The Efficacy of Administration of Intravenous Magnesium Sulfate for Improved Ventricular Rate Control or Rhythm Control in Patients with Non-postoperative Atrial Fibrillation and Atrial Flutter

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Abstract
INTRODUCTION: Standard treatment for atrial tachyarrhythmias, such as atrial fibrillation or atrial flutter, involves rate and rhythm control. Previous studies have looked at the electrophysiologic effects of magnesium on impulse formation and propagation, and theorized it could be beneficial in treatment for atrial tachycardias. There recently have been studies about magnesium sulfate and its utility in establishing rate and rhythm control in patients with atrial fibrillation or flutter.

METHODS: This systematic review used several databases to find five relevant articles regarding the use of intravenous magnesium sulfate in non-postoperative patients with atrial fibrillation or atrial flutter. The articles' outcomes were ventricular rate control and return to normal sinus rhythm. Only randomized control trials that were double or single-blinded were used to ensure validity.

RESULTS: Both studies that used magnesium sulfate bolus and infusion in conjunction with an antiarrhythmic medication such as a beta blocker, calcium channel blocker, or digoxin, had better ventricular rate control. Only one of the two studies using magnesium sulfate with an antiarrhythmic medications had a better conversion to normal sinus rhythm. Of the three studies that did not use antiarrhythmic medication with magnesium sulfate, the study that used only use a bolus of magnesium sulfate did not have a beneficial effect in rate or rhythm control. The other two studies that did use a bolus and infusion of magnesium sulfate, but no other antiarrhythmics, had better efficacy in returning the patient to a normal sinus rhythm.

CONCLUSION: Magnesium sulfate, in conjunction with typical antiarrhythmics, given as a bolus and infusion is found to have greater efficacy in ventricular rate control and return to normal sinus rhythm. Further randomized control trials regarding specific dose of magnesium sulfate and antiarrhythmic medication needs to be pursued.

Degree Type
Capstone Project

Degree Name
Master of Science in Physician Assistant Studies

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Subject Categories
Medicine and Health Sciences

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A Clinical Research Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Forest Grove, OR For the Masters of Science Degree August, 2009

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Abstract

INTRODUCTION: Standard treatment for atrial tachyarrhythmias, such as atrial fibrillation or atrial flutter, involves rate and rhythm control. Previous studies have looked at the electrophysiologic effects of magnesium on impulse formation and propagation, and theorized it could be beneficial in treatment for atrial tachycardias. There recently have been studies about magnesium sulfate and its utility in establishing rate and rhythm control in patients with atrial fibrillation or flutter. METHODS: This systematic review used several databases to find five relevant articles regarding the use of intravenous magnesium sulfate in non-postoperative patients with atrial fibrillation or atrial flutter. The articles’ outcomes were ventricular rate control and return to normal sinus rhythm. Only randomized control trials that were double or single-blinded were used to ensure validity. RESULTS: Both studies that used magnesium sulfate bolus and infusion in conjunction with an antiarrhythmic medication such as a beta blocker, calcium channel blocker, or digoxin, had better ventricular rate control. Only one of the two studies using magnesium sulfate with an antiarrhythmic medications had a better conversion to normal sinus rhythm. Of the three studies that did not use antiarrhythmic medication with magnesium sulfate, the study that used only use a bolus of magnesium sulfate did not have a beneficial effect in rate or rhythm control. The other two studies that did use a bolus and infusion of magnesium sulfate, but no other antiarrhythmics, had better efficacy in returning the patient to a normal sinus rhythm. CONCLUSION: Magnesium sulfate, in conjunction with typical antiarrhythmics, given as a bolus and infusion is found to have greater efficacy in ventricular rate control and return to normal sinus rhythm. Further randomized control trials regarding specific dose of magnesium sulfate and antiarrhythmic medication needs to be pursued.
Any sinus rhythm at a rate higher than one hundred beats per minute is considered supraventricular tachycardia, and atrial tachyarrhythmia is a specific type of supraventricular tachycardia. Atrial tachyarrhythmias originate in the atria and sustain a rate greater than one hundred. Abnormal impulse formation or propagation is the cause of atrial tachyarrhythmias.

