Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Effect of intraportal infusion to improve small for size graft injury in living donor adult liver transplantation

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Keywords
intra-portal infusion, living donor adult liver transplantation, small for size graft injury.

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Received: 1 September 2004
Revision requested: 15 December 2004
Accepted: 24 April 2005

doi:10.1111/j.1432-2277.2005.00159.x

Summary

The most important problem in the living donor adult liver transplantation (LDALT) is a small for size graft. Although a right lobe graft is used in many cases in order to avoid small for size graft, for a donor, the risk has few in left lobe graft. We evaluate the effect of an intraportal infusion treatment to the small for size graft. One hundred and twelve patients who underwent LDALT were studied. The graft weight recipient standard liver volume ratio (GV/SLV) of these patients were 50% or less. We divided the patients into following two groups; infusion group ($n = 53$) and control group ($n = 59$). For the infusion group, 16 G double lumen catheter was inserted into portal vein and nafamostat mesilate (protease inhibitor which stabilize coagulofibrinolytic state; 200 mg/day), prostaglandin E_1 (vasodilator and hepatoprotective effect; 500 μg/day) and thromboxane A_2 synthetase inhibitor (vasodilator and anticoagulant effect; 160 mg/day) were administrated continuously for 7 days. Small-for-size graft syndrome was defined as bilirubin >10 mg/dl and ascites >1000 cc on postoperative day (POD) 14. Comparison examination of a background factors and postoperative bilirubin and amount of ascites was carried out. The mean GV/SLV did not have the difference at 39.1% of infusion group, and 38.3% of control group ($P = 0.58$). By the control group, 15 patients (25.4%) were small-for-size graft syndrome, however, there was only two (3.8%) small-for-size graft syndrome in infusion group ($P = 0.04$). The bilirubin levels of infusion and control group on 7 and 14 POD were 9.9 and 7.8 vs. 9.5 and 10.5 mg/dl, respectively. The amount of ascites of infusion group on 7 and 14 POD were 870 and 430 cc, respectively. On the contrary, in control group, the amount of ascites on 7 and 14 POD were 1290 and 1070 cc, respectively. Bilirubin levels and the amount of ascites on 7 and 14 POD were lower in the patients with infusion group then those with control group. There were no differences between infusion group and control group in age, sex and Child's classification. The intraportal infusion had an effect in prevention of hyperbilirubinemia and loss in quality of excessive ascites in the patients with small for size graft. This was suggested to be what is depended on the improvement of the microcirculation insufficiency considered one of the causes of small-for-size graft syndrome.

Introduction

The first successful living donor adult liver transplantation (LDALT) patient was reported by Hashikura *et al*. in 1993 [1]. The major concern of LDALT is the adequacy of the size of the graft [2–4]. Harvesting a larger graft poses a higher risk for the living donor [5,6]. On the contrary, a small for size graft may not only be functionally inadequate for the recipient, but will also sustain injury characterized by cholestasis and histological features of ischemia after implantation [4]. The exact mechanism leading to injury of a small for size graft after liver transplantation remains unknown. It has been suggested that excessive portal flow secondary to relative portal hypertension may be the cause and that portal decompression may improve graft survival [7]. In experimental and clinical study, some drugs such as prostaglandin E_1 [8–11], thromboxane A_2 synthetase inhibitor [12–16] or nafamostat mesilate [17–19] have been reported to be effective on liver resection and posttransplant graft function. In this report, we evaluate the effect of an intraportal infusion treatment using such drugs to improve the small for size graft injury.

Patients and methods

One hundred twelve consecutive patients who underwent LDALT were studied. The graft weight recipient standard liver volume ratio (GV/SLV) of these patients were 50% or less. We excluded ABO incompatible case and auxiliary partial orthotopic liver transplantations (APOLT) case.

