The influance of intraoperative magnesium sulfate administration on postoperative morphine requirement in living donor during orthotopic liver transplantation

Thesis submitted for partial fulfillment of the MD degree in anaethesia

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Introduction

In 1989, the first successful living donor liver transplantation was performed. The donor is typically healthy individual therefore, minimizing post donation complications especially postoperative pain is very important. [1]

Adequate postoperative pain control is crucial to mitigate stress response, postoperative insulin resistance, and to reduce the incidence of postoperative chronic pain [2, 3].

A lot of recent trials emphasized that perioperative magnesium sulfate (MgSO4) infusion has general anesthetic properties that could reduce anesthetic drug consumption and postoperative analgesia requirements in several types of surgery. These effects mediated through its antinociceptive properties as a noncompetitive N-methyl-D-aspartate receptor antagonist [4, 5]. NMDA receptor antagonists give opiods the potential to have an analgesic effect and used widely as opiod adjuvant [6].

Magnesium is also known to antagonize the expression of inflammatory mediators (histamine, serotonin and cytokines) in peripheral tissues [7].

Optimal post-operative pain control is necessary for early mobilization, improved respiratory function and reduces incidence of deep venous thrombosis. Administration of multimodal analgesics could limit the excessive use of systemic opioid analgesia especially(morphine), which had a high rate of postoperative side effects as sedation, respiratory depression, ileus, nausea, vomiting, constipation, urine retention, and itching [8,9], Therefore, medications and adjuvant drugs reducing the need for opiods have become widely used as parts of multimodal analgesia.

Post-operative pain management begins with pre-operative planning and formulating a pain management plan that is tailored to an individual patient's liver function, respiratory and coagulation status, comorbidities and extent of resection [10].

Aim of the work

The aim of this study is to assess the effect of intraoperative use of magnesium sulfate in liver donating patients in reducing post-operative morphine requirements early postoperative 24 hour in adult living liver donor. Our hypothesis is that magnesium sulfate could be used to efficiently reduce postoperative morphine consumption in the early 24 hr postoperative as evident in other surgery types.

Patients and methods:

After ethical committee approval and written informed consent this prospective randomized control trial (double blind) study from both sexes undergoing right hepatotomy.

Inclusion criteria:

- Age (18-50).
- ASA physical state I or II.
- Normal liver functions, renal functions and serum electrolytes.

Exclusion criteria:

- Patients with impaired hepatic or renal functions.
- Various degree of heart block.
- Hypertension, Diabetes, Myopathy or any neurological disorder.

- History of long term opiod use, patients treated with calcium channel blockers and known allergy to drug used.
- Pregnant woman and obesity (BMI >30).

Patient preparations and anesthetic technique:

Patient will be randomly assigned to one of the two groups. The magnesium group (Group M) receives 40 mg/kg of magnesium sulfate in 100 ml of isotonic saline over 15 min immediately before induction of anesthesia and then 15 mg/kg/h by continuous I.V. infusion until the end of operation. Whereas patients in the saline group (Group S) receive the same volume of isotonic saline over the same period (placebo group).

An independent anesthesiologist who will not be participating in the study prepares the study medications.

Patients will be premedicated with tablet of alprazolam 0.25 mg the night before and 2 hours before surgery.

Upon arrival in operating room usual monitoring will be established including: heart rate, blood pressure electrocardiogram (ECG) and temperature.

After induction of anesthesia, arterial line will be inserted for continuous monitoring of blood pressure and frequent blood gas analysis and end tidal CO2(capneography) is attached.

General anesthesia will be administered using propofol 2 mg/kg , morphine 0.1 mg/kg and atracurium besylate 0.5 mg/kg followed by oral endotracheal intubation.

Maintenance of general anesthesia with a mixture of isoflurane and 50% oxygen in air, morphine 2 mg/h , mechanical ventilation will be

adjusted to keep SaO2 >95 % and end tidal Co_2 between 35 and 40 mmHg. Atracurium (0.15 mg/kg) will be administered every 30 min.

