath associated with wheezing, cough or chest tightness. The primary treatment for mild AEBA often required only β_2-agonist therapy via metered-dose inhaler (MDI). However, moderate to severe exacerbations of bronchial asthma mostly required repetitive administration of β_2-agonist via nebulizer, early introduction of glucocorticosteroids, and oxygen supplements in emergency department.

During moderate and severe AEBA, often β_2-agonist e.g. salbutamol alone is not enough to relieve bronchospasm. For this reason, researchers had discovered variety of additional agents to alleviate the AEBA symptoms. Ipratropium bromide an anticholinergic agent (Rodrigo et al.,2000) has been used as an adjuvant to salbutamol in the treatment of AEBA, inhaled glococorticosteroids (Rodrigo et al., 1998) which has been proven in their anti-inflammatory effect during an exacerbation. Theophylline is another potential but less favorable treatment for AEBA, because evidence has showed their narrow therapeutic index that possible harmful to the patient in acute exacerbations condition (Parameswaran et al., 2012). Intravenous β_2-agonist such as salbutamol and terbutaline are reserved for patient with life threatening AEBA (Travers et al., 2004). By looking back to the agents mention above, choices of agents in the treatment for moderate AEBA are limited. Therefore research for new agents for acute management in AEBA is encouraging.

Magnesium sulfate ($MgSO_4$) is a new agent that has been recommended as an additional treatment for AEBA since early of 21st century. Its intravenous use for severe life threatening AEBA has been proven to reduce hospital admission rates in certain patient. (Rowe et al., 2000). Global Initiative for Asthma (GINA) also recommended magnesium sulfate as an adjuvant to salbutamol nebulization in view of its benefits in improving pulmonary function and likewise reduces the rate of hospital admissions. (Evidence A) (Blitz et al., 2005).

1.2 Justification of the study

By understanding the pathophysiology of acute exacerbation of bronchial asthma, various treatment agents have evolved. Traditionally, repeated doses of β_2-agonist nebulization had been the common practice in the treatment of AEBA. As time goes by, new evidence has evolved. Anticholinergic agents together with β_2-agonist in nebulization for children and adults have been proven to reduce the risk of hospital admission by 49%. (Plotnick et al., 2000; Stoodley et al., 1999 and Rodrigo et al., 2000). In addition, Rowe et al, 2007 has also recommended the use of corticosteroid in the treatment of AEBA to reduce the risk of relapse.

Study by Fischl et al. in 1981 showed that, about 41% of AEBA patients in his study population had been hospitalized and experienced relapsed. Relapse and hospitalization of AEBA patient can be reduced or avoided if more bronchodilatory agents have been developed.

Since the last decade, Magnesium sulfate ($MgSO_4$) has gained some popularity as adjunct therapy in the management of AEBA. This agent is easy to use, safe, and inexpensive. In North America, intravenous dose of 2g to be given in 20 minutes infusion for severe AEBA had been widely accepted by their emergency physician (Rowe et al., 2000). Besides, intravenous $MgSO_4$ therapy for severe life threatening AEBA has also been recommended in the asthma management guidelines (British Thoracic Society, 2011).

Apart from this, numerous studies have been published worldwide regarding the efficacy of nebulized $MgSO_4$ in AEBA. However, there were different outcomes from these studies. The reasons for diverse outcomes mainly are due to small number of

study population and diversity in study design with different $MgSO_4$ concentration being used in the studies.

We are conducting this trial in our center by obtaining a larger sample population size; we wish to elicit the significant of mean difference improvement of pulmonary function in nebulization $MgSO_4$ with salbutamol group compare with salbutamol group alone. At the same time, we would like to observe for any significant improvement in time of discharge in these two groups of patient. In future, we hope this study may contribute in the evidence pools of efficacy of nebulization $MgSO_4$ in the management of AEBA.

We have chosen patients with moderate AEBA as the group of interest in our study. Patient with mild AEBA symptoms can resolve easily with MDI salbutamol at home. On the other hand, patient with severe AEBA need to be treated in critical care area with more intensive therapy. Besides research has shown the efficacy of IV $MgSO_4$ in the treatment for severe AEBA, this therapy has been adopted in most of the guideline in the treatment of AEBA. Therefore, patient with moderate AEBA is the most suitable group in our study.

