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Review Paper

Magnesium sulphate replacement therapy in cardiac surgery patients: A systematic review

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ABSTRACT

Objective: The objective of this review was to identify evidence to inform clinical practice guidelines for magnesium sulphate ($MgSO_4$) replacement therapy for postoperative cardiac surgery patients.
Data sources: Three databases were systematically searched: CINAHL Complete, MEDLINE Complete, and EmBase.
Review method used: A systematic literature review method was used to locate, appraise, and synthesise available evidence for each step of the medication management cycle (indication, prescription, preparation, administration, and monitoring) for $MgSO_4$ replacement therapy. Database searches used combinations of synonyms for postoperation or surgery, cardiac, heart, arrhythmia, atrial fibrillation, and magnesium sulphate. Search results were independently screened for inclusion by two researchers at title, abstract, and full-text stages with good statistical agreement (kappa scores of 0.99, 0.87, and 1.00, respectively).
Results: Twenty-four included studies reported varying methodologies, data collected, and medication management practices. Of these, 23 studies (95.8%) excluded patients with comorbidities commonly observed in clinical practice. This review identified low-level evidence for two practice recommendations: (i) concurrent administration of $MgSO_4$ with medications recommended as the best practice for prevention of postoperative atrial fibrillation and (ii) clinical and laboratory monitoring of magnesium blood serum levels, vital signs, and electrocardiography should be performed during $MgSO_4$ replacement therapy. Evidence to inform $MgSO_4$ replacement therapy for each medication management cycle step was limited; therefore, a guideline could not be developed.
Conclusions: Although $MgSO_4$ is routinely administered to prevent hypomagnesaemia in postoperative cardiac surgery patients, there was insufficient evidence to guide critical care nurses in each medication management cycle step for $MgSO_4$ replacement therapy. These findings precluded the development of comprehensive recommendations to standardise this practice. Poor standardisation can increase the risk for patient harm related to variation in clinical processes and procedural errors. In light of this evidence gap, consensus of expert opinion should be used as a strategy to guide $MgSO_4$ medication management.

1. Introduction

Inconsistencies in clinical practice for the indication, prescription, preparation, administration, and monitoring of intravenous (IV) magnesium sulphate ($MgSO_4$) can pose a medication safety risk for patients. As an electrolyte, $MgSO_4$ is a high-risk medication [1–3] often administered intravenously for the prevention of postoperative atrial fibrillation (POAF), one of the most common postoperative complications of cardiac surgery.[1–6] Between 10 and 50% of patients develop

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new atrial fibrillation (AF) as a complication after cardiac surgery and up to 60% of patients after concurrent valve and coronary artery bypass grafting (CABG) surgery.[6–10] AF is more common in older patients (>65 years) and in those having surgery involving cardiopulmonary bypass, valve repair or replacement.[7,11,12] Electrolyte imbalances are an independent factor for the development of AF in cardiac surgery patients with other contributing factors including fluid shifts and irritation of the heart's conduction system caused by inflammation or scarring from surgery.[13–15] Use of cardiopulmonary bypass during cardiac surgery results in a loss of potassium (K^+) and magnesium (Mg^{2+}), electrolytes that protect the heart's conduction system from arrhythmias by stabilising cardiac cells.[16] Given K^+ is more readily retained by the body when Mg^{2+} blood serum levels are within the normal range, normal Mg^{2+} levels are considered protective against arrhythmias.[17]

POAF is a relatively common complication of cardiac surgery which contributes to increased patient mortality, increased length of hospital stay, and high healthcare costs.[18–20] As the population ages and the frequency of cardiac surgeries increases, it is expected that the incidence of complications such as POAF will also increase. Effective prevention and proactive early management can mitigate the human and economic consequences of POAF, making this an important consideration for critical care nurses who have a key role in early detection and escalation of treatment.

Current best available evidence recommends a β-blocker medication should be used for primary prevention of POAF in cardiac surgery patients[19,21] and that $MgSO_4$ replacement therapy used as an adjunct to prevent hypomagnesaemia associated with increased risk for POAF. Guidelines suggest that this treatment is relatively inexpensive and low risk for patients with normal renal function[18,20] but provide little guidance about how it should be managed. Magnesium replacement therapy is becoming a routine practice in many critical care settings, routinely used for prevention against hypomagnesaemia and POAF in postoperative cardiac surgery patients. However, evidence to guide the steps for safe medication management of $MgSO_4$, such as indications, dose, administration regime, monitoring required, or goals for optimal blood serum levels, is lacking in current guidelines.[21,22] The current lack of evidence presents a clinical challenge for critical care nurses who manage postoperative cardiac surgery patients and contributes to variation in practice and clinical risk.

Standardisation of practice is an important component of medication safety in critical care patients. Standardisation of medication practices can be mediated through nursing education, evaluation of medication distributions systems, workloads, and environmental factors such as the effect of interruptions on healthcare staff.[23–25] Currently, inconsistencies in Mg^{2+} blood serum levels in postoperative cardiac surgery patients contribute to variability in electrolyte replacement practices and a lack of clarity about management and treatment goals. In particular, it is not clear when $MgSO_4$ replacement therapy is indicated or how it should be prescribed, prepared, administered, and monitored. Best practice recommendations for safe medication management state that standardisation of practice across each of the medication cycle steps (indication, prescription, preparation, administration, and monitoring) is important for medication safety.[24,26,27] Conversely, variability in clinical practice may contribute to medication errors and adverse patient outcomes. Patients in critical care units, such as cardiac surgery patients, are at high risk for adverse events, errors, and potential errors.[26,28,29]

2. Objectives

The purpose of this study was to identify, appraise, and synthesise best evidence to inform recommendations for practice guidelines to assist critical care nurses in safe medication management of $MgSO_4$ replacement therapy in postoperative cardiac surgical patients. The research aims were to (i) appraise current evidence about management of $MgSO_4$ replacement therapy in postoperative cardiac surgery patients by extracting data related to each step of the medication management cycle (indication, prescription, preparation, administration, and monitoring) and (ii) identify best practice evidence to inform guidelines to standardise each step of the medication management cycle for $MgSO_4$ replacement therapy in postoperative cardiac surgery patients. The intended outcomes of this review was to inform local policy, guidelines, and associated quality improvement strategies to standardise $MgSO_4$ replacement therapy for the prevention of AF in postoperative cardiac surgery patients.

