

Right-lobe Liver Transplant From Donors With Gilbert Syndrome

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Abstract

Objectives: Donor safety is one of the most important aspects of living-donor liver transplant. The preoperative evaluation of candidates for such transplants essentially starts with serologic and biochemical analyses. However, some potential liver donors with normal liver function test results may have isolated mild hyperbilirubinemia (serum indirect bilirubin level > 20.5 $\mu\text{mol/L}$ [1.2 mg/dL]). Gilbert syndrome is an autosomal recessive condition that is a common cause of nonhemolytic unconjugated hyperbilirubinemia, and its prevalence is 3% to 10% in the healthy US population. Mild hyperbilirubinemia episodes are expected in people with Gilbert syndrome when they are exposed to physical stress, such as operative intervention or low energy intake. The liver morphologic findings of these individuals are normal; however, there is a debate on the use of people with Gilbert syndrome as living-liver donors. The purpose of this study was to assess the results of right-lobe living-donor hepatectomy of liver donors with Gilbert syndrome.

Materials and Methods: Between 2004 and 2010, two hundred twenty-five living-donor liver transplants using right-lobe grafts were performed in our hospital. Donors with Gilbert syndrome were defined as those whose serum bilirubin level was greater than 20.5 $\mu\text{mol/L}$ (1.2 mg/dL). Six of 225 right-lobe living-donor liver transplants were performed using donors with Gilbert syndrome.

Results: The median follow-up after transplant was 34 months (range, 18 to 51 mo). One week after the operation, the median bilirubin level for right-lobe liver donors was 34.5 $\mu\text{mol/L}$ (2.02 mg/dL) (range, 17.1 to 51.3 $\mu\text{mol/L}$ [1 to 3 mg/dL]), and the median prothrombin time (international normalized ratio) was 1.36 (range, 1.1 to 1.7). The median bilirubin level of the donors after 6 months was 29 $\mu\text{mol/L}$ (1.7 mg/dL) (range, 20.5 to 41 $\mu\text{mol/L}$ [1.2 to 2.4 mg/dL]).

Conclusions: Living-donor liver transplant from Gilbert syndrome donors can be safely performed.

Key words: *Living-donor liver transplantation, Living-donor, Right hepatectomy, Gilbert syndrome, Hyperbilirubinemia*

Introduction

Liver transplant is the standard treatment of end-stage liver disease. In countries where organ shortage is a great problem, living-donor liver transplant has become the criterion standard treatment of end-stage liver disease.

One of the most important assays for preoperative evaluation of the liver donors is serum bilirubin level. Gilbert syndrome is an autosomal recessive disorder whose prevalence is reported as 3% to 10% in the US population.^{1, 2} Liver resection from patients with Gilbert syndrome³ and living-donor left hepatectomy from donors with Gilbert syndrome⁴ have been reported in the literature, but there are no clear data about safely using right-lobe liver grafts from this population.

The rapidly increasing number of liver transplant candidates force liver transplant centers such as ours to reassess their donor selection criteria. Nevertheless, the limits that might be successfully tolerated by donor grafts are potentially

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broad and require greater study. We report the results of a study of liver donors with Gilbert syndrome and the early graft outcomes in recipients based on liver function before and after the operation.

Materials and Methods

Between 2004 and 2010, two hundred twenty-five living-donor liver transplants using right-lobe grafts were performed in the Sisli Florence Nightingale Hospital, Department of General Surgery and Organ Transplantation. The recipients' and donors' data were collected from the Organ Transplantation Database. The preoperative donor evaluation included serologic and biochemical analyses, complete blood count, computed tomography (CT), and magnetic resonance cholangiopancreatography.

Donors with Gilbert syndrome were defined as those whose serum bilirubin level was greater than 20.5 $\mu\text{mol/L}$ (1.2 mg/dL) with indirect hyperbilirubinemia, normal serologic findings and transaminase levels, normal protein electrophoresis and imaging results, and no previous drug use in the last 3 months. Six of 225 right-lobe living-donor liver transplants were performed using donors with Gilbert syndrome. For these 6 transplants, the clinical course and laboratory values were studied preoperatively and postoperatively.