Normal impulses are formed due to the heart’s automaticity, which is caused by an action potential within the cardiac myocyte. The action potential allows the sinus node to depolarize, which then causes a heartbeat. The normal action potential of a cardiac myocyte has five different sequential phases. Each one of the phases represents different ions crossing the cell membrane of the cardiac myocyte. Phase 0 is depolarization by sodium ions crossing over the cell membrane into the myocyte. Slight repolarization in Phase 1, is due mostly to potassium ions leaving the cell. Phase 2 utilizes calcium and potassium. Calcium travels into the cell while potassium is still in a slow outward flux. Phase 3 is where most of the repolarization occurs, because more potassium is leaving the cell than calcium is entering. The resting phase of the action potential is in Phase 4. The sodium-potassium adenosine triphosphatase pump and sodium-calcium exchanger maintains Phase 4 of the action potential in the cardiac myocyte. The pump and exchanger return the balance of ions to their original state.

Normal impulse formation reaches threshold potential and then depolarizes spontaneously in the sinoatrial node. This process is called automaticity. Other cells such as the atrial cells, atrioventricular node, and the His-Pukinje fibers are capable of
automaticity if they are not suppressed by the more rapid firing sinoatrial node.\textsuperscript{3} The slope of Phase 4 and threshold potential determine the rate of impulse formation, and are regulated by the autonomic nervous system and ionic currents.\textsuperscript{2}

Normal propagation of a cardiac impulse originates from the sinus node; the sinus node activates first the atria, then atrioventricular node, then bundle of His, then bundle branches, and finally, the ventricles.\textsuperscript{4} This systematic traveling impulse allows for the atria to contract first and adequately fill the ventricles to maximize cardiac output.\textsuperscript{3}

There are two reasons why a patient would experience an atrial tachyarrythmia, abnormal impulse formation or abnormal impulse propagation. In case of abnormal impulse formation, this could be from a decreased threshold for the action potential. When the slope of phase 4 of the cardiac action potential is increased, this causes aberrant automaticity and reduces the threshold for the action potential.\textsuperscript{2} Electrolyte abnormalities can cause deviations in the cardiac myocyte action potential. Abnormal propagation in atrial tachyarrythmias could be due to reentry.\textsuperscript{4} Reentry is the phenomenon where a group of muscle fibers fails to be initially activated during normal wave propagation, but are activated in the retrograde direction by the same wave of depolarization.\textsuperscript{4} Atrial fibrillation is the most common tachyarrythmia, and is characterized by uncoordinated atrial electrical activation and atrial contraction.\textsuperscript{53} It is estimated that at least five million Americans have been diagnosed with atrial fibrillation.\textsuperscript{3} The prevalence of atrial fibrillation increases with age, with more men than women being affected. The prevalence has been found to be higher in whites than in blacks.\textsuperscript{4}
Atrial fibrillation has a specific etiology and pathology. Hypertension, coronary artery disease, heart failure, and valvular heart disease are usually associated with and thought to be a cause of atrial fibrillation.\(^6\) \(^4\) Rheumatic fever once played a greater role in its etiology, but successful prevention of the disease has limited its role. \(^4\) The two mechanisms that lead to the development of atrial fibrillation are abnormal impulse formation from rapidly firing foci which hit the atrioventricular node, and abnormal impulse propagation caused by multiple reentry circuits in the atria. The source of the rapidly discharging foci usually arises from the pulmonary veins that cause abnormal automaticity. \(^4\) Pulmonary veins in patients with atrial fibrillation have shorter refractory periods than healthy patients in control groups. \(^4\) Ionic changes due to altered atrial myocytes from stretched myocardial muscle can also lead to abnormal impulse formation. \(^3\) The repeated stimulation of the atrioventricular node causes an irregular, rapid ventricular response. \(^5\)

The second possible cause of atrial fibrillation is reentry due to multiple wavelets. The initial impulse travels around refractory tissue and become irregular wavelets that then can accelerate or decelerate upon encountering other tissue. \(^4\) Larger atrial mass is correlated with more refractory tissue. \(^4\) The normal progression is atrial tissue alteration due to heart disease or normal aging, leads to sinus node damage, and eventual atrial fibrillation. \(^4\)

In the case of atrial flutter, there is a regular rhythm has monomorphic P waves, no isoelectric baseline, and a rate of 240 to 340 beats per minute. \(^4\) The problem arises when a single macroreentry circuit in the right atrium leads to regular, but rapid, ventricular response. \(^5\) Basically, there is a narrow region of reentrant demarcated by
anatomic or functional barriers which can be from past surgical scars or nonsurgical fibrosis that generate reentrant pathways allowing atrial flutter, most often induced by a premature atrial beats, to occur. A patient is most commonly at risk for atrial flutter within one week after open heart surgery. Other diseases associated with atrial flutter are chronic obstructive pulmonary disease, mitral or tricuspid disease, atrial enlargement, and thyrotoxicosis.