2.0 LITERATURE REVIEW

2.1 Introduction to Bronchial Asthma

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. It is characterized by recurrent episodes of wheezing, breathlessness, chest tightness and coughing. During exacerbation of asthma, it is associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. A variety of airway alterations occur in asthma, but airway inflammation is the final common pathway limiting airflow. Therefore steroid has been recognized as the basis of asthma therapy.

Allergen and non-allergen (e.g. NSAID induced, exercise induced and cold induced) induce bronchoconstriction by triggering the release of mediators and metabolic products from inflammatory cells, in particular T-helper cells that release cytokines such as interleukin (IL)-4, IL-5, and IL-13 (Kips JC,2001); eosinophils (Kay AB.,2005), lymphocytes (Larche et al., 2003), mast cells (Peter et al.,2006), macrophages (Peter et al.,2004), dendritic cells (Kuipers et al.,2004), and myofibroblast (Descalzi et al.,2007) which contribute to prolonged bronchial smooth muscle spasm (Hirst et al.,2004), edema, and mucus production (Chung et a.,2000).

Airway remodeling refers to the persistent structural changes in airways seen in patients with asthma and is caused by the presence of repetitive or chronic airway inflammation. Microscopically the inflamed airways showed epithelial thickening, mucous gland metaplasia, subepithelial fibrosis, airway smooth muscles hypertrophy, loss of cartilage integrity, and angiogenesis. (Bergeron et al., 2010) Airway remodeling is observed in patients with prolonged asthma histories and their pulmonary function decline with age. Airway remodeling induced by chronic inflammation may lead to

development of chronic irreversible airflow. This group of patients has resistance to routine therapy and at risk of higher mortality.

Acute exacerbation of bronchial asthma refers to transient worsening of respiratory effort characterized by expiratory airflow limitation as a result of exposure to trigger factors such as environment antigens (pollen, dander, mites) or microbiological antigens (bacteria, viruses).

2.2 Diagnostic Strategies for Bronchial Asthma

2.2.1 History Components

The diagnosis of asthma is based on the recognition of a characteristic pattern of symptoms and signs. Most patients with AEBA have a constellation of symptoms, including cough, dyspnoea, chest tightness, and wheezing (Levy et al., 2006) Clinical features that increase probability of asthma are: Diurnal variation in symptoms severity; Symptoms in response to exercise, allergen exposure, and cold air; Patient or family history of atopic disorder; Low peak expiratory flow rate (PEFR); Peripheral blood eosinophilia; History of improvement with treatment.

The brief history pertinent to current exacerbation should include onset and possible triggers, severity of symptoms especially as compare previous exacerbations, and other comorbidities. Drug history is another crucial component, including time and amounts of recent used asthma medication which indicate severity and controlled of asthma; any other potential drug that will exacerbate the symptoms of asthma. Risk factors for death from asthma are important to determine and are listed as below (National Asthma Education, 2007), which facilitate physician in decision for patient disposition.

Risk Factors for Death from Asthma

Asthma History

Previous severe exacerbation which required intensive care for asthma

Two or more hospitalization for asthma in the past year

Three or more visits to emergency department in the past year for AEBA

Use of more than two MDI short acting β_2-agonist canisters in past one month

Hospitalization or visit to emergency department in the past month

Difficulty perceiving asthma symptoms or severity of exacerbations

Social History

Lower social economy group or living in rural area

Serious psychosocial problems

Illicit drug use, e.g. inhaled cocaine and heroin (Levine et al., 2005)

Comorbities

Cardiovascular disease

Other chronic lung disease

Chronic psychiatric disease

2.2.2 Physical Assessment

Patient with mild AEBA speak in sentence, those with moderate AEBA in phrases, and those with severe AEBA in words together with increase work of breathing. Cyanosis is uncommon in view of the left shift of the oxyhemoglobin dissociation curve produced by respiratory alkalosis.

