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Ionized calcium changes during living-donor liver transplantation in patients with and without administration of blood-bank products

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Abstract Exogenous citrate load from blood transfusion during orthotopic liver transplantation is thought to be the main cause of ionized hypocalcemia, which may result in hemodynamic instability. This implies that if no blood is transfused, chelation of free ionized calcium (Ca^{++}) by citrate is avoided and supplemental calcium need not be given. For this study, we divided 39 pediatric living-donor liver transplant patients into two groups according to the blood component replacement given: group I received packed red blood cells and fresh frozen plasma with and without 5% albumin, and group II received 5% albumin alone. The intra-operative serial ionized calcium level was recorded, and the amount of calcium chloride replacement to maintain acceptable blood Ca^{++} levels was compared between the groups. The mean serum ionized calcium level changes of both groups could be maintained within lower-to-normal limits intra-operatively. The amount of supplemental calcium chloride required to correct the hypo-ionized calcium was not significantly different between the groups. We can conclude that if an exogenous citrate load is eliminated by the avoidance of blood transfusion and 5% albumin infusion is used, instead, to replace the blood and ascites loss during OLT, the risk of ionic hypocalcemia still persists. Serum Ca^{++} monitoring and adequate replacement are, therefore, still required in this setting.

Keywords Liver surgery · Transplantation · Anesthesia · General · Monitoring · Serum ionized calcium · Transfusion · Blood-bank products · 5% Albumin

Introduction

Low ionized calcium and high citrate levels in the blood are common findings during orthotopic liver transplantation (OLT) [4, 9, 12, 14, 15]. Exogenous citrate load following transfusion with banked blood products during OLT is thought to be the main cause of ionized hypocalcemia. Serum ionic calcium (Ca^{++}) is, therefore, routinely monitored in liver transplantation. Failure of serum Ca^{++} levels to be checked and corrected intra-operatively may lead to citrate intoxication and hemodynamic instability [14]. Cardiac arrest induced by severe ionic hypocalcemia during OLT has been reported as a consequence [13]. Dupont et al. showed that infusion of 5% albumin instead of fresh frozen plasma (FFP) did not result in significant changes in coagulation factors during OLT [5]; furthermore, intra-operative blood loss during OLT was not correlated to the abnormality of the coagulation data [3, 8, 18], and excessive administration of FFP may cause hepatic

artery thrombosis after OLT [10]. In the living-donor liver transplantation (LDLT) series reported here, a number of patients did not require a transfusion of any banked blood components intra-operatively, but received 5% albumin instead. The precise effect of 5% albumin on free Ca^{++} in patients undergoing OLT for end-stage liver disease has not yet been reported.

With this retrospective study, we aim to test whether blood transfusion-induced ionized hypocalcemia can be avoided by not giving blood products but replacing with 5% albumin. For this purpose we compare and analyze serum Ca^{++} level changes and calcium replacement between patients who received banked blood-product transfusions during LDLT and those who received 5% albumin.

Materials and methods

Written informed consent for surgery and anesthesia was obtained from the parents of the patients. The anesthesia records of 44 LDLTs performed between June 1994 and June 2000 were reviewed. The patients were divided into two groups according to the kind of transfusion they had received. Group I(GI) comprised patients who received packed red blood cells (PRBCs) and/or FFP (both preserved in citrate phosphate dextrose adenine) with and without 5% albumin. (Biotest Pharma, Dreieich, Germany), while group II (GII) received only 5% albumin during OLT. Serum Ca^{++} levels were compared between the groups before the operation, 2 and 4 h after the operation, in the anhepatic phase, 10 min after reperfusion, and at the end of the operation.

