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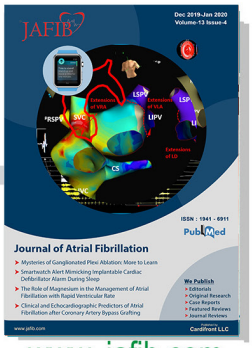

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The Role of Magnesium in the Management of Atrial Fibrillation with Rapid Ventricular Rate

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Abstract

Background: Atrial fibrillation is currently managed with a variety of rate controlling and antiarrhythmic agents. Often, magnesium is used as adjunctive therapy, however, the benefit it provides in managing Afib with RVR has been debated. This study aimed to determine if IV MgSO4 administration in conjunction with standard therapy provides any synergistic effect in acute and prolonged control of Afib with RVR.

Methods: This was a retrospective study involving ninety patients with episodes of Afib with RVR during their hospitalization. The treatment group included those that had received magnesium (n=32) along with standard management and the control group (n=58) received only standard management. Heart rates at different time intervals were collected. Dose dependent effects of IV MgSO4 on heart rates were also evaluated.

Results: Patients that received magnesium had a lower mean heart rate (85 BPM versus 96 BPM, P<0.05) 24 hours after onset of the episode. Also, in the last 16 hours of observation, it appeared that administration of higher levels of magnesium resulted in statistically lower heart rates. In the group of patients that received 2 grams of magnesium, the mean heart rate at 8 hours was 103.4 beats/min and 84.8 beats/min at 24 hours (p<0.01). This same trend was not seen in patients that received 1 gram of magnesium or in the control group.

Conclusion: Overall, the use of IV MgSO4 as an adjunctive treatment permitted normalization of the heart rate progressively that continued to at least 24 hours.

Introduction

Atrial Fibrillation (Afib) is the most commonly managed heart arrhythmia[1,2]. It is classified as a supraventricular arrhythmia which involves desynchronized atrial activation resulting in poor mechanical function. Characteristic identification of this arrhythmia on electrocardiogram (ECG) is highlighted by the lack of consistent P waves. Dependent on the condition of the AV node itself and its response to vagal and sympathetic tones, this rhythm can lead to a rapid ventricular response (RVR). Afib with RVR shortens ventricular filling time, increases myocardial oxygen demands and can potentially induce tachycardia cardiomyopathy[3].

A variety of rate controlling agents and antiarrhythmic agents including ß-blockers, calcium channel blockers, digoxin, and amiodarone are commonly used to control Afib with RVR[4]. Often, magnesium is seen being used as an adjunctive therapy, however, the benefit it provides in managing Afib with RVR has been debated. The rationale behind magnesium use is based on the physiological and pharmacological properties of the element[5]. Magnesium directly acts on myocardial potassium channels and has voltage dependent and indirect effects on sodium and calcium channels. Additionally, it can act as a calcium antagonist capable of inhibiting L-Type calcium current channels in myocardial cells. In theory, this property can lead to decreased frequency of sinus node depolarization and a prolonged refractory period of the AV node[6].

Evidence has emerged over the years supporting magnesium supplementation when trying to prevent or treat arrhythmias[6-9]. A meta-analysis by Onalen et al indicated that intravenous magnesium sulfate (IV MgSO4) provides a synergistic effect with standard rate controlling agents in acute management of Afib with RVR[10]. As a complement to rate control, a meta-analysis of 5 randomized trials (n=380) demonstrated that magnesium administration led to improved heart rates by a factor of 3 compared to placebo[11]. However, there are some studies that demonstrate that magnesium use does not provide any benefit in managing Afib with RVR[12-14]. For example, a meta-analysis of 10 randomized controlled trials by Kwok et al demonstrated that supplementing digoxin or ibutilide with IV MgSO4 provided no benefit in controlling Afib with RVR[13]. In addition, Lancaster et al., observed higher serum potassium and magnesium levels being associated with increased risk of postoperative atrial fibrillation[14].

