

A Randomized Controlled Trial of Magnesium Sulfate, in Addition to Usual Care, for Rate Control in Atrial Fibrillation

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Study objectives: We examine the safety and efficacy of magnesium sulfate infusion, in addition to usual care, for acute rate reduction in patients with atrial fibrillation and a rapid ventricular response rate.

Methods: This was a prospective, randomized, double-blind, placebo-controlled trial of intravenous magnesium sulfate in adult emergency department patients with rapid atrial fibrillation. Study solutions were given in addition to any therapy the treating physician would normally consider appropriate, including the use of standard rate-reduction agents. Patients received either 20 mEq (2.5 g, 10 mmol) magnesium sulfate over a 20-minute period, followed by 20 mEq (2.5 g, 10 mmol) over a 2-hour period intravenously, or placebo.

Results: One hundred ninety-nine patients were randomized, 102 to receive magnesium sulfate and 97 to receive placebo. The antiarrhythmic drug most commonly used by treating physicians was digoxin. Magnesium sulfate was more likely than placebo to achieve a pulse rate of less than 100 beats/min (63 [65%] of 97 versus 32 [34%] of 93, relative risk [RR] 1.89; 95% confidence interval [CI] 1.38 to 2.59; $P < .0001$) and more likely to convert to sinus rhythm (25 [27%] of 94 patients versus 11 [12%] of 91 patients; RR 2.20; 95% CI 1.15 to 4.21; $P = .01$). Comparative mean pulse rate reductions in the magnesium sulfate group did not reach predetermined clinical significance levels (≥ 15 beats/min reduction) at any of the measured time points. Magnesium sulfate was more likely to be associated with an adverse event (14 [15%] of 95 patients versus 5 [5%] of 92 patients; RR 2.71; 95% CI 1.02 to 7.23; $P = .04$).

Conclusion: Magnesium sulfate, when used to supplement other standard rate-reduction therapies, enhances rate reduction and conversion to sinus rhythm in patients with rapid atrial fibrillation. [Ann Emerg Med. 2005;45:347-353.]

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INTRODUCTION

Background

Atrial fibrillation is the most common sustained clinically significant arrhythmia.¹ The majority of patients with a rapid ventricular response rate (rapid atrial fibrillation) do not require immediate electrical cardioversion. However, if allowed to remain in sustained rapid atrial fibrillation for hours, tachycardia-induced left ventricular dysfunction may result.^{2,3} Ventricular rate control is generally the primary therapeutic objective. Early conversion to sinus rhythm is of secondary importance and, in many cases, may not be desirable until anticoagulation has been effected.^{4,5}

A variety of pharmacologic agents are used for early rate control. Calcium-channel blockers, β -blockers, sotalol, and Vaughan Williams Class 1C agents must be used with caution

in patients with poor left ventricular function—precisely the group in which pulse rate reduction is most urgent. For this group, digoxin or amiodarone has been recommended.^{4,6,7} Digoxin has recently been the mainstay of therapy, and although inexpensive, it has a slow onset of action and is significantly less effective in states of increased sympathetic tone.^{4,6,8-10} Despite the widespread use of amiodarone in this setting, the evidence for its efficacy is somewhat equivocal. It also has a high adverse-effect profile with chronic dosing.¹¹

Magnesium sulfate has a number of biochemical and electrophysiologic properties that might make it useful in the treatment of rapid atrial fibrillation. Specifically, its role as a coenzyme for the sodium-potassium ion exchange pump (the Na-K ATPase) and its effects on potassium channels and intracellular calcium accumulation all serve to decrease

Editor's Capsule Summary

What is already known on this topic

Many patients presenting to the emergency department with rapid atrial fibrillation require rate reduction.

What question this study addressed

This randomized controlled trial examined whether the addition of magnesium sulfate to standard therapies for patients with atrial fibrillation would enhance reduction in the pulse rate.

What this study adds to our knowledge

When added to other standard therapies, intravenous magnesium facilitated a reduction in pulse rate, and patients were more likely to reach a pulse rate below 100 beats/min within 2.5 hours after treatment was initiated.

