Effect of Graft Weight to Recipient Body Weight Ratio on Hemodynamic and Metabolic Parameters in Pediatric Liver Transplant: A Retrospective Analysis

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Abstract

Objectives: To analyze how graft-weight-to-body-weight ratio in pediatric liver transplant affects intraoperative and early postoperative hemodynamic and metabolic parameters.

Materials and Methods: We reviewed data from 130 children who underwent liver transplant between 2005 and 2015. Recipients were divided into 2 groups: those with a graft weight to body weight ratio > 4% (large for size) and those with a ratio ≤ 4% (normal for size). Data included demographics, preoperative laboratory findings, intraoperative metabolic and hemodynamic parameters, and intensive care follow-up parameters.

Results: Patients in the large-graft-for-size group (> 4%) received more colloid solution (57.7 ± 20.1 mL/kg vs 45.1 ± 21.9 mL/kg; P = .08) and higher doses of furosemide (0.7 ± 0.6 mg/kg vs 0.4 ± 0.7 mg/kg; P = .018). They had lower mean pH (7.1 ± 0.1 vs 7.2 ± 0.1; P = .004) and PO_2 (115.4 ± 44.6 mm Hg vs 147.6 ± 49.3 mm Hg; P = .004) values, higher blood glucose values (352.8 ± 96.9 mg/dL vs 262.8 ± 88.2 mg/dL; P < .001), and lower mean body temperature (34.8 ± 0.7°C vs 35.2 ± 0.6°C; P = .016) during the neohepatic phase. They received more blood transfusions during both the anhepatic (30.3 ± 24.3 mL/kg vs 18.8 ± 21.8 mL/kg; P = .013) and neohepatic (17.7 ± 20.4 mL/kg vs 10.3 ± 15.5 mL/kg; P = .031) phases and more fresh frozen plasma (13.6 ± 17.6 mL/kg vs 6.2 ± 10.2 mL/kg; P = .012) during the neohepatic phase. They also were more likely to be hypotensive (P < .05) and to receive norepinephrine infusion more often (44% vs 22%; P < .05) intra-operatively. More patients in this group were mechanically ventilated in the intensive care unit (56% vs 31%; P = .035). There were no significant differences between the groups in postoperative acute renal dysfunction, graft rejection or loss, infections, length of intensive care stay, and mortality (P > .05).

Conclusions: High graft weight-to-body-weight ratio is associated with adverse metabolic and hemodynamic changes during the intraoperative and early postoperative periods. These results emphasize the importance of using an appropriately sized graft in liver transplant.

Key words: *Hemodynamic changes, Large graft for size, Metabolic changes, Normal graft for size, Pediatric patients*

Introduction

Liver transplant for acute or chronic liver failure in pediatric patients is becoming more common.[1] Advances in surgical techniques, immunosuppressive therapy, and postoperative intensive care are resulting in increased success rates in these patients.[2,3] However, there also are increased complications in pediatric liver transplant patients compared to adult liver transplant patients, particularly related to vascular thrombosis-associated graft loss.[1,2]

There are 3 graft types used in pediatric patients: (1) whole organ deceased-donor transplant, (2) deceased-donor split liver transplant, and (3) living-donor liver transplant.[2] A mismatch in graft size versus patient size is a rare but critical issue in living-donor liver transplant.[4] Small-for-size grafts are associated with poor graft survival. Postoperative graft dysfunction caused by a graft that is insufficiently sized to maintain adequate liver function presents as cholestasis, coagulopathy, portal hypertension, sepsis, variceal bleeding, respiratory

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failure, acute kidney dysfunction, intestinal per-foration, and mortality. With a large-for-size graft, there is low portal blood flow, which impairs hepatic circulation, as well as size discordance between the vascular lumens, insufficient blood supply to the graft, and the insufficient size of the recipient's abdominal cavity.[5-8] Akdur and colleagues showed that large-for-size grafts may cause abdo1minal compartment syndrome and vascular problems as a result of the relatively small recipient size.[2]

We conducted this study to raise awareness of the metabolic and hemodynamic changes associated with graft-recipient size mismatching. We hypo-thesize that a high graft weight to recipient body weight ratio (> 4%) in pediatric liver transplant adversely affects intraoperative and early post-operative hemodynamic and metabolic parameters.

