DOES INTRAVENOUS MAGNESIUM REDUCE HOSPITAL ADMISSION RATES IN ADULTS WITH SEVERE ACUTE ASTHMA?

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Abstract

Does Intravenous magnesium reduce hospital admission rates in adults with severe acute asthma?

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Introduction: Asthma is a chronic respiratory disease characterized by bronchial hyper-responsiveness, airflow obstruction, and inflammation that presents with symptoms of cough, dyspnea, chest tightness, wheezing, and sputum production. Symptoms of asthma can range from mild to severe, resulting in hospitalization, intubation, and even death. In addition to inhaled beta agonists, nebulized ipratropium, oxygen, and systemic corticosteroids, magnesium sulfate has been used as an adjunctive treatment of acute severe asthma exacerbations. However, despite its use, its effectiveness has been inconclusive and controversial, with previous studies showing the greatest benefit in those having severe exacerbations. This literature review was conducted to determine if magnesium sulfate administration reduces hospital admission rates in adults with acute, severe exacerbations.

Methods: A literature search was conducted for research studies of adult patients who presented with an acute, severe asthma exacerbation and were treated with intravenous magnesium sulfate. Study dates were limited to the years 1989-2014, and were identified through PubMed, Scopus, Embase, and Google Scholar, with further studies identified through the search of reference lists of published articles. A total of 11 studies were found using the sources above. Of these 11 studies, 5 double blind, randomized, placebo controlled trials were selected for this review.

Results: Results from the five randomized controlled trials selected were mixed, with two studies showing a decrease in admissions (one had weak evidence of a decrease), and three studies showing no difference in admission rates.

Conclusion: Intravenous magnesium sulfate does not appear to decrease admission rates in adult asthmatics having a severe exacerbation.

Introduction

Asthma is a chronic respiratory disease characterized by bronchial hyper-responsiveness, airflow obstruction, and inflammation that presents with symptoms of cough, dyspnea, chest tightness, wheezing, and sputum production. Symptoms of asthma can range from mild to severe, resulting in hospitalization, intubation, and even death. According to Statistics Canada, 7.9% of Canadians over the age of 12 had asthma in 2013 (1). Asthma carries a significant burden in quality of life considerations, and is responsible for a significant number of emergency room visits.

Treatment of asthma focuses primarily on control of symptoms and prevention of exacerbations, however exacerbations still occur frequently. First line adult asthma exacerbation treatment is with inhaled beta agonists, nebulized iptratropium (atrovent), oxygen, and/or systemic corticosteroids depending on severity. Intravenous aminophylline/theophylline, as well as heliox are also occasionally used, but methylxanthines have fallen out of failure due to narrow therapeutic ranges. As systemic corticosteroids take 6-8 hours for effect, additional therapy for the treatment of asthma would be useful in the early stages of an exacerbation. One medication often considered as an adjunct in the treatment of asthma is magnesium sulphate ($MgSO_4$,) administered through nebulization or intravenously. Indeed, some guidelines even include IV $MgSO_4$ administration as a treatment for acute adult asthma exacerbations. Despite this, the research on magnesium's

effectiveness has been inconclusive and controversial. This paper will examine whether the use of intravenous magnesium leads to a decrease in admission rates in adults with acute, severe asthma exacerbations.

Methods

Literature Search

A literature search was conducted and research studies between the years of 1989-2014 were identified through PubMed, Scopus, Embase, and Google Scholar. Further studies were identified through the search of reference lists of published articles, as well as reference lists of systematic reviews.

Articles Included in Literature Review

A total of 11 studies were found using the sources listed above. Of these eleven, five studies were selected for this literature review. All included studies were double blind, randomized, placebo controlled trials that studied either a primary population or population subset of adult patients who presented with severe and/or life threatening acute asthma exacerbations and reported on admission rates as a primary or secondary outcome. Published dates of included studies ranged from 1995-2013. Of the excluded studies, two were excluded due to being unblinded with no placebo group (2)(3), another study was excluded due to single blinding (4). Other studies were excluded due to subjective means of assessing an asthma exacerbation (use of the FISCHL scale in (5), no admission rates reported (6), and brief duration of study (7)

Location of Study

Four of the five studies included in this review occurred in the emergency department, one study did not specify the practice setting, but occurred in a teaching hospital. Three of the studies were performed in the United States, two studies occurred in the United Kingdom. Most of the studies were multi center trials, ranging from 2-34 hospitals participating, however two studies occurred in a single hospital.

