The effectiveness of magnesium for neuroprotection during global cerebral ischemia associated with cardiac arrest or cardiac surgery

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Abstract

The objective of this systematic review derived thesis is to present the best available evidence on the use of magnesium for neuroprotection during global cerebral ischemia associated with cardiac surgery and cardiac arrest in adults. This systematic review utilizes the JBI methodology for quantitative reviews presenting JBI level of evidence 1.a (a systematic review of randomised controlled trials).

The presupposition of this thesis is that for patients who survive global ischemia, improved neurological outcome can improve quality of life. This review considered adults above 18 years of age without pre-existing neurological deficits. The intervention of interest was magnesium administered in doses of at least of two grams compared to placebo to adult patients within 24 hours of cardiac arrest or cardiac surgery.

Seven trials were included in this review with 988 participants meeting the inclusion criteria. To enable assessment of the available datum, neuroprotection was examined by breaking down neurological outcomes into three domains; functional neurological outcomes, neurophysiological outcomes and cognitive function.

The evidence presented in this review highlights the fact that magnesium may provide improved functional neurological outcome for patients with global cerebral ischemia. However, current evidence does not support the view that magnesium improves long-term cognitive function.

The individual studies investigating the neuroprotective effects of magnesium during cardiac arrest did not show statistical improvement on neurological outcome. Pooled datum using meta-analysis from the three trials favored magnesium to improve neurological outcome post cardiac arrest. There was no data available for neurophysiological and cognitive function post cardiac arrest.

For patients post cardiac surgery, there is limited evidence to suggest that magnesium administration may improve functional neurological and neurophysiological outcomes. There was no improvement noted in cognitive function, where cognitive decline is noted in both placebo and magnesium populations.

This review concludes that research into the neuroprotective properties of magnesium is somewhat fragmented, with no standard criteria to assess all of the neurological outcome domains. Future research on neuroprotection should involve outcomes from each of the neurological domains, at multiple time points in combination with imaging modalities.

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Chapter 1: Introduction

Chapter introduction

The focus of this chapter is to provide the context of this thesis, highlighting relevant physiology, importance of evidence based health care as a lead in to the presentation of the methods, results and discussion of findings from a systematic review. The review focuses on magnesium as a neuroprotective agent for populations at risk of global ischemia associated with cardiac arrest and cardiac surgery utilizing the methodology of Joanna Briggs Institute (JBI). JBI is a leading international organisation for evidence based health care, facilitating the synthesis, transfer and utilization of evidence from primary research to clinical practice, in a range of fields including health sciences, humanities and social sciences.[1] Synthesis through systematic review involves rigorous standardized methods to ensure transparency and auditability of the reporting and to enable verification of the results.

The context of this review is centred on the premise global cerebral ischemia is caused by hypoperfusion of the entire brain, resulting in diffuse ischemic injury. Myocardial dysfunction caused by cardiac arrest or cardiac surgery resulting in hemodynamic collapse is one of the many causes of global cerebral ischemia.[2, 3] In an ischemic environment, neurological cellular functions begin to fail within minutes, resulting in irreversible pathological damage due to a number of complex biochemical processes, (described in detail later).[4] Neurological decline is well documented in patients with global cerebral ischemia associated with cardiac surgery[5-8] and cardiac arrest.[2, 9, 10] It is clear that survival is not the only important patient outcome, because neurological dysfunction decreases quality of life and can increase morbidity and mortality considerably.

At the time of drafting this thesis, there were no other systematic reviews published that specifically focused on addressing the neuroprotective properties of magnesium during global cerebral ischemia associated with cardiac arrest and cardiac surgery in humans. Neurological injury due to global cerebral ischemia associated with both cardiac surgery and cardiac arrest shares common pathophysiological mechanisms, therefore studies from both clinical situations have been included in this review.

Cardiac surgery

The risk of global cerebral ischemia related to cardiac surgery is associated with surgical procedures requiring iatrogenically induced cardiac arrest,[8] and the use of cardiac bypass techniques.[7] Cardiac bypass, also referred to as a cardiopulmonary bypass, is a technique commonly used for surgeries including: coronary artery bypass surgery, aneurysm, valvular and ascending thoracic aortic repair and heart transplantations.[11] Circulation and tissue perfusion during ‘on pump’ cardiac surgery are maintained by extracorporeal cardiopulmonary bypass techniques.[11] This procedure involves surrogate technology temporarily performing external respiration, oxygenation and circulation of the patients’ blood, with redirection of blood from the heart and lungs during surgery.[11] *Figure 1.1* is a schematic representation of the typical cardiopulmonary bypass setup.

Whilst cardiac surgery is often performed to increase quality of life, neurological decline and cognitive changes after cardiac surgery have been noted in some patients.[12] Cognitive dysfunction is apparent in 50% to 80% of cardiac surgery patients at hospital discharge, 20% to 50% at six weeks and 10% to 30% at six months, post operatively.[5] The causes are thought to be multifactorial, including patient independent risk factors combined with the sequelae of global cerebral ischemic injury.[13]

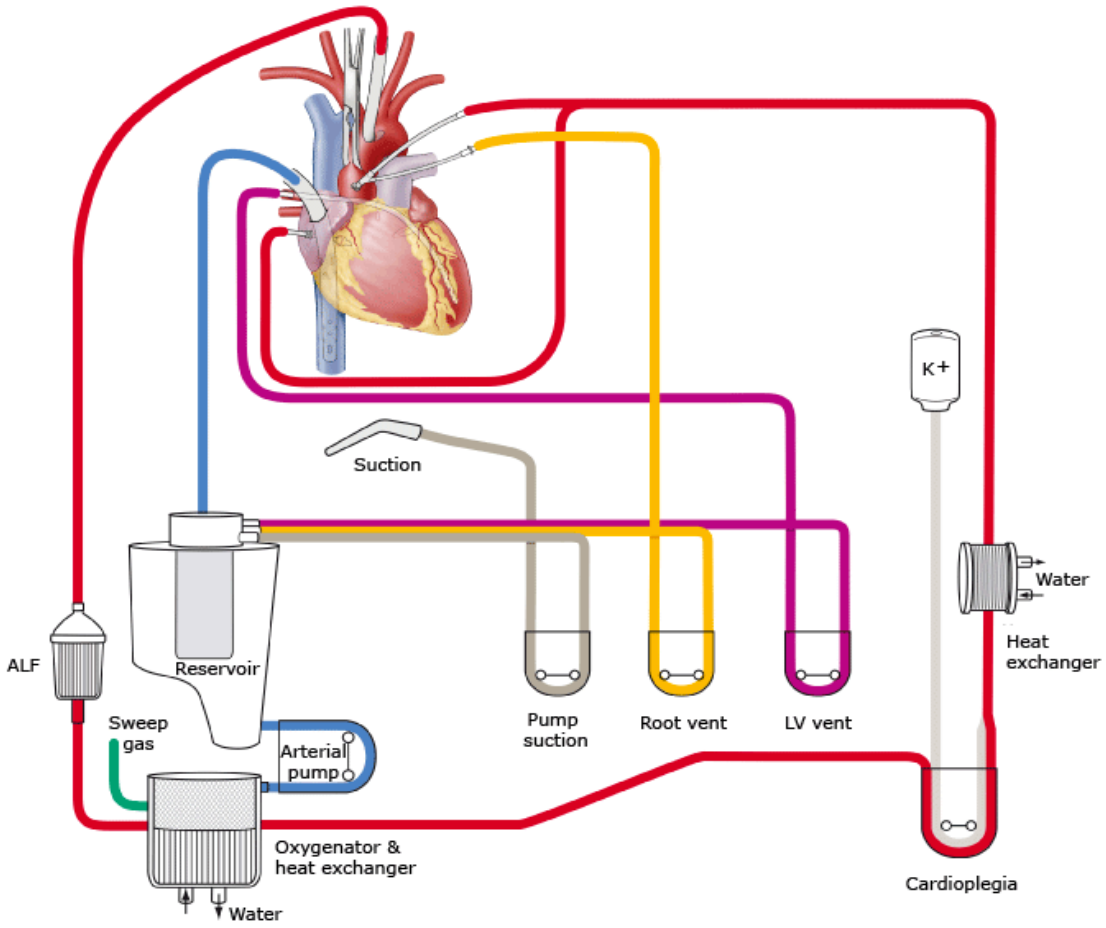

Figure 1.1: schematic representation of cardiopulmonary bypass[11] (ALF: arterial line filter, LV: left ventricular, K+ cardioplegia solution)

Cardiac arrest

Cardiac arrest is the spontaneous cessation of myocardial activity, usually precipitated by cellular insults such as hypoxia, toxic injury, metabolic disturbances or trauma. Survival outcomes post cardiac arrest are generally very poor.[2] For out-of–hospital cardiac arrest, survival (to 28 days) for bystander-witnessed incidents is 10.6%.[14] When cardiac arrest is witnessed by Emergency Medical Services (EMS), a 33% survival rate has been reported.[14] This data is limited to shockable rhythms only, including ventricular fibrillation (VF) or ventricular tachycardia (VT). Survival rates for in-hospital cardiac arrest are slightly higher. The survival rate at hospital discharge increases to between 14% to 32%, depending on initial rhythm.[15, 16] Patients may survive cardiac arrest due to resuscitation and advanced life support practices, however post cardiac arrest syndrome,[17] including extensive cerebral damage may prevent

full neurological recovery.[3, 10] Current estimations suggest only three to seven percent of cardiac arrest survivors return to their pre-cardiac arrest level of neurological functioning.[10]

Magnesium for neuroprotection

Several neuroprotective interventions have been investigated for capacity to improve neurological outcomes, patient quality of life and reduce morbidity and mortality associated with these conditions.[14] One of these interventions is administration of the endogenous electrolyte, magnesium. Magnesium is thought to be beneficial as a neuroprotective agent for global cerebral ischemia due to its multifaceted cellular mechanisms, which are described in detail in chapter 2.[18] Primary research in this area has produced inconsistent results and individual human trials have not reflected the efficacy of magnesium for neuroprotection reported in animal trials. This quantitative systematic review analysed randomized controlled trials investigating magnesium for neuroprotection during cardiac surgery and cardiac arrest.

Statement of the review objectives

The objective of this systematic review was to provide the best available evidence related to the neuroprotective effects of magnesium during a period of global cerebral ischemia in adults with cardiac arrest or cardiac surgery. Neurological outcomes were examined and an investigation of optimal magnesium dosing regimens was considered.

The Joanna Briggs Institute Model of Evidence Based Health Care

Established in 1996 as a joint initiative of the Royal Adelaide Hospital and the University of Adelaide, the JBI has become an international research institute and collaborative venture for evidence based health care, with over 70 centres globally.[19] The JBI approach considers EBHC to be dependent on the evidence as well as the context in which health care is delivered. It is reliant on diverse types of evidence (evidence of feasibility, appropriateness, meaningfulness and effectiveness) that are brought together after knowledge creation (evidence generation) through synthesis, then transferred to relevant settings and implemented within local contexts.[19, 20] Global health issues are a driver and reason for evidence based health care, and provide the framework for systematic reviews of international literature to inform local policy/practice domains; this approach recognises that international evidence is a more robust basis for decision making than local knowledge alone, or narrow conceptualisations of evidence. [19, 20]

Figure 1.2: The JBI Conceptual Model of evidence based healthcare.

The JBI conceptual model of evidence based health care is presented as an iterative process contributing to global health through four major programs:

I. Evidence generation;
II. Evidence synthesis;
III. Evidence (knowledge) transfer; and
IV. Evidence implementation

Health care evidence generation begins with gaps in knowledge that are potentially answered by the research question.[21] Whilst research from well-designed studies is known to be a credible source of information, the JBI model recognises that when studies with rigorous methodological study designs are not available, the best available evidence may include non-empirical evidence, including expert

opinion.[21] Evidence is not limited to effectiveness for a specific population. Domains of feasibility, meaningfulness and appropriateness are also important in evidence based healthcare, these being founded in economics, qualitative inquiry and ethics for healthcare policy and practice.[21]

The JBI has three established areas informing evidence synthesis,[21] theoretical knowledge, methodological development and systematic review methods. This overarching structure of theory, methodological development and methods provides the guidance for quantitative, qualitative and mixed method systematic reviews.[19] Evidence synthesis had traditionally been applied to numerical datum, however in JBI, interest in evidence from a wider range of sources has resulted in methodological developments for qualitative, economics and other forms of datum synthesis.[21] Evidence needs to be effectively transferred to the professions to facilitate evidence implementation. Within the model, there are three major areas of evidence transfer; education and training; information delivery; and through organizational teams.[20]

The Evidence Transfer Program in JBI has a focus on pedagogy to increase knowledge, skills and capacity for clinicians, academics, researchers and policy makers for evidence based healthcare. Evidence implementation is not only dependent on the individual clinicians, policy makers and managers of organizations, but also subject to organizational change and practice change, which is subsequently evaluated by the impact on patient outcomes.[20]

Overview of the science of evidence synthesis

Evidence based healthcare has been defined as the conscientious use of the current best evidence in making decisions about the care of individual patients or delivery of health services and is considered fundamental for best practice in clinical practice and policy development.[20, 23] For this to happen, gaps in knowledge need to be converted into answerable questions.[23] As the volume of valid evidence increases due to the rapid increase of clinical trials, it is essential that as health professionals we are able to assimilate, evaluate and use evidence in the most effective way for patients.[24] Systematic reviews and evidence-based clinical practice guidelines are methods for assimilating large volumes of primary research into synthesized evidence in order to increase the accessibility of research evidence and for facilitating the implementation of evidence into practice. It has been suggested that systematic reviews be conducted within a broader conceptual framework for evidence based healthcare which is focused on implementation. [19, 20]

There are several established centres for evidence based practice that focus on developing evidence in the form of systematic reviews covering areas in adult and paediatric medicine, surgery, nursing, pharmacotherapy and pathology. The leaders in the global, not for profit EBHC sector include the Joanna Briggs Institute,[19] the Cochrane Collaboration and Britain's Centre for Review and Dissemination in York.[25] This thesis reports the results of a quantitative systematic review informed by JBI methodology for evidence synthesis.

JBI methodological basis of quantitative systematic reviews

The Joanna Briggs Institute methodological guidance for the synthesis of primary research into systematic reviews has informed the conduct of the systematic review presented in this thesis, albeit with some variations to fit the reporting requirements of a conventional thesis.[19] The processes and steps in the JBI methodology for quantitative systematic reviews are as followed in the JBI Reviewers Manual.[1] These include:

I. Formulating the review objective and questions and defining the inclusion and exclusion criteria for the review protocol, which is then submitted for review and publication
II. Searching the evidence
III. Study selection: based on inclusion criteria as specified in the protocol
IV. Assessment of identified study quality by critical appraisal using standardized instruments by two reviewers
V. Data extraction, analysis and synthesis
VI. Drafting the systematic review report

Formulating the objective and question

The systematic review process begins with the development of a review protocol based on the review question.[19] The review question in quantitative reviews of effects is formulated using the mnemonic PICO (*Appendix 1*). The PICO based question is then expanded into a more detailed structure that includes detailed description of the relevant characteristics of the Population of interest, the Intervention, Control or comparison and Outcomes of interest to the review; in addition to which the preferred study designs are described, thus providing clarity to the direction and operationalisation of the review question.[1]

Data extraction, Analysis & Synthesis

The JBI SUMARI software (JBI System for the Unified Management, Assessment and Review of Information) (*Appendix 2*) is designed to facilitate each of the seven steps in a quantitative systematic review, from question development through comprehensive critical appraisal (*Appendix 3*), systematic data extraction (*Appendix 4*) and statistical analysis.[19] The standardisation of data extraction, analytic techniques and methods of synthesis is associated with increased quality of conduct and reporting of systematic reviews.[19]

Definitions of terms

Cardiac arrest:	a sudden, sometimes temporary cessation of cardiac functioning[2]
Cardiac surgery:	the field of medicine requiring surgical treatment of the organs inside the thoracic cavity[5]
Functional neurological:	adapted term to describe the branch of neurological outcomes concerned with purposeful motor movement, activities of daily living and independent living[26]
Global cerebral ischemia:	hypoxic injury to the entire brain[2]
Homogeneity:	studies considered similar enough to be classified together[19]
Independent living:	the state of living that does not rely on others for activities of daily living[16]
Neurophysiology:	the branch of neurological outcomes that is concerned with objective physiological measures related to the function of the neurological system[6]
Neuroprotection:	mechanisms and strategies used to prevent neurological dysfunction[10]
Pre-existing neurological condition:	Any congenital or acquired neurological event or condition that affects any aspect of neurological functioning (eg Stroke, Motor Neurone Disease, Multiple Sclerosis)[5]
Cognitive function:	the branch of neurological outcomes concerned with emotional disturbance, behavioral abnormality and cognitive function[7, 27]

Assumptions:

Quality of life

Measuring and assessing quality of life raises several challenges. The objective results in quantitative trials do not assess the subjective individual perception of outcomes. Health is defined by The World Health Organization as "a state of complete physical, mental and social wellbeing, not merely the absence of disease".[28] An individual's quality of life is often multifactorial; it is directly related to their perception of their position, received care and directly influenced by culture and beliefs.[28] The EQ-5D is a standardized instrument to measure quality of life, however this was not directly assessed by the studies in this review. For the purpose of this review, quality of life is considered to have declined where neurological injury impedes the ability to function independently as measured by functional, physiological and cognitive changes.

Functional neurological outcomes:

Functional neurological outcomes are assumed in this review to relate specifically to the ability of the body to exhibit functional neurological commands. It includes objective assessment of neurological function via instruments such as the Glasgow Coma Scale (GCS), Glasgow Outcomes Scale/ Cerebral Performance Category, and Karnofsky performance status. Other measures of neurological outcome include arousal and consciousness, voluntary controlled movement and co-ordination, and the activities of daily living such as the ability to toilet, dress and mobilise. Functional neurological outcome is directly related to quality of life, and the ability to perform daily life functions.

Neurophysiological outcome:

In the context of this thesis, neurophysiological outcome refers to the results of investigations which assess the physiological functioning of the neurological system. These include specific biochemical markers and proteins released by neurons, and direct markers of neurological activity. In the included trials, the neurophysiological outcomes were neuron specific enolase and P300 evoked potentials.[6, 8]

Cognitive function:

The term cognitive function is usually interchangeable with neuropsychiatric and neurocognitive terms. These measure cognitive and behavioural changes with tests including mini mental state examination (MMSE), mental state examination (MSE), Hopkins verbal learning test, Controlled Oral Word Association Test, Randt Memory Test, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Test, Wechsler Memory Scale, forward and backward digit span tests and the Boston naming test.[5, 27]

Chapter 2: The systematic review protocol

Chapter introduction

The review protocol provides an objective a-priori report of the proposed methods and decision-making processes within the systematic review. The essential components of the protocol include: the review question; the inclusion and exclusion criteria that will be used to select the literature; databases to be searched; JBI SUMARI module to be used; type of data extracted and strategies for datum synthesis.[19] The protocol for this systematic review has previously been peer reviewed and published in the Joanna Briggs Library of Reviews and Implementation reports.[29]

The focus of this chapter is on the presentation of selected existing evidence related to the topic to situate the context of the specific review topic within the wider field of study. There are therefore no methods specific to this section, and while some animal studies have been included, the overall focus is on human studies where in-vitro or in-vivo methods have led to findings that assist in positioning the relevance of this systematic review as a contribution to knowledge.