Preoperative donor remnant liver volume was calculated by volumetric CT scan, leaving a remnant greater or equal to 30% in the right-lobe liver donor.

Results

The median follow-up after transplant was 34 months (range, 18 to 51 mo). Five of the 6 donors were male (age range, 18 to 48 y; median age, 26 y). The recipients were 4 men and 2 women (age range, 30 to 63 y; median age, 46 y). Indications for living-donor liver transplant in these patients were

hepatitis B-related cirrhosis (n=2), hepatitis C-related cirrhosis (n=1), primary sclerosing cholangitis (n=1), and cryptogenic cirrhosis (n=2).

There were no medical or surgical complications in any of the donors. One week after the operation, the median bilirubin level for right-lobe liver donors was 34.5 $\mu\text{mol/L}$ (2.02 mg/dL) (range, 17.1 to 51.3 $\mu\text{mol/L}$ [1 to 3 mg/dL]), and the median prothrombin time (international normalized ratio) was 1.36 (range, 1.1 to 1.7). The median bilirubin level of the donors after 6 months was 29 $\mu\text{mol/L}$ (1.7 mg/dL) (range, 20.5 to 41 $\mu\text{mol/L}$ [1.2 to 2.4 mg/dL]). Postoperative laboratory values of the individual donors are presented in the Table.

All 6 recipients were discharged from the hospital, but 2 died during follow-up. One of these 2 recipients died of sepsis 6 weeks after the operation. The other recipient died 8 months after the operation as a result of biliary leakage and sepsis. All other recipients did well, without any complications. The median bilirubin level and prothrombin time were 20.5 $\mu\text{mol/L}$ (1.2 mg/dL) (range, 10.2 to 41 $\mu\text{mol/L}$ [0.6 to 2.4 mg/dL]) and 1.25 (range, 1 to 1.7) at the end of 2 years.

Discussion

Liver transplant is the criterion standard treatment of end-stage liver disease. In countries where organ supply stays under the demand, living-donor liver transplant has become the standard treatment of end-stage liver disease. Right-lobe living-donor liver transplant is performed more frequently in adults because of the metabolic demand of the recipient. Selection of right-lobe liver donors was reported in the literature by Marcos and associates.⁵ The authors defined suitable donors as having normal laboratory findings, excluding unrecognized infection, liver disease, metabolic disorders, and conditions representing undue

Table 1. Preoperative and postoperative laboratory values.

Patient No.	Age (y)	Preoperative values		Postoperative (week 1) values		Postoperative values (after 1 week)		
		Bilirubin, $\mu\text{mol/L}$ (mg/dL)	Prothrombin time (INR)	Bilirubin, $\mu\text{mol/L}$ (mg/dL)	Prothrombin time (INR)	AST, $\mu\text{mol/L}$ (U/L)	ALT, $\mu\text{mol/L}$ (U/L)	GGT, $\mu\text{kat/L}$ (U/L)
1	30	58.4 (3.4)	1.10	44.4 (2.6)	1.1	(32)	(66)	(150)
2	23	27.3 (1.6)	1.10	25.6 (1.5)	1.6	(40)	(28)	(27)
3	21	41 (2.4)	0.80	44.4 (2.6)	1.3	(35)	(75)	(190)
4	48	42.7 (2.5)	1.10	44.4 (2.6)	1.1	(60)	(112)	(159)
5	18	34 (2.0)	1.00	8.5 (0.5)	1.44	(36)	(66)	(68)
6	32	37.6 (2.2)	1.02	51.3 (3.0)	1.7	(150)	(161)	(62)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ -glutamyltransferase; INR, international normalized ratio

surgical risk. Imaging studies including abdominal CT and magnetic resonance cholangiopancreatography to assess the anatomy of the liver are mandatory. Valentin-Gamazo and associates⁶ reported an evaluation protocol for living-donor candidates for liver donation.