3. Methods

A systematic literature review methodology was used to identify, extract, and synthesise available evidence for each step of the medication management cycle for $MgSO_4$ replacement therapy in postoperative cardiac surgery patients. The efficacy of $MgSO_4$ as an adjunct for prevention of POAF is included in best practice guidelines[18,20] hence was not the focus of this review. Rather, as existing guidelines do not provide evidence for the safe medication management of $MgSO_4$ replacement therapy, the five stages of the medication management cycle (indication, prescription, preparation, administration, and monitoring) specific to $MgSO_4$ replacement therapy were used as a framework to extract data to address the research objectives. Existing literature was searched using the Population, Intervention, Comparison, and Outcome format:

- Population—adult postoperative cardiac surgery patients (age >18 years) who had undergone cardio-pulmonary bypass and at risk of developing AF.
- Intervention—administration of IV $MgSO_4$ replacement therapy.
- Comparison—no comparison was included.
- Outcome—evidence for the safe medication management of $MgSO_4$ replacement therapy.

Three databases selected for their reputable and comprehensive collection of peer-reviewed health sciences literature were independently searched using a strategy verified by an experienced health librarian in August 2016. The databases, CINAHL Complete (Cumulative Index to Nursing and Allied Health Literature), MEDLINE Complete, and EmBase were each searched for the Medical Subject Headings (MeSH) terms arrhythmia, atrial fibrillation, magnesium, magnesium sulphate, and cardiac surgical procedures using the following combination of keywords:

> ("post op*" OR "post surg*" OR (after N3 operation OR surg*)) AND (cardi* OR heart) AND (arrhythm* OR "atrial fibrillation") AND (magnesium OR "magnesium sulphate" OR "magnesium sulfate" OR "$MgSO_4$")

Peer-reviewed publications of primary research including randomised controlled trials, cohort studies, and observational research were included in this review to capture the highest levels of research evidence relevant to cardiothoracic nursing. Conference, poster, and oral abstracts were excluded as they were unlikely to provide the detail and data required to address the review question. Full-text studies needed to be available in the English language to enable thorough evaluation. A focus on research published between 2000 and 2016 ensured studies were current at the time of the review and therefore relevant for contemporary clinical practice.

Systematic reviews and meta-analyses examining the efficacy of $MgSO_4$ in the prevention of postcardiac surgery AF were excluded as these studies differed in focus, potentially introducing a source of bias. Studies reporting minimally invasive surgeries such as 'off-pump' cardiac surgery, which did not use cardiopulmonary bypass or minimal-access cardiac surgery, including robotics technology, were excluded because these introduced variables were not relevant to the clinical context of critical care nursing practice intended for the outcomes of the review. Studies in which $MgSO_4$ was only administered in the cardioplegia solution intra-operatively were excluded as this is not performed or managed by the nursing population who care for these patients postoperatively. Studies detailing the use of IV $MgSO_4$ in cardiac surgery patients perioperatively were included because of their relevance in their postoperative management by critical care nurses. Only human studies of adult populations who underwent cardiothoracic surgery were included; animal studies and studies on paediatric populations were excluded as they have specific care needs not relevant to the focus of this review.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were used as a framework to guide planning and documentation of the review.[30] The quality of evidence was appraised using combined criteria derived from the Cochrane Handbook, Assessment of Multiple Systematic Reviews, and Risk of Bias in Non-Randomised Studies of Interventions critical appraisal tools for quantitative evidence and systematic reviews.[31–33] The National Health and Medical Research Council definitions of levels of evidence and grades of recommendations were also used to guide interpretations of existing literature.[34]

The framework used for data extraction and critical appraisal was guided by existing medication safety frameworks from the Australian Commission on Safety and Quality in Health Care and the Australian Pharmaceutical Advisory Council.[28,35–37] At least two researchers independently screened all titles, abstracts, and full texts to identify studies that met the inclusion criteria (Fig. 1, PRISMA diagram). Removal of most studies at full-text level was due to a lack of detailed information about the type of magnesium ($MgSO_4$ not specified), timing of administration (only included in cardioplegia solution), arrhythmias other than AF examined, use of off-pump cardiac surgery, and methods of reporting (posters or presentations).

Strong statistical agreement was demonstrated by high Kappa (κ) scores calculated using the equation $\kappa = (Pr(a) - Pr(e))/(1-Pr(e))$, at each stage of exclusion by title ($\kappa = 0.99$), abstract ($\kappa = 0.87$), and full text ($\kappa = 1.00$). A third reviewer who was available to make the final decision on study disagreement was not required. Data extraction was independently verified by two members of the research team.

4. Results

4.1. Research characteristics, designs, and samples

Included in the review were 24 studies reporting varying methodologies, data collected, and medication management practices, summarised in Table 1. Of the 24 studies, the majority were experimental and randomised ($n = 19$, 79.2%). Examination of the study aims revealed most involved use of $MgSO_4$ to prevent POAF ($n = 14$, 58.3%). Twenty-one studies (87.5%) used concurrent medications, most often K^+ ($n = 8$), amiodarone ($n = 4$), or β-blockers ($n = 9$).

Just more than half of the 6617 patients included in the 24 studies received $MgSO_4$ ($n = 3346$, 50.6%). Most of these studies only included patients who underwent isolated CABG surgery

