Retrospective Study

Living donor liver transplantation with body-weight more or less than 10 kilograms

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Abstract

AIM: To compare the outcomes of pediatric patients weighing less than or more than 10 kg who underwent liver transplantation.

METHODS: Data for 196 pediatric patients who underwent liver transplantation between June 1994 and February 2011 were reviewed retrospectively. The information for each patient was anonymized and de-identified before analysis. The data included information regarding the pre-transplant conditions, intraoperative fluid replacement and outcomes for each patient. The 196 patients were divided into two groups: those with body weights of less than 10 kg were included in group 1 (G1; n = 101), while those with body weights of more than 10 kg were included in group 2 (G2; n = 95). For each group, the patients' ages, body weights, heights, pediatric end stage liver disease scores, anesthesia times, and warm and cold ischemic times were analyzed. In addition, between-group comparisons were also made. Mann-Whitney U tests were used to compare all the variables except for complications and survival rates, which were analyzed using chi-squared tests and Kaplan-Meier tests, respectively.

RESULTS: The general medical conditions of the G1
INTRODUCTION

Performing living donor liver transplantation (LDLT) for pediatric patients, especially those with body weights of less than 10 kg, poses a challenge for all the participants in the liver transplant team, including anesthesiologists[1-4]. The outcomes of such transplants for pediatric patients weighing less than 10 kg differ from those for pediatric patients weighing more than 10 kg[1-4]. We have previously reported that the average change in core temperature during an LDLT for pediatric patients weighing less than 10 kg is significantly different from that in heavier children[5]. Furthermore, a lower survival rate for lower weight children was reported by Arnon et al[6], and according to other studies, this poorer survival results from higher risks of perioperative vascular complications, bile duct complications and infections[4,6,7]. In pediatric kidney transplantation, the ideal body weight for a recipient has also been found to be greater than 10 kg[8]. Most of the previous reports regarding pediatric organ transplantation have primarily evaluated the outcomes in terms of the morbidity and mortality of the procedure in question[1-4]. However, little information can be found in the literature concerning the anesthetic fluid requirements for pediatric patients with different body weights undergoing LDLT. Thus, the aim of the current study was to evaluate, analyze, and compare data retrospectively regarding the anesthetic fluid requirements for pediatric patients weighing less and more than 10 kg who underwent LDLT, while at the same time also comparing and analyzing the complications and survival rates for such patients.

MATERIALS AND METHODS

Ethics approval

This retrospective study was approved by the Institutional Review Board for Human Studies of Chang Gung Memorial Hospital (101-1945B).

Patient selection and data collection

We collected and analyzed the data from the anesthesia records of pediatric patients who underwent LDLT between June 1994 and February 2011. The information for each patient was anonymized and de-identified before analysis. The general anesthesia, intraoperative monitoring and blood transfusion protocols used[9], as well as their documentation[10], were similar to those described in previously published reports[9,9,11-13]. Estimated blood losses were made through visual estimations of a small (250 mL) suction bottle (Receptal® Accurate Measurement Device, Hospira, Inc. Lake Forest, Il 60045, United States) and the weight of laparotomy sponges. The pediatric patients were divided into two groups: those with body weights of less than 10 kg were included in group 1 (G1), while those with weights of more than 10 kg were included in group 2 (G2). For each group, the patients’ ages, body weights, heights, pediatric end stage liver disease scores (PELDS), anesthesia times, and warm and cold ischemic times were analyzed. In addition, between-group comparisons were made.

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Core tip: Although pediatric patients weighing less than 10 kg who underwent living donor liver transplantation usually had worse pre-transplant conditions, more intraoperative bleeding and more portal vein complications, their three-year survival rate was 94%, a rate comparable to that achieved by children weighing more than 10 kg. A prerequisite for achieving these excellent results is good and effective teamwork. Cooperation between surgeons, plastic surgeons, and anesthesiologists in the operating theater is fundamental, but the contributions of radiologists are also critical. Radiologists should be available in the operating room to perform Doppler ultrasounds or place vascular stents, as required.