Atrial tachyarrhythmias can be asymptomatic or can produce symptoms such as palpitations, syncope, chest pain, shortness of breathe, dizziness, or a sense of a slowing heart rate. These symptoms are produced when there is decreased ventricular filling, which then causes a decreased cardiac output. Conditions such as atrial fibrillation or flutter are diagnosed by electrocardiogram (ECG). An echocardiogram is sometimes performed to monitor cardiac chamber size and function and valve abnormalities.

There are several appropriate treatment modalities for atrial tachyarrhythmias. The standard treatments for atrial fibrillation, alone or in combination, are ventricular rate control, rhythm control, and prevention of thromboembolism. To establish ventricular rate control, beta-adrenergic blockers, calcium channel blockers, or digoxin are useful. Normal sinus rhythm can be restored or maintained either pharmacologically or electrically. Flecainide, dofetilide, propafenone, ibutilide, or amiodarone can be used in chemical cardioversion. External synchronized DC cardioversion and radiofrequency catheter ablation are modalities for electrical cardioversion. The risk of thrombolytic events can be decreased by keeping the international normalized ration (INR) between 2.0 and 3.0 with an anticoagulant.
For atrial flutter, the treatment modalities are also pharmacologic or electric. Effective chemical cardioversion can be achieved with type IC antiarrhythmics in combination with atrioventricular nodal blocking agents like beta adrenergic blockers, type III antiarrhythmics, such as sotalol, dofetilide, ibutilide, and amiodarone, or class IA antiarrhythmics, for example quinidine, procainamide, or disopyramide. Electrical cardioversion involves overdrive pacing of the atria or direct current synchronization to the QRS complex. Catheter ablation is another option for the treatment of atrial flutter. There is a question when dealing with patients with atrial flutter as to whether efforts should be made to prevent thromboembolism as their risk is lower than those diagnosed with atrial fibrillation. However, there has been recent evidence of thrombogenic potential in patients with atrial rates greater than two hundred.

**Magnesium Sulfate**

Magnesium is an intracellular ion that participates in more than three hundred enzymatic reactions within the body, and is involved closely with the production and utilization of adenosine triphosphate. Patients with low intracellular levels of magnesium are predisposed to cardiac arrhythmias, as magnesium is needed for potassium and calcium channels to function properly in the myocardial cell. Magnesium is an important cofactor into the sodium-potassium adenosine triphosphate pump for Phase 4 of the cardiac action potential, accordingly it is standard treatment to give magnesium salts to patients with refractory ventricular arrhythmias.
Magnesium sulfate has historically been used to treat ventricular arrhythmias such as ventricular fibrillation or pulseless ventricular tachycardia in patients with suspected hypomagnesemia under the theory that hypomagnesemia can precipitate ventricular fibrillation and hinder the return of potassium to the myocytes. Magnesium imbalances may cause aberrant cardiac impulse generation and reentrant loop in the atria.

Recent studies have looked at the electrophysiological effect of magnesium on cardiac myocytes. The first electrophysiologic study compared magnesium sulfate to adenosine triphosphate for treating supraventricular tachycardia. It was hypothesized that, since magnesium sulfate prolongs atrioventricular node conduction and refractoriness, it could be used for atrioventricular node reentrant supraventricular tachycardias. It was concluded that magnesium sulfate did not terminate supraventricular tachycardias, but it did show some promise in blocking retrograde conduction in accessory pathways.

The second study looked at the differential effects of intravenous magnesium on atrioventricular node conduction in twenty-three patients with supraventricular tachycardia. Patients were given 2.47 grams of intravenous magnesium sulfate bolus over one minute. The study found that magnesium sulfate prolongs tachycardia cycle length in patients, from 340 to 370 milliseconds (8.8%) versus patients without magnesium sulfate from 347 to 350 milliseconds (0.8%), when compared to baseline. Since lengthening the tachycardia cycle length will delay the atrioventricular node conduction, and thereby decrease the number of impulses going to the ventricles, this will cause a decrease in ventricular rate. These two electrophysiologic studies have shown
that magnesium sulfate has the potential to stop retrograde reentry and slow cardiac conduction of patients in atrial fibrillation or atrial flutter.

