

Inhaled Versus Nebulized Magnesium Sulfate in Severe Acute Refractory Asthma in
Children

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Abstract

Introduction: Asthma is an extremely prevalent lung condition that comes with life-threatening exacerbations that are sometimes refractory to standard therapy regimens. Standard therapy regimens include short acting beta agonists, short acting muscarinic agonists, and inhaled corticosteroids. After initial therapy has failed there is a wide range of adjunctive medication that can be used. One medication that has demonstrated efficacy in these circumstances is intravenous magnesium sulfate. Magnesium sulfate toxicity may result in severe neurologic and cardiac conditions. Magnesium sulfate can be administered through a nebulizer machine; this route of administration would decrease the incidence of the adverse effects of magnesium sulfate toxicity and would negate the use of the intravenous catheter for administration of this medication. This review compares the efficacy of intravenous versus nebulized magnesium sulfate in the setting of severe acute asthma in a pediatric patient.

Methods: A literature search was conducted using PubMed and Google Scholar. Selected articles include six randomized controlled trials and one cohort study. Only studies that are recent and pertinent to the research were included.

Results: In four studies intravenous magnesium sulfate significantly improved outcomes of pediatric patients with acute asthma. In four studies nebulized magnesium sulfate significantly improved outcomes and in one study it did not significantly improve outcomes of pediatric patients with acute asthma. Lastly, in the two studies that directly compared the intravenous to the nebulized route of administration there was no significant difference in outcomes of the two samples.

Discussion: Results in this review are consistent with previously obtained results where there is acknowledged efficacy of an intravenous route of administration and mixed results surrounding nebulized route of administration. These inconsistent results for nebulized route of administration have led to a dismissal of the use of nebulized magnesium sulfate in clinical practice. A practitioner should not utilize a medication that is not supported by evidence, especially in a life-threatening situation. However, an important trend to note is that studies that found nebulized magnesium sulfate to be effective only included patients with severe asthma and the study that did not find it to improve outcomes included mild, moderate, and severe asthma.

Conclusion: These results actually demonstrate promise for the role of nebulized magnesium sulfate in severe acute refractory asthma, something that has previously lost favor. However, further randomized controlled trials are required to investigate the outcomes of pediatric patients with severe acute refractory asthma, as opposed to mild or moderate asthma, who receive nebulized magnesium sulfate in order to support this possibility. If further trials are performed it can have a great future impact on outcomes in this population by improving the patient's asthma, reducing magnesium toxicity occurrence, and reducing intravenous catheter utilization or complications.

Introduction

Asthma is one of the most prevalent health conditions in the world today. The latest reports from the WHO state that approximately 235 million people suffer from asthma worldwide [14]. Further, the WHO reports that 383,000 people died of asthma in 2015 [14]. Lastly, although it affects both pediatric and adult patients asthma is the single most common chronic condition in children [1]. Although asthma is so prevalent and serious, the future shows great promise for both pediatric and adult patients who suffer from asthma because it is a very treatable and reversible condition.

Standard acute asthma treatment currently involves the use of short acting beta agonists (SABA) like albuterol, short acting muscarinic antagonists (SAMA) such as ipratropium, and inhaled corticosteroids (ICS). Such methods are sufficient for symptom resolution in most but not all cases [2]. Recently, the use of Magnesium Sulfate (MgSO₄) has become an accepted treatment for severe asthma that is refractory to traditional asthma treatment consisting of a SABA, SAMA, and ICS [6]. Specifically, MgSO₄ has been found to be very effective in more severe cases of refractory asthma as opposed to mild cases [5].

There have been multiple studies that demonstrate the efficacy of intravenous (IV) MgSO₄ in treating severe asthma refractory to standard treatment regimens. Still there is no universally accepted dosage of IV MgSO₄, which makes it difficult to compare reviews of such studies. Conversely, literature on the efficacy of nebulized MgSO₄ is widely varying with some studies reporting no significant improvement of pulmonary function and others reporting that there indeed is a

significant improvement in pulmonary function. Upon further examination of these contradicting results about the efficacy of nebulized MgSO₄ it becomes apparent that many of the studies that report no benefit focus on mild to severe pediatric asthma [10]. Interestingly, studies that do report benefit from nebulized MgSO₄ focus solely on severe pediatric asthma [8].

Ultimately, it would benefit patients and providers clinically to administer this medication less invasively, that is via a nebulized route of administration, even if that may only be in severe cases. MgSO₄ has a reputation for its harsh side effects when provided at high doses. Toxic levels of MgSO₄ are known to cause nausea, vomiting, bradycardia, hypotension, heart block, hyporeflexia, lethargy, and even death. Nebulized MgSO₄ would be a better alternative, as it would act more locally, which could decrease the likelihood of these systemic adverse effects from occurring. Further, administration of nebulized MgSO₄ would allow for other interventions that require IV access to be administered concomitantly in a single IV rather than having to wait for completion of the course of the IV MgSO₄ and subsequently prolonging care in a critical patient who may have poor IV access. Lastly, it would reduce the required number of IV's and the possible complications that sometimes come with them such as infection.

In order to establish any role of nebulized MgSO₄ in treatment of severe refractory pediatric asthma one must first determine if nebulized MgSO₄ has similar effects on pediatric patients with asthma when compared to the effects of IV MgSO₄. With the need for a comparison between IV and nebulized MgSO₄ the purpose of this article is to address the following research question: In pediatric patients ages (2-

15) with severe acute asthma that are unresponsive to initial therapy, is adjunctive use of intravenous MgSO₄ more effective than adjunctive nebulized MgSO₄ in reducing admission rates to the PICU for symptoms of an asthma attack?