How this might change clinical practice

Patients with atrial fibrillation who require rapid pulse rate reduction may benefit from the addition of intravenous magnesium to other rate reduction therapies.

automaticity.¹²⁻¹⁴ Clinically, it has been found that atrioventricular nodal conduction is prolonged in patients treated with magnesium sulfate infusions.¹⁵ Such effects might serve to decrease the ventricular response rate to atrial fibrillation. It also has a high therapeutic to toxic ratio¹⁶⁻²⁰ and is relatively devoid of negative inotropic effects.²¹

Importance

To date, there have been 7 published clinical trials that have studied the effects of magnesium sulfate therapy in patients with supraventricular tachyarrhythmias, including patients in rapid atrial fibrillation.²²⁻²⁸ Each of the studies concluded that magnesium sulfate reduced ventricular response rates with minimal adverse sequelae. All but 1 concluded that the rate reductions were clinically significant.²⁷ The rate of conversion to sinus rhythm in patients treated with magnesium sulfate varied considerably in these studies. Unfortunately, the sample sizes of these studies were small (ranging from 15 to 57 patients), and differences in study design make it difficult to combine their results for analysis.

The question of whether magnesium sulfate is of particular benefit in hypomagnesemic patients with rapid atrial fibrillation has been examined in only 1 small clinical study that showed its effect to be independent of magnesium status.²⁷ Problematic in this determination is the fact that serum magnesium concentrations may not accurately reflect total body or intracellular magnesium. Patients receiving regular diuretics or patients who are chronic alcoholics may be total body magnesium deplete but may have normal serum magnesium levels.^{29,30}

Goals of This Investigation

This study aimed to answer the question of whether magnesium sulfate could, within the first 2.5 hours of presentation and when added to usual care, safely and effectively reduce the ventricular response rate in adult emergency department (ED) patients with rapid atrial fibrillation. Additionally, we wished to determine whether it increased the rate of conversion to sinus rhythm.

MATERIALS AND METHODS

Theoretical Model of the Problem

Magnesium sulfate is believed to reduce the rate of impulse transmission through the atrioventricular node. An intravenous infusion might augment the effect of coadministered antiarrhythmics and more rapidly reduce the rate of transmission of atrial impulses in atrial fibrillation. Because of its relatively wide therapeutic window, it would be expected that, at appropriate dosing, it would do this with few significant adverse effects. It might also be expected not to have a significant effect on the rate of conversion to sinus rhythm.

This study aimed to examine these questions in the clinical setting of acute presentations of atrial fibrillation in the ED. Endpoints of achieving a pulse rate of less than 100 beats/min, a relative reduction in pulse rate of 15 beats/min or more, and conversion to sinus rhythm were measured throughout the period of an infusion of magnesium sulfate. Administration of the study solution was in addition to any standard therapies thought appropriate by the treating physician.

Study Design

This was a randomized, prospective, double-blinded, placebo-controlled study. We compared the effects of magnesium sulfate and placebo on acute rate control in patients presenting to the ED with atrial fibrillation and with ventricular response rates greater than 120 beats/min. Study solutions were given in addition to any therapy the treating physician would normally consider appropriate, including the use of standard rate-reducing agents.

Setting

The study was conducted in 2 major academic, tertiary referral EDs of a city of 1 million inhabitants with a combined adult ED census of 80,000 per year. Patients were enrolled from August 1999 to June 2002. The study was approved by the ethics committees of both participating hospitals, and all patients consented to be involved.

Selection of Participants

Patients older than 18 years and presenting to the ED with atrial fibrillation and a ventricular response rate greater than 120 beats/min were eligible for inclusion. Exclusion criteria are listed in Figure 1. Randomization was achieved by block randomization of 50 consecutive study numbers as either solution "A" or "B" by drawing lots blindly from an equal number of marked tokens. The pharmacy department of each hospital

1. Hemodynamic instability defined as:
 - Requirement for cardioversion
 - Systolic blood pressure <90 mm Hg
 - Symptomatic hypotension
2. History of renal failure
3. History of atrioventricular node disease, including secondary and tertiary atrioventricular block, "tachy/bradycardia syndrome," but excluding primary atrioventricular block and patients with permanent pacemakers
4. Acute myocardial infarction with ECG criteria for thrombolysis

Figure 1. Exclusion criteria.

prepared all study solutions and determined which of "A" or "B" was to be the study and which the placebo solutions. Patients were then allocated consecutive study numbers as they were enrolled. Enrollment was convenience based, at the discretion of the ED treating physician.