Two retrospective studies that looked at the efficacy of ibutilide with or without magnesium sulfate found it efficacious in rate and rhythm control in patients with atrial fibrillation and atrial flutter. Both of the trials had an intervention consisted of intravenous magnesium sulfate two hours before or during ibutilide administration. The comparison was no magnesium sulfate, only the ibutilide. The first study had 229 patients with atrial fibrillation or atrial flutter received ibutilide for acute chemical conversion made up the study group. The trial found successful chemical conversion within six hours of ibutilide dose was seventy-eight percent with any dose of magnesium sulfate, compared to 59.8% with only ibutilide. The second retrospective trial had a population of 321 patients with supraventricular tachycardia who received ibutilide for acute chemical conversion. The study found magnesium sulfate enhanced the effect of ibutilide to establish rate control after six hours. Seventy-two percent of patients that received magnesium sulfate had a successful chemical cardioversion versus only sixty percent of patients that didn’t receive magnesium sulfate.

**Purpose**

The purpose of this systematic review is to determine whether the addition of intravenous magnesium sulfate aids in rate or rhythm control in patients with atrial fibrillation or atrial flutter. There are no current formal recommendations for the use of
magnesium sulfate in these particular arrhythmias, and its use is inconsistent in the medical community. There have been several studies of its utility of the past two decades in the management, of atrial tachyarrhythmia.

Hypothesis

Since most atrial tachyarrhythmias are due to abnormal impulse formation and propagation, and since magnesium is utilized by the cardiac myocyte action potential to control impulse formation and propagation, magnesium sulfate should therefore, improve rate or rhythm control. Magnesium plays a role in Phase 4 the action potential in a cardiac myocyte by being a cofactor in the sodium-potassium adenosine triphosphatase enzyme, and by its involvement in the calcium channels in the atrial myocytes. If the magnesium is already depleted, or becomes depleted due to the arrhythmia, it would make sense that replenishing this electrolyte would assist in the treatment of atrial tachyarrhythmia.

It would not be expected that magnesium sulfate to chemically cardiovert patients in atrial fibrillation or atrial flutter. However, it seems probable that it could be used in conjunction with other antiarrhythmics to provide a higher rate of successful conversion.

Magnesium sulfate may be able to be used to establish ventricular rate control by itself in patients with atrial arrhythmias, but it would most likely have a greater effect when used in combination with other rate controlling medication.

Significance
Atrial fibrillation and flutter are common types of arrhythmias that can result in serious complications. If left untreated, they can lead to electrophysiologic remodeling, which would predispose the heart to perpetuation of atrial fibrillation. Atrial fibrillation can also lead to loss of atrial myocardium with scarring and fatty infiltration. Eventually, heart failure can worsen from the added stress on the heart when it has a chronically decreased cardiac output. Restoring the heart to normal sinus rhythm or to a controlled ventricular rate, is crucial to the cardiovascular health of the patient.

Atrial fibrillation and atrial flutter confer an increased relative risk of mortality most commonly due to stroke. The risk of stroke is correlated with increased age in patients with atrial fibrillation.

**METHODS**

The search for relevant studies was detailed and exhaustive. Bibliographic databases used were MEDLINE-OVID, PUBMED, CINALH, and Web of Science. Only published articles were included. The terms searched to allow a comprehensive and representative review were (1) “supraventricular tachycardia”; (2) “magnesium sulfate”; (3) “magnesium sulphate”; (4) “atrial fibrillation”; (5) “atrial flutter”; (6) atrial arrhythmia; (7) or a combination of these terms.

Inclusion criteria for these selected studies are any type of atrial tachyarrhythmia, including atrial fibrillation or atrial flutter. Patients considered in this systematic review
had atrial tachyarrhythmia which was acute or chronic, since most studies were vague about the duration of arrhythmia. Any dosage of intravenous magnesium sulfate was included. Studies that used other common antiarrhythmic medications, in addition to the magnesium sulfate, were used for the review. The desired outcome was a decrease in heart rate and a conversion to normal sinus rhythm. Randomized, double-blinded, and single-blinded studies were included. Data from 1990 to the present was used and only full articles in English were accepted.