Background

Injury caused by global cerebral ischemia during cardiac arrest and cardiac surgery have different contributing factors yet both share common pathophysiological mechanisms. Each of these conditions has previously been investigated independently due to multiple confounding factors in the setting of each of these event and the effect on patient outcomes. The ceassation of myocardial activity is predicted and controlled within the cardiac surgery environment under medical guidance,[5] in comparison with spontaneous cardiac arrest where medical response may be delayed.[9] The following review of the literature will discuss the current understanding of the pathophysiology of global cerebral ischemia, as well as previously investigated neuroprotective therapies used during cardiac surgery and cardiac arrest and the current use of magnesium in clinical practice.

Cardiac surgery

Cardiac surgery is often performed to increase quality of life for patients with significant cardiac disease such as vascular or valvular pathology. However, for patients who suffer complications such as cognitive decline or neurologic dysfunction post surgery, quality of life may also decrease post-surgery.[7] Neurologic dysfunction is also associated with a reduction in independent living.[5] The most noted type of neurological decline is cognitive decline.[30]

The mechanisms for neurologic deterioration in the presence of cardiac arrest are similar to vascular or valvular pathology, where global cerebral ischemia occurs due to decreased perfusion pressures from use of cardiopulmonary bypass techniques or iatrogenically induced cardiac arrest.[5, 7, 8] Additional factors contributing to ischemia include genetic predisposition, transcerebral platelet activation, cerebral embolism, duration of surgery, systemic inflammatory responses, hemodilution, variations in blood glucose and fluctuating core body temperature.[5] Neurological deficits may include altered neurocognitive state and behavioral abnormalities.[5]

Perioperative cerebral injury is problematic, contributing to impaired postoperative recovery, increased postoperative costs and prolonged hospital stay. [30] Several pharmaceutical strategies have been investigated with the objective of reducing the clinical impact of perioperative neurological dysfunction and cognitive decline.[30] To date, results of these trials have failed to consistently demonstrate effective neuroprotective properties.

Cardiac arrest

During cardiac arrest, the cessation of organized myocardial activity results in hemodynamic collapse, causing hypoperfusion and hypoxia of neuronal cells.[5, 31] More than 50% of cardiac arrest survivors sustain some degree of permanent cerebral injury, with only three to seven percent of survivors returning to pre-arrest level of neurological functioning.[10, 32] Cerebral deficits range from memory loss and severe depression to brain death and cerebral necrosis, causing significant reduction of quality of life.[10]

Post cardiac arrest syndrome is the pathology which follows reperfusion after whole body ischemia.[3, 33] The four key sequela of post cardiac arrest syndrome include: post-arrest brain injury; post-arrest myocardial dysfunction; systemic ischemia and reperfusion response.[3] Precipitating pathology, pre-existing co-morbidities and duration of arrest also contribute to high morbidity and mortality rates in patients with return of spontaneous circulation (ROSC).[3, 17] Early mortality is often due to cardiovascular instability, whereas late mortality may be associated with cerebral injury. Cerebral dysfunction occurs due to a combination of anoxic cerebral conditions and reperfusion injury.[3]

The immediate post arrest phase is defined as the first 20 minutes after ROSC. Neuroprotective interventions are most effective during the early post arrest phase, occurring between 20 minutes and six to twelve hours after ROSC.[10] The intermediate phase is between six to twelve hours and 72 hours post ROSC. During this phase, injury pathways are still active and are a window where aggressive treatment can be initiated.[34]

Neurological injury during global cerebral ischemia

Neurological complications post cardiac surgery and cardiac arrest are common, resulting in neurological motor and sensory deficits, altered levels of arousal and consciousness, memory loss, depression and cognitive decline.[6, 9] As discussed, global cerebral ischemia may result from several aetiologies including reduced haemodynamic stability resulting in decreased cerebral perfusion pressures from cardiac arrest and certain cardiac surgical procedures.[2, 8] Hypoperfusion of the cerebrum results in decreased oxygen delivery causing hypoxic ischemic injury.[3] For these patients, survival is not the only important outcome, since neurological dysfunction impacts on quality of life.

The pathophysiology of global cerebral ischemia is complex, with much of the physiological knowledge originating from studies in animal models. Inflammatory responses and cytotoxic and cerebral oedema result in irreversible pathological damage due to a number of biochemical processes,[4] including glutamate excitotoxicity, calcium dysregulation, and reperfusion injury.[35, 36] The neurochemical consequences result in oxygen free-radical generation, membrane lipid breakdown, proteolysis, up

regulation of specific genes, apoptosis and necrosis.[37, 38] These processes present clinically with neurological dysfunction and psychiatric decline.[5]

Glutamate excitotoxicity is central to the pathophysiology of irreversible neuronal damage, resulting in calcium and sodium influx via ligand-gated channels causing alterations to the intracellular ionic environment.[5] Cellular cytotoxic oedema is mediated by an influx of water following sodium and calcium ions. The movement of extracellular calcium into the intracellular environment further exacerbates this process and initiates apoptotic cascades.[39] A subsequent result of hypoxia is anaerobic respiration. Secondary lactic acid accumulation and decreased cellular pH triggers lysosomal storage release, causing further cellular necrosis.[40]

Glia (neuronal support cells), including astrocytes and microglia, activate as the degree of neuronal damage increases. The interplay between cells with the cerebrum further contributes to neuroinflammation and neuronal cellular injury. Microglia are the active immunological defence cells of the central nervous system which normally protect neurons. During activation, they may inadvertently further damage neurons by activation of phagocytic oxidases, release of glutamate, production of reactive oxidative species and release of inflammatory cytokines.[41] Our understanding of these processes from animal models reflect similar processes which occur in humans, providing insights that may inform therapeutic targets and treatments in human studies.

Neuroprotection after global ischemia

In both cardiac surgery and cardiac arrest, measures to prevent brain injury have been studied, but the strategies to minimize brain injury have received less attention.[5] Survival outcome research has been prioritized over neurological outcome research, influencing research objectives and clinical practice.[2] There is some evidence that hemodynamic optimization, oxygenation and ventilation, circulatory support, management of acute coronary syndrome and treatment of the reversible causes (including metabolic control) can reduce global ischemia post cardiac surgery and post cardiac arrest neurological injury. The International Liaison Committee on Resuscitation recognizes the need to find a neuroprotective agent, although to date, there have been few pharmacological measures and clinical interventions introduced which elicit neuroprotection.[1, 12]

Therapeutic interventions

Therapeutic interventions for neuroprotection are centred around targeted temperature management, maximizing supportive measures, optimising blood glucose and maintaining haemodynamic stability and cerebral perfusion pressure. Targeted temperature management, also known as therapeutic hypothermia, has been extensively researched and clinical protocols are in place at many institutions. Therapeutic hypothermia is hypothesised to reduce cerebral oxygen consumption, thereby suppressing the biochemical and metabolic sequelae such as reducing destructive enzymatic reactions and reactive free-radical generation. Therapeutic hypothermia is recommended by the American Heart Association for patients with ROSC post out-of-hospital cardiac arrest, yet published research on this topic is contradictory and therefore inconclusive.[42] Some authors suggest therapeutic hypothermia itself may not be beneficial, but instead recommend the prevention of spiking fevers to reduce the risk of neuronal injury. Evidence supports the use of cooling and antipyretics to maintain normothermia, as each degree over 37°C has been correlated to a 2.26 increase in the odds ratio for neurological dysfunction.[43] One study found that inducing hypothermia (32°C) improved cognitive outcome - measured at one week and three months post coronary artery bypass graft surgery - suggesting a benefit of this intervention.[44] In contrast, others found no adverse effects; intraoperative hypothermia compared to normothermia did not improve neurological outcomes; hyperthermia, however, contributed to unfavourable outcomes.[45]

Pharmaceutical interventions

Several pharmaceutical agents have been investigated for potential benefits on neurological outcomes post cardiac arrest, including magnesium,[9, 16, 31] calcium channel blockers such as lidoflazine,[46] dexmetomidine, erythropoietin, lidocaine[30] and glucocorticoids.[47] The Brain Resuscitation Clinical Trial II[46] failed to replicate the neurological benefits of lidoflazine found in laboratory trials, with several complications arising such as hypotension and re-arrest.

Research into glucocorticosteroids has identified conflicting results. A retrospective study[47] found administrating glucocorticoids post cardiac arrest did not improve neurological outcome and may be associated with additional complications such as increased risk of infection or negative nitrogen balance.[47] Recent clinical trials have recognised early neuronal damage, (detected by measures of

serological neuron-specific enolase and S100beta protein)[48] has been shown to be reduced with administration of corticosteroids after cardiac pulmonary bypass. However, a corresponding clinical outcome of neurological improvement has yet to be observed.[48]

Interventions using dexmedetomidine, erythropoietin and lidocaine have elicited some degree of improved neurological outcome, however magnesium appears the safest, with a low risk of harm in specific populations.[30] The authors of a literature review on neuroprotection after major cardiovascular surgery noted that further research is required to determine the safety, efficacy and optimal dosing regimens for each of these interventions.[30]

Magnesium for neuroprotection

The neuroprotective mechanisms of magnesium on neurons and glia have been studied in animals since the 1980s as they are associated with several physiological processes relevant to cerebral ischemia.[4,49] These include vasodilatory regulation of cerebral blood flow,[6] inhibition of pre-synaptic excitotoxic neurotransmitters such as glutamate, mitochondrial stability[50] and anti-apoptogenic modulation of growth factors.[4]

Normal physiological mechanisms of magnesium homeostasis are not yet completely understood. Intracellular magnesium in both free and bound forms is essential for the regulation of numerous intracellular functions, including enzymes involved in ion channel transport, metabolic cycles and signaling pathways. Free magnesium has been shown to diminish during acute and chronic cerebral pathologies.[51]

Magnesium provides neuroprotection by non-competitive inhibition at post-synaptic glutamate N-methy-D-aspartate receptors (NMDA), sodium and calcium receptors, thereby inhibiting the release of calcium into neuronal cells.[6, 52]Inhibition of calcium influx reduces glutamate excitotoxicity and calcium dysregulation, central to the pathophysiology of cerebral ischemia. Increased intracellular magnesium also provides antagonist actions at voltage-gated channels, preventing entry of ions during ischemia including calcium, sodium and potassium.[4, 52] Figure 2.1 is a schematic representation of where magnesium inhibits the NMDA receptor on a post synaptic neuronal cell.

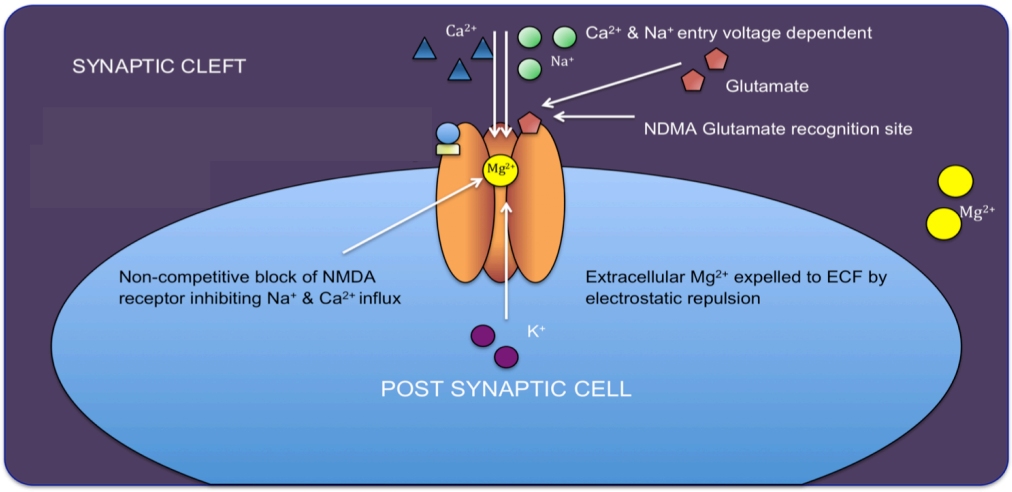

Figure 2.1: Schematic representation of the role of magnesium in neuroprotection by NMDA receptor inhibition (*Adapted from Clinical Anatomy & Neuroscience*[53])

The normal magnesium plasma and intracellular ranges are 0.70 to 0.85 mmol/L[54] and 0.6 mmol/L to 0.8 mmol/L[55] respectively. In normal homeostasis, magnesium is principally absorbed transcellularly through the small bowel, with 60-70% of magnesium reabsorption occurring in the ascending loop of Henle.[56] Cerebrospinal concentrations of magnesium are generally higher at 1.1 mmol/l compared to plasma serum concentrations at 0.8 mmol/l.[4]

Animal model studies demonstrate cortical extracellular concentrations of magnesium are higher than cerebrospinal fluid, indicating active transport across the blood-brain barrier (BBB).[18] The neuroprotective mechanisms of magnesium in mice are exhibited at physiological extracellular concentrations between 250 µmol and 1000 µmol/L.[57] These studies have not been replicated in humans, and whether these values have a similar effect in humans is unclear. Magnesium transport into the cerebral spinal fluid in humans is not yet fully understood, however, current hypotheses include transcellular and paracellular mechanisms.[18] Initial studies on pre-eclamptic patients receiving intravenous magnesium found a modest increase in the cerebral spinal fluid concentrations.[57] Both intramuscular and intravenous administration of magnesium increase cerebrospinal fluid concentrations by 20 to 25%, indicating the possibility of clinically effective therapy.[58]

Magnesium for neuroprotection in aligned fields of study

Focal ischemia associated with acute stroke is most closely aligned to the topic of this review. The FAST-MAG trial by Saver et al (2015) investigated the use of magnesium sulphate in patients with acute stroke. Whilst the study noted magnesium administration to be safe, no significant shift in the distribution of 90-day disability outcomes were measured using the global modified Rankin Scale for the 1700 patients enrolled.[35] Potential physiological explanations for the neutral results (no benefit, no harm) are attributed to the intact BBB, reducing conductance of magnesium into neural tissue.[35]

A review suggested the therapeutic role of magnesium in ischemic stroke, intra-cerebral haemorrhage, and subarachnoid haemorrhage (SAH) may be limited by late administration.[57] In the population with SAH, the authors proposed that when the time to magnesium administration was approximately 32 hours, pathological processes leading to ischemia from vasospasm may have already been present.[57]Clear definitions of "early" as compared with "late" administration are yet to be established, although the authors suggested that 32 hours might be too late. Further research into magnesium administration at onset of symptoms and throughout recovery is required if a definitive framework for "late versus early" is to be established. The authors suggest magnesium has future clinical promise as a neuroprotectant therapy, applied to conditions including preterm prevention of intraventricular haemorrhage, carotid endarterectomy, cardiac arrest and cardiac surgery. [57]

Research into the neuroprotective properties of magnesium during cardiac surgery has produced conflicting results. One trial[5] found improved functional neurological outcome in the magnesium group compared to placebo at 96 hours (P = 0.0001). Two other trials,[6,8] found magnesium did demonstrate neuroprotective properties when serum magnesium concentrations were increased. The small sample sizes of these studies, n = 28[8] and n=30[6], limits the power of these trials. In contrast to these results, another trial[7] found magnesium did not sustainably improve cognitive function at 6 weeks follow up.

Clinical trials investigating magnesium for neuroprotection during global cerebral ischemia after cardiac arrest have had promising results without adverse effects. One trial[31] noted the only participant to survive neurologically intact to hospital discharge from a small cohort was from the group who were administered magnesium, although it must be acknowledged that this result provides no clear evidence of association. Another trial[9] found improved functional neurological outcome in their magnesium group compared to placebo, three months post arrest.[9] A third trial found improved discharge status and independent living in the magnesium cohort compared to placebo, post arrest.[16]

Current clinical applications of magnesium

In Australia, magnesium is currently used for pre-eclampsia, eclampsia, preterm labour and acute severe asthma.[59, 60] Beneficial effects have been reported in cardiovascular diseases,[61] including unstable angina,[62] prolonged QT syndrome and dysrhythmias such as torsades de pointes ventricular tachycardia.[29] Other current clinical applications of magnesium include correction of hypomagnesia associated with digoxin toxicity, hydrofluoric acid poisoning and osmotic laxatives. Magnesium is currently an anticonvulsant treatment of choice for women with pre-eclampsia who are at risk of seizures to improve maternal and infant outcome and reduce mortality.[63] Other, potential therapeutic uses of magnesium which are being investigated globally include traumatic brain injury,[36, 64] sub-arachnoid hemorrhage[36, 64] and focal ischemia.[36, 64]

The clinical application of antenatal magnesium for neuroprotection of preterm infants has been reported to show beneficial neurological outcomes.[65, 66] Administration of magnesium sulphate reduces the risks of cerebral palsy; the odds ratio ((OR) (OR0.14;95% confidence interval (CI) 0.05 to 0.51)) however there is a lack of consensus among researchers in this field regarding the optimal magnesium

dosing regimen. Due to the lack of recent comparative trials, there is no consensus as to the regimen of choice in terms of dose and duration of magnesium.[65]

Adverse effects

The common side effects of hypermagnesia in conscious patients include nausea, flushing and vomiting, and, less frequently, headaches and dizziness.[59] Initial clinical signs are attributed to neuromuscular blockade, including loss of deep tendon reflexes and respiratory depression. Other reported effects include thirst, muscle weakness, hypotension, bradycardia, central nervous system depression and coma.[59] Adverse reactions from high doses are few, however, may include respiratory depression and cardiovascular effects such as sinoatrial node blockade, hypotension and circulatory collapse.[16]

Precautions and contraindications

Precautions regarding the administration of magnesium are warranted in some conditions such as in patients with myasthenia gravis and obstetric patients being treated with nifedipine. Magnesium is contraindicated in hypermagnesia or heart block.[59] In patients with myasthenia gravis, magnesium interferes with neuromuscular transmission, resulting in increased weakness; monitoring of respiratory function is required.[59] The effects of magnesium may be amplified in the obstetric population treated with nifedipine, putting these patients at risk of hypotension and other adverse effects of hypermagnesia. Patients with renal impairment may need dose adjustments to prevent hypermagnesia because magnesium is predominantly renally cleared.[59]

Variations in dosage, time of administration and combination with other therapies contribute to the varying results of clinical trials.[6] The therapeutic dose of magnesium administered for neuroprotection during global cerebral ischemia may be in the range of two to six grams.[9, 16, 31, 61]

Quality of life and neurological outcome

As discussed in chapter one, Quality of life is complex and multifactorial, directly affected by the state of health. The effects of neurological dysfunction are apparent in all aspects of health. Several areas of life are affected such as the ability to perform activities instrumental to daily living, which in turn affect social interaction. Quality of life is subjective to the individual and can be difficult to quantify objectively, however is usually evaluated by assessment tools that measure ability to walk and move, as well as continence and cognitive function and activities of daily living.