The main indications for LDALT were cholestatic diseases ($n = 20$), fulminant hepatic failure ($n = 28$), hepatocellular carcinoma ($n = 37$), liver cirrhosis ($n = 20$), and others ($n = 7$). Eighty-one patients received ABO identical grafts and 31 patients received ABO compatible grafts. The left plus caudate lobe as used for 102 cases, and the right lone was used for 10 cases.

A preoperative evaluation for potential living donors included a completed history and physical examination, an abdominal computed tomography scan, and angiogram. The computed tomography scan was used to calculate the size of the whole liver and the extended left lobe. The angiogram assessed the hepatic arterial supply, especially to the left lobe, and the diameters of the hepatic arteries. The SLV was calculated according to the formula, while the weight of the procured left lobe, labeled as GV, was measured on the back table. Subsequently the ratio GV/SLV could be calculated.

The donor hepatectomy was performed according to our standard technique [11–13]. Intraoperative cholangiography and ultrasonography ware performed, followed by cholecystectomy. The arteries supplying the left love were dissected and divided at their branching site from the either right or the proper hepatic artery. The transection of the liver parenchyma, after a dissection of the left hepatic artery and portal and hepatic veins, was performed with the liver fully perfused. The recipient operation was performed using our standard technique described before [13–17]. Using electromagnetic flow probes, the arterial blood flow was measured in recipients after performing anastomosis of all the vessels after 30 min of equilibration, but before biliary reconstruction. Biliary anastomosis was performed as an end-to-side hepaticojejunostomy on a Roux-en-Y loop, or end-to-end hepaticocholedochostomy. The initial immunosuppressive regimen consisted of tacrolimus or cyclosporin and steroids. Duplex Pulse Doppler ultrasonography was performed every postoperative day (POD) in all recipients to confirm the patency of the blood viscosity.

We divided the patients into following two groups; first 59 patients as control group and the other 53 patients as infusion group. For the infusion group, 16 G double lumen catheter was inserted into portal vein through umbilical vein or mesenteric vein and nafamostat mesilate (protease inhibitor which stabilize coagulofibrinolytic state) (200 mg/day), prostaglandin E_1 (vasodilator and hepatoprotective effect) (500 μg/day) and thromboxane A_2 synthetase inhibitor (vasodilator and anticoagulant effect; 160 mg/day) were administrated just after reperfusion continuously for 7 days. Median follow-uptime is 54 month in control group and 35 month in infusion group.

Small-for-size graft syndrome was defined as bilirubin >10 mg/dl and ascites >1000 cc on POD 14. Comparison examination of a background factors and postoperative bilirubin and amount of ascites was carried out.

Parametric variables were compared using the unpaired Student's *t*-test, while nonparametric variables were compared using a chi-square analysis. The survival probability of recipients was determined by the Kaplan–Meier methods. A *P*-value of <0.05 was considered significant.

Results

There was no complications related to infusion tube. Recipient characteristics were summarized in Table 1. No difference was seen in age, gender and Child's classification between the groups. In control group, 18 patients (30.5%) were fulminant hepatic failure and 14 patients (23.7%) were cholestatic diseases patients. On the contrary, in infusion group, 25 patients (47.1%) were hepatocellular carcinoma. The mean GV/SLV and GRWR did not have the difference at 39.3% and 0.78% of infusion group, and 38.3% and 0.77% of control group ($P = 0.58$; Table 1).

The bilirubin levels of infusion and control group on 7 POD and 14 POD were 9.9 and 7.8 vs. 9.5 and 10.5 mg/dl, respectively. There are no significant differences in bilirubin levels between control and infusion group on POD7 and 14. However, bilirubin levels and the amount of ascites on 7 and 14 POD were lower in the patients with infusion group then those with control group, and in the control group, bilirubin levels getting higher after 7 POD, although in the infusion group, bilirubin levels decreased after 7 POD (Fig. 1).

The amount of ascites of infusion group on 7 and 14 POD were 870 and 430 cc, respectively. On the contrary, in control group, the amount of ascites on 7 and 14 POD were 1290 and 1070 cc, respectively. The amount of ascites was significantly fewer in the infusion group than control group on POD 7 ($P = 0.07$) and 14 ($P = 0.02$; Fig. 2).

