

Magnesium Supplementation During Liver Transplantation

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Citation

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Abstract

Patients undergoing liver transplantation are prone to hypomagnesemia, with potential deleterious effects. This prospective observational study evaluated the efficacy and safety of routine intraoperative magnesium supplementation to prevent hypomagnesemia. Perioperative serum magnesium levels and electronic anesthesia records of 218 orthotopic liver transplant patients were recorded and analyzed. Data included patient demographics, magnesium dose, blood products infused and cardiac rhythm. The results showed lower prevalence of postoperative hypomagnesemia in patients administered magnesium supplementation compared to patients without supplementation, despite low preoperative serum levels ($p=0.03$). For patients without supplementation, a high preoperative level prevented hypomagnesemia. A magnesium dose of 3g effectively prevented hypomagnesemia. Magnesium supplementation was associated with 20% risk of mild hypermagnesemia. The prevalence of persistent arrhythmias was 27% and was not higher in hypomagnesemia. The study concludes that routine intraoperative magnesium supplementation reduces the occurrence of postoperative hypomagnesemia, but may not affect the occurrence of arrhythmias.

This work is attributed to the Departments of Anesthesiology and Surgery, University of Michigan, Ann Arbor, USA.

INTRODUCTION

Magnesium (Mg) is an important electrolyte that plays a key role in numerous physiological processes and in the pathophysiology of many diseases. The ionized fraction is the physiologically active form, and less than 1% of total body magnesium is present in circulating blood ¹. Serum magnesium exists in ionized (62%), protein-bound (33%) and anion-complexed (5%) forms.

Hypomagnesemia is common in surgical, and critically ill patients; with the prevalence as high as 20% ². It causes cardiovascular, neuromuscular and coagulation dysfunctions; and is associated with increased inflammatory response and mortality ^{3, 4}. Hypomagnesemia is common following cardiac, major gastrointestinal and liver transplant surgery ^{5, 6, 7}. Total hypomagnesemia invariably occurs during orthotopic liver transplantation (OLT) mostly because of transfusion-related citrate toxicity and chelation of magnesium during the anhepatic phase ^{8, 9}. Therefore, magnesium supplementation is recommended during OLT ^{8, 9, 10}. In response to the observation of significant perioperative hypomagnesemia associated with arrhythmias

in our OLT patients, we adopted the practice of magnesium supplementation during OLT in our hospital over the last 2 years.

This prospective observational study aimed to evaluate the efficacy and safety of intraoperative magnesium supplementation in the prevention of perioperative hypomagnesemia following orthotopic liver transplantation. The study also examined the influence of intraoperative transfusion and preoperative serum magnesium levels on the occurrence of hypomagnesemia in these patients.

MATERIALS AND METHODS

Following institutional approval, we conducted a prospective observation of the perioperative records of patients who underwent cadaveric OLT at the adult hospital of our tertiary institution, between February 2001 and January 2006. The electronic laboratory results of each patient were recorded, especially the immediate pre-transplant and post-transplant serum ionized magnesium levels. The post-transplant magnesium levels were checked at the end of surgery or upon arrival in the recovery room. The normal range of serum ionized magnesium was defined as 1.5 to 2.3mg/dl.

The electronic intraoperative records, including the Centricity anesthesia information system (Centricity, GE Technologies, Waukesha, WI) were also analyzed. The data

analyzed included patient demographics, the dose of intraoperative magnesium supplementation administered, the volume of magnesium-containing crystalloids administered, type of prevalent cardiac rhythm, amount of blood components transfused, prevalence of hypocalcaemia, and urine output.

The standardized anesthesia protocol used for the patients consisted of propofol-suxamethonium induction and isoflurane-fentanyl-atracurium maintenance. Rapid IV infusor, cell-saver and heating devices were used. Calcium was infused at 1g/hr and additional doses titrated to maintain normal serum ionized levels. Packed red blood cells were infused to maintain haematocrit above 25% and fresh frozen plasma was infused to maintain an international normalized ratio below 1.7. Platelets were infused to maintain the platelet count above $70 \times 10^9/L$. Cryoprecipitate infusion was indicated at fibrinogen level less than 150mg/dl. Clinical fibrinolysis, indicated by diffuse non-surgical haemorrhage, was treated with epsilon-aminocaproic acid infusion.

According to hospital protocol, magnesium supplement was infused intraoperatively to patients without preoperative hypermagnesemia or contraindications such as heart block. A dose of 2-grams of magnesium was infused after anesthesia induction and additional doses of 1-gram were infused to treat persistent arrhythmias or hypomagnesemia especially during massive blood transfusion or the anhepatic phase when citrate toxicity and magnesium chelation is most likely to occur.