Exclusion criteria included patients without atrial tachyarrhythmia, as well as patients less than one month postoperative from a cardiac or vascular surgery. Any study done before 1990 was not included in the systematic review. Commentaries, retrospective studies, and case studies were not included in this review. Validity was established by accountability for all patients in the studies, as well as similarity between groups at the start of the trials. Abstracts were not accepted. A Jadad score equal or less than 2 was not accepted for randomized control trials. (See Table 1 for Jadad Score.)

**RESULTS**

A total of five articles were used for the systematic review. Three of the trials were double-blinded, randomized controlled trials, and looked solely at atrial fibrillation.\textsuperscript{13,14,15} Two of the articles were single-blinded, randomized controlled trials performed on patients with atrial flutter or fibrillation.\textsuperscript{16,17} All of the articles looked at the use of intravenous magnesium sulfate and the efficacy of rate and rhythm control in
patients with non-postoperative atrial tachyarrhythmias. The articles were reviewed specifically for their study type, sample size, type of arrhythmia, duration of arrhythmia, dose of magnesium sulfate, dose of medication with which it was being compared, the reduction in ventricular rate, and the conversion to normal sinus rhythm. (See Table 1).

The first study looked at magnesium sulfate versus placebo for the treatment of paroxysmal atrial fibrillation. The study had forty-eight adults, eighteen years of age or older, with atrial fibrillation with an onset of less than forty-eight hours and with a sustained ventricular rate greater than one hundred beats per minute. The intervention was intravenous magnesium sulfate 2.5g over fifteen minutes compared to the placebo of normal saline. After two hours, there was no difference between intravenous magnesium sulfate and normal saline with regard for decreasing heart rate. For the magnesium sulfate group, the ventricular rate dropped by nine beats per minute versus the placebo group that showed a drop of twenty-six beats per minute. The P value was 0.124, which means the decrease in heart rate was not statistically significant. Of the magnesium sulfate group, 8.7% converted to normal sinus rhythm and 25.0% of the placebo group converted to normal sinus rhythm within the same time frame. The P value for rhythm conversion was 0.25, which means the outcome was not statistically significant.

The next study was a randomized, double-blinded control trial that looked at the effect of magnesium sulfate on ventricular rate control in atrial fibrillation in fifteen adults with newly recognized atrial fibrillation with a rapid ventricular response. Patients were given a two-gram bolus of intravenous magnesium sulfate over one minute, then four grams over four hours. The placebo group was given no magnesium sulfate. All patients were given 0.5mg of intravenous digoxin after thirty minutes. This study
found that magnesium sulfate decreased the ventricular rate more than the placebo after 3.5 hours. After five minutes, the heart rate declined seventeen percent in patients that were administered the magnesium sulfate compared to one percent in the placebo group in the same time period. The P value was 0.02, which was statistically significant. Once digoxin was administered thirty minutes later to both groups, the magnesium sulfate group had a twenty seven percent decrease in heart rate, versus the placebo group which had only an eighteen percent rate reduction. The P value was 0.08, which is not statically significant. Those patients who returned to normal sinus rhythm were excluded in the study; three from the placebo group and one from the magnesium group. The rate of conversion of the magnesium group after digoxin was administered was 14.2% and was 37.5% for the placebo.

The next double-blinded, randomized control trial studied the addition of magnesium sulfate to the usual care of atrial fibrillation for rate control. 14 One hundred and ninety-nine patients, eighteen and older, suffering from atrial fibrillation with a rapid ventricular response greater than 120 beats per minute were included. Patients were randomized to receive intravenous magnesium sulfate in a five gram bolus, followed by 2.5 grams in twenty minutes, and finally 2.5 grams over two hours or a placebo regimen that had no magnesium sulfate. The study found magnesium sulfate, in conjunction with standard therapy for atrial fibrillation, was more apt to decrease the heart rate to less than one hundred beats per minute after two and a half hours and to convert to sinus rhythm versus no magnesium sulfate. Sixty-five percent of patients that took magnesium sulfate had a favorable outcome versus only thirty-four percent of patients taking the placebo. The relative risk was 1.89 with a 95% confidence interval of 1.38 to 2.59; the P value was
less than 0.0001. Twenty-seven percent of patients receiving magnesium sulfate converted to normal sinus rhythm compared to twelve percent with placebo. The relative risk was 2.20 with a 95% confidence interval of 1.15 to 4.21; and the P value of less than 0.01.

