

**The effects of magnesium sulphate on intraoperative
blood loss in meningioma patient undergoing
craniotomy with tumor removal: A prospective
randomized study.**

NCT number: NCT03558516

Document date: 1 August 2018

Study protocol

The protocol was approved by the institutional ethics committee (SI 259/2018). After obtaining written informed consent from all patients, a randomized double-blinded placebo-controlled trial was conducted on 80 patients. This study was registered at Clinical Trials.gov (NCT03558516). The patients will be randomized into 2 groups in blocks of 4 by computer-generated numbers. The sequence numbers and groups will be placed inside concealed envelopes, which will be opened by researchers. The researchers will enroll the participants but will not take part in patient care.

We will enroll patients aged between 18-70 years, American Society of Anesthesiologist (ASA) grade I and II, diagnosed of supratentorial meningioma and underwent craniotomy with tumor removal at Siriraj hospital, Mahidol university. The exclusion criteria included all of the following conditions; preoperatively unstable hemodynamics requiring vasopressors or vasodilators, heart disease or heart block, liver disease Child Pugh Score C, Renal insufficiency or estimated glomerular filtration rate (e-GFR) < 60 mL/min, allergy history of magnesium or any drug use in study protocol, use calcium channel blocker before operation, pregnancy, receive magnesium sulfate to treatment other conditions, baseline serum magnesium more than 2.6 mg/dL, BMI > 30 kg/m², and prone to brain herniation from increased intracranial pressure.

On the day before surgery, the informed consent will be obtained and baseline cognitive function will be measured by Montreal Cognitive Assessment (MOCA) test.

At the operating room, standard monitorings will be used. General anesthesia will be inducted with propofol 1.5-2.0 mg/kg, fentanyl 1-2 mcg/kg, and then cis-atracurium 0.15 mg/kg will be given for facilitating tracheal intubation. Then, the extra-large bore intravenous lines will be accessed and radial artery will be cannulated for continuous arterial pressure monitoring. A baseline blood sampling for magnesium level will be obtained.

Group Mg (Study group) patients will receive 40 mg/kg of magnesium sulphate loading in 30 minutes at incision and then continuous drip 10 mg/kg/hr until dura will be closure. Group NSS (Control group) patients will receive normal saline with the same amount for loading and continuous infusion. Identical infusion syringes of magnesium (Mg) and placebo will be prepared and labeled by the research staff that will not provide care for the patients.

Anesthesia will be maintained with sevoflurane not exceeding 1 minimal alveolar concentration (MAC) with supplemental of intermittent fentanyl 0.5-1 mcg/kg, and continuous cis-atracurium 0.06-0.1 mg/kg/hr. If the depth of anesthesia is not adequate, propofol 2-6 mg/kg/hr continuous will be given.

Hematocrit levels will be measured every 2-3 hours. Intraoperative transfusion triggered for packed red cell is a hematocrit < 27%. Magnesium level will be measured at beginning and 4 hours. If magnesium level is more than 4 mg/dl, study drug will be stopped. Intraoperative bleeding will be measured by collection in suction bottle, plastic bags, drapes, and soaked gauzes subtracting the amount of irrigating fluid.

After the uneventful operation, the patients will be extubated and transferred to neurosurgical intensive care unit. Some patients will remain intubation and post-operative ventilation will be continued and reasons for remaining intubation will be noted.

Postoperative cognitive function test (MOCA) will be done at postoperative day 3-7 when patient has less pain and recover enough for comfortable testing.

The measure outcomes are intraoperative blood loss, amount of pack red cell (PRC) transfusion requirement, anesthetic requirement and postoperative MOCA score.

Study Protocol

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Special equipment preparation

1. Equipment for arterial line insertion for continuous BP monitoring
(A-line may be not required, according to anesthesiologist in charge)
2. Two syringe pumps for study drug and muscle relaxant administration
3. Study drug (be prepared by investigator)
4. Two heparin tubes (green capped tube)
5. Equipment for hematocrit assessment

Monitoring & IV access

- Standard monitoring (NIBP, Pulse oximetry, EKG, End tidal CO₂)
- Arterial line insertion (before or after induction)

Induction

- **Fentanyl 1-2 mcg/kg**
- **Propofol 1.5-2 mg/kg**
- **Cis-atracurium 0.15 mg/kg** then wait for 4 minutes before intubation
- Use Sevoflurane in Air:Oxygen 1:1, Sevoflurane < 1 MAC
- Positioning as usual
- Aspirate blood from A-line **3 ml** into heparin tube for assess baseline Mg level
(Aspirate from vein if no A-line)

Maintenance

- Prepare study drug in syringe pump
- At skin incision **Study drug 0.2 ml/kg loading drip in 30 minutes** for example BW 60 kg use drug $0.2 \times 60 = 12$ ml drip 24 ml/hr for 30 minutes then IV continuous **0.05 ml/kg/hr** for example BW 60 kg administer 3 ml/hr
- Use **Cis-atracurium IV continuous infusion 0.06-0.1 ml/kg/hr**
- Give intermittent **Fentanyl 0.5-1 mcg/kg/hr** according to anesthesiologist in charge
- If Depth of anesthesia is not adequate or brain is tight, you can use **Propofol 2-6 mg/kg/hr** according to anesthesiologist in charge
- Assess **Hematocrit before PRC transfusion**, PRC is transfused when Hct.<27%
- 4 hours after skin incision Aspirate blood from A-line **3 ml** into heparin tube for assess Mg level
(Aspirate from vein if no A-line)

Intraoperative hypotension	Intraoperative hypertension
SBP<90 mmHg or decrease <20% from baseline	SBP>140 mmHg or increase >20% from baseline
1. Fluid resuscitation or 2. Vasopressor according to anesthesiologist in charge	1. Increase Sevoflurane to 1 MAC wait for 5 min, if BP still high 2. Fentanyl 25 mcg not exceed 2 times, wait for 5 minute (total 10 mins) if BP still high 3. Propofol intermittent bolus or continuous drip if depth of anesthesia is not adequate 4. If depth of anesthesia is adequate, Nicardipine 0.2-0.4 mg in titration or Labetalol 2.5-5 in titration or Continuous drip according to anesthesiologist in charge

End of the case

- **Stop Study drug when dura was closure**
- Discontinue muscle relaxant at least 30 minute before operation finish
- **Record Intraoperative blood loss (Primary outcome)**

Reversal and Extubation

- **Use Glycopyrrolate 0.4 mg and Neostigmine 2.5 mg as reversal agents**
- If residual neuromuscular blocking effect is suspected, evaluate train of four before extubation
- Extubation when patients fully awake, open eyes and follow command
- **Record time when fully awake and extubation (Secondary outcome)**
- If remain intubation, please note the reason for remaining intubation

Step for sending lab investigation

- Send heparin tube to laboratory within 2 hours
- 8.00 am – 4.00 pm contact research officer
- After 6.00 pm contact Dr.Thanawut