This study aimed to determine whether IV MgSO4 provides a synergistic affect when combined with rate controlling or anti arrhythmic agents in achieving acute and prolonged control of episodes

Key Words
Atrial Fibrillation, Magnesium

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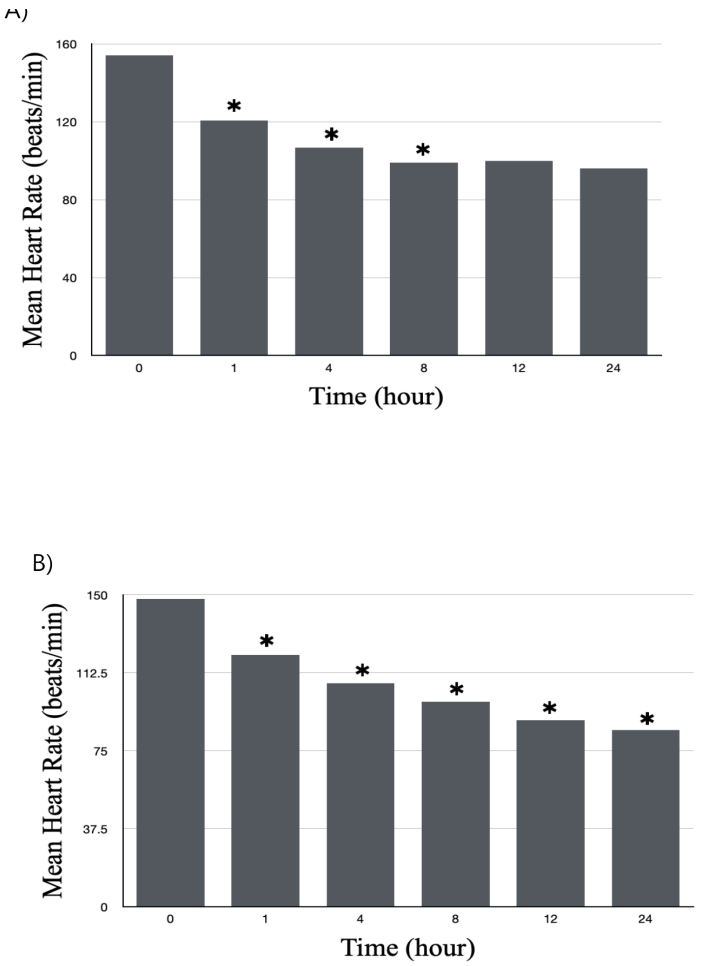

Figure 1: **A) Mean heart rate in relation to time for patients in the control group; patients that did not receive magnesium. B) Mean heart rate in relation to time in patients that received magnesium. *P<0.05**

of acute atrial fibrillation with rapid ventricular rate.

Methods

This was a retrospective study conducted at SUNY Upstate Medical University, Syracuse, NY. The patients selected for this study were those who had episodes of atrial fibrillation with RVR during their inpatient admission. A total of 90 patients were included for the study and data was collected through chart review. Each patient that was found to have Afib with RVR had a rapid response team come in to address the clinical situation. Heart rates for these patients were collected at onset of the episode, and subsequently at 1 hour, 4 hours, 8 hours, 12 hours and 24 hours after onset of the episode.

Patients were divided into two groups: those that received intravenous magnesium during the episode of atrial fibrillation with RVR and those that did not. Patients were given magnesium as per the preference of the physician in charge of care at the time. The patients that did not receive magnesium served as the control group for the study. Additional data gathered included whether patients in both groups were given any nodal blocking agents or antiarrhythmic agents. To determine whether the effect of magnesium is dose dependent, the heart rates of patients that received 1 gram of magnesium were compared to those that received 2 grams of magnesium.

Statistical analysis

The mean heart rate at onset of atrial fibrillation with RVR, at 1 hour, 4 hours, 8 hours, 12 hours and 24 hours were calculated. Student's T test was used to compare the means in group of patients that received magnesium to those in the control group. The decrease in heart rate from one-time interval to another within each group was also evaluated using paired student's T test analysis. The proportional receipt of beta blockers, diltiazem, digoxin and amiodarone among these two groups was calculated and their frequency of use was compared using the Chi-square method. The group of patients that received magnesium was further subdivided into groups based on the amount of magnesium given. One group was created of those patients that had received 1 gram of magnesium while another group was created of those that had received 2 grams of magnesium. The mean heart rates after magnesium administration in each group at onset of atrial fibrillation with RVR, at 1 hour, 4 hours, 8 hours, 12 hours and 24 hours were compared. A multiple linear regression analysis was also performed. A P value <0.05 was considered significant.

