A Multicenter Randomized Controlled Trial of Therapeutic Hypothermia plus Magnesium Sulphate (MgSO4) vs. Therapeutic Hypothermia plus Placebo in the Management of Term and Near Term babies with Hypoxic Ischemic Encephalopathy (The Mag Cool Study): Preliminary Safety Results.

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Introduction

Therapeutic Hypothermia has now become a standard of care, among NICU's worldwide, in the neuro-protective management of moderate to severe Hypoxic Ischemic Encephalopathy (HIE) in term and near term babies. Additional neuro-protection is possible by adding additional neuro-protective agents to hypothermia therapy. MgSO4 is known for its neuroprotective properties in newborn babies.

The Mag Cool Study is comparing Therapeutic Hypothermia plus Magnesium Sulphate with Therapeutic Hypothermia plus Placebo in the Management of Term and Near Term babies with Hypoxic Ischemic Encephalopathy. The current abstract presents the preliminary safety results of the combined use of Hypothermia and MgSO4.

Objective

To determine the safety of a combination of Magnesium Sulphate and therapeutic Hypothermia in the management of term and near term newborns with moderate to severe Hypoxic Ischemic Encephalopathy.

Methods

Study design: Multicenter, Prospective, Randomized, double blind, placebo controlled trial.

Study Duration: June 2012 to December 2013.

Funding: The study is funded by the Internal Research Grants Competition of Hamad Medical Corporation Doha Qatar (Grant # GC 1028A).

IRB Approval: The study, its data collection and consent forms are approved by the IRB of Hamad Medical Corporation Qatar and the relevant IRB's of all participating centers.

Randomization: Babies were randomized, using a web based randomization system provided by Sealed envelopes Inc. London UK, to Arm A (Magnesium Sulphate 250mg/k/dose for three doses at 24 hours interval or Arm B (an equivalent volume of normal saline as placebo) to be administered as soon as possible after birth; preferably within six hours of birth.

Method: Term and near term babies (≥35 completed weeks of gestation) with evidence of moderate to severe Hypoxic Ischemic encephalopathy using Inclusion and Exclusion criteria. All babies were provided standard hypothermia therapy as soon after birth as possible, using either a total body cooling machine or head cooling machine to maintain a rectal temperature of 33.5^0 C for a period of 72 hours followed by an eight hours period of gradual rewarming to normal body temperature and another 16 hours of observation (total duration 96 hours).

Definitions: Mild- moderate hypotension (requiring volume + one inotrope); Severe hypotension (requiring volume + two or more inotropes).

Safety outcome measures: Death or severe adverse events during the 96 hours of treatment including Hypotension, Coagulopathy, Thrombocytopenia , Intracranial hemorrhage, Pulmonary hemorrhage, Pulmonary hypertension, Necrotizing Enterocolitis, Cardiac arrhythmias and Major venous thrombosis.

Statistical Analysis

SPSS Version 20 was used for Data Analysis. Frequencies were run for the study variables. Cross tabulations with uni-variate analysis of the Intervention arm (MgSO4 and Placebo) was done with the adverse events such as the Hypotension, Abnormal coagulopathy, and thrombocytopenia. Chi-square test and Fischer Exact test was used, and a p-value of 0.05 was taken as significant.

Results

A total of **18** patients were enrolled in the safety study from 26th May 2012 till 15th November 2012. There were 9 patients in each of the trial arms MgSO4 vs. Placebo arm. Therapeutic hypothermia was successfully maintained between 33.5 and 34.5^0 C as per standard protocol. All 18 patients received intensive care including endotracheal intubation and ventilation.

7 (38.9%) patients had moderate HIE and **11 (61.9%)** had severe HIE. On univariate analysis the distribution of the severe and moderate HIE was similar amongst the two trial arms (p-value >0.9).

The overall proportion of hypotension was **83.33%** (n=15).There was no difference in the incidence and severity of hypotension between the two trial arms (p-value >0.9) Table 1.

The overall proportion of coagulopathy was **83.33%** (n=15). Although the incidence of coagulopathy was **66.7%** in the MgSO4 arm and 100% in the placebo arm, the difference was statistically non significant (Fischer Exact p value = 0.1) Table 2.

The overall proportion of thrombocytopenia was **61%** (n=11) with no difference in the incidence between the two trial arms.(Fischer exact p-value>0.9) Table 3.

Results

Adverse events: There was one reported death in the MgSO4 arm. This patient had evidence of severe perinatal asphyxia at birth (Apgar score less than 5 at ten minutes). The pH was 6.9 and base excess of -28.3 at the time of randomization (3 hours 45 minutes of age: the time required for the transfer of the patient to the managing hospital). His death was attributed to the severity of his condition as his clinical and laboratory parameters were worsening well before starting therapeutic hypothermia or receiving his first dose of medication (at 8 hours of age). Another patient in the MgSO4 arm developed severe bradycardia at 70 hours of therapeutic hypothermia requiring the termination of hypothermia.

There were no recorded cases, in any of the trial arms, of intracranial hemorrhage, Pulmonary hemorrhage, Pulmonary hypertension, Necrotizing Enterocolitis or Major venous thrombosis.

Table 1. Comparison of Hypotension as an adverse event between the two trial arms.

Trial Arm/Variable	No Hypotension	Mild-Moderate Hypotension	Severe Hypotension	Total	Fisher Exact P value
Arm A (MgSO4)	2 (22.2%)	5 (55.6%)	2 (22.2%)	9 (100%)	>0.9
Arm B (Placebo)	1 (11.1%)	6 (66.7%)	2 (22.2%)	9 (100%)	

Table 2.Comaprison of Coagulopathy as an adverse event between the two trial arms.

Trial Arm/Variable	Normal Coagulation	Abnormal Coagulation	Total	Fisher Exact Test P value
Arm A (MgSO4	3 (33.3%)	6 (66.7%)	9 (100%)	0.103
Arm B (Placebo)	0 (0%)	9 (100%)	9 (100%)	

Table 3. Comparison of Thrombocytopenia as an adverse event between the two trial arms.

Trial Arm/Variable	Normal Platelet Count	Thrombocytopenia	Total	Fisher Exact Test P value
Arm A (MgSO4	4 (44.4%)	5 (55.6%)	9 (100%)	>0.9
Arm B (Placebo)	3 (33.3%)	6 (66.7%)	9 (100%)	

Conclusion

The combined use of therapeutic hypothermia and MgSO4 appears to be safe in the patients recruited in the study so far particularly with respect to maintaining blood pressure and coagulopathy. Long term survival and neurodevelopmental outcomes remain to be evaluated.

References

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Participating Centers

Hamad Medical Corporation (Qatar), Zekai Tahir Burak Hospital, Diyarbakir Children's Hospital, Istanbul Medeniyet University Goztepe Hospital & Tepecik Hospital (Turkey), Mansoura University Children's Hospital, (Egypt), Habib Medical Group (Saudi Arabia), University Malaya Medical Center & Universiti Kebangsaan Malaysia (Malaysia), Tawam Hospital & Mafraq Hospital (UAE), The Children's Hospital & Institute of Child Health (Pakistan), SKIMMS(India), Khoula Hospital (Oman), Salmaniya Complex (Bahrain).