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MAGNESIUM SULFATE TREATMENT IMPROVES OUTCOME IN PATIENTS WITH SUBARACHNOID HEMORRHAGE: A META-ANALYSIS STUDY

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Abstract

Objective—To elucidate the role of magnesium sulfate in patients with subarachnoid hemorrhagic (SAH) brain injury

Method—Studies for the meta-analysis were identified from PubMed (1966 to 2009), Embase (1980 to 2009), and two Chinese journals (1989 to 2009). Paper selection was based on randomized controlled trials comparing magnesium sulfate to placebo treatment in patients with SAH. Two independent review authors extracted the data and assessed trial quality. Meta-analysis was performed using the Cochrane Review Manager software.

Results—Five trials involving 482 patients were included in the review. Magnesium sulfate reduced the risk of poor outcome and reduced the occurrence of delayed cerebral ischemia. In the treatment groups, relative risk for poor outcome was 0.73 (CI 0.57-0.93) and 0.66 (CI 0.47-0.92) for delayed cerebral ischemia. Case fatality assessment at three to six months did not show statistically significant data (RR 0.88; CI 0.61-1.29).

Conclusion—Magnesium sulfate appears to be an effective treatment option in the management of SAH. Further clinical trials are needed before magnesium sulfate can become a routine treatment for SAH.

Keywords

Magnesium Sulfate (MgSO₄); subarachnoid hemorrhage (SAH); vasospasm

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a devastating event accounting for five percent of all stroke types with an estimated incidence of nine per hundred thousand persons each year [1]. On average twelve percent of patients die before reaching medical attention with forty percent of those who survive, dying within the first month [2].

Yet despite the advances that have been made both surgically and medically for patients who experience an SAH, morbidity and mortality rates have failed to move appropriately

[3]. This is partly attributed to the lack of effective therapeutic approach in dealing with cerebral ischemia as a result of cerebral vasospasm, one of the major consequences seen in SAH [4]. Considered one of the most important causes of poor outcome in SAH, cerebral vasospasm most frequently develops between four and ten days after an injury [7-9]. Current prophylactic therapies include oral calcium channel blockers, rho-kinase inhibitors and cisternal irrigation with milrinone [5]. Despite aggressive prophylactic therapy, cerebral vasospasm continues to be as high as 67%. Once the onset occurs, very few therapies including hypertensive-hypervolemic hemodilution therapy, intra-arterial injection of papaverin, and transluminal balloon angioplasty are available. Therefore, a new therapeutic approach is warranted to combat the effects of cerebral vasospasm.

Magnesium sulfate has been suggested in several clinical studies to reduce the risks of delayed cerebral ischemia and with very limited adverse effects [12-15]. Theorized to block the release of excitatory amino acids as well as act as a vasodilator on cerebral arteries [21-23], magnesium sulfate has been used for years as an effective treatment for vasospasm in obstetric diseases, including pre-eclampsia and full blown eclampsia [10,11].

In this study, we performed a systematic review and meta-analysis of patients who experienced an SAH and assess the efficacy and safety of magnesium sulfate treatment. We hope to determine whether magnesium sulfate treatment will reduce the risk of delayed cerebral ischemia caused by cerebral vasospasm and improve morbidity and mortality among these patients.

METHODS

Search Methods

Literature search engines that were employed for this study include PubMed (limited from 1966 to May 2009) and Embase (limited from 1980 to May 2009). Two Chinese journals were manually searched from 1989 to May 2009 – *Chinese Journal of Neurosurgery* and *Chinese Journal of Neurology*. Databases were searched using key terms such as ‘magnesium sulfate’ and ‘subarachnoid hemorrhage’.

Selection Criteria

Randomized clinical trials looking directly at magnesium sulfate treatment and placebo in patients with SAH were included. Uncontrolled trials as well as quasi-randomized controlled trials were not employed. Participation was restricted to those individuals, male or female, older than eighteen years of age who presented within a four day time window after SAH. Patients who were pregnant, in renal failure, hypotensive, bradycardic, had signs of hypermagnesaemia, neuromuscular disease, or faced imminent death were excluded from the study.

The diagnosis of SAH had to be confirmed on proper imaging including computerized tomography and/or magnetic resonance angiography and cerebral angiography. All patients had to have received standard medical care and proper SAH management. Treatment with magnesium sulfate by intravenous infusion must have started within four days of hemorrhage onset and maintained for a minimum of twelve days.

Outcomes were assessed within six months of the event looking at clinical signs of ischemia and/or death. In addition, adverse effects including any case fatalities were measured.

Data Collection and Bias Assessment

Independent review was conducted by two authors who assessed the standardization of this study. These authors evaluated the level and method of randomization, presence of blinding, whether follow-ups/drop-outs were reported and if so, ensuring the rate was less than twenty percent [24]. The authors rated the quality of allocation concealment as adequate if there was a double blind treatment, unclear if the treatment concealment was unknown and inadequate if there was single or no blinding of treatment [25]. Further assessment of bias score risk was obtained using the modified Jadad scale [26].