Methods

A literature search was performed in November 2018 using PubMed. The search ultimately yielded the following search terms “(((asthma/drug therapy[MeSH Terms]) AND magnesium sulfate)) AND child”. This search yielded 75 results. This search can be obtained by simply copy and pasting the previous search into the PubMed search bar or stepwise by using Pubmed’s advanced search builder. The first line of the advanced search builder should include “asthma/drug therapy” with the field adjusted to “MeSH terms”. The second line of the builder should include “magnesium sulfate” using an “AND” connector and the field should read “all fields”. The third line of the builder should include “child” using an “AND” connector and the field should read “all fields”. Please find a screenshot of a completed advanced search bar as previously described in the appendix denoted as “figure 1- PubMed Advanced Search”. Lastly, ensure all filters are removed at this time. These 75 articles from the aforementioned search represent studies that meet inclusion criteria which were studies that involved 1) drug therapy for asthma AND 2) magnesium sulfate as part of the intervention AND 3) children in the study. Studies that were not clinical trials were excluded by selecting the filter “clinical trial” under “article types”. Excluding all studies that were not clinical trials narrowed results down to 23 articles. Next, studies that were done anytime before the past 10 years

were excluded by selecting the filter “10 years” under “publication dates”. Excluding all studies outside of 10 years from the date of this search narrowed results down to 12 articles. Of those 12 articles four were excluded for the various reasons. One was excluded because it pertained to asthma attacks that were not considered severe, a second article was excluded because it investigated cost efficacy of magnesium sulfate rather than the efficacy of the drug itself, a third article was excluded because it was an ongoing study that has not yet released any of its results, and a fourth article was excluded because it was a repeat of one of the studies already included. Ultimately, eight articles from this search were used in the investigation of efficacy of magnesium sulfate in severe asthma attacks.

A second search using Google Scholar was conducted in November 2018. The search can be found by entering the following search terms in the Google Scholar search bar, “Comparing Efficacy of Inhaled Magnesium Sulfate to Intravenous Magnesium Sulfate in Childhood Severe Asthma Exacerbation”. This search yielded “about 3,780 results”, but can be narrowed by including only articles published after 2014. This can be done by selecting “since 2014” on the filter, which lowered the number of results to 1,150 articles. Next, the articles are sorted by relevance so the top results were briefly reviewed for any appropriate studies. The fourth article listed is “Comparison Efficacy and Safety of Inhaled Magnesium Sulfate to Intravenous Magnesium Sulfate in Childhood Severe Asthma Exacerbation” by S. Watanatham, et al. In order to narrow results to studies similar to this one the link “related articles” was selected under the fourth article. Selecting “related articles” narrowed results down to just 15 articles. All of these 15 articles contain the

inclusion criteria, which are articles published after 2014 that discuss the utilization of either intravenous or nebulized magnesium sulfate as a therapy for severe asthma in children. Of those 15 articles 11 were immediately excluded because they were dated before 2012 despite the filter, which should have only included studies from 2014 or later, a twelfth was excluded because it was an article already included by the other search, a thirteenth was excluded because it pertained to bronchiolitis and not asthma. However, the two studies that were included from this search met all criteria.

Results

Daengsuwan T, Watanatham S. A comparative pilot study of the efficacy and safety of nebulized magnesium sulfate and intravenous magnesium sulfate in children with severe acute asthma. *Asian Pac J Allergy Immunol.* 2017;35(2):108-112.

This study looks to compare efficacy of nebulized vs. intravenous MgSO₄ in children with severe acute asthma. The study alludes to multiple articles demonstrating mixed results about the efficacy of nebulized MgSO₄ in severe asthma. As a result the study aims to establish a more refined understanding of the role of nebulized MgSO₄ in severe asthma while still comparing that to the influence of IV MgSO₄.

The sample size of this study was 28 patients. This study is considered a pilot study so 28 patients is an acceptable number. Ideally more patients should be evaluated in the future.

The study methods were appropriate for the most part with some minor flaws. The subjects were all candidates who underwent a standardized treatment

regiment for their asthma and were still considered to be suffering a severe asthma attack. This study is one of the most useful studies for this research question because it evaluates the target population, children with severe asthma who are refractory to initial treatment. Many other studies fail to specify the severity of the asthma and if the patients had any success with standardized interventions that would have already been used. The subjects were randomly given either nebulized MgSO₄ or IV MgSO₄. The asthma severity was evaluated using the Wood's Clinical Asthma Score, which creates objectivity in determination of severity. The researchers also monitored blood pressure and certain signs of magnesium toxicity such as deep tendon reflexes to ensure no patient reached a toxic level. Researchers also evaluated length of stay for each group. One flaw with the design was that the "standard of care for asthma was provided by the primary physician without any disruption by the researcher." Although allowing the primary physician to treat using the standard of care is necessary for the patient's safety it does confound the results some and one must question if any improvements may be attributable to this "standard of care." Another obvious issue with this study is its relatively small sample size.

Yes measurements of major variables are valid and reliable. Specifically, utilizing the Wood's Clinical Asthma Score created an objective measure of asthma severity to quantify and compare the influence IV vs. nebulized MgSO₄ had on the patients. Also, measuring length of stay is a useful way to measure long term outcome, which is something most other studies fail to monitor or report.

This study appropriately utilized separate t-tests for Wood's Clinical Asthma Score and length of stay respectively each with a p value of $p < 0.05$. T-tests are useful when comparing the means of two groups, which is exactly what this compares (ie. the mean Wood's Clinical Asthma Score in IV vs. Nebulized MgSO₄). The study also uses the Fisher's exact test to determine any demographic differences in non-numerical data between the two study groups.

There were no untoward events reported in the study. The authors explicitly detail that "no adverse symptoms of MgSO₄ toxicity" occurred. The study demonstrates a significant improvement in Wood's Clinical Asthma Score and length of hospital stay in both the IV MgSO₄ group and the nebulized MgSO₄ group. The study also demonstrates no significant difference between the two groups in either the Wood's Clinical Asthma Score or length of stay. The results of this study are consistent with previous research. First, a variety of studies have demonstrated the efficacy of IV MgSO₄ in children with severe asthma and this study was another example of its efficacy. Second, this study aligns with previous studies in demonstrating the efficacy of nebulized MgSO₄ in treating patients with severe acute asthma specifically when "treatment begins early, within 6 hours of an attack." Other studies that do not focus on severe asthma in children seem to indicate no role for nebulized MgSO₄. This study is comparable only to other studies that evaluate patients with severe asthma.

This study suggests nebulized MgSO₄ is equally effective as IV MgSO₄ in treating children with severe asthma that is refractory to standard protocols. However, as a clinician one should recognize the well-established role of IV MgSO₄

in severe asthma that is refractory to standard protocols and compare that to this pilot study, which only tested 28 patients. Ultimately, more trials need to be conducted before a clinician should utilize nebulized MgSO₄ in place of IV MgSO₄. However, if further trials solidify the role of nebulized MgSO₄ in severe asthma that is refractory to standard protocols it should be the preferred route of administration due to less risk of magnesium toxicity.