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The gender and age specific Z-scores of the height and weight measurements in both groups were calculated. Likewise, intraoperative blood loss, ascitic loss and fluid replacement amounts were recorded and compared. Laboratory data, including hemoglobin (Hb) levels, serum albumin levels, platelet counts, activated partial thromboplastin time (APTT), international normal ratios (INRs), serum creatinine levels, total bilirubin levels and pH levels were also collected, analyzed, and compared between groups. All data related to body weight were converted to a per-kg basis for comparison. The frequency of perioperative morbidity and one- and three-year survival rates were also compared between the groups.

**Statistical analysis**

Mann Whitney U tests were used to compare data for all the variables, except for the morbidity and one- and three-year survival rates. The incidences of morbidity were compared by $z^2$, while the one- and three-year survival rates were compared by Kaplan-Meier tests. A $P$ value < 0.05 was regarded as statistically significant.

Data are presented as mean ± SD.

The statistical methods used in this study were reviewed by Dr. Shao-Chun Wu of Chang Gung University, Taiwan.

**RESULTS**

The patient etiologies (for G1 and G2, respectively) were as follows: biliary atresia (92 patients and 70 patients), neonatal hepatitis (7 and 4), glycogen storage disease (0 and 12), Alagille syndrome (1 and 5), urea cycle disease (1 and 0), fulminant hepatitis (0 and 1), cryptogenic (0 and 1), Wilson’s disease (0 and 1) and hepatitis C virus (0 and 1). Table 1 shows the gender- and age-specific Z-scores for the height and weight measurements in both groups. The Z-score in G1 was < -3, which indicated that the patients had suffered from moderate to severe malnutrition. Table 2 shows the characteristics of the patients in G1 and G2. The PELD scores were significantly higher for the G1 patients, while the pre-operative Hb and serum albumin levels were all lower for the G1 patients. The coagulation test results indicated that APTT and INR were both significantly prolonged in G1 patients and that the G1 patients had higher total bilirubin levels and platelet counts before the operation. Table 3 shows that the average anesthesia time for G1 was longer than the average time for G2, but also that the warm and cold ischemic times were similar between the groups. The extubation times were significantly longer among the G1 patients compared with the times for the G2 patients (Table 4). The absolute amount of blood loss for the two groups was similar. When body weight was taken into consideration and the data were converted to a per-kg basis, it was revealed that the G1 patients had significantly more ascites and greater blood loss per kilogram. Therefore, the G1 patients received significantly more crystalloids, 5% albumin and red blood cells to replace their losses (Table 3). Table 4 shows that the G1 patients also required more fluid and weight measurements were also calculated.

### Table 1 The gender and age specific Z-scores of the measurements in height and weight in both groups

| Z-score | Male height | Male weight | Female height | Female weight |
|---------|-------------|-------------|---------------|---------------|
| < 10 kg (group 1) | -3.364 (n = 51) | -2.977 (n = 51) | -3.266 (n = 50) | -3.277 (n = 50) |
| > 10 kg (group 2) | -2.43 (n = 53) | -1.07 (n = 53) | -1.504 (n = 42) | -0.046 (n = 42) |

The calculation of Z-score follows that used by the National Health and Nutrition Examination Survey (NHANES) 2000-04.

### Table 2 Patients’ characteristics between groups

| G1 (n = 101) | G2 (n = 95) | P value |
|--------------|-------------|---------|
| Age (mo)     | 16.1 ± 25.1 | 67.6 ± 49.1 | < 0.001 |
| Weight (kg)  | 7.8 ± 1.2 | 18.6 ± 11.2 | < 0.001 |
| Height (cm)  | 69.4 ± 6.0 | 103.1 ± 23.9 | 0.006 |
| PELD score   | 15.9 ± 10.9 | 6.8 ± 8.9 | < 0.001 |
| Hemoglobin (g/dL) | 9.2 ± 1.7 | 10.0 ± 1.7 | 0.003 |
| Serum albumin (g/L) | 3.1 ± 0.6 | 3.5 ± 0.7 | < 0.001 |
| Serum creatinine (mg/dL) | 0.8 ± 0.3 | 0.7 ± 0.14 | 0.113 |
| Total bilirubin | 18.4 ± 11.0 | 8.4 ± 9.3 | < 0.001 |
| INR          | 1.45 ± 0.8 | 1.07 ± 0.2 | < 0.001 |
| APTT (S)     | 44.4 ± 18.9 | 37.3 ± 13.2 | 0.001 |
| Platelet (1000/μL) | 191.0 ± 110 | 163.1 ± 117 | 0.015 |

PELD: Pediatric end stage liver disease; INR: International normal ratios; APTT: Activated partial thromboplastin time; G1: Those with body weights of less than 10 kg were included in group 1; G2: Those with body weights of more than 10 kg were included in group 2.