Intravenous Magnesium Dosage, Timing of administration, infusion time

Four studies provided a dosage of 2g IV $MgSO_4$, with one study providing a dose of 1.2 g IV $MgSO_4$. All participants were given $MgSO_4$ within 30 minutes of randomization to placebo or control groups. Infusion time varied in the studies from 10-20 minutes.

Patient Selection

Patients in all five studies were randomly assigned to placebo vs. control group. Two studies (8)(9) were randomly assigned through pharmacy using a random number generation; one study used a 1:1 ratio randomization table (10). Two studies were randomized either through a random number generator (11) or an internet or telephone generated randomization sequence (12)**.**

Blinding

All studies blinded patients to treatment with IV $MgSO_4$ vs. placebo. Four studies described blinding of placebo vs. $MgSO_4$ as being identical in appearance and performed under the guidance of the hospital pharmacy. Goodacre (12) described participants being allocated to numbered treatment packs kept in the emergency department which participants, hospital staff, and research staff were blinded to.

Follow-Up

Three of the studies (9)(12)(8), had low attrition rates that were documented clearly; rates were similar in both placebo and control groups. Porter (11) did not disclose attrition rates in his study; Silverman (10) disclosed a fairly high rate of participants who had protocol violations but stayed in the intention-to-treat data set, however a detailed attrition rate for placebo vs. treatment groups was not disclosed.

Classification of Severe Asthma

All studies defined severe acute asthma using either peak expiratory flow rate (PEFR), or forced expiratory volume in 1 second (FEV_1). In addition to a PEFR of <50% of best or predicted, Goodacre (12) also

defined severe acute asthma as either a respiratory rate >25 breaths per min, heart rate >110 beats per min, or inability to complete sentences in one breath. Two studies used FEV1 criteria ranging from ≤25% (9) to ≤30% predicted (10). Bradshaw (8) separated subjects into life threatening (PEF <33% predicted), and severe (PEF 34-50% predicted), whereas Porter (11) defined severe exacerbation as PEF <100 L/min or <25% predicted flow.

Study Ages

Three studies included in this review studied mostly adult asthmatics between the ages of 18-65. One study Included individuals between the ages of 17-73 (8) and one included those 16-88 years of age (12). The decision to include patients whose age was 16 and over was made as the mean age in the Goodacre (12) study was 35.6 (IV $MgSO_4$ arm) and 36.4 (placebo arm), and in the Bradhshaw (8) study the average age was 36 (IV $MgSO_4$ arm) and 38.8 (placebo arm). In addition, the inclusion of individuals 16 and over would not be expected to alter results, as there is theoretically little difference between those aged 16 as compared to 18.

Study Size

Goodacre (12) had the largest total number of participants at 1109 allocated to intravenous $MgSO_4$, nebulized $MgSO_4$, or placebo. Of the 1109 total participants, there were 394 allocated to the intravenous $MgSO_4$ group, and 358 in the placebo group. Silverman (10) had the second largest study patients, with a total of 248 patients. Bloch (9) had 135 total patients, with 35 allocated to the severe group, 94 classified as moderately ill. Porter (11) included 42 patients, Bradshaw (8) had a total of 129 patients (29 life threatening group, 61 severe group, 39 moderate group). For the purposes of this paper, only the results of the patients classified as severe and life threatening were included.

Baseline Characteristics of Study Participants

The Goodacre (12) study had a greater portion of white patients in the IV $MgSO_4$ group (94%), and more patients who had never smoked in the nebulized magnesium group. In the Bloch(9) and Silverman(10)

studies, there were no significant differences between placebo and magnesium groups. In the Porter (11) study, there was a higher heart rate in the magnesium group versus placebo, `and only 25% males in the placebo group. Bradshaw (8) had a disproportionate number of females (57%) in the severe IV $MgSO_4$ treated group and the life threatening group (71% placebo, 67% $MgSO_4$ group); there were no other significant differences.

Only two of the studies included ethnicity in their baseline characteristics of participants. The Goodacre (12) trial had almost exclusively white participants (90%), with 70% of the total participants being female. The Silverman (10) study included 30% blacks, 35% Hispanic, 10% whites, the majority of the study patients were male at 58%.