The results of this study are mostly reliable. Obviously, one must recognize its shortcomings with a small sample size and the confounding influence the primary physician's unrestricted care may have. However, the study did properly randomize patients into the two groups. Also, by evaluating length of stay the researchers are including unintended or unexpected influences that either treatment modality may have. Lastly, this study is one of the most valid studies that pertain to this research question. This study is so valid and reliable because of its focus on children with severe asthma that are refractory to standard protocols. The study utilized an inclusion and exclusion criteria that only targeted the population in question. There were no significant differences between groups, which demonstrates that the intervention is more likely to be what caused differences in the results.

Egelund TA, Wassil SK, Edwards EM, Linden S, Irazuzta JE. High-dose magnesium sulfate infusion protocol for status asthmaticus: A safety and pharmacokinetics cohort study. *Intensive Care Med.* 2013;39(1):117-122.

The study was done to evaluate what effect high levels of magnesium sulfate (MgSO₄) have on patients who are experiencing an acute severe asthma exacerbation. This is appropriate because these patients are already in significant

distress and any adverse effect from a medication could be life threatening. The study pertains to this research question because it establishes the safety profile of infused MgSO₄ in patients with severe asthma. The safety profile of MgSO₄ has been explored in other conditions but it has not been extensively explored in severe asthma.

The sample size of this study is 57 patients. The subjects were 57 patients admitted to the PICU with a severe asthma exacerbation. The design and methods are appropriate but this study has a few flaws that must be considered when interpreting the results. 57 Patients aged 2-18 years of age were designated to receive either MgSO₄ at the treating physician's discretion or a placebo. All patients who received the MgSO₄ were given a loading dose of 75 mg and then a weight based continuous infusion. The patients were evaluated for respirations, blood pressure, heart rate, troponin level, serum magnesium and ionized magnesium, nausea and vomiting, skin flushing, and pain at the IV site. Results were recorded and statistically evaluated as discussed later.

One flaw is that patients were only given MgSO₄ at the discretion of the treating physician. Whenever a study picks and chooses who receives the intervention one must always consider the fact that this can influence results. Another issue with this study is the relatively small sample size of only 57 patients. As with any study more participants yield more powerful results. Otherwise the study remained consistent once interventions were administered which helps attribute effects of an intervention directly to the intervention itself. Also, the study

addresses the important bodily systems that pertain to asthma, which is certainly important.

The measurements of major variables are a strength of this study because they are so valid. All variables that are measured are directed at systems affected with hypermagnesemia. Also, most of these effects are measured simply with vital signs such as respiratory rate, heart rate, and blood pressure, metrics that are very reliable and part of why they are so routinely used. Also, measuring both serum and ionized magnesium will give very reliable results as to the patients' magnesium levels.

The authors utilized t-tests and chi-square analysis at 95% confidence intervals. The authors compare means of each vital sign or lab value individually i.e. systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, troponin, etc. This method is useful because it investigates each area of possible adverse effects individually to ensure each one is addressed and not overshadowed. Also, a p of 0.05 is a reasonable level of confidence that will be truly representative of any differences present.

Three patients reported adverse events that are associated with elevated magnesium. The adverse effects that were experienced were nausea, vomiting, and pain at the injection site. However, none of these adverse effects correlated to elevated serum magnesium.

The study demonstrates no significant difference in systolic blood pressure, diastolic blood pressure, or oxygen saturation but did demonstrate a statistical difference in heart rate and respiratory rate which were both lower in the treatment

group. There is little to no evidence in literature evaluating the safety profile of MgSO₄ in asthma, but no studies have reported adverse effects in asthma treatment groups receiving MgSO₄. Results of this study suggest that MgSO₄ may slow heart rate and respiratory rate when administered in very high doses, which has not been reported in patients with severe asthma receiving MgSO₄ but is consistent with generally accepted adverse effects of hypermagnesemia.

The important factor to consider with this study is that it investigates high dose infusion of MgSO₄. The dosages utilized in this study had noteworthy but very minimal effects at dosages well above what a severe asthmatic patient would be receiving. A clinician should recognize that MgSO₄ is relatively safe to administer in severe asthma and generally shouldn't be concerned with any adverse effects. However, if an excessively large dose is administered the patient's vitals should be monitored with emphasis on heart rate and respiratory rate.

The study results are valid but should be considered with a small level of skepticism with respect to the population that was selected to receive treatment as it was at the discretion of the treating physician. Specifically, outcome criteria were very objective as previously mentioned with the reliability of vital signs as a metric. Experimenters were sure to monitor patients for the duration of the infusion, which ensured that the patient was being evaluated at the patient's drug concentrations.

Powell CV, Kolamunnage-Dona R, Lowe J, et al. MAGNEsium trial in children (MAGNETIC): A randomised, placebo-controlled trial and economic evaluation of nebulised magnesium sulphate in acute severe asthma in children. *Health Technol Assess.* 2013;17(45):v-vi, 1-216.

The study was done to more accurately assess the efficacy of nebulized magnesium sulfate (MgSO₄). The article alludes to just four other studies being

performed on the efficacy of MgSO₄ but points out the lack of consistency in the previous studies. Specifically, the inconsistencies in previous studies were the level of severity of asthma, primary outcomes, what treatment protocols were utilized, and what groups were compared. The MAGNETIC trial sets out to focus solely on the effect of nebulized MgSO₄ in severe asthma with standardized treatment protocols, using consistent outcome measures and comparisons of the study's groups. Further, this study adds to a very small body of literature that needs more investigation. This study perfectly fits the aspect of the research question pertaining to efficacy of nebulized MgSO₄.

The sample size is 508 children, ages 2-16 who presented to an emergency room actively symptomatic with a severe acute asthma exacerbation.

The study design and methods are for the most part appropriate with one exception that is more suitably discussed in the next question referencing the validity and reliability of measurements of major variables. The 508 children selected were presenting to one of 30 hospitals involved in the study and were actively symptomatic with severe acute asthma. Patient's were only included if they met requirements of severe asthma as defined by BTS/SIGN guidelines. Patient's received "local hospital-defined" conventional treatment for 20 minutes, were reassessed with the same guidelines, and if patients were still considered severe then they were officially part of the 508 active participants. The 508 patients were then randomly stratified into two categories. One group (n=252) received nebulized isotonic MgSO₄ plus a standardized amount of salbutamol and ipratropium bromide while the other group (n=256) received nebulized isotonic saline plus a

standardized amount of salbutamol and ipratropium bromide. The three drugs for each group were mixed into one nebulizer and administered over 15-20 minutes. Patients were given a total of three nebulizer treatments at a specific frequency that was determined by the severity of their systems based on the Yung Asthma Severity Score. Yung Asthma Severity Score was recorded when the patient presented to the ED, when the patient met the final inclusion criteria after twenty minutes of conventional treatment, 20 minutes after first nebulizer treatment, 40 minutes after second nebulizer treatment, and then 60 minutes, 120 minutes, 180 minutes, and 240 minutes after their third nebulizer treatment. Data was collected until discharge from hospital.

