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Research Protocol

Intravenous magnesium compared with sotalol for prevention of atrial fibrillation after coronary artery bypass surgery

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1 Project title

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2 Details of project team

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3 Planned investigation

3.1 Background

3.1.1 Patients, underlying disease and treatment

Atrial fibrillation (AF) is a supraventricular arrhythmia characterised by uncoordinated atrial activation with consequent deterioration of atrial mechanical function and is one of the most common complications after coronary artery bypass grafting (CABG). Its incidence ranges from 20% to 40%[1] and it is an important cause of morbidity. AF increases the risk of mortality and morbidity from stroke, heart failure, myocardial infarction, thromboembolism, and bleeding from anticoagulation. [1] This results in prolonged hospitalisation, hospital readmission and excess utilisation of hospital resources and increased costs.[2] Consequently primary prevention of AF after CABG is of great importance.

Although the cause of AF after CABG is not clear it is thought to be multifactorial. Risk factors include advanced age, previous history of AF, and low magnesium levels. Magnesium is essential to the functioning of the cardiovascular system and patients with cardiac problems often exhibit abnormal magnesium metabolism. Cardiac surgical procedures may also cause rapid and acute changes in magnesium status.

Approximately 23,000 CABG operations are performed annually in the England.[3] For adults undergoing elective CABG the procedure may be on- or off-pump (the patient's circulation is, or is not, diverted through a pump oxygenator machine). During surgery the heart is beating when a patient is off-pump and can be either be beating or artificially stopped when the patient is on-pump.

3.1.2 Technology to prevent complications

Various pharmacological agents have been used to prevent AF after CABG including magnesium sulphate, magnesium chloride, lidocaine, beta-blockers, digoxin, calcium channel blockers, class I and class III anti-arrhythmics (AARs). Sotalol is a unique beta-blocker with potassium channel blocking properties (Class II and III antiarrhythmic effects) and has been used for the prevention of AF after cardiac surgery. It has an appreciable Class III action only at high doses (240-480 mg/day) and at low doses commonly prescribed in the UK (80–160 mg/day), the main antiarrhythmic effect is its Class II (ie beta-blocker) action. Side effects may include ventricular proarrhythmias.[2]

Because magnesium is required physiologically for cardiac function it has long been used in the treatment of arrhythmias although its mechanism of action has not been fully explained. Magnesium sulphate is well tolerated by patients and is unlikely to cause drug reactions such as plaques associated with AAR use and the side effects of drowsiness and lethargy from using beta-blockers. However, it has wide effects on basic biological mechanisms and is unlikely to be particularly targeted in action.

3.1.3 Current UK practice

Current UK guidelines recommend beta-blockers, in particular sotalol, should be used routinely as first choice for the prophylaxis of AF in all patients undergoing cardiac surgery, unless contraindicated.[1] Amiodarone should be used in patients for whom beta blocker therapy is not possible. In high-risk patients receiving beta-blocker therapy for prophylaxis of AF, amiodarone may also be used as additional prophylaxis. Magnesium is also recommended and may be given in addition to other strategies to reduce the incidence of AF. One acceptable strategy for prophylaxis with magnesium is 6 mmol magnesium sulphate infusion pre-operatively, just after cardiopulmonary bypass and once daily for 4 days after surgery.[1]

Sotalol is therefore routinely used for prophylaxis of AF. In UK clinical practice, sotalol is often used at low doses (80–160 mg/day), at which it essentially acts in a similar manner to a standard beta-blocker (Class II) in terms of antiarrhythmic activity. In people with low body mass index, renal impairment, etc, some Class III activity may be manifest at low doses. When used as an antiarrhythmic agent, sotalol is often started at 80 mg twice daily for the first week and thereafter titrated to 160 mg twice daily (or higher subsequently), after checking for adverse effects and QT prolongation on the electrocardiogram.{BMJClinical Evidence http://www.clinicalevidence.com/ceweb/conditions/cvd/0210/0210_I9.jsp}

Magnesium administration is not a first-line choice for prophylaxis of AF and it is not known to what extent it is used in current practice. It may be used in combination with other drugs.[2] Magnesium sulphate is usually administered intravenously. 1 to 4g magnesium sulphate may be given intravenously in 10% to 20% solution at a rate not exceeding 1.5 mL of 10% solution or equivalent per minute or intravenous infusion of 4g in 250 mL of 5% dextrose at a rate not exceeding 3 mL per minute. It may also be given as an intravenous bolus, intramuscularly or orally in the form of magnesium glycerophosphate.