The next randomized, single-blinded trial studied intravenous magnesium sulfate versus diltiazem in paroxysmal atrial fibrillation. The population was forty-six patients with atrial fibrillation that received intravenous magnesium sulfate bolus of 2.5g over fifteen minutes and 7.5g infusion over the next six hours or intravenous diltiazem bolus of 25mg over fifteen minutes, then an infusion of 12.5 mg over six hours. After six hours, there was no difference in heart rate reduction between the two groups, but both did see a statistically significant decrease. The P value was less than 0.001 at six hours. There was a fifty-seven percent conversion rate to normal sinus rhythm in the magnesium sulfate group opposed to twenty-two percent of patients who received diltiazem. It appears that magnesium sulfate helps with ventricular rate control and conversion to normal sinus rhythm in patients with atrial fibrillation after twelve hours. Although diltiazem helped with rate control as much as magnesium sulfate, it didn’t have as high a rate of conversion to normal sinus rhythm.

The final study was a randomized, single-blinded trial that reviewed the effect of magnesium versus verapamil on atrial tachyarrhythmias. The sixty-four patients included in the trial had atrial fibrillation or atrial flutter of a duration of less than one week. Patients were given intravenous magnesium sulfate at a dose of 1.2 grams over five minutes, and the same dose was repeated over ten minutes if there was no response. After the boluses, an infusion of magnesium sulfate was started at a rate of 0.6 grams per
hour. The control group was given an intravenous verapamil bolus of five milligrams over a five minute period, then five milligrams after ten minutes if there was no response. Verapamil was then infused at a rate of 0.6 milligrams per hour. After four hours, conversion to normal sinus rhythm occurred in 57.1% of patients who received magnesium sulfate versus 12.5% who received verapamil. A ventricular rate of less than one hundred was achieved in 23.8% percent of the magnesium sulfate group versus 58.3% of those treated with verapamil, demonstrating that magnesium sulfate was better at converting atrial tachyarrhythmias than verapamil, yet verapamil was better at decreasing the ventricular rate to under one hundred beats per minute than was magnesium sulfate.

**DISCUSSION**

The goal of this literature review was to use current medical literature to determine whether intravenous magnesium sulfate was beneficial for patients with new onset atrial fibrillation or flutter. The inclusion and exclusion criteria set forth during the search limited the available studies to only a few and made it necessary to include two trials that were single-blinded. The Chu study was a double-blinded, randomized clinical trial with a Jadad score of five. The methods of randomizing and blinding were well explained. The Jadad score for the Hays study was a three since the methods of randomization and blinding were not described, and validity was in question. The Davey study was a double-blinded, randomized control trial, and its methods were described in
detail, earning a Jadad score of five. The Gullestad study was a single-blinded, randomized trial with a Jadad score was three. The Chiladakis trial, with a low Jadad score of two, was also a single-blinded, randomized trial.

The characteristics of each study’s population varied slightly, as did its size. All of the trials used adults eighteen or older, and some had no upper age limit stated. The average age of a participant was 63.5 years old and only two studies had a significantly different average age. The Chu and Davey study had an average age of fifty-two and seventy-two, respectively. Population sizes ranged from fifteen to 199 patients, and the median population size was forty-eight for the five trials. The Hays study had the lowest number of participants.

The dose of magnesium sulfate varied for each study. Some studies used boluses, some had boluses plus an infusion. The Chu study was the only trial without an infusion of magnesium sulfate after the initial bolus. The Gullestad study had the smallest bolus of magnesium sulfate at 1.2 grams. The Chiladakis study had the longest infusion of magnesium sulfate, at six hours.

Some of the studies looked at magnesium sulfate use in conjunction with an antiarrhythmic or with other medications. For the Chu study, magnesium sulfate was not used in addition with other antiarrhythmic medication while, in the Hays study magnesium sulfate was given with digoxin. The Davey study used a variety of other antiarrhythmics with magnesium sulfate at the physician’s discretion versus one standard therapy. The Chiladakis study compared magnesium sulfate with diltiazem, but did not use an antiarrhythmics in addition to the magnesium sulfate. The dose of diltiazem was maximized in the Chiladakis study. In the Gullestad study, the verapamil dose was small
and not titrated, and the magnesium dose was given alone, rather than in conjunction with another medication.