Tachypnoea and tachycardia are associated with severe obstruction. The respiratory rate poorly correlate with PEFR and indicates severe obstruction if it is higher than 40 breaths per minute.

A pulsus paradoxus or inspiratory fall in systolic blood pressure greater that 10mmHg usually signifies severe AEBA. However, its absent does not exclude severe disease

.

Wheezing does not designate the presence, duration and severity of asthma. It correlates poorly with the degree of functional derangement and may be absent in life-threatening condition. Physical assessment is crucial to identify signs from complication of asthma such as pneumothorax, pneumomediastinum or pneumonia.

2.2.3 Test for Diagnosis and Monitoring of Bronchial Asthma

The severity of airflow obstruction cannot be accurately assessed from symptoms and physical examination alone (Silverman et al., 2007). Physician tends to underestimate the degree of airflow obstruction in acute asthma. Therefore measurements of lung function, and particularly the demonstration of reversibility of lung function abnormalities, greatly enhance diagnostic confidence. PEFR in litres per minute and force expiratory volume in 1 second from spirometry (FEV_1) are available and gained widespread acceptance methods to assess airflow limitation in patients over 5 years of age. Predicted values of FEV_1, FVC and PEFR based on age, sex and height have been obtained from population studies. (Nunn et al., 1989 and Radeos et al., 2004) An increase in of FEV_1 ≥12% and 200ml after administration of bronchodilator agent specifies reversible airflow limitation which is consistent with diagnosis of asthma (Pellegrino et al., 2005). In peak expiratory flow measurement,

patient post administration of bronchodilatory agent show improvement of PEFR of 60L.min or ≥ 20% of pre-bronchodilator PEFR suggests a diagnosis of bronchial asthma. (Dekker et al., 1992) Both measurements require the patient's cooperation for maximal effort and are effort dependent. The best of three consecutive values should be recorded. Any patient unable to perform pulmonary function test should be considered to have severe airflow obstruction.

Spirometry is a preferable method in measuring lung function, because its result is reproducible, reliable but unfortunately it is effort dependent. Therefore most assessments in the emergency department use single-patient-use peak flow meter. Peak flow meter is relatively inexpensive, durable, portable and ideal for patient to use in home settings for day-to-day monitoring. The identical device should be used to assess then reassess an individual patient, and different meters should not be used interchangeably. Lastly, the FEV_1 and PEFR measurements are not interchangeable in assessing acute airway obstruction.

Arterial blood gas is rarely clinically useful in AEBA unless oxygen saturation cannot be obtained reliably via pulse oximetry or saturation drop below 92%. Because neither pretreatment nor post-treatment arterial blood gases correlate with pulmonary function test or predict clinical outcomes. Occasionally, despite improvement in pulmonary function test values with bronchodilator therapy, some patients have transient fall in partial pressure of oxygen in arterial blood (Pao_2) secondary to pulmonary vasodilatation and worsening ventilation-perfusion match.

The assessment of ventilation may be simplified nowadays, because there is a high concordance between end-tidal partial pressure of CO_2 (Pco_2) measured by

capnography and the $Paco_2$ obtained with ABG measurement. (Corbo et al., 2005) Continuous monitoring patient's response to bronchodilatory therapy in AEBA can now be easy and effortless using capnographic waveform analysis. (Nik Hisamuddin et al., 2009)

Chest radiograph is of little value in most AEBA and should be restricted to patients with suspected complication from the primary disease such as pneumonia, pneumothorax, pneumomediastinum, congestive heart failure, life-threatening asthma with poor response to treatment, and patient who required mechanical ventilator support.

2.2.3 Assessment of severity of AEBA in Emergency Department

A patient with acute exacerbation of bronchial asthma when presented to emergency department, assessment of the severity of exacerbation is crucial because it determines the types of treatment that need to be administered and the care facility level a patient needed in different severity. Most patient with severe to life threatening exacerbation need to be referred to hospital with acute intensive care facilities. Table below is adopted from GINA guideline 2012 which classify the severity of AEBA.

