CHANGES OF SERUM MAGNESIUM AND PHOSPHATE CONCENTRATIONS DURING AND AFTER HEPATIC RESECTIONS FOR CIRRHOTIC PATIENTS

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ABSTRACT

A prospective study to evaluate alternations in serum concentrations of total magnesium (TMg), ionized magnesium (iMg), inorganic phosphorus (PO₄), lactic acid (LA), aspartate aminotransferase (AST), alanine aminotransferase (ALT) during and after liver resections in liver cirrhotic patients and their inter-relationships. Twenty-five patients were included with Child-Pugh's B classification. Samples were taken before anesthesia induction, during liver resection, thirty minutes after resection and reperfusion and daily for 3 days. TMg was adjusted for albumin concentration. Mg and PO₄ supplementations were not given intraoperatively except for the magnesium found in the normal composition of Plasmalyte A, a multiple electrolyte fluid composition of pH 7.4 (6.5-8) used for volume replacement. Results showed a significant decline in TMg, iMg and PO₄ during liver resection (p=0.005 p= 0.008 p=0.068 respectively) and after resection (p=0.005 p=0.005 p=0.021 respectively). The decline of TMg exceeded the decline of iMg to below the normal laboratory reference ranges intraoperatively and postoperatively on day 1 in 15 patients. TMg correlated positively with iMg (r=0.55 p=0.01). Significant perioperative increase in LA, AST and ALT (p<0.05) were observed with a gradual decreased on day2 and 3. LA correlated positively with both AST and ALT (r=0.54, p<0.01 and r=0.53, p<0.01, respectively) but negatively with both TMg and iMg (r=-0.31, p=0.01, r=-0.22, p=0.09). Hypoalbuminaemia was frequently reported among this population. In conclusion total magnesium over estimated the incidence of hypomagnesaemia when significant hypoalbuminemia is present, ionised magnesium should be used instead. Intra-operative and post-operative hypophosphataemia occurs frequently. Monitoring and intravenous replacement is hence recommended. Lactate could be used as an indirect indicator for liver function. Possible preventive measures need to be investigated in future studies.

INTRODUCTION

Liver resection induces a derangement of liver function that persist for several days or weeks depending on the size of resection. Several studies reported significant electrolyte blood changes particularly among magnesium and phosphorus as a result of the liver resections. Severe hypophosphataemia has been reported postoperatively after major liver resections, but few studied the intra-operative changes during and immediately after the surgical procedure of the resection. Magnesium is the fourth most common mineral salt in the human body and the second among intracellular cations. It is involved in the regulation of different ion channels and phosphorylation reactions, and serves as a cofactor in many enzymatic systems within the liver. In serum magnesium exists in three fractions: protein-bound, complex bound and free ionized magnesium. Only the free ionized fraction is biologically active.

The aim of this prospective study is to evaluate the alternations in serum concentrations of total magnesium (TMg), ionized magnesium (iMg), inorganic phosphorus (PO₄), lactic acid (LA), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and albumin during and after hepatic tumour resections in patients suffering from liver cirrhosis due to viral hepatitis and their inter-relationships.

PATIENTS AND METHODS.

Twenty-five adult patients (ASA-II-III) were included with Child-Pugh’s B classification. Following Ethics Committee approval and
informed consent arterial blood samples were taken preoperatively before general anaesthesia induction, during liver resection, thirty minutes after completion of resection and reperfusion and daily for 3 days. Serum TMg (ref. range 0.65-1.05 mmol/l) and PO4 (ref. range 0.87-1.45) were measured with the use of a colorometric method by Advia 1650 analyser (Bayer Diagnostic) and corrected for albumin, while the iMg (ref.range 0.45-0.65 mmol/l) was measured by an ion selective electrode analyzer, AVL 988-4 (Roche Diagnostics). Reference ranges were adjusted for albumin concentration. TMg was adjusted for albumin concentration (35-45 g/l). Lactic acid (LA) was measured with an enzymatic method by Advia 1650 analyser (Bayer Diagnostic). Mg and PO4 supplantations were not given intraoperatively except for the magnesium in the normal composition of the Plasmalyte A crystalloid infusion used for the intraoperative fluid replacement. Plasmalyte A is a multiple electrolyte fluid of a pH of 7.4 (6.5-8) and osmolarity of 294 mOsmol/L. Plasmalyte A is composed of Sodium 140 mEq/L, Potassium 5 mEq/L, Magnesium 3 mEq/L, Chloride 98 mEq/L, Acetate 27 mEq/L and Gluconate 23 mEq/L. Human plasma protein solution 5% and blood products were used when necessary. General anaesthesia was induced with Propofol 2mg/kg, Rocuronium 0.6 mg/kg and fentanyl 1 microgram/kg. Sevoflurane and mixed air/oxygen were used for maintenance. Intraoperative incremental doses of muscle relaxants guided by peripheral nerve stimulation as well as repeated doses of fentanyl was used to mainataine a state of balance anaesthesia and analgesia during the surgery. Postoperative pain was controlled by the use of intravenous morphine patient controlled analgesia (PCA) regimes. The postoperative patient pain control status was followed and the parameters of the PCA adjusted to provide the best pain control status. A left radial artery cannule was also inserted for monitoring the systemic blood pressure invasively. The central venous pressure was kept near to 5 cmH2O with monitoring and intravenous fluid replacement. Elective hepatic vascular occlusion was applied during the surgical procedure. Collected data also includes operative time, urine out put, blood loss and both crystalloid and blood transfusion requirements. Data presented as median [interquartiles] for statistical analysis by Wilcoxon-Signed Ranked test, using the SPSS computer software (SPSS 10 for Window; SPSS Inc., Chicago, IL). A p value of <0.05 was considered to be statistically significant.