Not all the studies looked at the same outcome nor the same period of time. The Chu study only looked at rate control, and conversion to normal sinus rhythm two hours after the intervention. For the Davey study, the outcomes measured were, the ventricular rate control and rhythm conversion after 2.5 hours. In the Hays study, ventricular rate control was measured after 3.5 hours, and those that converted to normal sinus rhythm were subsequently excluded. The Chiladakis study only looked at the first six hours for rate or rhythm control. It is possible for both magnesium sulfate and diltiazem to work up to twenty-four hours after administration, and this study did not take that into account. The Gullestad study looked at both outcomes after four hours.

It was predicted that magnesium sulfate given without the addition of an antiarrhythmic, would not significantly decrease ventricular rate or convert the arrhythmia to a normal sinus rhythm. The Chu study concluded that magnesium sulfate alone did not cause significant ventricular rate control or return of normal sinus rhythm. The Hays trial exclude patients that converted to normal sinus rhythm, but it does appear that the control group had a better rate of conversion. The Davey study found the use of magnesium sulfate, in addition to other antiarrhythmic medication, was efficacious in controlling the ventricular rate and returning the rhythm to normal sinus. The Chiladakis and Gullestad trials actually found magnesium sulfate alone could increase the number converted to normal sinus rhythm. However, both studies failed to control ventricular rate.
LIMITATIONS

There were several limitations for this systematic review. The weakness of this systematic review is the broad population. All patients with chronic or paroxysmal atrial tachyarrhythmia were included. The validity of the results this systematic review may have been easier to validate in a more specific population, for example had the population been limited to those with either atrial fibrillation or atrial flutter. Most studies appeared to be on patients with acute onset atrial tachyarrhythmia. However, the underlying pathophysiology of atrial fibrillation and atrial flutter is similar in nature, making this diverse population pertinent. Ventricular arrhythmias or other supraventricular tachycardias were not included, since their pathophysiology is quite different to an atrial tachyarrhythmia.

Either a decreased ventricular rate or rhythm control was accepted as an outcome. This endpoint was not very specific, nor was it an easy endpoint to measure. Another area that could decrease the validity the studies of this review is the range of dosage of intravenous magnesium sulfate in each of the studies. The bolus range was between 1.2 and 5 grams. Some studies included an infusion of magnesium sulfate as well as a bolus, and those ranges also varied. The discrepancy between dosages could vary the outcomes significantly. The timing of the bolus and infusion of the magnesium sulfate also could affect the endpoint. The bolus of the magnesium sulfate varied, as did the infusion of the medication.
The comparison was magnesium sulfate versus no magnesium sulfate (placebo, saline, or other medication).

The studies selected for this review were not all double-blinded, randomized control trials. However, all of them appear to be legitimate in their blinding and randomizing. Certain articles state they are randomized or blinded, but fail to explain how that was achieved and their Jadad score of less than five reflect this.

By applying less strict criteria to their outcomes, some of the studies tended to overestimate the efficacy of magnesium sulfate. If the endpoint was not precise and ventricular rate was just stated as lowered instead of below an exact beat count per minute, the study may actually overestimate have over-exaggerated the effectiveness of the medication. For example, the Davey study is alone in having a specific outcome that looked at a ventricular rate of less than one hundred beats per minute.

The heterogeneity of the populations is the degree of difference between the groups and is defined as the P value. If the P value is less than 0.05 (or saying there is one in five hundred chance of these being just a coincidence), the heterogeneity is small and makes chance an unlikely explanation for the differences. Heterogeneity tests are less meaningful if the sample sizes are small. A P value of less than 0.05 is statistically significant, meaning that the results are unlikely to be due to chance alone.

Recommendations for further study would primarily look at the dosing of magnesium sulfate. Finding an optimal dose for the bolus and infusion of magnesium sulfate would make the comparison to other medications more standard across the board.

CONCLUSION
Magnesium sulfate has a history in treating ventricular arrhythmias and has recently been studied to look at its efficacy in rate and rhythm control in atrial tachyarrhythmias.

The use of magnesium sulfate is beneficial in the treatment of atrial fibrillation and atrial flutter if it is used in conjunction with another antiarrhythmic medication. Magnesium sulfate tends not to be as effective in chemical cardioversion or rate control when administered by itself. At least a two milligram bolus of magnesium sulfate followed by an infusion leads to higher likelihood of cardioversion. A dose of four milligrams appears to be even more efficacious than lower doses at cardioversion. Magnesium sulfate alone was not as effective as verapamil or diltiazem in lowering the ventricular rate.

