CME Information: Low-dose Magnesium Sulfate Versus High Dose in the Early Management of Rapid Atrial Fibrillation: Randomized Controlled Double-blind Study (LOMAGHI Study)

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CME Low-dose Magnesium Sulfate Versus High Dose in the Early Management of Rapid Atrial Fibrillation: Randomized Controlled Double-blind Study (LOMAGHI Study)

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ABSTRACT

Objectives: We aim to determine the benefit of two different doses magnesium sulfate ($MgSO_4$) compared to placebo in rate control of rapid atrial fibrillation (AF) managed in the emergency department (ED).

Methods: We undertook a randomized, controlled, double-blind clinical trial in three university hospital EDs between August 2009 and December 2014. Patients > 18 years with rapid AF (>120 beats/min) were enrolled and randomized to 9 g of intravenous $MgSO_4$ (high-dose group, *n* = 153), 4.5 g of intravenous $MgSO_4$ (low-dose group, *n* = 148), or serum saline infusion (placebo group, *n* = 149), given in addition to atrioventricular (AV) nodal blocking agents. The primary outcome was the reduction of baseline ventricular rate (VR) to 90 beats/min or less or reduction of VR by 20% or greater from baseline (therapeutic response). Secondary outcome included resolution time (defined as the elapsed time from start of treatment to therapeutic response), sinus rhythm conversion rate, and adverse events within the first 24 hours.

Results: At 4 hours, therapeutic response rate was higher in low- and high-$MgSO_4$ groups compared to placebo group; the absolute differences were, respectively, 20.5% (risk ratio [RR] = 2.31, 95% confidence interval [CI] = 1.45–3.69) and +15.8% (RR = 1.89, 95% CI = 1.20–2.99). At 24 hours, compared to placebo group, therapeutic response difference was +14.1% (RR = 9.74, 95% CI = 2.87–17.05) with low-dose $MgSO_4$ and +10.3% (RR = 3.22, 95% CI = 1.45–7.17) with high-dose $MgSO_4$. The lowest resolution time was observed in the low-dose $MgSO_4$ group (5.2 ± 2 hours) compared to 6.1 ± 1.9 hours in the high-dose $MgSO_4$ group and 8.4 ± 2.5 hours in the placebo group. Rhythm control rate at 24 hours was significantly higher in the low-dose $MgSO_4$ group (22.9%) compared to the high-dose $MgSO_4$ group (13.0%, p = 0.03) and the placebo group (10.7%). Adverse effects were minor and significantly more frequent with high-dose $MgSO_4$.

Conclusions: Intravenous $MgSO_4$ appears to have a synergistic effect when combined with other AV nodal blockers resulting in improved rate control. Similar efficacy was observed with 4.5 and 9 g of $MgSO_4$ but a dose of 9 g was associated with more side effects.

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Atrial fibrillation (AF) is the most frequent cardiac arrhythmia and its incidence increases with age.[1–3] For the management of AF in emergency department (ED), the physician must decrease the ventricular rate (VR) with or without restoration of sinus rhythm. Several drugs are recommended such as calcium channel blockers, beta-blockers, and digoxin, but the ultimate one is unknown.[4] The use of magnesium as an alternative drug or in addition to usual care has been previously investigated.[5–7] The rationale for its use was based on its physiologic and pharmacologic properties to decrease the frequency of sinus node depolarization, to prolong the refractory period of the atrioventricular (AV) node. It acts as a calcium antagonist by inhibiting L-type calcium current in heart cells.[8,9] If not treated promptly, rapid AF can be associated with significant complications including congestive heart failure, hypotension, and cardiac ischemia. Intravenous magnesium is safe and cheap and may have a synergistic effect with usual antiarrhythmic drugs. A previously published meta-analysis conducted by Onalan et al.[10] suggested that intravenous magnesium compared to placebo or standard rate control agents is an effective and safe strategy for the acute management of rapid AF. However, most of the included trials had small sample size or were performed in post–cardiac surgery patients.[11,12] In addition, the dose of magnesium used in previous studies varied widely, which could influence its efficacy as AF rate control may be dose dependent.[6,13–15] We are unaware of any study comparing two different doses of intravenous magnesium on the outcome of VR of AF. Accordingly, a definitive conclusion regarding the benefit of $MgSO_4$ in the rapid management of rapid AF is still uncertain and available results could not be extrapolated to patients treated in the ED.