Materials and Methods

Patients
In this retrospective study, we reviewed data from 130 pediatric patients who underwent an isolated liver transplant between 2005 to 2015 at Baskent University Hospital. Demographic data included age, sex, and cause of liver disease (viral, biliary, idiopathic). Child-Pugh and pediatric end-stage liver disease scores were recorded. The intraoperative and postoperative inotropic agents that were used, intraoperative complications, and incidence of mortality were also noted.

Donor and grafts
Grafts were recovered from healthy adult living donors. The donors included 111 parents (40 fathers and 71 mothers) and 19 other relatives of the patients.

Intraoperative and postoperative intensive care management
We divided the transplant operation into 2 phases based on liver function: the anhepatic phase, from the beginning of the operation to liver activation by reflow of graft portal vein and hepatic artery; and the neohepatic phase, from reflow of portal vein and hepatic artery circulation to the end of the operation. All patients had a radial arterial catheter in place for invasive blood pressure monitoring, a femoral arterial catheter for pulse contour cardiac output monitoring, and a central venous catheter for fluid replacement. After induction of anesthesia, patients received infusions of desflurane, remifentanil, rocuronium, and norepinephrine. Intraoperative data, including the use of blood products, urine output, central venous pressure, body temperature, systolic-diastolic arterial pressures, pH, PO_2, lactate, potassium, and blood glucose levels, for both the anhepatic and the hepatic phases were recorded.

Graft size was evaluated by graft-weight-to-recipient-body-weight ratio (G/R ratio = graft weight [kg] / recipient body weight [kg]). We assigned patients into 2 groups based on their G/R ratio: recipients with a G/R > 4% (large for size) and those with a G/R ≤ 4% (normal for size).

The immunosuppressive drug regimen consisted of tacrolimus and steroids. Methylprednisolone (10 mg/kg) was administered during the reflow of graft portal vein and hepatic artery anastomosis. After transplant, methylprednisolone was started at a dose of 2 mg/kg per day and was continued for 6 months. Acute rejection was diagnosed when clinical signs of fever and increased levels of transaminases and/or bilirubin with or without histologic diagnosis were observed. A steroid bolus injection was given with or without a change in tacrolimus dose if acute rejection occurred.

Statistical analyses
Values are shown as mean plus or minus standard deviation or as median and range. For statistical comparison, the Mann-Whitney test for continuous data and the chi-squared test for categorical data were used. *P* values less than .05 were regarded as statistically significant.

Results

Data from 130 pediatric liver transplant recipients were included in the analyses. There were 61 female patients (47%) ranging in age from 5 months to 14 years (4.6 ± 3.8 y), and the body weight of all patients ranged from 5 to 37 kg (15.7 ± 8.5 kg). Age (1.0 ± 0.3 y vs 5.5 ± 3.8 y; *P* < .001) and body weight (6.8 ± 0.7 kg vs 178 ± 8.1 kg; *P* < .001) were statistically significantly different between the 2 groups. Patient demographics are shown in Table 1.

Mean Child-Pugh and pediatric end-stage liver disease scores were 8.7 and 17.1, respectively. Child-Pugh (9.6 ± 1.3 vs 8.5 ± 2.1; *P* = .013) and pediatric end-stage liver disease (27.8 ± 11.3 vs 14.5 ± 15.2; *P* < .001) scores also were significantly different

between the groups. Patients in the G/R > 4% group received more colloid solution and higher doses of furosemide than did patients in the G/R ≤ 4% group. They also received norepinephrine infusion intraoperatively more often (44% vs 22%; $P < .05$) and had higher blood glucose values (352.8 ± 96.9 mg/dL vs 262.8 ± 88.2 mg/dL; $P < .001$) than did patients in the G/R ≤ 4% group (Table 2).

