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Intravenous Magnesium For Pediatric Sickle Cell Vaso-occlusive Crisis: Methodological issues of a randomized controlled trial

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Abstract

Background—Multiple recent Sickle Cell Disease studies have been terminated due to poor enrollment. We developed methods to overcome past barriers and utilized these to study the efficacy and safety of intravenous magnesium for vaso-occlusive crisis (VOC). We describe the methods of the Intravenous Magnesium in Sickle Vaso-occlusive Crisis (MAGiC) trial and discuss methods used to overcome past barriers.

Procedure—MAGiC was a multicenter randomized double-blind placebo-controlled trial of intravenous magnesium versus normal saline for treatment of VOC. The study was a collaboration between Pediatric Hematologists and Emergency Physicians in the Pediatric Emergency Care Applied Research Network (PECARN). Eligible patients were randomized within 12 hours of receiving intravenous opioids in the emergency department (ED) and administered study medication every eight hours. The primary outcome was hospital length of stay. Associated plasma studies elucidated magnesium's mechanism of action and the pathophysiology of VOC. Health-related quality of life was measured. Site-, protocol- and patient-related barriers to prior studies were identified and addressed.

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CONFLICT OF INTEREST

The authors have indicated they have no financial relationships or conflicts of interest relevant to this article to disclose.

Results—Limited study staff availability, lack of collaboration with the ED, and difficulty obtaining consent were previously identified barriers. Leveraging PECARN resources, forging close collaborations between Sickle Cell Centers and EDs of participating sites, and approaching eligible patients for prior consent helped overcome these barriers.

Conclusion—Participation in the PECARN network and establishment of collaborative arrangements between Sickle Cell Centers and their affiliated EDs are major innovative features of the MAGiC study that allowed improved subject capture. These methods could serve as a model for future studies of VOCs.

Keywords

Sickle Cell Disease; Sickle Cell Anemia; Hemoglobinopathies; Vaso-occlusive Crisis; Randomized Controlled Trial; Enrollment; Pain Medicine; Hematology

INTRODUCTION

Each year in the United States (US), approximately 2,000 children are born with Sickle Cell Disease (SCD), one of the most commonly inherited hemoglobinopathies in the world [1, 2]. While SCD affects multiple organ systems, much of the morbidity of the disease is due to recurrent vaso-occlusive (VOC) pain crises which often result in hospitalizations and adversely affect quality of life [3, 4]. In the US alone, there are over 18,000 hospitalizations and 75,000 hospitalization days annually for children suffering vaso-occlusive pain episodes secondary to SCD [5]. Up to 28% of SCD patients admitted for VOC are readmitted within 30 days for another crisis [6].

Despite noteworthy advances in the management of other comorbidities of SCD [7, 8] and significant progress in the understanding of the pathophysiology of VOC [9], little has changed in the management of acute SCD pain in recent decades. Current management is based primarily on expert opinion [10–12], with evidence-based acute management derived from small, often inadequately powered SCD-specific studies [13] or studies of non-SCD pain [14]. Robust multi-center clinical trials for VOC are few in number and recent attempts have been plagued with multiple challenges leading to poor patient enrollment [15–18]. Within the past 5 years, 16 clinical trials for patients with SCD have been closed prematurely due to inadequate patient accrual; many were large multicenter randomized controlled trials funded by the National Institutes of Health [16–21].

Challenges to enrollment of SCD patients noted in these and other trials can be categorized broadly into three groups: 1) Site-related factors, e.g. lack of research staff during off-hours or limited communication and collaboration between treatment teams (especially between the Emergency Department and Hematology teams), leading to delayed identification of eligible patients; 2) Protocol-related factors, e.g. complicated protocols or limited participation in planning from potential stakeholders; 3) Patient-related factors, e.g. patient mistrust of research, difficulty obtaining consent during an acute pain episode or absence of parents to provide consent once the patient is admitted [15–20].

To address these challenges and the need for initiation of an effective intervention as early as feasible during a painful episode [16, 17] the current study of Intravenous Magnesium in Sickle Vaso-occlusive Crisis (MAGiC) forged a unique partnership. This partnership between the Sickle Cell Centers and Emergency Departments (EDs) of participating study sites allowed close collaboration through all stages of study development and implementation. The partnership specifically provided the capacity to address the three broad groups of challenges outlined above. In this manuscript, we provide the rationale for the use of magnesium for the acute treatment of sickle cell VOC, describe the study protocol, and propose a methodology to address enrollment problems identified in previous studies.

