**The utility of Magnesium in the Management of Atrial fibrillation with Rapid ventricular response: A randomised controlled trial (MagMAR study)**

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**ABSTRACT**

High dose magnesium is often utilized in the management of atrial fibrillation with rapid ventricular response, however randomised controlled trials have shown conflicting results in regards to its efficacy. We aim to further examine the relationship between the ventricular response rate in rapid atrial fibrillation and magnesium therapy in acute emergency department presentations. MagMAR is a randomised, prospective, double blind, placebo controlled trial. We aim to enrol patients at a single centre tertiary level emergency department whose presenting complaint can be attributed to atrial fibrillation with rapid ventricular response, defined as a rate > 120bpm with either new or pre-existing (permanent, persistent or paroxysmal) atrial fibrillation. Patients will be randomized into one of two treatment arms, receiving either high dose intravenous magnesium, or intravenous placebo (normal saline). This will be in addition to the usual emergency department management with the primary end point being reduction of ventricular rate. Secondary endpoints include reversion to sinus rhythm, time to achieve target heart rate, number of additional treatments required to achieve heart rate target, length of stay in emergency department, rate of inpatient hospital admission and 30 day mortality and readmission rates.

**BACKGROUND**

Atrial fibrillation (AF) is an often-encountered presentation in emergency departments worldwide with its prevalence increasing due to increasing life expectancy and improved detection and diagnosis. As a result, this is translating to increased rates of patient presentations to emergency departments with AF. A recent analysis of national data in Australia confirmed a 7.9% annual increase in hospitalisations due to AF (as a principal diagnosis), with almost 45 000 hospitalisations attributable to AF per annum. The estimated prevalence of AF in Australian adults aged older than 55 years as at June 2014 was estimated to be 5.35%, with projections that by 2034 this will increase by a further 20%1. Atrial fibrillation is not a benign entity; left untreated and uncontrolled, it can causes significant morbidity and has the potential to precipitate acute heart failure, stroke and long term can result in tachycardia induced cardiomyopathy and subsequent chronic heart failure2,3.

High dose intravenous magnesium is a commonly utilised treatment in atrial fibrillation with rapid ventricular response (AF with RVR). Early studies suggested magnesium was safe, affordable and easily accessible and as a result has been widely used. It is thought to have a number of favourable biochemical and electrophysiological properties that may aid in ventricular rate reduction. Specifically, its role as a facilitator for the sodium potassium exchange pump (the Na-K ATPase) and its effects on potassium channels and intracellular calcium accumulation all serve to decrease automaticity, prolonging the atrial and atrioventricular nodal refractory period and thus potentially decreasing ventricular rates 4-6. Although these pathophysiological mechanisms are theoretically sound, randomised controlled trials have shown conflicting results with regards to magnesium’s clinical efficacy.

A small number of randomised controlled trials have assessed magnesium’s efficacy when compared to placebo. Initial small studies provided the rationale for a clinical trial in which 199 patients presenting with AF (mean baseline ventricular rate 142 beats per min) were treated with usual AV nodal blocking therapy, most often digoxin, and were also randomly assigned to intravenous magnesium sulfate (2.5g over 20 minutes followed by 2.5 g over two hours) or placebo7. This study showed the addition of magnesium therapy increased the likelihood of achieving a ventricular rate <100 beats/min compared to placebo (65% versus 34%, p<0.0001) and conversion to sinus rhythm (27% versus 12%, p=0.01). However, the study did have a number of limitations. Firstly, the benefit of magnesium was modest (a reduction of 12 beats per minute) and secondly, digoxin was the main agent used for rate control with the current standard of care, (calcium channel blocker, beta blocker) used in only 12-13% of patients.

Other studies however have shown conflicting results. In a similar study conducted in Queensland, Australia, comparing IV magnesium sulfate (MgSO4) to placebo given as an initial bolus with heart rates monitored every 15 minutes for 2 hours, it failed to demonstrate a difference between the two groups for reducing heart rate or conversion to sinus rhythm8. This study however only enrolled a small sample of only 24 patients and only moderate doses of magnesium were given (10mmol or 2.5g). This trial however likely represents the more contemporary management strategy adopted, at least throughout Australia.