Data Analysis

All data analysis was conducted using the Review Manager 5.01 software (Cochrane Collaboration, www.cc-ims.net, Oxford, UK). A heterogeneity test was conducted using either a model with fixed effects if the test was not statistically significant ($p > 0.05$) or with random effects if the test was statistically significant ($p < 0.05$). Treatment outcomes were estimated using relative risk (RR) with a 95% confidence interval (CI).

RESULTS

Five studies published between 2002 to 2008 comparing magnesium sulfate treatment with placebo in patients with SAH were obtained and included in the analysis. These studies reported on a total of 482 patients of whom 243 (50.4%) received treatment and 239 (49.6%) received placebo. The studies descriptions can be found in tables one and two. All five studies scored four or more stars on the modified Jadad scale with the method quality descriptions found in table two.

Meta-Analysis

There was a statistically significant difference reported in six month outcome between the placebo and treatment groups (RR 0.73; p -value 0.01; CI 0.57-0.93; Figure 1) as well as among the data collected from the delayed cerebral ischemia assessment (RR 0.66; p -value 0.01; CI 0.47-0.92; Figure 2). Case fatality assessment at three to six months did not show statistically significant data (RR 0.88; p -value 0.52; CI 0.61-1.29; Figure 3).

Adverse Effects

Four of five studies reported adverse effects with the treatment group including one patient experiencing hypotension, two with bradycardia, one with atrial fibrillation, three with hypermagnesemia and one with renal failure. In another study two patients reported a warm feeling during the start of magnesium sulfate infusion while another patient complained about acute injection site pain (Table 1).

DISCUSSION

The aim of this study was to investigate the role of magnesium sulfate in subarachnoid hemorrhagic brain injury by collecting and analyzing data from previously published works. In this meta-analysis, five papers were reviewed looking at the effects of magnesium sulfate versus placebo treatments. Two points were established after completion of the analysis. First, treatment with magnesium sulfate reduces poor outcome, including mortality and morbidity, associated with SAH. Second, prophylactic treatment with magnesium sulfate significantly decreases the risk of delayed cerebral ischemia after SAH. To the best of our knowledge, this is the first meta-analysis looking at the effects of magnesium sulfate on SAH outcome.

The improvements with magnesium sulfate treatment are consistent in all five studies. However the mechanism behind its effects still remains unclear. Hypotheses allude to the possibility of an N-methyl-D-aspartate (NMDA) receptor causing relaxation of the cerebral arteries [17,18]. This can be explained by the magnesium ion having a key binding position on the receptor. Other studies have proposed that magnesium may act as a nonspecific antagonism of all subtypes of voltage-sensitive calcium channels [19,20]. This could explain a previously published study comparing magnesium sulfate to nimodipine therapy in SAH which found magnesium sulfate had similar if not, better efficacy compared to nimodipine [28]. Determining the mechanism behind treatment with magnesium sulfate is beyond the scope of this study; however, it is recognized that the need to understand how it exerts its effects is important to understanding both improved and adverse outcomes.

Magnesium sulfate has been shown to be beneficial in treatment management of patients with SAH. Based on the results collected in this review, the authors of this paper suggest prophylactic magnesium sulfate treatment as an effective option in the management of SAH. Understandably, the need for larger scale studies is warranted.

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Figure 1.
 Meta-Analysis of Poor Outcome (Morbidity & Mortality)

Figure 2.
Meta-analysis of case fatality

Figure 3.
 Meta-analysis of DCI (delayed cerebral ischemia)

Table 1

Characteristics of Studies Included in Analysis

Trials	No. of patients		Interventions		Poor Outcome		Case Fatality		DCI		Adverse effects
	MG	CG	MG	CG	MG	CG	MG	CG	MG	CG	
Boet R 2005	23	22	Magnesium sulfate	NS	8/23	12/22	3/23	3/22	6/23	12/22	Not mentioned
Muroi C 2008	31	27	Magnesium sulfate Ringer's solution		11/31	14/27	4/31	6/27	4/31	4/27	Hypotension (n=5), Bradycardia (n=2), Respiratory failure (n=1), Hypocalcemia (n=8)
Veyna RS 2002	20	16	Magnesium sulfate	NS	7/20	8/16	4/20	2/16	6/20	5/16	No serious side effects
van den Bergh 2005	139	144	Magnesium sulfate	NS	38/139	51/144	27/139	31/144	21/122	31/127	Hypotension (n=1), bradycardia (n=2), atrial fibrillation (n=1), hypermagnesaemia (n=3), renal failure (n=1)
Wong GK 2006	30	30	Magnesium sulfate	NS	10/30	14/30	4/30	5/30	7/30	13/30	Warm feeling (n=3), Pain (n=1)

CG: control group, DCI: delayed cerebral ischemia, MG: magnesium sulfate group, NS: normal saline

Table 2

Method Characteristics Employed by Studies Included in the Analysis

Trials	Randomization	Allocation concealment	Blinding	Withdraws	Jadad score
Boet R 2005	RCT	Adequate	Double-blind	Unclear	6
Muroi C 2008	RCT	Inadequate	Single-blind	Unclear	4
Veyna RS 2002	RCT	Inadequate	Single-blind	10%	5
van den Bergh WM 2005	RCT	Adequate	Double-blind	12.01%	7
Wong GK 2006	RCT	Adequate	Double-blind	Unclear	6