Interventions

Enrolled patients were randomized to receive either 40 mEq (5 g, 20 mmol) of magnesium sulfate in 100 mL of 5% dextrose solution, with 20 mEq (2.5 g, 10 mmol) given intravenously over a 20-minute period, followed by the remaining 20 mEq (2.5 g, 10 mmol) intravenously over the next 2 hours, or an equivalent volume of 5% dextrose solution at the same rates of infusion. Patients, staff, treating physicians, and investigators were blinded to the study solution contents. Statistical analysis was also performed blinded to which arm of the study received magnesium sulfate.

Methods of Measurement

Enrolled patients received continuous electronic vital sign monitoring, with half-hourly automatic recording of pulse rate, oxygen saturation, and noninvasive blood pressure. Before infusion of the study solution, an ECG was performed, and blood was drawn for serum creatinine and electrolyte concentrations, including magnesium and calcium.

The treating physicians and nurses recorded data on a preformatted data collection sheet and in the case records. Where data were incompletely recorded on the study data sheet, the principal investigator at each site reviewed the case records to extract results. Predetermined validity of data extracted from the case record included pulse rate data if recorded on the hospital nursing chart, conversion to sinus rhythm if documented by an ECG with a time stamp indicating when it was performed or documentation by the treating physician, chronic alcoholism if documented in the current medical history by the admitting physician, and current use of diuretics if listed by the admitting physician as "current medication."

Data collected included duration of symptoms (<24 hours, >24 hours, or unknown); history of heart disease or alcohol

abuse; current use of diuretics, digoxin, and antiarrhythmics; drug therapy administered during the trial period; pulse rates at baseline and half hourly for 150 minutes after commencement of the infusion; whether there was conversion to sinus rhythm and the time it occurred; and adverse effects and their nature. Creatinine clearance was calculated using the formula: $\text{creatinine clearance} = (140 - \text{age}) \times \text{weight (kg)} \times 0.85$ (if female) / $\text{serum creatinine (mmol/L)} \times 815$. Hypomagnesemia was defined as a measured serum concentration of less than 1.4 mEq/L (0.70 mmol/L).

Outcome Measures

Outcome measures during the infusion were a pulse rate of less than 100 beats/min; mean changes in pulse rate at 30, 60, 90, 120, and 150 minutes; and conversion to sinus rhythm. A 20% absolute greater incidence (25% versus 5%) of pulse rate reduction to less than 100 beats/min and a difference in the mean pulse rate of 15 beats/min at the measured points were predetermined to be clinically significant. Using these criteria with a significance level of 0.05, 45 and 39 patients (assuming an SD of approximately 25 beats/min), respectively, would be needed in each group to achieve a power of 80%. A predetermination of clinical significance for differences in the rates of conversion to sinus rhythm and of adverse effects was not made.

Primary Data Analysis

All analyses were performed on the basis of intention to treat. The effect of treatment on the binary outcomes "any pulse rate less than 100," conversion to sinus rhythm, and any adverse effects was analyzed using χ^2 tests, and the results were reported as relative risks (RRs) and 95% confidence intervals (CIs). Log-binomial regression was used to adjust the analyses for confounders. Log-binomial regression is a generalized linear model similar to logistic regression, except that the log of the probability is analyzed rather than the logit. Log-binomial regression was used because we wished to report results in terms of RRs rather than odds ratios.

The effect of treatment on pulse rate measured at various points was analyzed using mixed model analysis of variance (with a random intercept and slope for each subject), with contrasts to test preplanned hypotheses of interest. Confounders were added to the model as necessary. The effect of treatment on the time taken to achieve a pulse rate of less than 100 beats/min was analyzed using a log-rank, with life-table estimates of the probability of achievement. Cox's proportional hazards regression was used to adjust the previous analysis for confounding factors.