More recently, a large randomized trial of 450 patients recruited to either low dose (4.5g), high dose (9g) or placebo in addition to standard AV nodal blocking agents has been reported10. At 4 hours, this showed a significant reduction in ventricular rate with both the low and high dose groups when compared to placebo with a reduction of ventricular rates of 20.5% and 15.8% respectively in addition to standard medical therapy when compared to placebo, suggesting magnesium may have a synergistic effect. Again however, the AV nodal blocking agents utilized do not represent contemporary practice with approximately 50% of patients receiving digoxin, and only approximately 20% beta blockers, the current mainstay of treatment.

As a result of the conflicting results we decided to undertake a double blinded, randomised placebo controlled trial assessing the efficacy of intravenous magnesium in addition to the use of contemporary AV nodal blocking agents for the treatment of AF with rapid ventricular response.

**STUDY DESIGN**

***Study Design Rationale***

Following a detailed literature search we reviewed all RCT’s and mechanistic studies published in the literature to determine the optimal dose of magnesium, duration of administration, side effects profile, monitoring protocols, adjunctive treatments and clinical endpoints of each study. Given this and in conjunction with clinical experience we have determined the following. The study protocol is summarised in Figure 1.

***Outcomes***

**Primary outcome:**

 • Reduction of ventricular rate to <100 beats per minute or 20% from initial

**Secondary outcomes:**

* Reversion to sinus rhythm.
* Time elapsed from commencement of treatment to target rate reduction.
* Number of/dose of rate/rhythm control agents required to achieve target rate reduction.
* Length of stay in the emergency department
* Need for admission to hospital
* Mortality and rehospitalisation at 30 days

***Magnesium Dosing and Protocol***

Throughout the literature different dosing and magnesium administration regimens have been employed. These include:

• Walker 1996 - 5g MgSO4 administer stat. This showed a significant reduction in HR at 30 minutes but not at 240 minutes when compared to placebo

• Chu 2009 utilised 2.5g MgSO4 given over 15 minutes, with no subsequent infusion. Heart rate was measured every 15 minutes for 2 hours and was compared to placebo. This study showed no difference between the two groups.

• Bouida 2018 – Low dose (4.5g) and high dose (9g) with administration within 30 minutes with no ongoing infusion. Showed significant reduction in ventricular rate with both low and high dose groups compared to placebo.

 • Davey 2005 - 2.5 g over 20 minutes followed by 2.5 g over two hours.

Intravenous magnesium sulfate is routinely administered in patients with AF with RVR in Australia with 10mmol (~2.5g) being the most commonly used dose, administered as a continuous infusion over a 30-60 minute period. Given the above findings, with moderate doses (4.5g-5g) being found to be as effective as higher doses (9g) and more effective than low doses (2.5g) patients, we will therefore give 5g (20mmol) of IV magnesium over a 30 minute period in our study.

Studies in other patient cohorts such as those with pre-eclampsia or acute asthma have shown that high doses of magnesium are safe. For instance, the most common magnesium sulphate regimen used in pre-eclampsia is a loading dose of 6 g of a 10% solution intravenously over 15 to 20 minutes followed by 2g/hour as a continuous infusion. Magnesium toxicity is uncommon in those with normal renal function, however potential side effects may include diaphoresis, flushing, and warmth, likely related to peripheral vasodilation and a drop in blood pressure. Nausea, vomiting, headache, muscle weakness, visual disturbances, and palpitations may also occur. Should any severe reactions occur the infusion would be ceased immediately.