Baseline intravenous infusion rate of lactated ringers solution will be set at (6ml/ kg/h) in both group, additional solution will be infused if required.

Magnesium sulfate infusion and anesthetic agents will be discontinued at the end of operation.

Postoperative residual neuromuscular blockade will be reversed by using neostigmine 0.04 mg/kg and atropine 0.02 mg/kg.

Then the patient will be extubated and transfer topost anesthesia care unit(PACU) for 1hr observation.

Postoperative analgesia will be attained by using morphine titration protocol as follow, on patient request 3 mg i.v morphine injection administered(maximum 15 mg/4hr or 45mg/24hr).

Data for assessments:

Age, height, weight, sex, body mass index(BMI), duration of surgery and duration of anesthesia (from the time of induction to withdrawal of all anesthetics) will be recorded.

Mean arterial pressure (MAP) and heart rate (HR) will be measured at the following times before induction, before intubation and at 5, 15,30,60,90,120 min thereafter and in 30 min, 4, 24, 48 hours after surgery.

A postoperative rescue analgesia with intravenous morphine per a titration protocol (3 mg morphine sulfate IV as a bolus dose that could be repeated every 5 minutes

with a maximum dose of 15 mg per 4 hours or 45 mg per 24 hours) was employed if visual analog pain scale (VAS) ≥ 4. The morphine titration protocol will be suspended with Oxygen saturation < 95%; respiratory rate < 10 / min; the development of sedation (Ramsay sedation scale >2); development of acute adverse effects (allergy, marked itching, excessive vomiting, and hypotension with systolic blood pressure ≤ 20% of baseline values); or attaining adequate level of analgesia.

Total and interval morphine consumption at 30 min and at 4, 24 and 48 hours after operation will be recorded. If necessary rescue analgesia (ketorolac 30 mg) will be administered .Pain score using Visual analogue scale (VAS, starting from 0 – no pain to 10- worst pain) will be recorded at emergence from anesthesia and at 30 min ,4,24,48 hours after surgery.

Sedation will be assessed at 30min, 4,24, and 48 hours postoperatively on a 5-point sedation Ramsay's score[11](5, aroused only by shaking; 4, asleep, difficulty responding to verbal commands; 3, mostly sleeping but easily aroused; 2, drowsy or dozing intermittently; 1, awake). Over-sedation is defined as having a sedation score ≥ 4 combined with a respiratory rate < 8 breaths per minute. Patients with oversedation were transferred to the intensive care unit for close monitoring and observation, and patients with nausea and vomiting were treated by Ondansetron 0.15 mg/kg intravenously over 15 minutes.

Patient satisfaction levels will be reported using five point scale (1-very unsatisfactory, 5- excellent) 48hr postoperative.

In addition, opiod related adverse effects as shivering, nausea, vomiting, respiratory depression, somnolence, oversedation, itching, constipation, ileus and any other side effect will be also reported.

Blood samples for serum magnesium concentration determination will be obtained before and immediately after surgery.

Levels of IL6, IL8 and TNFα will be reported after 24hr postoperative.

Statistical analysis:

Statistical analysis will be done using "SPSS 19 for Windows" software. Data will be collected from all patients during and after anesthesia. Descriptive statistics (mean, standard deviation "SD", or median and ranges) will be calculated. Comparative statistics between the two groups will be applied. Unpaired t-test will be used to compare the mean values between the two groups. The Kolmogorov-Smirnov test was implemented to check the normality of continuous data distribution ($P \leq 0.05$) Mann-Whitney-U test will be used to compare the di□erence between the two groups for non parametric variables (e.g.VAS).While, Chi-square test will be used to compare the categorical variables between both groups. Signifcant result will be considered when P value was less than (0.05).

Sample Size:

Sample size calculations of this trial will be done upon the following assumption, $\alpha = 0.05$ $\beta = 0.2$, effect size will be =0.7.The effect size is calculated by using G*Power software version 3.1.9.2 (Institute of Experimental Psychology, Heinrich Heine University, Dusseldorf, German) we found 25 patients in each group have a power of 80% .We plan to recruit 30 patients per Group to account for possible dropout.

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