Summary

The necessity of neuroprotective interventions is evident since global cerebral ischemia associated with both cardiac surgery and cardiac arrest results in neurological dysfunction. The clinical consequences of which may severely impact patients, ranging from functional neurological impediments to cognitive decline. Magnesium is a promising neuroprotective agent due to its safety, known adverse effects and currently approved applications in clinical practice. The doses required for neuroprotection during global cerebral ischemia are similar to those currently administered for pre-eclampsia and eclampsia, therefore providing an avenue for expansion of its use.

Review objectives

The objective of this systematic review was to provide the best available evidence related to the neuroprotective effects of magnesium during a period of global cerebral ischemia in adults with cardiac arrest or cardiac surgery. Neurological outcomes were examined, and an investigation of optimal magnesium dosing regimens will also be reported.

Review Questions

Does therapeutic magnesium admistraion improve neurological outcome in patients with global ischemia in the setting of cardiac bypass surgery or cardiac arrest.

Criteria for considering studies for this review

The inclusion criteria were formulated using the PICO mnemonic, and published in the a-priori protocol as reported in Chapter one (*Appendix 1, Table 2.1)*.[67] The pathophysiological mechanisms of global cerebral ischemia are similar between cardiac arrest and cardiac surgery, therefore both populations were included in this study. The intervention of magnesium administration in either of these conditions with measured neurological outcomes was considered in this review.

Table 2.1: Summary of the PICO used to formulate inclusion and exclusion criteria in the systematic review

Population	Adults at risk of global cerebral ischemia associated with: • cardiac arrest, either pre-hospital or the in-hospital setting; or • elective cardiac surgery utilizing cardiopulmonary bypass or iatrogenic cardiac arrest
Intervention	Magnesium administration of a minimum 2 g
Comparison	Placebo administration
Outcome	Measurable neurological outcomes

Types of studies

The primary study designs of interest in this quantitative systematic review were experimental study designs including randomized controlled trials, controlled non-randomized trials, and quasi-experimental trials. In the absence of such trials, this review would also have considered analytical epidemiological studies or descriptive study designs. However, the search revealed sufficient randomized controlled trials to limit study selection to experimental designs. Study selection was based upon initial screening for experimental methods, then detailed reading and checking against the inclusion criteria, for whether randomization was reported, and which methods of allocation were described. All types of randomization were considered appropriate to this review, including individual

patient, block, and/or stratified methods. Quasi-randomized trials are those where randomization is not truly random but rely on methods that involve sequential allocation. While at a higher risk of allocation bias than double blinded trials with truly random allocation, the inclusion of control groups, with "before and after" measurement provides suitable baseline data for comparative analysis that is of a higher level of evidence than study designs with no controls. Risk of bias was carefully evaluated throughout critical appraisal (reported below).

Types of participants

This review considered any adults above 18 years of age with global cerebral ischemia who received the intervention of interest as described below. Participants may have experienced global cerebral ischemia due to cardiac arrest or cardiac surgery. The following exclusion criteria were applied when screening the literature. Participants receiving multimodal treatment were excluded from this review. Participants were also excluded if there was pre-existing neurological injury or co-morbid conditions. Pre-existing neurological deficits were defined as clinical neurological diagnoses or co-morbidities; papers were read in detail at study selection to screen out those where the participants had identified pre-existing neurological deficits. Additionally, papers were also excluded if neurological outcomes were not assessed.

Types of intervention

The intervention of interest was magnesium in doses of at least two grams compared to placebo administered to adult patients within 24 hours of cardiac arrest or cardiac surgery.[9] The immediate effect of magnesium for acute emergencies has been demonstrated in current clinical applications such as patients with severe asthma or Torsardes de Pointes.[59] Ideally, investigation of the immediate administration of magnesium would be appropriate for this population. Evidence from Bhudia et al(2006)[5] and Thel et al (1997)[16] suggests magnesium administration up to 24 hours post global ischemia is beneficial, therefore the timeframe of 24 hours was chosen to include a wider scope of research in this area. Magnesium formulation was not specified in order to incorporate all trials utilizing magnesium in this review. The majority of trials use magnesium sulphate, however, other formulations have similar clinical effects.

Types of Comparators

The comparator to the intervention of interest was passive placebo administration within the same timeframe and over the same period as the intervention. All the included trials reported 0.9% Sodium Chloride (Normal Saline) as the placebo of choice.

Types of outcomes

The primary outcome of interest was neurological status post-cardiac arrest or cardiac surgery as measured by objective scales, such as, but not limited to: cerebral performance category, brain stem reflex, Glasgow Coma Scale and independent living or dependent living status. Secondary measures assessed optimal magnesium dosing regimen and timing.

Neurological outcome

Neurological assessment is used commonly in both clinical and research practices, however, in this review, neuroprotective outcomes were measured differently across the included studies. Accurate assessment is essential for long-term and short-term patient outcomes, interventions and assessing quality of life, therefore both short-term and long-term assessment were considered for inclusion. Several parameters are required to give an overview of neurological function, including independent living, communication, motor and sensory function, cognitive and behavioural domains and consciousness. The research presented in the included trials tends to only assess selected portions of these parameters. To assist in analysing outcomes, neurological outcome has been considered in three subsets: functional neurological, neurophysiological and cognitive outcomes. Each of these terms are defined in Chapter 1.

Magnesium dosing regimen

Magnesium dosing occurred at various time points post cardiac arrest, and pre and post cardiac surgery. Investigating patterns of magnesium dosing regimen with neurological outcome will provide insight to optimal dosing regimens, including evidence to inform decision making on bolus versus infusion for administration.

Timing of reported neurological outcomes

The trials included in this systematic review measured neurological outcome at different time points. These included 24 hours, three days (72 hours), four days, six weeks, three months and at discharge from hospital. Time points of reported outcomes were reviewed to determine if time point affected neurological outcome.

Review methods

Search strategy

The JBI literature search strategy was applied during this systematic review and included a three-step approach. The search strategy attempted to identify all experimental research (randomized controlled trials, non-randomized controlled trials, and quasi-experimental reports) relevant to the review question. The literature search was completed by the corresponding author.

A preliminary search using the search terms ‘magnesium’, ‘neuroprotection’, ‘cardiac arrest’, and ‘cardiac bypass surgery’ was undertaken in the PubMed, EMBASE, CINHAL and Cochrane Central Register of Controlled Trials (CENTRAL) databases to identify the database-specific thesaurus and free text terms (*Appendix 5.1*). This was followed by a comprehensive systematic search using appropriate indexing terms and medical subject headings specific to each included database. To complete the literature search, the reference list of studies meeting the PICO inclusion criteria was screened for additional studies. Selected studies for inclusion were critically appraised by two reviewers. [19]

The title and abstract for each article was assessed for eligibility prior to critical appraisal to determine inclusion in this review, the reference list of all included trials was reviewed for additional trials. Email

alerts were arranged by the corresponding author to ensure new publications meeting the search strategy were considered in the review. Only trials published in English were considered for inclusion in this review.

After advice from a librarian, logic grids were used to inform search strategy development for each database. Details of the search strategy for published and unpublished trials can be found in *Tables 3.2* and *3.3* respectively. International registers searched for unpublished literature included the Australian Clinical Trials Register (www.australianclinicaltrials.gov.au), Australian and New Zealand Clinical Trials Register (www.anzctr.org.au), Clinical Trials (https://clinicaltrials.gov/), European Clinical Trials Register (www.controlledtrials.com) and ISRCTN Registry (http://www.isrctn.com/). Keywords "magnesium" and "neuroprotection" were used when searching these databases (*Appendix 5.2*).

Because the clinical implications of magnesium therapy for neuroprotection have been investigated since the early 1980s, the search strategy for consideration of inclusion in this review was limited to trials published between 1st January 1980 and 1st August 2014. The selected trials were managed using EndNote bibliographic software. Duplicates were screed for and removed manually. Only the primary reviewer (AP) was involved in selection of the papers (described below), in accordance with the degree requirements of the Master of Clinical Science. However, two reviewers were involved in independent critical appraisal of the selected papers.

Study selection

Article titles and abstracts identified in the search strategy were reviewed to establish whether the paper met the inclusion criteria and needed to be retrieved for more detailed reading to confirm relevance and applicability through comparison with the inclusion criteria. Papers were selected for review which studied adults aged 18 years and older with global ischemia, either by spontaneous or iatrogenic cardiac arrest. Participants of the studies needed to receive magnesium within the first 24 hours of arrest and have neurological outcome measured. The study selection process followed the PRISMA guidelines and reported in figure 3.1, which identifies the number of records retrieved from database searching, duplicates and full text eligibility for qualitative synthesis and meta-analysis.[68] Included published and unpublished trials can be found in *Appendix 6* and *Appendix 7* respectively.

Assessment of methodological quality and critical appraisal

Two independent reviewers conducted critical appraisal to assess methodological quality (internal validity) of each of the selected trials prior to inclusion, using JBI-MAStARI. JBI-MAStARI includes an established critical appraisal tool facilitating assessment of the internal validity, quality and risk of bias of the included studies. In the event of disagreements arising between reviewers, a third reviewer was available to resolve disagreements. No disagreements occurred between the reviewers.

The critical appraisal instrument in JBI-MAStARI comprises ten questions, to which possible answers are Yes, No, Unclear or Not Applicable. The JBI- MAStARI critical appraisal questions and checklist for

randomised control/ pseudo-randomised trials can be found in *Appendix* 3. This systematic review only included RCTs or pseudo RCTs. The review itself was formulated using CReMS software version 5.02.

Based on the population group studied, a "yes" was required in six out of the ten JBI-MAStARI questions. Therefore, trials with a score equal or greater than six out of ten were included in the review. Randomization of participants needed to be stated but was not required to be explicitly detailed (questions one, three and five). Because of the nature of cardiac arrest, it is not practical to blind participants to the intervention (question 2). It was important the trials had objective measures of neurological assessment, measured in a reliable way with the appropriate statistical analysis (questions eight, nine and ten). For RCT models, participants of both the control and treatment groups had to be treated identically, except for the magnesium intervention.

Datum extraction

The type of data extracted was predetermined by the protocol.[29] Datum was extracted from the trials included in this review using the JBI-MAStARI standardized data extraction tool that can be found in *Appendix 4.* The data for each study included the study method, population characteristics and sample sizes, study setting and location, interventions used, study outcomes and author conclusions. Datum specific to the review question was firstly extracted. The extractions were then reviewed multiple times against the original studies to ensure accuracy and reliability of the data. Where sufficient data was not available, authors were contacted requesting the primary data. Of the four authors contacted for additional details, only one (Professor Fatovich) returned correspondence.

Datum synthesis

Quantitative datum from comparable trials was pooled, where possible, in statistical meta-analysis using Review Manager 5.3. Effect sizes expressed as odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals were calculated for analysis. Heterogeneity was assessed statistically using the standard chi-square and I^2. RevMan 5.3 software was chosen for meta-analysis since MAStARI does not report I^2, a measure of the consistency between trials in meta-analysis.[69] The three trials suitable for meta-analysis using this software evaluated functional neurological outcomes, post-cardiac arrest.

The remainder of the trials included in this review had both extensive clinical and methodological heterogeneity.[67] As statistical pooling was not possible for all outcomes, the findings of heterogeneous studies are reported in narrative form, including tables and figures to aid in datum presentation where appropriate. Trials were subdivided into categories investigating cardiac arrest and those investigating cardiac surgery. Further subdivision of trials includes subcategories of neurological outcomes, magnesium dosing regimen and timing of reported neurological outcomes.

Software

This review write-up was guided by templates embedded in the JBI software Master of Clinical Science students are required to use; the System for the Unified Management, Assessment and Review of Information (SUMARI).[19] The module of SUMARI applied was the "Meta Analysis of Statistics Assessment and Review Instrument" (JBI MAStARI) component. SUMARI includes the Comprehensive Review Management System (CReMS) software version 5.03. This software is designed to assist researchers to manage and document the steps and phases of the systematic review. Advantages of using CReMS software include the programs' capabilities of incorporating the review protocol, search results, review findings, and study characteristics. Additionally, the software is able to create either word-rich files or portable document format (PDF). However, Review Manager by the Cochrane collaboration was used to facilitate the analysis because it incorporated analytic methods not available in CReMS or MAStARI.

Chapter 3: Results

Chapter introduction

The premise of this review is that for patients who survive global cerebral ischemia, administration of intravenous magnesium can improve neurological outcomes. Commencing with a description of the included trials, and decisions related to inclusion and exclusion, followed by a critical summary of the methodological strengths and weaknesses of the included literature; the "results" chapter then presents the key results for the outcome measures that were established a-priori in the published protocol.[29]

Description of Studies

Included trials

A total of 325 potentially relevant records were identified through database searching*;* the detailed search strategies for each database are reported in *Appendix 5*. Following the removal of eight duplicates, 317 studies were retrieved for examination of title and abstract. A further 291 articles were excluded after evaluation of title and abstract for being incongruent with the review inclusion criteria, leaving 13 trials for detailed examination. Subsequently, seven full text articles were excluded based on evaluation against the appraisal criteria.[70-76] During bibliographical review, one additional record was identified,[31] resulting in seven randomized controlled trials being included for analysis in this systematic review (Table 3.1). Four trials investigated magnesium during cardiac surgery (*Appendix* 6.1) and three trials during cardiac arrest (*Appendix* 6.2). Details of excluded studies are listed in *Appendix 7*. The process of study selection followed PRISMA guidelines[68] (*Figure 3.1).*

Table 3.1 Potentially relevant records identified by database searching

Database Search		**Other resources**	
PubMed	28	Australian Clinical Trials Register	0
CINHAL	5	Australian & New Zealand Clinical Trials Register	0
EMBASE	275	Clinical Trials	1
CENTRAL	16	European Clinical Trials Register	0
Total	**324**	ISRCTN Registry	0
		Total	**1**
		Combined total	**325**

After eligibility assessment, seven randomized controlled trials with data from 988 participants in total were considered. The outcomes for the methodological quality assessment of the included trials using the JBI critical appraisal tool are reported in *Table 3.2.* Study details of methodological design, including neurological outcome measures, timeframes and location, number of participants and mean age, are described in *Tables 3.3 and 3.4 for c*ardiac surgery and cardiac arrest respectively. Prospective randomization occurred in four trials which investigated the neuroprotective properties of magnesium during elective cardiac surgery.[5-8] Patients were randomized during treatment in the three trials investigating the neuroprotective properties of magnesium during cardiac arrest.[9, 16, 31]

Demographic characteristics of participants were similar among all trials. Included trials were conducted in the metropolitan pre-hospital setting,[9] hospital emergency department[31] or non-emergency hospital wards.[5-8, 16] The trials were conducted in metropolitan areas with high index of population in the United States of America,[5, 7, 9, 16] Australia,[31] Egypt[6] and Austria.[8]

It should be noted that the study by Rinosl et al (2013)[8] was originally identified as a conference abstract paper published in 2009.[52] Critical appraisal was conducted on the original conference piece.[52] After contact with the authors, the outcomes and results presented in the article published in 2013 were included in this review.[8]

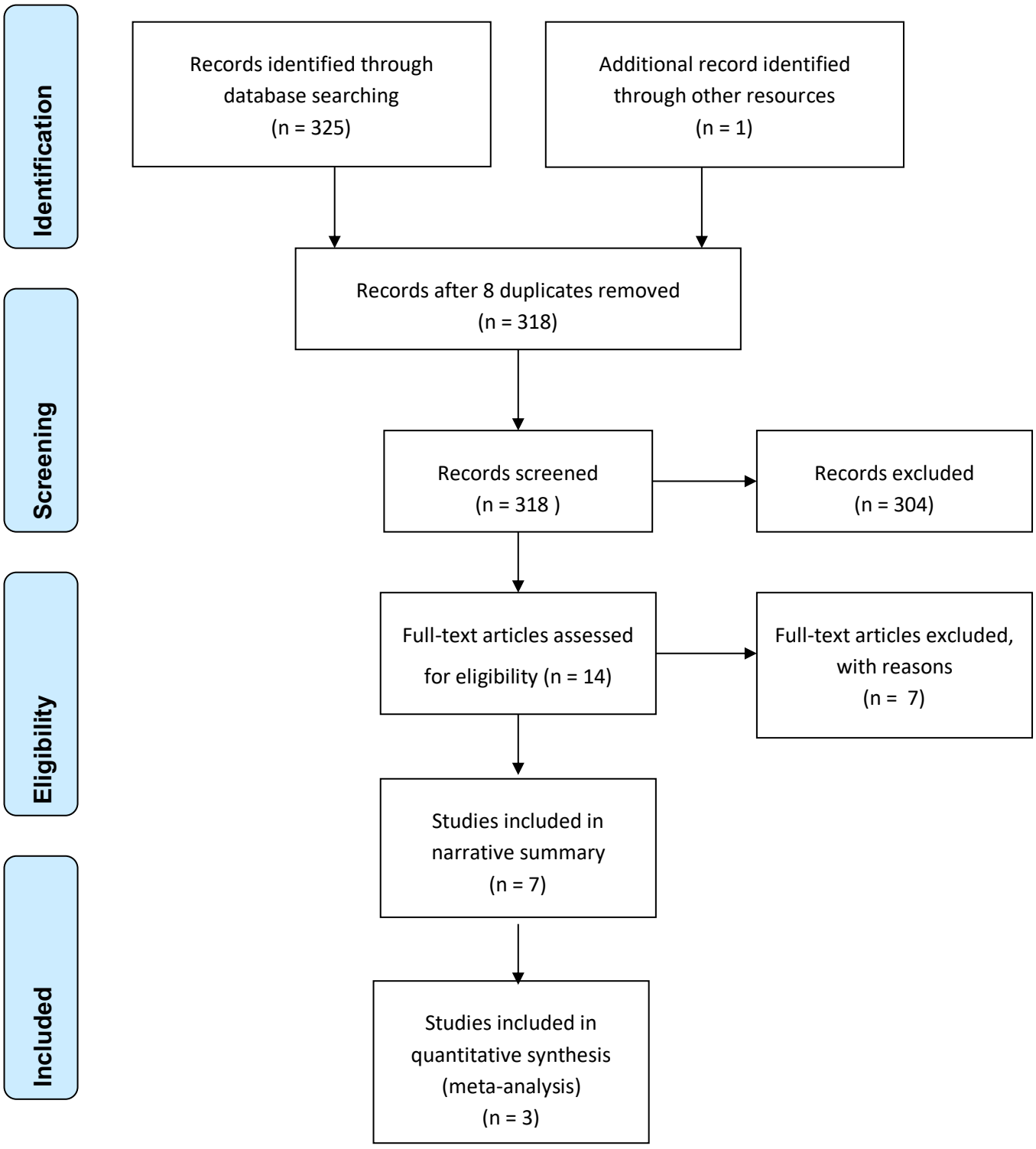

Figure 3.1: PRISMA flowchart reporting study management[68]

Methodological quality of included trials

The seven trials included in this review were critically appraised for methodological quality using the JBI-MAStARI critical appraisal tools (*Appendix 3)*. The quality threshold score during critical appraisal was six out of ten, including a requirement that the study stated randomization had guided participant allocation. Questions requiring "yes" in the JBI-MAStARI critical appraisal tool in order for the study to be included were questions six, seven, eight, nine and ten. Trials were required to have the following characteristics:

- To be of RCT design, but not required to specifically state randomization techniques.
- The magnesium and placebo treatment groups comparable at entry, in terms of disease processes and demographic characteristics
- Participant blinding in the studies of cardiac surgery
- The magnesium and placebo groups needed to be treated identically except for the named intervention
- The outcomes of participants who withdrew are described and included in the analysis
- Neurological outcomes were measured in the same ways for participants in the intervention and placebo groups
- Neurological outcomes were measured in reliable ways
- Appropriate statistical analysis used

Randomized Controlled Trials (RCT) were the preferred study design for inclusion in this systematic review. Evidence of reporting of specific details on the method for patient randomization were preferred but not required for inclusion, based on the stated study design. Methods of randomization were well described in seven trials. In the remaining trials, randomization methods were not clearly reported.