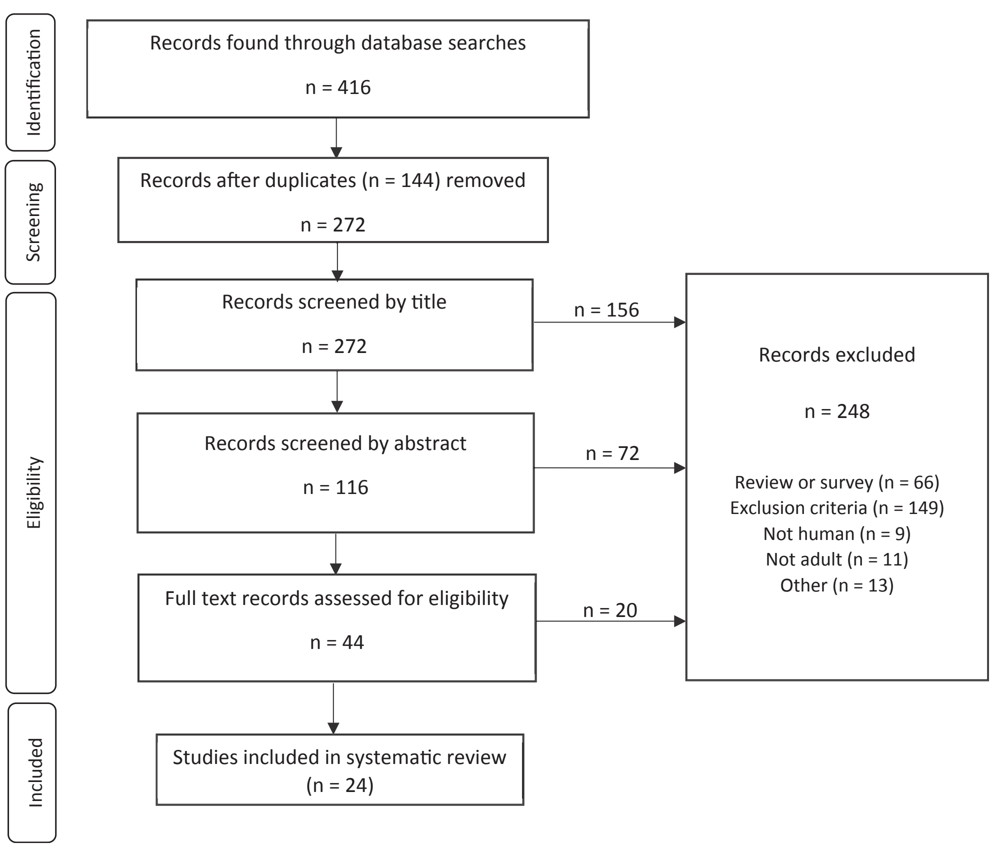

Fig. 1. PRISMA diagram of study selection process.

Table 1
Characteristics of included studies.

Study citation	Study design	Sample size + study arms	Study aim	Medication cycle–relevant findings
Allen, Heimansohn, Robison, Schier, & Griffith, 2006	Quasi-experimental (consecutive patients)	Sample size: 1068 2 arms—592 patients in the Mg^{2+} and amiodarone group and 476 patients in the control Mg^{2+} group	To reduce POAF by incorporating amiodarone into an existing POAF prevention pathway	**Indication**: Routine as per postcardiac surgery pathway for POAF prevention **Prescription**: 4 g of IV $MgSO_4$ intraoperatively and postoperatively 2 g per day **Preparation**: 2 g of $MgSO_4$ in 50 ml of 0.9% sodium chloride (NaCl) **Administration**: IV infusion over 2 h, each morning **Monitoring**: Clinical monitoring—NS Laboratory tests—Existing AF prevention protocol (stop $MgSO_4$ and use potassium sliding scale depending on serum creatinine levels) but NS when these were to be checked Mg^{2+} serum levels/ranges—NS
Bakhsh, Abbas, Hussain, Ali Khan, & Naqvi, 2009	Randomised controlled trial	Sample size: 220 2 arms—110 in the Mg^{2+} intervention group and 110 patients in the control group	To prevent POAF with 3-day Mg^{2+} infusion after CABG	**Indication**: Study protocol—patients randomised to the intervention group **Prescription**: 10 mmol (2.47 g) IV $MgSO_4$ **Preparation**: Five ampoules of 500 mg of $MgSO_4$ in 100 ml of NaCl **Administration**: IV infusion over 4 h, once daily for Three days **Monitoring**: Clinical monitoring—Standardised anaesthesia and surgical procedures for all patients Laboratory tests—NS Mg^{2+} serum levels/ranges—NS
Behmanesh et al., 2006	Randomised controlled trial	Sample size: 100 2 arms—50 patients in the prophylaxis bisoprolol and Mg^{2+} group and 50 patients in the control group	To prevent POAF after CABG	**Indication**: Patients in the prophylaxis group **Prescription**: Single dose of 2 g of $MgSO_4$ **Preparation**: 2 g of $MgSO_4$ in 100 ml of NaCl **Administration**: Single dose **Monitoring**: Clinical monitoring—Continuously monitored by bedside alarm-triggered monitors for the first 72 h, then monitored with an alarm-triggered 3-lead telemetry until morning of postoperative day 7 Laboratory tests—NS Mg^{2+} serum levels/ranges—NS
Brackbill & Moberg, 2005	Descriptive (retrospective chart review)	Sample size: 234 2 arms—99 in the Mg^{2+} group and 135 patients in the control group	To decrease frequency of POAF	**Indication**: Nil **Prescription**: 2 g of IV $MgSO_4$ **Preparation**: 2 g of $MgSO_4$ in 100 ml of NaCl **Administration**: 2 g of IV $MgSO_4$ intraoperatively, and 2 g every 12 h, over at least 1 h, postoperatively for at least two consecutive days **Monitoring**: Clinical monitoring—NS Laboratory tests—NS Mg^{2+} serum levels/ranges—NS
Cagli et al., 2006	Randomised controlled trial	Sample size: 136 3 arms—44 patients in the amiodarone and Mg^{2+} group, 44 patients in the amiodarone group, and 48 patients in the control group	To prevent POAF using a combination of low-dose amiodarone and $MgSO_4$	**Indication**: Consecutive patients randomised to the treatment group **Prescription**: 1.5 g of IV $MgSO_4$ **Preparation**: NS **Administration**: IV bolus over 10 min **Monitoring**: Clinical monitoring—Continuous ECG monitoring for at least 48 h immediately postoperatively. Then until discharge, blood pressure (BP) and 12-lead ECG performed every 8 h, and heart rate (HR) measured every 4 h Laboratory tests—Arterial blood gases and electrolytes (K^+ and Ca^{2+}) were measured 12-hourly Mg^{2+} serum levels/ranges—Stated serum Mg^{2+} normal range 1.95 ± 0.22 mEq/L
Carrió et al., 2012	Randomised controlled trial	Sample size: 216 2 arms—105 patients in the Mg^{2+} group and 111 in the control group	To assess whether immediate postoperative supplementation of $MgSO_4$ improves patient outcomes	**Indication**: Patients randomised to the treatment group **Prescription**: 1.5 g of IV $MgSO_4$ **Preparation**: 1.5 g of IV $MgSO_4$ bolus, then 12 g of IV $MgSO_4$ infusion (prepared by pharmacy staff) **Administration**: IV bolus over 5 min and then IV infusion over 24 h