Intravenous (IV) magnesium sulfate, a safe and effective drug for many pediatric conditions including asthma, acts as a vasodilator through both endothelial-dependent and endothelial-independent mechanisms. Vascular function is known to be impaired in SCD [22–24]. Patients with SCD have both increased circulating levels of vasoconstrictors, e.g., endothelin and thromboxane, and increased production and consumption of nitric oxide [24]. There is evidence that, at baseline, individuals have a compensatory increase in nitric oxide production that is overwhelmed by scavenging by cell-free hemoglobin and increased reactive oxygen species in plasma lipids and the vascular wall [22, 24–26]. Magnesium can cause vasodilation through at least two independent mechanisms: a direct inhibition of calcium in the vascular smooth-muscle wall and an endothelial dependent release of nitric oxide [27–32]. Magnesium can also modulate endothelial inflammation; magnesium deficiency is associated with increased levels of the inflammatory cytokines IL-1 β , IL-6 and TNF α , and increased expression of endothelial VCAM 1 [33–35]. This modulation of endothelial inflammation may be beneficial in SCD, a proinflammatory disease with increased circulating levels of the above cytokines [36, 37].

A pilot study using IV magnesium sulfate for acute pain crisis showed a statistically and clinically significant decrease in hospital length of stay (LOS) when magnesium was added to standard therapy. The median LOS with magnesium was 3.0 days, compared with 5.0 and 4.0 days for the 2 previous hospitalizations for each patient ($p = 0.006$). In addition, there was a 34% decrease in morphine equivalents used ($p = 0.002$), suggesting that magnesium also decreased severity of pain [38]. Given these preliminary data, we designed a randomized, double-blind, placebo-controlled multi-center trial to assess the efficacy and safety of the addition of IV magnesium sulfate to standard therapy for sickle cell pain episodes (referred to as the MAGiC study).

METHODS OF THE MAGIC STUDY

The overall goals of the MAGiC study were to determine the efficacy and safety of IV magnesium sulfate for the management of acute SCD VOC, to understand the impact of treatment on health related quality of life (HRQL) and short term outcomes in patients, and to elucidate potential mechanisms of action of IV magnesium sulfate in SCD VOC.

Study Hypotheses

Our primary hypothesis is that IV magnesium is an effective and safe agent for the treatment of children hospitalized for an acute sickle cell pain episode. The secondary hypotheses are: HRQL and short term outcomes will be improved in those treated with magnesium and: the beneficial effect of IV magnesium is, in part, due to increased endothelial cell nitric oxide production, improvement of endothelial dysfunction and/or reduction in inflammation.

Overall Design

The MAGiC study was a multi-center randomized controlled double-blind trial. Sickle Cell Centers and their associated EDs in eight large pediatric hospitals within the PECARN network participated. All patients four to twenty-one years of age with Hb SS or Hb S β° thalassemia disease presenting with VOC and being admitted for pain management were assessed further for eligibility (Table 1). Institutional Review Board approval was obtained at all participating sites, and an Investigational New Drug application (IND # 78,057) was approved by the Food and Drug Administration. The study was registered at ClinicalTrials.gov (study identifier: NCT01197417).

Outcome Measures

Efficacy outcome measures—The primary efficacy outcome measure was hospital LOS. Consistent with previous studies, LOS was recorded in hours from the time of the start of the first study medication until the time of discharge from the hospital, or 12 hours after the last IV opioid, whichever occurred first [35–37]. The main discharge criterion for VOC was the ability of the patient to control his/her pain with orally administered opioid medication or non-steroidal anti-inflammatory medications (NSAIDs). The 12-hour interval after the last IV opioid is the only previously published marker for the ability to control pain off IV opioids [39–41]. Using this alternate LOS outcome allowed us to account for hospitalizations that were prolonged for reasons not related to pain medication use; in particular, transportation difficulties and social situations.

The secondary efficacy outcome measure was the number of morphine equivalents per kilogram of body weight used following administration of the first dose of study medication. This included both IV and oral doses of opioid and aided in assessing the effect of the intervention on the patient's pain without relying on subjective pain scores which have proven to be problematic in prior studies [15, 40]. Non-morphine opioid medication doses were converted to morphine equivalents using previously published conversions [42].

Patient-reported outcomes: Health-related quality of life (HRQL)—HRQL was measured by the validated PedsQL™ Generic core scales, Sickle Cell Disease module and fatigue module [3]. In addition, short term outcomes affecting quality of life were assessed, specifically, days of school missed, days of continued pain, and missed days of work for parents.

