Effects of Intraoperative Magnesium Sulfate Administration on Postoperative Tramadol Requirement in Liver Transplantation: A Prospective, Double-Blind Study

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ABSTRACT

Background. Magnesium is an *N*-methyl-D-aspartate receptor blocker and is known to have analgesic effect. Hypomagnesemia can often be seen in liver transplantation and may be associated with higher morbidity and mortality. The objective of this study was to investigate the effects of intraoperative magnesium sulfate administration on postoperative tramadol requirement in liver transplant patients.

Methods. Liver transplant patients >18 years of age were screened prospectively from October 2014 to April 2015. Of these, 35 randomly selected patients with normal blood magnesium level (≥1.8 mmol/L) were included in a control group and another 35 randomly selected patients with low magnesium level (<1.8 mmol/L) were given 50 mg/kg intravenous magnesium sulfate replacement in the last 30 minutes of the operation. All patients received standard anesthesia induction and maintenance. Patient's age, sex, body mass index, Model for End-Stage Liver Disease and Acute Physiology and Chronic Health Evaluation II scores, 24-hour tramadol requirement, mechanical ventilation duration, and time of 1st tramadol need were recorded.

Results. In the magnesium group, mean 24-hour total tramadol requirement (3.7 mg/kg/d) and duration of mechanical ventilation (6.3 h) were significantly lower and time of 1st tramadol need (17.5 h) was significantly higher than in the control group ($P < .001$ for each). In the multivariate analysis, duration of mechanical ventilation was decreased by the usage of magnesium sulfate ($P < .001$).

Conclusions. Intraoperative use of magnesium sulfate in liver transplantation reduces the need for postoperative tramadol and duration of mechanical ventilation and therefore it is a candidate to be adjuvant agent.

HYPOMAGNESEMIA can be observed in end-stage liver disease because of malnutrition, malabsorbtion, and the usage of diuretics [1,2]. It is known that hypomagnesemia in liver transplantation (LT) is associated with citrate accumulation due to blood transfusion and magnesium chelation in the anhepatic phase [1,3]. Because hypomagnesemia is related to morbidity, mortality, organ dysfunction, pulmonary hypertension, and systemic inflammatory response syndrome (SIRS) in critically ill patients [4–6], it is important that hypomagnesemia should be fixed at the time of LT. In energy metabolism, magnesium is the cofactor of all enzymes in their phosphate transfer reactions [7]. Also, magnesium is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist and has been linked as the cause of pain and inflammatory response modulations [8–10]. NMDA receptor antagonists prevent evoked central sensitization and peripheral nociceptive stimulation [8–11]. In the preanesthesia

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Table 1. Demographic Data and Outcomes

Variable	Control ($n = 35$)	Magnesium ($n = 35$)	*P* Value
Age (y)	48 ± 4.9	49 ± 4.0	.681
Male, *n* (%)	27 (77.1)	26 (74.3)	.780
BMI (kg/m^2)	26.9 ± 1.6	26.0 ± 1.7	.418
MELD score	13.3 ± 0.6	13.7 ± 0.6	.512
APACHE II score	11.6 ± 0.8	12.0 ± 0.8	.473
Magnesium level (mmol/L)	2.2 ± 0.03	1.7 ± 0.04	<.001
Operation duration (h)	9.9 ± 0.8	10.2 ± 0.8	.601
Duration of MV (h)	10 ± 0.9	6.3 ± 0.9	<.001
Length of ICU stay (h)	21.1 ± 1.1	22.0 ± 1.4	.578
Length of hospital stay (d)	17.2 ± 1.1	17.4 ± 0.7	.749

Abbreviations: BMI, body mass index; MELD, Model for End-Stage Liver Disease; APACHE, Acute Physiology and Chronic Health Evaluation; MV, mechanical ventilation; ICU, intensive care unit.

induction period, it was shown that in non-LT patients, the need for intraoperative anesthesia and analgesia and postoperative mechanical ventilation period were decreased by administering intravenous (IV) magnesium sulfate [11–13]. The purpose of the present study, therefore, was to investigate the effects of the use of intraoperative IV magnesium sulfate in liver transplant patients and how it is related to postoperative analgesia requirement and outcome.

