

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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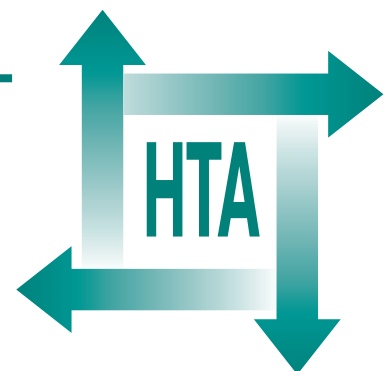
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Executive summary

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Executive summary

Background

Atrial fibrillation (AF) is a supraventricular arrhythmia characterised by abnormal heart rhythm, with symptoms such as palpitations and nausea. It is one of the most common complications after coronary artery bypass graft (CABG) and 20–40% of patients experience AF following cardiac or thoracic surgery. AF increases the risk of mortality and morbidity from stroke, heart failure, myocardial infarction and thromboembolism. This can result in prolonged hospitalisation, hospital readmission, excess utilisation of hospital resources and increased health service costs. Risk factors include advanced age (particularly over the age of 50), previous history of AF, male gender, hypertension, diabetes, smoking, myocardial infarction and valvular heart disease.

Clinical guidelines recommend that β -blockers are used routinely as first choice for the prophylaxis of AF in all patients undergoing cardiac surgery. It is also recommended that sotalol hydrochloride, a β -blocker with class III antiarrhythmic activity, is used. Magnesium may also be given to patients undergoing cardiothoracic surgery to reduce hypomagnesaemia, a common occurrence following this kind of surgery. However, it is not a first line choice for prophylaxis and it is not known to what extent it is used in current practice.

Objective

The aim of this research is to conduct a systematic review and economic evaluation of the clinical and cost-effectiveness of magnesium sulphate compared with sotalol, and to assess the clinical effectiveness of magnesium sulphate compared with placebo in the prevention of atrial fibrillation in patients who have had a CABG.

Methods

Methods for assessing clinical effectiveness

A systematic review was conducted to compare intravenous magnesium sulphate with placebo (or

control), and intravenous magnesium sulphate with sotalol given as prophylaxis before the onset of AF, in patients over 18 years, undergoing elective isolated CABG. Studies of other magnesium compounds (e.g. chloride, hydroxide or unspecified) were excluded. The primary outcome was incidence of postoperative AF. Supraventricular arrhythmias other than AF (e.g. tachycardias and atrial flutter) and all other non-atrial arrhythmias were excluded. Patient length of postoperative stay and the total length of hospital stay were additional outcomes.

A comprehensive search strategy was developed to identify relevant randomised controlled trials (RCTs) and systematic reviews. As this systematic review updates a previous published systematic review the searches were limited to studies published after the cut-off date for literature searching in that review (December 2003). The strategy was applied to ten general and specialist health and biomedical databases. Titles and abstracts were screened systematically against the inclusion criteria and full papers were ordered for further investigation. All included trials were subjected to data extraction using a standard template and quality assessment using published criteria. Data were analysed by narrative synthesis and quantitative meta-analysis, with sensitivity analyses where necessary. *A priori* defined subgroup analyses were performed to assess the effects of different delivery strategies for intravenous magnesium, including different total doses, timing of the initiation of prophylaxis and total duration of prophylaxis.

Methods for assessing cost-effectiveness

A systematic literature search was undertaken to identify economic evaluations of intravenous magnesium sulphate alone as prophylaxis against AF following CABG compared with sotalol as prophylaxis or no prophylaxis. A secondary aim of this review was to identify economic evaluations of other agents used for prophylaxis against postoperative AF or studies that reported cost/resource-use differences for patients undergoing CABG who developed AF. The purpose of reviewing these studies was to identify the scope and methods adopted in previous economic evaluations of prophylaxis against postoperative

AF and to identify the impact of postoperative AF on patients' resource use, which would inform the development of an economic model.

A comprehensive search strategy was developed to identify relevant economic evaluations and costing studies. The strategy was applied to a number of general and specialist health and biomedical databases. Titles and abstracts were screened against the inclusion criteria and full papers were ordered for further investigation. Included studies were discussed in a narrative review.