Results

Characteristics of Patients Enrolled in the Study

A total of 90 patients were enrolled in this study; of these, 32 patients had received magnesium during episodes of atrial fibrillation with RVR while 58 patients did not.

Patient baseline characteristics were similar in both groups (Table 1). A beta blocker was administered to 25 (78%) patients that

Table 1: Demographic and Clinical Characteristics of Patients

	Control (n=58)	Magnesium (n=32)
Age (years), median, SD	68 + 11.2	71 + 9.0
Sex		
Male	36 (53%)	19 (59%)
Female	32 (47%)	13 (41%)
History of heart disease No. (%)	26 (38%)	13 (41%)
Mean Estimated GFR (ml/min/1.73m^2)	43.5*	51†
Paroxysmal atrial fibrillation	19 (33%)	11 (34%)
Chronic atrial fibrillation	19 (33%)	7 (22%)
Valvular atrial fibrillation	2 (3.6%) **	1 (3.6%) ††
Average left atrial diameter (cm)	3.71**	3.85††
No prior history of atrial fibrillation	25 (43%)	18 (56%)
Diuretics No. (%)	16 (28%)	8 (25%)
Mean Serum magnesium (mg/dl)	1.79	1.8
Beta blockers No. (%)	40 (69%)	25 (78%)
Calcium channel blocker No. (%)	23 (40%)	7 (22%)
Digoxin No. (%)	4 (7%)	2 (6%)
Amiodarone No. (%)	3 (5%)	3 (9%)
Patients with repeat episodes of atrial fibrillation with RVR No. (%)	15 (26%)	7 (22%)

SD, Standard Deviation
*14 patients were not included in this calculation as they were above 80 years of age. GFR was estimated using the CKD-EPI equation which may not provide accurate assessments in patients greater than 80 years of age.
†7 patients were not included in this calculation as they were above 80 years of age.
**3 patients were not included as they did not have any cardiac imaging.
††4 patients were not included as they did not have any cardiac imaging.

Table 2: Mean heart rate in relation to time in patients that received magnesium compared to those that did not.

Time interval (hour)	Mean Heart Rate in the Control Group, beats/min (SEM)	Mean Heart Rate in the Magnesium group, beats/min (SEM)	Significance
0	154.21 (+2.54)	148.19 (+3.29)	NS
1	120.57 (+3.31)	121.23 (+3.93)	NS
4	106.86 (+3.24)	107.45 (+4.45)	NS
8	99.13 (+2.74)	98.72 (+4.55)	NS
12	99.87 (+2.94)	89.66 (+5.25)	NS
24	96.00 (+2.92)	85.03 (+4.44)	p<0.05

NS, no significant difference between the two groups

received magnesium and to 40 (69%) patients that did not receive any magnesium. In addition, 7 (22%) patients that received magnesium and 23 (40%) patients that did not receive magnesium were given calcium channel blockers. Digoxin and amiodarone were used less frequently, regardless, the frequency of use of these medications was comparable in both groups. Overall, when comparing the two groups of patients, there was no significant difference in the number of patients who received beta-blockers, calcium channel blockers, digoxin, or amiodarone.

Furthermore, the mean serum magnesium level was observed to be similar in both group of patients. Specifically, the group of patients that was given magnesium had a mean serum magnesium level of 1.8 mg/dl prior to the episode of Afib with RVR, while the control group was noted to have a mean of 1.79 mg/dl.

Lastly, the mean estimated GFR in the group of patients that received magnesium was noted to be 51 ml/ min/ 1.73m2, compared to a mean of 43.5 ml/min/1.73m2 in the control group. It should be noted that 7 patients from the group treated with magnesium and 14 patients from the control group were excluded from the calculation above as they were above 80 years of age.

Main results

Patients that received magnesium had a lower mean heart rate after 24 hours of the onset of the atrial fibrillation with RVR episode compared to the patients that did not receive magnesium. The average heart rate 24 hours after the episode in patients that received magnesium was 85 beats/min, whereas the average heart rate for patients that did not receive magnesium was 96 beats/min (P<0.05) (Table 2).