Four studies commented on asthma medications used prior to study enrollment by participants. In Bradshaw(8), inhaled steroids were used by 62% in life threatening group , and 75% of severe asthmatic group. In the severe group in Bloch(9), 20% used oral steroids in previous 24 hours, 20% had used inhaled steroids, and 58% had used Theophylline. In Silverman (10), 13% used oral steroids in past 24 hours, 27% had used theophylline, and 26% had used inhaled steroids. In Goodacre (12), 88% had used salbutamol, 33% had used prednisolone, and 14% had used iptratropium.

Of the studies that reported smoking history (either current or previous smokers), results ranged from 29%-31%, up to 47% in the Silverman study(10). One study (11) did not provide information on asthma medications used prior to enrollment or smoking history.

Decision to Admit – Timing and Criteria

Timing of the decision for admission to hospital, discharge from the emergency department, or further observation in the emergency department ranged between the studies from a low of 60 minutes (8) (11), to a high of 4 hours (9) (10). Goodacre (12) also recorded admission data on study participants in the following 7 days after treatment,; the Bloch (9) study also followed up at 24 hours and one week after emergency department discharge. Admission criteria also varied between the studies. Guidelines for admission were not disclosed in two studies (12) (11). Of the remaining three studies, admission criteria were as follows in the Bradshaw (8) study: PEF <50% predicted, respiratory rate >25/min, pulse >110 beats/min or inability to

complete sentences in 1 breath. Bloch (9) study criteria for admission included shortness of breath at rest or minimal exertion, respiratory rate greater than or equal to 28, or FEV1 less than 50% of predicted. In the Silverman (10) study, an FEV1<50% predicted, respiratory rate ≥26/min, no improvement in shortness of breath or wheezing, or significant dyspnea on ambulation were the admission criteria.

Other Treatments Provided

Study patients received nebulized salbutamol and corticosteroids in all included studies. Corticosteroid dosages varied throughout the study, with studies administering corticosteroids intravenously; only the Goodacre (12) study administered oral prednisolone. Oxygen use was described in three of five studies, however it was presumably administered as necessary in all studies. Two studies described the use of nebulized atrovent (8) (12), there were also additional treatments described as nebulized bronchodilators or IV aminophylline administered at the discretion of the attending physician in the Bradshaw (8) study. See Table 1 for specific dosage and frequency of medications provided.

Exclusion Criteria

Exclusion criteria were generally the same across the five studies. Exclusion criteria included those with chronic lung disease, COPD, or suspected pneumonia; other criteria were congestive heart failure, previous myocardial infarction, known hypertension currently on medication and hypertension or hypotension on presentation. Other excluded individuals were pregnant patients, diabetics, and febrile individuals. Those with life-threatening features (such as silent chest, cyanosis, poor respiratory effort, bradycardia) and those requiring intubation or were highly likely to require intubation were excluded.

Side Effects

None of the studies reported life threatening side effects or major side effects. Minor side effects of flushing, mild fatigue, burning at the IV site, and one episode of transient urticarial were described in Bloch (9). Other minor side effects include a decrease in blood pressure as described in three studies, with Porter (11)

describing a decrease in mean arterial pressure of 8.7 mm Hg. Nausea, vomiting, headache, dizziness were also described; no decrease in patellar deep tendon reflexes was noted in one study. Some of the side effects are likely not due to $MgSO_4$ infusion itself, and may be due to effects of other medications administered.

Table 1 – Comparison of study treatments and protocols

Treatments	Study Authors and Protocols				
	Porter	**Goodacre**	**Silverman**	**Bradshaw**	**Bloch**
Ventolin (Dose, route, frequency)	2.5 Mg nebulized at 20, 40, 60 minutes (additional nebulization treatments at physician discretion after 60 minutes)	5 Mg Nebulised during recruitment, followed by up to 5 Mg every 20 minutes (added to each trial nebulizer)	2.5 Mg Nebulized with 100% Oxygen at 0, 30, 60, 120, 180 minutes after ED arrival	5 mg Nebulised, followed by up to 3 additional nebs	2.5 Mg Nebulized at 0, 30, 60, 120, 180 minutes
Iptratropium		500 mcg Nebulised total		500 mcg Nebulised total	
Corticosteroids	Methylpredniso-lone 125 mg IV (at start of study)	Prednisolone Orally	Methylpredni-solone 125 mg IV	Hydrocortisone 200 mg IV	Methylpredniso-lone 125 mg IV within 30 minutes of presentation (if FEV1 <40% predicted or had received oral steroids in past 6 months)
Oxygen	To maintain pulse oximetry reading of >91%	Not Described	100% with Mg Nebulization	35% for all patients	Did not describe in study
Aminophylline				Intravenous given at the discretion of the attending physician (7 in MgSO4 group, 5 in placebo group)	