Description of allocator blinding was well described in all trials except one.[7] This paper was originally assessed as a conference abstract, and detailed study methods were not described, hence it was not clear whether blinding had been undertaken, and if so, how it had been undertaken.

Two trials described those assessing outcomes as being blinded to treatment allocation. Trials were still included where description of allocator and assessment blinding was insufficient, if the critical appraisal score met the threshold.[9, 16] The outcomes of people who withdrew during trials were included in the analysis in five trials. [5, 7, 9, 16, 31] One trial stated participants did not complete the trial but not specifically state reasons of withdrawal.[6] The only trial that did not state if participants withdrew was the conference abstract.[8] The decision to include this study was based on the comparable participant number at entry and completion of the study. Based on these criteria, all trials that met the appraisal criteria were included in this review. Results of critical appraisal can be found in *Table 3.2* and details of questions one to ten in *Appendix 3*.

Table 3.2: JBI-MAStARI critical appraisal results of included trials

Author, date	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Rinosl H, Skhirtladze K, Birkenberg B, Mora B, Steinlechner B & Dworschak M, 2014	U	Y	Y	N	U	Y	Y	Y	Y	Y
Fatovich DM, Prentice DA & Dobb GJ, 1997	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y
Thel MC, Armstrong AL, McNulty SE, Califf RM & O'Connor CM,, 1997	U	Y	Y	Y	Y	Y	Y	Y	Y	Y
Hafez HS, Abdelkader AA, Elagaty AE, Bakry MA, Nawito AM & Elw, 2013	U	Y	Y	U	U	Y	Y	Y	Y	Y
Longstreth W, Fahrenbruch C, Olsufka M, Walsh T, Copass M & Cobb L, 2002	U	Y	Y	Y	Y	Y	Y	Y	Y	Y
Mathew HP, White WD, Schinderle DB, Podgoreau MV, Berger M, Milano C, Laskowitz DT, Stafford-Smith M, Blumenthal JA ; Newman MF, 2013	Y	Y	U	Y	N	Y	Y	Y	Y	Y
Bhudia S, Cosgrove D, Naugle R, Rajeswaran J, Lam B, Walton E, Petrich J, Palumbo R, Gillinov M, Apperson-Hansen C & Blackstone E, 2006	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
%	57.14	100.00	85.71	83.33	40.00	100.00	100.00	100.00	100.00	100.00
Y = yes, N= No, U = Unclear, N/A = Not applicable. See *Appendix 3* for details on the questions										

Assessment of heterogeneity

The Joanna Briggs Institute methodological guidance indicates heterogeneity can be attributed to clinical, methodological or statistical factors. Clinical heterogeneity is present when there are differences in participant characteristics, clinical interventions or how participants were treated in the study. Methodological heterogeneity is present when included studies are of varied design or quality, while statistical heterogeneity is considered present when variability in summary treatment effects between trials is identified.[1] Heterogeneity is measured on a scale, and ranges from high to low. Low may indicate an absence of heterogeneity, or that while present, it was not significant enough to be considered as confounding the results.[19]

In this systematic review, demographic characteristics for populations were similar for trials investigating cardiac arrest and cardiac surgery. In each study, neurological outcomes were measured reliably, participants were treated identically in terms of the type of intervention in either magnesium or placebo groups. The homogeneity of populations, treatment/intervention and outcomes measured was the premise of the use of meta-analysis in this review for appropriate studies.

Whilst the overarching principles were similar in all trials, not all measures of neurological outcomes were the same. There were variations in the timing of recorded outcomes and dosing regimens. In all included studies except one,[9] neurological outcomes were measured using validated neurological assessment tools in similar populations. To organize the trials based on the assessment outcomes, the neurological measures were categorised into functional, physiological and cognitive outcomes. Categorization of the trials based on their neurological measure enabled similar trials to be analysed using meta-analysis.

Characteristics and validity of the neurological measurements for cardiac surgery and cardiac arrest can be found in *Tables 3.3* and *3.4* respectively. Further discussion of the reliability of these assessment tools is in Chapter four. The trial that did not use a validated assessment tool evaluated neurological function by living status, and awakening by three months. The Living status categorisation used directly reflected quality of life, measured as independent, dependent or vegetative.

Table 3.3 Description of neurological measures and validity of outcomes measured for studies investigating cardiac surgery

Author, date	Test Category	Neurological measure	Description of Neurological measure	Validity
Bhudia et al 2006[5]	**Functional Neurological Assessments**	**Western Perioperative Neurological Scale**	Score calculated based on the following domains: Mentation: 4 tests: level of consciousness, orientation to time, place, short term memory & speech Motor function: 5 tests limbs, cranial nerves Sensory: 4 tests: sensation in R & L upper & lower limbs Cerebellar function: 4 tests: movement, gait, reflexes, primitive reflexes (glabellar tap, snout response, suck response, palmonmental reflex, grasp reflex)	Validated for neurological assessment in populations at risk of stroke during coronary artery bypass surgery.[77] The scale was originally designed to detect and quantify anatomically discrete neurological abnormalities for patients preoperatively.[77]
	Cognitive Assessment	**Hopkins Verbal Learning Test (HVLT)**	Brief assessment of verbal learning, memory, discrimination, recognition and recall.	Studied in populations with vascular dementia and Alzheimer's disease. Validated in populations with suspected dementia as a test of learning and memory.[78]
		Controlled oral word association test	Test of verbal fluency and spontaneous production of words. COWAT scores correlate with measures of executive functioning, learning and working memory.	Validated in populations with traumatic brain injury.[79] Some authors are concerned the ability to retrieve words is affected by habitual responses.[80]
		Boston Naming Test	Verbalising names in response to visual stimulus.	Validated screening tool for cognitive function in populations at risk of dementia.[81]
		Grooved Pegboard & digit symbol search	Visual motor assessment using pegboard and symbol searches. Test of executive control capabilities.	Difference in gender and age noted. Stratified normative estimates are required to provide accurate clinical assessment.[82]
Hafez et al 2013[6]	**Neurophysiological test**	**Cognitive P300 Evoked Potentials**	Neuronal response to an auditory stimulus was calculated by: ▪ The latency: time taken to reach the peak component (in milliseconds). ▪ The amplitude: measured in microvolts from the peak of the P3 component to the preceding wave.	P300 cognitive auditory evoked potentials are valid measures of cognitive function in populations which undergo cardiac pulmonary bypass.[83]

Table 3.3 continued

Mathew et al 2014[7]	**Cognitive assessment**		Cognitive tests comprised of 5 tests to determine score: ▪ Short Story module of the Randt Memory Test ▪ Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Test ▪ Modified Visual Reproduction Test from the Wechsler Memory Scale ▪ Digit Symbol Test from the Wechsler Memory Scale ▪ Trail making test part B	Well-validated series of cognitive tests in accordance with the Consensus statement on Assessment of Neurobehavioural Outcomes after cardiac Surgery.[7]
Rinosl et al 2013[8, 52]	**Neurophysiological Assessment**	Neuron-specific enolase	The dominant enolse enzyme found in neural and endocrine neuronal tissue.	Raised concentrations of neuron specific enolase reflects proportion of neuronal damage.[84]
		P300 cognitive evoked potentials	As above	As above
	Cognitive	Mini-mental State Exam	30-point questionnaire to measure cognitive impairment	The MMSE is a validated clinical and research tool to investigate cognitive dysfunction. It cannot be used to make diagnoses, but used to identify patients needing further investigations.[27]
		Forward and Backward Digit Span Tests	Visual motor assessment	Validated cognitive assessment tool. Variations in results between age and gender, therefore stratified normative estimates are required to provide accurate clinical assessment.[82]

Table 3.4 Description of neurological measures and validity of outcomes measured for studies investigating cardiac arrest

Author, date	Test Category	Neurological measures	Description of Neurological measure	Validity
Fatovich et al 1997[31]	**Functional Neurological Assessment**	Glasgow Outcome Scale, also known as the Cerebral Performance Category (CPC)	A scale that grades patients' response to advanced life support practices.	The CPP is a validated instrument to measure outcomes after cardiac arrest.[85]
Longstreth et al 2002[9]	**Functional Neurological Assessment**	Time to awakening Living status	Awakening, defined as patient having comprehensible speech or following commands, and based on the review of medical records and telephone contact. Living status assessed by 3 months and categorised as either neurologically intact (independent) or neurological dysfunction (dependent, vegetative or dead).	No validated objective neurological assessment tool used. Datum obtained from audited patient files and follow up by direct phone contact with the patients.
Thel et al 1997[16]	**Functional Neurological Assessment**	Glasgow Coma Score (GCS)	Practical measure of the conscious state of an individual in response to a defined stimuli. Minimum score of 3, maximum 15 from 3 domains (eye, voice, motor).	Validated for predicting mortality but not regarded as a comprehensive neurological assessment.[86].
		Karnofsky performance status	A score that measures an individual's overall performance status or ability to perform activities of daily living. Scores range from 0 to 100 in increments of 10.	Validated research tool for neurological assessment.[87]
		Discharge status:	Discharge of patient to: • Home self care and independent living • Home – assisted care • Skilled nursing facility	No validated objective assessment neurological tool used. Neurological outcome based on audit of discharge living status.

Overview of review findings & main results

This systematic review included a total of seven trials, randomizing 988 participants. Two trials[5, 16] found a statistically significant effect of magnesium, three trials[7, 9, 31] found no significant statistical difference between groups, and the remaining two trials[6, 8] noted neuroprotective effects of magnesium during administration, with neuroprotective properties decreasing as serum magnesium levels decline.

Trials were firstly categorized into either cardiac surgery or cardiac arrest. Four trials[5,6-8] randomizing 797 participants investigated the intervention during cardiac surgery and three trials[9, 16, 31] randomizing 191 eligible participants during cardiac arrest. The main results section is then reported across three key domains of neuroprotective effects: functional neurological assessment, neurophysiological assessment and cognitive assessment. *Tables 3.5* and 3.6 describe the results and authors' conclusions of included trials during cardiac surgery and cardiac arrest.

Neurological outcomes

Functional neurological outcomes

Four trials[5, 9, 16, 31, 88] including 541 participants assessed functional neurologic outcomes. Functional neurological outcome is not limited to arousal or level of consciousness, but also encompasses the ability to perform activities of daily living, and independence. For each trial, functional assessment varied between Western Perioperative Neurologic Scale (WPNS),[5] measured days of awakening and independence,[9] Glasgow Outcome Scale or Cerebral Performance Category (CPC),[31] Glasgow Coma Scale (GCS) and Karnofsky performance status.[16]

Three[5, 9, 16] of the four[31] trials that measured functional neurological outcome found improved neurological recovery in the magnesium group. Two of these studies were post cardiac arrest[9, 16] and one, post cardiac surgery.[5] The fourth trial,[31] also a post cardiac arrest investigation, noted improved neurological recovery in several patients from the magnesium cohort, however, these patients did not survive to discharge.

Functional neurological outcomes after cardiac surgery

One study of 350 participants investigated functional neurological outcome after cardiac surgery.[5] This study found that maintaining magnesium plasma levels of 3.6 to 4.8 mg/dL was effective in improving functional neurological outcome. This was achieved by administering 3.1780mg of magnesium per 100ml of normal saline. In this trial, data was collected from patients undergoing elective on-pump coronary artery bypass grafting (CABG), valve surgery, or combined CABG and valve surgery. Functional neurological outcome was measured at 24 hours, 96 hours and psychological data at 3 months.[5] The study utilized scores from the Western Perioperative Neurological scale to measure functional neurological outcomes. Neurological assessment was based on the following domains: mentation, motor, sensory and cerebella function. Refer to *Table 3.4* for further details.

WPNS scores decreased post-operatively in both groups at 24 hours ($p<0.0001$). The WPNS score coefficient ± standard deviation (SD) was 1.6 ± 0.42. At 96 hours, significant improvement was maintained in the magnesium group, which had returned to pre-operative WPNS scores, whereas the placebo group did not ($p=0.003$), with the magnesium group regaining neurological function before the placebo group ($p=0.01$).

Sensory domain and motor function tests remained relatively unaffected compared to the baseline for both magnesium ($p<0.3$) and placebo ($p=0.0$) groups. The mentation score returned to pre-operative levels in the magnesium group prior to the placebo group, which remained depressed from the baseline at 96 hours. Authors were contacted for raw data to enable re-analysis, however, no additional data was provided. The placebo group had decreased cerebellar function scores compared to pre-operative levels, and increased primitive reflexes ($p<0.002$). Cerebellar function tests remained at pre-operative levels in the magnesium group ($p>0.5$). The differences between groups for cerebellar function were statistically significant and unlikely to be due to chance ($p=0.003$).

Functional neurological outcomes after cardiac arrest

Three trials were suited for meta-analysis.[9, 16, 31] Dichotomous datum from these three trials investigating functional neurological outcome post cardiac arrest by assessing independent living was extracted and combined. The rationale for including these studies in meta-analysis was the overarching similar characteristics of each study for patients post cardiac arrest. The participants received the intervention or placebo as allocated in the protocol and each of the participants had a neurological assessment. Each of these trials included neurological assessments categorized as functional neurological outcomes for adults, post cardiac arrest.

There were notable differences in the settings of these three trials. Two trials[9, 31] investigated patients with out-of-hospital cardiac arrest brought into the emergency department by paramedics, undergoing cardio-pulmonary resuscitation. One trial investigated patients with in-hospital cardiac arrest.[16] Since none of these trials was completed in a critical care environment, each was considered similar in terms of environmental capacity. Whilst the magnesium dosing regimen varied in each trial, all three trials met the inclusion criteria of a minimum 2g magnesium within 24 hours of cardiac arrest. Although there were differences in effect sizes, the outcomes were measured using similar methods and the $I^2 = 0\%$ indicates when pooled, there was low risk of heterogeneity.

Meta-analysis included 187 participants. In one trial,[31] only the eight participants who had neurological assessment were included in meta analysis instead of the original 67 participants from this study. Only single treatment modes with magnesium were considered, resulting in 33 participants being included from the original 150 participants in another trial.[16] Results were analysed using a random effects statistical analysis model. The Mantel-Haenszel test for variance was the most appropriate model for categorical data with small sample sizes.

Mantel-Haenszel is the default fixed-effect method of meta-analysis programmed in Review Manager.[89] When datum are sparse, either in terms of event rates being low or study size being small, the estimates of the standard errors of the effect estimates that are used in the inverse variance methods may be poor. Mantel-Haenszel methods use a different weighting scheme that depends on which effect measure (e.g. risk ratio, odds ratio, risk difference) is being used. They have been shown to have better statistical properties when there are few events, such as in the case of the included studies. Because this is common in Cochrane reviews, the Mantel-Haenszel method is generally preferable to the inverse variance method and was applied in this review. In other situations, the two methods give similar estimates.[89]

Neurological deficits were found to be lower in the magnesium cohort than the placebo participants, suggesting magnesium may improve functional neurological outcome, post cardiac arrest (OR 0.44, 95% CI 0.24-0.81). Individually, studies did not favour magnesium and lacked statistical significance. Pooled data in meta-analysis, however, favours magnesium administration to improve functional neurological outcome, post cardiac arrest, compared to placebo (*Figure 3.2)*.

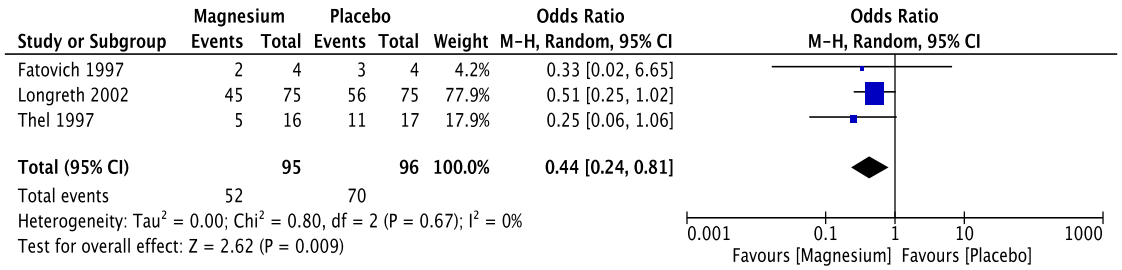

Figure *3.2:* Meta-analysis of trials investigating the neuroprotective properties of magnesium on functional neurological outcome post cardiac arrest

Participants in one study of out-of-hospital cardiac arrest patients brought into the emergency department (ED) by paramedics received a 5g magnesium bolus on arrival.[31] The outcome of interest was the level of neurological intactness as measured by the Glasgow Outcome Scale. Of the participants who survived to leave the ED, two of four participants from the magnesium group were neurologically intact, whereas one of four of the placebo group participants was neurologically intact. An additional two participants from the magnesium group were neurologically intact but did not survive to leave the ED, due to septicaemia.[31] The second study included a magnesium regimen involving a 2g bolus en route to hospital.[9] No significant difference (p=0.25) was found between the magnesium 46.7% (n=35) and placebo group 37.3% (n=28) in awakening by 3 months. There were significantly higher rates of (p=0.05) independent living in the magnesium group at 40%, (n=30) compared to placebo at 25.3% (n=27.9). At the final three-month assessment, there were no significant differences in independence between groups (p=2.9).[9] In the final study, the magnesium treatment regimen included a 2g bolus followed by an 8g infusion.[16] At 24 hours, this study found no significant difference in GCS between the magnesium and placebo groups GCS 11 (8-15) and GCS 11 (6-14) respectively. Median Karnofsky Performance Status was significantly higher in the magnesium group: 70 (64-80) versus placebo: 40 (30-70), (p=0.041). At discharge, the number of participants with independent living was significantly higher in the magnesium group at 60% (n=11/16), compared to the placebo group at 35% (n=6/17), p=0.052). Comparative description of these results is reported in *Table 3.6.*

Neurophysiological outcome after cardiac surgery

Two studies[6, 8] with a total of 58 participants investigated neurophysiological outcomes. Two trials[6, 8] measured neurophysiology using cognitive P300 evoked potentials and one trial[6] assessed biochemical measures of neurological damage using neuron-specific enolase (NSE).[8] In these studies, 4mg magnesium was administered shortly after anaesthesia was effective. The effectiveness of the intervention declined as serum magnesium levels decreased towards the baseline.[8] The limited samples sizes of these studies' trials demonstrates the need for a larger trial.