METHODS

Study Design

The study, which was approved by the local Ethics Committee, was designed as prospective double-blind. From October 2014 to May 2015, 70 liver transplant patients who were ≥18 years old with operation duration of 10–12 hours and clamping duration of <80 minutes were included in the study. To detect a decrease of 0.4 mg/kg/d (10%) of the 24-hour tramadol requirement (accepting an alpha error of 5% and beta error of 10%), the required study size was 35 patients per group.

Patients <18 years of age, not consenting, with known allergy to magnesium, diagnosed with hepatorenal syndrome, with serum creatinine level of >1.2 mg/dL, requiring preoperative and/or postoperative high-dose sympathomimetic support (using >10 μg/kg/min dopamine or adrenaline infusion), or using analgesic, sedative, or muscle relaxant medication other than tramadol in the postoperative period were excluded. A standard general anesthesia induction (1.5 μg/kg fentanyl, 2 mg/kg propofol, and 0.6 mg/kg rocuronium bromide) and maintenance (minimum alveolar concentration 0.7% sevorane, 0.05–0.25 μg/kg/min remifentanil, and 0.15 mg/kg/h rocuronium bromide) was used on all patients. Magnesium sulfate, 50 mg/kg IV [14], was administered in the last 30 minutes of operation to the patients whose level of serum magnesium 5 minutes after reperfusion was <1.8 mmol/L. Placebo infusion was administered to the patients with ≥1.8 mmol/L serum magnesium. Magnesium levels and given infusions were not known by the intensive care unit (ICU) team. All patients were taken intubated to the ICU in the postoperative period and received IV tramadol (0.2 mg/kg IV bolus and 0.15 mg/kg/h infusion) for postoperative analgesia. In the 1st 24 hours, hourly visual analog scale (VAS) was made by the intensive care nurses who were not familiar with the group assignments. Additional 0.2 mg/kg IV tramadol was administered when VAS was >3. Age, sex, body mass index (BMI), Model for End-Stage Liver Disease (MELD) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores, duration of mechanical ventilation (MV), length of ICU stay (LOS-ICU), length of hospital stay (LOS-hospital), 24-hour total tramadol requirement, and time of the 1st additional tramadol use for the patients were recorded by the intensivist team.

Serum Magnesium Measurements and Limits

Blood samples were stored in a vacuum tube with silica gel. A Siemens Dimension device that used a modified methylthymol blue complexometric procedure was used to determine serum magnesium level. Normal serum magnesium level was 1.8–2.4 mg/dL.

Statistical Analysis

The characteristics of patients were summarized with the use of mean, SD, median, interquartile range, and range; categoric variables were summarized with the use of count and percentage. Continuous variables were compared with the use of Mann-Whitney *U* test; categoric variables were compared with the use of chi-square or Mantel-Haenszel test.

Multivariate linear regression model was used to evaluate the effect of variables such as age (y), BMI, MELD score, APACHE II score, operation duration, and the use of magnesium (g) on the following variable of MV duration. Type 1 error was set at 0.05. Analyses were performed with the use of Wizard Pro version 1.7.17(150).

RESULTS

In both groups, age (y), sex (male), BMI (kg/m^2), operation duration (h), MELD score, APACHE II score, LOS-ICU (h), and LOS-hospital (d) were similar ($P > .05$ for each). In the magnesium group, mean 24-hour total tramadol requirement (3.7 mg/kg/d) and duration of MV (6.3 h) were significantly lower and time of 1st tramadol need (17.5 h) was significantly higher than in the control group ($P < .001$ for each; Tables 1 and 2). There were positive correlation of duration of MV with 24-hour tramadol requirement and LOS-ICU ($r^2 = 0.14$ [$P = .002$]; $r^2 = 0.17$ [$P < .001$]; respectively). However, there was a negative correlation of duration of MV with the time of 1st tramadol need and the use of magnesium ($r^2 = 0.31$ [$P < .001$]; $r^2 = 0.28$ [$P < .001$]; respectively; Fig 1).

Multivariate Linear Regression Model

Age, BMI, MELD and APACHE II scores, and operation duration did not have any impact on the duration of MV ($P > .05$ for each). According to this model, duration of MV was decreased by the use of magnesium ($P < .001$; Table 3).

Table 2. Postoperative Tramadol Requirements in Both Groups

Variable	Control ($n = 35$)	Magnesium ($n = 35$)	*P* Value
24-hour total tramadol requirement (mg/kg/h)	4.1 ± 0.07	3.7 ± 0.05	<.001
Time of 1st tramadol need (h)	3.2 ± 0.7	17.5 ± 2.5	<.001