Overall, these methods are appropriate and the authors do a good job of keeping evaluation of severity consistent using the Yung Asthma Severity Score and BTS/SIGN guidelines consistently. Also, it is important to ensure that other therapies administered were consistent so it was well thought out to use salbutamol and ipratropium bromide for both the placebo group and the intervention group. This makes any results more attributable to the intervention in question and not other therapies like salbutamol and ipratropium bromide. Lastly, it was very appropriate for the authors to follow patients until discharge in order to note any acute changes that may have occurred after just the first two hours post therapy.

The measurements of major variables are mostly valid and reliable. The assessment of validity and reliability should be based on all the reasons mentioned in the previous question that make the measures valid, which include the consistency of severity assessment, adjunctive drugs used, and post therapeutic

follow up. However, one caveat that should be considered when assessing the validity is that the first twenty minutes of intervention were “local-hospital defined”. While one would imagine hospitals have relatively standardized protocols for asthma exacerbation there is certainly room for variability in what treatments were provided especially when considering there were 30 different hospitals utilized. Nonetheless, the patients were still refractory and required further treatment so results from this study can be considered fairly reliable but not perfect.

Data, which are specified as Yung Asthma Severity Score at 60 minutes after the third nebulizer treatment, are analyzed using an intention to treat analysis with a p value of 0.05 and 95% confidence intervals. Authors then used an analysis of covariance to compare their results to baseline Yung Asthma Severity Score. The authors stated that their study had a power of 80%, which is a considerable level of power. The authors correctly utilized the intention to treat analysis, which is considered the gold standard of evaluating compared treatments in a randomized controlled trial.

The authors acknowledge 21 types of adverse events. No results are attributed to treatment and a majority of the events are, “felt to be related to the disease under study.” There was also no substantial between group difference in the two treatments.

The study demonstrates no statistically significant difference in asthma severity improvement between the group that received MgSO₄ and the group that received saline. The authors did note that the clinical effect was larger in children with a more severe asthma exacerbation and when symptoms were present for less

than six hours. Previous research has yielded mixed results as to the efficacy of nebulized MgSO₄. Some studies have found nebulized MgSO₄ to be statistically effective and others like this study have found that it is not. Previous studies have also recognized a more drastic effect when the asthma is more severe. When considering the results of this study with previous studies it seems to direct nebulized MgSO₄ as a modality of treatment that could be effective in very severe asthma but is not very effective in moderate to severe asthma.

The results of this study, especially when considered with previous studies suggest nebulized MgSO₄ is a therapy that is not effective in even moderately severe asthma but may have a role in extremely severe asthma. Further study is required to determine its efficacy in extremely severe asthma before it should be routinely used in clinical practice.

The results of this study are valid as patients were properly randomized, appropriate reasons were given as to why patients dropped out, and patients were followed until discharge to further study effects of the intervention.

Singh AK, Gaur S, Kumar R. A randomized controlled trial of intravenous magnesium sulphate as an adjunct to standard therapy in acute severe asthma. *Iran J Allergy Asthma Immunol.* 2008;7(4):221-229.

This study was done to establish the role of IV MgSO₄ in treating patients with severe acute asthma who have received both beta-2-agonists and ipratropium bromide. This study acknowledges how previous studies have addressed the efficacy of IV MgSO₄ with beta-2-agonists alone. However, the article demonstrates a clear lack of research on the effect IV MgSO₄ with both beta-2-agonists and ipratropium bromide.

The sample size of the study is 60 patients. 75 were initially screened and only five were initially excluded but another 10 patients had to be excluded due to protocol violations.

Overall, the study methods are moderately appropriate but there are some facets of the study that could be improved upon. Patients who presented to an ED with dyspnea solely related to asthma were included and researchers immediately measured multiple variables to include spirometry, respiratory rate, heart rate, BP, the presence of cyanosis, SPO₂, and dyspnea based on the Borg dyspnea score. Each subject received albuterol and ipratropium bromide. Next, each subject was randomly assigned to either a control group or a group that received IV MgSO₄. The patient was unaware what group they entered into but the researchers knew whether the patient was receiving IV MgSO₄ or a similar looking placebo. All of the aforementioned clinical variables were measured in 30 minute increments from 0 minutes to 120 minutes. Patients were then either admitted or discharged at the discretion of the ED providers. Most of the variables utilized in the study are both valid and reliable measures in evaluating a patient's oxygenation and perfusion status such as spirometry, SPO₂, respiratory rate and heart rate. However, the Borg dyspnea scale is subjective, which leaves ample room for patients to be underestimating or overestimating their current level of dyspnea. Also, the researchers decided to make this a single-blinded study rather than a double-blinded study. A double-blinded study would have been more ideal in this situation as it would have yielded less biased results if the researchers were ignorant of what group was receiving the IV MgSO₄ vs. placebo.

The measures utilized in this study are mostly valid and reliable. Spirometry such as FEV₁, respiratory rate, SPO₂, and heart rate are all commonly accepted measures utilized when determining a patient's level of oxygenation and perfusion. SPO₂ has been shown to sometimes be less accurate than more invasive measures, but more invasive measures are not indicated in this instance. Also, the patients assessed their level of dyspnea using the Borg dyspnea scale. The Borg dyspnea scale is a subjective measurement that may allow a patient to underestimate or overestimate their current level of dyspnea. Conversely, the patient's subjective assessment of their dyspnea is almost exactly what needs to be improved so while it is not totally accurate it certainly warrants merit as well.

The changes in FEV₁ and multiple other variables such as HR, SPO₂, RR, etc. were calculated and statistically analyzed using a repeated measures ANOVA at a level of $p < 0.05$. An ANOVA was appropriate in this instance as the researchers were evaluating the change in FEV₁ at multiple time increments (0, 30, 60, 90, and 120). This was also done for other variables such HR, SPO₂, RR, and others. The F value demonstrated differences between the control group and the experimental group specifically in patient height.