Table 1: Assessment of severity of AEBA

	Mild	Moderate	Severe and life threatening
Altered conscious level	No	No	Yes
Respiratory rate	Increase	Increase	>30/min
Talk in	Sentences	Phrases	Words
Pulses paradoxus	Absent	May be present	Often present
Wheezing intensity	Moderate	Loud	Loud or silent chest
Accessory muscles	Absent	Moderate	Marked
Pulse	<100/min	100-120/min	>120/min
Initial PEFR	>80%	60-80%	<60%
Oxygen saturation	>95%	91-95%	<90%

2.3 Management of AEBA in Emergency Department

2.3.1 Oxygen therapy

Oxygen supplement should be given to patient with saturation less than 90% (95% in pregnant and coexisting heart disease), titrated to maintain arterial oxygen between 94-98%.

2.3.2 β_2-agonist

Rapid acting inhaled β_2-agonists either via nebulizers or holding chamber are the medication of choice use in AEBA for relief of bronchospasm e.g. salbutamol and terbutaline. (Cates et al., 2004) Their use should be on an as-needed basis with the

lowest dose and frequency as possible. Increase daily use of β_2-agonist is an indicator for poor asthma control. Similarly, failure of β_2-agonist use to relief bronchospasm symptoms during AEBA warrants an emergency treatment and short term oral glucocorticosteroids. Inhaled β_2-agonist has less side effects such as tremor and tachycardia than occur in oral β_2-agonist.

2.3.3 Glucocorticosteroids

Inhaled glucocorticosteroids are currently the most effective anti-inflammatory therapy for persistent bronchial asthma. Evidence has shown in their efficacy in reducing asthma mortality (Suissa et al., 2000), improving lung function test of patient, has better quality of life, reducing asthma symptoms (Juniper et al., 1990), reducing episodes of AEBA (Pauwels et al., 1997), and controlling airway inflammation. (Jeffery et al., 1992)

Systemic glucocorticosteroids are indicated for all moderate to severe AEBA or those experiencing incomplete response to initial β_2-agonist therapy. The benefits of steroids include reduces the rate of relapse, speeds the resolution of airflow obstruction, and may decrease the hospital admission rate in severe AEBA. (Rowe et al., 2007) Steroid effects begin at 4-6 hours and peak at 24 hours. Oral glucocorticosteroid is favorable and is as effective as intravenous hydrocortisone. (Harrison et al., 1986)

2.3.4 Anticholinergic Agents

Ipratropium bromide is one of the most commonly used anticholinergic drug in the treatment of AEBA. It has bronchodilator effect and reduces airway secretion. However, the maximum effect of inhaled ipratropium bromide is in 30 to 120 minutes and lasting up to 6 hours. In addition to this, its bronchodilating potency is lower and

onset of action slower than β_2-agonists, therefore it should not be used alone in acute exacerbation of asthma. Clinical trial has shown that ipratropium bromide in combination with β_2-agonists for severe AEBA modestly improve lung function test result and a reduction in hospitalization. (Rodrigo et al., 1999)

2.3.5 Magnesium Sulfate ($MgSO_4$)

Magnesium is the second most abundant intracellular cation in human body. Normal serum magnesium level is 1.5-2.5mEq/L. It plays a major roles in physiology function in the body, e.g. as cofactor of more than 100 enzymes in intracellular phosphorylation processes, DNA and protein synthesis, ATP function, neurotransmission, cardiac conduction and smooth muscle relaxation effect. A research paper published in 1990, demonstrated a significant smooth muscle relaxation property of magnesium (Spivey et al, 1990). Another study proposed by (Lindeman et al, 1989) revealed that magnesium plays a role in airway smooth muscle relaxation by acting as a voltage-sensitive calcium channel blocker. In explanation, Cation Magnesium has a 2+ valence comparable to cation calcium. Consequently when $MgSO_4$ is given as a therapy in acute asthma attack, magnesium acquires a competitive effect with calcium in the body which inhibit intake of calcium cation into smooth muscle cells in airway. Therefore airway smooth muscle relaxation occurred.