Patients in the G/R > 4% group received more packed red blood cell transfusions during both the anhepatic (30.3 ± 24.3 mL/kg vs 18.8 ± 21.8 mL/kg; $P = .013$) and the neohepatic (17.7 ± 20.4 mL/kg vs 10.3 ± 15.5 mL/kg; $P = .031$) phases and more fresh frozen plasma (13.6 ± 17.6 mL/kg and 6.2 ± 10.2 mL/kg; $P = .012$) during the neohepatic phase. During the anhepatic phase, urinary output was lower in the G/R > 4% group than in the G/R ≤ 4% group (6.3 ± 4.6 mL/kg vs 9.3 ± 6.9 mL/kg; $P = .024$). The G/R > 4% group also was more likely to be hypotensive intraoperatively during all phases ($P < .05$) and to have lower mean pH (7.1 ± 0.1 vs 7.2 ± 0.1; $P = .004$) and PO_2 (115.4 ± 44.6 mm Hg vs 147.6 ± 49.3 mm Hg; $P = .004$) values and lower mean body temperatures (34.8 ± 0.7°C vs 35.2 ± 0.6°C; $P = .016$) during the neohepatic phase (Table 3 and Table 4).

More patients in the G/R > 4% group were mechanically ventilated in the intensive care unit (56% vs 31%, $P = .035$). There were no significant differences between the groups in postoperative acute renal dysfunction, graft rejection or loss, infections, length of intensive care stay, and mortality ($P > .05$) (Table 5).

Discussion

In this retrospective study, a G/R > 4% was associated with metabolic and hemodynamic adverse outcomes in pediatric living-donor liver transplant recipients. Recipients with a large-for-size graft were more likely to be hypotensive and hypothermic and to need greater amounts of colloid fluid replacements, blood product transfusions, and norepinephrine intraoperatively. More patients in this group were mechanically ventilated postoperatively.

Whereas the small-for-size syndrome is associated with poor graft survival, inferior outcome, and significant mortality compared to a normal-for-size

Table 1. Patient Demographics (N = 130)

	Value[†]
Age (y)	4.6 ± 3.8
Sex (female)	61 (47)
Weight (kg)	15.7 ± 8.5
Child-Pugh score	8.7 ± 2.0
PELD score	17.1 ± 15.4

Abbreviations: PELD, pediatric end-stage liver disease
[†]Data are mean ± standard deviation or number (%).

Table 2. Comparison of Demographics, Scores, and Intraoperative Parameters

Parameter	G/R ≤ 4%*	G/R > 4%*	P Value
Age (y)	5.5 ± 3.8	1.0 ± 0.3	< .001
Sex (female)	51 (49)	10 (40)	.508
Weight (kg)	17.8 ± 8.1	6.8 ± 0.7	< .001
Child-Pugh score	8.5 ± 2.1	9.6 ± 1.3	.013
PELD score	15. ± 15.2	27.8 ± 11.3	< .001
Colloid (mL/kg)	45.1 ± 21.9	57.7 ± 20.1	.008
Furosemide (mg/kg)	0.4 ± 0.7	0.7 ± 0.6	.018
Norepinephrine	23 (22)	11 (44)	.040
Blood glucose (mg/dL)	262.8 ± 88.2	352.8 ± 96.9	< .001

Abbreviations: G/R, graft-weight-to-recipient-body-weight; PELD, pediatric end-stage liver disease
*Data are mean ± standard deviation or number (%).

Table 3. Comparison of Intraoperative Parameters During Anhepatic Phase

Parameter	G/R ≤ 4%*	G/R > 4%*	P Value
PRBC transfusion (mL/kg)	18.8 ± 21.8	30.3 ± 24.3	.013
FFP transfusion (mL/kg)	15.5 ± 16.0	26.4 ± 28.6	.130
Urinary output (mL/kg)	9.3 ± 6.9	6.3 ± 4.6	.024
pH	7.3 ± 0.1	7.3 ± 0.1	.474
Blood pressure (mm Hg)			
Systolic	67.0 ± 13.9	63.3 ± 12.8	.143
Diastolic	35.4 ± 8.6	31.5 ± 8.5	.026
PO_2 (mm Hg)	151.7 ± 52.9	124.5 ± 51.3	.021
Body temperature (°C)	35.4 ± 0.8	35.1 ± 0.6	.082

Abbreviations: FFP, fresh frozen plasma; G/R, graft-weight-to-recipient-body-weight; pH, power of hydrogen; PO_2, partial pressure of oxygen; PRBC, packed red blood cells
[a]Data are mean ± standard deviation.