We also compared the total amount of supplemental calcium chloride (milligram per kilogram) that was required to maintain normocalcemia intra-operatively between the groups. The total blood and ascites loss (milliliter per kilogram), the amount of PRBC (milliliter per kilogram), FFP (milliliter per kilogram) and/or albumin infusion (milliliter per kilogram) during the OLT procedure were also compared between the groups. Further parameters, such as patient characteristics, anesthesia time, crystalloid infusion (milliliter per kilogram per hour), urine output (milliliter per kilogram per hour), and body temperature after induction of anesthesia and at the end of the operation, pre-operative and postoperative hemoglobin (Hb), hematocrit (Hct), platelet count, international normalized ratio (INR), and serum albumin, were likewise compared between groups. The arterial blood gases including serum Ca^{++}, Hb and Hct were measured approximately hourly by a blood gas machine (288 Blood Gas System, Ciba Corning Diagnostics, Metfield, Mass., USA). If serum Ca^{++} dropped below 0.8 mmol/l at any single point of determination, we gave 5–10 mg/kg of calcium chloride, to correct the deficit, aiming at a level of about 1.0 mmol/l. We also administered 5–10 mg/kg of calcium chloride routinely, as pretreatment against the negative effect of potassium flux during reperfusion.

The indication for blood transfusion was determined by the anesthesiologists according to the hemodynamic condition of the patients, the actual central venous pressure, Hb, Hct, urine output, and blood loss during the operation, but regardless of the coagulation parameters. The Hb and Hct were allowed to decrease to as far as 6–7 g/dl and 20%, respectively, provided the patients remained hemodynamically stable, and CVP was 5–12 cm H2O. The amount of PRBC transfusion was calculated with the aim of an Hb level being achieved of approximately 8 g/dl after transfusion. The decision to replace the blood and ascites loss with FFP or 5% albumin was not made at random. In the first 12 cases FFP was purposely given as colloid replacement for the initial loss, and PRBCs were added if necessary. In the last 32 cases 5% albumin solution was used instead. Anesthesia was induced with mask inhalation and maintained with isoflurane combined with fentanyl, as required, in an O_2/air mixture, and atracurium was used as muscle relaxant. All patients received dopamine at 2 μ/kg per h throughout the operation to support renal function and maintain a urine output > 1 ml/kg per h. Intravenous heparin at 20 IU/kg was administered, one dose before ligation of the native hepatic artery, and another just before completion of hepatic artery reconstruction of the allograft. The surgical procedure was performed without a veno–venous bypass being used. No autotransfusion, blood salvage or anti-fibrinolytic agents were used.

All data are given as mean + SD and compared by use of the Mann–Whitney U test; commercial statistics computer software (SPSS for Windows, SPSS, Chicago, Ill. USA) was employed. A P value < 0.05 was regarded as significant.

Results

Forty-four LDLTs were performed between June 1994 and June 2000 at the Chang Gung Memorial Hospital, Kaohsiung Medical Center, Taiwan. Three adults and one adolescent were excluded because their physiology differed from that of children. A further child was excluded, who received neither banked blood products nor 5% albumin. A 2-year-old boy underwent LDLT for biliary atresia with minimal blood and ascites loss. He received only 7.8 ml/kg per h crystalloids, his pre-operative and postoperative Ca^{++} was 1.12 and 1.26 mmol/l, respectively. No supplemental calcium chloride was required for the maintenance of an appropriate Ca^{++} level, except for a single dose of 9 mg/kg, given as pretreatment against the negative effects of potassium flux during reperfusion.

Twenty-three patients met the criteria for and were included in GI and 16 in GII. Table 1 shows that there was no significant difference in the demographic data of the patients. There was, furthermore, no difference in anesthetic time, crystalloid requirement, urine output, and pre-operative and postoperative body temperature. Table 2 shows that there was no difference in the total loss of blood plus ascites, the volume of replacement with and without red blood cells, calcium chloride replacement, pre-operative and postoperative serum Ca^{++} levels, pH, serum albumin, INR, Hb, Hct and platelet count. Figure 1 shows that no difference was found in the changes of the serum Ca^{++} level during OLT between the groups. The only significant difference noted was in the administration of PRBCs and FFP in GI (Table 2). The hemodynamics of both groups could be maintained within acceptable range, and no patient in any group required additional vaso-active drugs, except for a 2-μg/kg per h dopamine drip for stimulation of renal dopaminergic receptors to maintain adequate diuresis. No patient required platelet transfusion during the operation. All the patients, including the five who were excluded from analysis, recovered fully and are

alive and well at a mean follow-up time of 2.8 ± 1.7 years (0.8–6.9). Graft and patient survivals remain at 100%.

Discussion

The currently most widely accepted concept of the cause of ionic hypocalcemia during OLT is the binding of calcium by citrate [4, 9, 12, 14, 15]. Since a patient with end-stage liver disease is less capable of metabolizing citrate, exogenous citrate following blood transfusion can indeed reach toxic levels and induce cardiac arrest [13].