We defined small for size graft syndrome as the as bilirubin >10 mg/dl and ascites >1000 cc on POD 14. By the control group, 15 patients (25.4%) were small-for-size graft syndrome, on the contrary, there was only two (3.8%) small-for-size graft syndrome in infusion group ($P = 0.04$; Fig. 3, Table 2).

Table 1. Recipient and operative characteristics.

Factors	Control ($n = 59$)	Infusion ($n = 53$)	*P*-value
Recipient			
Age	44.7 ± 14.8	42.2 ± 13.7	0.34
Male/female	27/32	21/32	0.64
Child A/B/C	3/14/24	0/16/27	0.19
Indication			
Cholestatic diseases	14	6	0.02
Fulminant hepatic failure	18	10	
Hepatocellular carcinoma	12	25	
Liver cirrhosis	10	10	
Others	5	2	
Graft and operation			
LL/RL	51/8	51/2	0.14
GV/SLV (%)	38.3 ± 7.8	39.3 ± 7.6	0.58
GRWR (%)	0.77 ± 0.15	0.78 ± 0.16	0.59
Operation time (min)	751 ± 231	742 ± 223	0.84
Blood loss (g)	7184 ± 8831	7798 ± 9697	0.72

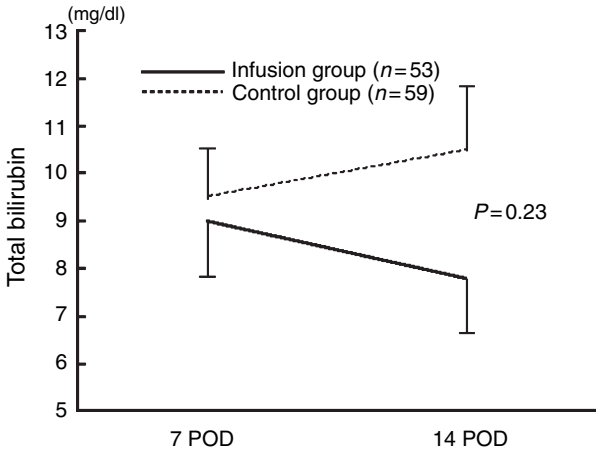

Figure 1 Change in total bilirubin levels after LDALT. The bilirubin levels of infusion and control group on 7 and 14 POD were 9.0 and 7.8 vs. 9.5 and 10.5 mg/dl, respectively. There is no difference between infusion and control group.

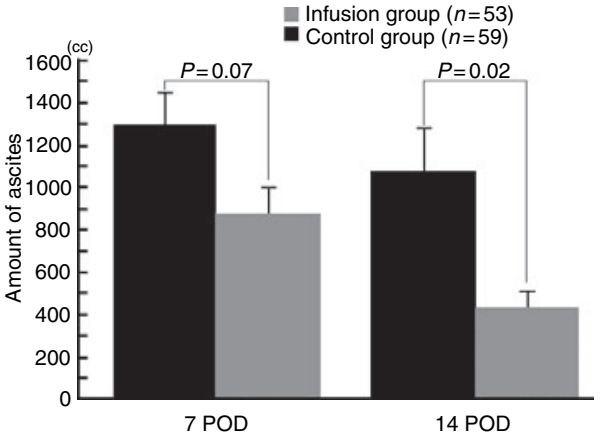

Figure 2 Change in amount of ascites after LDALT. The amount of ascites of infusion group on 7 and 14 POD were 870 and 430 cc, respectively. On the contrary, in control group, the amount of ascites on 7 and 14 POD were 1290 and 1070 cc, respectively. The difference is statistically significant in amount of ascites on POD 7 and 14 ($P < 0.05$).