We hypothesize that intravenous magnesium may have synergistic action with currently used rate-control agents in the treatment of patients with rapid AF. In addition, this action would depend on the dose of magnesium. The aim of this study was to investigate the efficacy and tolerance of magnesium sulfate ($MgSO_4$), administered at two different doses, to reduce VR in patients admitted to ED with rapid AF.

METHODS

Study Design and Setting

This is a prospective randomized, controlled, double-blind study carried out in three EDs of tertiary referral Tunisian hospitals with annual census of 90,000 to 110,000 adult patients. There are a total of 14 senior doctors and 36 residents working in the three participating EDs. Patients were enrolled between August 2009and December 2014. The trial was registered on ClinicalTrials.gov registry (NCT00965874) and approved by the human research ethics committees of the participating centers. The study was not supported by any funding organization.

Selection of Participants

Consecutive patients over 18 years old admitted to the ED for rapid AF (>120 beats/min) were eligible for enrollment. Patients were ineligible in presence of arterial hypotension (systolic arterial pressure < 90 mm Hg) if they had impaired consciousness, renal failure (serum creatinine > 180 μmol/L), wide-complex ventricular response, or contraindication to $MgSO_4$. We also excluded patients with acute myocardial infarction, acute congestive heart failure (New York Heart Association functional class 3 or 4), sick sinus syndrome, or rhythm other than AF. Informed consent was obtained from the patients or their relatives. All the treating physicians working in the three participating EDs have the prerogative not to enroll a patient if they deemed the individual too unstable for the trial.

Methods and Measurements

On arrival in the emergency department, all patients were administered oxygen as needed and an intravenous line inserted. A detailed history was taken including associated illness details and clinical examination was performed. Any medications received by the patient within 24 hours of their visit were recorded. After initial assessment, standard laboratory tests were performed and baseline serum magnesium was measured. Patients were then randomized to receive one of three treatments: 4.5 g intravenous $MgSO_4$ in 100 mL of normal saline (low-dose group), 9 g intravenous $MgSO_4$ in 100 mL of normal saline (high-dose group), or 100 mL of intravenous normal saline (placebo group). Protocol treatments were administered within 30 minutes. Study packs were prepared by the pharmacy department of Fattouma Bourguiba University Hospital. Each contained vials of experimental or placebo treatment and patient identification code. Randomization using random-number tables was achieved by blocks of three packs (one for each arm) by a pharmacist not involved with patient enrolment, data collection, or data analysis. The

$MgSO_4$ and placebo solutions were identical in appearance. Physicians and patients were both blinded to the randomization, which was done by random number. Physicians did not wait for the serum magnesium results before they started the protocol. All patients were monitored with continuous electrocardiographic monitoring. Blood pressure, respiratory rate, and pulse arterial oxygen saturation were recorded every hour. The same methods were used to record the VR data. Additional AV nodal blocking agents given at the same time as $MgSO_4$ were left at the discretion of the treating physicians and not mandated by the study protocol. In the three participant EDs, usual-care antiarrhythmics were not given, nor was electrical cardioversion done unless AF onset was diagnosed with certainty as a recent event (<48 hours). Any adverse effects noted by the patient or physicians were recorded on case report forms. Common adverse effects including flushing, nausea, vomiting, headache, dizziness, and hypotension were specifically sought and recorded. Patients were managed in the ED and data collected until 24 hours after randomization. If the patient was discharged or admitted prior to the 24 hours, data were no longer collected and the patient was excluded from the study. At this point, if not already undertaken, a final decision regarding hospital admission or home discharge was made. The decision to discharge the patient was taken by the attending emergency physician.

Outcome Measures

Primary endpoints of the study were VR control within the first 4 hours defined as reduction of baseline VR to 90 beats/min or less or reduction of VR by at least 20% from baseline (therapeutic response). Only patients who maintained these changes until the end of the protocol were considered to have achieved therapeutic response. Secondary endpoints included elapsed time from start of treatment to therapeutic response (resolution time), sinus rhythm conversion rate, and adverse events defined as major if they required treatment discontinuation or caused death.

