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Review

Magnesium sulfate for non-eclamptic status epilepticus

F.A. Zeiler [a,*], M. Matuszczak [b,1], J. Teitelbaum [c,2], L.M. Gillman [d,e,3], C.J. Kazina [a,4]

[a] Section of Neurosurgery, Dept. of Surgery, University of Manitoba, Winnipeg, Canada
[b] Undergraduate Medicine, University of Manitoba, Winnipeg, Canada
[c] Section of Neurology, Montreal Neurological Institute, McGill, Montreal, Canada
[d] Section of Critical Care Medicine, Dept. of Medicine, University of Manitoba, Winnipeg, Canada
[e] Section of General Surgery, Dept. of Surgery, University of Manitoba, Winnipeg, Canada

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ABSTRACT

Background: Our goal was to perform a systematic review of the literature on the use of intravenous magnesium sulfate ($MgSO_4$) for non-eclamptic status epilepticus (SE) and refractory status epilepticus (RSE).

Methods: Articles from MEDLINE, BIOSIS, EMBASE, Global Health, Scopus, Cochrane Library, the International Clinical Trials Registry Platform, clinicaltrials.gov (inception to June 2015), reference lists of relevant articles, and gray literature were searched. The strength of evidence was adjudicated using both the Oxford and GRADE methodology by two independent reviewers.

Results: We identified 19 original articles. A total of 28 patients were described in these articles with 11 being adult, 9 being pediatric, and 8 of unknown age. Seizure reduction/control with IV $MgSO_4$ occurred in 14 of the 28 patients (50.0%), with 2 (7.1%) and 12 (42.9%) displaying partial and complete responses respectively. Seizures recurred upon withdrawal of $MgSO_4$ therapy in 50% of the patients whom had reduction/control of their SE/RSE. Three patients had recorded adverse events related to $MgSO_4$ therapy.

Conclusions: Oxford level 4, GRADE D evidence exists to suggest a trend towards improved seizure control with the use of intravenous $MgSO_4$ for non-eclamptic RSE. Routine use of IV $MgSO_4$ in non-eclamptic SE/RSE cannot be recommended at this time. Further prospective study of this drug is required in order to determine its efficacy as an anti-epileptic in this setting.

1. Introduction

Magnesium sulfate ($MgSO_4$) is a drug that has garnered some interest within the epilepsy community [1]. Whether administered orally, or intravenous (IV), $MgSO_4$ has displayed some efficacy in the animal and human seizure literature [1,2].

Though its mechanism of action as an anti-epileptic drug (AED) is not well understood, it is believe to derive its anti-epileptic properties from N-methyl D-aspartate (NMDA) receptor inhibition. To date, a few animal models support this concept [3–6].

Clinically, $MgSO_4$ has seen much attention within the obstetrics literature as an effective prophylactic and therapeutic agent for pre-eclampsia and eclampsia, respectively [7]. Furthermore, the lack of significant side effects is appealing due to concerns about fetal toxicity. The efficacy of $MgSO_4$ as an AED in the setting of eclampsia is well documented since the early 1900s, with the mechanism of action attributed to both NMDA receptor antagonism and cerebral vasodilation. In addition, systematic reviews have demonstrated the superiority of $MgSO_4$ over diazepam, phenytoin and lytic cocktails in the setting of eclampsia [8–10].

During status epilepticus (SE) and refractory status epilepticus (RSE) the NMDA receptor plays a key role in pharmaco-resistance and epileptigenicity. As seizures remain uncontrolled, there is an up-regulation of the NMDA receptor, leading to a glutamate mediated excitotoxicity and seizure potentiation [11,12]. This has lead to the interest in NMDA receptor antagonists as AED in the

* Corresponding author at: GB-1 820 Sherbrook Street, Winnipeg, MB, Canada R3A1R9. Tel.: +1 204 228 6623; fax: +1 204 787 3851.
E-mail addresses: umzeiler@myumanitoba.ca (F.A. Zeiler), matuszcm@myumanitoba.ca (M. Matuszczak), jteitelbaum@hotmail.com (J. Teitelbaum), gillmanlm@gmail.com (L.M. Gillman), ckazina@exchange.hsc.mb.ca (C.J. Kazina).
[1] Address: Undergraduate Medicine, University of Manitoba, Winnipeg, MB, Canada R3A 1R9.
[2] Address: Montreal Neurological Institute, 3801 rue University, Montréal, QC, Canada H3A 2B4.
[3] Address: Section of General Surgery and Critical Care Medicine, Z3053 St. Boniface General Hospital, Winnipeg, MB, Canada.
[4] Address: Section of Neurosurgery, GB-1 820 Sherbrook Street, Winnipeg, MB, Canada R1A1R9.

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setting of SE/RSE. Ketamine is an example of one such drug which has displayed some efficacy in this setting [13].

The use of $MgSO_4$ in the setting of non-eclamptic SE/RSE has been mentioned in protocols and reviews of therapies [14–16]. To date however there are only a small number of cases describing the use of IV $MgSO_4$ for non-eclamptic SE/RSE [17–37].

Our goal was to perform a systematic review of the literature on the use of IV $MgSO_4$, a NMDA receptor antagonist, for non-eclamptic SE/RSE.

2. Materials and methods

A systematic review using the methodology outlined in the Cochrane Handbook for Systematic Reviewers [39] was conducted. The data was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [40]. The review questions and search strategy were decided upon by the primary author and supervisor.