A simple short-term economic model was developed, informed by the systematic review of economic evaluations and populated with data from the review of costing/resource-use studies and other published studies. The cost-effectiveness of magnesium sulphate as prophylaxis was estimated for a set of base-case assumptions and the robustness of these results was assessed using deterministic and probabilistic sensitivity analysis.

Results of the assessment of clinical effectiveness

The review identified 206 potentially relevant references. Of these, 22 papers met the inclusion criteria, comprising 17 papers that reported parallel-group RCTs (15 RCTs altogether) and five systematic reviews.

Of the 15 trials included, all compared magnesium sulphate with placebo or control. No trials were identified that specifically aimed to compare magnesium sulphate with sotalol. The 15 trials ranged in size from 15 to 176 patients randomised, and were conducted in Europe, the USA and Canada. The standard of reporting was generally poor, with details of key methodological attributes (e.g. method of randomisation and concealment of allocation) difficult to elucidate.

Of 1070 patients in the pooled magnesium group, 230 (21%) developed postoperative AF, compared with 307 of 1031 (30%) patients in the placebo or (control) group. Meta-analysis using a fixed-effects model generated a pooled odds ratio (OR) that was significantly less than 1.0 [OR = 0.65, 95% confidence interval (CI) 0.53 to 0.79, test for overall effect $p < 0.0001$], but with statistically significant heterogeneity ($I^2 = 63.4%$, $p = 0.0005$). Two RCTs were notable as they had relatively lower ORs in favour of magnesium sulphate. When these were removed from the analyses the pooled OR remained statistically significant, but

heterogeneity no longer remained significant. These two studies tended to impart a highly significant reduction in the odds of AF to whichever subgroup they were analysed in.

When studies were ordered by total duration of prophylaxis, an apparent relationship between duration and odds of AF was evident, with decreasing odds of AF as duration of prophylaxis increased. This was confirmed by linear regression analysis ($R^2 = 0.743$, $p < 0.001$). When the data were grouped into three classes according to whether duration of prophylaxis was 1 day or less, 2–4 days, or 5 days or greater, a statistically significant intervention effect was only present for the longest duration group (OR = 0.12, 95% CI 0.06 to 0.23, $p = 0.00001$).

Statistically significant intervention effects were associated with the initiation of prophylaxis 12 hours or more before surgery (OR 0.26; 95% CI 0.16 to 0.44, test for overall effect $p = 0.00001$, fixed-effects model) and less than 12 hours before surgery or during the surgery itself (OR = 0.73, 95% CI 0.56 to 0.97, test for overall effect $p = 0.03$, fixed-effects model), but not when prophylaxis was initiated at the end of surgery or postsurgery (OR = 0.85, 95% CI 0.59, 1.22, $p = 0.37$, fixed-effects model).

When studies were ordered by total dose of intravenous magnesium sulphate (<25 g), the odds of AF were independent of the dose. A notable exception was that for a total dose of 9 g magnesium sulphate, the odds of AF were significantly reduced relative to the control group, based on three studies that used this dose, including the two RCTs mentioned above that appeared to contribute to heterogeneity. This may be explained by the fact that each had excluded patients who were on antiarrhythmic drugs. They may have been at higher risk of AF compared with patients in other studies and, if so, might have benefited more from prophylactic magnesium. Within the subgroup of eight studies that maintained a constant dose rate there appears to be a relationship between the dose rate of magnesium sulphate and the odds of AF, with the largest prophylactic effects being seen at the lowest dose rates.

Results of the assessment of cost-effectiveness

Sixty-three potentially relevant references were found. No economic evaluations of intravenous ►

magnesium alone as prophylaxis against AF following CABG, compared with sotalol as prophylaxis or no prophylaxis, were identified. Four studies were included in the secondary review. One of the included studies was a report of an economic evaluation of oral amiodarone for prophylaxis against AF following CABG. The evaluation suggested that the principal determinant of the cost-effectiveness of prophylaxis against AF is likely to be the length of stay in the intensive care unit (ICU) and on hospital wards. A simple economic model, using a decision tree, was constructed. A flow diagram developed from this decision tree was assessed for its relevance to UK clinical practice and applicability to modelling the cost-effectiveness of magnesium sulphate prophylaxis. The diagram was taken to be a reasonable representation of current practice for patients developing AF following CABG, subject to modifications that would make it more consistent with current UK and European clinical guidelines.