Table 2 – Overview of studies included in analysis

Study	Participants	Type of Study	Outcomes	Results
Goodacre, 2013	1109 total 394 IV $MgSO_4$ group 358 placebo group between ages of 16-88	DB, PC, RCT	2 Primary outcome measures: 1. Proportion of patients admitted to hospital within 7 days 2. Breathlessness measured on a visual analogue scale in the 2 h after initiation of treatment	No clinically significant difference in breathlessness, weak evidence of a decrease in hospital admissions
Bradshaw, 2007	129 total 29 "life threatening" 61 severe between ages of 17-73	DB, PC, RCT	Primary outcome: % predicted PEF at 60 min Secondary outcome: Hospital admission rates	No significant difference in % predicted PEF or admission rates in "life threatening" or severe group (numbers in life threatening group may be too small to detect a significant difference)
Silverman, 2002	248 total between ages of 18-60	DB, PC, RCT	Primary outcome - % FEV1 predicted at 240 min Secondary outcomes: PEFR, hospital admission rates, change in pulse, Borg dyspnea ratings, accessory muscle usage, and respiratory rate	No change in admission rates (but many refused admission who would have been admitted), pulmonary function improved, especially in those with most severe airway compromise
Porter, 2001	42 patients between ages of 18-55	DB, PC, RCT	Primary outcome: PEF at 60 minutes Secondary outcomes: hospital admission, and subjective symptoms of dyspnea (measured by Borg dyspnea scale)	PEFR worse in MgSO4 group, no improvement in subjective symptoms or admission rates (although insufficient numbers?)
Bloch, 1994	135 total 35 severe between ages of 18-65	DB, PC, RCT	Primary outcomes: FEV1 at 2 hours after baseline and hospital admission rates	Decreased admission rate and improved FEV1 in severe asthma

Results

Results from the studies were mixed. The Goodacre (12) study showed no clinically significant difference in breathlessness (measured on a visual analogue scale), with weak evidence of a decrease in admission rates to hospital between IV $MgSO_4$ and placebo. There was no difference in physiological measures noted, nor was there any difference in use of respiratory support, ICU admission rates, length of stay, or improvement in PEFR.

Bloch (9) showed a decreased admission rate and improved FEV1 in patients with acute severe asthma. Despite seven patients leaving the emergency department (ED) at 120 minutes (five of which received $MgSO_4$ and were presumably doing well), the results remain statistically significant. There was no benefit from $MgSO_4$ in patients with moderate asthma exacerbations.

Bradshaw (8) showed no significant difference in admission rates in either "life-threatening" or severe groups, but the numbers in the "life-threatening" group may have been too small to detect a significant difference; there was also no significant change in % predicted PEF.

Silverman (10) found that patients with the lowest initial FEV1 had the greatest improvements in pulmonary function after receiving IV $MgSO_4$. Those with an initial FEV1 <25% predicted who received $MgSO_4$ had a final FEV1 of 45.3% compared to 35.6% for placebo, and the higher the initial FEV1, the less the benefit. Those with an FEV1 on ED arrival closer to 30% predicted had no apparent benefit. It was also found that magnesium did not decrease hospitalization rates; however, the majority of patients advised admission refused, and post hoc analysis did reveal actual hospital admission rates to be lower in magnesium-treated patients with the lowest ED arrival FEV1. Admission rates for those treated with magnesium were actually higher when FEV1 initially was closer to 30% for unexplained reasons.

Porter (11) found that PEF were actually worse in the magnesium group versus placebo, didn't appear to decrease admission rate to hospital, and did not decrease subjective dyspnea as measured on the borg dyspnea scale. However there were only 10 total admissions that resulted in a confidence interval that was very wide. The results of the studies have been summarized in Table 2.

Conflicts of Interest

Only three studies reported funding or sponsoring information for their trial. The Goodacre (12) research trial received funding from the UK National Institute for Health Research Health Technology Assessment Programme and declared no conflict of interest. Bloch (9) was partly supported by the Nina Weisman Pulmonary Research Fund, and Silverman (10) was supported in part by a grant from the Max and Victoria Dreyfus Foundation.