The statistics package used for analyses was the SAS version 8.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Characteristics of Study Subjects

One hundred ninety-nine patients were enrolled in the study. Seventeen patients were withdrawn from the study

Table 1. Study withdrawals.

Reason	No.	MgSO ₄ / Placebo
Creatinine clearance <30 mL/min	3	1/2
Unknown	2	1/1
Hypermagnesemia	1	1
Patient or treating physician request		
Hypotension	4	3/1
Other, minor adverse effect	5	2/3
Other	2	1/1
Total	17	9/8

MgSO₄, Magnesium sulfate.

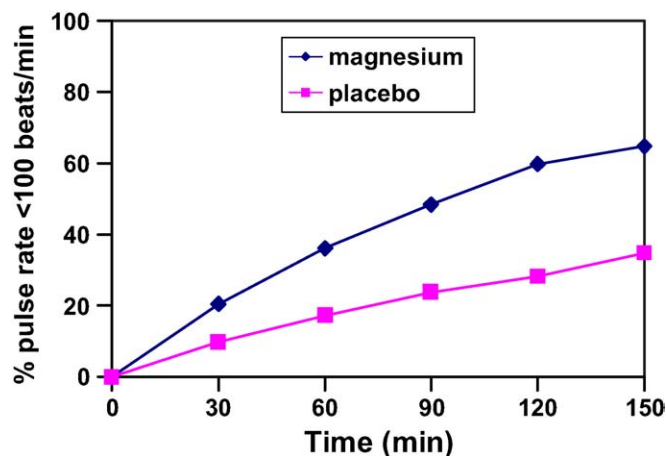
Table 2. Comparison of characteristics between treatment groups.*

Characteristic	MgSO ₄	Placebo
No. randomized	n=102	n=97
Sex, No. (%)		
Unknown	3 (2.9)	1 (1.0)
Male	46 (45.1)	45 (46.4)
Female	53 (52.0)	51 (52.6)
Age, y, median (IQR)	72.0 (60.0–80.0)	73.0 (61.0–81.0)
History of alcohol abuse, No. (%)	8 (8.2)	10 (10.8)
History of heart disease, No. (%)	46 (46.9)	47 (50.5)
Currently receiving diuretic, No. (%)	13 (13.4)	25 (26.9)
Currently receiving digoxin, No. (%)	14 (14.4)	12 (12.9)
Currently receiving other antiarrhythmics, No. (%)	28 (27.5)	29 (29.9)
Duration of symptoms, No. (%)		
Unknown	13 (12.7)	15 (15.5)
<24 h	70 (68.6)	54 (55.7)
≥24 h	19 (18.6)	28 (28.9)
Digoxin given, No. (%)	76 (77.6)	81 (86.2)
Verapamil given, No. (%)	2 (2.0)	4 (4.3)
β-Blocker given, No. (%)	11 (10.8)	9 (9.3)
Mean serum magnesium, mmol/L (SD)	0.85 (0.10)	0.88 (0.14)
Magnesium <0.7 mmol/L, No. (%)	5 (5.7)	5 (6.0)
Low magnesium or alcohol abuse or diuretic, No. (%)	22 (22.2)	34 (36.2)
Baseline pulse rate, beats/min (SD)	141.6 (17.7)	143.2 (16.9)
Protocol violation, No. (%)	7 (6.9)	7 (7.2)
Withdrawn, No. (%)	9 (8.8)	8 (8.2)

IQR, Interquartile range.

*Percentages may be calculated from less than 102 or 97 due to missing data.

treatment, but their data were included in analyses (Table 1). There were 14 protocol violations, the majority the result of too-rapid infusion of the test solution. Three of the 14 were randomized but converted to sinus rhythm before the test

**Figure 2.** Cumulative total percentage of patients achieving a pulse rate of less than 100 beats/min from onset of study solution.

solution was administered, and in 3 further cases no pulse rate or reversion status data were available. Subjects were enrolled at the discretion of the physician treating them in the ED, and the total number and characteristics of patients who were eligible for inclusion in the study but not included are unknown.