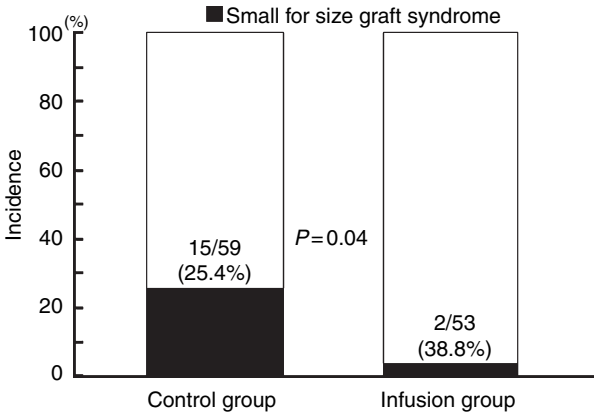

Figure 3 Small for size graft syndrome. We defined small for size graft syndrome as the as bilirubin >10 mg/dl and ascites >1000 cc on postoperative day (POD) 14. By the control group, 15 patients (25.4%) were small-for-size graft syndrome, on the contrary, there was only two (3.8%) small-for-size graft syndrome in infusion group ($P = 0.04$).

Table 2. Postoperative complications.

Complications	Control ($n = 59$)	Infusion ($n = 53$)	*P*-value
Bilirubin on POD 14 >10 mg/dl	19 (32.2)	15 (28.3)	0.81
Ascites on POD 14 >1000 cc	14 (23.7)	2 (3.8)	0.01
Acute cellular rejections	22 (37.3)	16 (30.2)	0.55
Biliary complications	20 (33.9)	7 (13.2)	0.02
Vascular complications	5 (8.5)	2 (3.8)	0.52
Infections	35 (59.3)	30 (56.6)	0.92
Small for size graft syndrome	15 (25.4)	2 (3.8)	0.04

Values in parenthesis are percentage.

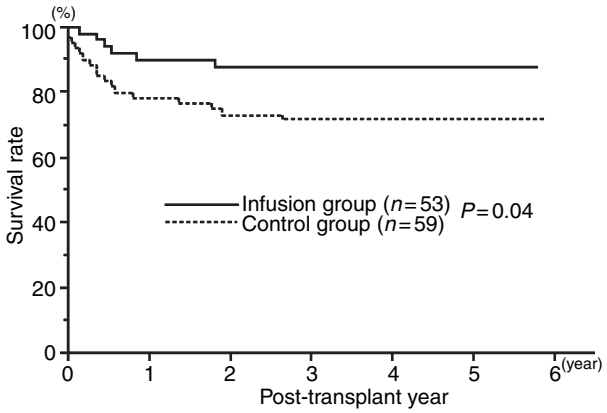

Figure 4 Kaplan–Meier patient survival curves of 112 patients with LDALT according to intraportal infusion treatment. In control group, the 1, 3 and 5 year patients' survival rates were 74.1%, 72.3% and 72.3%, respectively. And in infusion group, the 1, 3 and 5 year patients' survival rates were 86.6%, 86.6% and 86.6%, respectively. The patient survival rate was higher in the patients with infusion group than those with control group and the difference is statistically significant ($P = 0.04$).

Figure 4 demonstrates the Kaplan–Meier patient survival curves of 112 patients with LDALT according to intraportal infusion treatment. In control group, the 1, 3 and 5 year patients' survival rates were 74.1%, 72.3% and 72.3%, respectively. And in infusion group, the 1, 3 and 5 year patients' survival rates were 86.6%, 86.6% and 86.6%, respectively. The patient survival rate was higher in the patients with infusion group than those with control group and the difference is statistically significant ($P = 0.04$).

Discussion

Living donor adult liver transplantation can be performed successfully using a smaller graft [20–24]. Our previous report [2] described that a graft estimated as 26% of the recipient SLV was transplanted successfully to a patients with fulminant hepatic failure. Lo *et al.* [3] also reported that a graft estimated as 25% of the recipient SLV was successfully transplanted to patients with fulminant hepatic failure. But the minimal graft volume for successful LDALT depends on the pretransplant condition and disease of the recipient in each case.