Discussion

Magnesium use in bronchial asthma has been studied as early as the 1930's (13) and has been shown to be a bronchial smooth muscle relaxant in vitro (14). A number of studies have also confirmed $MgSO_4$'s bronchodilating properties, including Okayama (15), Noppen (3) and Rolla (16); the bronchodilating peak effect of magnesium in these studies ranged from 10 minutes to 30 minutes. The exact mechanism for the pulmonary benefits seen with administration of $MgSO_4$ are not clear, however, a number of different mechanisms have been proposed. There is evidence that magnesium has an anti-inflammatory effect through decreasing superoxide production in neutrophils (17). Magnesium results in smooth muscle relaxation by acting as a calcium antagonist, as intracellular magnesium reduces calcium uptake directly and modulates smooth muscle contractions (18). Treatment of acute asthmatic patients with beta agonists has been reported to decrease serum levels of magnesium by 15% through either intracellular shifting or increasing urinary losses (19). As magnesium is primarily stored intracellularly (principally within bone), serum levels may not accurately detect a deficit of magnesium, and magnesium deficiency may lead to bronchoconstriction due to increased excitation of bronchial smooth muscle (20).

There is also anecdotal evidence of magnesium's effectiveness characterized in the literature, including one case study which reported the effectiveness of high-dose IV $MgSO_4$ (5 g IV over 5 minutes) in avoiding re-

intubation in severe bronchospasm with hypoxia (21). In addition to case studies, a number of randomized controlled studies have been performed related to magnesium use in asthmatic patients. The results of these studies have been mixed, with some failing to show improvement with magnesium administration. Of the studies that had a positive outcome, the greatest benefit appears to be in those having severe exacerbations. There have also been a number of systematic reviews addressing $MgSO_4$ use in asthma. A Cochrane review (22) found that IV $MgSO_4$ reduced hospital admission compared with placebo, and translated to a reduction of seven hospital admissions for every 100 adults treated. Other systematic reviews have concluded that IV MgSO4 may be beneficial as an adjunct to standard treatment in adults with severe or life threatening exacerbations (23), and may result in a modest decrease in admissions among adult asthmatic patients (24). Route of administration does appear to matter, as inhaled $MgSO_4$ has not been shown to reduce hospital admissions, and there was no clear evidence of improved pulmonary function in a recent cochrane review (25). Long term (6.5 months) oral magnesium supplementation has also been show to reduce bronchial reactivity to methacholine and PEFR, as well as subjective asthma control measures and quality of life in a randomized placebo controlled trial in adults with mild to moderate asthma (26).

As a result of the conflicting reports related to the efficacy of $MgSO_4$ use in adult asthmatic patients, this paper sought to address one important aspect in the treatment of acute asthma: does intravenous magnesium sulfate reduce hospital admission rates in adults with severe acute asthma? The results from the five randomized controlled trials selected were mixed, with two studies showing a decrease in admissions (one showed a weak decrease), and three studies showing no difference in admission rates. Of the three studies showing no change in admission rates, one had insufficient numbers in the “life threatening” group to come to a conclusion, and in one study patient’s who were advised admission refused. In the latter study however, there would have been a trend toward a reduction in admission rates had a standard FEV1 cutoff been used for admission.

Five studies were reviewed for this paper. The studies varied in the number of participants, other treatments provided (as well as dosage of treatments provided), dosage of IV $MgSO_4$, as well as admitting criteria and timing of decision to admit. Additional differences were the classification of severe asthma, and length of the studies. The number of study participants ranged from 35 to 752 (see Table 2 for particulars). Two

studies had 35 and 42 total patients with severe asthma enrolled, with treatment and placebo groups as small as 14 in some cases. Therefore, the low number of participants makes it difficult to determine if the results can be extrapolated to the larger group of adult asthmatics. In the largest study (and likely the largest study of $MgSO_4$ use in acute asthma), the study had 87% power to detect a 10% difference in admission rate for IV $MgSO_4$ versus placebo, with results showing only weak evidence of a decrease in hospital admissions.

Duration of study also varied significantly, from a length of 60 minutes in two studies up to 240 minutes. As described previously, the bronchodilating effect of $MgSO_4$ is thought to be peak between 10-30 minutes. However, beneficial effects of $MgSO_4$ on pulmonary function have persisted well beyond this time period in some studies. Silverman (10) found a sustained improvement in pulmonary function even several hours after magnesium was administered, as did Bijani (6), who reports an increased PEFR at 30 minutes and 3 hours after stopping $MgSO_4$ infusion. Noppen (3) also describes a persistent bronchodilating effect, which persisted beyond 30 minutes post infusion. Therefore, study duration may have affected the findings, as studies which had a shorter duration may have seen a beneficial effect if the study had continued.