				Monitoring: Clinical monitoring—Continuous bedside ECG monitoring. 12-lead ECGs performed the day before surgery on admission to the ICU and daily until discharge Laboratory tests—Serum Mg^{2+} concentrations measured on the ICU admission and 6, 24, and 48 h later Mg^{2+} serum levels/ranges—Reference range 0.65–1.05 mmol/L
Cook et al., 2009	Randomised controlled trial	Sample size: 927 4 arms—CABG surgery, 347 patients in the Mg^{2+} group, 347 in the control group; valve ± CABG surgery, 115 in the Mg^{2+} group and 118 in the control group	To prevent postoperative atrial arrhythmias	**Indication**: Patients randomised to treatment group or "standard of care" treatment **Prescription**: 5 g of IV $MgSO_4$ bolus by an anaesthetist on cross-clamp removal and then 5 g of IV $MgSO_4$ on postoperative days 1–4 **Preparation**: NS (prepared by pharmacy staff) **Administration**: IV bolus and then IV infusion over 4 h daily **Monitoring**: Clinical monitoring—Telemetry monitoring for the first five days postoperatively Laboratory tests—Serum Mg^{2+} levels checked on arrival to the ICU Mg^{2+} serum levels/ranges—Normal range stated as 0.70–1.1 mmol/L
Dabrowski et al., 2008	Quasi-experimental	Sample size: 120 6 arms—Patients with and without preoperative Mg^{2+} supplementation further divided into three groups of Mg^{2+} replacement (varying concentrations). The number of patients in each arm: NS	To assess the effect of Mg^{2+} doses on serum Mg^{2+} levels and incidence of POAF	**Indication**: Patients selected to treatment **Prescription**: 3.33 mg/min of IV $MgSO_4$, 6.66 mg/min of IV $MgSO_4$, or 10 mg/min of IV $MgSO_4$ **Preparation**: NS **Administration**: NS **Monitoring**: Clinical monitoring—HR continuously monitored postoperatively Laboratory tests—Arterial blood tests performed locally Mg^{2+} serum levels/ranges—Range 0.80–1.2 mmol/L
Dagdelen, Toraman, Karabulut, & Alhan, 2002	Randomised controlled trial	Sample size: 148 2 arms—93 patients in the Mg^{2+} group and 55 control patients	To examine the effect of Mg^{2+} on P-wave duration and dispersion	**Indication**: Patients randomised to treatment group **Prescription**: 1.5 g/day of $MgSO_4$ infusion **Preparation**: NS **Administration**: IV infusion over 4 h the day before surgery, just after surgery, and once daily for four days after surgery **Monitoring**: Clinical monitoring—12-lead ECG performed on the day before surgery, just after surgery, and once daily for four days postoperatively. Patients continuously monitored with alarm-triggered bedside monitors during ICU stay and then with an alarm-triggered 7-lead telemetry system until postoperative day 4 Laboratory tests—Mg^{2+} level measured before treatment and daily for postoperative days 1–4 Mg^{2+} serum levels/ranges—Reference range 1.58–2.55 mg/dL
Forlani et al., 2002	Randomised controlled trial	Sample size: 207 4 arms—54 in the Mg^{2+} group, 51 in the sotalol group, 52 in the Mg^{2+} and sotalol group, and 50 patients in the control group	To prevent POAF	**Indication**: Patients randomised to Mg^{2+} groups **Prescription**: 1.5 g of IV $MgSO_4$ daily **Preparation**: NS **Administration**: Given daily from just before CPB until day five postoperatively **Monitoring**: Clinical monitoring—Haemodynamics continuously monitored during operation and for the first 48 h postoperatively. Cardiac monitored until the morning of postoperative day 2, then 12-lead ECG performed every 8 h until discharge Laboratory tests—Stated that Ca^{2+} and K^{+} levels similar among groups but NS details or aims. Monitoring of blood serum levels for electrolytes was performed preoperatively and every day after the operation Mg^{2+} serum levels/ranges—NS

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Table 1 (*continued*)

Study citation	Study design	Sample size + study arms	Study aim	Medication cycle–relevant findings
Hamid et al., 2008	Randomised controlled trial	Sample size: 104 2 arms—53 patients in the Mg^{2+} group and 51 patients in the control group	To prevent POAF	**Indication**: Patients randomised to the Mg^{2+} group **Prescription**: 2 g of $MgSO_4$ (coded) **Preparation**: 2 g of $MgSO_4$ in 100 ml of NaCl **Administration**: IV administered over 30 min **Monitoring**: Clinical monitoring—Cardiac monitoring before induction of anaesthesia and continued for 24 h Laboratory tests—Serum Mg^{2+} levels measured preoperatively, on shift to the ICU and at 6, 12, and 24 h postoperatively Mg^{2+} serum levels/ranges—NS
Hazelrigg et al., 2004	Randomised controlled trial	Sample size: 202 2 arms—105 patients in the Mg^{2+} group and 97 patients in the control group	To examine the effects of prophylactic Mg^{2+} on arrhythmias	**Indication**: Patients randomised to the Mg^{2+} group **Prescription**: 80 mg/kg ideal body weight $MgSO_4$ preoperatively, then 8 mg/kg ideal body weight $MgSO_4$ postoperatively **Preparation**: 80 mg/kg ideal body weight $MgSO_4$ in 100 ml of 5% glucose (preoperative), then 8 mg/kg ideal body weight $MgSO_4$ in 100 ml of 5% glucose (postoperative) **Administration**: 80 mg/kg given over 30 min pre-CPB, then 8 mg/kg over 24 h twice **Monitoring**: Clinical monitoring—Continuous cardiac telemetry monitoring Laboratory tests—Blood and tissue samples were taken preoperatively, immediately post-operative day of surgery in PM, day one postoperatively AM and PM, day two postoperatively AM, and then daily postoperative days 3, 4, and five (times not specified) Mg^{2+} serum levels/ranges—NS
Kiziltepe et al., 2003	Randomised controlled trial	Sample size: 100 2 arms—50 patients in the Mg^{2+} group and 50 patients in the control group	To examine $MgSO_4$ as an antiarrhythmic drug	**Indication**: Arrhythmia development **Prescription**: 1.5 g of $MgSO_4$ over 5–10 min **Preparation**: NS **Administration**: Bolus over 5–10 min, repeated if no response after 15 min **Monitoring**: Clinical monitoring—Arrhythmias monitored during ICU care Laboratory tests—NS Mg^{2+} serum levels/ranges—Normal levels between 1.8 and 2.5 mEq/L
Klinger et al., 2015	Randomised controlled trial	Sample size: 363 2 arms—186 patients in the Mg^{2+} group and 177 patients in the control group	To evaluate whether high-dose Mg^{2+} decreases new POAF	**Indication**: Patients randomised to Mg^{2+} group and standard $MgSO_4$ postoperative therapy **Prescription**: 50 mg/kg bolus over 20 min after induction of anaesthesia, followed by 50 mg/kg over 3 h (coded) **Preparation**: NS **Administration**: Bolus over 20 min after induction of anaesthesia, followed by infusion over 3 h **Monitoring**: Clinical monitoring—Telemetry monitoring until hospital discharge Laboratory tests—Blood tests at baseline, post bolus, on admission to the ICU, and 24- and 48-h after initial bolus Mg^{2+} serum levels/ranges—$MgSO_4$ replacement given when serum level ranges 1.8–2.0 mg/dL (no reference)
Laiq, Khan, Mailk, & Ahmad, 2013	Randomised controlled trial	Sample size: 100 2 arms—50 patients in the Mg^{2+} group and 50 patients in the control group	To prevent POAF	**Indication**: Patients randomised to Mg^{2+} group and hypomagnesaemia **Prescription**: 40 mg/kg of $MgSO_4$ 30 min preoperatively and then repeated 30 min intraoperatively (coded) **Preparation**: 40 mg/kg of $MgSO_4$ in 100 ml of NaCl **Administration**: IV infusion given 30 min preoperatively and 30 min intraoperatively **Monitoring**: Clinical monitoring—Routine haemodynamic monitoring and daily ECG