In the first study, patients admitted for elective on-pump coronary bypass grafting were administered a 4g infusion and neurophysiologic testing using cognitive P300 visual evoked potentials at 3 days, postoperatively. In the magnesium group, there was a significant decrease in P300 latency post operatively, compared to the baseline (preoperative: 449 msec ± 35.87 and postoperative: 404.83 msec

± 49.59; p=0.008) but no difference in amplitude (preoperative: 11.97μv ± 4.48 and postoperative: 12.55μv ± 3.69; p=0.701), compared to baseline. The placebo group had no significant difference between baseline and post-operative latency (preoperatively: 415.6 msec ± 60.77 and postoperatively: 433.2 msec ± 46.49; p=0.38) or amplitude (preoperatively 9.16 μv ± 3.98 and postoperatively 9.14 μv ± 4.13; p=0.99). The post operative P300 amplitude was significantly higher in the magnesium group compared to the placebo group (magnesium 12.55 msec ± 3.69 versus placebo: 9.14 msec ± 4.13; p=0.0241).

P300 latency evoke potentials were also measured at three months[8]. The authors noted an increase in latency in both magnesium and placebo groups at three months (magnesium; 459 msec ± 120 versus placebo: 410 msec ± 67; p<0.05). The methodological heterogeneity between the two trials, particularly the time point for measurement of outcomes, contraindicated meta analysis of these trials. The clinical significance of these results are discussed in chapter 5.

Only one study measured neuron specific enolase (NSE) levels at two, six and 24 hours, post operatively.[8] NSE remained suppressed post-operatively (10.0μg/L), compared to the baseline (9.8μg/L) in the magnesium group. No data was available for comparison from the placebo group, however, the authors reported that NSE remained suppressed whilst magnesium remained elevated. The authors concluded that treatment with magnesium in this study did not show a clear neuroprotective effect, however, serum magnesium >1.2mmol/L temporarily suppressed NSE release from damaged neurons. No studies measured neurophysiological outcomes following cardiac arrest, hence reporting in this thesis is limited to outcomes following surgery.

Cognitive outcomes after cardiac surgery

Three trials[8, 13, 52] with a total of 386 patients investigated cognitive outcomes after cardiac surgery. Magnesium was not effective in reducing postoperative cognitive decline. Magnesium dosing concentrations varied between each of the trials, with one study measuring by weight,[7] another study administered all patients a 4g bolus followed by 0.6g infusion,[8] and the third trial aimed to maintain plasma concentrations of 3.6 to 4.8 mg/dL.[5] One study had invalid results due to familiarity with testing methods resulting in detection bias, and will not be discussed further. [5]

The types of cognitive assessments varied between studies. One study included a series of five tests which provided each participant with an individual score.[7] The tests used by this study included the Short Story module of the Randt Memory Test, the Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Test, the Modified Visual Reproduction Test from the Wechsler Memory Scale, Digit Symbol subtest of the WAIS-R, and the Trail Making Test.[7] Another paper performed cognitive testing using the mini mental state exam and the forward and backward digit span tests.[8] *Table* 3.3 and *Table 3.4* provide a detailed description of neurological outcomes in cardiac surgery and cardiac arrest respectively.

Results from the final study on cognitive outcomes concluded magnesium administered intravenously during cardiac surgery does not reduce postoperative cognitive dysfunction.[7] Patients undergoing elective cardiac surgery received a magnesium treatment regimen consisting of a 50mg/kg bolus

followed by 50mg/kg infusion over three hours. Cognitive assessments were made at 6 weeks. No significant difference was found in cognitive tests (p=0.93) or neurocognitive change scores between the magnesium and placebo groups (magnesium: 0.07 ± 0.28 versus placebo: 0.13 ± 0.28; p=0.31).

It should be noted that no studies measured cognitive outcomes following cardiac arrest, hence reporting in this thesis is limited to outcomes following cardiac surgery.

Summary of Results

A large RCT using the WPNS to measure changes in functional neurological outcomes following cardiac surgery found no difference between magnesium and placebo groups for three of the four domains, although a positive, persistent change favouring magnesium was noted for cerebellar functioning.[5]

Meta-analysis of functional neurological outcomes across three trials of cardiac arrest patients favoured intravenous magnesium.[9, 16, 31] The analysis was not confounded by heterogeneity, but there were inconsistencies in how patients were selected for analysis in two of the three studies, therefore caution is needed in interpreting these findings, and further research that adheres to CONSORT requirements (including intention to treat analysis) is needed.

Only two studies investigated neurophysiological outcomes following cardiac surgery, both were limited by small sample sizes.[6, 8] There were no clinically significant differences between groups, although there was a significant decrease in P300 latency associated with magnesium in one study. Neither study was able to demonstrate clinical benefit for neurophysiological outcomes following cardiac arrest or cardiac surgery.

In terms of cognitive outcomes following cardiac surgery, three trials with 386 patients were included in this review.[8, 13, 52] Administration of magnesium was not associated with a protective effect against cognitive dysfunction at six week follow-up. There was highly significant heterogeneity between these three studies which again highlights the need for research that enables meaningful comparisons between studies. Outcomes for each of the included trials are described in *tables 3.5* and *3.6* for cardiac surgery and cardiac arrest respectively.

Table 3.5: Results for included trials investigating the outcomes of magnesium for neuroprotection during cardiac surgery

Study	Category	Neurological measure	Time point	Results	Summary
Bhudia et al 2006[5]	Functional assessment	Western Perioperative Neurological Scale	24 hours 96 hours	No significant difference between Mg & placebo group (p<0.0001) at 24 hours Mg group significantly improved compared to placebo (p=0.01) at 96 hours	No significant difference between Mg & placebo group at 24 hours (p<0.0001) Mg group significantly improved compared to placebo at 96 hours (p=0.01)
	Cognitive assessment	Hopkins verbal learning test Controlled oral word association test Boston Naming Test (BNT) Digit symbol & symbol search: processing index speed Grooved pegboard	3 months	Invalid results	Conclusion cannot be drawn due to invalid results
Hafez et al 2013[6]	Neurophysio-logical outcome	Cognitive P300 Visual Evoked potentials in response to stimulus	72 hours	Significant difference between Mg & placebo (p=0.0241)	Evidence of decreased neuron excitability at 3 to 4 days Magnesium may have a neuroprotective effect. Neuroprotective effects of magnesium evidence whilst serum magnesium elevated
Mathew et al 2014[7]	Cognitive assessment	Short Story module of the Randt Memory Test, Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Test, Modified Visual Reproduction, Digit Symbol subtest of the WAIS-R, and Trail Making Test	6 weeks	No significant difference (p=0.31)	No significant difference between groups. Magnesium does not improve perioperative cognitive dysfunction
Rinosl et al 2013[8]	Neurophysio-logical assessment	Blood samples: neuron-specific enolase (NSE) surrogate marker of neuronal injury P300 cognitive evoked potentials	96 hours	No significant difference (p<0.05)	No significant difference between groups Magnesium temporarily suppresses neurological damage and may have a neuroprotective effect. Neuroprotective effects of magnesium evidence whilst serum magnesium elevated
	Psychiatric assessment	Mini-mental stae examination Digit span test (forward & backward) Trail-making test	3 months	Significant decrease in both groups (p<0.05)	Cognitive decline is evident in both magnesium and placebo groups

Table 3.6: Results for included trials investigating the outcomes of magnesium for neuroprotection during cardiac arrest

Study	Category		24hours	Results	Summary
Fatovich et al 1997[31]	Functional assessment	Cerebral Performance Category	At discharge	Neurologically appropriate: Mg 6.5% and Placebo 2.8% No significant difference between groups (p<0.5)	At discharge, Neurologically appropriate: Mg 6.5% and Placebo 2.8%. No statistical significant difference between groups (p<0.5) Only neurologically intact participant was from magnesium group.
Longstreth et al 2002[9]	Functional assessment	Awakening at any time by 3 months Independent: Measured by comprehensible speech, following commands and based on medical records and telephone contact Days to awakening: Calculated by 25% of the group awake	3months	Increased independent living in Mg group compared to placebo (p=0.05)	At 3 months, increased independent living in Mg group compared to placebo (p=0.05) Magnesium improved functional neurological outcome up to 3 months post arrest however the study lacks the power
Thel et al 1997[16]	Functional assessment	Median (IQR) Glasgow Coma Score (GCS) Median (IQR) Karnofsky performance status Discharge status: home, assisted or nursing facility	24 hours At discharge	No difference in mean GCS at 24 hours Median KPS higher in Mg group (p=0.041) Increased independent living in Mg group (p=0.52)	At discharge, median Karnofsky performance status significantly higher in Mg group (p=0.041) Significantly increased independent living in magnesium group (p=0.52). Quality of life in cardiac arrest survivors due to functional neurological outcome was improved in the magnesium group.

Variance in magnesium dosing regimen

Magnesium treatment regimens varied significantly between included trials (with the exception of those studies included in meta-analysis) in terms of both dose and timing of administration. All doses were given via the intravenous route. Two trials of cardiac arrest patients included a bolus dose of magnesium either enroute[9] or on arrival to the emergency department,[31] three trials gave a bolus dose followed by infusion[7, 52,16] and two trials administered an infusion only.[5, 6] Dosing regimes are described in detail in *Table 3.7.*

Magnesium dosing regimen in cardiac surgery

For patients undergoing cardiac surgery, it is difficult to determine a beneficial pattern from a therapeutic dosing regime, in terms of pre-operative magnesium dose, timing and post-operative magnesium administration due to the lack of significant findings for most outcomes across the included studies.

Two trials[5, 6] showed significant statistical improvement in functional neurology and physiological neurological recovery within two to three days when the first dose of magnesium was administered during anaesthesia. The larger trial[5] administered 1g magnesium during anaesthesia, followed by a 3g infusion over 24 hours; and whilst the second trial[6] administered a 4g infusion over 20 minutes. Two trials[7, 52] found no significant statistical improvement in neurological outcome when magnesium was administered during cardiac surgery. Both studies administered a 4g bolus during surgery, followed by either a 1g infusion over 2 hours or a 4g infusion over 3 hours. However, questions regarding what the optimal dosing regimen remain a research priority.

Magnesium dosing regimen in cardiac arrest

For patients in cardiac arrest, the most effective dosing regimen involved 2g magnesium administered at the point of ROSC and/or immediately during the post arrest period, followed by a 24-hour infusion. Two trials[9, 16] found a significant statistical improvement in neurological recovery when magnesium was administered during ROSC. No statistical difference in neurological outcomes was recorded in the trial[31] that administered magnesium during advanced life support.

Table 3.7. Magnesium dosing regime

Author, date	Magnesium	Route	Regimen	Magnesium compound	Placebo
Cardiac Surgery					
Bhudia et al 2006[5]	780mg Mg/100ml normal saline	IV Infusion	15 minutes during anaesthesia induction	$MgSO_4$	Normal saline administered in same quantities as magnesium treatment
	3.160g Mg/100ml of normal saline Plasma Mg 3.6 to 4.8 mg/dL	IV Infusion	24hours		
Hafez et al 2013[6]	4g Mg	IV Infusion	20 minutes	$MgSO_4$	Normal saline administered in same quantities as magnesium treatment
Mathew et al 2014[7]	50mg/kg Mg	Bolus	20 minutes after anaesthesia induction	Not specified	Normal saline administered in same quantities as magnesium treatment
	5 mg/kg Mg (approximately 4.2g for an 85kg person)	IV Infusion	3 hours		
Rinosl et al 2013[8, 52]	4g Mg	Bolus	30minutes prior to induction of VF	$MgSO_4$	Placebo (n=14) Placebo regime not specified
	0.6g Mg	Infusion	2 hours		
Cardiac Arrest					
Fatovich et al 1997[31]	5g Mg in 10ml	Bolus	On arrival to ED department	$MgSO_4$	10ml normal saline bolus
Longstreth et al 2002[9]	2g Mg/ 4ml 2ml normal saline	Bolus	En route to hospital	$MgSO_4$	4ml Normal saline 2ml Normal saline
Thel et al 1997[16]	2g Mg bolus	Bolus	At arrest	$MgSO_4$	Normal saline administered in same quantities as magnesium treatment
	8g Mg	IV infusion	24 hours		
Mg = magnesium, kg = kilograms, g = grams, ml = millilitres, $MgSO_4$ = magnesium sulphate, VF = ventricular fibrillation, IV = intravenous					

Variance in reporting timeframes between trials of neurological measurement

Outcomes were measured at various time points for each of the seven included trials. Three trials assessed outcomes at 24 hours,[5, 8, 16] however only one of these trial[16] was included in meta-analysis. One trial measured outcomes at six weeks,[7] two trials between three to four days,[5, 6] two trials at three months,[5, 9] and two trials at discharge from hospital. There is no clear association between outcomes and specific time points of measured neurological outcomes for studies investigating either cardiac arrest or cardiac surgery.

For cardiac surgery, the four included trials measured preoperative baseline levels followed by postoperative neurological outcomes, including psychological status, biochemical markers and neurophysiological assessment at day three to four. The remainder of the studies had outcome measures at 24 hours,[5] three to four days,[8] six weeks[7] and three months.[5] For cardiac arrest, findings were noted at 24 hours, at hospital discharge and at three months. [16,9]

Chapter 4: Discussion and Conclusions

Chapter introduction

Evidence based health care is essential for clinical practice to keep evolving to ensure the best outcomes for the patient.[23] The Joanna Briggs Institute model of evidence based healthcare has established several validated tools for the translation of primary research and clinician expertise into knowledge for clinical practice via the synthesis of evidence as systematic reviews.[20] Neurological assessment is used commonly in both clinical and research practices to assess functional staus. Accurate assessment is essential for long-term and short-term patient outcomes and interventions. Several parameters are required to give an overview of neurological function, including independent living, communication, motor and sensory function, cognitive and behavioural domains and consciousness.

Summary of review protocol

The study objective

The objective of this review was to present the best available evidence related to the neuroprotective effects of magnesium during a period of global cerebral ischemia associated with cardiac arrest or cardiac surgery. Magnesium dosing variances and timeframes were also investigated.

Inclusion criteria

This review considered adults aged above 18 years. Studies of patients with existing neurological deficits or aged below 18 were excluded. Pre-existing neurological deficits were defined as diseases or conditions already existing in an individual which would interfere with the clinical assessment. The intervention of interest was magnesium administered in doses of at least of 2g compared to placebo in adult patients within 24 hours of cardiac arrest or cardiac surgery. This review considered experimental designs, including randomized controlled trials, non-randomized controlled trials, and quasi-experimental designs.

The outcome of interest was neurological recovery, post-cardiac arrest or cardiac surgery, as measured by objective scales, such as but not limited to cerebral performance category, brain stem reflex, Glasgow Coma Score (GCS) and measures of independent living or dependent living status. The effect of magnesium on mortality has been extensively studied, therefore mortality was not considered an outcome of interest.

Search strategy

The search strategy aimed to find both published and unpublished studies between January 1980 and August 2014 utilizing the Joanna Briggs Institute three-step search strategy. Databases searched for published studies included PubMed, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL). Unpublished studies were searched for using

Australian Clinical Trials Register, Australian and New Zealand Clinical Trials Register, Clinical Trials, European Clinical Trials Register and ISRCTN Registry.

Data extraction

Quantitative datum was, where possible, pooled in statistical meta-analysis using the Cochrane software Review Manager. Where statistical pooling was not possible, the findings were presented in narrative form, including tables and figures, to aid in datum presentation, where appropriate. Heterogeneity was noted in neurological outcome measures, magnesium dosing regimen and timing of reported neurological outcome, and will be discussed in the following section.

The studies included in this review were critically appraised using the JBI-MAStARI critical appraisal tool. Using this tool, all studies met the inclusion threshold of a score of six out of ten. Observed differences between trials were identified in population groups, measures of neurological outcome, dosing regimens and intervention environments. The populations included were similar across the different trials in terms of mean age, and the exclusion criteria predominantly including pre-existing neurological injury and multimodal treatments. The studies included in this systematic review each investigated neurological outcomes, however, each used different definitions, reporting methods and measures of neurological outcome. The validity of each of the reported outcomes was assessed (Tables 3.3 and 3.4).

To understand the causes of heterogeneity, studies were reported based upon populations with cardiac arrest, and those with cardiac surgery. There was significant heterogeneity among four of the seven studies investigating patients with cardiac arrest, therefore these were analysed narratively. Sufficient homogeneity was evident in three studies investigating cardiac surgery to perform meta-analysis (I^2=0%).

Neuroprotective effects measured by neurological outcome were categorized into three subsets: functional neurological, neurophysiological and cognitive assessment. There is significant overlap between these domains, and several neurological measures are likely to be used across these three discrete categories. The categorisation of studies was useful to understand measured outcomes and clinical implications. Studies investigating neuroprotective outcomes post cardiac surgery, included all three domains, whereas only functional neurological outcome was assessed in studies that were post cardiac arrest.

Discussion of main results

Functional neurological outcomes after cardiac surgery

The data from one trial reporting on neurological outcomes, post cardiac surgery found the magnesium group significantly improved 3 to 4 days post surgery compared to placebo when maintaining plasma magnesium levels of 3.6 to 4.8 mg/dL for 24 hours, post operatively. Whilst

the study power is significant and the study design robust, this data needs to be interpreted cautiously. Thee western perioperative neurological scale (WPNS) used to assess neurological function has previously only been validated in the setting of pre-operative cardiac patients. The WPNS is a tool for preoperative neurological assessment of cardiac patients used clinically in North America, with several similarities to clinical neurological examination domains used in Australia. Scored tests are used to provide a comprehensive overview of neurological assessment, including four main domains: mentation, motor, sensory and cerebellar domains.[5] Details of the WPNS can be found in *Appendix 8.1.* The nature of the WPNS provides extensive insight to functional capacity assessing several domains, including mentation, motor and sensory function and primitive reflexes; however, an ideal tool to assess neurological outcome in research, however is yet to be validated.[90]

Data on the validity of the tool within the literature is limited and has only been referenced in the study included. Citation review revealed no insight to the previous use of this tool. The authors of this scale were contacted to establish the validity of the tool, however, no response was received.[5] Issues determining the credibility of this neurological measure are a significant barrier to accurately interpreting the results of this trial.

The addition of magnesium to the intra-operative regimen could potentially improve patient recovery. The long-term effects of magnesium administration intra-operatively are yet to be established, however the short-term effects have potential benefits. The magnesium group in one study was noted to have improved recovery in short-term memory and reduced re-emergence of primitive reflexes. The outcomes of this study suggest intra-operative elevated magnesium levels enable patients to recover more quickly and completely, improving neurological recovery. Implementing intra-operative magnesium needs further research to determine the efficacy and safety.