Although right-lobe hepatectomy in a living donor potentiates a challenging and complex procedure, the risk of expanding donor selection criteria is being discussed among organ transplant centers because of the organ shortage. The use of extended-criteria donors dates to 1987.⁷ However, the definition of extended-criteria donors has not been done clearly.

Some authors' recent investigations supported a relation between the graft quality and transplant outcome. Cameron and associates⁸ defined a scoring system for extended-criteria donors, which includes donor age greater than 55 years, donor hospital stay more than 5 days, cold ischemia time more than 10 hours, and warm ischemia time more than 40 minutes. The results showed an increased mortality risk for donors with high scores. On the other hand, Feng and associates⁹ defined a donor risk index, which precludes donor age greater than 40 years (particularly more than 60 years), donation after cardiac death or partial grafts, African American race, shorter height, cerebrovascular accident, and "other" causes of brain death. Some studies demonstrated that hepatosteatosis exceeding 30% is associated with a marked increase in graft failure.^{10, 11} A more-recent study, however, demonstrated similar 60-day mortality rates and similar 3-year patient survival rates (83% vs 84%) comparing the transplant of steatotic livers with nonsteatotic livers.¹² These results conclude that the criteria used to select appropriate liver donors must be reevaluated in the settings of improved surgical technique, preoperative patient management, and immunosuppression.¹² In those 3 reports,¹⁰⁻¹² Gilbert syndrome is not a risk factor or an extended criterion in living-donor liver transplant.

Gilbert syndrome (also called *familial nonhemolytic nonobstructive jaundice*) is an autosomal recessive disorder caused by reduction in the glucuronidation activity of the enzyme uridine diphosphate-glucuronosyltransferase.² The prevalence of Gilbert syndrome in the US population is reported as 3% to 10% and up to 12% in the male population.¹³ Because the diagnosis of Gilbert syndrome varies according to

bilirubin levels, fasting periods, and methods of analysis, the range may vary among 3% to 36% in different communities (eg, Asians and Africans). Gilbert syndrome is considered a benign condition with no morbidity and mortality. It affects men more often than women, varying among populations (2:1 to 7:1). The diagnosis of Gilbert syndrome usually is made during puberty because of inhibition of bilirubin glucuronidation by endogenous steroid hormones. Diagnosis in elderly patients often occurs when results of routine biochemical testing (serum unconjugated bilirubin levels) reveal hyperbilirubinemia.

It is not clear whether a liver graft from a donor with Gilbert syndrome could result in a normal outcome for the recipient. Henne-Bruns and Kremer¹⁴ reported the first case of Gilbert syndrome in a liver transplant recipient as a cause of hyperbilirubinemia after liver transplant in 1988. They described a 33-year-old woman having an increased unconjugated bilirubin level with normal results of liver function tests. Hemolysis, rejection, biliary obstruction, and infection were excluded, and Gilbert syndrome was suspected. They defined the metabolic disorder as a harmless condition to the liver transplant recipient. Furthermore, Miyake and associates¹⁵ reported living-donor liver transplant from a donor with Gilbert syndrome to a cirrhotic patient. The recipient, a 22-year woman, died 16 months after the operation owing to subacute fulminant hepatitis, but the authors concluded that liver graft from a donor with Gilbert syndrome could be transplanted safely.¹⁵ Similarly, Arita and associates³ reported that liver resection in 2 patients with Gilbert syndrome could be performed safely. In addition, Gates and associates¹⁶ reported that the recipients who did seem to have Gilbert syndrome after liver transplant had excellent long-term survival and completely normal graft function among their 229 recipients.¹⁶

In conclusion, according to the literature and our experience, it seems that transplant of a partial right-lobe liver graft from a living donor with Gilbert syndrome does not lead to poor outcomes. However, to achieve more satisfactory results, more prospective randomized trials are needed.

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