Data Analysis

Analysis was undertaken on an intention-to-treat basis. Patients were removed from analysis after randomization only if recruitment was an unequivocal protocol violation (i.e., no consent had been recorded or if they had previously been recruited) or if the patient withdrew from the trial prior to any treatments having been administered. In all other cases, participants were analyzed in accordance with the groups they were allocated to regardless of whether or not they actually completed their allocated treatment. The study was designed to test the superiority of adjunctive low-dose $MgSO_4$ over placebo group. We estimated that a sample size on the basis on the following assumptions: with 145 patients on control treatment and 145 patients on $MgSO_4$, there will be a 80% chance of detecting a significant difference at a one-sided 0.05 significance level. This assumes that the response rate of control treatment is 0.5 and the response rate of $MgSO_4$ treatment is 0.65. The sample size was inflated by 3% to account for missing data, attrition, and protocol violations. Patient characteristics and outcome measures were reported as means with standard deviations (SDs) or medians and 95% confidence intervals (CIs), as appropriate. Descriptive and inferential statistical analyses (Kruskal-Wallis, Mann-Whitney rank sum, or Friedman tests for continuous variables; Fisher's exact or chi-square tests for categorical data) were performed as appropriate. Pairwise comparisons were used in our analysis with Bonferroni adjustment. Nonparametric statistical techniques were used for the continuous data, as these data were not normally distributed. The risk ratio (RR) and 95% CI were calculated. Data obtained in this study have been recorded and analyzed with the SPSS computer software (Version 17). A p-value of <0.05 level was used to determine significant differences.

RESULTS

Characteristics of Study Subjects

A study enrollment flow diagram is displayed in Figure 1. A total of 469 patients underwent randomization; of these, 19 were withdrawn from the study prior to receiving the study medications. Of the 19 withdrawals, 11 patients withdrew consent before treatment, seven patients did not receive study medication because it was not available, and one patient left the ED for a procedure in the cardiology department. A total of 450 patients ultimately received the study medications, 149 in the placebo group, 148 in the low-dose $MgSO_4$ group, and 153 in the high-dose $MgSO_4$ group. Summary demographic and clinical characteristics for patients in the three study groups are presented in Table 1. There were no