Functional neurological outcomes after cardiac arrest

Three trials[9, 16, 31] measured functional neurological status to investigate the effect of magnesium on neurological outcomes during cardiac arrest. The individual studies did not show statistical benefit of magnesium administration on neurological outcomes during cardiac arrest. However, pooled datum using meta-analysis from the three trials[9, 16, 31] favoured magnesium to improve neurological outcomes, post cardiac arrest.

The rationale for including these studies in meta-analysis was the overarching similar characteristics of each study for patients post cardiac arrest. The participants received the intervention or placebo as allocated in the protocol, and each of the participants included had a functional neurological assessment. Whilst different neurological outcome scales were used for each trial, each type of measure was concerned with purposeful motor movement, activities of daily living and independent living.

This review concluded that magnesium administration does not improve the survival rate of resuscitation,[16] therefore advanced resuscitation practices such as advanced airway

management, compressions and defibrillation should not be delayed for magnesium administration.[2] The potential benefits of magnesium could easily be incorporated by administering supplementation during return of spontaneous circulation (ROSC) care. Since the outcomes of patients who suffer cardiac arrest are generally poor, and the safety profile of magnesium is strong, this intervention has the potential to improve patient outcome and improve functional outcome for those who survive. Further clinical studies are required to determine the optimal clinical regimen.

The administration of magnesium during the ROSC period could be incorporated during fluid administration. Electrolyte profiles are regularly monitored in critically unwell patients. Magnesium as an additive to fluid sequences could be titrated to maintain the optimum serum level. Dosing regimen and optimum serum levels are an area for future research. This would influence clinical practice, not only during in-hospital treatment of cardiac arrest, but including other areas of healthcare using resuscitation practices such as pre-hospital care.

One trial measured neurological outcome using the Cerebral Performance Category (CPC) (*Appendix 8.2)* post cardiac arrest.[31] This alignes with recommendations by the International Liaison Committee on Resuscitation (ILCOR) as part of Utstein data reporting methods.[2] This five-tier scale incorporates assessment of consciousness and independent status, long-term survival and quality of life, post cardiac arrest.[92] One trial directly assessed functional living status by using discharge destination (nursing home or independent living), the Karnofsky performance status (KPS) (*Appendix 8.3*) and the Glasgow Coma Scale (GCS) (*Appendix 8.4)*,[16] whilst the other assessed the ability to perform activities of daily living.[9]

The CPC scale has previously been criticised for poorly defined, subjective criteria.[91] CPC1[93] scores have been found to overestimate patients' ability, providing inaccurate assessment of cognitive and functional neurological outcome. Discrepancies in discharge status have been found in patients post cardiac arrest with a CPC 3, who discharged to a range of facilities from "home with no services" to long-term acute care".[85] Furthermore, several impairments and disability disparate concepts are grouped together, suggesting the need for patient subcategories *Appendix 9.2*.

Discharge status reflects the individual's functional status. The facility (home, nursing home) patients are discharged to correlates with a measure of independence and therefore functional ability. Multiple factors affect discharge status, including insurance coverage,[85] family members,[85] pre-existing morbidity, lower socio-economic status, health literacy and geographic location.[85] Discharge position correlates poorly with CPC[85], indicating future research could incorporate discharge status with clinical assessment. This limiting factor reduces the accuracy of comparison these two studies.

The KPS measures the level of care required by assessing the activities of daily living, which increase the accuracy of functional status when combined with discharge status.[16] This tool is currently used in clinical practice to determine the effectiveness of different therapies and assess the prognosis of patients with a range of serious diseases such as stroke, cancer and

palliative medicine.[94] Advantages of the KPS include a comparable measure of functional outcome and independence, however, it could also be criticised for subjective clinical assessment.[95]

The predominant factor limiting comparison of trials during this review was the variances in assessment of neurological outcome. The three validated neurological assessment tools are: GCS, Canadian Neurological Scale (CNS) and the National Institute of Health Stroke Scale (NIHSS). Future research could be centred on recommendations from The National Health and Medical Research council of Australia (NHMRC) and aim to use recommendations from the expert groups such as the NHMRC and ILCOR when deciding on neurological assessment measures.

Neurophysiological outcomes after cardiac surgery

For the purpose of this systematic review, neurophysiological measures were defined as objective measures of changes in physiological functioning. This is an emerging field which does not have the same limitations as functional neurological outcome and cognitive outcome measures, which can be unreliable due to subjectivity of the examiner. An objective neurophysiological measure such as neuronal activation or a biochemical marker is thus justified.

Neurophysiological datum was obtained from two studies[6, 8] using P300 evoked potentials and one study[8] using neuron specific enolase. Neuron specific enolase (NSE) is a relatively neuron specific isoenzyme of enolase, found in the cytoplasm of both neurons and neuroendocrine cells.[96] During neuronal injury, membrane disruption causes leakage of proteins, including NSE, into the extracellular space, which transports to the cerebral spinal fluid (CSF). The CSF directly transports components into the venous circulation at the villi of the arachnoid space, allowing NSE levels to be directly quantified from plasma samples.

Reduced NSE levels correlate with reduced neuronal injury. NSE levels are suppressed during elevated magnesium serum levels, suggesting magnesium dosing regimen needs to be increased and prolonged post operatively to improve neuroprotective effects of magnesium.[8] The clinical implication of maintaining raised serum levels is that it would require prolonged magnesium infusion administration. Regular clinical examination and serum electrolyte sampling would be required to monitor for side effects associated with raised serum levels.

Currently in clinical practice, NSE is used to monitor the progress of neural crest tumours, including small cell carcinoma of the lung, melanoma, seminoma and neurblastoma.[97] Whilst testing does not have 100% sensitivity for diagnostic purposes, levels are used to monitor response to therapy.[98] Conditions resulting in central nervous system disease and damage which report increased NSE in the CSF include cardiac arrest, traumatic brain injury, ischemic stroke including transient episodes, haemorrhagic stroke, multiple sclerosis and brain neoplasms.[99] NSE is not routinely measured for these conditions in clinical practice.

NSE could potentially be used in the clinical setting of patients with cardiac arrest or cardiac injury to monitor neuronal injury. It is known that increased NSE correlates with the degree of neuronal damage, yet clinical intervals have not been established in humans. Serum NSE >33 µg/L in the first three days has been associated with delayed return to consciousness in patients who survive cardiac arrest but remain comatose. [100] Further investigation to NSE levels in patient with global ischemia is required to assess the reliability of this measure.

Cognitive P300 evoked potentials are typically used in research rather than clinical practice. The voltage and speed of neuronal excitability is measured in response to a direct stimulus, producing a waveform that represents the physiological response of neurons in the process of decision-making. Results are validated for specifying changes in cognitive function, changes in decision-making and alterations in neurotransmitter and electrophysiological abnormalities.[101] Neuron excitability is affected by reduced atrophy, where the degree of structural atrophy correlates with reduced neuron excitability.[101] Patient factors such as age and pre-existing neurological decline would influence the outcome of this measure, and these determinants need to be considered prior to further use of this tool.

Cognitive outcomes after cardiac surgery

Short-term and long-term neurocognitive decline has been well established after cardiac bypass surgery[12] and in patients with left ventricular failure.[102] Cognitive testing encompasses behavioural and psychiatric evaluation. Cognitive decline leading to impaired functioning and psychosocial impairments has been documented in patients requiring cardiac surgery and following cardiac arrest. Hypoperfusion of the cerebrum had previously been thought to contribute to this decline.[7]

Several hypotheses for short-term and long-term decline could explain the lack of improvement in cognitive outcome. In addition to hypoperfusion of the cerebrum, these reasons could also include microemboli, anaesthesia and systemic inflammatory responses.[12, 13] Other postulated mechanisms include cerebral oxygen desaturation[6] and platelet activation. Cardiac conditions are often associated with cerebrovascular pathology due to the similarity of risk factors to coronary disease including hypertension, hyperlipidaemia and hypercholesterolemia. In addition to the cellular neuroprotective mechanisms, magnesium may improve cerebral blood flow via vasodilatory mechanisms.[13]

Of the cognitive datum investigated in 3 studies,[5, 6, 8] there was no significant difference in cognitive function between the magnesium and placebo groups in 2 studies. The results from the third study,[5] have been omitted from analysis as the data was found to be unreliable. Decline in cognitive function has been associated with inadequate serum magnesium levels <1.2mmol/L.[8] Future trials using adequately powered studies involving prolonged magnesium administration could clarify whether there is an association, its strength and direction.

Inconsistency among cognitive reporting methods has resulted in difficulties in comparing trials. Currently, there are numerous cgnitive tests to assess cognitive function. The tests used in this

review included a combination of validated tests such as the Randt Memory Test, subsets of the digit span test, Mini-Mental State Examination, Weshler Memory Scale and Trail making test.[6] There is debate among researchers in the field whether future testing should isolate the dominant and non-dominant hemispheres. Without consistency in reporting against standardised methods, comparisons among research trials will continue to be limited.

Newer brief cognitive screening instruments used in dementia screening may be useful in assessing cognitive decline in patients with global ischemia, due to increased sensitivity and specificity. [103] Screening instruments recommended in primary care due to validity and reliability, efficacy and sensitivity include the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE) Memory Impairment Screen (MIS) and General Practitioner Assessment of Cognition (GPCOG).[103] Ideally, comprehensive testing involves cognitive, motor and perceptual functions including orientation, visual-spatial organisation, executive decision making, memory and planning functions such as concentration, attention and comprehension.

The MMSE is a widely used cognitive screening tool in clinical practice, usage of the MMSE has identified several limitations, requiring adjustment for age and education status.[103] Participants with high intelligence or education demonstrate a ceiling effect, leading to false negatives.[103] False positives occur with increased age, limited education, foreign cultures and sensory impairment.[103] The MMSE has been criticized for limited sensitivity to frontal and subcortical changes, requiring additional testing for frontal and executive function. Yet this tool has many advantages, allowing correlation between different population groups and reduces administration time.

Variability in the incidence of cognitive decline could be attributed to numerous factors including demographic differences, variance in surgical procedures, study inclusion and exclusion criteria, time interval for measuring follow-up, statistical analysis variation and variations in control groups.[12] Surgical procedural variation reflects differences in technique, which may influence cerebral blood flow. These include the cross clamping technique, degree of hypothermia, rate of rewarming, and the use of cardiotomy suction.[12] The limited control of numerous factors contributing to cognitive decline in these patients support the need for long-term cognitive follow-up and ongoing support for this patient population.

For this population, cardiac surgery with implantation of artificial devices reduces cognitive decline, supporting the hypothesis of long-term cerebral hypoperfusion.[102] Assessing neurophysiological decline is difficult due to variations in ischaemic time, variations in cognitive assessment and limitations of assessing reperfusion injury.[8] A number of these patients have arteriosclerosis vascular disease, which potentially will affect cerebral arteries. Vascular induced cognitive decline cannot be resolved with a neuroprotective agent administered during surgery, but requires a prolonged management plan.

Magnesium dosing regimen

Timing of magnesium dosing

Magnesium dosing regimen varied significantly between studies. For both cardiac surgery and cardiac arrest, magnesium dosing was most effective when a loading bolus was followed by an infusion at the earliest possible point, however, there is not enough evidence in this review to make clinical recommendations for the timing of magnesium administration. In the population with cardiac surgery, favourable outcomes were observed when magnesium was administered during anaesthesia,[5, 6] and continued for 24 hours, post procedure.[5]

In populations during cardiac arrest, magnesium was most effective during return of spontaneous circulation (ROSC)[9, 16] not during the resuscitation period. Previous studies[31, 104] have found that administration of magnesium does not reduce mortality during cardiac arrest, therefore magnesium administration should not precede normal resuscitation practices such as CPR and defibrillation. As discussed earlier, the future clinical application of magnesium supplementation could be incorporated as a magnesium additive during fluid resuscitation in the early post-arrest period.

Formulation of magnesium dosing regimen

For cardiac surgery patients, there is no clear beneficial pattern for magnesium dosing between bolus and infusion administration. Two studies reported neurophysiological protection during magnesium administration, therefore it may be postulated that prolonged infusion of magnesium increases neuroprotection.[6, 8] While another study found the potentially detrimental effects of magnesium and slight increase in mortality rate in populations with stroke and traumatic brain injury.[13] Future research should aim to identify a safe and effective regimen for prolong elevated serum magnesium levels post administration. It may be necessary to continue magnesium supplementation during the postoperative period.

In Australia, magnesium treatment is currently indicated for severe asthma, pre-eclampsia, eclampsia, neuroprotection for a pre-term foetus less than 30 weeks, some cardiac arrhythmias including torsades de pointes and rhythms associated with hypokalemia.[59] The dosage of magnesium sulphate is highest for pre-eclampsia and eclampsia (4g given over 5 to 10 minutes followed by an infusion of 1g per hour for 24 hours). The dose for asthma is diluted to 10mmol, approximately 2.5g.

From the evidence included in this systematic review, we cannot recommend an optimal dosing regimen. In the studies presented, the most effective dose of magnesium during cardiac arrest was found to be 2g during ROSC, followed by 8g infusion over 24 hours. Further research is required to determine the optimal patterns of dosing that could be applied to patients who undergo cardiac surgery and cardiac arrest.

Adverse effects of magnesium

The trials included in this review noted the safety of magnesium in doses up to 5g for cardiac surgery and 10g for cardiac arrest within a 24-hour period. The adverse events reported in the included trials were due to pre-existing co-morbidities and medical complications, not due to the magnesium administration.

Previously reported common adverse effects of magnesium include hypotension, flushing, nausea and vomiting.[59] More serious effects include bradycardia, central nervous system depression and cardiac arrest, although none of these were reported in the included studies. The problems in particular for the populations discussed include and increased risk of cardiac rhythm disturbances, particular heart block, negative ionotropic effects and concurrent kidney injury contributing to the risk of overdose. Continuous clinical monitoring is required in all patients with this therapy, in combination with regular clinical examination to detect the effects of hypermagnesia, including the loss of deep tendon reflexes and respiratory depression.[59]

Conclusions

The evidence in this systematic review suggests magnesium administered during anaesthesia may provide improved functional neurological outcome for patients with cardiac surgery, however, additional studies are required to support this. The neuroprotective effect of magnesium occurs while serum levels remain elevated with limited adverse effects. Magnesium was not shown to improve long-term cognitive function and cognitive testing has noted a steady decline in all intervention and control participants of populations included in this systematic review.

The evidence from this systematic review suggests magnesium administration at the point of return of spontaneous circulation (ROSC) after cardiac arrest is effective in improving functional neurological outcomes. Further research is required to investigate the optimal dosing regimen, however, the most effective formulation used in the trials included in this review was 2g magnesium administered during ROSC followed by 8g infusion over 24 hours. Data is not available on neurophysiological or cognitive outcomes after cardiac arrest, and is an area for future research.

The limitations of this review are centred around the different measures of neurological outcome. Each trial included in this systematic review investigated neurological outcomes, however, each trial uses different definitions, reporting methods and measures of neurological outcome. Accurate interpretation of the results is difficult in the absence of validated comparative data between neurological measures. Congruity of both definitions and neurological measures is required among researchers and clinicians to propagate knowledge in this area. Currently, terminology and outcome measures are quite different, suggesting the need for a common model. Further research into optimal magnesium dosing regimen is required.

Recommendations for clinical practice

Cardiac Surgery

Magnesium administration may improve short-term ceebeller functioning in patients who suffer global cerebral ischemia associated with cardiac surgery **(Grade B)**

Magnesium administration may confer a functional neuroprotective effect in some patients whilst serum magnesium levels are elevated **(Grade B)**

Magnesium administration does not improve cognitive outcome in patients who suffer global cerebral ischemia associated with cardiac surgery **(Grade A)**

The optimal dosage, and mode of administration of Magnesium has not been established **(Grade B)**

Cardiac arrest

Magnesium administration improves functional neurological outcome in patients who suffer global cerebral ischemia associated with cardiac arrest **(Grade A)**

Magnesium administration appears to be effective when given as a bolus during return of circulation followed by an infusion over 24 hours **(Grade B)**

There is insufficient evidence to comment on neurophysiological or cognitive outcomes

Implications for research

- Further research is needed in specific domains of functional neurological, neurophysiological and cognitive outcomes to determine the effectiveness of neuroprotective properties of magnesium during global cerebral ischemia associated with cardiac surgery
- Where possible, researchers should report neurological outcomes using similar standards from expert groups such as ILCOR and the NHMRC. Sub categorization of measures into functional neurological, neurophysiological and cogntive measures allows comparison of studies and comprehensive neurological assessment.
- Consensus on reporting standards for outcome measurement time points and consistent adherence to CONSORT requirements is recommended to enable meaningful comparison between studies, ideally including short and longer term timeframes.

Conclusions

This systematic review critically reviewed and evaluated evidence from experimental studies on possible benefits in terms of neuroprotection from intravenous administration of Magnesium. The evidence from this systematic review indicates that magnesium may improve functional neurological outcomes in some patients who suffer global ischemia associated with cardiac surgery and cardiac arrest.

For patients undergoing elective cardiac surgery, neurophysiological data indicates magnesium provides short-term neuroprotection during elevated serum levels with limited adverse effects. To date, there are no known additional benefits of magnesium on long-term cognitive function. For cardiac arrest patients, magnesium administration offers promise for protection of functional neurological outcomes.

Standardisation of methods, timeframes and adherence to CONSORT requirments in primary research are required if future trials are to enable useful comparisons. Researchers should consider neurological assessment methods recommended by the NHMRC and ILCO to allow comparative research of future trials.

Future research should incorporate testing of neurological outcome in the domains of functional outcome, neurophysiological markers and cognitive tests. Suitable dosing regimens should be investigated prior to introduction into clinical practice. Further research is required to investigate the optimal magnesium dose and timing of reported outcome.

Conflicts of interest

There are no conflicts of interest to declare

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References

1. JBI. Joanna Briggs Institute Reviewers' Manual: 2014 edition. In: Institute JB, (ed.). 2014.

2. Jacobs I, Nadkarni V, Bahr J, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). *Resuscitation*. 2004; 63: 233-49.

3. Nolan JP, Neumar RW, Adrie C, et al. Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication: A scientific statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke (Part 1). *International Emergency Nursing*. 2009; 17: 203-25.

4. Muir KW. Magnesium in stroke treatment. *Postgraduate Medical Journal*. 2002; 78:641-5

5. Bhudia SK, Cosgrove DM, Naugle RI, et al. Magnesium as a neuroprotectant in cardiac surgery: a randomized clinical trial. *The Journal of Thoracic and Cardiovascular Surgery*. 2006; 131: 853-61.

6. Hafez H, Abdelkader A, Elagaty A, Bakry M, Nawito A and Elwahab Y. Cerebral protective effect of magnesium during CABG assessed by cerebral oximetry and cognitive P300 visual evoked potentials. *World Journal of Medical Sciences*. 2013; 8: 339-44.