				Laboratory tests—ABG performed postoperatively just after arrival to the ICU, then every 4 h and as needed. Formal blood levels monitored 12 h preoperatively, 1 h postoperatively, and on postoperative days 1, 2, and 3 Mg^{2+} serum levels/ranges—Normal limits stated 1.8 −2.5 mg/dL (no reference)
Mariscalco, Cederlund, & Engström, 2007	Randomised controlled trial	Sample size: 893 2 arms—49 patients in the sotalol and Mg^{2+} group and 844 patients in the control group	To assess the compliance of the suggested prophylactic treatment	**Indication**: Patients randomised to the Mg^{2+} and sotalol group **Prescription**: 20 mmol $MgSO_4$ **Preparation**: NS **Administration**: NS **Monitoring**: Clinical monitoring—Telemetry for minimum 48 h after operation, then daily ECG until 96 h after operation Laboratory tests—Electrolyte levels measured preoperatively and every day postoperatively Mg^{2+} serum levels/ranges—Only stated suggested toxic level of Mg^{2+} is 2.5 mmol/L (with a reference)
Najafi, Haghighat, & Tafti, 2007	Quasi-experimental	Sample size: 170 1 arm—170 patients in the Mg^{2+} group	To evaluate the relationship between total Mg^{2+} blood level and perioperative arrhythmias	**Indication**: Nil (all patients received Mg^{2+}) **Prescription**: NS **Preparation**: NS **Administration**: Patients received 2.5 g of $MgSO_4$ on average (range between 1 and 6 g) **Monitoring**: Clinical monitoring—Monitored for three days from the time of surgery (NS type of monitoring) Laboratory tests—Serum Mg^{2+} measured preoperatively just before anaesthesia, on arrival to the ICU and on the first morning postoperatively Mg^{2+} serum levels/ranges—Hypomagnesaemia defined as serum Mg^{2+} level <1.5 mg/dL
Najafi, Hamidian, et al., 2007	Randomised controlled trial	Sample size: 345 2 arms—166 patients in the Mg^{2+} group and 179 patients in the control group	To examine the effects of prophylactic Mg^{2+} on post-CABG arrhythmias	**Indication**: Patients randomised to Mg^{2+} group **Prescription**: 10 g of IV $MgSO_4$ continuous infusion at a constant rate **Preparation**: NS **Administration**: Continuous infusion at constant rate (2 g after induction of anaesthesia until the start of cardiopulmonary bypass (CPB) and 8 g after CABG until 24 h postoperatively) **Monitoring**: Clinical monitoring—Continuous ECG monitoring for those who required interventions Laboratory tests—Serum Mg^{2+} levels checked at the onset of induction, 0, 24, and 48 h after ICU admission Mg^{2+} serum levels/ranges—Hypomagnesaemia defined as serum Mg^{2+} level <1.6 mg/dL
Solomon, Berger, Trivedi, Hannan, & Katz, 2000	Randomised controlled trial	Sample size: 167 2 arms—82 patients in the propranolol group and 85 patients in the Mg^{2+} and propranolol group	To test the hypothesis that adjunctive $MgSO_4$ improves efficacy of β-blockers in POAF prevention	**Indication**: Patients randomised to intervention group **Prescription**: 2 g of IV bolus $MgSO_4$ over 10 min and then continuous infusion of 16 g over the next 24 h **Preparation**: NS **Administration**: Bolus over 10 min and then continuous infusion over 24 h **Monitoring**: Clinical monitoring—Continuous alarm-triggered ECG monitoring in the ICU Laboratory tests—NS Mg^{2+} serum levels/ranges—NS
Svagzdiene, Sirvinskas, Benetis, Raliene, & Simatoniene, 2009	Randomised controlled trial	Sample size: 165 2 arms—55 patients in the Mg^{2+} group and 110 patients in the control group	To assess the incidences of AF	**Indication**: Patients randomised to Mg^{2+} group **Prescription**: 40 mg/kg of $MgSO_4$ after anaesthesia induction and then 500 mg/h maintenance infusion **Preparation**: NS **Administration**: 40 mg/kg of $MgSO_4$ after anaesthesia induction and then 500 mg/h maintenance infusion

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Table 1 (*continued*)

