Procedural Manual

Intravenous Magnesium sulfate in Aneurysmal Subarachnoid Hemorrhage

www.surgery.cuhk.edu.hk/imash-trial

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1. Trial summary

1.1 Aim of the trial

The aim of this randomized, placebo-controlled, double-blinded, multi-center trial is to evaluate the effect that intravenous magnesium sulfate infusion on the clinical outcome of patients with aneurismal subarachnoid hemorrhage (ASAH).

1.2 Trial flow chart

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**Target sample size**

348 patients with proven aneurysmal Subarachnoid hemorrhage

**MgSO₄ Infusion**  
*(n = 174)*

**Saline infusion**  
*(n = 174)*

**Study duration = 7 years**

**Outcome assessment**

**Primary outcome:**  
Glasgow Outcome Scale-Extended at six months

**Secondary outcome**  
1. Incidence of clinical vasospasm,  
2. Barthel Index,  
3. Modified Rankin score,  
4. Modified national institute of Health Stroke Scale,  
5. MCA velocities,  
6. Other major complications.
2. Organization of *The IMASH Trial*

**Steering Committee**

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Consultant neurosurgeon, Department of Neurosurgery, Christchurch Hospital, New Zealand

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**Web-site Design & Maintenance**

Dr George Wong

[www.surgery.cuhk.edu.hk/imash-trial](http://www.surgery.cuhk.edu.hk/imash-trial)
3. **Ethics requirement**

3.1 The study will conform to the Declaration of Helsinki. Approval from various Institution Review Boards should be obtained before the start of the trial. Suitable patients or their guardian/relative will be approached by one of the investigators. Written informed consent will be obtained. A member of the study team should be available to answer any question pertaining to the study. Patients may withdraw from the trial at any time. Each individual participating center has to establish the required guidelines for the conduction of this study in their environment.

3.2 Ethics approval from individual hospital should be obtained before the commencement of the trial. Copy of the ethics approval letter should be faxed to the trial office +852 26469296

3.3 All patients must sign (and date) a written informed consent before randomization (see appendix). Two photocopies should be made, one for the patient and the other one for the case notes. The local centre coordinator (or his/her delegate) should keep the original in the trial folder labeled as “Consent Forms”.

3.4 Patients who refuse participation should have their refusal recorded in the “Patient refusal log.”
4. **Patient Selection**  
Subjects should be recruited according to the following inclusion and exclusion criteria.

4.1 **Inclusion criteria:**  
(1) ASAH (as indicated by CT scan or lumbar puncture and an intracranial aneurysm confirmed by computer tomographic or conventional angiography)  
(2) Within 48 hrs of ictus (hemorrhage event)

4.2 **Exclusion criteria:**  
(1) Pregnancy  
(2) Major renal, hepatic or pulmonary disease  
(3) Major cardiac disease or recent myocardial infarct (< 6 months)  
(4) Age less than 18 years  
(5) Moribund condition on admission (defined as a patient that is in such a poor clinical condition that further active neurosurgical management would not be anticipated)

4.3 **Grade 5 and Geriatric SAH**  
Members of the Steering committees have considered the issues of Grade 5 SAH and geriatric (age > 80) patients (who would be considered for further neurosurgical treatment). Since there is much uncertainty, we have decided that they should be included in the trial. The main analysis will be carried out with these groups of patients. Separate sensitivity analyses will also be performed.
5. Randomization procedure

5.1 The randomization procedure will be completely web-based. (www.surgery.cuhk.edu.hk/imash-trial)

5.2 When a suitable patient has been identified and informed consent obtained, please go to the web for randomization.

5.3 To complete the randomization procedure, you need to know
(1) your center’s name,

(2) the patient’s identification (hospital) number

(3) the time of hemorrhagic event. The time from hemorrhage to randomization must be < 48 h.