The control group demonstrated a statistically significant progressive decrease in the heart rates between onset of the episode to 1 hour after episode (p<0.001), 1 hour to 4 hours after episode (p<0.001) and 4 hours to 8 hours after episode (p<0.001) (Figure 1A). However, the decrease in heart rate between 8 hours to 12 hours and 12 hours to 24 hours was not statistically significant. On the other hand, the magnesium group showed similar trends as there were also significantly lower heart rates at the intervals of 1 hour, 4 hours and 8 hours after the onset of episode (Figure 1B). Unlike the control group however, the magnesium group continued to demonstrate a statistically significant decline in the heart rate beyond 8 hours. The average heart rate at 12 hours was 89.66 beats/min and was statistically lower than the average heart rate of 98.72 beats/min at 8 hours (p<0.05). Also, at 24 hours, the average heart rate was 85.03 beats/min and was lower than the average heart rate of 89.66 beats/min at 12 hours (p<0.05). In brief, it appears that that the addition of magnesium permits normalization of the cardiac rate in a progressive way that continues up to 24 hours.

A deeper comparison was done on the 34 patients that received magnesium; 17 patients were given 1 gram of magnesium and 17 were given 2 grams of magnesium. Upon comparison, it was noted that the mean heart rate after 24 hours in the low magnesium group was 87.1 beats/min, whereas in the high magnesium group, the mean heart rate at 24 hours was 84.8 beats/min; this difference did not achieve statistical significance (Table 3). However, in the last 16 hours of observation, between 8 hours of the onset of the episode and 24 hours, it appeared that administering higher levels of magnesium had an advantage (Figure 2). The mean heart rate in the control group and the low magnesium group at 8 hours was 99.2 beats/min and 94.1 beats/min, respectively. At 24 hours, the mean heart decreased to 96 beats/min in the control group and to 87.1 beats/min the in low magnesium group, and these decreases in heart rate were not statistically significant. On the other hand, in the group of patients that received 2 gm of magnesium, the mean heart rate at 8 hours was 103.4 beats/min and 84.8 beats/min at 24 hours (p<0.01). In brief, the mean heart rate decreased by 3 beats/min in patients that did not receive any magnesium, 7 beats/min in those that received 1 gram of magnesium and 18.2 beats/min in those that received 2 grams of magnesium between 8 and 24 hours after onset of Afib with RVR.

As this study involved the use of other rate controlling agents in association with magnesium, a multiple linear regression analysis was also performed to determine whether magnesium has an independent effect on rate response. An analysis including all rate controlling agents and magnesium at 24 hours resulted in R=0.29 (p<0.05). A backward stepwise regression analysis, removing the effect of one rate controlling agent at a time, concluded that magnesium alone was still important in determining the heart rate (R=0.22, p<0.05). Furthermore, it was determined that the effect magnesium had on rate response is dependent on the amount of magnesium administered. A significant regression equation was found (95.6-0.77(milliequivalents of magnesium)) with a R of 0.27 (p<0.05). The heart rate decreased by

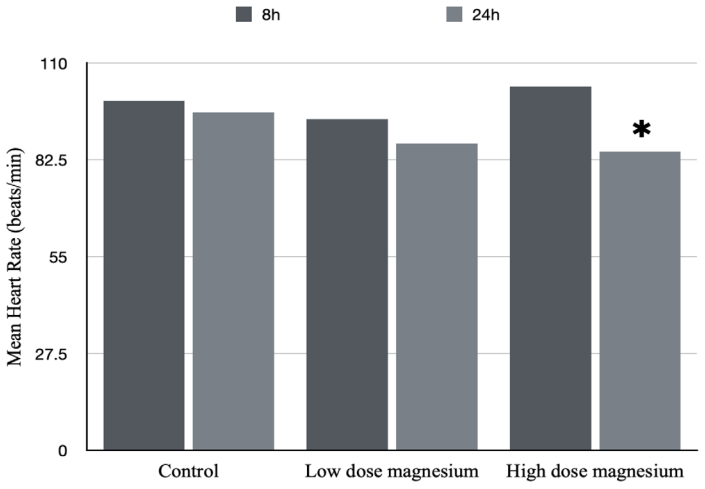

Figure 2: Mean heart rates in the control group, the low dose magnesium group, and the high dose magnesium group at 8 hours and 24 hours after onset of Afib with RVR. *P<0.01

Table 3: Mean heart rate over time in patients that received 1 gram of magnesium (low dose magnesium group) and 2 grams of magnesium (high dose magnesium group).

