# Prospective Randomized Controlled Trial of Magnesium During Carotid Endarterectomy

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### A. Statement of Study Purpose and Rationale

Many patients undergoing carotid endarterectomy (CEA) develop cognitive dysfunction due to the procedure. The incidence is approximately 25% on post-operative day 1, and 28% on post-operative day 30. Cognitive dysfunction is determined by a battery of neuropsychological tests administered before and after the procedure. Similar declines in cognitive performance are absent in a control group of patients undergoing spine surgery. In addition, the concentrations of serum markers of cerebral injury neuron specific enolase and protein S I OOB are elevated in patients undergoing CEA, but not in spine surgery patients. The cause of this neurocognitive injury is likely due to perioperative emboli and/or cerebral hypoperfusion.

Our goal is to test the hypothesis that intravenously administered magnesium sulfate (MgS04) will reduce the incidence of cognitive dysfunction in CEA patients. This therapy may work through a variety of mechanisms associated with magnesium's action as a calcium antagonist. MgSO4 blocks vasoconstriction, increases coronary and cerebral blood flow, and reduces ischemic brain injury in animal models of stroke. Possible mechanisms for this cerebroprotective effect include an increase in cerebral blood flow (CBF) due to cerebral vasodilation, antagonism of voltage-sensitive calcium channels, blockage of NMDA glutamate receptors, inhibition of glutamate release and enhanced mitochondrial calcium buffering.

Our study will compare two groups of patients, one treatment group receiving intravenous MgS04 and a placebo group receiving saline solution. A research pharmacist will randomly assign patients to the treatment or placebo group. Patients will be stratified according to the asymptomatic or symptomatic nature of their carotid artery disease. Outcome measures include change in performance on a battery of 5 neuropsychometric tests on post-operative day I and post-operative day 30, compared to preoperative performance.

### B. Study Design and Statistical Analysis/ Study Procedure

Patients will be assigned to either a MgS04 treatment group, or a saline placebo group. The treatment group (group A) will receive a bolus containing 2g of Mg over 15 minutes immediately after induction and a continuous maintenance dose containing l6g Mg over the next 24 hours. The target serum Mg level in group A is 3-4 mEq1L. Serum Mg levels will be measured before and six times after the bolus dose is administered according to the following blood drawing schedule: pre-induction, 15 minutes, I hour, 2 hours, 6 hours, 12 hours, and 24 hours post-bolus. An individual not involved in the study will record and monitor the Mg. An alert will be initiated when the serum Mg level exceeds 4 mEq/L, with subsequent reduction in the rate of infusion, and the infusion will be discontinued in the event the serum Mg level exceeds 6 mEq/L. These patients will be removed from the study. The placebo group (group B), will receive a bolus and continuous maintenance dose of saline solution over the next 24 hours. These groups will be randomly chosen by the research pharmacist and will not be revealed to the anesthesiologist, surgeon or neuropsychometrist. The patient's assigned treatment will only be revealed for the following reasons: hemodynamic instability defined as an inability to maintain systolic blood pressure within 25% of the patient's normal values with crystalloid fluids or phenylephrine for longer than 15 minutes, cardiac ischemia as determined by EKG changes, stroke, seizure or failure to regain consciousness.

Study size and statistics: Under control conditions, 25% of patients have significant cognitive decline within 48 hours of CEA. If we wish to detect a 50% reduction in this incidence with the administration of MgS04, we will need 168 patients in each group to power the study to 0.8 with an alpha of 0.05. Since the group will be stratified into asymptomatic and symptomatic patients, a total of 672 patients will be needed. The mean changes in performance on each neuropsychometric test between the two groups will be compared by t-test. Additionally, a composite score will be calculated for each patient by generating a Z-score for each test and adding them. A conservative definition for injury is a composite score that falls at least 2 standard deviations below the mean composite score of the placebo group. This will generate a dichotomous variable reflecting overall injury. The proportions of this dichotomous variable will be between the two groups by the chi-square or Fisher's exact test.