3.1.4 Costs

According to BNF 51, March 2006:
Injection, magnesium sulphate 20% (Mg2+ approx. 0.8 mmol/mL), net price 20-mL (4-g) amp = £2.75; 50% (Mg2+ approx. 2 mmol/mL), 2-mL (1-g) amp = £2.59, 4-mL (2-g) prefilled syringe = £6.50, 5-mL (2.5-g) amp = £2.50, 10-mL (5-g) amp = £3.35; 10-mL (5-g) prefilled syringe = £4.95.

Sotalol (non proprietary) tablets sotalol hydrochloride 40mg, net price 56 = £1.34; 80mg, 56 = £1.99; 160mg 28 = £3.84.

3.1.5 Rationale for the study

Despite published guidelines outlining different treatment options,[1] uncertainty remains as to the most appropriate intervention to prevent AF after CABG. A systematic review comparing magnesium sulphate with Sotalol is required.

Although a recent systematic review concluded that the use of magnesium sulphate is associated with a significant reduction on post-operative AF, the best delivery strategy is not known and a systematic review of the different delivery strategies of magnesium sulphate is required.

From the perspective of the patient the clinical issue is to effectively prevent AF and avoid the side effects of beta-blockers which may lead to reduced quality of life. The wider NHS perspective is concerned with identifying and providing the most cost effective method of preventing AF after CABG.

3.2 Research Aim

The aims of this project are to compare the effectiveness and cost effectiveness of magnesium sulphate and Sotalol to prevent atrial fibrillation after coronary artery bypass surgery and to evaluate the delivery strategies of peri-operative magnesium sulphate.

3.3 Objectives

The main objectives will be as follows:

- To assess the effectiveness of perioperative intravenous magnesium sulphate in preventing AF after CABG compared with Sotalol.
- To determine the optimum dosage, duration, timing and administration method of magnesium sulphate in preventing AF after CABG.
- To assess the cost effectiveness of magnesium sulphate compared with sotalol by using a simple economic model.

Existing research

A systematic review suggests that the use of intravenous magnesium is associated with a significant reduction in the incidence of atrial fibrillation after CABG with a relative risk of 0.64 (95%CI 0.47, 0.87, p=0.004).[4] Two subsequent RCTs suggest that magnesium has no effect in preventing AF after CABG.[5;6]

3.4 Research Methods

3.4.1 Systematic Review

The systematic review will be undertaken in accordance with the NHS Centre for Reviews and Dissemination guidelines.[7]

3.4.1.1 Literature search

Literature will be identified by searching electronic databases, bibliographies of retrieved articles and consultation with experts in the area. A comprehensive database of relevant published and unpublished articles will be constructed using the Reference Manager software package.

The searches carried out will include:

- General health and biomedical databases: Medline; Embase; PubMed (previous 6 months)
- Specialist electronic databases: Database of Abstracts of Reviews of Effectiveness (DARE); Cochrane Library; Health Technology Assessment Database (HTA); NHS Economic Evaluation Database (NHS EED); EconLit
- Contact with individual experts and those with an interest in the field
- Checking of reference lists

- Research in Progress: National Research Register (NRR); Current Controlled Trials; Clinical Trials.gov

All databases will be searched from inception to the current date for studies comparing intravenous magnesium and sotalol. Searches for literature on intravenous magnesium sulphate compared with placebo or no intervention will be restricted to 2004 onwards in order to update the existing systematic review,[4] and results stored in a separate reference database. Searches will be limited to English language articles.

3.4.1.2 Study inclusion

Specific inclusion criteria will be defined for each element of the systematic review. The full literature search results will be screened by one reviewer and checked by a second reviewer to identify all citations that may meet the inclusion criteria. Full manuscripts of all selected citations will be retrieved and assessed by two reviewers against the inclusion criteria. Disagreements over study inclusion will be resolved by consensus or if necessary by arbitration by a third reviewer.

The planned inclusion/exclusion criteria for the systematic review are shown in Table 1.