No magnesium specific side effects were reported during the study. Patients complained of anxiety, palpitations, tremors, headache, dry mouth, and non-specific nausea. One patient withdrew due to excess anxiety, one patient withdrew due to excess tremors, and three patients withdrew due to severity of illness.

The results demonstrated that both the placebo and experimental (IV MgSO₄) group had significant improvements in FEV₁. The results are consistent

with previous studies that demonstrate the efficacy of beta-2-agonists and ipratropium bromide, which is likely why both the control and experimental group demonstrated improvements. Further examination reveals that patients who received IV MgSO₄ had higher rates of discharge at 60 minutes, 90 minutes, and 120 minutes than the control group. The fact that the patients who received IV MgSO₄ had higher rates of discharge is consistent with previous research in the area and demonstrates efficacy of IV MgSO₄.

This article in conjunction with many other studies demonstrates the necessity for IV MgSO₄ to be included in protocols for patients with severe asthma who are refractory to other treatments. This study demonstrates the fact that IV MgSO₄ is both safe and effective when utilized with a beta-2-agonist and ipratropium bromide. When this is considered with other research in the field a clinician must recognize that IV MgSO₄ is safe and effective when patients are refractory to beta-2-agonist and ipratropium bromide.

One major concern is that the study was blind only to the patients and not the experimenters. The study would have been much more valid if the trial was double-blinded. However, the researchers did appropriately randomize the patients into either the control group or the experimental group. Also, the primary metric of change in FEV₁ is a reliable and valid way of assessing bronchodilatory effects in patients with asthma. Lastly, aside from height the two groups had no other differences, which demonstrate that the differences in results are less likely to be random, and are more attributable to the intervention.

Sun YX, Gong CH, Liu S, et al. Effect of inhaled MgSO₄ on FEV₁ and PEF in children with asthma induced by acetylcholine: A randomized controlled clinical trial of 330 cases. *J Trop Pediatr.* 2014;60(2):141-147.

This study aims to investigate the role of nebulized magnesium sulfate (MgSO₄) in asthma. This article focuses on how MgSO₄ affects patients with asthma induced by acetylcholine (Ach). This is a practical study because studies like the previously mentioned MAGNETIC trial have only investigated the role of nebulized MgSO₄ in all subsets of asthma where this study focuses on only on asthma induced by Ach. This study is pertinent to the research question because it may highlight a subpopulation of pediatric patients that can benefit from MgSO₄ therapy. It should be noted this study includes all levels of asthma severity but MgSO₄ may be useful in severe Ach induced asthma, which this study can give a certain level of insight to.

The sample size of this study is 330 patients. Patients ranged from 4-16 years of age. The design methods of this study are appropriate. The 330 patients were selected using inclusion criteria specifically requiring a previously positive Ach provocation test. The test itself investigated baseline FEV₁ and peak expiratory flow (PEF) that were measured before a second Ach provocation test performed under the supervision of the experimenters. FEV₁ and PEF were then measured again immediately after the Ach test, 10 minutes after a nebulizer treatment and 20 minutes after the nebulizer treatment. The 330 patients were broken into three groups who received either MgSO₄ alone, albuterol alone or albuterol and MgSO₄. Patients were monitored for any adverse effects and appropriate intervention protocols were in place should any adverse events be too severe.

This study does a very good job at developing a standard procedure that does not allow for any confounding variables. By being so structured and simplistic the study

ensures that the results are indeed an accurate measure of how MgSO₄ influences Ach induced asthma.

The measures in this study are mostly valid and reliable. FEV1 and PEF have long been utilized in the evaluation of asthma and are no different in this instance. They are great measures of the level of obstruction and if the intervention is successful, these pulmonary function tests would accurately reflect that. While this study does not use a large variety of variables the few that it does use are indeed sufficient enough to accurately measure the effects of the interventions. It is important to note that FEV1 and other PFT's are actually not recommended in severe asthma as they can exacerbate symptoms.

The data are analyzed using a two-tailed ANOVA with a significance of $p=0.05$ that compared the mean FEV1 and PEF values for the three different groups. This is the appropriate test at a meaningful significance to compare mean pulmonary function test values of multiple groups of interventions. There was also a chi-square analysis utilized in assessing male versus female effects with a significance level also set at $p=0.05$.

The study acknowledges seven patients had poor responses to inhalation of MgSO₄ but deems MgSO₄ safe in children as no adverse effects were reported. The study is ambiguous when it states that there were no adverse effects to MgSO₄ but there were seven patients with a poor response. The study needs to elaborate on what "poor responses" indicates. This ambiguity pertaining to what "poor responses" means should be considered when interpreting the safety profile of MgSO₄.

The study demonstrated that nebulized MgSO₄ alone did not significantly reduce bronchoconstriction in patients with Ach induced asthma when compared to nebulized albuterol alone. However, the study did note that nebulized MgSO₄ does have a bronchodilatory effect, just not more significantly than albuterol. Also there was no evidence of a synergistic effect when nebulized MgSO₄ and albuterol are combined. This is consistent with previous research that acknowledges nebulized MgSO₄ has some bronchodilating activity but no statistically significant effect even in Ach induced asthma.

Similar to the first article, this article confirms the notion that nebulized MgSO₄ is not an optimal treatment in asthma but may have some bronchodilating effect. Ultimately, it demonstrates that nebulized MgSO₄ is not an ideal asthma therapy but it is safe and could be considered if no other more successful and clinically supported medications have been successful in treatment.

The results of this study are fairly valid. The process of randomization was appropriately performed, control groups were appropriate, the instruments to measure outcomes were valid and reliable. Lastly, the study included representation of both male and female patients to make results more generalizable and not specific to only males or females.

Wang H, Xiong Y, Gong C, et al. Effect of inhaled magnesium sulfate on bronchial hyperresponsiveness. *Indian J Pediatr.* 2015;82(4):321-327.

This study was done to see if inhaled MgSO₄ alone or if MgSO₄ plus a beta-2-agonist could improve FEV-1 in children with asthma. The article points out how reviews have highlighted inconsistencies in studies examining the effect of inhaled MgSO₄. This article particularly aims to add to that body of research by more

accurately detailing the role of inhaled MgSO₄ in order to rid academia of the mixed and seemingly unpredictable results.