There was also significant variability in the use of asthmatic medications prior to study enrollment as described in the baseline characteristics section above. For example, in the Bloch (9) study only 20% had used inhaled steroids in the previous 24 hours, whereas in Bradshaw (8), inhaled steroids were used by 62% in life threatening group , and 75% of severe asthmatic group. There were also significant differences in the use of oral steroids ranging from a reported low of 13% up to a high of 33%. Most of the differences in medication use likely reflect a change in the treatment of asthma over the years as the study periods ranged from 1995 to 2013. The significant differences between studies in the pre-treatment medications may affect the response to $MgSO_4$ administration, including blunting the potential anti-inflammatory response of magnesium.

The majority of the studies used a dose of 2 grams of IV $MgSO_4$, however one study used a dose of 1.2 grams. The lower dose of magnesium may have contributed to the lack of response seen in this study, and it is unclear what the maximally effective dose of $MgSO_4$ is in acute asthma. It is possible that doses higher than 2 grams may provide further benefit as case reports have described the beneficial use of doses as high as 5 grams. In addition, research has shown that in response to $MgSO_4$, pulmonary function is improved in a dose

dependent manner, which suggests higher doses of $MgSO_4$ may provide more optimal bronchodilation (27). Continuous infusions or repeated doses of $MgSO_4$ may also be beneficial in acute severe asthma, however the use of higher doses may be limited by potential hypotension.

Treatment of severe asthma exacerbations has evolved in the past few years, and now call for the use of inhaled beta agonists such as salbutamol, inhaled anticholinergics (atrovent), and the use of corticosteroids. Inhaled beta agonists are known to decrease serum magnesium levels and may result in bronchoconstriction. As a result, it is possible that studies that used higher doses of inhaled salbutamol may result in even lower magnesium levels, and the administration of $MgSO_4$ in these settings may be more effective in relieving bronchospasm. Unfortunately, the total dose of inhaled salbutamol was not always clearly stated in the studies, with published doses ranging from a low of 7.5 mg to potentially 30 mg. However, even at the highest level dosing of potentially 30 mg, the result was still only weakly positive for a reduced admission rate. It is also possible that the opposite effect may occur; that higher dosing of inhaled beta agonists may blunt any further bronchodilating effect from administration of $MgSO_4$ and negate any further benefit.

All studies included in this review have described the use of beta agonists, as well as either oral or intravenous corticosteroids. As treatment guidelines have changed to include atrovent, efficacy of $MgSO_4$ needs to be reevaluated in the current practice setting. Atrovent has been shown to produce a greater bronchodilator effect when combined with inhaled beta agonists than that observed with beta agonists alone. For $MgSO_4$ to be useful when combined with atrovent and beta agonist therapy, it would have to be providing additional benefit to that already seen with these two agents. Of the studies reviewed, only Goodacre (12) and Bradshaw (8) described the use of atrovent, both at a dose of 500 mcq total. Of these two studies, only Goodacre (12) showed evidence of a decrease in hospital admissions, and the evidence was weak. Additional research studies have examined the use of IV $MgSO_4$ in acute severe asthma combined with salbutamol, ipratropium, and corticosteroids. One study (4) was a randomized, single blinded, placebo controlled study of 60 patients. In this study, there was found to be an absolute risk reduction in hospitalization of 23%, with a number needed to treat of only 4 to prevent one admission.

Definition of Acute Severe Asthma Exacerbation

When choosing appropriate studies to review for this paper, I decided to include studies where objective definitions of acute severe asthma were used. These definitions included either the FEV1 or PEFR as objective measures of asthma severity. The rationale for this decision was that results could be compared using standard values, and these values could be potentially reproducible in future studies. Although definitions of severe asthma vary, an FEV1 30-50% and PEFR <40% (<200L/min) are generally used as to categorize a severe obstruction, with an FEV1 <30% indicating very severe obstruction according to the American Thoracic Society (28). The use of spirometry and peak expiratory flows are not without limitations however, as results are often variable and unreliable, and can be difficult to obtain. Additionally, research performed on PEFR in adult asthmatics in the ED show no improvement in outcomes, do not reliably predict need for admission, and do not limit morbidity or mortality in acute exacerbations (29). Therefore, in order to characterize severe acute asthma in the emergency department, other measures other than PEFR and spirometry should be used, such as accessory muscle use, chest wall retractions, agitation, profound diaphoresis, rapid, shallow breathing (respiratory rate >25-30 breaths/minute), etc. Unfortunately, there can be significant variability in inter-rater reliability using these criteria, making comparison between study participants classified with severe asthma difficult.

