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LOW dose MAGnesium sulfate versus High dose in the early management of rapid atrial fibrillation: randomised controlled double blind study

(LOMAGHI study)

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Low dose MAGnesiumsulfate versus High dose in the early management of rapid atrial fibrillation: randomised controlled double blind study (LOMAGHI study)

ABSTRACT

Objectives: We aim to determine the benefit of two different doses magnesium sulfate (MgS) 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 3 university hospital EDs between August 2009 and December 2014. Patients >18years with rapid AF (>120 bpm) were enrolled and randomized to 9g intravenous MgS (High dose group, n=153), 4.5 g intravenous MgS (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 MgS groups compared to placebo group, the absolute difference was respectively 20.5% (risk ratio [RR] 2.31; 95% 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 MgS, and +10.3% (RR 3.22; 95% CI 1.45-7.17) with high dose MgS. The lowest resolution time was observed in Low dose MgS group (5.2±2 hours) compared to 6.1±1.9 hours in High dose MgS group and 8.4±2.5 hours in placebo group. Rhythm control rate at 24 hours was significantly higher in Low dose MgS group (22.9%) compared to High dose MgS group (13.0%, p=0.03) and placebo group (10.7%). Adverse effects were minor and significantly more frequent with high dose MgS.

Conclusions: Intravenous MgS 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 9g of MgS but a dose of 9g was associated with more side effects.

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia and its incidence increases with age¹⁻³. For the management of AF in emergency department, the physician has to decrease the ventricular rate 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 unknown⁴. The use of magnesium as an alternative drug or in addition to usual care has been previously investigated⁵⁻⁷. The rationale for its use was based on its physiological and pharmacological properties to decrease the frequency of sinus node depolarization, to prolong the refractory period of the atrioventricular 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. suggested that intravenous magnesium compared to placebo or standard rate control agents is an effective and safe strategy for the acute management of rapid AF¹⁰. However, most of the included trials had small sample size or were performed in post-cardiac surgery patients¹¹⁻¹². In addition, the dose of magnesium used in previous studies varied widely which could influence its efficacy as AF rate control may be dose dependent¹³⁻¹⁶. We are unaware of any study comparing two different doses of intravenous magnesium on the outcome of ventricular rate of AF. Accordingly, a definitive conclusion regarding the benefit of MgS in the rapid management of rapid AF is still uncertain and available results could not be extrapolated to patients treated in emergency department (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 (MgS), administered at two different doses, to reduce ventricular rate 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 2009 and 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 <90mmHg), if they have impaired consciousness, renal failure (serum creatinine >180 μ mol/L), wide-complex ventricular response or contraindication to MgS. 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 3 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 room, 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 randomised to receive either one of three treatments: 4.5g intravenous MgS in 100 mL normal saline (Low dose group); 9g intravenous MgS in 100 mL normal saline (High dose group) or 100mL intravenous normal saline (placebo group). Protocol treatments were administered within 30 min. Study packs were prepared by the pharmacy department of F.B university hospital. Each contained vials of experimental or placebo treatment and patient identification code. Randomisation using random number tables was achieved by block of 3 packs (1 for each arm) by a pharmacist not involved with patient enrolment, data collection, or data analysis. The MgS and placebo solutions were identical in appearance. Physicians and patients were both blinded to the randomisation 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 ECG monitoring. Blood pressure, respiratory rate, and pulse arterial oxygen saturation were recorded every hour. The same methods were used to record the ventricular rate data. Additional AV nodal blocking agents given at the same time as MgS were left at the discretion of the treating physicians and not mandated by the study protocol. In the 3 participant EDs, usual care antiarrhythmics were not given, nor 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 randomisation. If the patient was discharged or admitted prior to the 24h, 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 endpoint of the study were ventricular rate (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 endpoint 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.

Statistical Analysis

Analysis was undertaken on an intention-to-treat basis. Patients were removed from analysis post randomisation 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 analysed 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 MgS 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 MgS, 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 MgS 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 (CI), 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 was calculated. Data obtained in this study have been recorded and analysed with the computer software SPSS (version 17, Chicago, IL). A p value <0.05 level was used to determine significant differences.

RESULTS

Characteristics of Study subjects

A study enrolment flow diagram is displayed in figure 1. Four hundred sixty-nine 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, 7 patients did not receive study medication because it was not available, and 1 patient left the ED for a procedure in the cardiology department. Four hundred fifty patients ultimately received the study medications, 149 in placebo group, 148 in Low dose MgS group, and 153 in High dose MgS group. Summary demographic and clinical characteristics for patients in the three study groups are presented in Table 1. There were no significant differences among the three treatment groups with respect to baseline demographic or clinical characteristics. Utilization of rate control medications in the 3 groups was similar in the 3 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 MgS study groups which reached statistical significance at time 4 hours (figure 2). The superiority of Mg S 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 Low MgS group and placebo group [absolute difference 20.5% (RR [risk ratio] 2.31; 95% CI 1.45-3.69), and between High MgS group and placebo group [absolute difference 15.8% (RR 1.89; 95% CI 1.20-2.99)] (figure 3). The difference was not significant between both MgS groups [absolute difference 4.7% (RR 0.81; 95% CI 0.51-1.30)]. At 24 hours, therapeutic response rate was significantly higher in Low MgS group [absolute difference 14.1% (RR 9.74; 95% CI 2.87-17.05)] and in High MgS group compared to 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 placebo group, 6.1±1.9 hours for the Low dose group and 5.2±2.0 hours for the High dose group; the