Baseline characteristics were similar between the randomized groups, except for duration of symptoms, whether digoxin was given, presence or likelihood of hypomagnesemia, and baseline pulse rate (Table 2). Digoxin was the most commonly coadministered antiarrhythmic drug selected by treating physicians (157 patients [78.9%]). A β-blocker was administered to 20 (10%) patients and verapamil to 6 (3%) patients. For 24 patients, the first dose of antiarrhythmic was administered more than 20 minutes after the study solution (10 having received magnesium sulfate, 14 placebo). For 11 patients, no antiarrhythmic, other than the study solution, was recorded as being administered (7 having received magnesium sulfate and 4 placebo). For 9 patients (2 having received magnesium sulfate and 7 placebo), multiple doses of antiarrhythmic were administered during the study.

Main Results

Patients who received magnesium sulfate were more likely to achieve a pulse rate of less than 100 beats/min during the study period (63 [65%] of 97 versus 32 [34%] of 93; RR 1.89; 95% CI 1.38 to 2.59; $P<.0001$) (Figures 2 and 3). Adjusting for baseline differences between the 2 groups for duration of symptoms and baseline pulse rate made little difference to the result (adjusted RR 1.74; 95% CI 1.25 to 2.41; $P=.001$).

Subjects in the magnesium sulfate group were more likely than those in the placebo group to convert to sinus rhythm (25 [27%] of 94 versus 11 [12%] of 91; RR 2.20; 95% CI 1.15 to 4.21; $P=.01$) (Figure 4). Adjustment for baseline differences in duration of symptoms, hypomagnesemia, and baseline pulse rate made little difference to the result (adjusted RR 2.05; 95% CI 1.05 to 4.03; $P=.04$).

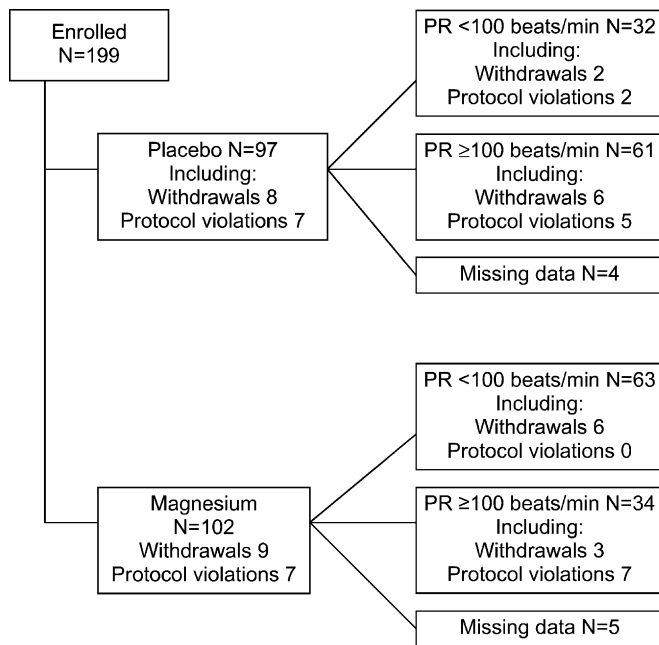


Figure 3. Flow diagram of patients achieving a pulse rate less than 100 beats/min at any time during the study. PR, Pulse rate.

Subjects in the magnesium sulfate group were more likely than those in the placebo group to have an adverse event (14 [15%] of 95 versus 5 [5%] of 92; RR 2.71; 95% CI 1.02 to 7.23; $P=.04$). The majority of adverse events were considered minor, with flushing the most frequently reported (Table 3).

There was a statistically significant reduction in mean pulse rate in the magnesium sulfate group relative to placebo at points 30 through 150 minutes on the unadjusted analysis and the analysis adjusting for duration of symptoms, digoxin given, and hypomagnesemia (Figure 5). However, our predetermined criteria for clinical significance of a mean pulse rate of greater than or equal to 15 beats/min difference between the groups was not achieved, although it did lie within the CIs at points 120 and 150 minutes (Table 4).