**Figure 1** Three-year survival rate (%) between groups.
Our results showed that the G1 patients had significantly different preoperative conditions compared with the G2 patients (Tables 1 and 2). Although the current study included only living donor liver transplantation, organ allocation has nothing to do with PELDS[15]. However, when PELDS were applied to the patients in this study, the G1 patients were indeed found to have higher average PELDS values, with mean values of 15.9 ± 10.9 and 6.8 ± 8.9 for G1 and G2, respectively. PELDS provide a useful model consisting of five objective parameters: total serum bilirubin, INR, albumin, growth failure and age. PELDS can predict death or deterioration in the condition of the patient that may require transfer to the intensive care unit while the patient awaits liver transplantation[16]. The PELDS and the Z-score, an anthropometric parameter for malnutrition[17], indicated that the medical conditions of the G1 patients were indeed worse and that their indications for liver transplantation were relatively urgent compared with those for the G2 patients. Furthermore, more challenging complications and difficulties are to be expected in LT for pediatric patients weighing less than 10 kg[4,18-20]. Table 3 further revealed that the total anesthesia time for G1 patients was significantly longer than that for G2 patients, most likely because of more difficult placement of arterial lines and the central venous catheter. In addition, more surgical time was needed for G1 patients to solve the intraoperative vascular complications, such as portal vein thrombosis[4,18]. Significant differences in ascites and blood loss were also noted when body weight was taken into consideration. High blood loss index is a risk factor that contributes to poor outcomes of the graft in pediatric LT[19]. The mean blood loss values for G1 and G2 were 28.6 ± 36.7 and 15.0 ± 21.2 mL/kg, respectively. Higher blood loss in infants weighing less than 10 kg has also been reported in open heart surgery[20]. Indeed, blood loss and transfusion requirements were correlated inversely with age and body weight[20]. More blood loss may cause more labile hemodynamic changes, the development of metabolic acidosis and higher incidences of ionized hypocalcemia[12]. Table 3 shows that the G1 patients received significantly more crystalloids (16.8 ± 5.5 vs 12.1 ± 5.5), more RBC (29.0 ± 29.0 vs 10.0 ± 17.3) and more 5% albumin (8.8 ± 6.8 vs 2.3 ± 1.9).
Fluid homeostasis differs between infants and children, with the body’s water content decreasing gradually from neonate to infant and from child to adult[23]. G1 patients received more crystalloids, based not only on more blood and ascitic fluid loss, but also on the recommended fluid requirements reported by Holiday and Segar[24] and the massive intraoperative fluid shift in liver transplantation setting (Table 3).

Table 5 shows that the postoperative complications, except for portal vein thrombosis, and the one- and three-year survival rates, were similar between the groups. Portal vein thrombosis is a serious complication of LT, which is associated with high morbidity and mortality in pediatric liver transplantation[19,25,29]. In this study, we experienced 13 cases (12 in G1 and 1 in G2) of perioperative portal vein thrombosis, detected by routine perioperative Doppler ultrasound[4]. Early detection and surgical intervention are crucial in treating portal vein complications. Seven patients with portal vein complications were detected intraoperatively by Doppler ultrasound[9,18]; immediate surgical interventions, such as graft reposition, collateral shunt ligation, thrombectomy and reconstruction of the portal vein, local infusion of heparin through inferior mesenteric vein catheter and endovascular stenting rescued 5/7 patients’ grafts, as well as ensuring the patient’s survival[18]. Multivariate analysis showed that body weight less than 10 kg and age less than one year old were important risk factors of portal vein thrombosis[4]. Although the exact mechanism of portal vein thrombosis is not clear, it is probable that both mechanical factors and hypercoagulopathy contribute to these thrombotic events[9,26], despite the patients having profound coagulation defects[27]. The hemostasis system of chronic or end-stage liver disease is complex: the pro- and anti-hemostatic pathways can change concomitantly in liver disease, but the change of the anti-hemostatic pathways is usually not well reflected in the routine coagulation tests, because in the latter measures, only the quantity of the procoagulant factors of the complex hemostatic system[27,28]. End-stage liver disease patients may be in hemostatic balance or a rebalanced condition, providing good hemostatic function, but on the other hand, both bleeding and thrombotic complications in the same patient can be encountered[27,28], as seen in our G1 patients (Table 5). The concern for the high incidence of intraoperative portal vein thrombosis in patients weighing less than 10 kg[4] resulted in the administration of significantly less FFP in G1 compared with G2, despite having more bleeding (Table 3).