2.1. Search question, population, inclusion and exclusion criteria

The question posed for systematic review was: What is the effectiveness of IV $MgSO_4$ for non-eclamptic SE/RSE? The definition of SE and RSE was as per the Neurocritical Care Society guidelines on the management of SE [41]. The definition for RSE was as follows: any patient(s) whom continue to experience either clinical or electro-graphic seizures after receiving adequate doses of an initial benzodiazepine followed by a second acceptable antiepileptic drug (AED) will be considered refractory [41]. Non-eclamptic SE was defined as SE in the absence of pregnancy, or SE in the setting of pregnancy but in the absence of the other features of eclampsia such as hypertension and multi-organ dysfunction. The term generalized refractory status epilepticus (GRSE) was used to refer to generalized tonic-clonic RSE. The term focal refractory status epilepticus (FRSE) was used to refer focal tonic-clonic RSE. The term multi-focal refractory status epilepticus (MFRSE) was used to refer to RSE that had a mutli-focal tonic-clonic nature. The term non-convulsive refractory status epilepticus (NCRSE) was used for non-convulsive seizures that fulfilled the criteria for RSE.

All studies, prospective and retrospective of any size based on human subjects were included. The reason for an all-inclusive search was based on the small number of studies of any type identified by the primary author during a preliminary search of MEDLINE.

The primary outcome measure was electrographic seizure control, defined as: complete resolution, partial seizure reduction, and failure. This qualitative seizure response grading was used given the lack of detail around the electroencephalographic response reported within the studies found. Secondary outcome measures were patient outcome (if reported), and adverse effects of the administration of $MgSO_4$.

Inclusion criteria were: All studies including human subjects whether prospective or retrospective, all study sizes, any age category, the documented use of IV $MgSO_4$ for the purpose of seizure control in the setting of SE/RSE, and the absence of pre-eclampsia/eclampsia as the cause of neurological deterioration or seizures. Exclusion criteria were: animal and non-English studies, treatment with oral $MgSO_4$, and any studies describing patients with pre-eclampsia/eclampsia.

2.2. Search strategy

MEDLINE, BIOSIS, EMBASE, Global Health, SCOPUS, and Cochrane Library from inception to June 2015 were searched using individualized search strategies for each database. The search strategy for MEDLINE can be seen in Appendix A of the supplementary material, with a similar search strategy utilized for the other databases. In addition, the World Health Organizations International Clinical Trials Registry Platform and ClinicalTrials.gov were searched looking for studies planned or underway, with none identified.

As well, meeting proceedings for the last 10 years looking for ongoing and unpublished work based on $MgSO_4$ for SE/RSE were examined. The meeting proceedings of the following professional societies were searched: Canadian Neurological Sciences Federation (CNSF), American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), European Neurosurgical Society (ENSS), World Federation of Neurological Surgeons (WFNS), American Neurology Association (ANA), American Academy of Neurology (AAN), European Federation of Neurological Science (EFNS), World Congress of Neurology (WCN), Society of Critical Care Medicine (SCCM), Neurocritical Care Society (NCS), World Federation of Societies of Intensive and Critical Care Medicine (WFSICCM), American Society for Anesthesiologists (ASA), World Federation of Societies of Anesthesiologist (WFSA), Australian Society of Anesthesiologists, International Anesthesia Research Society (IARS), Society of Neurosurgical Anesthesiology and Critical Care (SNACC), Society for Neuroscience in Anesthesiology and Critical Care, and the Japanese Society of Neuroanesthesia and Critical Care (JSNCC).

Finally, reference lists of any review articles or systematic reviews on seizure management were reviewed for relevant studies on $MgSO_4$ usage for SE/RSE that were missed during the database and meeting proceeding search.

2.3. Study selection

Utilizing two reviewers (FZ and MM), a two-step review of all articles returned by our search strategies was performed. First, the reviewers independently screened all titles and abstracts of the returned articles to decide if they met the inclusion criteria. Second, full text of the chosen articles was then assessed to confirm if they met the inclusion criteria and that the primary outcome of seizure control was reported in the study. Any discrepancies between the two reviewers were resolved by a third party (CK).

2.4. Data collection

Data was extracted from the selected articles and stored in an electronic database. Data fields included: patient demographics, type of study (prospective or retrospective), number of patients, dose of $MgSO_4$ used, timing to administration of $MgSO_4$, duration of $MgSO_4$ administration, time to effect of drug, how many other AED were utilized prior to implementation of $MgSO_4$, degree of seizure control (as described previously), adverse effects, and patient outcome.

2.5. Quality of evidence assessment

Assessment of the level of evidence for each included study was conducted by a panel of two independent reviewers, utilizing the Oxford criteria [42] and the Grading of Recommendation Assessment Development and Education (GRADE) criteria [43–48] for level of evidence. We elected on utilizing two different systems to grade level of evidence given that these two systems are amongst the most commonly used. We believe this would allow a larger audience to follow our systematic approach in the setting of unfamiliarity with a particular grading system.

The Oxford criteria consist of a 5 level grading system for literature. Level 1 is split into subcategories 1a, 1b, and 1c which represent a systematic review of randomized control trials (RCT) with homogeneity, individual RCT with narrow confidence interval, and all or none studies respectively. Oxford level 2 is