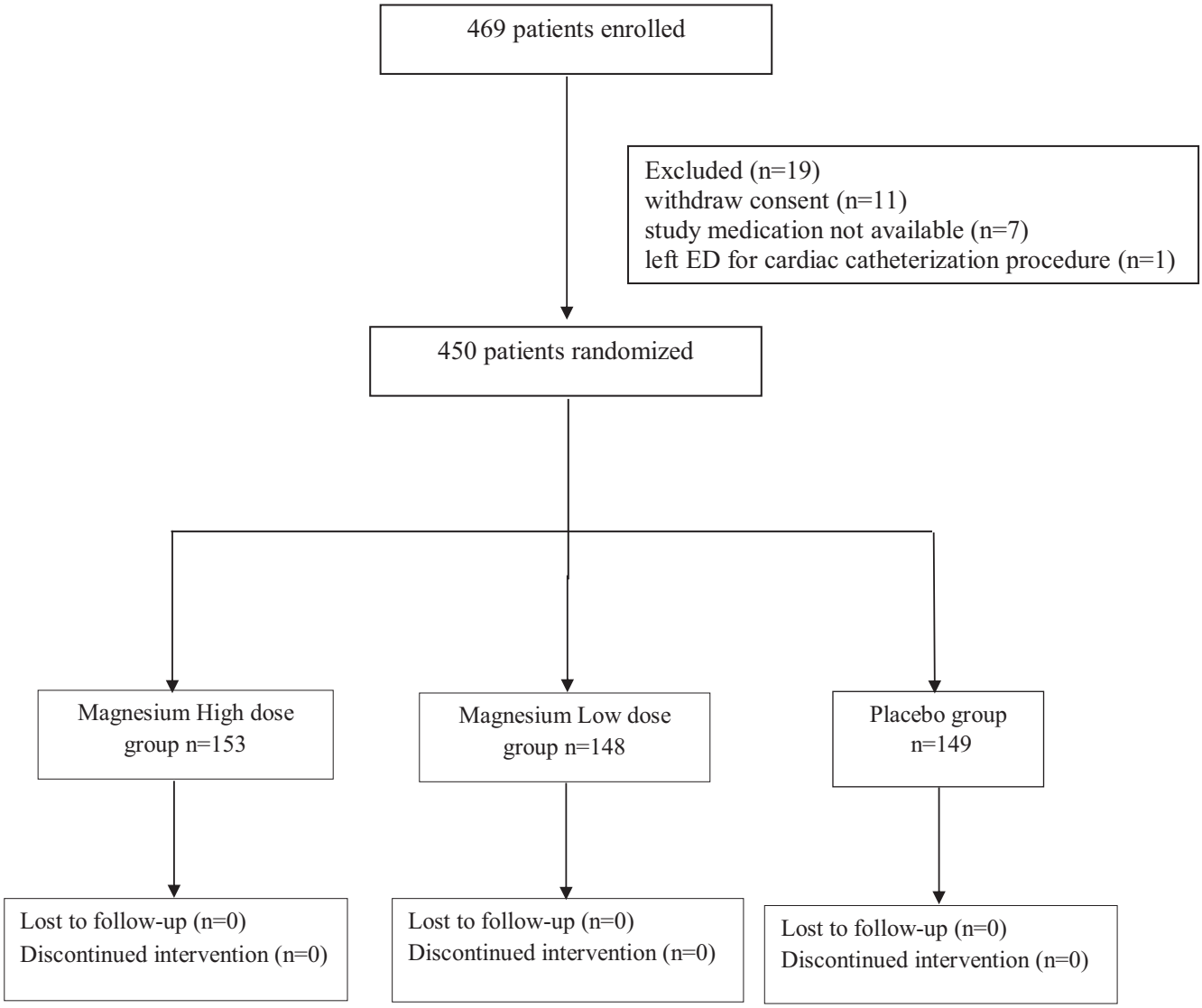

Figure 1. Patients' flow chart.

significant differences among the three treatment groups with respect to baseline demographic or clinical characteristics. Utilization of rate-control medications in the three groups was similar in the three groups. Digoxin was the most used rate-control agent as usual care (47.5%).

Main Results

All groups showed reductions in VR relative to baseline as shown in Figure 2. At each time point there is a similarity in VR decrease from baseline across both $MgSO_4$ study groups, which reached statistical significance at time 4 hours (Figure 2). The superiority of $MgSO_4$ treatment groups compared to placebo group in decreasing HR was significant at 4 hours and persisted during all the protocol period. Therapeutic response rates at 4 and 24 hours are summarized in Table 2. The absolute difference was significant between the low-$MgSO_4$ group and the placebo group (absolute difference = 20.5%, RR = 2.31, 95% CI = 1.45–3.69) and between the high-$MgSO_4$ group and the placebo group (absolute difference = 15.8%, RR = 1.89, 95% CI = 1.20–2.99; Figure 3). The difference was not significant between both $MgSO_4$ groups (absolute difference = 4.7%, RR = 0.81, 95% CI = 0.51–1.30). At 24 hours, the therapeutic response rate was significantly higher in the low-$MgSO_4$ group (absolute difference = 14.1%, RR = 9.74, 95% CI = 2.87–17.05) and in the high-$MgSO_4$ group compared to the placebo group (absolute difference = 10.3%, RR = 3.22, 95% CI = 1.45–7.17; Figure 3). Mean resolution time was 8.4 ± 2.5 hours in the placebo group, 6.1 ± 1.9 hours for the low-dose group, and 5.2 ± 2.0 hours for the high-dose group;