We have reported that 8.4% of our pediatric LDLT had acquired hyponatremia at the end of the operation. The cause is not related to the body weight, but the only risk factor was administration of more than 3.5 ml/kg per hour of hypotonic solution[29].

In conclusion, the G1 patients had worse preoperative conditions, as shown by their lower Z-scores and higher PELDS compared with the G2 patients. The G1 patients also had more ascites and more blood loss intraoperatively, and required more intensive fluid resuscitation. G1 patients also had more incidences of perioperative portal vein thrombosis, indicating that infants with body weights of less than 10 kg have more surgical and anesthesia risks compared with infants weighing more than 10 kg. When a life-saving procedure can achieve a three-year survival rate of over 94%, it is worthwhile to perform it, no matter how difficult and complicated the procedure may be, even with known high potential lethal complications, such as portal vein thrombosis. A prerequisite for achieving these excellent results is good and effective teamwork. Cooperation between surgeons, plastic surgeons, and anesthesiologists in the operating theater is fundamental; however, the contributions of radiologists are also critical. Radiologists should be available in the OR to perform Doppler ultrasounds before closing the abdomen at the end of the LT procedure to assure sufficient flow in the portal and hepatic arteries[30], and they should also be able to insert a portal vein stent at the operating table if necessary. When a patient has indications requiring an LT, a low body weight of less 10 kg should not be viewed as a reason to delay performing the procedure.