To avoid small for size graft syndrome, right lobe graft has been used for LDALT [25–29]. Marcos *et al.* [25] and many other surgeons concluded that right lobectomies for living donation can be performed safety with minimal risk to both donor and recipient although providing adequate liver mass for an average size adult patient. Lo *et al.* [30] reported that LDALT using the extended right lobe living graft can extend the donor is relatively small compared with the recipient. However, concerning the safety of the donor, Sakamoto *et al.* and Sugawara *et al.* [26,28,31] reported that right lobectomy from living donors is a safe procedure with acceptable morbidity, but some care should be taken early after the operation for donors with small residual liver and aged donors. We also reported that postoperative liver functions including total bilirubin and ALT levels of the right lobe donors were significantly higher than those of left lobe donors [5]. From these findings, we use left lobe with caudate lobe graft to minimize the risk of the donor [21,32]. Recipient survival may depend on not only size and quality of the graft but recipient status. Our previous report suggested that intractable ascites was characteristics of small-for-size graft and small for size grafts <30% of SLV can be used careful intraoperative and postoperative management until the grafts regenerate [21].

Man *et al.* [33] reported that in a rat model, the portal hemodynamic changes in small for size grafts are transient, and the progressive damage of the graft may result from microcirculatory failure because of irreversible endothelial injury after reperfusion. To minimize the small for size graft injury, several methods were used. Ku *et al.* [7] reported an improved of canine liver transplantation using a quarter-graft with the aid of a porthepatic vein shunt. The effect of a porthepatic vein shunt on portal vein decompression should be an important factor for preventing graft injury after circulation in an extremely small graft. Clinically, Boillot *et al.* [34] completely divided the superior mesenteric venous flow by a mesocaval shunt with downstream legation of the superior mesenteric vein in order to avoid graft congestion and failure by overperfusion. To avoid outflow disturbance, De Villa *et al.* [27] recommended a recipient venoplasty with a, aching venoplasty of multiple graft hepatic veins to create a singlewide outflow orifice.

Different from these surgical methods, we performed intraportal infusion to improve small for graft injury. Recently, Tanabe *et al.* [35] and Shimazu *et al.* [36] showed the feasibility of controlling rejection and other

complications in adult-ABO incompatible liver transplantation under intraportal infusion therapy. They performed intraportal infusion therapy after transplantation with methylpredonisolone, prostaglandin E_1, and gabexate mesilate.

Our previous report also demonstrated that the regeneration rate of small graft was over 2.0 in 1 week after transplantation [21]. From this finding, we supported small grafts by intraportal infusion treatment first 1 week after transplantation. In our study, the drugs we used were prostaglandin E_1, thromboxane A_2 synthetase inhibitor and nafamostat mesilate. The effects of prostaglandin E_1 are hepatoprotective effect and improve microcirculation. We have reported that prostaglandin E_1 improves hepatocyte and sinusoidal cell function on isolated perfused rat liver [8,9]. The effects of thromboxane A_2 synthetase inhibitor are to improve microcirculation, hepatoprotective effect and inhibit platelet aggregation. We also reported that thromboxane A_2 synthetase inhibitor improves hepatocyte and sinusoidal cell function on isolated perfused rat liver [12–16]. The effects of nafamostat mesilate is to stabilize coagulant and fibrinolytic system and anti-inflammatory effect, and we reported that nafamostat mesilate stabilized coagulation and fibrinolysis in hepatic resection [17,18].

In summary, from our results of 112 LDALTs using intraportal infusion treatment, intraportal infusion treatment had an effect in prevention of hyperbilirubinemia and loss in quality of excessive ascites in the patients with small for size graft. Intraportal infusion also reduced in incidence of small for size graft syndrome in LDALT.

In conclusion, intraportal infusion treatment is suggested to be useful to improve small for size graft function. This was suggested to be what is dependent on the improvement of the microcirculation insufficiency considered one of the causes of small foe size graft syndrome.

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