Data analysis was performed using SPSS v.13 (SPSS, Chicago, IL). Pearson's Chi-Square test and Fisher's Exact test were used to analyze group comparisons. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 218 orthotopic liver transplant cases were reviewed and analyzed. The demographics of the study sample are presented in Table 1.

Figure 1

Table 1

Age	Number of cases	Percentage
13-17 years	9	4.1
18-64 years	195	89.4
65-71 years	14	6.4
Gender	Number of cases	Percentage
Male	148	67.9
Female	70	32.1

The prevalence of postoperative ionized hypomagnesemia was similar in all age groups. About 22% of the adolescents, 27.6% of adults, and 28.6% of the elderly patients developed postoperative hypomagnesemia. Preoperative serum magnesium levels were low (<1.5mg/dl) in 9 patients or 4%, normal (1.5-2.3mg/dl) in 188 patients or 86%, and high (>2.3mg/dl) in 21 patients or 10%. Twenty percent of patients (n=45) received magnesium supplementation. The overall prevalence of postoperative hypomagnesemia in patients administered magnesium supplement was 10.3%, compared to 31.3% in patients without supplement ($p=0.009$). Analysis of serum magnesium levels revealed a significantly lower prevalence of postoperative hypomagnesemia in patients administered magnesium supplement, despite low preoperative serum magnesium: $p=0.03$ (Table 2).

Figure 2

Table 2

Preoperative Magnesemia	Intraoperative supplement	% Prevalence postop. hypomagnesemia
Low	Supplementation	10
	None	100
Normal	Supplementation	11
	None	30

$p=0.03$
 $p=0.03$

For patients without magnesium supplementation, a preoperative serum ionized magnesium <2mg/dl was associated with a 46.8% prevalence of postoperative hypomagnesemia, while a high serum level >2.3mg/dl was not associated with postoperative hypomagnesemia: $p=0.002$ (Table 3).

Figure 3

Table 3

Preoperative magnesemia	% Prevalence postop. hypomagnesemia	
<2mg/dl	46.8	
≥2mg/dl	4.6	<i>p</i> =0.001
≤2.3mg/dl	34.6	
≥2.4mg/dl	0	<i>p</i> =0.002

The total dose of intraoperative magnesium administered in 69% of supplemented patients (n=29) was 2g; and the remaining 31% (n=16) received 3g or more. A dose of 2g was associated with a 30% incidence of postoperative hypomagnesemia, whereas a dose of 3g was not associated with hypomagnesemia (Table 4).

Figure 4

Table 4

Magnesium dose	% Prevalence postop. hypomagnesemia	
<2g	31.3	
≥2g	8.3	<i>p</i> =0.004
<2.9g	29.2	
≥3g	0	<i>p</i> =0.02

Patients who received intraoperative magnesium had a higher prevalence of postoperative hypermagnesemia, compared to patients without supplementation (20% vs 1.7% respectively, *p*=0.0001). However, no patient had severe hypermagnesemia (>3mg/dl) or associated clinical complications of cardiovascular depression. Following supplementation, serum magnesium increased by 27% in patients who developed postoperative hypermagnesemia, and by 12.2% in other patients: *p*=0.003. The degree of elevation was 11% in patients administered ≤2g of magnesium and 14% in patients administered >2g: *p*=0.013. There were no reported complications during intravenous magnesium administration, such as cardiovascular depression.

The overall prevalence of frequent or persistent perioperative arrhythmias was 27% and there was no statistical difference between the hypomagnesemia, hypermagnesemia or normal magnesemia groups. Despite infusion and bolus administration of calcium, persistent perioperative hypocalcaemia occurred in 40% of patients and did not correlate with magnesemia state.

There was no significant association between the amount of hemoderivatives transfused intraoperatively and the frequency of postoperative hypomagnesemia in the OLT patient population studied (*p*=0.5). All adult patients were infused with 1-2 liters of Normosol®-R (Hospira, Lake Forest, IL), a crystalloid solution containing 300mg of magnesium per liter. Normosol®-R was the standard solution used for priming the rapid IV infusor.

DISCUSSION

Patients with end-stage liver disease (ESLD) are prone to hypomagnesemia as a result of malnutrition, malabsorption, diarrhea, secondary hyperaldosteronism and diuretic treatment^{9, 11}. Although only 3.7% of our patients had low preoperative serum ionized magnesium levels, most of the patients had normal values which in the absence of magnesium supplementation, increased their risk of perioperative hypomagnesemia significantly. This finding suggests that despite normal preoperative magnesium levels, OLT patients are at a significant risk of postoperative hypomagnesemia.