Time interval (hour)	Mean Heart Rate in the Low Magnesium Group, beats/min (SEM)	Mean Heart Rate in the High Magnesium Group, beats/min (SEM)	Significance
0	147.5 (+4.0)	147.4 (+5.0)	NS
1	117.4 (+5.4)	124.5 (+5.5)	NS
4	104.2 (+4.7)	111.7 (+7.6)	NS
8	94.1 (+5.3)	103.4 (+7.2)	NS
12	91.1 (+8.5)	90.7 (+5.9)	NS
24	87.1 (+7.0)	84.8 (+5.2)	NS

NS, no significant difference between the two groups

0.77 beats/min for each milliequivalent (mEq) of magnesium used;of note, 8 mEq of magnesium is equivalent to 1 gram of magnesium. In brief, the infusion of magnesium leads to a predictable decrease in heart rate and this response is independent of the other medications butis dependent on the dosage of magnesium used.

Lastly, the number of repeat episodes of atrial fibrillation during the patient's hospitalization were also analyzed. In the group of patients that received magnesium, 7 (22%) patients had repeat episodes before discharge, compared to 15 (26%) patients in the control group.

Discussion

Atrial fibrillation has become a major public health burden and its prevalence is projected to continuously increase[18]. The associated costs continue to strain a struggling healthcare system with increasing needs in medications, management of the extensive complications such as heart failure and stroke, and the significant morbidity and mortality caused simply due to the prevalence of the condition. Additional options for management of this arrhythmia may help with the overall burden, and magnesium, being a drug that is easily available and uncostly, may provide some support.

Magnesium is viewed to act as a calcium channel blocker; hence, it should theoretically function as an AV nodal blocker. However, there have been mixed results regarding the benefit of magnesium use in helping control atrial fibrillation with RVR in prior studies. Most of these studies have also been limited to post-cardiac surgery patients, limiting the generalizability of their findings[14-17]. With such contrasting studies, electrolyte supplementation for management of atrial fibrillation remains conflicting in both medical and surgical wards.

The patients included in this study were not post-surgical, rather patients from all wards within the hospital that developed acute episodes of atrial fibrillation with rapid ventricular rate. The results of this study indicate that magnesium may play an important role in helping maintain a lower heart rate for longer periods of time. Also, it seems that magnesium may help decrease heart rates at a faster rate. In the different groups that were analyzed, when magnesium was given, there was a greater decrease in heart rates 1 hour from the onset of the episode and onwards. In addition, it should be noted that the mean serum magnesium levels prior to the onset of the episode, were within normal range for both the control group and the group of patients that received magnesium. Interestingly, the patients that did receive magnesium still achieved a statistically significant lower mean heart rate after 24 hours of the onset of the atrial fibrillation with RVR episode compared to control group despite normal serum magnesium levels. This study also indicates that there is a possibility that the impact of magnesium may be dose dependent as the rate of decrease in heart rate was noted to be higher in patients that were given a higher dose of magnesium.

Limitations

There were limiting factors that played a role in this study. For instance, patients had received other drugs during their episodes of Afib with RVR; some received rate controlling agents, while others received antiarrhythmic agents. The dosage administered for these other drugs may have also varied in the different groups. To further add to the limitations, some patients that had repeat episodes of Afib with RVR, were administered additional medications and this may have hindered the overall response to magnesium administration.

Conclusions

Overall, our results seem to indicate that magnesium has a role to play in the management of atrial fibrillation with RVR. Larger randomized studies are still needed to further support and clarify its role. Additional areas for future studies that may be worth looking into include determining the impact of magnesium when combined with specific AV nodal blockers or antiarrhythmics. Last but not least, further studies are needed to determine effective dosages of magnesium and to help determine whether there are any adverse effects of high dose magnesium use in such patients.

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