Table 4. Comparison of Intraoperative Parameters During Neohepatic Phase

Parameter	G/R ≤ 4%*	G/R > 4%*	P Value
PRBC transfusion (mL/kg)	10.3 ± 15.5	17.7 ± 20.4	.031
FFP transfusion (mL/kg)	6.2 ± 10.2	13.6 ± 17.6	.012
Urinary output (mL/kg)	9.9 ± 9.2	10.3±12.2	.688
pH	7.2 ± 0.1	7.2 ± 0.1	.045
Blood pressure (mm Hg)			
Systolic	77.9 ± 19.3	61.5 ± 20.0	.001
Diastolic	36.2 ± 11.1	30.6 ± 8.5	.009
PO_2 (mm Hg)	200.1 ± 71.7	172.3 ± 44.0	.141
Body temperature (°C)	35.2 ± 0.6	34.8 ± 0.7	.016

Abbreviations: FFP, fresh frozen plasma; G/R, graft-weight-to-recipient-body-weight; pH, power of hydrogen; PO_2, artial pressure of oxygen; PRBC, packed red blood cells
*Data are mean ± standard deviation.

Table 5. Comparison of Postoperative Parameters

Parameter	G/R ≤ 4%*	G/R > 4%*	P Value
Mechanical ventilation	33 (31)	14 (56)	.035
Tracheostomy	6 (6)	0 (0)	.595
Revision surgery	35 (34)	10 (40)	.641
Acute kidney injury	13 (13)	0 (0)	.127
Graft rejection	16 (16)	2 (8)	.523
Graft loss	9 (9)	0 (0)	.204
Mortality	13 (13)	2 (8)	.734

Abbreviations: G/R, graft-weight-to-recipient-body-weight
*Data are number (%).

liver transplant,[4,5] there are also serious adverse outcomes related to a large-for-size graft, including increased intra-abdominal and intrathoracic pressures, atelectasis formation, prolonged intubation, decreased cardiac output, hypotension, and kidney and graft injury related to decreased perfusion. In addition, the need for high levels of antigen in large-for-size grafts is associated with a high incidence of rejection.[4,6]

Consistent with these findings, in our study, intraoperative hypotension was observed more frequently in patients with a G/R > 4%. Because the large graft receives relatively low portal blood flow due to the small recipient size, impairment in hepatic microcirculation may occur. Furthermore, external compression due to the small abdominal cavity also may lead to hepatic hypoperfusion. This hypoperfusion leads to prolonged warm ischemia time. Release of inflammatory mediators by the ischemic tissue and distribution of volume into the graft may explain this hemodynamic instability.[4] This mechanism may also explain the greater need for colloid fluids and furosemide administration in these patients.

In a retrospective study by Levesque and colleagues, more pediatric and adult liver transplant recipients in the higher G/R group developed respiratory failure compared with patients in the normal-for-size group.[7] In our study, more patients in the large-for-size group were mechanically ventilated postoperatively. This finding may be explained by an increase in intra-abdominal and intrathoracic pressures, atelectasis, and respiratory failure.[4] In addition, the large-for-size group in our study received more blood product transfusions. This finding may be explained by hypotension due to external compression of the venous system and distribution of volume into the graft. This greater need for blood product transfusions may lead to a higher rate of respiratory failure and the need for mechanical ventilation postoperatively. It also may be the reason these patients were more hypothermic.

The superior results with normal-sized grafts may be attributable to vascular factors. Akdur and colleagues reported vascular kinking with large grafts that required treatment with the Bogota bag technique.[2]

Living-donor liver transplant remains the treatment option for liver failure for many patients owing to the shortage of deceased-donor organ donation in our country. Success of the transplant surgery largely depends on matching the graft size to the recipient's body weight. The G/R ratio is used to determine the minimum graft volume in living-donor liver transplant.[4]

Conclusions

The importance of the appropriate relation between graft size and recipient body weight in liver transplant is becoming more apparent. The use of indexes such as the G/R ratio make it possible to transplant an appropriately sized graft and thereby to reduce postoperative adverse outcomes and improve survival. While the outcomes with small-for-size grafts are now well established, the effects of large-for-size grafts in pediatric living-donor liver transplant need to be studied further.

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