***Heart Rate Primary Outcome***

The numerous RCTs published have used varying degree of reduction or target heart rate as their primary endpoint 7,8,11. These include:

The target heart rate, our primary outcome, was determined both on the available research showing clinical outcomes, along with what other trials have utilised. The RACE-II trial showed that strict heart rate control (<80bpm) did not have any benefit when compared to a heart rate of less than 110bpm10 in patients with permanent AF. We felt a heart rate of less than 100bpm as a target was a reasonable compromise where ED physicians would also be happy for patients to be discharged home should they be able to be rate controlled and would not be aggressively aiming to achieve unnecessarily strict control.

***Study Setting***

The study will take place in Melbourne, Victoria, the second largest city in Australia with an estimated population of 4.5 million people with healthcare provided predominantly through a public system, with no or minimal charges to patients. It will be conducted from the emergency department of Box Hill Hospital, a tertiary level hospital that had over 67,000 patient presentations last year and is the main hospital of the Eastern Health network, one of Melbourne’s largest metropolitan public health services. Every year approximately 750 patients present to Box Hill Hospital emergency department for the treatment AF with rapid ventricular response.

***Patient recruitment***

Patients will be recruited through the emergency department with emergency department physicians being responsible for identifying, recruiting and consenting suitable patients. A proforma detailing inclusion and exclusion criteria for the trial with consent and data collection forms attached will be circulated within the emergency department. Collaboration with emergency department staff through personalised education with regards to the trial protocol and utilisation of data collection tools will be undertaken to maximise patient recruitment. Patient recruitment will commence on the 1st of April 2019 with full recruitment of 200 participants expected to be completed within a 12-month timeframe.

***Consent***

Patients will be invited to participate in the study and will be required to give informed consent to take part in the trial once they have been deemed to meet the inclusion criteria and none of the exclusion criteria. Emergency department staff will explain the study and provide participants with the Participant Information and Consent Form (PICF) outlining the purpose of the study and potential complications retaining a signed original. The patient must exhibit good understanding of the trial and provide a signature to confirm their willingness to participate.

***Data acquisition at index procedure***

Data will be collected in paper format on a pre-printed proforma to ensure accurate, consistent and complete data collection. Once collected, data will be collated and entered manually into RedCaps to ensure secure and accurate data storage. Original documentation will be stored in a safe and secure location within the research department ensuring patient confidentiality. Information collected will include a full medical history, including specific history of cardiovascular disease, thyroid or kidney disease, a full list of medication with particular attention paid to rate or rhythm control medication, antihypertensives and magnesium or potassium replacement in particular those that may have been taken in the preceding 24 hours. Vital signs with particular attention paid to heart rate and a baseline electrocardiogram will be taken at time of enrolment.

A standard blood panel including full blood count, urea and electrolytes and serum magnesium along with additional blood tests ordered at the discretion of the treating emergency physician. Thyroid function tests are to be ordered in the case of first presentation atrial fibrillation.

***Randomisation***

Once consent has been obtained and all necessary information collected randomisation will take place. This will be done through the use of sequentially numbered magnesium and normal saline bags which will be identical in appearance and numbered from 1-200, randomly ordered. These will be prepared in advance in batches of 10 by the hospital pharmacy department with random allocation of each unit to either contain the control drug or placebo. Only the pharmacy will be aware of which number corresponds to placebo or magnesium and both bags will be identical in appearance. Once a bag has been taken sequentially, this will become the study participants ID number to ensure accurate data analysis post hoc. This method will ensure blinding and allocation concealment.

***Observation and Administration Protocol***

Prior to commencement of the infusion over a 30-minute period, a baseline set of observations and ECG will be taken. On commencement of the infusion patients will remain on telemetry, which will be used to document heart rate. Additionally, 12-lead ECG monitoring will remain connected with 30 minutely ECGs and observations recorded to the digital medical record for the first 2 hours following administration od either intervention or active control arm normal saline. During this time, unless clinically required due to patient instability, AV nodal blocking agents or cardioversion will not be allowed. Following the initial one hour period, AV nodal blocking agents will be able to be administered at the discretion of the emergency department doctors. Following administration of medications, patients will continue to be monitored for the remainder of their emergency department stay with regular observations and an ECG every 1 hour until the 4 hour mark post infusion commencement then telemetry and usual nursing observations thereafter.

