Use of intravenous magnesium to treat acute onset atrial fibrillation: a meta-analysis

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CRD summary
This well-conducted review found that intravenous magnesium is not effective in converting acute onset atrial fibrillation to sinus rhythm in patients with a normal serum magnesium concentration. The addition of intravenous magnesium to digoxin reduces fast ventricular response rates, but is less effective than other calcium antagonists or amiodarone. These findings are likely to be reliable.

Authors' objectives
To determine the effectiveness of intravenous magnesium in the conversion of acute onset atrial fibrillation (AF) to sinus rhythm, and in reducing ventricular response and risk of bradycardia.

Searching
The Cochrane CENTRAL Register, EMBASE and MEDLINE were searched to May 2006; the search terms were reported. The reference lists of relevant editorials, reviews and retrieved articles were screened. The websites of the International Network of Agencies of Health Technology Assessment and International Society of Technology Assessment in Health Care were also searched. No language restrictions were applied.

Study selection
Randomised controlled trials (RCTs) comparing intravenous magnesium with placebo, or alternative anti-arrhythmic drugs, in adult patients with acute onset AF (onset of symptoms or electrocardiography documented AF of less than 7 days before trial enrolment) were included in the review. If studies included patients with AF, atrial flutter or other supraventricular arrhythmia, only the subset of patients with AF were included. Studies of prophylactic magnesium for the prevention rather than treatment of AF were excluded. Inclusion criteria were not defined in terms of the outcomes.

The trials compared magnesium (3 to 10 g in most studies; 25 g in one trial) with placebo, intravenous calcium antagonists or amiodarone. Placebo-controlled trials used digoxin or ibutilide as the concurrent anti-arrhythmic drug in both treatment arms. The studies were conducted in emergency departments, intensive care units and cardiology departments. Most of the trials excluded patients with unstable blood-pressure and renal dysfunction. Where reported, baseline serum magnesium concentrations were normal. The outcomes were assessed 20 minutes to 24 hours after treatment initiation. The primary review outcomes were the proportion of patients with AF converted to sinus rhythm within 24 hours of treatment and the proportion of patients in whom ventricular response slowed to less than 100 beats/minute. The secondary outcomes assessed were the proportion of patients who developed symptoms of flushing, tingling and dizziness, the proportion of patients with significant bradycardia or atrioventricular block (pause >3 seconds, hypotension or symptomatic), hypotension (systolic blood-pressure <100 mmHg or symptomatic) and the proportion of patients who required rescue anti-arrhythmic drugs at the end of the trial.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
Study quality was assessed using the Jadad scale, with studies assigned an overall quality score ranging from 0 to 5. Allocation concealment was graded on the basis of the Cochrane approach.

Two reviewers independently assessed the quality of the studies, and a third reviewer checked the quality assessment.

Data extraction
Differences in categorical outcomes were extracted as odds ratios (ORs) with 95% confidence intervals (CIs). The author of one trial was contacted for clarification of trial data.
Two reviewers independently extracted the data from the included studies, and a third reviewer checked the data extraction.

Methods of synthesis
A random-effects model was used to pool ORs and calculate summary 95% CIs. Trials were stratified according to whether the comparator was a placebo or anti-arrhythmic agent. The interaction between the two strata was tested using the ratio of ORs. Heterogeneity was assessed using the $I^2$ and $\chi^2$ statistics. Sensitivity analyses were conducted with the exclusion of trials that included some patients with atrial flutter or other supraventricular tachyarrhythmias and trials that did not document duration of AF. Publication bias was assessed using a funnel plot, based on the outcome of conversion to sinus rhythm.

Results of the review
Ten RCTs (n=515) were included in the review: five placebo-controlled and five comparing magnesium with alternative anti-arrhythmic drugs.

Study quality scores ranged from 2 to 5. All trials were randomised, but only the 5 placebo-controlled studies were double-blinded. All except one of the trials conducted an intention-to-treat analysis. The proportion of patients lost to follow-up was less than 10% in all trials.