RESULTS.

Twenty five patients were involved with male : female ratio 17:8 and median age of 53 [38.5-55.7] years. Major to minor liver resections ratio was 16:9. The median operative time was 4[3-7.5] hours. Viral hepatitis constituted the main cause for the liver cirrhosis for most of the patients with hepatitis C constituting the majority. Twenty one patients suffered from cirrhosis of the liver as a result of viral hepatitis, while the remaining four patients had mixed schistosomiasis and hepatic C. The blood concentrations of TMg, iMg and PO4 decreased during liver resection (p=0.005, p=0.008, p=0.68 respectively) and afterwards (p=0.005, p=0.005, p=0.021 respectively) as shown in table 1. The decline of TMg exceeded the decline of iMg to below normal laboratory reference ranges intraoperatively and postoperatively on day 1 in 15 patients. TMg correlated positively with iMg (r=0.55, p=0.001). Postoperatively on day 1 the significant decline in TMg and PO4 required intravenous repletion of magnesium and phosphate for 15 patient. Significant perioperative increase in LA, AST and ALT (p<0.05) were observed with a gradual decreased on day2 and 3 as shown in tables 1 and 2. LA correlated positively with both AST and ALT (r=0.54, p<0.01 and r=0.53, p<0.01, respectively) but negatively with both TMg and iMg (r = -0.31, p=0.01, r = -0.22, p=0.09). Preoperative hypo-albuminaemia was frequently reported among this population 25.5 [23.7-28.5] g/l. Haemoglobin concentration dropped from 11.4[10.9-13.07] to 9.85[9.3-10.42], (p=0.007) with a median Blood loss of 400[200-500] and a median blood transfusion requirement of 1.5 unit. During surgery the median crystalloids infusion was 2250[2000-5187] mls with median urine out put of 1025[737-1140] mls.
Table (1): Perioperative blood concentrations of total magnesium, ionised magnesium, lactate and phosphate.

<table>
<thead>
<tr>
<th></th>
<th>TMg (mMol/L)</th>
<th>iMg (mMol/L)</th>
<th>LA (mMol/L)</th>
<th>PO₄ (mMol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperatively</td>
<td>0.66 [0.61–0.73]</td>
<td>0.58 [0.53–0.65]</td>
<td>1.43 [1.27–1.93]</td>
<td>1.03 [0.90–1.20]</td>
</tr>
<tr>
<td>Middle</td>
<td>0.59 [0.56–0.63]*</td>
<td>0.54 [0.47–0.57]*</td>
<td>1.95 [1.75–2.31]*</td>
<td>1.11 [0.95–1.17]</td>
</tr>
<tr>
<td>After</td>
<td>0.56 [0.53–0.60]*</td>
<td>0.50 [0.43–0.53]*</td>
<td>2.40 [2.12–3.58]*</td>
<td>0.89 [0.82–1.01]*</td>
</tr>
<tr>
<td>Day 1</td>
<td>0.51 [0.41–0.59]*</td>
<td>0.49 [0.42–0.51]*</td>
<td>2.07 [1.80–2.62]*</td>
<td>0.63 [0.49–0.70]*</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.59 [0.54–0.65]*</td>
<td>0.50 [0.45–0.60] *</td>
<td>1.70 [1.48–2.20]</td>
<td>0.79 [0.70–0.81]*</td>
</tr>
<tr>
<td>Day 3</td>
<td>0.66 [0.55–0.67]</td>
<td>0.50 [0.48–0.56]</td>
<td>1.17 [1.08–1.82]</td>
<td>0.89 [0.79–1.10]</td>
</tr>
</tbody>
</table>

Data presented as median [interquartiles]. *Significant (P < 0.05) when compared to preoperative values. Middle = Middle liver resection; After = 30 minute after liver resection and reperfusion; TMg = Total Magnesium; iMg = Ionised magnesium; LA = Lactate; PO₄ = Phosphate.

Table (2): Perioperative blood concentrations of aspartate aminotransferase, alanine aminotransferase and serum albumin.

<table>
<thead>
<tr>
<th></th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
<th>ALBUMIN (g/l)</th>
</tr>
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<tbody>
<tr>
<td>Preoperatively</td>
<td>21.5 [19.0-29.0]</td>
<td>24.0 [20.0-40.0]</td>
<td>25.5 [23.7-28.5]</td>
</tr>
<tr>
<td>Day 1</td>
<td>257.0 [211.0-376.0]*</td>
<td>367.0 [263.0-464.0]*</td>
<td>24.2 [22.4-26.9]</td>
</tr>
<tr>
<td>Day 2</td>
<td>149.0 [91.0-183.0]*</td>
<td>210.0 [172.0-293.0]*</td>
<td>24.7 [23.1-27.4]</td>
</tr>
<tr>
<td>Day 3</td>
<td>58.0 [34.0-89.0]*</td>
<td>89.0 [67.0-116.0]*</td>
<td>25.2 [21.9-27.8]</td>
</tr>
</tbody>
</table>

Data presented as median [interquartiles]. *Significant (P < 0.05) when compared to preoperative values. AST = aspartate aminotransferase; ALT = Alanine aminotransferase; ALBUMIN = Serum Albumin.

**DISCUSSION**

A significant decrease in magnesium blood concentration was reported previously in several studies during the peri-operative period of most abdominal and orthopedic surgery. Few studied intraoperative and immediate postoperative blood concentration changes of magnesium. One study by Kuplman et al involving only seven patients undergoing liver resection came to the conclusion that both total and ionized magnesium declined during and after the surgery, the results of our current research agree with this finding and with the conclusion that monitoring and replacement is essential in this population of patients. In our study group patients, the blood transfusion requirements were low and hence can not be considered as a source for citrate as is the case during massive blood transfusion, where citrate overload could be considered as a chelating agent for magnesium and calcium as well. The reason behind the drop of magnesium during and after liver resection seems to be multi-factorial and can involve many factors such as the stress response. This disorder is often overlooked, although it should probably be searched for systematically because of it’s significance for the prognosis of the patients.

Hypophosphataemia can develop after major liver resection for tumour resection, as reported by the George and Shiu retrospective study. The mechanism by which phosphorus in blood decreases after major surgery have not been elucidated, but several studies suggest that the rapid changes of the extracellular phosphorus pool are probably related to a complex interplay.
of various factors, including phosphate flux into the liver for regeneration and energy metabolism and movement into skeletal muscle, under the effect of stress related hormones like insulin, glucagons, and cytokines. We agree with George and Shiu study that the extraordinary regenerative state after major resections and the biochemical derangements that commonly occurs after these surgeries make these patients prone for acute hypophosphataemia and hence the recommendation that serum phosphorus concentration need to be frequently checked and replaced. Liver resection involving ischemic / reperfusion injury because of the temporary hepatic vascular clamping (Pringle technique) as shown by several studies lead to a local and systemic complex inflammatory process and an associated release of various stress related hormones and endogenous interleukins, this leads to a metabolic milieu favoring an increase in cellular phosphorus uptake with the consequent development of hypophosphataemia.

Sharp increases in blood concentration of several biochemical parameters such as LA, AST and ALT were observed intraoperatively and in the immediate postoperative period, reflecting a degree of transient impairment in metabolic liver function as a result of liver transection and the depressant effect of anaesthesia and surgery on hepatic function. A slow normalization postoperatively could be taken as an indication of hepatic tissues recovery or it’s ability to regenerate. A study by Kato M et al study concluded that the induction of ischaemia to the liver tissues by the Pringle's maneuver during liver resection in cirrhotic patients leads to an increase in blood concentrations of lactic acid, with a subsequent decrease postoperatively after reperfusion. Our results were in line with the above study, in addition to our finding of a negative correlation between the decline in magnesium serum concentrations both total and ionized and the increase in serum lactic acid concentration. This correlation need to be studied and the mechanism behind to be explored further. The reduction in hepatic function as a results of the trauma from the liver resection procedure leads to an increase in lactate as well as citrate in the blood due to the reduction in their metabolism by the liver cells. This increase in citrate load during liver resection as shown by Kulpmann et al study can lead to a decrease in both magnesium and calcium due to its chelating effect to both, this increase in citrate load was found even in cases when no citrate was administered to the patients in the form of blood transfusions.

From another prospective it is well known that magnesium correlates with several important enzymes utilizing high-energy phosphate bonds, as in case of glucose metabolism which is mainly situated in liver cells. This is shown in Sanders et al study where intracellular magnesium deficiency and hypomagnesaeemia were found to correlate with the impaired function of many hepatic enzymes utilizing high energy phosphate bonds. Magnesium is known to activate most of the enzymes involved in energy metabolism and may be a rate-limiting factor in oxidative phosphorylation.

In conclusion total Magnesium over estimated the incidence of hypomagnesaemia when significant hypoalbuminemia is present, ionised magnesium should be used instead. Intra-operative and postoperative hypophosphataemia occurs frequent-ly. Monitoring and intravenous replace-ment is hence recommended. The causes of hypophosphataemia and hypomagnes-aemia are mutifactorial. Further investiga-tions are needed to correlate the different contributing factors. Lactate could be used as an indirect indicator for liver function both during and after liver resection. Possible preventive measures need to be investigated in future studies.

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REFERENCES