**Statistical and Data Analysis**

All data will be collated using RedCaps. Analysis will be undertaken on an intention-to-treat analysis. All binary outcomes such as hospital admission, conversion to sinus rhythm and mortality at 30 days will be analysed using a chi-squared test with results reported as relative risk with a 95% confidence interval. To compare the heart rate at set time points between the placebo and control groups a Student’s t-test will be used.

**RESOURCES AND FUNDING**

Full funding for this trial has generously been provided by the Eastern Health Foundation.

**EXPECTED VALUE OF RESULTS**

In patients presenting with AF with rapid ventricular response, rapidly reducing heart rate in the ED through safe and proven strategies may facilitate early discharge. This could reduce hospital admission rates and length of stay, which are known to be associated with potential complications and adverse clinical events. Importantly, it may hasten patient recovery and reduce symptoms and the long-term consequences of a prolonged tachycardia.

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**Figure 1.** Study flow chart.

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**Table 1.** Patient baseline demographics

|  |  |
| --- | --- |
| Baseline Data |  |
| Participant Study ID |  |
| Enrolment Date |  |
| Hospital UR |  |
| Full Name |  |
| Date of Birth |  |
| Contact Number | (T) (M) |
| Alternative Contact | Name: (T) |
| General Practitioner | Name: |
| Address: |
| Contact: (T) (F) |
| Date of Discharge |  |
| Demographics |  |
| Medical History | Heart Failure Yes NoPrevious AF Yes NoPrevious Stroke Yes No Smoking Current Ex-Smoker NeverHypertension Yes NoDiabetes Yes No |
| Age / Sex |  Male Female Age |
| Pathology (On Admission apart from Cardiac Enzymes) |
| Full Blood Count | Hb Platelet |
| Renal Function |  Creatinine eGFR |
| Thyroid Function |  TSH T4 |
| Serum Potassium |  |
| Magnesium |  |
| Baseline Obs |
| ECG Done | Time Date |
| Saturations |  |
| Blood Pressure |  |
| Heart Rate (Time 0) | Bpm |
| Heart Rate |  |
| Time 30 Minutes | ECG Done |
| Time 60 Minutes | ECG Done |
| Time 90 Minutes | ECG Done |
| Time 120 Minutes | ECG Done |
| Time 180 Minutes | ECG Done |
| Time 240 Minutes | ECG Done |
| Medications |  |
| Beta Blocker |  Yes No Total Dose: |
| CCB |  Yes No Total Dose: |
| Digoxin |  Yes No Total Dose: |
| Sotalol |  Yes No Total Dose: |
| Flecainide |  Yes No Total Dose: |
| Amiodarone |  Yes No Total Dose: |
| Outcome |   |
| Hospital Admission |  Yes No |
| Reversion |  Yes No Time: |

**Table 2.** Patient baseline demographics – Emergency department data collection form

|  |  |
| --- | --- |
| Data |  |
| Enrolment date  |  |
| Participant Study ID from Infusion Bag Number |  |
| Hospital UR Sticker |  |
| Time Infusion Started |  |
| Baseline Heart Rate (bpm) |  | Baseline BP |  |
| Heart Rate 30 minutes |  | BP 30 minutes |  |
| Heart Rate 60 minutes |  | BP 60 minutes |  |
| Heart Rate 90 minutes |  | BP 90 minutes |  |
| Heart Rate 120 minutes |  | BP 120 minutes |  |
| Outcome |   |
| Reversion |  Yes No Time: |

Checklist of investigations

* FBE, UEC, serum Mg (result not required prior to commencing infusion)
* TFTs only if first presentation
* ECG baseline
* ECG 30 min
* ECG 60 min
* ECG 90 min
* ECG 120 min
* ECG 3 hours
* ECG 4 hours
* Telemetry for duration of patient stay