Table 1 Inclusion criteria for the systematic review

	Systematic review of sotalol vs magnesium sulphate	**Systematic review of delivery strategies of magnesium sulphate**
Patients	Adults (age over 18) undergoing elective CABG Either on-pump or off-pump CABG techniques; any number of grafts; any conduit type.	Adults (age over 18) undergoing elective CABG (defined as isolated coronary revascularization operation that does not need to be performed at the same hospital admission). Either on-pump or off-pump CABG techniques; any number of grafts; any conduit type.
Intervention	Magnesium sulphate, as bolus or continuous infusion, of a specified dose and duration, given as a prophylactic measure before the onset of AF.	Magnesium sulphate, as bolus or continuous infusion, of a specified dose and duration, given as a prophylactic measure before the onset of AF.
Comparator	Sotalol, given as a prophylactic measure before the onset of AF	Any different delivery strategy including: • Different method (bolus/infusion) • Different dosage • Different duration • Different timing If there are no head to head studies of different delivery strategies then indirect comparisons of magnesium sulphate vs placebo/no intervention will be included (update of Alghamdi review)
Outcomes	Primary outcome: Incidence of AF after CABG Economic outcomes	Primary outcome: Incidence of AF after CABG (defined as totally irregular atrial rhythm leading to irregular ventricular rhythm, measured using a continuous electrocardiogram (ECG) and confirmed by standard 12-lead ECG). Incremental cost, incremental cost-effectiveness and cost-utility ratio

	Systematic review of sotalol vs magnesium sulphate	**Systematic review of delivery strategies of magnesium sulphate**
Design	RCTs	RCTs Full economic evaluations (cost-minimisation, cost effectiveness, cost utility, cost benefit analyses)
Exclusions	n/a	Studies that meet any one of: Unspecified methods of detection of AF; Unspecified period of follow-up; Participants with chronic or paroxysmal AF; Participants with history of arrhythmias (any rhythm other than normal sinus rhythm).

Secondary outcomes, such as incidence of stroke or mortality, quality of life and length of hospital stay, will not be used for inclusion/exclusion purposes but will be reported if mentioned in included studies.

3.4.1.3 Data extraction

The extraction of studies' findings will be conducted by two reviewers using a pre-designed and piloted data extraction form to avoid any errors. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration by a third reviewer.

3.4.1.4 Quality assessment

The methodological quality of included studies will be assessed using formal tools specific to the design of the study and focusing on possible sources of bias. Quality assessment of RCTs will be conducted using criteria developed by NHS Centre for Reviews and Dissemination[7] (Appendix 1). Study quality will be assessed by two reviewers. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration involving a third reviewer.

3.4.1.5 Data synthesis

The methods of data synthesis will be determined by the nature of the studies identified through searches and included in the review. Quantitative synthesis of results through meta-analysis will be considered if there are several high quality studies of the same design and sources of heterogeneity will be investigated by subgroup analyses if applicable. The results of any included studies suitable for quantitative synthesis will also be summarised in a narrative form along with a narrative synthesis of the results from studies for which quantitative synthesis is not possible. All results will also be tabulated (see Appendix 2).

3.4.2 Economic evaluation

An economic model will be developed to assess the costs and consequences of using magnesium sulphate to prevent atrial fibrillation after CABG compared with sotalol. Modelling will be conducted according to accepted methodology for economic evaluations.[8;9] The model will describe the pathway of individuals following CABG and receiving prophylaxis with either magnesium sulphate or sotalol, focussing on drug dosing, duration of treatment and method of administration (and, where data allow, combination strategies), the probability of developing AF, probability of adverse effects of prophylaxis and their associated morbidity, as well as duration of hospital stay with or without AF or adverse effects. The structure of the model will be informed by the systematic review of clinical effectiveness, previous economic evaluations (if any) identified by the systematic review of economic literature by expert opinion.

Data to populate the model will come primarily from the systematic review of clinical effectiveness, but will be supplemented by targeted searches for key parameters (for example, quality of life impact of adverse events, costs of managing AF and adverse events) which may not be adequately addressed in studies included in the systematic review. Where data cannot be identified through searches, estimates will be based on expert opinion. The sources for all parameter estimates will be clearly identified.

The perspective of the costing will be that of the NHS and Personal Social Services. Cost data will include the direct costs associated with providing prophylaxis with magnesium sulphate or sotalol, costs of managing AF and adverse events. This will include an estimate of AF or adverse events on inpatient stay. Quantity of resources used will be identified from the literature using targeted searches and expert opinion. Unit cost data will be extracted from the literature, routine sources (for example, NHS Reference Costs) or maybe developed in collaboration with hospital trusts.