Studies reporting resource use by patients with AF following CABG suggest that, while AF significantly increased inpatient stays, by up to 2.3 days in the ICU and 3.4 days on the ward, differences in length of stay and costs between patients receiving prophylaxis and those not receiving prophylaxis were not statistically significant. The lack of significant findings, with respect to differences in length of stay or cost, may reflect clinical trials being powered to detect differences in clinical outcome and not differences in resource use. However, the lack of significant differences may also reflect the fact that, since postoperative AF affects a minority of patients (albeit a large minority), the difference in resource use between patients with and without AF may be diluted when looking at mean values across a cohort of patients.

A simple economic model was developed to estimate the cost-effectiveness of magnesium sulphate prophylaxis against AF following CABG. This was populated with data on the baseline risk of AF following CABG and the relative risk of AF with magnesium sulphate prophylaxis from the meta-analysis, along with cost and resource-use data from published sources. In the base-case analysis, magnesium sulphate prophylaxis resulted in 0.081 fewer cases of AF at an incremental cost of £2.55. That is, the cost of prophylaxis was slightly higher than the expected savings due to reduced ICU and ward stays resulting from the reduction in AF cases. The incremental cost-

effectiveness ratio (ICER) was £32 per AF case avoided. The estimated difference in average length of stay between the prophylaxis and no-prophylaxis strategies was only 0.24 days, despite a large assumed difference of 3 days for patients experiencing AF in each group (1 extra day in the ICU and 2 extra days on the ward). In the deterministic sensitivity analysis the greatest variation in ICERs was observed for input parameters relating to the baseline risk of AF following CABG and the effectiveness of prophylaxis, the cost of prophylaxis and the resource consequences of postoperative AF. The largest ICER (£2092) in the sensitivity analysis was associated with increasing the length of patients' preoperative stay. In the base case it was assumed that admission routines would be identical under both strategies. However, patients receiving prophylaxis by intravenous infusion may have longer preoperative stays.

In the probabilistic analysis the majority of the simulations were associated with improved outcomes (in this case fewer cases of AF), but also higher costs. Prophylaxis was the dominant strategy (better outcome at lower cost) in about 41% of the simulations using the base-case assumptions. Under an alternative scenario where patients receiving prophylaxis are admitted for longer before their operation, to receive their initial infusion, the proportion of simulations where prophylaxis dominates falls to around 5%. Analysis using an acceptability curve showed that the probability of magnesium sulphate prophylaxis being cost-effective, compared with surgery with no prophylaxis, increases 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. Under the alternative scenario of longer preoperative stays the probability of being cost-effective at these two threshold values fell to 48% and 93%, respectively. It is unclear what the appropriate decision threshold should be, given that this model used intermediate rather than final outcomes.

Conclusions

No RCTs were identified that specifically aimed to compare intravenous magnesium with sotalol as prophylaxis for AF in patients undergoing CABG. Such a comparison does not appear to be clinically meaningful. Intravenous magnesium, compared

with placebo or control, is effective in preventing postoperative AF, as confirmed by a statistically significant intervention effect based on pooled analysis of 15 RCTs. It was also found that AF was less likely to occur when a longer duration of prophylaxis was used, and the earlier that prophylaxis is started; however, this finding was associated with two RCTs that had more favourable results than the other trials, but with no clear explanation as to why. No clear relationship between dose and AF was observed, although a lower constant dose rate was associated with the lowest odds of AF.

In the base-case analysis in the economic model, magnesium sulphate prophylaxis reduced the number of postoperative AF cases at a modest increase in cost. The results of the economic analysis are highly sensitive to variation in certain key parameters. Prophylaxis is less likely to be a cost-effective option if it requires changes in admission routines that result in longer preoperative stays than would be the case without prophylaxis.

Recommendations for further research

Further research should investigate the relationship between dose, dose rate, duration of prophylaxis, timing of initiation of therapy and patient characteristics, such as degree of risk for AF. This will provide stronger evidence for the optimum delivery of intravenous magnesium in patients undergoing CABG.

Publication

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NIHR Health Technology Assessment Programme

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The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA Programme as project number 07/18/01. The contractual start date was in April 2007. The draft report began editorial review in August 2007 and was accepted for publication in February 2008. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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