Safety Outcome Measures—Hypotension (defined as a greater than 20% reduction in systolic blood pressure from the measurement taken just prior to the study drug infusion), weakness, and a warm sensation associated with study drug infusions were the primary

safety concerns; re-hospitalizations were also recorded. To monitor for magnesium toxicity, serum magnesium levels were evaluated prior to the first study drug infusion and one hour after the start of the fourth infusion (at hour 25). With the exception of the site pharmacy, all study personnel were blinded to the results of the hour 25 magnesium levels as knowledge of these results could have revealed whether the patient was receiving magnesium or placebo. Finally, adverse events, coded using the Medical Dictionary for Regulatory Activities (MedDRA) vocabulary, were recorded from the time of enrollment through hospital discharge, or day seven of hospitalization, whichever occurred first.

Plasma studies—These studies explored the pathophysiology of crisis and mechanism of action of magnesium sulfate and included: plasma nitrite, cell-free hemoglobin, LDH, and plasma levels of sVCAM-1, sP-selectin, IL-1 β , IL-6, TNF α and IFN- γ as markers of endothelial injury and the systemic response to inflammation.

Study flow

Screening and Enrollment—Patients with SCD were screened and enrolled in the ED where possible. Informed consent was also obtained in advance of a qualifying ED visit where feasible, for example, during a hematology clinic visit or an admission to the hospital. In these instances, verification of eligibility and of prior consent was performed prior to subject enrollment in the ED. Equal allocation randomization, stratified by age (4–11 years and 12–21 years), study site, and hydroxyurea use during the past three months (yes/no) in randomly varying block sizes was utilized. Randomization tables were provided by the PECARN Data Coordinating Center to each study site research pharmacy where the study drug was prepared according to the assigned study arm.

Study Drug Administration—Enrolled children were randomized to receive 40 mg/kg (max 2.4 grams) of IV magnesium sulfate infused at a concentration of 40 mg/ml (1 ml/kg, max 60 ml), or the equivalent volume of normal saline placebo administered over 20 minutes. The first dose was ideally given in the ED but may also have been administered on the inpatient floor for those patients already admitted at the time of randomization. Study drug infusions were given every eight hours for a total of six doses or until discharge, whichever occurred earlier. Continuous cardiorespiratory monitoring was performed during and after each infusion.

Other standard therapy—Throughout their hospital stay, all subjects continued to receive standard therapy for VOC. Initial opioid treatment at each institution was structured to aid in comparison of the effects of magnesium on pain and LOS while still allowing institutional flexibility. Other SCD-specific medications (e.g., opioids during the inpatient stay, intravenous non-steroidal anti-inflammatory drugs) were administered at the discretion of the blinded treating physician.

Patient-reported outcomes—The HRQL outcomes were assessed at four time points: study enrollment in ED, time of last study medication dose (40 hours), one week post hospital discharge, and one to three months post discharge. Short term outcomes were assessed one week post hospital discharge.

Plasma studies—Blood sampling occurred just prior to the first study drug infusion, one hour after the start of the fourth infusion and again at the 1–3 month post-discharge follow-up visit. Complete blood count (CBC), reticulocyte counts, serum lactate dehydrogenase (LDH), blood urea nitrogen (BUN), creatinine, and calcium were processed in the clinical site's clinical laboratory. For the remaining plasma studies, 5.5 ml of whole blood was collected in 3.2% citrate, centrifuged immediately to isolate the platelet-poor plasma and frozen at -80°C for shipment on dry ice to the main study lab at the Medical College of Wisconsin.

Follow-up—Enrolled children and their caregivers were contacted by telephone 7–10 days after discharge and were seen in clinic 1–3 months following discharge to determine re-hospitalization or unscheduled care and to determine patient-reported outcomes within the seven days and 28 days following discharge from the hospital (Figure 1).

Statistical Considerations

All analyses were conducted on a modified intention-to-treat basis, with all patients who were randomized and received any study drug included and analyzed in the treatment arm to which they are randomized. Median LOS and interquartile ranges were reported for each arm. A van Elteren test, stratified in the same manner as randomization, was used to compare the distribution of the LOS for subjects in each treatment arm. A van Elteren test was also used to compare the total number of morphine equivalents per kilogram of body weight between subjects in each arm. The proportions of subjects who experienced hypotension, weakness, a warm sensation during infusion, or all-cause re-hospitalization within seven and 28 days, were compared between treatment arms using a Mantel-Haenszel test. HRQL scores between children in the two arms were compared using t-test or Wilcoxon rank sum test. Longitudinal analysis of HRQL scores was performed using a linear mixed-effects subject specific model.