The sample size was 84 children who suffer from asthma and did not take a bronchodilator agent one day before the experiment was performed. The study randomly divided the 84 subjects into three groups with randomization software. The three groups received either inhaled MgSO₄, inhaled albuterol, or both inhaled MgSO₄ and inhaled albuterol. Initially, all subjects were asked to perform baseline FEV₁ measurements. Subjects were then given a provocation test via four separate doses of acetylcholine to induce their asthma and FEV₁ was measured after every dose to ensure there was not too significant of a drop. Subjects then received either inhaled MgSO₄, inhaled albuterol, or both inhaled MgSO₄ and inhaled albuterol, which was nebulized over 5 minutes. All subjects were then tested for their FEV₁ at 10 and 20 minutes after the bronchodilator treatment. Researchers monitored SPO₂ and deep tendon reflexes to ensure patients did not suffer from hypoxia or magnesium toxicity respectively. Researchers then recorded change in FEV₁ by taking $(FEV_{1\text{Post bronchodilator}} - FEV_{1\text{Post provocation test}}) / (FEV_{1\text{ post provocation test}}) \times 100$. These methods are indeed appropriate as they used proper techniques for randomization in order to ensure that subjects were appropriately stratified into different groups. Also, utilizing an albuterol group as a control group is useful because it can demonstrate how an already accepted medication influences FEV₁ in this situation. One major issue with the design is that there is no placebo group. Having a placebo group would have demonstrated that the improvements after the bronchodilators were due to the bronchodilators and not some other process.

Ultimately, the study design was basic and somewhat effective in trying to determine the impact of inhaled MgSO₄ in a patient with asthma.

Yes the measurements of major variables are valid and reliable in this study. Specifically, this study examines the effect of MgSO₄ or Albuterol or both by determining change in FEV₁. Effectively, this metric evaluates how much air can forcefully be expelled in one second, which is the ideal measurement when investigating an obstructive disease such as asthma. Also, using the change in FEV₁ from post provocation test to post bronchodilator is the best way to demonstrate affects that can be directly attributable to the intervention. Next, the researchers recorded vitals using the almost unanimously accepted methods of obtaining them. Of note, the researchers did use a pulse oximeter for SPO₂ concentration, which has been shown to be inaccurate at times but is more practical than the use of more invasive techniques.

The study used two forms of statistical analyses. First, a two-tailed chi-squared analysis of numerical means with a p- value of <0.05 was used to determine differences between each group to ensure no group was unique or different from the others. The differences in the groups were expressed as numerical data. The data was represented as a mean value +/- standard deviation. This is the ideal method of analysis for evaluating three groups with nominal data and ultimately demonstrated that there were no differences between the groups. Secondly, the mean change in FEV₁ of each group is analyzed via an ANOVA with a two-tailed p value of <0.05. This method is useful when determining differences in repeated measures of numerical data between more than two groups and it demonstrated

that the albuterol group and albuterol + MgSO₄ group had statistically significantly improved FEV₁ where p was <0.05 , while the MgSO₄ alone resulted in an improvement but one that was not statistically significant (p was >0.05).

There were seven patients who had a “poor response” to inhalation of MgSO₄ but the author does not elaborate on what these responses were. The author does disclose that none of the patients demonstrated any adverse effects of MgSO₄, which demonstrates the drugs safety. Otherwise, the study does not indicate the occurrence of any untoward events.

The study demonstrates that there was an improvement in change in FEV₁ in the MgSO₄ group but the change was not statistically significant ($p >0.05$). However, the study does demonstrate a statistically significant improvement in change in FEV₁ in the albuterol group and the albuterol +MgSO₄ group. The results of this study are relatively consistent with previous studies that have shown efficacy for albuterol, which is why it is so commonly utilized. Also, the results are consistent with previous studies that have found inhaled or nebulized MgSO₄ is not totally effective in treating less than severe asthma. Specifically, this study does not specify the severity of asthma, which seems to be an important factor when evaluating MgSO₄ in asthma. In general previous studies have shown that MgSO₄ yields improvement only when the patient has more severe asthma.

This study has further demonstrated to clinicians that there is almost no role for nebulized MgSO₄ in treating mild or even moderate asthma in children. One should not conclude that MgSO₄ is also ineffective in severe asthma. Previous studies evaluating inhaled MgSO₄ in severe asthma have yielded mixed results and

this study does not focus on severe asthma exacerbations. Ultimately, a clinician treating a patient suffering from an asthma attack should not use nebulized MgSO₄ if the attack is considered mild or moderate in severity, as it has been shown to be ineffective.

The results of this study are valid as the subjects were properly randomized and the experimenters properly blinded. There were no significant differences between groups, which demonstrates that the intervention is more likely to be what caused differences in the results. Patients were properly followed until resolution of their asthma exacerbation, which ensured there was no other unintended or unexpected affect of the intervention. Lastly, proper inclusion and exclusion criteria were discussed to ensure this study targeted the correct population.

Watanatham S, Pongsamart G, Vangveeravong M, Daengsuwan T. Comparison efficacy and safety of inhaled magnesium sulfate to intravenous magnesium sulfate in childhood severe asthma exacerbation. *J Allergy Clin Immunol.* 2015;135(2):AB241.

This study was done to see if there was any difference in asthma severity or length of hospital stay in groups who received nebulized versus IV MgSO₄ in the setting of children who were suffering from a severe acute asthma attack. This was measured by determining asthma severity scores 60 minutes after administration of medication and measuring length of hospital stay.

The sample size was 12 patients. This is a small sample size. The study design and methods are mostly appropriate. Twelve children who presented to the hospital for acute severe asthma were given three intermittent treatments of either nebulized or IV MgSO₄. The wood's asthma severity score was measured at 20 min, 40 min, 60 min, 120 min, 180 min, and 240 min as well as the duration of hospital

stay. Of the twelve 4 received IV MgSO₄ and 8 received nebulized MgSO₄. The sample size is very small and as in most studies the study could be more generalizable if they included a larger sample size. Also, the authors used the woods asthma severity score, which is a way to objectify the severity of the asthma attack. However, the score is not perfectly accurate at assessing the level of severity of a patient's asthma. Also, the study does not mention if other drugs were given such as inhaled or IV corticosteroids or nebulized albuterol. If these other drugs were not used this limits the application of this study to the research question as the research question refers to MgSO₄ as an adjunctive and not primary treatment.

The measurements of variables are as reliable as possible. The Wood's asthma severity score and hospital duration are for the most part entirely objective. When considering other metrics to use for the evaluation of asthma severity and outcomes, these are much more reliable options than subjective assessment of outcomes.