7. Mathew JP, White WD, Schinderle DB, et al. Intraoperative magnesium administration does not improve neurocognitive function after cardiac surgery. *Stroke; a Journal of Cerebral Circulation*. 2013; 44: 3407-13.

8. Rinosl H, Skhirtladze K, Felli A, Ankersmit HJ and Dworschak M. Ther neuroprotective effect of magnesium sulphate during iatrogenically-induced ventricular fibrillation. *Magnesium Research*. 2013; 26: 109-19.

9. Longstreth WT, Fahrenbruch CT, Olsuffka M, Walsh TR, Copass MK and Cobb LA. Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest. *Neurology*. 2002; 59: 506-14.

10. Geocadin RG, Koenig MA, Jia X, Stevens RD and Peberdy MA. Management of brain injury after resuscitation from cardiac arrest. *Neurologic clinics*. 2008; 26: 487-506, ix.

11. Fitzsimons MG. In: Mark J and Nussmeier N, (eds.). *Weaning from cardiopulmonary bypass (CPB)*. Waltham WA: UpToDate, 2015.

12. Selnes OA and McKhann GM. Neurocognitive complications after coronary artery bypass surgery. *Ann Neurol*. 2005; 57: 615-21.

13. Mathew JP, Laskowitz DT and Newman MF. Response to letter regarding article, "Intraoperative magnesium administration does not improve neurocognitive function after cardiac surgery". *Stroke*. 2014; 45: e45.

14. Finn J, Jacobs I, Holman C and Oxer H. Outcomes of out-of-hospital cardiac arrest patients in Perth, Western Australia, 1996-1999. *Resuscitation*. 2001; 51: 247-5.

15. Peters R and Boyde M. Improving survival after in-hosptial cardiac arrest: the Australian experience. *American Journal of Critical Care*. 2007; 16: 240-6.

16. Thel MC, Armstrong AL, McNulty SE, Califf RM and O'Connor CM. Randomised trial of magnesium in in-hospital cardiac arrest. Duke Internal Medicine Housestaff. *Lancet*. 1997; 350: 1272-6.

17. Stub D, Bernard S, Duffy SJ and Kaye DM. Post cardiac arrest syndrome: a review of therapeutic strategies. *Circulation*. 2011; 123: 1428-35.

18. Ghabriel M and Vink R. Magnesium transport across the blood-brain barriers. In: Vink R and Nechifor M, (eds.). *Magnesium in the Central Nervous System*. The University of Adelaide: The University of Adelaide Press, 2011, p. 59-76.

19. Institute TJB. *Joanna Briggs Institute Reviewers Manual: 2014 edition*. The Joanna Briggs Institute: Adelaide, 2014.

20. Pearson A, Wiechula R, Court A and Lockwood C. The JBI model of evidence-based healthcare. *International journal of evidence-based healthcare*. 2005; 3: 207-15.

21. Pearson A, Jordan Z and Munn Z. Translational science and evidence-based healthcare: a clarification and reconceptualization of how knowledge is generated and used in healthcare. *Nursing Research Practice*. 2012; 2012: 792519.

22. Munn Z, Porritt K, Lockwood C, Aromataris E and Pearson A. Establishing confidence in the output of qualitative research synthesis: the ConQual approach. *BMC Medical Research Methodolology*. 2014; 14: 108.

23. Sackett DL and Rosenberg WM. The need for evidence-based medicine. *Journal of the Royal Society of Medicine.* 1995; 88: 620-4.

24. Rosenberg WM and Sackett DL. On the need for evidence-based medicine. *Therapie*. 1996; 51: 212-7.

25. Sackett DL, Rosenberg WM, Gray JA, Haynes RB and Richardson WS. Evidence based medicine: what it is and what it isn't. 1996. *Clinical orthopedics and related research*. 2007; 455: 3-5.

26. Knot S and Tirschwell DL. Long-term neurologiclal complications after hypoxic-ischemic encephalopathy. *Seminars in Neurology*. 2006; 24: 422-31.

27. O'connor D, Pollitt P, Hyde J, et al. The reliability and validity of the Mini-Mental State in a British community survey. *Journal of psychiatric research*. 1989; 23: 87-96.

28. Organization TWH. WHOQOL: Measuring quality of life. *Health statisics and information systems*. Geneva 2018.

29. Pearce A, Lockwood C and Van Den Heuvel C. The use of therapeutic magnesium for neuroprotection during global cerebral ischemia associated with cardiac arrest and cardiac bypass surgery in adults: a systematic review protocol. *JBI Database of Systematic Reviews and Implementation Reports*. 2015; 13: 3-13.

30. Torres J and Ishida K. Neuroprotection after major cardiovascular surgery. *Current treatment options in neurology*. 2015; 17: 357.

31. Fatovich DM, Prentice DA and Dobb GJ. Magnesium in cardiac arrest (the magic trial). *Resuscitation*. 1997; 35: 237-41.

32. Dougherty CM. The natural history of recovery following sudden cardiac arrest and internal cardioverter-defibrillator implantation. *Progress in Cardiovascular Nursing*. 2001; 16: 163-8.

33. Chalkias A, Kuzovlev A, Noto A, d'Aloja E and Xanthos T. Identifying the role of cytochrome c in post-resuscitation pathophysiology. *American Journal of Emergency Medicine*. 2015.

34. Binks A and Nolan JP. Post-cardiac arrest syndrome. *Minerva Anestesiologica*. 2010; 76: 362-8.

35. Saver JL, Starkman S, Eckstein M, et al. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. *The New England Journal of Medicine*. 2015; 372: 528-36.

36. Cook NL, Corrigan F and van den Heuvel C. The role of magnesium in traumatic brain injury. In: Vink R and Nechifor M, (eds.). *Magnesium in the Central Nervous System*. The University of Adelaide: The University of Adelaide Press, 2011, p. 167-80.

37. Saver JL and Starkman S. Magnesium in clinical stroke. In: Vink R and Nechifor M, (eds.). *Magnesium in the Central Nervous System*. The University of Adelaide: The University of Adelaide Press, 2011, p. 205-16.

38. Saver JL, Kidwell C, Eckstein M, Starkman S and Investigators F-MPT. Prehospital neuroprotective therapy for acute stroke: results of the Field Administration of Stroke

Therapy-Magnesium (FAST-MAG) pilot trial. *Stroke; a Journal of Cerebral Circulation* 2004; 35: e106-8.

39. Goldberg MP and Choi DW. Combined oxygen and glucose deprivation in cortical cell culture: calcium-dependent and calcium-independent mechanisms of neuronal injury. *Journal of Neuroscience*. 1993; 13: 3510-24.

40. Kumar V, Abbas A, Fausto N, Robbins S and Cotran R. *Robbins & Cotran patholoIgic basis of disease*. Philadelphia: Elsevier Saunders2005.

41. Brown GC and Vilalta A. How microglia kill neurons. *Brain Research*. 2015.

42. Mangus DB, Huang L, Applegate PM, Gatling JW, Zhang J and Applegate RL, 2nd. A systematic review of neuroprotective strategies after cardiac arrest: from bench to bedside (Part I - Protection via specific pathways). *Medical Gas Research*. 2014; 4: 9.

43. Puttgen HA, Pantle H and Geocadin RG. Management of cardiac arrest patients to maximize neurologic outcome. *Current opinion in critical care*. 2009; 15: 118-24.

44. Nathan HJ, Wells GA, Munson JL and Wozny D. Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: a randomized trial. *Circulation*. 2001; 104: I85-91.

45. Boodhwani M, Rubens F, Wozny D, Rodriguez R and Nathan HJ. Effects of sustained mild hypothermia on neurocognitive function after coronary artery bypass surgery: a randomized, double-blind study. *The Journal of Thoracic and Cardiovascular Surgery*. 2007; 134: 1443-50; discussion 51-2.

46. Abramson A, Tyrrell K, Safar P, et al. A Randomized Clinical Study of a Calcium-Entry Blocker (Lidoflazine) in the Treatment of Comatose Survivors of Cardiac Arrest. *New England Journal of Medicine*. 1991; 324: 1225-31.

47. Jastremski M, Sutton-Tyrrell K, Vaagenes P, Abramson N, Heiselman D and Safar P. GLucocorticoid treatment does not improve neurological recovery following cardiac arrest. *JAMA : The Journal of the American Medical Association*. 1989; 262: 3427-30.

48. Salameh A, Dhein S, . , Dähnert I and Klein N. Neuroprotective strategies during cardiac surgery with cardiopulmonary bypass. . *International Journal of Molecular Sciences*. 2016; 17: 1945.

49. Aslanyan S, Weir CJ, Muir KW, Lees KR and Investigators IS. Magnesium for treatment of acute lacunar stroke syndromes: further analysis of the IMAGES trial. *Stroke; a Journal of Cerebral Circulation.* 2007; 38: 1269-73.

50. Romani A. Intracellular magnesium homeostasis. In: Vink R and Nechifor M, (eds.). *Magnesium in the Central Nervous System*. 1 ed. The University of Adelaide: The University of Adelaide Press, 2011, p. 13-58.

51. Vink R, Cook NL and van den Heuvel C. Magnesium in acute and chronic brain injury: an update. *Magnesium research : official organ of the International Society for the Development of Research on Magnesium*. 2009; 22: 158S-62S.

52. Rinosl H, Skhirtladze K, Birkenberg B, Mora B, Steinlechner B and Dworschak M. The neuroprotective effect of magnesium sulphate during brief cardiac arrest. *European Societry of Intensive Care Medicine 22nd annual congress*. Vienna, Austria 2009.

53. Fitzgerald M, Gruener G and Mtui E. *Clinical Neuroanatomy & Neuroscience*. 6th edition ed. Washington, USA: Saunders, Elsevier, 2012.

54. Yu A. Regulation of magnesium balance. In: Goldfarb S and Forman J, (eds.). Waltham, MA.: UpToDate, 2014.

55. Dai LJ and Quamme GA. Intracellular Mg2+ and magnesium depletion in isolated renal thick ascending limb cells. *Journal of Clinical Investigation.* 1991; 88: 1255-64.

56. Quamme GA. Renal magnesium handling: new insights in understanding old problems. *Kidney International*. 1997; 52: 1180-95.

57. Chang JJ, Mack WJ, Saver JL and Sanossian N. Magnesium: potential roles in neurovascular disease. *Frontiers in Neurology*. 2014; 5: 52.

58. Fuchs-Buder T, Tramer MR and Tassonyi E. Cerebrospinal fluid passage of intravenous magnesium sulfate in neurosurgical patients. *Journal of Neurosurgical Anesthesiology*. 1997; 9: 324-8.

59. Australian Medicines Handbook, Chapeter 17: Obstetric and Gynaecological drugs: Magnesium Sulphate. AMH, 2015.

60. Kew KM, Kirtchuk L and Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. *The Cochrane Database of Systematic Reviews*. 2014; 5.

61. Muir KW, Lees KR, Ford I, Davis S and Intravenous Magnesium Efficacy in Stroke Study I. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. *Lancet*. 2004; 363: 439-45.

62. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. *Circulation*. 2004; 110: 588-636.

63. Trial M. The Magpie Trial Collaborative Group. Do Women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomized placebo-contolled trial. *Lancet*. 2002; 59: 1877-90.

64. van den Bergh W. Magnesium in subarachnoid hemorrhage. In: Vink R and Nechifor M, (eds.). *Magnsim in the Central Nervous System*. The University of Adelaide: The University of Adelaide Press, 2011, p. 193-204.

65. Bain E, Middleton P and Crowther CA. Different regimens for neuroprotection of the fetus for women at risk of preterm birth (Review). *The Cochrane Database of Systematic Reviews*. 2012.

66. Kent A and Kecskes Z. Magnesium sulphate for term infants following perinatal asphyxia. *The Cochrane Database of Systematic Reviews*. 2009; 1.

67. Munn z, Tufanaru C and Aromataris E. JBI's Systematic Reviews: Data Extraction and Synthesis. *American Journal of Nursing*. 2014; 114: 49-54.

68. Moher D, Liberati A, Tetzlaff J and Alltman DG. Preffered reporting items for systematic meta-analysis: The Prisma Statement. 2009.

69. Higgins JPT, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. *BMJ : British Medical Journal*. 2003; 327: 557-60.

70. Dabbagh A, Bastanifar E, Foroughi M, Rajaei S and Keramatinia AA. The effect of intravenous magnesium sulfate on serum levels of N-terminal pro-brain natriuretic peptide (NT pro-BNP) in elective CABG with cardiopulmonary bypass. *Journal of Anesthesia*. 2013; 27: 693-8.

71. Ito H, Saito S, Mikyahra K, Takemura H, Toyama M and Matsuura A. Retrograde cardioplegia revisited: open technique for long aortic cross clamping. *Heart Lung Circulation*. 2013; 9: 742-5.

72. Carrio ML, Ventura JL, Javierre C, et al. Does post-cardiac surgery magnesium supplementation improve outcome? *Magnesium research: official organ of the International Society for the Development of Research on Magnesium*. 2012; 25: 159-67.

73. Aktas MK, Aguila A, Daniels LA, et al. Therapeutic hypothermia in seven year old patient with long QT syndrome and cardiac arrest. *Heart Rhythm*. 2009; 6: S389-S90.

74. Meloni BP, Campbell K, Zhu H and Knuckey NW. In search of clinical neuroprotection after brain ischemia: the case for mild hypothermia (35 degrees C) and magnesium. *Stroke; a Journal of Cerebral Circulation.* 2009; 40: 2236-40.

75. Iandau M, Schneider S, Machado C, et al. Randomized clinical trial of magnesium, diazepam or both after out of hospital cardiac arrest, multiple letters. *Neurology*. 2003; 60: 1868-9.

76. Mohseni M, Ziaeifard M and Abbasi Z. *ARYA Atherosclerosis*. 2013; 10: 227.

77. Murkin J, Martzke J, Buchan A, Bentley C and Wong C. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery:: II. neurologic and cognitive outcomes. *The Journal of Thoracic and Cardiovascular Surgery*. 1995; 110: 349-62.

78. Shapiro AM, Benedict RH, Schretlen D and Brandt J. Construct and concurrent validity of the Hopkins Verbal Learning Test–revised. *The Clinical Neuropsychologist*. 1999; 13: 348-58.

79. DesRosiers G and Kavanagh D. Cognitive assessment in closed head injury: Stability, validity and parallel forms for two neuropsychological measures of recovery. *International Journal of Clinical Neuropsychology*. 1987.

80. Ross TP, Calhoun E, Cox T, Wenner C, Kono W and Pleasant M. The reliability and validity of qualitative scores for the Controlled Oral Word Association Test. *Archives of Clinical Neuropsychology*. 2007; 22: 475-88.

81. Fastenau PS, Denburg NL and Mauer BA. Parallel short forms for the Boston Naming Test: psychometric properties and norms for older adults. *Journal of Clinical and Experimental Neuropsychology*. 1998; 20: 828-34.

82. Ruff RM and Parker SB. Gender-and age-specific changes in motor speed and eye-hand coordination in adults: normative values for the Finger Tapping and Grooved Pegboard Tests. *Perceptual and Motor Skills*. 1993; 76: 1219-30.

83. Grimm M, Czerny M, Baumer H, et al. Normothermic cardiopulmonary bypass is beneficial for cognitive brain function after coronary artery bypass grafting—a prospective randomized trial☆. *European Journal of Cardiothoracic Surgery*. 2000; 18: 270-5.

84. Persson L, Hårdemark H, Gustafsson J, et al. S-100 protein and neuron-specific enolase in cerebrospinal fluid and serum: markers of cell damage in human central nervous system. *Stroke; a Journal of Cerebral Circulation*. 1987; 18: 911-8.

85. Rittenberger JC, Raina K, Holm MB, Kim YJ and Callaway CW. Association between Cerebral Performance Category, Modified Rankin Scale, and discharge disposition after cardiac arrest. *Resuscitation*. 2011; 82: 1036-40.

86. Marion DW and Carlier PM. Problems with initial Glasgow Coma Scale assessment caused by prehospital treatment of patients with head injuries: results of a national survey. *Journal of Trauma and Acute Care Surgery*. 1994; 36: 89-95.

87. Mor V, Laliberte L, Morris JN and Wiemann M. The Karnofsky performance status scale: an examination of its reliability and validity in a research setting. *Cancer*. 1984; 53: 2002-7.

88. Landau WM, Schneider S, Machado C, et al. Randomized clinical trial of magnesium, diazepam, or both after out-of-hospital cardiac arrest [1] (multiple letters). *Neurology*. 2003; 60: 1868-9.

89. Collaboration TC. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. 2011.

90. Bilotta F, Gelb AW, Stazi E, Titi L, Paoloni FP and Rosa G. Pharmacological perioperative brain neuroprotection: a qualitative review of randomized clinical trials. *British Journal of Anesthesia.* 2013; 110 Suppl 1: i113-20.

91. Cummins RO, Chamberlain DA, Abramson NS, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Circulation*. 1991; 84: 960-75.

92. Phelps R, Florence D, Maynard C, Silver J and Rea T. Cerebral Performance Category and long-term prognosis following out-of-hospital cardiac arrest. *Critical Care Medicine*. 2013; 41: 1252-7.

93. Raina K, Callaway C, Rittenberger J and Holm M. Neurological status following cardiac arrest: Method and tool utility. *Resuscitation*. 2008; 79: 249-56.

94. Altilio T and Otis-Green S. *Oxford Textbook of Pallative Medicine*. Oxford University Press, 1993.

95. Abernethy A, Shelby-James T, Fazekas B, Woods D and Currow D. The Australian-modified Karnofsky Performance Status (AKPS) Scale: A revised Scale for contemporary pallative care clinical practice. *BioMed Central Pallative Care*. 2005; 4: 1-12.

96. Laskowitz DT, Grocott H, Hsia A and Copeland KR. Serum markers of cerebral ischemia. *Journal of Stroke and Cerebrovascular Diseases*. 1998; 7: 234-41.

97. Cooper E. Neuron-specific enolase. *Europe PubMed Central*. 1994; 9: 205-10.

98. Labdenne P and Heikinheimo M. Clinical use of tumour markers in childhood malignancy. *Annuals of Medicine* 2002; 43: 316-23.

99. Barone FC, Clark RK, Price WJ, et al. Neuron-specific enolase increases in cerebral and systemic circulation following focal ischemia. *Brain Research*. 1993; 623: 77-82.

100. Hirsch KG, Mlynash M, Jansen S, et al. Prognostic value of a qualitative brain MRI scoring system after cardiac arrest. *Journal of Neuroimaging : official journal of the American Society of Neuroimaging*. 2015; 25: 430-7.

101. Braverman ER, Blum K, Hussman KL, et al. Evoked Potentials and Memory/Cognition Tests Validate Brain Atrophy as Measured by 3T MRI (NeuroQuant) in Cognitively Impaired Patients. *PLoS One*. 2015; 10: e0133609.

102. Zimpfer D, Wieselthaler G, Czerny M, et al. Neruocognitive function in patients with ventricular assisted devices. *American Society for Artificial Internal Organs*. 2006; 52: 24-7.