Study citation	Study design	Sample size + study arms	Study aim	Medication cycle–relevant findings
				Monitoring: Clinical monitoring—ECG monitoring throughout the study Laboratory tests—Electrolyte concentrations examined before CPB, immediately postoperatively, on arrival to the ICU and, the next morning after surgery Mg^{2+} serum levels/ranges—Hypomagnesaemia defined as serum Mg^{2+} level <0.7 mmol/L
Tiryakioglu et al., 2009	Quasi-experimental	Sample size: 192 3 arms—64 patients in the Mg^{2+} group, 64 patients in the amiodarone group, and 64 patients in the control group	To assess prophylactic $MgSO_4$ and amiodarone in treating post-CABG arrhythmias	**Indication**: Patients in Mg^{2+} group **Prescription**: 3 g of IV $MgSO_4$ for 2 h **Preparation**: 3 g of IV $MgSO_4$ in 100 ml of NaCl **Administration**: 3 g given 12 h before surgery, immediately after surgery, and on postoperative days 1, 2, and 3 **Monitoring**: Clinical monitoring—Patients were monitored for at least 24 h postoperatively, with ECG at 0, 6, and 12 h postoperatively and on postoperative days 1, 2 and 3 Laboratory tests—Venous Mg^{2+} blood levels checked immediately after surgery and on postoperative days 1, 2, and 3 (K^+, Na^+, and Ca^{2+} also tested at these times and replaced as required) Mg^{2+} serum levels/ranges—NS
Toraman et al., 2001	Randomised controlled trial	Sample size: 200 2 arms—100 patients in the Mg^{2+} group and 100 patients in the control group	To assess intermittent Mg^{2+} infusion on POAF	**Indication**: Patients randomised to Mg^{2+} group **Prescription**: 6 mmol $MgSO_4$ over 2 h **Preparation**: 6 mmol $MgSO_4$ in 100 ml of NaCl **Administration**: Infusion over 4 h the day before surgery, after CPB and then once daily for four days postoperatively **Monitoring**: Clinical monitoring—Continuous alarm-triggered bedside monitoring in the ICU, then alarm-triggered 7-lead telemetry until the morning of day five postoperatively. ECGs preoperatively and postoperatively on days 0–5 Laboratory tests—Serum Mg^{2+}, K^+, and Ca^{2+} taken the day before surgery, 12 h post-CPB, and each morning for the first four days postoperatively. Blood gases were monitored but timing NS Mg^{2+} serum levels/ranges—Reference range 0.7–1.05 mmol/L
Treggiari-Venzi et al., 2000	Randomised controlled trial	Sample size: 155 2 arms—100 patients in the Mg^{2+} group and 100 patients in the control group	To assess whether amiodarone and $MgSO_4$ prevent POAF post-CABGs	**Indication**: Patients randomised to Mg^{2+} group **Prescription**: $MgSO_4$ 4 g per 24 h **Preparation**: NS (done by pharmacy staff) **Administration**: 4 g per 24 h for 72 h **Monitoring**: Clinical monitoring—Holter ECG during 72 h postoperatively and 12-lead ECGs every 12 h Laboratory tests—6-hourly ABGs and electrolytes (K^+, Na^+, and Ca^{2+}) and 12-hourly formal plasma Mg^{2+} levels Mg^{2+} serum levels/ranges—NS
Wilkes, Mallett, Peachey, Di Salvo, & Walesby, 2002	Randomised controlled trial	Sample size: 85 2 arms—43 patients in the Mg^{2+} group and 42 patients in the control group	To prevent arrhythmias after CABG	**Indication**: Patients randomised to Mg^{2+} group with measured ionised Mg^{2+} levels **Prescription**: $MgSO_4$ 10 mmol over 20 min **Preparation**: $MgSO_4$ 10 mmol in 50 ml of NaCl over 20 min **Administration**: Infusion over 20 min **Monitoring**: Clinical monitoring—Holter monitoring for 72 h Laboratory tests—Ionised and total plasma Mg^{2+} measured before surgery, twice during CPB cold, CPB warm, after CPB in surgery and within 1 h after surgery Mg^{2+} serum levels/ranges—0.45–0.6 mmol/L for ionised plasma Mg^{2+} and 0.7–1.0 mmol/L for total plasma Mg^{2+} (NS rationale or reference for either of these)

Legend: AF, atrial fibrillation; CABG = coronary artery bypass grafting; ECG = electrocardiogram; ICU = intensive care unit; NS = not stated, Ca^{2+} = calcium, Na^+ = sodium; IV = intravenous; POAF = postoperative atrial fibrillation.

(n = 18, 75%), and 23 out of the 24 studies (95.8%) excluded patients with common comorbidities typically observed in clinical practice. In total, 53 exclusion criteria were identified in the included studies, with between 3 and 15 exclusions in each study. Common exclusion criteria were as follows: <50 or >75 years old, emergency surgery, previous CABG or heart surgery, female, left ventricular ejection fraction less than normal, concomitant procedure or surgery, hemodynamically unstable, pacemaker or automated implantable cardioverter defibrillator, valvular disease, congestive heart failure, unstable angina pectoris, history of AF or arrhythmias, previous antiarrhythmic drug use, or history of diuretic use. These extensive exclusion criteria included common comorbidities and clinical conditions experienced by a large majority of the cardiac surgery patient population, demonstrating a disconnect between these studies and current clinical practice.

Risk of bias was assessed and found to be evident in all studies at the preintervention, intervention, or postintervention stages, as outlined in Table 2. Potential for selection bias was most common and related to restrictive patient inclusion criterion, small sample sizes, and concurrent administration of electrolyte and antiarrhythmic medications. This risk of bias analysis contributed to the overall quality appraisal of the included studies, presented in Table 3 (Supplementary Material). Owing to the nature of this research, which examined $MgSO_4$ medication safety practices rather that its efficacy, it was not necessary to exclude any studies because of poor quality.

4.2. Indication

In a third of the studies (n = 8, 33.3%), the timing of $MgSO_4$ administration during the postoperative period was not stated.[38–45] In the majority, $MgSO_4$ was administered as part of routine postoperative care for cardiac surgery patients (n = 21, 87.5%). In three studies (12.5%), criteria were used as indications for Mg^{2+} administration: two (8.3%) used hypomagnesaemia,[46,47] and one used arrhythmia development (4.2%).[42]

4.3. Prescription

In 21 (87.5%) of the 24 included studies, the method of communicating the Mg^{2+} prescription was not specified. Nearly all studies included prescription details (n = 23, 95.8%) in which $MgSO_4$ doses ranged from 6 to 40 mmol/L. In a small number of studies, patient weight was used to calculate the $MgSO_4$ doses (n = 4, 16.67%) with doses ranging between 40 and 80 mg/kg.[41,43,45,46] Administration duration also varied between 5 min and 24 h. No studies provided a justification or clinical rationale for the prescription used.

4.4. Preparation

Eleven studies (45.8%) provided insufficient information to determine how the $MgSO_4$ was prepared.[40,42–45,48–53] The other 13 reported varying concentrations of $MgSO_4$ used, although nine specified it was diluted in normal saline (0.9% NaCl). Four studies reported that $MgSO_4$ was prepared by pharmacy staff (16.7%) to ensure blinding;[39,53–55] however, in the remaining 20 studies (83.3%), it was not stated who prepared the $MgSO_4$ for administration.

4.5. Administration

The regimen used to administer $MgSO_4$ to the patient was reported in all but one study (n = 23, 95.8%). Only 14 (58.3%) studies included details about $MgSO_4$ administration during each of the three time periods, 0–24 h, 24–48 h, and 48–72 h postoperatively.

4.6. Monitoring

Most studies reported that clinical monitoring, including electrocardiography, was used postoperatively (n = 22, 91.7%). Laboratory monitoring was reported in 18 studies (75%), with six not stating if any was used (25%). Details of the Mg^{2+} blood serum

Table 2
Domains of bias for each included study.