The primary and secondary outcomes are asthma severity score 60 minutes after intervention and hospital duration respectively. A two tailed t-test was performed to see if there was a significant difference in either result between the nebulized and IV group.

There were no reported untoward events in this study. This study demonstrates no difference in outcomes of patients who received nebulized versus IV MgSO₄. This is consistent with other studies that restrict the inclusion criteria to include only severe asthma attacks. However, the previous studies have yielded mixed results when including mild, moderate, and severe attacks so this is a study

that promotes the idea that these routes of administration may be equally beneficial. Ultimately this is another example that academics should consider larger studies that include only severe acute asthma attacks to determine the efficacy of nebulized MgSO₄.

This study suggests that nebulized MgSO₄ may be just as effective as an IV route of administration. This is good for many reasons such as no need for IV access when it is difficult to obtain. Also this can free up an IV to be used for other medications that may have been otherwise held if the IV was being utilized to administer MgSO₄. Lastly, there is less chance of MgSO₄ toxicity with the nebulized version and this study supports the idea that the safer route of administration may just as effective.

The results of this study are indeed valid. However, one must consider that this was a small sample size and that including a larger sample would increase the validity of this study. Otherwise, the study used the most objective measures it could have for determining severity of asthma. Also, they used consistent and reliable methods and study design that minimized any risk for undue error in the study.

Discussion

The use of MgSO₄ in asthma is not a novel idea; however, it is not universally used and is generally utilized only in severe cases because it is not a first line medication. Further, the research behind the efficacy and safety of MgSO₄ is limited. Finally, studies comparing a nebulized vs. IV route of administration of MgSO₄ are relatively rare. At first glance, review of these few, limited studies may prompt one

to dismiss the efficacy of nebulized MgSO₄ altogether. Although, deeper analysis of these same studies actually yields valuable information that suggests nebulized MgSO₄ may be just as safe and effective as IV MgSO₄ and it may reduce PICU admission rates for severe acute asthma that is refractory to standard treatment. The deeper analysis that supports the efficacy of nebulized MgSO₄ in severe acute asthma that is refractory to standard treatment will be discussed in this section.

When considering all the articles explored in this analysis one should first consider the types of study designs that are included. This analysis utilizes six randomized controlled trials and one cohort study. Randomized controlled trials are the preferred study design when evaluating efficacy or safety of a medication because they can both manipulate variables and controls as well as evenly distribute extraneous or anomalous data, reducing the chance of biased or skewed results. The cohort study is also a useful design and it is considered the best observational study because one is able to observe if certain precipitating factors are related to a disease in any way. Ultimately, this analysis includes studies that only use appropriate designs and methods and excludes less accurate modalities.

Next, one should evaluate the validity of the studies included. Validity in this review is discussed in regards to generally accepted principles of research and statistics along with relevance to the research question at hand. This analysis explores the validity of each included study based on six criteria as seen in Appendix B. Each individual criterion will be explained in further detail and how the studies included meet or fail the criterion.

The first criterion is blinding, or did the researchers inform the patients if they were receiving MgSO₄ rather than a placebo. Blinding prevents placebo effect from confounding results and all the studies included in this article were appropriately blinded. Second, is if there is any evidence of bias or skewing of the data for any reason and there is no evidence of any bias upon review of each article. Third, is how appropriate each study methods and design are for the research question. Five of the seven studies were considered “adequate” and appropriate for this research question. The two that were not considered appropriate and were considered “marginal” had some deviations in protocol such as allowing non-standardized initial drug regimens upon ED entry or not using a placebo group. Fourth, is if the inclusion criteria was reflective of the research population. In this review the research population is pediatric patients with acute severe asthma that is refractory to initial therapy. Any study that was considered “marginal” or “inadequate” either included adults, or patients who had what was considered to be mild or moderate asthma along with severe asthma. Fifth, is data analysis and is evaluating if the researchers used appropriate statistical studies to interpret the data involved in their respective studies. All studies fulfilled the fifth criterion. Lastly, the power, or the overall measure of whether the statistical testing adequately rejects the null hypothesis, of each study was evaluated. Again each study fulfilled this criterion, although some studies certainly had more power than others. None of the studies included are perfectly valid and reliable as such a study does not exist. However, given the research question and how each study employs

accepted principles of research, design, and statistics the included studies are acceptable in terms of validity.

Lastly, one must consider the results of the studies. The table in Appendix C discusses whether each study had results that demonstrated IV MgSO₄ alone, or Nebulized MgSO₄ alone, improved asthma to a degree that is statistically significant. Also, in studies that utilized both routes of administration it was evaluated if there was a statistically significant difference in outcomes in each sample. IV MgSO₄ yielded significant improvement in four of the studies. Nebulized MgSO₄ yielded significant improvement in four studies and insignificant improvement in one study. In the two studies that directly compared IV vs. nebulized route of administration there was no significant difference between the outcome of the IV group or the nebulized group.

When interpreting these results they are fairly consistent with previous results that yield an overall accepted efficacy of IV route of administration and mixed results with nebulized route of administration. When considering the unanimous efficacy of IV MgSO₄ and split results of nebulized MgSO₄ it begs the question, "Why is there not a statistically significant difference between the groups in the studies where IV and nebulized route of administration of MgSO₄ are directly compared."

The answer to this question may lie within the inclusion criteria. The single study that found nebulized MgSO₄ did not improve the asthma included patients that had mild, moderate, and severe asthma. It is important to remember this research question is only considering severe asthma not mild or moderate. Also,

upon a brief review of other articles in academia not included in this review, articles that have found no significant improvement with the nebulized route of administration also included mild and moderate cases. Further, cases that only include severe asthma more commonly found that nebulized MgSO₄ did have significant improvement. This highlights two important factors about research and design. First, is that one must always interpret results with respect to the population studied and the population in question. Second, more studies are needed corroborate this possibility, as is always the case in research. More studies will always yield stronger support for or against the claim in question, or in this case the efficacy of a drug.

Conclusion

As previously mentioned there was evidence that IV MgSO₄ improved patient outcomes, nebulized MgSO₄ improved outcomes in some trials and in others it did not, and there were no significant differences in the two studies that directly compared IV to nebulized MgSO₄. Upon closer examination of the studies where nebulized MgSO₄ alone is investigated, it is revealed that the studies that demonstrate significant improvement included only patients with severe acute refractory asthma. The sole study that did not find a significant improvement with nebulized MgSO₄ included patients with a wide range of asthma severity having mild, moderate, and severe asthma attacks.