More randomized control studies need to be done on the dosage of magnesium sulfate. The optimal amount and rate of the bolus and infusion need to be established before further comparisons are made. Studies comparing different antiarrhythmic medications in combination with magnesium sulfate for the treatment of atrial tachyarrhythmias would also be useful.
FIGURES

FIGURE 1

Jadad scores

1. Was the study described as randomized? Yes:1 No: 0
2. Was the method used to generate the sequence of randomization described adequately? Yes:1 No: 0
3. Was the study described as double-blind? Yes:1 No:0
4. Were those lost to follow-up adequately addressed? Yes:1 No:0
5. Deduct one point if the method of randomization was described but was not appropriate. Yes:-1 No or N/A:0
6. Deduct one point if the method of blinding was described but was not appropriate. Yes: -1 No or N/A:0
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Jadad or SS Score</th>
<th># of Pts</th>
<th>Type of Arrhythmia</th>
<th>C, A, or specific time</th>
<th>Dose of MgSO4</th>
<th>Comparison/Control</th>
<th>Other med used with MgSO4</th>
<th>Change in VR w/ MgSO4</th>
<th>Change in VR w/ Control</th>
<th>Conversion rate to NSR w/ MgSO4</th>
<th>Conversion rate to NSR w/ Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chu</td>
<td>DB, R</td>
<td>5</td>
<td>48</td>
<td>AF</td>
<td>&lt;48 hrs</td>
<td>2.5g x 15 min</td>
<td>Placebo</td>
<td>No</td>
<td>At 2 hrs, 9 bpm</td>
<td>At 2 hrs, 26 bpm</td>
<td>8.7%</td>
<td>25%</td>
</tr>
<tr>
<td>Davey</td>
<td>DB, R</td>
<td>5</td>
<td>199</td>
<td>AF</td>
<td>A</td>
<td>5g B, 2.5g x 20 min, 2.5g x 2 hrs</td>
<td>Placebo</td>
<td>BB, verapamil or digoxin</td>
<td>65% &lt;100 bpm</td>
<td>34% &lt;100 bpm</td>
<td>27%</td>
<td>12%</td>
</tr>
<tr>
<td>Hays</td>
<td>DB, R</td>
<td>3</td>
<td>15</td>
<td>AF</td>
<td>A, 5 day ave.</td>
<td>2gB x 1 min, 4g x 4 hrs.</td>
<td>Placebo</td>
<td>Yes, Digoxin</td>
<td>BD=16 % AD=26%</td>
<td>BD= 1% AD=18%</td>
<td>14.2%</td>
<td>37.5%</td>
</tr>
<tr>
<td>Chiladakis</td>
<td>R, SB</td>
<td>2</td>
<td>46</td>
<td>AF</td>
<td>&lt;12 hrs</td>
<td>2.5gBx15 min, 7.5g x 6hrs</td>
<td>Diltiazem 25mgBx15 min, 75mg x 6hrs</td>
<td>No</td>
<td>NA, no difference</td>
<td>NA, no difference</td>
<td>57%</td>
<td>22%</td>
</tr>
<tr>
<td>Gullestad</td>
<td>R, SB</td>
<td>3</td>
<td>64</td>
<td>AF and AFL</td>
<td>&lt;1 week</td>
<td>1.2gBx5min x2, then 0.6g/hr</td>
<td>Verapamil</td>
<td>No</td>
<td>At 4hrs, 23.8% &lt;100bpm</td>
<td>At 4 hrs, 58.3% &lt;100bpm</td>
<td>57.1%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

A= acute; AD: after digoxin; AF= atrial fibrillation; AFL= atrial flutter; B= bolus; BD=before digoxin; bpm=beats per minute; C= chronic DB=double blind; g= gram; hrs=hours; J= Jadad Score mg=milligrams; MgSO4=Magnesium sulfate; min= minutes; NA= not available; NSR= normal sinus rhythm; P= prospective; Pts=patients; R= randomized; Retro= retrospective; SB= single blind; SS= Schindeler Score; SVT= supraventricular tachycardia; VR=ventricular rate
References

1. Irwin RS, Rippe JM, eds. *Irwin and Rippe's Intensive Care Medicine*. 6th ed. 530 Walnut Street, Philadelphia PA 19106 USA: Lippincott Williams & Wilkins (Copyright 2008 by Richard S. Irwin, M.D. and James M. Rippe, M.D.); 2008.