(4) You must click YES to questions (2), (4) and (5)

2. Does the patient have aneurysmal SAH? Yes ☐ No ☐
   (as proven by CT scan or lumbar puncture and an intracranial aneurysm confirmed by computer tomographic or conventional angiography)

4. Has informed consent been obtained? Yes ☐ No ☐

5. Have all the following exclusion criteria been discounted?
   Yes ☐ No ☐
   * Patients who are pregnant
   * Patients with major renal, hepatic or pulmonary disease
   * Patients with major cardiac disease or recent myocardial infarct (< 6 months)
   * Patients who are moribund on admission (defined as a patient that is in such a poor clinical condition that further active neurosurgical management would not be anticipated)
(5) Other data include age, gender and WFNS grade (these data will be used for stratification of treatment allocation)

6. Age: [ ] (Value must be in 18)
7. Gender: Male ☐ Female ☐
8. WFNS Clinical grade: [Choose one only]

<table>
<thead>
<tr>
<th>Grade</th>
<th>GCS</th>
<th>Motor Deficit or Aphasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>absent</td>
</tr>
<tr>
<td>2</td>
<td>13-14</td>
<td>absent</td>
</tr>
<tr>
<td>3</td>
<td>13-14</td>
<td>present</td>
</tr>
<tr>
<td>4</td>
<td>7-12</td>
<td>present or absent</td>
</tr>
<tr>
<td>5</td>
<td>3-6</td>
<td>present or absent</td>
</tr>
</tbody>
</table>

(6) You should confirm the accuracy of the information and then click submit.

Please confirm the following information is correct

- Center name: Prince of Wales Hospital, Hong Kong, China
- Hospital (or patient identification) number: a1234567
- Does the patient have aneurysmal SAH? Yes
- What was the time of ictus (hemorrhagic event)? 11/1/2003 1:01:00 AM
- Has informed consent been obtained? Yes
- Have all following exclusion criteria been discounted? Yes
- Gender: Male
- WFNS Clinical grade: 1

Confirm or click back button to modify.

(7) A randomization code will be generated; you are encouraged to print the slip for reference. You should keep this in a safe place so that the randomization outcome is concealed from the investigators.

Randomization outcome:

The trial number for the patient is: pwh001-19

This patient is going to have: Saline

5.4 For practice, a web-site ([www.surgery.cuhk.edu.hk/imash-trial/testing](http://www.surgery.cuhk.edu.hk/imash-trial/testing)) has been set up for testing the randomization procedure.
6. Study drug administration

6.1 Each center should nominate an independent medical staff dedicated to look after study drug administration. He/she will adjust study drug infusion according to the plasma magnesium concentration, \([\text{Mg}^{2+}]\).

6.2 This independent medical staff should not be directly involved with the day to day management of the patient except to check \([\text{Mg}^{2+}]\).

6.3 Study drug should be administered at two phases:
   (1) **Bolus dose** (20 mmol over 30 min) followed by,
   (2) **Maintenance infusion** (80 mmol/day) for 14 days.

6.4 The aim will be to raise the plasma magnesium concentration to 2.0-2.5 mmol/L or twice the serum baseline level.

6.5 **Bolus study drug administration:**
   Add \(\text{MgSO}_4 \text{ 20 mmol}\) to a volume of 50 ml with normal saline.
   The volume (50 ml) should be infused over 30 min at 100 ml/h.

6.6 **Maintenance study drug administration:**
   Maintenance study drug should be started after completion of the bolus dose.
   Add \(\text{MgSO}_4 \text{ 80 mmol}\) to a bag of 500 ml fluid. The choice of fluid can be “0.9% saline” or “0.45% saline and 4.5% dextrose” or other appropriate fluid depending on the plasma sodium concentration. A label should be attached to each bag of fluid.

   \image{image.png}

   Study drug infusion should be started as 20 ml/h. The infusion should then be adjusted according to the plasma magnesium concentration, \([\text{Mg}^{2+}]\).

6.7 **During study drug administration, \([\text{Mg}^{2+}]\) should be checked regularly to avoid magnesium toxicity.**

6.8 This infusion regime is based on our previous research, changes in infusion rate is rarely required.
6.9 Drug infusion in the control group

Bolus: Draw up saline 50 ml and infuse at 100 ml/h as the bolus.  
Maintenance: Add \textbf{80 ml} saline to a bag of 500 ml fluid. The choice of fluid can be “0.9% saline” or “0.45% saline and 4.5% dextrose” or other appropriate fluid depending on the plasma sodium concentration. Study drug infusion should be started as 20 ml/h. In order to mimic the fluctuation of study drug administration in the treatment group, the infusion rate in the control group should be varied according to the last patient in the treatment group (i.e. receiving MgSO₄).

6.10 \textbf{Frequently asked question regarding study drug administration}

- **How often should I check the [Mg²⁺]?”**
  We recommend you check [Mg²⁺] everyday. The main purpose of measuring daily [Mg²⁺] is to avoid unintentional magnesium toxicity.