REFERENCES
1 Ardiles V, Ciardullo MA, D’Agostino D, Pekolj J, Mattera FJ,
Baldurin GH, Brandi C, Beskov AF, Molmenti EP, de Santibañes E. Transplantation with hyper-reduced liver grafts in children under 10 kg of weight. *Langenbecks Arch Surg* 2013; 398: 79-85 [PMID: 23909008]  
2 Uribe M, Alba A, Hunter B, González G, Godoy J, Ferrario M, Buckel E, Cavalleri S, Heine C, Rebellodo R, Auad H, Acuña C. Liver transplantation in children weighing less than 10 kg: Chilean experience. *Transplant Proc* 2013; 45: 3733-3733 [PMID: 24315011 DOI: 10.1016/j.transproced.2013.08.092]  
3 Arnon R, Annunziato R, Milóth T, Sagawa H, Nostrand KV, Florman S, Suchy F, Kerkar N. Liver transplantation in children weighing 5 kg or less: analysis of the UNOS database. *Pediatr Transplant* 2011; 15: 650-658 [PMID: 2179756]  
4 Cheng VF, Chen CL, Huang TL, Chen TY, Chen YS, Takatsuki M, Wang CC, Chiu KW, Tsang L, Sun PL, Jawan B. Risk factors for intraoperative portal vein thrombosis in pediatric living donor liver transplantation. *Clin Transplant* 2004; 18: 390-394 [PMID: 15233815]  
5 Jawan B, Luk HN, Chen YS, Wang CC, Cheng VF, Huang TL, Eng HL, Liu PP, Chiu KW, Chen CL. The effect of liver graft-body weight ratio on the core temperature of pediatric patients during liver transplantation. *Liver Transpl* 2003; 9: 760-763 [PMID: 12872566]  
6 Castañeda-Martínez AL, Alcaide-Ortega RI, Fuentes-García CL, Segar WE, Alba A, Hunter B, González G, Godoy J, Ferrario M, Buckel E, Cavalleri S, Heine C, Rebellodo R, Auad H, Acuña C. Liver transplantation in children weighing less than 10 kg: Chilean experience. *Ann Surg* 2012; 256: 586-591 [PMID: 22448749]  
7 Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, Mei H, Curtin LR, Arnow BH, Johnson CL. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 21* 2002; (246): 1-190 [PMID: 12043359]  
8 Freeman RB, Wiesner RH, Roberts JP, McDermid S, Dykstra DM, Merion RM. Improving liver allocation: MELD and PELD. *Am J Transplant* 2004; 4 Suppl 9: 114-131 [PMID: 15133360]  
9 McDermid SW, Anand R, Lindblad AS. Development of a pediatric end-stage liver disease score to predict poor outcome in children awaiting liver transplantation. *Transplantation* 2002; 74: 173-181 [PMID: 12157128]  
10 Biend A. Is diarrhoea a major cause of malnutrition among the under-fives in developing countries? A review of available evidence. *Eur J Clin Nutr* 1990; 44: 611-628 [PMID: 2261894]  
11 Lin TL, Chiang LW, Chen CL, Wang SH, Lin CC, Liu YW, Yong CC, Lin TS, Li W, Jawan B, Cheng VF, Chen YS, Concejero AM, Wang CC. Intra-operative management of low portal vein flow in pediatric living donor liver transplantation. *Transpl Int* 2012; 25: 1460-1466 [PMID: 22795858]  
12 Boldt J, Knothe C, Zickmann B, Wege N, Dapper F, Hemmelmann G. Aprotinin in cardiac surgical operations: platelet function, blood loss, and use of homologous blood. *Ann Thorac Surg* 1993; 55: 457-461 [PMID: 8355571]  
13 Martin TJ, Kang Y, Robertson KM, Virji MA, Marquez JM. Ionization and hemodynamic effects of calcium chloride and calcium gluconate in the absence of hepatic function. *Anesthesiology* 1986; 65: 475-481 [PMID: 3535571]  
14 Sieders E, Peeters PM, Ten Vergert EM, de Jong KP, Porte RJ, Zwaveling JH, Bijleveld CM, Gouw AS, Slooff MJ. Graft loss after liver transplantation. *Ann Surg* 2002; 235: 125-132 [PMID: 11753051]  
15 Boldt J, Knothe C, Zickmann B, Wege N, Dapper F, Hemmelmann G. Aprotinin in cardiac surgical operations: platelet function, blood loss, and use of homologous blood. *Ann Thorac Surg* 1993; 55: 457-461 [PMID: 8355571]  
16 Martin TJ, Kang Y, Robertson KM, Virji MA, Marquez JM. Ionization and hemodynamic effects of calcium chloride and calcium gluconate in the absence of hepatic function. *Anesthesiology* 1986; 65: 475-481 [PMID: 3535571]  
17 Marquez J, Martin D, Virji MA, Kang YG, Warty VS, Shaw B, Sassano JJ, Waterman P, Winter PM, Pinsky MR. Cardiopulmonary depression secondary to ionic hypocalcemia during hepatic transplantation in humans. *Anesthesiology* 2005; 102: 823-832 [PMID: 15341307]  
18 Bekker J, Ploem S, de Jong KP. Early hepatic artery thrombosis after liver transplantation: a systematic review of the incidence, outcome and risk factors. *Am J Transplantation* 2009; 9: 746-757 [PMID: 19298450]  
19 Ooi CY, Brandão LR, Zolpys L, De Angelis M, Drew W, Jones N, Ling SC, Fecteu A, Ng VL. Thrombotic events after pediatric liver transplantation. *Pediatr Transplant* 2010; 14: 476-482 [PMID: 19849008]  
20 Lisman T, Caldwell SH, Burroughs AK, Northup PG, Senzolo M, Stravitz RT, Tripodi A, Trotter JF, Valla DC, Porte RJ. Hemostasis and thrombosis in patients with liver disease: the ups and downs. *J Hepatol* 2010; 53: 362-371 [PMID: 20546962]  
21 Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood* 2010; 116: 878-885 [PMID: 20406681]  
22 Yang SC, Wang CH, Chen CL, Cheng KW, Wu SC, Shih TH, Jawan B, Huang CJ, Acquired hyponatremia in pediatric living donor liver transplantation. *Ann Transplantation* 2014; 19: 609-613 [PMID: 25418023 DOI: 10.12659/AOT.892191]  
23 Cheng VF, Huang TL, Chen CL, Lee TY, Chen YS, Liu PP, Chiang YC, Eng HL, Wang CC, Cheung HK, Jawan B, Goto S. Intraoperative Doppler ultrasound in liver transplantation. *Clin Transplant* 1998; 12: 292-299 [PMID: 9686322]  

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