Increased serum citrate concentrations 20 to 100-times higher during OLT than those measured pre-operatively have been reported [9, 14]. In several studies, serum citrate and ionized calcium level were found to be inversely correlated [4, 9, 12, 14, 15]. In this report, serum Ca^{++} was maintained near low-to-normal limits (normal value: 1.02–1.26 mmol/l) during the operation in both groups (Fig. 1), regardless of blood-product replacement used (Table 2).

Notably, we found that in the absence of an exogenous load of citrate, effected by avoiding banked-blood transfusion such as in GII, the requirement of supplemental calcium chloride during operation, which is aimed at preventing the development of ionized hypocalcemia, was not significantly different from that of the citrate-loaded group (GI).

These observations indicate that other factors may be as important as exogenous citrate in causing ionic

Table 1 Comparison of patients' characteristics, anesthesia time, crystalloids, and body temperature changes of the two groups. Data are given as mean + SD. *1* pre-operative, *2* postoperative

Characteristic		GI ($n=23$)	GII ($n=16$)	P
Age (months)		33.6 ± 18.4	47.6 ± 29.2	0.151
Weight (kg)		12.1 ± 3.55	13.8 ± 4.32	0.252
Height (cm)		89.0 ± 24.7	92.4 ± 14.24	0.137
Gender (n)				
Male		10	11	
Female		12	5	
Disease				
Biliary atresia		20	12	
Glucogen storage disease		2	2	
Hepatitis		1	1	
Alagille's syndrome			1	
Anesthesia time (h)		14.8 ± 3.0	12.9 ± 1.6	0.65
Crystalloids infusion (ml/kg per h)		10.2 ± 3.4	8.2 ± 3.7	0.84
Urine output (ml/kg per h)		2.7 ± 1.0	2.1 ± 1.2	0.76
Body temperature (°C)	1	35.9 ± 0.6	35.8 ± 0.76	0.42
	2	36.3 ± 0.74	36.6 ± 0.78	0.332

Table 2 Comparison of the serum ionized calcium, calcium chloride substitution, and related parameters of the two groups. Data are given as mean + SD. *$CaCl_2$* calcium chloride, *1* pre-operative, *2* postoperative

Parameter		GI ($n=23$)	GII ($n=16$)	P
Blood + ascites loss (ml/kg)		25.0 ± 21.5	13.1 ± 8.1	0.219
Volume replacement	PRBC (ml/kg)	11.1 ± 10.7	0	0.000
	FFP (ml/kg)	12 ± 14.4	0	0.000
	Albumin (ml/kg)	37.8 ± 44.7	44.9 ± 29.5	0.224
	Total (ml/kg)	62.1 ± 40.7	44.9 ± 29.5	0.236
$CaCl_2$ (mg/kg)		27.8 ± 15.1	28.2 ± 17.5	0.932
Serum Ca^{++} (mmol/l)	1	0.95 ± 0.14	0.84 ± 0.2	0.137
	2	0.91 ± 0.12	0.87 ± 0.18	0.475
pH	1	7.34 ± 0.01	7.25 ± 0.04	0.167
	2	7.39 ± 0.06	7.33 ± 0.03	0.1
Serum albumin	1	3.47 ± 0.7	3.7 ± 0.5	0.112
	2	3.1 ± 0.6	3.7 ± 0.5	0.12
INR	1	1.1 + 0.58	1.3 ± 0.8	0.879
	2	2.2 ± 0.8	1.89 ± 0.6	0.210
Hb (g/dl)	1	8.8 ± 1.9	10.3 ± 1.6	0.35
	2	7.8 ± 1.2	7.9 ± 1.9	0.679
Hct (%)	1	26.8 ± 6.3	30.2 ± 4.9	0.170
	2	23.1 ± 4.4	23.9 ± 5.8	0.830
Platelet count ($\times 10^4/mm^3$)	1	14.1 ± 8.7	14.9 ± 12.0	0.853
	2	14.0 ± 7.3	13.2 ± 7.8	0.558

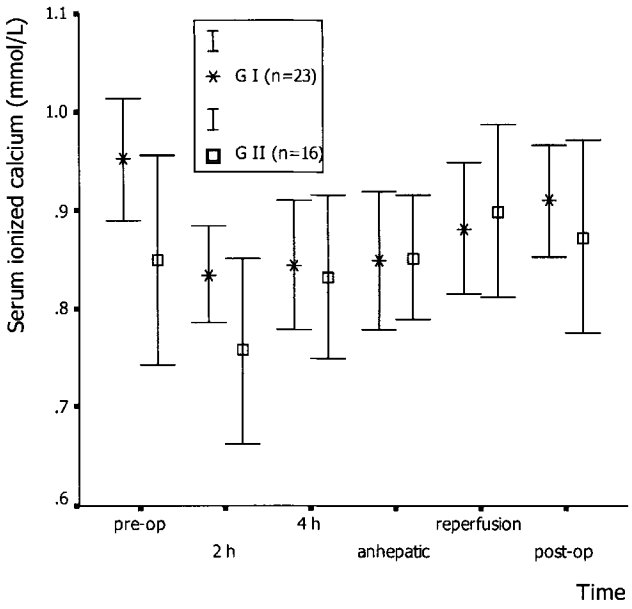

Fig. 1 No significant difference in intra-operative changes of serum ionized calcium between the two groups

hypocalcemia during OLT. In the group that received no banked-blood components (GII), 5% albumin was used instead, as colloid replacement for the blood and ascites losses, to maintain the intravascular volume and stabilize hemodynamics. The commercial 5% albumin preparation, which is free of citrate, contains 96% albumin, plus caprylate, *N*-acetyltryptophanate, sodium, chloride and potassium ions, and aluminum. In fact, albumin is not only known to bind drugs, hormones, and bilirubin, but also mineral ions [7], with at least 30 different binding sites, various association constants and H^+ interactions [6]. Howland et al. showed that the use of 5% albumin alone, to replace blood loss in non-liver transplantation surgery, caused a significant decrease in ionic calcium levels [11]. Infusion of albumin to treat hypoproteinemia in neonates also causes a significant decrease in serum Ca^{++} [16]. Historically, OLT surgery was associated with such excessive blood losses that blood-component transfusion with subsequent exogenous citrate loading was almost unavoidable. With increasing expertise and improvement of the surgical technique, surgeons can now perform OLT with minimal blood loss [8] and without blood transfusion [2, 17]. Table 2 shows that the blood and ascites losses in our LDLT patients were not excessive, and 21 patients (GI and GII) out of 39 of our cases (53%) did not require PRBCs intra-operatively. When the pre-operative Hb was higher than 10 g/dl, and the blood and ascites loss was less than 14 ml/kg, replacement with FFP, or 5% albumin alone without red blood cells, was deemed sufficient. As FFP transfusion bears a greater risk of disease transmission and hepatic artery thrombosis, the use of FFP for volume replacement is now regarded as inappropriate [1, 10].

Commercial 5% albumin is osmotically equal to plasma, and hypovolemia and/or hypo-albuminemia are the indications for its use. Infusion of 5% albumin instead of FFP did not result in significant changes in coagulation factors during OLT [5], but added the risk of development of ionized hypocalcemia in end-stage liver disease patients undergoing OLT, as shown by our data. Other possible factors, such as hemodilution, which may be encountered in the anhepatic phase, should be considered. Hemodilution during veno–venous bypass may also cause ionized hypocalcemia [19], but none of our patients needed the veno–venous bypass for hemodynamic support during the anhepatic phase. Likewise, the total amount of crystalloid and colloids infused was not different between groups.

In conclusion, provided that the blood loss during LDLT is not massive and the coagulopathy is not so severe that it has to be corrected, 5% albumin alone or 5% albumin combined with PRBC can safely be used in pediatric LDLT. The results reported here suggest that if the exogenous citrate load is excluded by the avoidance of transfusion with banked-blood components, and 5% albumin is used, instead, to replace blood and ascites loss during OLT, the risk of ionic hypocalcemia still persists.

Consequently, it is important to note that if 5% albumin alone is used instead of banked-blood components, regular intra-operative monitoring of serum Ca^{++} levels and adequate correction of deficits—the latter to prevent ionized hypocalcemia—are still necessary in OLT.

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