103. Ismail Z, Rajji TK and Shulman KI. Brief cognitive screening instruments: an update. *International Journal of Geriatric Psychiatry*. 2010; 25: 111-20.

104. Allegra J, Lavery R, Cody R, et al. Magnesium sulfate in the treatment of refractory ventricular fibrillation in the prehospital setting. *Resuscitation*. 2001; 49: 245-9.

Appendices

Appendix 1: the PICO, PICOH, PICo and SPICE frameworks for developing the systematic review question

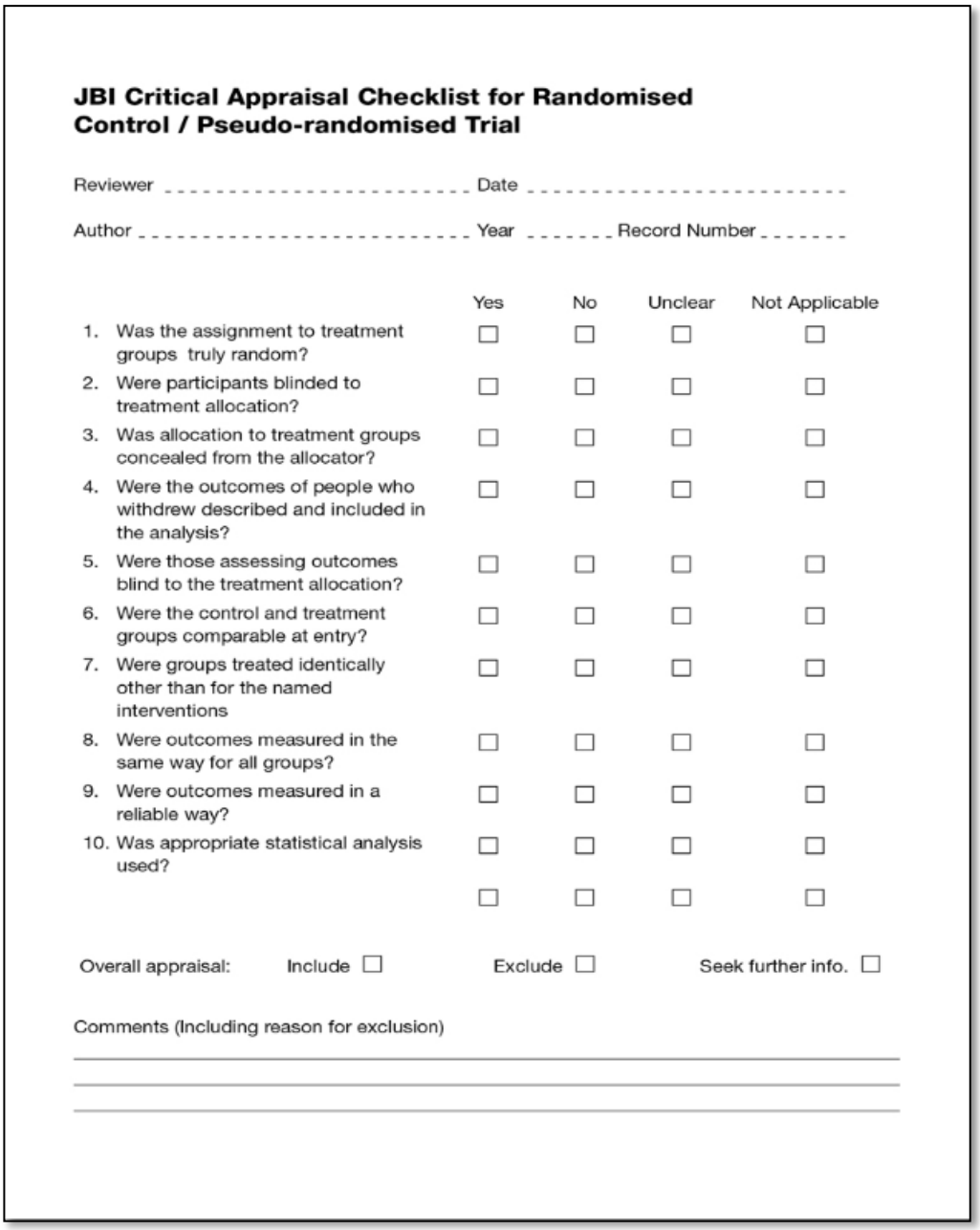
P = Problem/ Patient/ Population I = Intervention C = Control/ Comparison/ Context O = Outcomes	P = Population I = Intervention P = Professionals O = Outcomes H = Healthcare setting
P= Population I = Phenomena of Interest Co = Context	S = Setting P = Perspective I = Intervention C = Comparison E = Evaluation

Appendix 2: characteristics of JBI - SUMARI modules QARI, MAStARI, ACTUARI and NOTARI[1]

Acronym	Module	Primary research designs included	Type of Systematic Review	Module components
QARI	Qualitative Assessment and Review Instrument	Qualitative studies	Qualitative review	Critical appraisal tool Data extraction Meta-aggregation
MAStARI	Meta-Analysis of Statistics Assessment and Review Instrument	Comparable cohort (RCT, pseudo RCT) Time series Descriptive studies	Quantitative review	Critical appraisal tool Data extraction Meta- analysis
ACTUARI	Analysis of Cost, Technology and Utilisation Assessment and Review Instrument	Cost effectiveness, cost minimization, Cost benefit or Cost utility	Economic Evaluation	Critical appraisal Data extraction & synthesis of economic data
NOTARI	Narrative, Opinion and Text Assessment and Review Instrument	Expert opinion texts	Qualitative review	Critical appraisal Meta extraction Data synthesis

Appendix 3: Critical Appraisal Instruments

JBI critical appraisal template for randomized controlled trials and pseudo-randomized controlled trials



JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

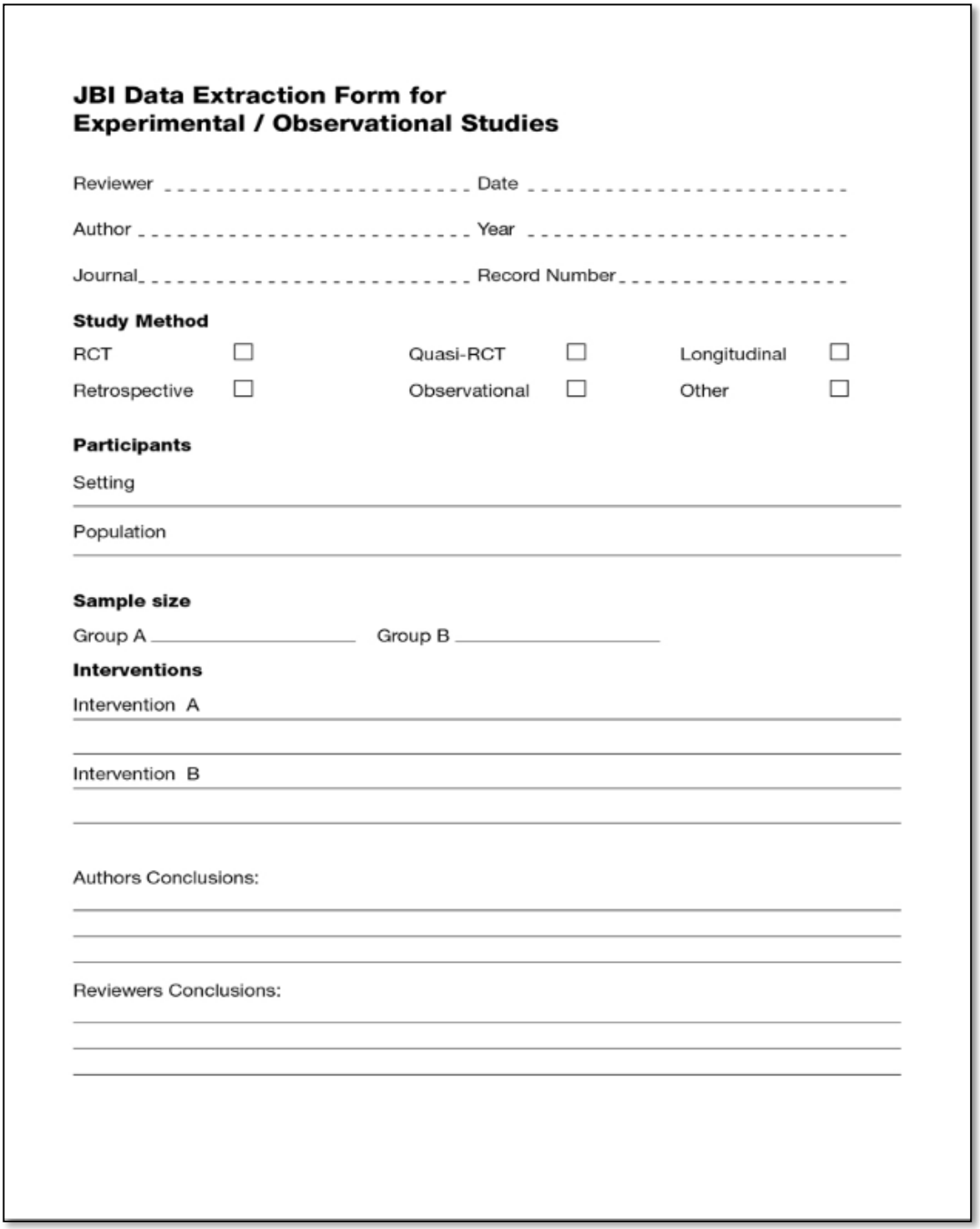
Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix 4: Data Extraction Instruments



JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal _____ Record Number _____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting _____

Population _____

Sample size

Group A _____ Group B _____

Interventions

Intervention A _____

_____

Intervention B _____

_____

Authors Conclusions:

_____

_____

_____

Reviewers Conclusions:

_____

_____

_____

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Appendix 5: Detailed Search Strategy

Appendix 5.1: The search strategy used for published trials

Database	Search strategy: key words identified	Number of Results
PubMED	Heart arrest[mh] OR sudden cardiac death*[tiab] OR out-of-hospital cardiac arrest*[tiab] OR Resuscitation[mh] OR resuscitation[tiab] OR cardiopulmonary[tiab] advanced cardiac life support[tiab] OR Cardiac Surgical Procedures[mh] OR cardiac surgical procedure* [tiab] OR heart bypass*[tiab] OR coronary artery bypass*[tiab] OR cardioplegia[tiab] AND Magnesium[tw] OR Magnesium compound[mh] AND Neuroprotective agents[mh] OR neuroprotect*[tw]	28
CINHAL	MH Heart arrest+ OR TI 'Heart arrest*' OR AB 'heart arrest' OR TI sudden cardiac death* OR AB sudden Cardiac death OR TI 'out-of-hospital cardiac arrest*' OR AB 'out-of-hospital cardiac arrest' OR Resuscitation[mh] OR resuscitation[tiab] OR cardiopulmonary[tiab] advanced cardiac life support[tiab] OR Cardiac Surgical Procedures[mh] OR cardiac surgical procedure* [tiab] OR heart bypass*[tiab] OR coronary artery bypass*[tiab] OR cardioplegia[tiab] AND Magnesium[tw] OR Magnesium compound[mh] AND MH neuroprotective agents+ OR TI neuroprotect* OR AB Neuroprotect*	5
EMBASE	Resuscitation'/syn OR 'cardiopulmonary':ti OR 'cardiopulmonary':ab OR 'sudden cardiac death':ti OR 'sudden cardiac death':ab OR 'out of hospital cardiac arrest':ti OR 'out of hospital cardiac arrest':ab OR 'cardiac surgical procedure':ti OR 'cardiac surgical procedure':ab R 'heart bypass':ti OR 'heart bypass':ab OR 'coronary artery bypass':ti OR 'coronary artery bypass':ab AND 'magnesium'/syn AND 'neuroprotection'/syn OR 'neuroprotective':ti OR 'neuroprotective':ab OR 'neuroprotection':ti OR 'neuroprotection':ab	275
CENTRAL	"magnesium" AND "cardiac arrest"	16
	"magnesium" AND "Neuroprotection"	0

Appendix 5.2: The search strategy used for databases of unpublished trials

Database	**Search strategy: key words identified**	**Number of Results**
Australian Clinical Trials Register	Magnesium AND Neuroprotection	0
Australia & New Zealand Clinical Trials Register	Magnesium AND Neuroprotection	0
Clinical Trials	Magnesium AND Neuroprotection	1
European Clinical Trials Register	Magnesium AND Neuroprotection	0
ISRCTN Registry	Magnesium AND Neuroprotection	0

Appendix 6: Included trials

Appendix 6.1: Included trials investigating the neuroprotective properties of magnesium during cardiac surgery

	Population		**Intervention**	**Comparison**	**Outcomes**		
Author, date	Population characteristics	Mean Age	Intervention (Magnesium)	Placebo	Outcomes measured		Results
Bhudia et al 2006[5]	Adult patients 18 years older admitted for elective on-pump cardiac surgery (CABG, valve surgery or both)	64 ± 12	n=174	n=176	Neurologic Assessment (WPNS)	24 hour 4 days	At 24 hours, No significant difference between Mg & placebo group (p<0.0001) At 96 hours, Mg group significantly improved compared to placebo (p=0.01)
					Psychiatric Assessment	3 months	
Hafez et al 2013[6]	Adult patients 18 years older admitted for on elective on pump cardiac surgery (coronary artery bypass grafting)	54 ± 5	n=15	n=15	Cerebral oximetry	0 hours	
					Cognitive P300 evoked potentials	3 days	At 3-4 days, Significant difference between Mg & placebo cohorts (p=0.0241)
Mathew et al 2014[6]	Adult patients 18 years older admitted for elective cardiac surgery	68 ± 8	n=198	n=191	Neurocognitive tests	6 weeks	At 6 weeks, No significant difference between magnesium cohort and placebo (p=0.31)
Rinosl et al 2013[8, 52]	Adult patients 18 years older admitted for elective cardiac surgery (internal cardio/defibrillator implantation requiring induction of VF)	60 ± 9	n=14	n=14	Neuron-specific Enolase Cognitive P300 evoked potentials	0 hours 2 hours 6 hours 24 hours	At 96 hours, No significant difference between magnesium and placebo (p<0.05) At 3 months, Significant decrease in both magnesium and placebo groups (p<0.05)
Totals			401	396			

Appendix 6.2: Included trials investigating the neuroprotective effect of magnesium during cardiac arrest

	Population		**Intervention**	**Comparison**	**Outcome**		
Author, date	Population characteristics	Mean Age	Intervention (Magnesium)	Placebo	Outcomes measured		Results
Fatovich et al 1997[31]	Adult patients 18 years older with cardiac arrest. Out-of hospital-cardiac arrest receiving CPR on arrival to ED department	64 ± 11	n=4	n=4	Neurological appropriateness defined by CPC	At discharge	At hospital discharge, patients who were neurologically appropriate: Mg 6.5% and Placebo 2.8%. No significant difference between groups (p<0.5)
Longstreth et al 2002[9]	Adult patients 18 years older with cardiac arrest Out-of-hospital cardiac arrest and ROSC achieved with minimum systolic blood pressure of 90mmHg	69.2 ± 14.2	n=75	n=75	Awakening and lifestyle level: (independent, dependent, vegetative, death) by 3 months	3 months	Increased independent living in Mg group compared to placebo (p=0.05)
Thel et al 1997[16]	Adult patients 18 years older In-hospital cardiac arrest in non-emergency department wards	63 (50-71 IQR)	n=16	n=17	GCS	24 hours	
					Karnofsky performance status, discharge status	At discharge	At discharge, median Karnofsky performance status significantly higher in Mg group (p=0.041) Significantly increased independent living in magnesium group (p=0.52)
Totals			95	96			

Appendix 7: Excluded studies

Table of excluded studies with reasons why they did not meet the inclusion criteria

Study	Reason for exclusion
Dabbagh et al 2013[70]	Study outcomes were based on post-operative pain, bleeding and extubation time. Neurological outcome was not measured.
Ito et al 2013[71]	Study did not use magnesium during procedure.
Carrio et al 2012[72]	Study outcomes were based on hours of intubation, cardiac arrhythmias and mortality. Neurological outcome was not measured.
Aktas et al 2009[73]	Case report using several pharmacological interventions in addition to magnesium.
Meloni et al 2009[74]	Not primary research. Review article discussing neuroprotection after brain ischemia.
Iandau et al 2003[75]	Not primary research. Responding letter to original authors Longstreth et al.
Mohseni et al 2013[76]	Case report using several pharmacological interventions in addition to magnesium.

Appendix 8: Details of neurological assessment

Appendix 8.1: The Western Neurological Perioperative Scale (WNPS)

Domain	**Tests**
Mentation	Level of consciousness Orientation to time place and person Short-term memory Speech
Motor function	Motor strength: bilateral upper & lower limbs Facial motor strength: cranial nerve testing
Sensory function	Sensation in upper & lower limbs
Cerebellar function	Movement Gait Reflexes: • Upper limb • Lower limb Primitive reflexes: • Glabellar tap • Snout response • Suck response • Palmomental reflex • Grasp reflex

Appendix 8.2: The Cerebral Performance Category

CPC 1	Good cerebral performance: normal life • Conscious, alert, able to work • May have minor neurological or psychological deficit including mild dysphagia, non incapacitating hemiparesis, minor cranial nerve abnormalities
CPC 2	Moderate cerebral disability: disabled but independent • Conscious, sufficient cerebral function for independent activities of daily life • Able to work in sheltered environment • May have moderate neurological or psychological impairment including hemiplegia, seizures, ataxia, dysarthria, dysphasia and memory changes
CPC 3	Severe cerebral disability: conscious but disabled and dependent • Conscious but dependent on others for daily support due to limited brain function • Limited cognition • Ranges from ambulatory state to severe dementia or paralysis
CPC 4	Com/ vegetative state: Unconscious • Unconscious, unaware of surroundings • No cognition • No verbal or psychological integration with the environment
CPC 5	Brain death • Certified brain death by traditional criteria
CPC: Cerebral Performance Category	

Appendix 8.3: Australian Modified Karnofsky Performance Status Index

AKPS Criteria	Score
Normal, no complaints; no evidence of disease	100
Able to carry on normal activity: minor sign or symptom of disease	90
Normal activity with effort; some signs or symptoms of disease	80
Cares for self: unable to carry on normal activity or to do active work	70
Able to care for most needs; but requires occasional assistance	60
Considerable assistance and frequent medical care required	50
In bed more than 50% of the time	40
Almost completely bedfast	30
Totally bedfast and requiring extensive nursing care by professionals and/or family	20
Comatose or barely rousable	10
Dead	0

Appendix 8.4 Glasgow Coma Scale

Behavior	Response	Score
Eyes opening	Spontaneous	4
	To speech	3
	To pain	2
	No response	1
Voice	Orientated to time, place, person	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Motor	Obeys commands	6
	Moves to localized pain	5
	Flexion withdrawal to pain	4
	Decorticate posturing	3
	Decerebrate posturing	
	No response	1