Rhythm conversion (10 RCTs): 5 placebo-controlled trials showed no benefit of adding magnesium to digoxin or ibutilide (OR 1.22, 95% CI: 0.56, 2.65, p=0.61). There was little evidence of heterogeneity ($I^2$=25.8%; p=0.24). There was no difference in rhythm conversion in 5 trials that compared magnesium with alternative anti-arrhythmic drugs (OR 2.82, 95% CI: 0.64, 12.43, p=0.17). There was strong evidence of heterogeneity ($I^2$=66.7%, p=0.02).

Ventricular response rate (5 RCTs): 3 placebo-controlled trials reported a beneficial effect of adding magnesium to digoxin (OR 3.23, 95% CI: 1.93, 5.42). However, 2 trials that compared magnesium with alternative anti-arrhythmic drugs found that magnesium was less effective than verapamil (OR 0.19, 95% CI: 0.09, 0.44). There was no evidence of heterogeneity for either meta-analysis ($I^2$=0%, p=0.47 and p=0.99).

Risk of significant bradycardia (7 RCTs): 3 placebo-controlled trials showed no benefit of adding magnesium to digoxin (OR 3.47, 95% CI: 0.54, 22.22, p=0.19). Four trials that compared magnesium with alternative anti-arrhythmic drugs found that magnesium was less effective (OR 0.13, 95% CI: 0.02, 0.76, p=0.02). There was no evidence of heterogeneity for either meta-analysis ($I^2$=0%, p=0.74 and p=0.96).

Risk of atrioventricular block (5 RCTs): 2 placebo-controlled trials showed no benefit of adding magnesium to digoxin (OR 3.92, 95% CI: 0.43, 35.69, p=0.23). Four trials that compared magnesium with alternative anti-arrhythmic drugs found that magnesium was less effective (OR 0.09, 95% CI: 0.01, 0.77, p=0.02). There was little evidence of heterogeneity ($I^2$=0%, p=0.05).

Incidence of flushing, tingling and dizziness (4 RCTs): magnesium was associated with an increased risk of minor adverse effects in 3 placebo-controlled trials and one trial comparing magnesium with diltiazem (OR 14.52, 95% CI: 3.72, 56.72). There was no evidence of heterogeneity ($I^2$=0%, p=0.63).

Proportion of patients requiring rescue anti-arrhythmic drugs (number of studies unclear): there was no difference in the proportion of patients requiring rescue anti-arrhythmic drugs among placebo-controlled trials or among those that compared magnesium with alternative anti-arrhythmic drugs (OR 0.84, 95% CI: 0.25, 2.81).

The funnel plot showed slight asymmetry.

Cost information
The authors stated that two of the trials provided a cost analysis, but no further information was presented.

Authors’ conclusions
Intravenous magnesium is not effective in converting acute onset AF to sinus rhythm in patients with a normal serum
magnesium concentration. The addition of intravenous magnesium to digoxin reduces fast ventricular response rates, but is less effective than other calcium antagonists or amiodarone. Intravenous magnesium is a safe adjunct to digoxin for controlling the ventricular response in AF.

CRD commentary
The review addressed a focused question and inclusion criteria were defined clearly in terms of the study design, intervention and participants. The literature search was adequate, but did not include specific attempts to locate unpublished studies. There is therefore a possibility of publication bias, which was assessed in the review. Appropriate steps were taken to minimise bias and error at all stages of the review process. Study quality was assessed using appropriate criteria and the results of this assessment were reported clearly in tables, together with other relevant study details. The decision to pool studies stratified on comparator treatment was appropriate given the data, and heterogeneity was formally assessed. This was a well-conducted review and the findings are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that intravenous magnesium is a safe adjunct to digoxin for controlling the ventricular response in AF.

Research: The authors stated that a large RCT is needed to confirm the review findings.

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