Magnesium relaxes bronchial smooth muscle and dilates asthmatic airway in vitro. Mechanism of actions include calcium channel blocking properties as mention above (Lindeman 1989), inhibition of cholinergic neuromuscular transmission (Del Castilo et al., 1954), stabilization of mast cells and T-lymphocyte (Bois, 1963), and increase β_2-agonist bronchodilatory effect by enhancing the receptor affinity (Classen et al., 1987).

Intravenous $MgSO_4$ therapy in severe AEBA patient improves airflow limitation, prevent intubation and decrease hospital admission. (SIlverman et al., 2002) Side effects of magnesium infusion are dose related, toxicity occurred at serum magnesium level of 9mg/dL and above. However, 2g of intravenous magnesium bolus only increase the serum magnesium level from 2.2 to 2.8mg/dL 30 min after the infusion. (Elliott et al., 2009) Somehow it is still crucial to monitor for toxicity features such as warmth, flushing, sweating, nausea and vomiting, muscle weakness and loss of deep tendon reflex, hypotension and respiration distress. Magnesium nebulization still remains controversial even though a few publications supported for its efficacy use in adult and children with mild to moderate AEBA. (Blits et al., 2005 and Mahajan et al., 2004

2.4 Benefits of Nebulised $MgSO_4$ in AEBA

Theoretically, Magnesium has shown bronchodilatory effect based on few published hypothesis. $MgSO_4$ can induce bronchial smooth muscle relaxation by blocking the voltage-dependent calcium channels, subsequently it inhibits the uptake of calcium into cytosol of bronchial smooth muscle (Gourgoulianis et al., 2001). $MgSO_4$ can decrease the histamine release from the mast cells (Bois et al., 1963) and inhibit acetylcholine release from cholinergic nerve endings (Del custilo et al.,1954), in which both mechanism contribute to bronchial muscle relaxation. According to paper publishe in 1987 by Classen et al., magnesium has synergistic bronchodilator effect when given together with salbutamol.

There were two meta-analysis on the efficacy of nebulized $MgSO_4$ published in two years apart showed contradict results. (Blitz et al., 2005 and Mohammed et al., 2007) Among the 7 reviewed trials, only 3 trials with Jadad score of 5. Largest trial with total sample of 100 was from Aggrawal et al., 2006, showed no benefit of nebulized

$MgSO_4$ in management of AEBA. A recent study by Gallegos et al., 2010 (n=60), showed improvement in lung function test, oxygen saturation and reduces admission rate at 90 minutes. Base on the reviewed trials, there were heterogeneity of $MgSO_4$ treatment dose, different severity of AEBA and small number of pooled studies, the experts have concluded that the evidence is still insufficient to recommend the use of nebulized $MgSO_4$ in the treatment of AEBA. (Woo et al., 2012)

Table 2: Summary of systemic reviews and meta-analysis on the efficacy of $MgSO_4$ as an adjunct therapy for AEBA

Study	Sample size	Outcome measure	Results	Conclusion
Blits et al (2005)	6 trials (296 patients)	• Pulmonary function test • Admission to hospital	• Pulmonary function test: SMD 0.30 (95% CI ,0.05 to 0.55) five studies • Admission to hospital: RR 0.67 (95% CI,0.41 to 1.09) four studies	Benefit using $MgSO_4$ as an adjuvant to β_2-agonists in AEBA Reduce hospital admission
Mohammed et al (2007)	7 trials (430 patients)	• Pulmonary function test at 20min and 60min • Admission rate	• Pulmonary function test: SMD 0.17 (95% CI, 0.02 to 0.36, p=0.09) • Admission rate: RR 2.0 (95% CI,0.19 to 20.93, p=0.56)	Poor evidence for $MgSO_4$ to improve pulmonary function test Not significant to reduce admission rate

2.5 Methodological Quality of a Clinical Trail

Randomized controlled trial has been recognized as the most powerful and revolutionary forms of research, which has contributed great importance in medical sciences advancement. (Jadad et al., 2007) Jadad scale/Jadad scoring or also known as Oxford quality scoring system has been described by a Columbian physician Alenjandro Jadad-Bechara. The purpose of this scoring was to standardize the quality of clinical trial. Jadad scoring was described as a three-point questionnaire, each question carried a single point if the answer is yes and zero point if the answer is no, the question as shown below. (Jadad et al., 1996)

1. Was the study described as randomized?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

To receive the corresponding point, an article should describe the number of withdrawals and dropouts, in each of the study groups, and the underlying reasons. Additional points were given if:

- The method of randomisation was described in the paper, and that method was appropriate.
- The method of blinding was described, and it was appropriate.