Table 1
Demographic and Clinical Characteristics of Patients at Admission

	Placebo (*n* = 149)	Low-dose Magnesium (*n* = 148)	High-dose Magnesium (*n* = 153)
Age (years)	66.7 ± 12.3	66.1 ± 13.3	68.6 ± 13.7
Sex female	63	60	58
Hypertension	75 (50)	71 (47)	74 (49)
Diabetes	33 (21)	32 (21)	40 (27)
AF	84 (56)	88 (59)	82 (55)
Chronic heart failure	32 (21)	30 (20)	41 (27)
Stroke	9 (6)	10 (6.7)	13 (8.7)
The initial ED triage vitals			
Systolic blood pressure (mm Hg)	135 ± 28	136 ± 28	132 ± 33
Diastolic blood pressure (mm Hg)	84 ± 20	83 ± 19	80 ± 22
Temperature (°C)	37.2 ± 0.1	37.1 ± 0.4	37.0 ± 0.3
Heart rate (beats/min)	136 ± 21	138 ± 19	137 ± 15
Respiratory rate (breaths/min	20 ± 12	20 ± 5	20 ± 7
Oxygen saturation (%)	95 ± 7	94 ± 5	93 ± 9
Serum potassium (mmol/L)	4.1 ± 0.7	4.2 ± 0.2	4.2 ± 0.4
Serum magnesium mean (mmol/L)	0.99 ± 0.2	0.95 ± 0.24	1.07 ± 0.36
Rate-control agents			
Digoxin	71 (47.7)	75 (50.7)	8 (44.5)
Diltiazem	45 (30.2)	43 (29.0)	51 (33.3)
Beta-blockers	33 (22.1)	30 (20.3)	34 (22.2)

Data are reported as mean ± SD or *n* (%).
AF = atrial fibrillation.

the difference was statistically significant only between the placebo and the $MgSO_4$ groups. Conversion to sinus rhythm at 4 hours was achieved, respectively, in 10 patients from the placebo group (6.7%), in 18 patients from the low-dose group (12.1%), and in 12 patients from the high-dose group (7.8%); the difference was not statistically significant between the three groups. At 24 hours, rhythm control was achieved, respectively, in 16 patients from the placebo group (10.7%), in 34 patients from the low-dose group (22.9%), and in 20 patients from the high-dose group (13.0%). The difference was statistically significant between the low-dose group and the placebo group ($p = 0.005$) and between the low-dose group and the high-dose group ($p = 0.03$). It was not statistically significant between the high-dose group and the placebo group. In a secondary analysis including only patients receiving beta-blockers and calcium channel blockers, the obtained results were not significantly different compared to those found in the overall group. Adverse effects were more frequent in the two $MgSO_4$ groups compared to the placebo group ($p = 0.03$). Subjects in the high-dose group were more likely to have adverse events (21 patients vs. eight in the low-dose group and three in the placebo group [$p = 0.02$]). The most frequent adverse effect was transient flushing reported in 25 patients. The other adverse effects are transient hypotension observed in four patients (two in the high-dose group, one in the low-dose group, and one in the placebo group) and bradycardia observed in three patients, one in each group (Table 3). There was no death reported during the study, and in no patient was the protocol treatment stopped because of an adverse effect.

DISCUSSION

In this study, intravenous $MgSO_4$ appears to have a synergistic effect when combined with other AV nodal blockers resulting in improved rate control. Similar efficacy was observed with the 4.5 and 9 g of $MgSO_4$ but a dose of 9 g was associated with more side effects. Based on our findings, it seems that the logical approach is to combine $MgSO_4$ with usual rate-control agents to obtain efficient and more rapid action.

In the management of AF in ED, the objective is to rapidly decrease VR with or without restoration of sinus rhythm. Several drugs such as calcium channel blockers, beta-blockers, and digoxin are now the standard of care of rapid AF. However, current evidence