**Neurologic and Neuropsychometiric Evaluations**:

Preoperative neurological and neuropsychological evaluation will be performed before surgery along with a detailed medical and neurologic history and physical examination. The neuropsychometric tests are not intended to be diagnostic of specific neuropsychiatric disorders, but rather are designed to establish a baseline for later comparison. The specific neuropsychometric tests were selected because they measure higher cerebral function associated with the anterior circulation. These tests can be divided into four types:

1.) Two tests to determine focal functions: Boston Naming Test and Controlled Oral Word association Test
2.) An evaluation of mental processing speed: Reitan Trail-Making Test Part A and B
3.) An evaluation of verbal memory using a list of words: Bushke Selective Reminding Test
4.) An evaluation of visual memory: Rey Complex Figure

The left middle cerebal artery (MCA) territory is associated with language and two highly sensitive and specific tests will be used: the Boston Naming Test and the Controlled Oral Word Association Test. Right MCA territory supports visual-spatial tasks, and to assess function of this region, the Rey Complex Figure task will be administered. The Reitan Trail Making Test Parts A and B assesses mental tracking and the ability to switch mental set. Part A measures the time it takes for a subject to connect circles numbered 1-25 in sequence. Part B required the subject to connect circles that are labeled with number and letters, alternating between the two. The Bushke Verbal Selective Reminding Test asks a patient to learn a list of 12 words. This test scores the number of words learned and is an excellent measure of verbal memory. These tests will require approximately 30 minutes to administer.

**C. Study Drugs**

The material to be used in this study will be Magnesium Sulfate or saline placebo. MgS04 will be administered intravenously. It is given to treat patients with eclampsia and myocardial infarction. Normal serum levels are 1.6-2.6 mEq/L. Significant side effects include sedation, cardiac depression and suppression of neuromuscular junctions. Side effects occur when serum levels exceed 9-10 mEq/L.

**D. Medical Devices**

N/A

**E. Study Questionnaires**

N/A

**F. Subjects/Recruitment**

**a. Inclusion criteria**

1. age 18 years or older
2. admitted to hospital for elective CEA
3. ability to speak English
4. written informed consent obtained

**b. Exclusion criteria**

1. pregnancy
2. history of permanent neurologic impairment
3. Axis I disorder
4. Drug abuse
5. significant CAD

**G. Recruitment**

Patients will be recruited by an attending anesthesiologist, neurologist or neurosurgeon upon admission to the hospital. The investigator will give a detailed explanation of the risks and benefits of participation.

**H. Confidentiality**

All data will be kept confidential with a unique study number. Identifying data will be recorded at the local site for follow-up purposes, but not entered in the study charts. Charts will be maintained in a locked office which is accessible to authorized personnel only. All electronic data will be stored in a password protected database. Only th PI and key study personnel will have access to it.

**I. Potential Conflict of Interest**

No investigator has a proprietary interest in a drug, device or procedure under investigation.

**J. Location**

The study will be conducted at Columbia University Medical Center (Milstein Hospital Building). Patients will be given the option of being admitted preoperatively the night before surgery and stay up to two additional postoperative days. The first postoperative exam will be conducted in the NICU prior to discharge. The final exam will be conducted in the surgeon's waiting area.

**K. Potential Risks**

Magnesium is an important cation for enzymatic functioning, vascular tone, neuromuscular transmission and myocardial function. The actions of magnesium of concern are on vascular tone with resultant hypotension, on blockage of neuromuscular junctions with resultant weakness, and on the myocardium. with resultant myocardial depression. At the dosages administered in this study, we do not anticipate any harmful effects.

**L. Potential Benefits**

Potential benefits include a possible reduction in the risk of experiencing neurocognitive decline due to the procedure.

**M. Alerternatives**

No other therapies are currently given to prevent cognitive dysfunction following CEA. The alternative is not to participate in the study.

**N. Compensation**

N/A

**O. Costs**

N/A