- **What happen if [Mg²⁺] > 2.5 mmol/L?”**
  You should stop the infusion for 12 h and then restart the infusion at a rate that is half to the previous infusion rate (i.e. 10 ml/h), you should check [Mg²⁺] again in the next morning. Renal failure should be excluded.

- **What should I do if [Mg²⁺] is below target?”**
  You should give 50 ml of the maintenance study drug (i.e. the same bag of study drug containing MgSO₄ \textbf{80 mmol} or \textit{Equal volume of saline} in 500 ml fluid) quickly over 30 min and then increase the infusion rate by 5 ml/h, i.e. 25 ml/h. You should recheck [Mg²⁺] the next morning. If the [Mg²⁺] remains low, the same procedure could be repeated, i.e. another 50 ml of the maintenance study drug over 30 min then increase the infusion rate by 5 ml/h, this time it should be 30 ml/h. You should exclude salt losing nephropathy at this stage.

- **What should I do if [Mg²⁺] in the control group is lower than the normal limit?”**
  We think you should top up [Mg²⁺] to the normal limit by using the minimal amount of MgSO₄ salt (e.g. 5 mmol in 20 ml saline over 30 minutes). We believe it is unethical to leave patient alone with hypomagnesaemia. This regimen will not cause overshoot in the plasma magnesium concentration.

- **Should study drug be continued if vasospasm continued for longer than 14 days?”**
  If the patient still has evidence of clinical vasospasm at the end of day 14, the infusion will be continued until the period of clinical vasospasm resolves/stabilizes.
7. **TCD measurements**

7.1 TCD should be performed daily or more frequently if indicated. The purpose of TCD measurement is to detect vasospasm as early as possible.

7.2 If the temporal bone cannot be penetrated, you may use the orbital window and measure the flow velocity at the siphon of MCA. You should record the maximum flow velocity.
8. Clinical management

8.1 Clinical management should be in accord to standard international protocol for ASAH

8.2 At least one dose of nimodipine* (either oral or intravenous) should be included.

8.3 Treatment of established vasospasm may include:
   (1) Hypertension
   (2) Hypervolaemia
   (3) Hemodilution
   (4) Endovascular angioplasty
   (5) Vasodilator infusion, including nimodipine and intravascular paparverine.

8.4 Definitive treatment of the ruptured aneurysm:
   Either surgical or endovascular or combined treatments can be included.

8.5 Intraoperative therapy
   (1) Hypothermia, barbiturate and/or propofol coma may be included.
   (2) The duration of temporary artery occlusion (if used) should be documented
       (or at least estimated).

9. Outcome definitions

9.1 Episodes of CLINICAL VASOSPASM are defined as
   (i) a drop in Glasgow Coma Scale (GCS) Score of more than one for more than six hours,
   or (ii) focal neurological deficits such as hemiparesis not caused by:
      1. Rebleed (as confirmed by CT scan)
      2. Progressive hydrocephalus (as confirmed by CT scan)
      3. Electrolyte or metabolic disturbance

9.2 Possible neurologic events related to ASAH:
   1. Rebleed (as confirmed by CT scan)
   2. Seizure (EEG or clinical convulsion)
   3. Hydrocephalus (as confirmed by CT scan and requiring VP shunts)
   4. Cerebral infarction (as confirmed by CT scan with or without neurologic deficit)
   5. Post treatment (coiling or surgery) sequel (as confirmed by history and/or CT scan)

9.3 Possible extracranial events related to ASAH:
   1. Myocardial infarction
      Confirmed by ECG and/or troponin (cTnT or cTnI) or CK-MB enzyme rise
   2. Venous thromboembolism
      Deep vein thrombosis or pulmonary embolism, confirmed by venography, duplex
      ultrasonography, V-Q scan or spiral CT, or autopsy
   3. Pneumonia
      Two or more of temperature > 38 °C, white cell count > 12,000/ml, positive sputum
      culture
   4. Acute renal failure
      Plasma creatinine > 200 µmol/L or twice the preoperative value
   5. Sepsis
      New postoperative infection, positive microbial culture, requiring antibiotics
   6. Cardiac failure
      Any of the following signs (elevated jugular venous pressure, respiratory rales,
      crepitations, or presence of S3) plus radiographic evidence (e.g. vascular
      redistribution, interstitial pulmonary edema, or frank alveolar pulmonary edema).
   7. Gastrointestinal bleed
      Confirmed by endoscopy.
   8. Arrhythmia (not related to myocardial ischemia)
      Include arrhythmia that required treatment (e.g. antiarrhythmics or pacing) only.
   9. Hypotension
      Persistent systolic blood pressure < 90 mmHg requiring vasopressor or inotropes
(10) Abnormal electrolytes
   Include symptomatic hyper- or hyponatraemia requiring treatment (e.g. hypertonic saline, dDAVP, water infusion, …)