Results from the model will be presented as a cost-consequences analysis, reporting costs of interventions and their consequences – both in terms of cases of AF avoided and in terms of adverse events. Consequences will be identified in terms of morbidity and additional NHS treatment costs. It is anticipated that the model would be able to provide estimates of the cost-effectiveness of magnesium sulphate relative to sotalol in terms of the incremental cost per case of AF avoided.

The model will be developed using standard software such as Microsoft Excel or TreeAge Pro. The robustness of model results to plausible variation in key parameters will be addressed through appropriate sensitivity analyses.

3.4.3 Ethical arrangements

No specific ethical arrangements necessary.

3.4.4 Outputs of the review

In addition to the preparation of the HTA monograph, papers will be submitted to relevant peer reviewed journals and for presentation at conferences.

4 Project management and milestones

Project management and milestones

Milestones	**Week**
Project Initiation	
Development and peer review of protocol	1 – 2
Systematic Review	
Literature searches	1 – 2
Study selection	2 – 3
Study retrieval	2 – 4
Data extraction	3 – 5
Data analysis	5 – 6
Economic Evaluation	
Specify model	1 – 3
Data collection	3 – 7
Model and sensitivity analysis	6 – 9
Final Report	
Drafting of final report	9 – 10
Peer review and updating of report	11 – 12
Submission and dissemination of report	12

Competing Interests: No member of the team has registered any competing interests.

5 Advisory Group

Representatives and other potential users of the review from different professional backgrounds and opinions, including academics, clinicians, health economists, patient groups, professional organizations, will be invited to provide expert advice to support the project where possible. Experts will be asked to provide comments on a version of the protocol and of the final report, as well as advising on the identification of relevant evidence. All experts will be asked to register competing interests and to keep the details of the report confidential.

6 References

(1) Dunning J, Treasure T, Versteegh M, Nashef SAM. Guidelines on the prevention and management of de novo atrial fibrillation after cardiac and thoracic surgery. European Journal Cardio-thoracic Surgery 2006; 30:852-872.

(2) Shantsila E, Watson T, Lip GYH. Atrial fibrillation post-cardiac surgery: changing perspectives. Current Medical Research and Opinion 2006; 22(8):1437-1441.

(3) NHS HESonline. Hospital Episode Statistics. NHS England 2004-05. HES data 2006.

(4) Alghamdi AA, Al-Radi OO, Latter DA. Intravenous magnesium for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and meta-analysis. J Card Surg 2005; 20:293-299.

(5) Zangrillo A, Landoni G, Sparicio D, Pappalardo F, Bove T, et al. Perioperative magnesium supplementation to prevent atrial fibrillation after off-pump coronary artery surgery: a randomized controlled study. J Cardiothoracic and Vascular Anesthesia 2005; 19(6):723-728.

(6) Hazelrigg SR, Boley TM, Celindag IB, Moulton KP, Trammell GL, et al. The efficacy of supplemental magnesium in reducing atrial fibrillation after coronary artery bypass grafting. Annals Thoracic Surg 2004; 77(3):824-830.

(7) NHS Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness: CRD guidelines for those carrying out or commissioning reviews. CRD Report 4. 2001.
Ref Type: Report

(8) Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2004; 8(36):iii-iiv.

(9) Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996; 313(7052):275-283.

Appendix 1: Quality assessment

a. Quality criteria for assessment of experimental studies (NHS CRD)

Item	**Judgement***
1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	
10. Were withdrawals and dropouts completely described?	

* adequate, inadequate, not reported, unclear

Appendix 2: Data extraction form – Generic Sample

Reference and Design	Intervention	Participants	Outcome measures
Author: Year: Country: Study design: RCT Number of centres: ? Funding:	Intervention: Control: Other interventions used:	Number of Participants: Intervention: Control: Sample attrition/dropout: Sample crossovers: Inclusion criteria for study entry: Exclusion criteria for study entry: Characteristics of participants:	Primary outcomes: Secondary outcomes: Method of assessing outcomes: Adverse symptoms: Length of follow-up: Recruitment dates:

Results

Primary Outcomes	Intervention	Control	P Value

Comments:

Secondary outcomes	Intervention	Control	P value
			P=0.87

Comments:
Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE
Methodological comments Allocation to treatment groups: Blinding: Comparability of treatment groups: Method of data analysis: Sample size/power calculation: Attrition/drop-out: General comments Generalisability: Outcome measures: Inter-centre variability: Conflict of interests: