The role of magnesium sulphate in the management of Irukandji Syndrome: A Systematic Review

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JR and RF conceived of the idea, JR and RF developed the methodology, JR and RF undertook the initial review of the papers, all authors review the final papers, JR undertook the first draft, all authors contributed to final draft.

Introduction

Irukandji Syndrome (IS) came to the public attention with the report of the deaths of two tourists in 2002^{1,2} attributed to a small box jellyfish in tropical Queensland, Australia. Both fatalities were attributed to a hypertensive induced cerebral haemorrhage, stressing the importance of controlling the acute hypertensive state that can arise in some cases of this painfully debilitating marine envenomation³. This reduction could also reduce the likelihood of the patient developing cardiac dysfunction.

In 1961 Dr Jack Barnes identified two small carybdeid specimens that caused IS³. In honour of Jack Barnes, Southcott named the carybdeid *Carukia barnesi*⁴.

To date there are nine Australian species of carybdeid that have been formally identified that cause IS⁵. Even though this syndrome was first recognized in Australia, there have been reports of IS elsewhere across the globe, Hawaii⁶, Thailand⁷, Florida⁸, Philippines⁹, even in the cool waters of Northern Wales, UK¹⁰ and Victoria, Australia¹¹. Most of the species held responsible are still yet to be formally identified, and therefore IS refers to a group of systemic symptoms resulting from a carybdeid sting.

Fenner¹² and Carrette¹³ describe in detail the signs and symptoms of IS. The initial sting from the jellyfish is likely to be innocuous with minimal contact symptoms and indeed some individuals not noticing it at all, while species such as *Malo maxima* from Western Australia and *Morbakka fenneri* from Queensland cause immediate notable pain upon contact¹⁴. There is a delay before the onset of systemic symptoms from 5 to 120 minutes (n=30 minutes)¹⁵ after which the patient begins to experience systemic pain.

There may be minimal skin markings with localized piloerection and sweating, but this often goes unnoticed. Systemic symptoms can range from; low back pain, limb muscle/cramping pain, chest pain/tightness, sweating (localized or general), piloerection (localized or general), anxiety/feeling of impending doom, restlessness, headache, nausea, vomiting, increased respiratory rate, tremor, pallor, oliguria, tachycardia and hypertension¹². The symptoms of IS resemble that of a hyperadrenergic state and in animal modelling with crude *Carukia barnesi* venom, shows gross elevation in systemic noradrenaline and adrenaline, 200-fold & 100-fold respectively¹⁶.

Occasionally a 'second phase' may appear in severe cases of IS. These patients appear to develop severe hypertension with pressures as high as 300/180 mmHg being recorded¹².

Approximately 6-18 hours after the sting, patients can develop pulmonary oedema, which may be associated with depressed ejection fraction, reduced cardiac output and raised serum cardiac enzymes^{12,14}. The two documented fatalities attributed to IS have both been off shore stings, GBR and Whitsunday Islands, and both were due to intracranial hemorrhages, presumed secondary to severe hypertension^{1,2}. The first a 58 year old male stung in the Whitsunday Islands, who developed critical hypertension (260/160 mmHg) and had a raised troponin T (27 ug/L). This gentleman had an extensive medical history including an aortic valve replacement due to aortic stenosis, he was taking 8 mg warfarin daily and a week prior to the incident he had an international normalized ratio (INR) of 5.0¹. The second was a 44 year old male was stung on the GBR who also developed critical hypertension (230/90 mmHg) and had a raised troponin T (34 ug/L)^{2,14}.

The administration of Magnesium Sulphate (MgSO_4) for the treatment of hyperadrenergic conditions, such as phaeochromocytoma, pre-eclampsia but also in cardiology and asthma is a well-established therapy¹⁷. MgSO_4 has not only a depressant effect on the release of systemic catecholamines but is also known to produce a fall in systemic vascular resistance in hyperadrenergic settings¹⁷. However, magnesium toxicity can develop when serum concentrations exceed 1.74-2.61 mmol/L leading to nausea, vomiting, facial flushing, hypotension, urinary retention, ileus, lethargy and eventually muscle weakness, shortness of breath, arrhythmias and cardiac arrest¹⁸. Based on this premise and his extensive experience in managing severe pre-eclampsia, Corkeron¹⁹ reported the successful use of MgSO_4 in a 26 year old male diagnosed with IS. Although this patient had previously received morphine and diazepam which had 'settled his pain somewhat', he was still profusely diaphoretic, agitated and had continued abdominal discomfort. In the setting of persistent hypertension (170/100 mmHg), it was decided to start a therapeutic trial of MgSO_4 some 5 hours after the envenomation. A loading dose of 10 mmol MgSO_4 was given, followed immediately by an infusion of 5 mmol per hour. Towards the end of the initial loading dose, it was reported that the patient had resolution of systemic symptoms, agitation and pain had nearly subsided¹⁹.

There is, however, controversy over the use of MgSO_4 in the management of IS, and some physicians and research scientists recommend the use of MgSO_4 needs to be reconsidered until there is good evidence to support this²⁰. In order to evaluate the evidence base we have conducted a critical review of the literature, focusing on the data which either supports or contraindicates the effectiveness of the use of MgSO_4 in the treatment of pain and/or hypertension among patients with IS, and whether or not successful use has been dose-dependent.

Aims

The aim of this study was to explore the literature on the effectiveness of the use of magnesium in the treatment of pain and/or hypertension in the setting of IS, and whether it's partial success has been dosage dependent.

Methods

Articles relevant to IS and the use of magnesium were collected from three data bases; Scopus, Medline and ScienceDirect. Each data base was searched using the word 'Irukandji', the returned result was then searched again using the word 'magnesium'. A further hand search was conducted both of the references of the papers and through Google Scholar for citing papers. Also a search of Google Scholar for the words 'irukandji and magnesium' was also undertaken.

There were 177 results identified and entered into EndNote X7™ (Thomson Reuters, New York), duplicates removed and then reviewed firstly via title description, then abstracts, and finally reading the whole paper. All searches were conducted on the 2nd March 2014 with no date restrictions. This resulted in a total of nine papers (Figure 1)

[Insert Figure 1 about here]

Only nine were identified as to having sufficient detail to be included in the systematic review. Inclusion was based on having information regarding the dose and method of administration of MgSO_4 and/or patients outcomes such as: reduction in pain and/or blood pressure or the recurrence of pain and/or other symptoms; after its administration.

The methodological quality level evidence of the eight articles was reviewed with reference to the Australian Resuscitation Council evidence-based guidelines²¹ (Table 1).

Results

There were nine papers included in the review (Table 2). Of these, one article (RCT) does not support the use MgSO_4 until further evidence supports its benefit²⁰, another reports its failure based upon anecdotal evidence²², whilst the remaining seven^{19,23-28}, which are case series, report some success in managing IS with MgSO_4 .

[Insert Table 2 about here]

Articles supportive or negative for the use of MgSO_4 in the management of pain and or hypertension in IS are listed in the Table 3 according to the ARC Methodological Quality of Studies. (REFERENCE)

[Insert Table 1&3 about here]

In 2004 a group from several medical centers in Northern Australia reported success in managing IS with MgSO_4 in a case series of ten patients. No standardized dosing regimen for MgSO_4 was prescribed although dose range was recommended on the current management of pre-eclampsia. Of the ten patients, five had marked reduction in pain during the initial loading dose, and one reported minor pain which was augmented with a further 10 mmol bolus. The remaining four had the word 'improved' documented on their charts. Two patients with serious symptoms initially (pain scores of ten), had pain reduction to three and four respectively with bolus therapy, but required opiate therapy during the maintenance phase of MgSO_4 due to the recurrence of pain²³. They also noted a modest but significant reduction in systolic and mean arterial blood pressure after the administration of MgSO_4 , with a mean difference of -18.1 and -18.0 mmHg respectively²³. Four patients reported pain upon injection. However, one patient who had received a total of 166 mmol MgSO_4 over an 18 hour period, had evidence of ptosis and diplopia which resolved once the infusion was withdrawn.

Little²² reported two cases from Broome, Western Australia (WA) where MgSO_4 failed. It appears that one of those patients seems to have had some initial success with MgSO_4 (20 mmol Bolus, 10 mmol/hour infusion) but experienced a breakthrough in pain, requiring further management with opiate analgesics. The second patient continued to experience an increase in pain despite the use of MgSO_4 (16 mmol bolus and 4 mmol/hour infusion)²². These two patients required further significant pain management with opiates after receiving MgSO_4 . Eventually both patients required intubation and ventilation with the second patient developing pulmonary oedema, hypotension and raised troponin (0.4µg/l: normal <0.1µg/l). Macrokanis briefly reports the initial success of MgSO_4 in three cases from Broome, WA, in all three patients there was significant pain reduction within minutes of receiving MgSO_4 , from 10 to less than 5. Although MgSO_4 infusions was established, all three patients reported the reoccurrence of pain between 15 and 35 minutes²⁴. It also mentions a further seven cases that improved without the use of MgSO_4 . A case series of eight patients was reported from the Torres Strait Islands, Queensland in 2011, with one