Points would however be deducted if:

- The method of randomisation was described, but was inappropriate.
- The method of blinding was described, but was inappropriate.

3.0 HYPOTHESIS AND OBJECTIVES

3.1 RESEARCH HYPOTHESIS

- Nebulized isotonic magnesium sulfate as an adjunct to salbutamol has significant mean difference of PEFR improvement in the treatment of moderate AEBA in adults.

3.2 OBJECTIVE

3.2.1 General objective :

- To determine the effectiveness of isotonic magnesium sulfate as an adjunct to nebulized salbutamol compare to salbutamol only group as a treatment in moderate AEBA in adults.

3.2.2 Specific objectives :

- To compare the mean differences improvement of pulmonary function (PEFR) in this two groups of patient.

- To compare the mean discharge time in this two groups of patient.

4.0 METHODOLOGY

4.1 STUDY DESIGN, SETTING AND DURATION

This was a double-blinded, randomised control trial study with a goal to determine the mean difference improvement of PEFR in the treatment group and the control group with moderate AEBA. This study was conducted in Hospital Universiti Sains Malaysia (HUSM) for 12 months duration, from 1st October 2013 until 30th Sep 2014. This study consisted of 120 patients who presented with moderate AEBA.

4.2 REFERENCE POPULATION

Patients who presented with moderate AEBA as defined by GINA guideline 2012 in Kelantan.

4.3 SOURCE POPULATION AND SAMPLING FRAME

Adult patients who presented to emergency department of HUSM in Kelantan with moderate AEBA.

4.4 SAMPLE SIZE CALCULATION

Calculation of sample size was based on data presented from the similar study by Nannini et al, 2000 in which to detect the difference in mean percentage improvement in PEFR between control and treatment group.

The sample size was calculated using the two proportion formula as below (Pocok's formula):

$$n = \frac{p_1(1 - p_1) + p_2(1 - p_2) \times (z_\alpha + z_\beta)^2}{(p_1 - p_2)^2}$$

P_1 = 0.61 Percentage increase in PEFR of treatment groups from literature review (Nannini et al., 2000)

P_2 = 0.31 Percentage increase in PEFR of control groups from literature review (Nannini et al., 2000)

Z_α = 1.96 for α = 0.05 (two-tailed)

Z_β = 1.28 for 90% power

n = 56 with PS software

n = 67 in each arm with added 20% drop out.

4.5 INCLUSION AND EXCLUSION CRITERIAS

Patients with the below criteria were included into the study:

1) Patient with history of bronchial asthma
2) Fulfil the criteria for moderate exacerbation as defined by GINA guideline 2012. Characters of moderate AEBA include increase respiratory rate but not altered in conscious level, talking in phrases, moderate usage of accessary muscles, pulserate of 100 - 120bpm, loud wheezing, oxygen saturation between 91% to 95%, may be present of pulses paradoxus, initial PEFR between 60% to 80% of predicted value.

The present of several characters, but not necessaryly all indicates the classification of exacerbation.

3) Age between 18 – 65 years old
4) Consented patient
5) First visit for current exacerbation who has not been enrolled in study

However, those with any of the below criteria were excluded:

1) Age < 18 or > 65 years old
2) High grade fever with suspected pneumonia
3) Chronic obstructive pulmonary disease
4) Cardiac arrythmias
5) Heart failure
6) Chronic kidney disease
7) Pregnancy
8) First presentation with wheezing
9) Patient who deteriorated during the trial

4.6 ETHICS AND CONSENT

This study was approved by the Health and Human Medical Research and Ethics Committee of USM in 26th September 2013. Written consents were obtained from patients after they fulfilled the inclusion and exclusion criteria.