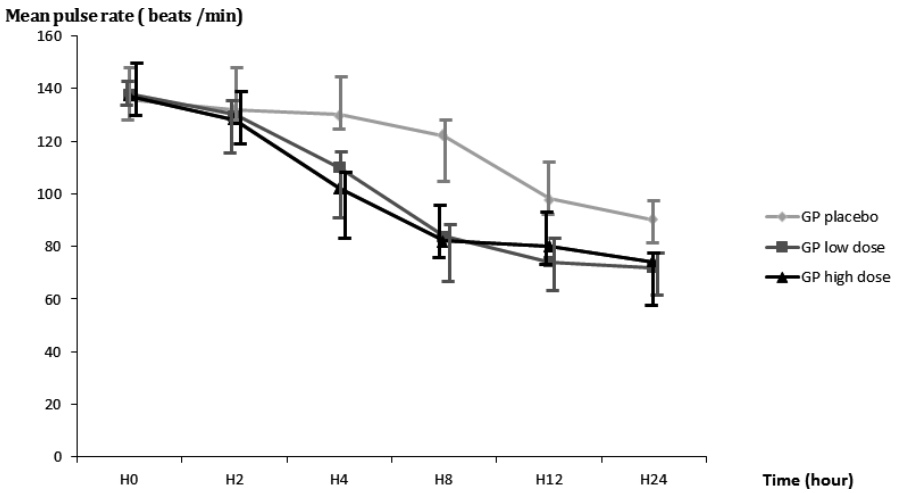

Figure 2. Mean heart rate in relation to time in patients treated with low-dose $MgSO_4$, high-dose $MgSO_4$, and placebo. Repeated heart rate monitoring showed a significant and greater reduction of heart rate in both magnesium groups compared to placebo. *p < 0.05 versus baseline; §p < 0.05 versus placebo. GP = group; $MgSO_4$ = magnesium sulfate.

Table 2
Rate Response from Baseline

	Placebo	Low-dose Magnesium	High-dose Magnesium
4 hours	43.6% (35.7%–51.6%)	64.2% (56.5%–71.9%)*	59.5% (57.1%–67.3%)*
24 hours	83.3% (77.2%–89.2%)	97.9% (95.7%–100%)	94.1% (90.4%–97.8%)

*p ≤ 0.05 versus placebo.

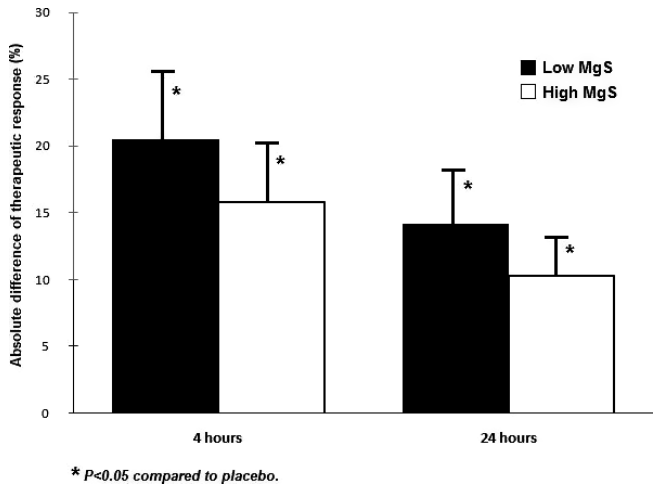

Figure 3. Mean (and standard error) absolute difference of therapeutic response (as reduction of baseline VR to 90 beats/min or less or reduction of VR by at least 20% from baseline) between $MgSO_4$ groups and placebo group 4 and 24 hours after the start of the study protocol. *p < 0.05 compared to placebo. $MgSO_4$ = magnesium sulfate; VR = ventricular rate.

regarding the optimal VR control agents is limited. The benefits of magnesium have been suggested for both rate and rhythm control acting synergistically with antiarrhythmic drugs. However, prior research in this issue has focused predominantly on patients whose arrhythmia followed cardiac or thoracic procedures. It is likely that the etiology and pathology of postoperative AF in such patients differs from that of ED population. Additionally, small population sizes of earlier investigations may have resulted in type 2 statistical errors. So far, there are only four randomized controlled double-blind trials assessing $MgSO_4$ for rate control of rapid AF in non–cardiac surgery patients.[10,16] Only two trials were performed in ED setting. These trials evaluated different alternative drugs and different protocols with regard the dose (4 to 6 g) and the duration (2 to 6 hours). In the largest study including 199 ED patients, Davey and Teubner[6] found that $MgSO_4$ added to standard treatment was more likely than placebo to achieve a pulse rate of less than 100 beats/min (65% vs. 34%) and more likely to convert to sinus rhythm (27% vs. 12%) within the 150 minutes of study protocol. Their results were close to those observed in our study within the 4-hour period with regard to rate control. Importantly, our study showed that superiority of $MgSO_4$ regarding rate and rhythm control continued until 24 hours with a faster onset. Additionally, we demonstrated that using $MgSO_4$ at a dose of 9 g was not associated with greater efficacy on rate control compared to 4.5 g. Perhaps the more limited response