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difference was statistically significant only between placebo and MgS groups. Conversion to sinus rhythm at 4 hour was achieved respectively in 10 patients from the placebo group (6.7%) and 18 patients from Low dose group (12.1%) and in 12 patients from the High dose group (7.8%); the difference was not statistically significant between the 3 groups. At 24 hour, rhythm control was achieved respectively in 16 patients from the placebo group (10.7%) and 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 Low dose group and placebo group ($p=0.005$) and between Low dose group and High dose group ($p=0.03$). It was not statistically significant between High dose group and 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 MgS groups compared to placebo group ($p=0.03$). Subjects in the High dose group were more likely to have adverse events [21 patients versus 8 in the Low dose group and 3 in the placebo group, ($p=0.02$)]. The most frequent adverse effect was transient flushing reported in 25 patients. The others adverse effects are transient hypotension observed in 4 patients (2 in High dose group, 1 in Low dose group, and 1 in placebo group) and bradycardia observed in 3 patients, one in each group (Table 3). There was no death reported during the study, and in no patient the protocol treatment was stopped because of for adverse effect.

DISCUSSION

In this study, intravenous MgS 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 9g of MgS but a dose of 9g was associated with more side effects. Based on our findings, it seems that the logical approach is to combine MgS with usual rate-control agents in order to obtain efficient and more rapid action.

In the management of AF in ED, the objective is to decrease rapidly VR with or without restoration of sinus rhythm. Several drugs as calcium channel blockers, beta-blockers and digoxin are now the standard of care of rapid AF. However, current evidence 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 post-operative 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 is only 4 randomized controlled double blind trials assessing MgS for rate control of rapid AF in non-cardiac surgery patients^{10, 17}. Only 2 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 Teubner⁶ found that MgS 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 MgS regarding rate and rhythm control continued until 24 with a faster onset. Additionally, we demonstrated that using MgS at a dose of 9g was not associated with greater efficacy on rate control compared to 4.5g. Perhaps the more limited response 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 electrophysiological effects of magnesium are probably dose related. In fact, Christiansen et al¹⁸ demonstrated in a dose-response study that 5 mmol intravenous magnesium induced prolongation of atrioventricular node conduction but no further prolongation was observed with higher doses. Accordingly, we think that there is no need to use high dose of MgS 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 MgS has a relatively wide toxic therapeutic window, the risk of adverse effects is possible^{6,19} and potentially more frequent with high MgS 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 demonstrated that intravenous MgS 10 mmol was not different from placebo for reducing VR or conversion to sinus rhythm at 2 hours post treatment in ED patients with AF of less than 48 hours duration²⁰. The improved efficacy of MgS 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 which 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 opinions²¹. It should also be

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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 bpm was used by other studies. In the present study, a VR control of 90bpm 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. Lastly, we acknowledge that the choice of MgS doses in this study may lack some objectivity. However, available data indicated that MgS posology differs according to indications and several dosage recommendations have been proposed. In the rate control of atrial fibrillation, MgS was used at a dose ranging from 1.2 to 10 g. The usual dose seems between 4 and 5g. Based on these findings, we chose 4.5g as the reference dose and 9g as the high dose.

CONCLUSIONS

Intravenous MgS 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 9g of MgS but a dose of 9g was associated with more side effects.

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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 mean \pm SD	66.7 \pm 12.3	66.1 \pm 13.3	68.6 \pm 13.7
Gender Female n(%)	63	60	58
Hypertension n (%)	75(50)	71 (47)	74 (49)
Diabetes n (%)	33 (21)	32 (21)	40 (27)
Atrial fibrillation n (%)	84 (56)	88 (59)	82 (55)
Chronic heart Failure n (%)	32 (21)	30 (20)	41 (27)
Stroke n (%)	9(6)	10(6.7)	13(8.7)
The initial ED triage vitals			
Systolic blood pressure (mmHg) \pm SD	135 \pm 28	136 \pm 28	132 \pm 33
Diastolic blood pressure (mmHg) \pm SD	84 \pm 20	83 \pm 19	80 \pm 22
Temperature $^{\circ}$ C \pm SD	37.2 \pm 0.1	37.1 \pm 0.4	37.0 \pm 0.3
Heart rate b/min \pm SD	136 \pm 21	138 \pm 19	137 \pm 15
Respiratory rate c/min \pm SD	20 \pm 12	20 \pm 5	20 \pm 7
Oxygen saturation % \pm SD	95 \pm 7	94 \pm 5	93 \pm 9
Serum potassium (mmol /L) \pm SD	4.1 \pm 0.7	4.2 \pm 0.2	4.2 \pm 0.4
Serum magnesium mean (mmol/L) \pm SD	0.99 \pm 0.2	0.95 \pm 0.24	1.07 \pm 0.36
Rate control agents			
Digoxin n (%)	71 (47.7)	75 (50.7)	68 (44.5)
Diltiazem n (%)	45 (30.2)	43 (29.0)	51 (33.3)
Beta-blockers n (%)	33 (22.1)	30 (20.3)	34 (22.2)

Table.2 Rate response from Baseline

	Placebo	Low dose magnesium	High dose magnesium
4 H	43.6% [35.7-51.6]	64.2% [56.5-71.9]*	59.5% [57.1-67.3]*
24 H	83.3% [77.2-89.2]	97.9% [95.7-100]	94.1% [90.4-97.8]

* $p \leq 0.05$ vs Placebo

Table.3 Adverse effects

	Placebo	Low dose magnesium	High dose magnesium
Flushing n (%)	1	6	18*
Hypotension n (%)	1	1	2
Bradycardia n (%)	1	1	1
Total	3	8	21*

* $p \leq 0.05$ vs Placebo and Low dose group