9.4 Possible adverse events related to MgSO₄ infusion
   (1) Hypotension (requiring vasopressor or inotropes and is not related to septic shock)
   (2) Weakness (causing respiratory compromise and require ventilation)

9.5 Other outcome measurements
   Scoring instructions for
   (1) Modified National Institute of Health stroke scale (mNIHSS)
   (2) Modified Rankin Scale
   (3) The Barthel index
   (4) The health survey short form-36 (SF-36)
   (5) Glasgow outcome scale-extended
   Are available in the appendix section
10. Guidelines for completing case report form

10.1 Please ensure every question is answered. Make sure the centre code and patient number is entered in each page.

10.2 Please write clearly, within the boxes and in BLOCK letter for each field, or fill in circles to indicate appropriate response. Enter zero in first box for each item not requiring data to indicate that the question has not been overlooked.

(2) e.g. 0 [ ] [ ] mg

10.3 To correct errors: draw a line through entire field and write correct entry above or beside error. Initial and date the change. E.g. 20 10
   a. L C 10/04/2003

10.4 Page A1
   Q.3 Body Weight - please estimate the body weight if the exact body weight could not be obtained.
   Q.7 Time of Hemorrhage events - if the exact time of hemorrhage events (Ictus) could not be obtained, write the estimate time.
   Q.8 Time of hospital admission, please enter the time of the first hospital admission.
   Q.9 Verbal score - please write “T” if the patient’s trachea is intubated.
   Q.13 Please circle CTA, MRA or DSA to indicate where aneurysms were seen.
   Q.14 Size of the ruptured aneurysm - please write the maximal diameter of the size of the ruptured aneurysm.

10.5 Page A 3
   Q.4 Enter the start time for the first procedure only.
   Q. 5 Estimate the duration of temporarily artery clipping

10.6 Page B1
   If the patient died before discharge, enter the date of death as the date of hospital discharge. You should complete the DEATH report.

10.7 Page B2
   Q. 8 Please complete the VASOSPASM report if the patient develop vasospasm.

10.8 Page B3
   Q.12 Please enter surgery that is related to neurosurgery only.

10.9 Page C1
   Q.2 If the patient has been re-hospitalized more than once, please enter the first re-admission only.
10.10 **Serious Adverse Event Report**

SAE is NOT part of natural history of the condition or a primary or secondary outcome of this trial. The serious adverse event is defined as: fatal, life threatening, requiring or prolonging hospitalization or others. Please remember to complete the date of onset of the event, the study drug information, action taken and relationship to study drug and outcome of this serious adverse event. If the patient died due to the serious adverse event, please also complete the **DEATH** report. Please write clearly in **BLOCK** letter and fax to +852 26469296.
11. Data management

11.1 Data should be faxed to the data management center (DMC)

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11.2 CRF A1–A3 should be faxed together to DMC within 48 hours after surgery/randomization

11.3 Fax B1–B3 within 48 hours after hospital discharge

11.4 Fax C1–C3 within 48 hours after 3 months follow-up

11.5 Fax D1–D3 within 48 hours after FINAL 6 months follow-up
12. Experimental paradigm

Day 0, Ictus, study infusion started within 48 hours

Day 14, study infusion stopped

Magnesium or saline infusion

Daily [Mg^{2+}], TCD

Admission
mNIHSS, Fisher's CT grade
WFNS grade
(CRF A1-3)

Discharge
mNIHSS, clinical events
(CRF B1-3)

3 months
Barthel index, modified Rankin score
GOSE
clinical events
(CRF C1-3)

6 months
Barthel index, modified Rankin score
GOSE
SF-36
clinical events
(CRF D1-3)

mNIHSS = modified National Institute of Health Stroke Scale
WFNS = World Federation Neurological Surgeons
SF 36 = Quality of health survey, short form 36