LIMITATIONS

The fact that we compared magnesium sulfate to placebo in addition to any other agents selected at the discretion of the treating physician as opposed to using standardized additional therapy might be viewed as a limitation. A majority of patients enrolled in the study received digoxin for rate control. Other drugs commonly used in clinical practice were infrequently used in the study, and some not at all. Subgroup analysis to draw conclusions about the utility of magnesium sulfate specifically with these other agents was therefore impossible.

The study did not examine the effect on pulse rate beyond the 2.5 hours of the study infusion. It is possible that the observed effects were rapidly reversed once the magnesium infusion had ceased.

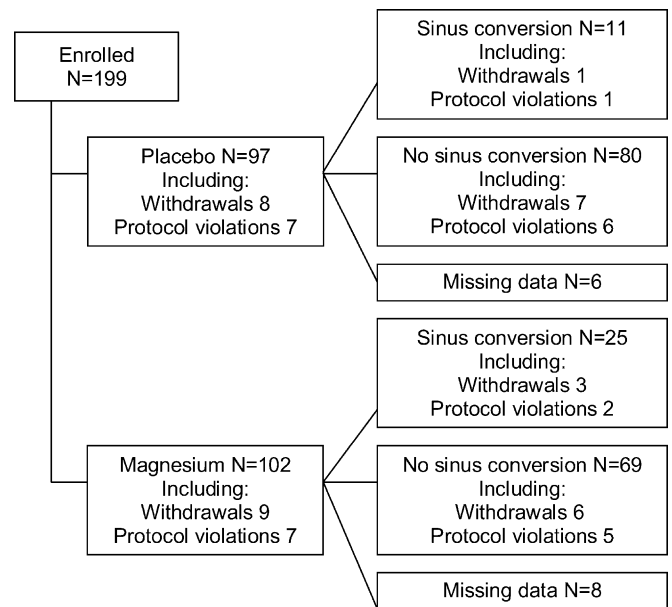


Figure 4. Flow diagram of patients converting to sinus rhythm.

Table 3. Reported adverse effects.

Adverse Effect	Nature	MgSO ₄	Placebo	
Minor	Flushing sensation	6		
	Local pain/irritation	3		
	Nausea		2	
	Abdominal discomfort		2	
	Headache		1	
	Dizziness	1		
	Hypotension (blood pressure >100 mm Hg systolic and not withdrawn)	1		
	Bradycardia (transient, no intervention required)	1		
	Major	Hypotension (blood pressure <100 mm Hg systolic, withdrawn from study, or other intervention)	4	1
		Bradycardia (intervention required)	1	
Total		23 Adverse effects in 21 patients		

The selection of achieving a pulse rate of 100 beats/min and of a relative reduction of 15 beats/min compared with placebo as clinically significant endpoints was somewhat subjective. It could be argued that a rate reduction to 80 or 90 beats/min and a greater relative reduction compared with placebo might be more appropriate. However, we could find little evidence supporting a specific rate within this range and believe the levels chosen are valid.

The total number of patients who were eligible for inclusion in the study is unknown, and there is a possibility of inclusion bias because the enrolled subjects did not represent consecutive patients but were enrolled at the discretion of the treating physician in the ED. It is possible that patients most likely to benefit from magnesium sulfate were somehow selected.