These results actually support that nebulized MgSO₄ may have similar efficacy to IV MgSO₄ in the setting of severe acute asthma that is refractory to

standard treatment. This claim is supported by the four out of four studies that only investigated patients experiencing severe asthma attacks, which demonstrate improvement with nebulized MgSO₄. It is also supported by the two out of two studies that directly compared IV and nebulized route of administration that found no significant difference in clinical outcomes.

If one looks at the potential clinical impact the role nebulized MgSO₄ could have if it becomes more commonly used there is a wide array of possible benefits. The first and foremost benefit is simply the patient's condition improving, any time one can demonstrate that a drug or route of administration is effective when it was previously thought to be ineffective a practitioner adds to their treatment arsenal. Second, is a nebulized route of administration will strongly reduce the potential that a patient may develop magnesium toxicity, something that is very possible with an IV route of administration. Last, is the potential benefit of freeing up the IV. Not running the magnesium sulfate through the IV will allow access for other medications to run through an IV that may have otherwise been held because the site was already in use.

There is an important caveat to all of these potential benefits that may be reaped if nebulized magnesium sulfate becomes more commonly used in the setting of severe acute refractory asthma. That caveat is simply the fact that in order to be more commonly used it must first garner stronger support in the literature. As the results of this review suggest that nebulized MgSO₄ may indeed have similar efficacy to IV MgSO₄ it would be naïve to now go freely use nebulized MgSO₄ in the life-threatening circumstances the patient population in question will be facing. Many

more studies that perform randomized controlled trials of nebulized MgSO₄ in severe acute refractory asthma in pediatric patients need to be conducted in order to determine if nebulized MgSO₄ is similar in efficacy to IV MgSO₄.

The gap in the literature remains, is the efficacy of nebulized MgSO₄ similar to IV MgSO₄ in pediatric patients with severe acute refractory asthma and is there any difference in PICU admission rates when one is used over the other? Based on this review and the seven studies explored in this review there is now a small amount of support suggesting nebulized MgSO₄ may have similar efficacy to IV MgSO₄. So, the next step is to perform more trials to get support. Further trials and studies will either support the role nebulized MgSO₄ or it will demonstrate that it is not as effective. Either outcome is important. The benefits have already been discussed and will certainly help clinical practice. If future studies demonstrate that there is not comparable efficacy of nebulized MgSO₄ that will inform the clinician that they should not administer MgSO₄ via nebulizer. Knowing what not to do is equally important because the clinician won't waste valuable time or resources pursuing a certain treatment if it is supported in the literature that this treatment modality is not as effective. Ultimately, more studies will yield the biggest benefit going forward.

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Appendices

Appendix A: Comparison of Study Designs

Study	Design	Total N	Population Demographics	Asthma Severity	MgSO ₄ ROA	Outcome Measures
Daengsuwan et al (2017)	RCT	N=28	14 Female 14 Male Mean Age= 5.4 +/-2.61 years (group 1) 5.15+/-3.34 years (group 2)	Acute asthma status for inclusion: Severe	Both NEB and IV	Asthma Severity Score and Vitals (RR, HR, O ₂ saturation, and BP)
Egelund et al (2013)	CS	N=57	19 Female 38 Male Mean Age= 8.9 +/-4.2 years (group 1) 5.6 +/-3.8 years (group 2)	Acute asthma status for inclusion: Severe (Status Asthmaticus)	IV only	Vitals (RR, HR, O ₂ saturation, and BP) Serum MgSO ₄
Powell et al (2013)	RCT	N=508	215 Female 293 Male Mean Age= 4.0 years (total)	Acute asthma status for inclusion: Severe	NEB only	Yung asthma severity score
Singh et al (2008)	RCT	N=60	31 Female 29 Male Mean Age= 34.79 +/-8.05 years (group 1) 35.9 +/- 8.76 years (group 2)	Acute asthma status for inclusion: Severe	IV only	FEV ₁ , peak expiratory flow, and discharge rates
Sun et al (2014)	RCT	N=330	148 Female 182 Male Mean Age= 6.3 +/-2.3 years (group 1) 5.77+/-2.10 years (group 2) 6.13 +/- 2.32	Acute asthma status for inclusion: Mild to Severe	NEB only	FEV ₁ , and peak expiratory flow

			years (group 3)			
Wang et al (2015)	RCT	N=84	35 Female 49 Male Mean Age= 6.18 +/-2.63 years (group 1) 5.86 +/- 1.8 years (group 2) 7.07+/- 2.62 years (group 3)	Acute asthma status for inclusion: Mild to Severe	NEB only	FEV ₁
Watanatham et al (2015)	RCT	N=12	4 Female 8 Male Mean Age= 5.5 +/-2.6 years (total)	Acute asthma status for inclusion: Severe	Both NEB and IV	Asthma severity score and length of stay at hospital

CS= Cohort Study, IV=Intravenous Administration, NEB=Nebulized Administration, ROA=Route of Administration, RCT= Randomized Controlled Trials

Appendix B: Validity Assessment

Study	Blinding	Biases	Appropriate Design for PICO Question	Inclusion Criteria Targets Correct Population	Data Analysis	Power
Daengsuwan et al (2017)	A	A	A	A	A	M
Egelund et al (2013)	A	A	A	A	M	A
Powell et al (2013)	A	A	M	A	A	A
Singh et al (2008)	M	A	A	I	A	A
Sun et al (2014)	A	A	A	M	A	A
Wang et al (2015)	A	A	M	A	A	A
Watanatham et al (2015)	A	A	A	A	A	M

Key: A=Adequate, M=Marginal, I=Inadequate

Appendix C: Summary of Results IV and Nebulized MgSO₄

Study	IV MgSO ₄ Improved Asthma	Nebulized MgSO ₄ Improved Asthma	IV Vs. Nebulized MgSO ₄ Outcome Difference
Daengsuwan et al (2017)	S	S	NS
Egelund et al (2013)	S	X	X
Powell et al (2013)	X	S	X
Singh et al (2008)	S	X	X
Sun et al (2014)	X	NS	X
Wang et al (2015)	X	S	X
Watanatham et al (2015)	S	S	NS

Key: S=Statistically Significant, NS= Not Statistically Significant, X= Not appropriate from study design