Table 3
Adverse Effects

	Placebo	Low-dose Magnesium	High-dose Magnesium
Flushing	1	6	18*
Hypotension	1	1	2
Bradycardia	1	1	1
Total	3	8	21*

*$p \leq 0.05$ versus placebo and low-dose group.

to a higher dose of magnesium was due to the lower baseline serum magnesium levels but this was not the case in this study. Our findings could also suggest that electrophysiologic effects of magnesium are probably dose related. In fact, Christiansen et al.[17] demonstrated in a dose–response study that 5 mmol intravenous magnesium induced prolongation of AV node conduction but no further prolongation was observed with higher doses. Accordingly, we think that there is no need to use high dose of $MgSO_4$ in rapid AF and that using a dose of 4.5 g as in the present study would be effective. Whether using lower doses would be as effective, the question should be specifically investigated. Although $MgSO_4$ has a relatively wide toxic therapeutic window, the risk of adverse effects is possible[6,18] and potentially more frequent with high $MgSO_4$ dose as shown in our study. Another important question should be discussed. Can magnesium be used as a single first-line agent or as an adjunctive treatment in rapid AF? In a double-blind, placebo-controlled clinical trial, Chu et al.[19] demonstrated that 10 mmol intravenous $MgSO_4$ was not different from placebo for reducing VR or conversion to sinus rhythm at 2 hours posttreatment in ED patients with AF of less than 48 hours' duration. The improved efficacy of $MgSO_4$ when added to standard treatment might also reduce the need to use higher doses of these agents, which is worthwhile regarding their potential adverse effects.

LIMITATIONS

First, we did not define a priori standard treatment that was left to the discretion of the ED physician. Of note, evidence-based treatment of rapid AF is still not well defined and current guidelines are mainly based on results of small studies or expert opinions.[20] It should also be highlighted that most of our patients received one or more of the recommended rate-control agents in this setting with similar repartition in the three protocol groups. Nonetheless, we acknowledge that digoxin is no longer a commonly used acute rate-control agent and was the most commonly used agent in this study, which may impact the generalizability of our results. Second, we excluded patients with hemodynamic instability, those with severe left ventricular dysfunction, and patients with acute AF associated with and/or other cardiovascular comorbidities such as myocardial infarction; such exclusion will limit the generalization of our findings to these patients. Third, we did not conduct data collection in the patients included once they left the ED after the protocol. As such, no information regarding longer-term variables or complications was readily available. Fourth, there is a lack of consensus regarding optimal rate control in acute AF. The 2014 AHA/ACC/HRS guidelines described heart rate control as a resting heart rate of less than 80 bpm for symptomatic management of rapid AF. An outcome goal less than 100 beats/min was used by other studies. In this study, a VR control of 90 beats/min was between these values. Fifth, in this study we did not try to correlate serum magnesium to clinical response. An adequately powered study is needed to establish this correlation and its clinical relevance. Finally, we acknowledge that the choice of $MgSO_4$ doses in this study may lack some objectivity. However, available data indicated that $MgSO_4$ posology differs according to indications and several dosage recommendations have been proposed. In the rate control of AF, $MgSO_4$ was used at a dose ranging from 1.2 to 10 g. The usual dose seems between 4 and 5 g. Based on these findings, we chose 4.5 g as the reference dose and 9 g as the high dose.

CONCLUSIONS

Intravenous magnesium sulfate appears to have a synergistic effect when combined with other atrioventricular nodal blockers resulting in improved rate control. Similar efficacy was observed with the 4.5 and 9 g of magnesium sulfate but a dose of 9 g was associated with more side effects.

The authors acknowledge all of our colleagues at the three emergencies departments who contributed greatly to this study.

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