For plasma studies, differences over time between the groups (during VOC) were tested using two-factor repeated-measures ANOVA. Means were compared using Tukey's Honestly Significant Difference (HSD) test for multiple comparisons adjustment. To evaluate differences between subjects at VOC onset compared to during steady state when well, results within each individual obtained during VOC and at the follow up visit were compared using paired t-tests.

Power and Sample Size Calculations—The sample size requirements for this trial reflected the power analysis for the primary endpoint, length of stay (LOS) in hours. A sample size of approximately 91 subjects per arm was needed to detect a 20-hour difference in length of stay, with $\alpha = 0.05$ and 80% power. Twenty hours was determined to be the minimally important difference in LOS due to the clinical significance of that decrease in stay resulting in a significant number of children leaving the hospital a calendar day earlier [39–41]. The sample size calculation assumed a standard deviation of 2.0 days for LOS, based on the pilot study. To account for up to 5% noncompliance (subjects who are assigned magnesium but do not get all infusions), the planned sample size was increased to 101

subjects per arm. An additional 2% increase to account for interim monitoring boundaries gave 104 per arm, or 208 total.

Interim Analyses and Stopping Rules

The MAGiC study was monitored by a Data and Safety Monitoring Board (DSMB) approved by the National Institutes of Health. The DSMB was composed of five doctorate-level members not affiliated with the study, including experts in Pediatric Emergency Medicine, Pediatric Hematology, Hematology, Bioethics, and Biostatistics. Interim monitoring for superiority or detrimental effect of one treatment approach was conducted using O'Brien-Fleming-type boundaries implemented using the Lan-DeMets flexible alpha-spending function approach. The projected accrual period was three years. The DSMB met prior to study launch, and planned meetings occurred after the accrual of approximately 69 subjects, and after the accrual of approximately 138 subjects. The DSMB made recommendations regarding study conduct, data quality, participant safety, and continuing or stopping the trial. For instance, after 75 patients were enrolled, the DSMB, with statistical support from the Data Coordinating Center, recommended that hour 25 blinded magnesium level monitoring was no longer required given that no magnesium toxicity had thus far occurred.

RESULTS

Overcoming Barriers to Enrollment

Site-related Factors—Limited staff availability and delay in initiation of study medications have been problematic in prior studies. To test the acute intervention, enrollment and study drug infusions needed to start within 12 hours of first pain medication administration in the ED. To achieve this, an innovative collaboration was forged between the Sickle Cell Centers and EDs of participating sites. Personnel from both departments were involved at all stages of the study from design to implementation, providing an increase in active study personnel and ensuring timely completion of study procedures. The study was conducted through the highly successful Pediatric Emergency Care Applied Research Network (PECARN), a network of 18 major pediatric hospitals with a proven track record of conducting high-quality, high-impact Pediatric Emergency Medicine research [43–45]. Leveraging of the PECARN infrastructure allowed for active patient screening, approach for consent, enrollment, drawing of pre-dose serum samples and infusion of the first dose of study medication to occur in the ED. PECARN research assistant staff provided in-person ED coverage over 16 hours per day, seven days per week, in addition to on-call coverage for enrollment and administration of study procedures during night hours.

Protocol-related Factors—Active participation of key personnel from other departments (pain medicine/anesthesia, pharmacy, nursing, etc.) at all sites through identification of study champions from the earliest stages of the study ensured that enrollment, randomization and safety monitoring were accomplished. Input from these key personnel during the design of the protocol also helped to streamline it. For example, the study drug was commercially available at a concentration of 40 mg/ml. To minimize errors during dose calculations and

study drug infusions, a study drug dose of 40 mg/kg (well within the known therapeutic range of magnesium) was chosen which resulted in a final drug volume of 1 ml/kg.

Patient-related Factors—The unique MAGiC study infrastructure has especially improved the opportunity for consent as legal guardians are almost always present in the ED but not consistently present on the inpatient floor following admission. In addition to this, another important feature of the protocol was that eligible patients and their families were approached for prior consent when they presented for routine care in the Hematology clinic or when seeking ED care during a non-eligible visit (e.g., fever or VOC not requiring admission). This allowed consent and assent to be obtained when patients and families were under less duress, a factor which was of significant ethical benefit in the attempt to obtain true informed consent [46]. Families could sign consent or simply receive education about the study at these times. This opportunity also gave patients more time to become acquainted with the study and to ask questions of their primary Hematologist before being eligible for enrollment, thus addressing patient mistrust of research and challenges with obtaining consent noted in prior studies.

DISCUSSION

Large-scale inpatient therapeutic studies for SCD have historically been difficult to complete [9, 11, 15–21]. Currently available data are limited, studies often underpowered, and results sometimes difficult to interpret [13, 17]. Poor patient enrollment has been cited as major limitations in most studies [16, 17, 47]. Reasons for this are most likely multifactorial.