Study citation	Pre-intervention	At intervention	Post-intervention				
	Selection bias	Detection bias	Performance bias	Detection of problems	Attrition	Attrition bias	Reporting bias
Allen, Heimansohn, Robison, Schier, & Griffith, 2006	+	+	+	+	+	+	+
Bakhsh, Abbas, Hussain, Ali Khan, & Naqvi, 2009	+	+	+	+	+	+	–
Behmanesh et al., 2006	+	+	+	+	+	–	–
Brackbill & Moberg, 2005	+	+	+	NS	NS	–	+
Cagli et al., 2006	+	+	+	NS	+	–	+
Carrió et al., 2012	+	+	+	+	NS	+	+
Cook et al., 2009	+	+	+	+	+	+	+
Dabrowski et al., 2008	+	+	+	NS	NS	–	+
Dagdelen, Toraman, Karabulut, & Alhan, 2002	+	+	+	+	NS	–	–
Forlani et al., 2002	+	+	+	+	+	+	+
Hamid et al., 2008	+	+	+	+	NS	NS	+
Hazelrigg et al., 2004	+	+	+	+	NS	NS	+
Kiziltepe et al., 2003	+	+	+	NS	+	+	+
Klinger et al., 2015	+	+	+	NS	+	+	+
Laiq, Khan, Mailk, & Ahmad, 2013	+	+	+	+	+	–	+
Mariscalco, Cederlund, & Engström, 2007	+	+	+	+	+	+	+
Najafi, Haghighat, & Tafti, 2007	+	+	–	+	+	NS	+
Najafi, Hamidian, et al., 2007	+	+	+	NS	+	+	+
Solomon, Berger, Trivedi, Hannan, & Katz, 2000	+	+	+	+	+	+	+
Svagzdiene, Sirvinskas, Benetis, Raliene, & Simatoniene, 2009	+	+	+	NS	+	–	+
Tiryakioglu et al., 2009	+	+	+	NS	–	–	–
Toraman et al., 2001	+	+	+	+	+	–	–
Treggiari-Venzi et al., 2000	+	+	+	+	+	+	+
Wilkes, Mallett, Peachey, Di Salvo, & Walesby, 2002	+	+	+	+	+	+	+

Legend: + = bias present; - = bias not present; NS = bias not stated.

levels, the ranges used for reference, or the clinical aims were reported in 14 (58.3%) studies, but these varied considerably, with low-end ranges of normomagnesemia from 0.65 to 0.8 mmol/L and high-end ranges from 1 to 1.2 mmol/L.

5. Discussion

This review found limited evidence to inform guidelines to standardise Mg^{2+} replacement therapy administered by nurses to postoperative cardiac surgical patients. Meta-analysis or direct comparison of studies could not be performed because ofthe high variability between studies in the clinical conditions examined, use of concurrent medications, and differing research aims which addressed the efficacy of $MgSO_4$ in POAF prevention rather than the safety and management of $MgSO_4$ replacement therapy.

5.1. Relevance to current clinical practice

Most of the included studies were limited in their relevance to current clinical practice because of the high number of patient exclusions. Up to 15 exclusion criteria were used, suggesting that the data obtained may not represent typical patient populations seen in current nursing practice. For example, older people, females, and patients with comorbidities and chronic diseases were underrepresented in the clinical trials included in this review, a finding consistent with previous reports of limitations of clinical trials.[56]

In Australia, 66% of the adult population has three or more risk factors for cardiovascular disease, and as those with multiple comorbidities have a higher risk for cardiovascular disease, these patients are more likely to undergo cardiac surgery.[57] Patients with additional characteristics that are common in cardiac patient populations, such as renal impairment, diabetes, and concurrent surgeries, were also often excluded in the published studies.[39]

The significance of renal failure and patient diuretic use in cardiac surgery patients is that Mg^{2+} elimination by the body primarily occurs in the kidneys[58]; therefore potential for harm to the kidneys from medications such as diuretics should be clinically monitored.[59] Measurable signs of chronic kidney disease were found in approximately 10% of adult Australians in 2011–2012, with 97% of these being early signs.[60] The clinical importance of renal function monitoring among cardiac surgery patients was not apparent in most of the included studies. Complex patients were underrepresented in the studies but are overrepresented in the population for which the recommendations of this review are expected to be relevant.

5.2. Indication

In most (n = 21, 87.5%) of the included studies, patients were randomised or assigned to receive $MgSO_4$ with no specific indications. This makes it difficult to develop recommendations about definitive indications for $MgSO_4$ replacement therapy. However, as adverse events were rare with routine administration of $MgSO_4$, it may be considered part of usual postoperative care rather than requiring specific indications, as seen in previously published guidelines.[18,20]

5.3. Prescription

Significant discrepancies between studies in the prescribed doses of $MgSO_4$ were concerning. These ranged between 6 and 40 mmol/L, and authors did not provide any evidence or explanation to justify doses. Similarly, the four studies that used patients' body weights to calculate $MgSO_4$ doses reported wide variation and failed to provide any evidence to support their decisions.[41,43,45,46] Despite the variations seen in $MgSO_4$ prescriptions, few adverse effects were reported, suggesting that the doses of $MgSO_4$ may not have directly contributed to patient adverse outcomes in these studies. Again, these findings make it difficult to draw conclusions or make recommendations about doses for $MgSO_4$ prescriptions.

5.4. Preparation

Unfortunately, most of the included studies did not specify how or by whom the $MgSO_4$ was prepared. Safe medication management requires a qualified person to prepare the medication to the correct concentration for delivery to the patient.[28] Previous research has shown that when medication preparation is performed by registered nurses, there is improved medication management, reduced errors, and fewer interruptions to medication handling.[23,28,61]

5.5. Administration

As POAF is most likely to occur within 72 h of cardiac surgery,[6] data extraction focussed on $MgSO_4$ administered in three time periods; 0–24 h, 24–48 h, and 48–72 h after surgery. Data about Mg^{2+} administration in these time periods were infrequently reported; hence, findings are inconclusive. In the 24 examined studies, the duration of administration ranged from 5 min to 24 h with no explanations provided. Again, insufficient data made it difficult to draw conclusions or make recommendations in relation to duration of administration. Most of the examined studies used concurrent medications with $MgSO_4$, including antiarrhythmics and other electrolytes. This is consistent with existing clinical practice recommendations for POAF prevention in cardiac surgery patients, reinforcing that concurrent electrolyte and β-blocker administration is safe.[18–20]

5.6. Monitoring

Clinical and laboratory monitoring is recommended to detect complications and treat abnormalities in critical care patients receiving $MgSO_4$ replacement therapy.[14,28,62] Of the 24 studies included in this review, two did not report on the clinical monitoring used,[38,63] and six did not report on laboratory monitoring (including blood tests).[38,42,48,52,63,64] Details provided about clinical monitoring use in the studies were variable. For example, Dabrowski[49] used only continuous heart rate monitoring, whilst other studies specified observations and alarm reviews.