patient receiving MgSO₄ as an infusion post opiate management. Details on dosage and infusion duration are not available but the author's state that the patient had improvement in pain but remained hypertensive²⁵. Of the eight patients, four were discharged the same day, whilst the remainder were discharged the following day. Nickson²⁶ also reported three cases from the Northern Territory that had initial success during the loading phase but experienced pain break through during the infusion stage of MgSO₄. One of those patients required further administration of morphine (10 mg IV during the next 7 h), whilst a second patient received further MgSO₄ (10 mmol IV during 2 h) when pain recurred at 20 h²⁶. A clinical practice update from the Townsville Hospital Emergency Department lists in detail their current management plan for the care of patients with IS²⁸. The Emergency Department identified a total of 15 cases of IS from Jan 2006 and Dec 2008. Of those, twelve were given MgSO₄, two of which were given MgSO₄ as a first line treatment. The article reports that in all twelve cases there was improvement in the patient's pain and or blood pressure.

From November 2003 to May 2007 a group based in Cairns Hospital (CH) ran a double blinded randomized controlled trial with MgSO₄ in the treatment of IS. Over this period a total of 121 patients were treated for IS in the CH Emergency Department (ED), of which 39 patients were recruited into the trial²⁰. The trial concludes that there appears to be no beneficial difference in those patients that received the MgSO₄ with those who received the placebo. Although upon receiving MgSO₄ one patient developed tachycardia (125 bpm), flushing and sweating during the initial dose. Four further patients who received MgSO₄ went on to develop pulmonary oedema, compared with none receiving saline. Four patients receiving MgSO₄ and one who received the placebo were admitted to the CCU due to their clinical condition. The study model demonstrated that there was no significant difference between the placebo group and those that received MgSO₄. See Table 4 for Summary..

Insert Table 4 about here

The study excluded more patients than that were enrolled; 21 patients being less than 16 years (RCT min age); 13 received no opiates prior to arrival at ED; 18 due to staff not being available; and 30 having to be excluded due to them receiving MgSO₄ prior to their arrival in ED. MgSO₄ dosage was based on Corkeron²² original description, with a 10 mmol bolus followed by a 5 mmol/hour infusion for 6 hours²⁰. The largest published series regarding the use of MgSO₄ in IS comes from Rathbone²⁷, describing the use of a specific protocol of MgSO₄ for the pre-hospital management of IS by Queensland Ambulance Service (QAS). In their protocol, MgSO₄ is administered if the initial use of parenteral opiates has not resulted in clinically adequate analgesia. Their adult dosing is a 20 mmol bolus followed by infusion

of 20 mmol/hour. In children, a 0.1 mmol/kg bolus dose is given over ten minutes, and is repeated once if required (total max dose 10 mmol), but no infusion is administered³⁰.

From 2007 to 2011, fifty four patients in Queensland were treated with combined opiate analgesia and MgSO₄ therapy by QAS. Their results suggest that the combination of opiate and MgSO₄ demonstrate a degree of efficacy in pain management and hypertension. Three patients alone with initial pain scores of 10/10 recorded no pain post administration of the loading dose. Of the 54 patients reviewed, 33 were initially hypertensive. Of these 33, 17 returned to normotensive, 9 were considered to be still hypertensive but had a reduction in their blood pressure and had no change at all upon their arrival at the receiving hospital,²⁷. The published letter has limited data for analysis and all patients received morphine prior to receiving MgSO₄, leaving the question of whether it was the opiate, MgSO₄ or a combination of the both that gave the end results

Discussion

This systematic review found insufficient evidence to support any clear recommendation regarding the use of magnesium but nor was there clear evidence to recommend against its use in Irukandji envenoming. It was also inconclusive in determining whether the partial success of magnesium has been dosage dependent. A large number of papers were excluded due to a lack of discussion regarding the use of MgSO₄, and due to insufficient details regarding patient's condition, their treatment and outcomes.