4.7 SAMPLING METHOD

All patients who presented to emergency department of HUSM with moderate AEBA were triaged to asthma bay. Brief history taking, physical examination and PEFR were performed on patient involved. Patients who had symptoms with medical history

of asthma as mentioned in GINA 2012 were selected as research candidates. Candidates who fulfill the inclusion and exclusion criterias and consented were recruited into the study.

4.8 STUDY METHOD

Each patient presented to emergency department of HUSM with AEBA was evaluated in the primary and secondary triage counter. Patient fulfilled the criterias for severe AEBA (GINA, 2012) was sent to critical care area. However, patients with mild to moderate asthma were triaged to asthma bay for further assessment and treatment. Each patient was evaluated using a simple clerking sheet. Pulse, blood pressure, oxygen saturation, respiratory rate, and pre-nebulization PEFR were recorded. Patient who fulfilled the criteias for moderate AEBA was selected as our study population. Finally, only patient who fulfilled the inclusion criteria and consented was selected as research candidate. Patient who was exluded was given AEBA standard treatment as per protocol.

Patients who were recruited into our study were randomly allocated into two groups. Best of three readings of Pre-bronchodilator PEFR was recorded at 0 minute using a mini Wright's (standard range) peak flow meter (Clement Clerk International, United Kingdom). Patient subsequently recieved medication via nebulization using a jet nebulizer. The research medication was prepared by pharmacist in HUSM. We use block randaomization, which will be explained in the later part. Post treatment, pulse, blood pressure, oxygen saturation, respiratory rate, and post-bronchodilator PEFR were again recorded at 20 minutes.

4.8.1 Randomization and research medication preparation method:

Block randomization was choosen, total of 20 blocks were prepared by pharmacist in HUSM. Each block contained 6 syringes with equal number of treament A and B at any time of study. When study subjects were recruited, the treatment in the block were allocated. The content in the sryinges were blinded to the researcher and patient during the sampling period. The list of content in syringes were reviewed to the reseacher only after completed the study.

Patients who were recruited into the study were randomly allocated into two types of medication group as describe below:

1. Group A – 3 mls of 0.9% normal saline

2. Group B – 3 mls of prepared $MgSO_4$ isotonic solution (7.5g or 3 ampules of $MgSO_4$ were mixed into 100mls of 0.9% normal saline)

At 0 minute, patients were allocated in one of the two groups stated above, 1 ml of salbutamol solution (5mg) were added in the nebulizer chamber in both groups. The drugs were delivered using jet nebulizer over a period of 5 to 8 minutes. At 20 minutes post treatment, pulse, blood pressure, oxygen saturation, respiratory rate, and post-bronchodilator PEFR were recorded. Patients' condition were reassesed at 20 minutes post treatment, standard AEBA treatment was continued as per protocol. Patients were allow to discharge home if their PEFR achieved >80% of predicted PEFR value for age, sex and height. Time from treatment initiated until patient discahged was recorded.

4.8.2 Data collection

Primary objective for this study was to determine the mean difference of PEFR improvement in this two study groups describe as absolute percentage improvement of PEFR post treatment (post nebulization PEFR minus pre nebulization PEFR divided by expected/best PEFR then multipled by 100).

Secondary objective for this study was to compare the means treament duration for this two groups, it is recorded as total minutes needed for treatment.

4.9 STATISTICAL ANALYSIS

All the data collected were entered and analyzed using SPSS version 22.0 licenced to HUSM. Descriptive statistic of the variables was calculated and presented. The mean and standard deviations for numerical variables and frequency and proportion for categorical variables were reported along with histogram, pie chart or bar chart.

For univariable analysis, the mean difference of improvement in PEFR described as percentage in PEFR from the baseline were analysed using a parametric independent t-tests. P value of ≤ 0.05 was considered to indicate statistical significance, two tailed. The mean changes of PEFR before and after treatment of each group and means difference of vital signs of each group was analysed using paired t-test, with statistically significance set at p value ≤ 0.05, two-tailed. Pearson's correlation was used to determine the relation between pre-nebulization PEFR and outcome PEFR in two study groups. P value of <0.05 was considered statistically significant.

4.10 FLOW CHART OF STUDY