The Improving Pain Management and Outcomes with Various Strategies of Patient-Controlled Anesthesia (IMPROVE) study, for example, was prematurely terminated after six months of enrollment due to poor patient accrual. This study of the NIH funded multicenter SCD clinical research network had an enrollment target of 278 patients. While lack of eligible subjects was not a problem, at study termination, only 38 patients had been enrolled across 31 participating sites. A thorough analysis revealed multiple obstacles to patient accrual including: difficulty obtaining consent during a painful episode, lack of staff to conduct the study 24 hours a day, delayed notification of admission from the ED, problems with interdepartmental collaboration, treatment team concerns about the study protocol, and complicated study protocol dosing schedules [17].

Limited study staffing and difficulty obtaining consent within a 14-hour window were similarly identified as barriers in the Preventing Acute Chest Syndrome by Transfusion Feasibility Study (PROACTIVE), another trial which reported difficult patient enrollment. The study's goal of randomizing 40 subjects in the intervention arm over a 12-month period across 26 study sites was not attained and only 10 patients were randomized [16].

These studies of acute interventions for SCD (and many others not specifically cited [18–21]) encountered site-, protocol-, and patient-related barriers to enrollment. Several innovative steps were taken in the MAGiC study to address the challenges identified. Participation in the PECARN network and the establishment of collaborative arrangements between the Sickle Cell Centers and their affiliated EDs are major innovative features of the

MAGiC study that allowed improved subject capture, preventing the prolonged delays that have previously existed in studies treating acute VOC.

In conclusion, based on the pilot study [38], intravenous magnesium is a potentially novel therapy for the management of acute VOC in patients with SCD, a common complication for which few therapeutic modalities have been developed in recent decades. The MAGiC study will elucidate the mechanisms by which IV magnesium may decrease the duration of VOC and, subsequently, hospital LOS for children admitted for VOC. The associated plasma studies will give further insight into the underlying pathophysiology of the disease and clarify the roles of hemolysis, endothelial injury, inflammation, and the nitric oxide pathway in the development and resolution of acute VOC. In addition, patient reported outcome data will describe the trajectory of patient functioning and any effects of magnesium treatment. The collaboration of Sick Cell Centers and their associated Emergency Departments and the infrastructure of the Pediatric Emergency Care Applied Research Network were leveraged in an attempt to overcome barriers identified in previous studies. This collaboration could serve as a strong model for future studies of acute pain in SCD.

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Figure 1.
Study flow diagram.

Table I**Patient Eligibility**

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> ■ age 4–21* years, inclusive; AND ■ Hb SS or Hb Sβ° thalassemia disease; AND ■ failed intravenous opioid pain management in ED prior to decision to admit; AND ■ decision to admit to the inpatient unit for sickle cell pain crisis. 	<ul style="list-style-type: none"> ■ patient received >12 hours of IV pain medication prior to enrollment; OR, ■ patient discharged from an inpatient unit within 72 hours of arrival in ED for current pain crisis, OR ■ previous enrollment in this study (only one admission per child is eligible); OR ■ history of allergy/intolerance to both IV morphine and hydromorphone; OR ■ known other cause for current pain – (avascular necrosis, gall bladder disease, priapism, etc.); OR ■ patient with > 10 admissions for pain crisis in the past year; OR ■ patient maintained on daily opioids or chronic transfusions for chronic sickle cell pain; OR ■ transfusion within the previous two months; OR ■ known kidney or liver failure (elevation of LFTs would not warrant exclusion); OR ■ known pulmonary hypertension; OR ■ patient known to be pregnant; OR ■ diagnosis of bacterial infection, fever ≥ 39.5°C, acute chest syndrome, hemodynamic instability or sepsis; OR ■ current oral magnesium supplementation or current enrollment in another therapeutic study protocol; OR ■ previously diagnosed clinical stroke**; OR ■ current or planned use of neuromuscular blocker, nifedipine, ritodrine, or terbutaline; OR allergy to magnesium sulfate.

* Maximum age of eligibility increased from 18 to 21 during the study to increase the eligible patient pool and to reflect the fact that many SCD patients are treated at pediatric facilities until age 21.

** Evidence of prior silent stroke was initially an exclusion criterion based on the concern that such patients may be at higher risk of repeat stroke if exposed to significant hypotension. However during the course of the study a multi-center investigation of risk factors for silent stroke in SCD patients revealed that hypertension, not hypotension, was a risk factor for stroke [48].