In 14 studies, Mg^{2+} blood serum level reference ranges or criteria used to detect hypomagnesaemia were specified;[39,42–51,54,65,66] however, no evidence to support the use of these values was provided. Insufficient data were found to inform recommendations about laboratory monitoring, such as specific timing and parameters for blood serum level measurements.

Potential for reporting, interpretation and publication biases, and risks of error in interpretation of clinical conditions was evident in studies that used local laboratory testing,[49] and the use of nonstandard, inconsistent values for Mg^{2+} blood serum levels was evident in the included studies.

5.7. Limitations

Several limitations of this research are worth noting. First, protocols were not evaluated in this review, and heterogeneity between studies, inconsistencies in data collection, and gaps in reporting limited the data available to examine the five steps in medication management. Hence, few recommendations could be made from this review.[67]

Examining the medication cycle steps, as well as study quality and risk of biases, were integral for the interpretation of the data and ensuring the findings were relevant for informing clinical practice guidelines to standardise nurse administration of $MgSO_4$ replacement therapy. Most studies examined a different research question which investigated the efficacy of $MgSO_4$ replacement therapy, rather than medication management and safety practices that are important for nurse administration. This made it difficult at times to extract useful data from the studies and meant that no studies were excluded using quality criteria as they addressed a different primary research question.

The comprehensive search of reputable databases identified three studies not available in English and full text[68–70] and seven studies with only abstracts available.[71–77] Data from these studies were inaccessible or incomplete, despite assistance from specialist nursing research librarians, and were therefore excluded from this review. It is not known if the inclusion of these studies would have resulted different findings. Similarly, the exclusion criteria used for study selection were another limitation. Inclusion and exclusion criteria were chosen to best reflect the clinical context of nursing practice that was the focus of the review, limiting the findings of this review in their relevance to other clinical environments.

5.8. Clinical practice implications

Overall, the quality of the information extracted from the included studies had significant gaps in relation to current nursing practices relevant to medication safety for $MgSO_4$ replacement therapy. Despite this, recommendations for two of the steps in the management of $MgSO_4$ replacement therapy in postoperative cardiac surgery patients were identified:

Administration—It is safe to administer $MgSO_4$ concurrently with other medications as recommended as the best practice for prevention of POAF in cardiac surgery patients (NHMRC Level III evidence).[34]

Monitoring—Patients receiving $MgSO_4$ should have clinical and laboratory monitoring (including vital signs, electrocardiography, and blood serum levels) to prevent hypomagnesaemia (NHMRC Level III evidence).[34]

Despite limited evidence, patterns identified after data synthesis suggest that routine $MgSO_4$ replacement therapy is safe for use in postoperative cardiac surgery patients; however, there is a lack of evidence to guide standardisation of practice, and this should be the subject of further investigation:

Indication—$MgSO_4$ can be considered in routine management of postoperative cardiac surgery patients (NHMRC Level IV evidence).[34]

Most importantly, this review identified significant gaps and insufficient research evidence to guide nursing practice in several medication cycle steps. Further research is needed to address these gaps before guidelines to standardise nursing management of $MgSO_4$ replacement therapy can be developed. The following factors could be considered for further research:

Indication—studies in which sample characteristics and research protocol are reflective of current clinical practice; specifically, fewer exclusion criteria, consistent study protocol and concurrent medication administration, as well as specific Mg^{2+} blood serum levels as indication for $MgSO_4$ replacement therapy.

Prescription—prescriber decision-making in electrolyte replacement, including Mg^{2+} and K^+ blood serum levels, renal function and concurrent medications; body weight-dependent dosage versus standardised prescriptions for $MgSO_4$ replacement therapy.

Administration—timing of $MgSO_4$ administration postoperatively, including use of bolus doses.

Monitoring—standardised hypomagnesaemia and normomagnesemia definitions with timing of Mg^{2+} blood serum levels before and after electrolyte replacement.

6. Conclusions

This systematic literature review revealed limited evidence to support standardisation of nursing management of $MgSO_4$ replacement therapy in postoperative cardiac surgery patients. A systematic review method was used to synthesise evidence relevant to the five steps of the medication cycle where IV $MgSO_4$ was given as prevention for POAF in cardiac surgery patients. It identified two clinical practice recommendations, as well as a number of gaps in the available evidence. The two recommendations for clinical practice are as follows: (i) $MgSO_4$ replacement therapy can be concurrently administered with other medications recommended as the best practice for prevention of POAF and (ii) clinical and laboratory monitoring, including vital signs, electrocardiography, and Mg^{2+} blood serum levels, should be performed for patients receiving $MgSO_4$ replacement therapy to prevent hypomagnesaemia.

Insufficient evidence limited development of a guideline to standardise $MgSO_4$ replacement therapy by nurses. On the basis of this research, which identified inconsistent, incomplete, and at times contradictory data from the examined studies, low-level evidence was identified for only two recommendations. Further studies addressing the indication, prescription, preparation, administration, and monitoring gaps in research evidence are required.

Limited evidence and variability in medication management practices may pose a safety risk for patients. Nurses, especially those working in critical care settings with cardiac surgical patients, need high-level evidence-based resources to ensure standardisation of care which decreases the risks of clinical or procedural errors. Expert opinion and current clinical practice should be examined in future studies to help fill this gap, and further clinical trials should be undertaken to inform recommendations for practice and development of clinical guidelines to standardise $MgSO_4$ replacement therapy for postoperative cardiac surgery patients.

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Authors' contributions

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CRediT authorship contribution statement

Rebecca Jedwab: Conceptualisation, Methodology, Validation, Formal Analysis, Investigation, Writing – Original Draft, Writing – Review & Editing. **Alison Hutchinson:** Conceptualisation, Methodology, Validation, Writing – Original Draft, Writing – Review & Editing, Supervision. **Bernice Redley:** Conceptualisation, Methodology, Validation, Formal Analysis, Investigation, Writing – Original Draft, Writing – Review & Editing, Supervision.

Appendix A. Supplementary data

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