Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation

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CRD summary
RCTs directly comparing intravenous magnesium sulphate with sotalol were not identified, but the authors did conclude that intravenous magnesium is effective in preventing atrial fibrillation in patients undergoing coronary artery bypass graft when compared to controls. This was a well conducted piece of research, which considered limitations with the included studies. The authors’ conclusions are likely to be reliable.

Authors’ objectives
To assess the clinical effectiveness of magnesium sulphate compared with sotalol or placebo in the prevention of atrial fibrillation (AF) in patients who have undergone coronary artery bypass graft (CABG).

Searching
DARE, Health Technology Assessment, Centre for Reviews and Dissemination, National Research Register, and Current Controlled Trials were searched from December 2003 to May 2007. The Cochrane Library (2007, Issue 2), MEDLINE (1950 to May 2007, week 1), EMBASE (1980 to 2007, week 19), and the MRC Trial Database and Clinical Trials website were also searched. References of retrieved publications were scanned for relevant articles. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) comparing intravenously administered magnesium sulphate with other strategies of intravenously administered magnesium sulphate, placebo or sotalol, in patients aged 18 years or more who had undergone CABG, were eligible for inclusion. Eligible studies were required to report on the incidence of AF after CABG as the primary outcome and duration of postoperative stay plus total hospital stay as secondary outcomes. Studies of patients receiving other medications such as B-blockers were only eligible for inclusion if the medications were administered as usual patient care to both treatment groups. The majority of included studies were conducted in Turkey but also in other European countries and North America. Included patients had undergone CABG, with or without valvular surgery. Definitions and methods for detecting AF varied between the different studies and incidences were reported directly or inferred indirectly. Magnesium sulphate was administered at different time points and treatment duration ranged between 30 minutes and six days. The majority of trials administered magnesium sulphate by intravenous infusion in doses ranging between 2.5 and 25 grams. Some studies reported length of stay in the intensive care unit (ICU) and adverse events as additional outcome measures.

Two reviewers independently screened studies for relevance, with disagreements resolved by discussion or referral to a third reviewer if necessary.

Assessment of study quality
The quality of the included studies was assessed using previously published criteria, including items on randomisation, allocation concealment, participant homogeneity, assessor blinding, presentation of outcome data, intention-to-treat analysis (ITT) and withdrawals.

Two reviewers assessed studies for validity and any disagreements were resolved by consensus or through discussions with a third reviewer.

Data extraction
Predesigned and piloted data extraction forms were used to extract the number (percent %) of patients experiencing AF and other relevant AF outcomes. Odds ratios (ORs) were calculated with 95% confidence intervals (CIs).
One reviewer extracted data and this was checked by another reviewer. Any disagreements were resolved by consensus or discussion with a third reviewer.

**Methods of synthesis**
Where possible, a fixed effect or random effects model (when heterogeneity was detected) was used to pool ORs. Where quantitative analysis was not possible, data were presented as a narrative synthesis. Heterogeneity was assessed using the $X^2$ and $I^2$ tests, with a $p$ value greater than 0.10 for $X^2$ and a figure greater than 50% for $I^2$ indicating statistical heterogeneity.

A priori subgroup analyses were undertaken to assess the effects of different delivery schedules for intravenous magnesium including different doses, durations and initiation of treatment. Sensitivity analyses were performed by removing studies of lower quality.

**Results of the review**
Fifteen RCTs (17 study arms) ($n=2,209; 1,175$ receiving intervention and $1,034$ receiving placebo/control) were included in the review. The quality of the included studies was unclear due to the poor standards of reporting in the included studies.

**Magnesium sulphate versus sotalol (two study arms):**
Incidences of postoperative AF in patients receiving magnesium sulphate compared to patients receiving sotalol were 15% versus 12%, respectively.

**Magnesium sulphate versus placebo/control (15 study arms):**
Patients receiving magnesium sulphate experienced significantly fewer incidences of AF compared to patients in the control/placebo group; OR 0.65 (95% CI: 0.53, 0.79, $p<0.0001$). However, there was significant statistical heterogeneity between studies ($I^2=63.4\%, p=0.0005$).