Magnesium supplementation is indicated during OLT to prevent the deleterious effects of hypomagnesemia and to produce many beneficial effects of magnesium such as coronary vasodilation, reduced dysrhythmias, reduced afterload, sympatholysis, reduced reperfusion injury, improved coagulation, neuromodulation, bronchodilation, reduced inflammatory response, and efficient energy metabolism^{1, 4, 10, 12}. Our study revealed significant prevention of postoperative hypomagnesemia following intraoperative magnesium supplementation despite low preoperative serum level. However, hypomagnesemia still occurred in 10% of supplemented patients all of whom received a dose of 2g. This may be related to post-transplant fluid and magnesium shifts between body compartments, and may also reflect the fact that only 1% of total body magnesium exists in circulating blood.

Hypomagnesemia was effectively prevented with supplemental dose of 3g, and despite varied recommendations on magnesium therapy, this indicates that a dose of 3g may be adequate for most OLT patients without high preoperative serum magnesium levels. However, this dose or mode of supplementation may not apply to all OLT patients. Further experience and studies are required to ascertain the optimal dose range of magnesium supplementation in adult OLT patients. The best mode of supplementation is titrated replacement based on serum

ionized magnesium monitoring especially during the anhepatic phase and massive transfusion. However, many hospitals do not or are unable to monitor serum ionized magnesium intraoperatively.

Our study revealed that only patients with high preoperative magnesium level may not require intraoperative supplementation. Although this sub-group constitutes less than one-tenth of the patients; nonetheless it is advisable to withhold routine supplementation from them in order to prevent hypermagnesemia. It is possible that the postoperative hypermagnesemia that was observed in 20% of supplemented patients may be due to incomplete equilibration with other body compartments. Ionized and total magnesium levels increase proportionally with supplementation, but the serum ionized level may not always correlate with other tissue stores ².

Hypermagnesemia can be problematic if severe (>3mg/dl). Severe hypermagnesemia can exert an anti-calcium effect on the cardiovascular system, causing vasodilatation, which is deleterious during reperfusion. Furthermore, cerebral vasodilatation may be unfavorable in encephalopathic patients. However, none of our patients who were administered magnesium supplementation developed severe hypermagnesemia, and the patients who developed mild hypermagnesemia (2.4-3mg/dl) did not have significant cardiovascular depression. We support the recommendation that monitoring of serum ionized magnesium should be conducted during magnesium supplementation ^{7, 8, 9, 11}. However, magnesium monitoring is expensive and not always immediately available ². Therefore, it may be cheaper, easier, quicker and relatively effective to administer appropriate intraoperative supplementation to patients without high preoperative serum magnesium levels. This method is also relatively safe and does not cause severe hypermagnesemia. Moreover, magnesium levels usually continue to fall for more than 24 hours following OLT and major abdominal surgery ⁵.

Although persistent or frequent arrhythmias were observed in 27% of patients, the occurrence was not significantly higher in hypomagnesemic patients. This may be due to the fact that the degree of hypomagnesemia was not severe enough in most of the patients. Furthermore, occurrence of arrhythmias depends on other factors including acid-base balance, intravascular volume status, temperature, and levels of many electrolytes.

Contrary to previous reports ¹¹, our study failed to show a

significant correlation between hypomagnesemia and massive transfusion. This may be due to intraoperative magnesium supplementation, and it is possible that patients who received massive transfusion were hypomagnesemic during the anhepatic phase from citrate overload. However, it is known that major abdominal surgery without massive transfusion causes hypomagnesemia ⁶. Although all our adult patients received additional 300-600mg of magnesium via the Normosol®-R infusion, this dose has been shown to be inadequate in preventing hypomagnesemia following abdominal surgery^{5, 6}.

In conclusion, this retrospective study confirms that postoperative hypomagnesemia is a frequent finding immediately following OLT, even in patients with normal preoperative magnesemia. However, there appears to be minimal clinical consequences of perioperative hypomagnesemia. Routine magnesium supplementation significantly reduces the occurrence of postoperative hypomagnesemia compared to no supplementation, but did not change the incidence of arrhythmias. Supplementation was associated with a 20% incidence of mild hypermagnesemia, but without clinical complications. From the presented data, it is unclear if routine magnesium supplementation for OLT is an appropriate approach for intraoperative electrolyte management during OLT, and if and how it would affect outcome. Further studies and clinical reports are required.

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