Overall the evidence for or against is weak with all studies bar one being case series. The single RCT undertaken in this area found no difference in analgesia requirements but it is a small trial of limited recruitment and methodological challenges. The authors note the limitations of the study; the magnesium dose during the trial was less than the now recommended dose given by the Irukandji Taskforce²⁹; pain scores were not always collected; classifying the severity of the syndrome is difficult and it is possible that the two groups had different severities of the syndrome. There is also the high patient exclusion criteria, only 39 of a possible 121 patients were recruited into the trial. Unfortunately the study had to be terminated early as QAS and other health care providers adopted the use of MgSO₄ for IS in 2006 (during the trial)²⁸. The early termination of the trial due to external influences may be an explanation as to why the data concludes that there appears to be no difference between the two study groups³¹. However, the authors need to be commended upon their efforts in recruiting suitable patients, when one has to consider the multiple agencies involved in the pre-hospital management of patients prior to arrival at the hospital.

The article from Townsville Hospital²⁸ mentions some success in patients who have received MgSO₄ and that medical treatment was consistent with the Irukandji Taskforce Guidelines.

However it lacks specific details such as; the severity of the syndrome, quantity of opiates received prior to receiving MgSO_4 , specific vital signs and pain score. It also discusses the limited knowledge in nursing staff with regards to the signs and symptoms of IS, the underlying pathophysiology and the appropriate monitoring for patients who are receiving MgSO_4 .

QAS initial success²⁷ may be due to a number of factors, including early pain management, which is reported to have a greater success in controlling pain in the acute setting³². Morphine is readily available to all QAS paramedics, and MgSO_4 has been shown to increase the analgesic effects of morphine in animal models³³. The relatively high dose of MgSO_4 in the QAS protocol may also be a factor. However this letter fails to mention specific details such as blood pressure and pain score.

A multi-agency randomised controlled trial using standardised diagnostic definitions and treatment regimens is needed to establish whether MgSO_4 has a role in managing this debilitating syndrome. Involving all prehospital agencies and receiving facilities will enable an overall control in drug use and dosage but will also allow for maximum patient capture. Such a trial should consider a relatively higher dose of MgSO_4 over previous trials and documented cases of recrudescence of symptoms which suggest a dose response relationship.

There also needs a greater understanding on causative species and their geographic localities. Venom variability amongst species and within the same species, such as between juveniles and mature specimens or seasonal and/or geographical changes may affect the response of IS to magnesium. This would require the combined efforts of the scientific communities and medical facilities, enabling a combined effort to produce and maintain management protocols based on current research and understanding.

The retrieval and management of IS patients costs the health services in northern Australia approximately AU\$1-3 million per year¹⁴ and with potentially added indirect costs through loss of tourism. The publicity of the two IS related fatalities in Queensland, Australia in 2002 cost the government an estimated AU\$65 million in lost tourism revenue and work time³⁴.

Furthermore a recognised descriptive definition of IS needs to be devised, that is accepted not only within the medical society but also within the scientific community. Fenner¹³ and Carrette¹⁴ list in detail the variable signs and symptoms that can arise in IS, highlighting the need for an accepted definition. This will reduce the confusion of 'what is IS' or the use of the term 'unknown marine toxidrome' and will help identify the true scope this syndrome has along the popular tropical and subtropical regions of the world.

At the time of publication a multicentre, prehospital and Emergency department randomised controlled trial has received QEMRF funding and ethics approval for Townsville

Hospital, Mackay Base Hospital, Cairns Hospital, Care Flight Retrieval Medicine and QAS (C. Gibbs 2015, pers. Comm., 23rd December).

Limitations

Irukandji is an Australian term and as such searching data bases might have missed similar syndromes from elsewhere around the world, however we do not think we have missed any other foreign language terminology. The significant variance in magnesium dosage and the limited recording of patient outcomes in some papers confines the limits of this review as does the small number of articles in the area.

Conclusion

This systematic review found that there is a lack of clinical trial evidence to support the use of MgSO₄ in IS. Current use in practice is based upon efficacy reported in case series. Further randomised trials are necessary to define the role of MgSO₄ in the management of this envenoming. The reporting of recrudescence of symptoms with reduction of dose does suggest a dose response relationship. The definitions of IS and study treatment protocols vary markedly, which is a limitation of the published data.

Until such time as a multi-agency RCT is undertaken, IS patients should continue to be managed as per local protocols and policies. The use of MgSO₄ should be considered where other treatment fails to produce clinically adequate analgesia and/or reduction in hypertension.

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Figure 1. Search strategy and results

Table 1 Level of Evidence.

Level of Evidence	Definitions	
I	Evidence obtained from a systemic review of all relevant randomised controlled trials.	
II	Evidence obtained from at least one properly designed randomised controlled trial.	
III-1	Evidence obtained from well-designed properly pseudo-randomised controlled trials (alternate allocation or other method).	
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted times series with a control group.	
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.	
IV	Evidence obtained from case series, either post-test or pre-test and post-test.	