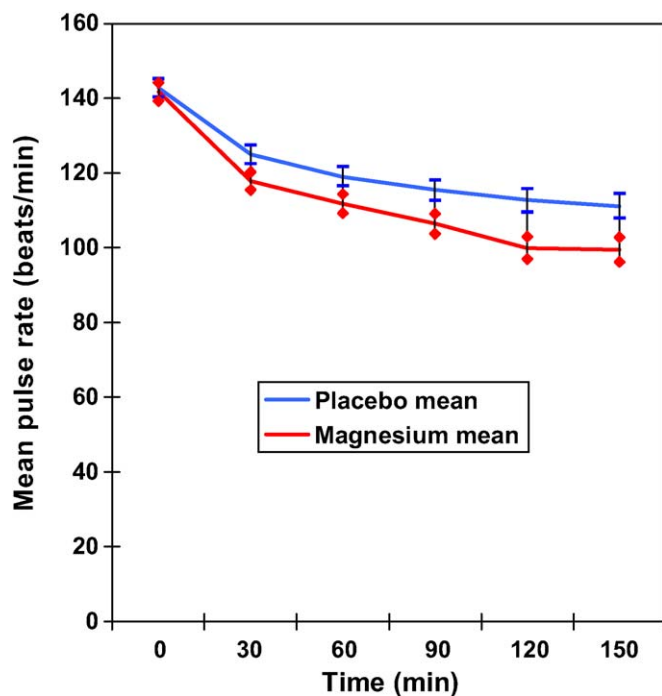


Figure 5. Mean pulse rate (with standard error bars) over time from commencement of the study.

DISCUSSION

Our study represents the largest single trial of the use of magnesium sulfate for ventricular response rate control in atrial fibrillation. We showed that the use of magnesium sulfate solution, in the doses given and when used in conjunction with other agents, results in an absolute increase of 31% of patients achieving a pulse rate of less than 100 beats/min compared with placebo.

We also demonstrated that magnesium sulfate increases the rate of conversion from atrial fibrillation to sinus rhythm when added to standard therapies. This increase in conversion to sinus rhythm is not necessarily desirable because of the risk of embolic events in patients who have longer duration of atrial fibrillation and who are not anticoagulated.

Although we demonstrated that magnesium sulfate produced a statistically significant reduction in ventricular response rates at all measured intervals up to 150 minutes, this did not reach our pretest definition of clinical significance of a relative reduction of 15 beats/min. Although there were more adverse effects in the magnesium sulfate-treated group, the majority of these were minor. There were, however, 5 patients in the magnesium sulfate group who had bradycardia or hypotension requiring treatment or cessation of the study solution, which emphasizes that close monitoring of patients receiving magnesium sulfate is essential.

Determining the degree of left ventricular dysfunction clinically at presentation in the ED to select an appropriate rate-reducing agent can be difficult. The majority of patients who present to the ED with atrial fibrillation are elderly, many have

Table 4. Mean pulse rate differences (beats/min) between treatment groups, placebo versus magnesium sulfate, adjusted repeated-measures analysis.

Time Point	Mean Pulse Rate Difference, Beats/Min (95% CI)
Change at 30 min	-5.94 (-11.66 to -0.23)
Change at 60 min	-6.06 (-12.08 to -0.05)
Change at 90 min	-7.79 (-14.54 to -1.05)
Change at 120 min	-11.61 (-19.01 to -4.14)
Change at 150 min	-10.58 (-18.87 to -2.30)

underlying heart disease,¹ and it is often difficult to rapidly confirm the reliability of a medical history in this setting. Published reviews of the management of atrial fibrillation have examined the evidence for the use of the pharmacologic agents commonly used to treat rapid atrial fibrillation.^{4,6,7} Broad consensus is seen in the recommendations of these reviews insofar as they recommend that calcium-channel blockers and β -blockers be considered first-line agents for rate control in patients with preserved left ventricular function, but caution their use in the presence of poor left ventricular function. We believe that many emergency physicians use digoxin despite its slow onset of effect because of uncertainty of their patients' underlying cardiac status. Although magnesium sulfate has a high therapeutic-to-toxic ratio and is relatively devoid of negative inotropic effects, we did not specifically investigate this group of patients, and the 5% incidence of hypotension represents a cause of some concern.

In Retrospect

Reliance on the clinical staff treating the patient to record data proved less reliable than hoped. Having a dedicated study data recorder might have resulted in more complete results. To simplify interpretation, the effects of magnesium sulfate in conjunction with other specific antiarrhythmics would be better examined separately.

In summary, we have demonstrated that an infusion of magnesium sulfate marginally improves early ventricular response rate control and increases rates of conversion to sinus rhythm in patients in rapid atrial fibrillation when added to usual treatment. A small risk of significant hypotension and bradycardia accompanies these effects.

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