Sensitivity analyses significantly altered the results, with the intervention effect no longer statistically significant when studies with adequate allocation concealment were pooled (two study arms); OR 0.84 (95% CI: 0.57, 1.26, $p=0.40$) and heterogeneity was no longer evident. Similar findings were reported for studies with adequate randomisation (four study arms) and studies with adequate blinding (six study arms). Removal of the two studies that appeared to be contributing to the statistical heterogeneity increased the pooled OR 0.78 (95% CI: 0.63, 0.97, $p=0.02$), indicating a significant treatment effect in the intervention group.

Subgroup analyses indicated significant intervention effects for studies commencing prophylaxis 12 hours or more pre-surgery; OR 0.26 (95% CI: 0.15, 0.44, $p<0.0001$), and within 12 hours of surgery (including during surgery itself); OR 0.73 (95% CI: 0.56, 0.97, $p=0.03$). However, significant statistical heterogeneity was reported in the first group of studies ($I^2=89.7\%$).

Mortality rates were reported in the review, but statistical analysis was not possible due to the small numbers of deaths observed. Other subgroup analyses of the dose rate of magnesium sulphate and adverse events were reported in the review.

**Cost information**
An economic model was used to inform the clinical effectiveness of magnesium sulphate prophylaxis. Base-case analysis showed 0.081 fewer cases of AF using magnesium sulphate prophylaxis, at an incremental cost of £2.55, which translates into an incremental cost-effectiveness ratio (ICER) of £32 per AF case avoided. Deterministic sensitivity analysis reported that the greatest ICER (£2092) was associated with increasing the length of patients' stay prior to operation.

Probabilistic analysis showed that most simulations were associated with fewer cases of AF, but at greater cost. Analysis using an acceptability curve showed that the probability of magnesium sulphate prophylaxis being cost-effective, compared with surgery with no prophylaxis, increased with willingness to pay (WTP) for a unit of outcome.
The probability of being cost-effective was 99% at a WTP threshold of £2000 per AF case avoided and 100% at a WTP threshold of £5000 per AF case avoided under the base-case assumptions.

Authors' conclusions
There were no RCTs directly comparing intravenous magnesium sulphate with sotalol for the prevention of AF in patients undergoing CABG. However, pooled analysis indicated that intravenous magnesium sulphate is effective in preventing postoperative AF when compared with placebo or control. Early initiation and longer duration of prophylaxis were associated with fewer incidences of AF but there are uncertainties surrounding these findings.

CRD commentary
The review question was clear and was supported by relevant inclusion criteria. A comprehensive search was undertaken using 10 electronic databases and another appropriate source. Attempts were made to identify unpublished articles, thus reducing the possibility that relevant papers were missed. However, as there was no mention of the language(s) in which papers were searched, the potential for language bias cannot be ruled out. Validity was assessed but the quality of the studies could not be determined due to the generally poor reporting in the studies. Attempts were made to minimise the potential for reviewer error or bias at each stage of the review process. Appropriate methods were used to assess statistical heterogeneity and reasonable steps were taken to explore significant heterogeneity. This was a generally well conducted piece of research and the authors appeared to consider and acknowledge the limitations with the included studies. Their cautious conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors stated that it may be beneficial for future systematic reviews to include RCTs that directly assess the clinical effectiveness of magnesium sulphate and sotalol combination therapy. Further research should also attempt to determine the optimum delivery of intravenous magnesium in patients undergoing CABG by investigating the relationship between dose, dose rate, duration of prophylaxis, timing of initiation of therapy and patient characteristics, such as degree of risk for AF.

Funding
Health Technology Assessment Programme.

Bibliographic details

PubMedID
18547499

Original Paper URL
http://www.hta.ac.uk/fullmono/mon1228.pdfCRD summary

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Arrhythmia Agents /administration & dosage /economics /therapeutic use; Atrial Fibrillation /prevention & control; Coronary Artery Bypass; Cost-Benefit Analysis; Databases, Factual; Humans; Infusions, Intravenous;
Magnesium Sulfate /administration & dosage /economics /therapeutic use; Randomized Controlled Trials as Topic; Sotalol /administration & dosage /economics /therapeutic use

**AccessionNumber**
12008104811

**Date bibliographic record published**
03/11/2008

**Date abstract record published**
02/03/2009

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.