Table 2 Summary of the 9 Reviewed Articles.

Reference	Year	Type of study	No of Cases	Did receive MgSO ₄	MgSO ₄ Dosage Intravenous	Out Comes Pain/BP	Health Care Facility	Geographical Location	Comments
Rathbone <i>et al.</i> ²⁷	2013	Retrospective	54	54	20mmol bolus 20mmol/h	N<54 Pain↓ N < 33 BP↓	Prehospital	QLD State.	Largest review of irukandji patients and the use of MgSO ₄ to date. All patients had received an opiate prior to the use of magnesium. Data 2007-2011.
McCullagh <i>et al.</i> ²⁰	2012	Double Blinded RCT	121	22	10 mmol bolus 5 mmol/h	No Demonstrated Benefit	Hospital Emergency Department	Cairns Region, QLD.	The only RCT to date on the use of magnesium in IS. Large exclusion criteria and minimum MgSO ₄ dose used. Data 2003-2007.
McIver <i>et al.</i> ²⁵	2011	Case Series	8	1	Not Documented	Not Documented	Hospital	Torres Strait Islands, Australia.	8 cases of IS. One patient reportedly received magnesium with improvement in pain. No change in the patient's hypertensive state, no dose recorded.
Clarkson ²⁸	2010	Case Series	15	12	0.15 mmol/kg bolus 0.1-0.15 mmol/kg/h	N<12 Pain ↓ N<12 BP ↓	Hospital	Townsville, QLD	12 cases of IS all received MgSO ₄ . Improvement on pain and reduction in BP recorded. But no specific details available regarding pain score, BP or total dose received.
Nickson <i>et al.</i> ²⁶	2009	Case Series	87	3	10 mmol/30 minutes	Pain↓	Multiple Health Facilities	Northern Territory, Australia.	Of the 87 cases of IS, three received magnesium. All documented subsiding pain post administration. Dose, rate and time of administration recorded. Data 1990-2007.
Macrokanis <i>et al.</i> ²⁴	2004	Retrospective	88	3	10-80 mmol	Pain↓	Hospital Emergency Department	Broome, Western Australia.	Of the 88 cases, three received magnesium. All three reported dramatic reduction in pain within minutes. All three had pain breakthrough during the infusion stage. Data 2001-2003
Little ²²	2005	Case Series	2	2	16-20 mmol bolus 4-10 mmol/h	Breakthrough in Pain	Hospital Facility	Broome, Western Australia.	2 reported cases of magnesium failure. One case reports a breakthrough in pain, suggesting an initial positive response. The second case reports a worsening pain. Both cases record magnesium dose.

Corkeron <i>et al.</i> ²³	2004	Non Randomized Case Series	13	10	10-20 mmol bolus 20 mmol/h	Pain↓ BP↓	Hospital Facility	Townsville QLD, Australia	Of the 13 cases, three were excluded due to insufficient details. 3 cases reported from Broome, WA, the remaining from N QLD. Detailed patients outcomes recorded i.e. Pain score, Blood pressure, MgSO ₄ dose.
Corkeron <i>et al.</i> ¹⁹	2003	Case Series	1	1	10mmol bolus 5 mmol/h	Pain↓ BP↓	Hospital Facility	Townsville, Australia	First recorded case of IS receiving magnesium. 2003 data.

Table 3 Methodological Quality of Studies

Methodological Quality of Studies							
	Good The methodological quality of the study is high with the likelihood of any significant bias being minimal		Fair The methodological quality of the study is reasonable with the potential for significant bias being likely		Poor The methodological Quality of the study is weak, possessing considerable and significant biases		
Supportive						Corkeron 2003, Corkeron 2004, Macrokanis 2004, Nickson 2009, McIver 2011, Rathbone 2013	
Negative		McCullagh 2012				Little 2005	
Level of Evidence	I	II	III-1	III-2	III-3	IV	Other

Table 4 RCT Summary Overview

Overview of the Results of the 39 RCT patients with Irukandji Syndrome		
	Placebo	Magnesium
Mean Morphine equivalent dose (mg) once entry into trial.	53	50
Median Length of Stay (h)	19	20.7
Mean Peak Pulse (bpm)	101	101
Mean Peak Troponin I Level (mcg/L)	2.4	8.3
Mean Percentage MAP rise	138	135
Mean Peak CK (U/L)	499	537
Serum Mg Level (mmol/L)	1.03	1.83

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