While the studies included in this review had various definitions of severe asthma, the FEV_1 criteria used for admission ranged from ≤25-30% in 2 studies, and 2 additional studies used PEFR that ranged from <25% to <33% predicted. In the largest study performed by Goodacre (12), severe acute asthma was defined as either a peak expiratory flow rate of <50% of best or predicted, respiratory rate >25 breaths per min, heart rate >110 beats per min, or inability to complete sentences in one breath. As a result, admission criteria for the Goodacre (12) study does not meet the criteria for severe asthma, and would be better characterized as a moderate asthma exacerbation. It is therefore difficult to compare the findings from this study to the other 4 studies, which in some cases had studied people whose PEFR was half that of patients included in the Goodacre (12) study. Additionally, early studies have indicated that those with the most severe disease may show the most benefit from $MgSO_4$ administration, and the Silverman (10) study also found that patients with the lowest initial

FEV_1 had the greatest improvements in pulmonary function after receiving magnesium, and the higher the initial FEV_1, the less the benefit. Therefore, it is possible that the people studied in the Goodacre (12) study did not have bronchospasm severe enough to show benefit from magnesium.

Studying hospital admission rates as the primary outcome of this paper can be challenging when a number of factors affect the decision to admit in addition to the actual presenting condition and treatment provided. Some of these factors include age, supports at home (including home environment), comorbidities, type of insurance, anticipated compliance rates, treating provider bias, as well as the ability to obtain medication. In order to reduce the subjective nature of admission decisions, three of the five studies reviewed in this paper listed criteria required for admission. These criteria included an objective measure of respiratory function, such as the FEV_1 or PEFR, as well as vital signs measurements, such as respiratory rate and heart rate. As all studies were placebo controlled, double blinded, randomized trials, the admission criteria used should not have affected results as the individual making the admission decision would not know whether they were admitting a member of the placebo or magnesium group. However, it is possible that a number of patients in either the placebo or magnesium group were admitted for reasons which were more related to their home environment, for example, than the severity of asthma exacerbation.

The studies reviewed in this paper took place in various locations throughout the United States and United Kingdom. Only two of the five studies reported on ethnic characteristics of the included participants. Of these two studies, one had a 90% white population which was studied, whereas the other study reported a much more diverse population and reported only a 10% white population. As the Canadian population is quite diverse in ethnicity, studies performed on ethnicities largely confined to one ethnic group may not be replicable in Canada as response to magnesium may vary within ethnicities. As an example, one systematic review references a study performed on Japanese adult patients which found that aminophylline treatment was found to be highly safe among this population (in contrast with other populations), with a toxicity occurring in only 0.29% of patients, all of which were mild (23).

Conclusion

This review found that, overall, IV administration of $MgSO_4$ did not reduce hospital admission rates in adults with severe asthma exacerbations. However, the results from the studies were not unanimous in this finding; in fact, in the most severe asthmatics two studies showed a decrease in admission rates when magnesium was used. When combined with an additional study showing weak evidence of a decrease in hospital admissions with $MgSO_4$ use, the majority (3 of 5) of the studies would actually show an overall benefit to magnesium administration. Limitations of the studies, such as a low number of participants, participant's refusal of admission, differences in study design and definition of terms make comparing the various research study findings challenging.

However, despite a lack of consensus on the use of IV $MgSO_4$ as an effective adjunct treatment in acute severe asthma, it remains readily available, inexpensive, easy to administer, and has a low rate of side effects, which are transient and relatively minor such as flushing, and hypotension. This is in contrast to aminophylline, a medication previously used more commonly in asthma treatment that has a narrow therapeutic window with potential for more serious side effects. Magnesium administration appears to show the most benefit in those who present with severe exacerbations. Further studies are needed to determine the optimal dose of $MgSO_4$ in this population, and whether $MgSO_4$ administration shows benefit in the current practice setting recommendations where ipratropium is now included.

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