Pretransplant Serum Hyaluronic Acid Can Be a Biomarker as a Prognostic Predictor in Adult-to-Adult Living Donor Liver Transplantation

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ABSTRACT

Objective. The goal of this study was to evaluate whether pretransplant serum hyaluronic acid (HA) levels can predict outcomes after adult-to-adult living donor liver transplantation (LDLT).

Methods. In study I, 21 patients who underwent LDLT (March 2002-February 2004) were divided into 2 groups: the H-I group (HA $\geq$500 ng/mL; n = 12) and the L-I group (HA <500 ng/mL; n = 9). The influence of pretransplantation HA levels on short-term surgical outcome was investigated. In study II, 77 LDLT patients (May 2004-December 2014) were also divided into 2 groups: the H-II group (HA $\geq$500 ng/mL; n = 40) and the L-II group (HA <500 ng/mL; n = 37). We compared long-term survival and investigated prognostic factors.

Results. In study I, HA levels significantly decreased after LDLT, and those in the H-I group were significantly higher compared with the L-I group at 1, 3, 5, and 7 days after LDLT. There were significant differences in postoperative peak total bilirubin levels (H-I vs L-I, 17.2 vs 6.2 mg/dL; $P = .013$), peak ascitic fluid volume (1327 vs 697 mL/d; $P = .005$), and the hepatocyte growth factor levels at 3 days after LDLT (1879 vs 1092 pg/mL; $P = .03$). In study II, the 1- and 5-year survival rates were significantly lower in the H-II group than in the L-II group (H-II vs L-II, 65.0% and 48.5% vs 86.5% and 80.8%; $P = .004$). In multivariate analysis, significant prognostic factors were preoperative HA $\geq$500 ng/mL ($P = .004$) and graft to recipient body weight ratio <0.8 ($P = .042$).

Conclusions. Preoperative HA level can be a prognostic risk factor. Patients with high HA levels are vulnerable and should be carefully managed after LDLT.

HYALURONIC ACID (HA) is a high-molecular-weight polysaccharide that is widely distributed in connective tissue. It is produced by fibroblasts and enters the circulation via lymph [1]; it is taken up by hepatic sinusoidal endothelial cells (SEC) and degraded by hyaluronidase enzyme [2]. Liver disease is associated with increased levels of HA [3,4]. Significant correlations between serum HA levels and degree of liver damage have been found in primary biliary cirrhosis, alcoholic liver disease, and chronic hepatitis C [5–7]. Therefore, HA levels can be used to assess liver function status.

In a previous study, we showed that serum HA levels successfully predicted liver failure after hepatectomy in 100 consecutive patients with cirrhosis or obstructive jaundice

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[8]. In terms of liver transplantation (LT), however, only a few studies have assessed the relationship between pretransplant serum HA levels or correlating effluent HA levels from perfusion solution and early graft function and/or primary nonfunction of the liver after LT [9,10]. The present study was therefore performed to assess the relationship between pretransplant serum HA levels and short- and long-term outcomes after adult-to-adult living donor liver transplantation (LDLT).

PATIENTS AND METHODS

Study I: Influence of Pretransplant HA Levels on Short-Term Surgical Outcome

Twenty-one patients (mean age, 51 years; range, 20–64 years; 13 male subjects and 8 female subjects) who underwent adult-to-adult LDLT between March 2002 and February 2004 were retrospectively studied. The etiologies for LDLT were cirrhosis (hepatitis C virus, hepatitis B virus, and alcohol) complicated by hepatocellular carcinoma (HCC) in 15 patients, primary biliary cirrhosis in 3, primary sclerosing cholangitis in 1, and fulminant hepatic failure in 2. Grafts comprised a right lobe graft in 20 patients and a left lobe graft with middle hepatic vein in 1. ABO blood group compatibility was identical in 17 patients, compatible in 3, and incompatible in 1. The patients were divided into 2 groups according to the pretransplant HA level: the H-I group (HA $\geq$500 ng/mL; n = 12) and the L-I group (HA <500 ng/mL; n = 9). The cutoff value of serum HA 500 ng/mL was chosen because this value was associated with liver failure after hepatectomy in our previous study [8]. The following perioperative factors regarding short-term surgical outcome were compared: postoperative liver function, changes in serum HA levels, hepatocyte growth factor (HGF) levels, and postoperative complications and outcome.

Blood samples were obtained from a peripheral vein preoperatively and at 1, 3, 5, and 7 days after LDLT. Samples were collected into a serum separator tube and centrifuged for 10 minutes at 3000*g*, and serum was stored at −80°C until assayed. Serum HA levels were measured by using a sandwich enzyme method according to manufacturer instructions (Funakoshi Co, Ltd, Tokyo, Japan) preoperatively and at 1, 3, 5, and 7 postoperative days (PODs). The data regarding serum HGF levels measured by using an enzyme immunoassay method on 3 PODs were collected from patients' record files. Data regarding serum alanine transaminase, bilirubin, prothrombin time, international normalized ratio (INR), and ascitic fluid volume were also collected from patients' record files.

Study II: Influence of Pretransplant HA Levels on Long-Term Surgical Outcomes

Based on the results of study I, adult LDLT patients (May 2004-December 2014) were reviewed and divided into 2 groups: the H-II group (HA $\geq$500 ng/mL; n = 40) and the L-II group (HA <500 ng/mL; n = 37). We compared the liver regeneration ratio based on CT volumetry (liver volume at 1 month after LDLT/standard liver volume) and overall survival, and investigated the prognostic risk factor of survival in this series. Standard liver volume was calculated according to the formula proposed by Urata et al [11]. To justify the cutoff value of a pretransplant HA level of 500 ng/mL, the cutoff value of HA for 1-, 2-, and 3-year survival was determined by using the receiver operating characteristic (ROC) curve.

LDLT Procedures

All LDLT procedures for both donors and recipients were performed according to details from our previously articles [12,13]. The right hepatic vein or common trunk of the left and middle hepatic veins was anastomosed to the inferior vena cava in an end-to-side fashion. Reconstruction of the hepatic arteries was performed with end-to-end anastomosis by using a surgical microscope. The bile duct was basically reconstructed with duct-to-duct anastomosis, and hepaticojejunostomy was used in patients with primary sclerosing cholangitis.

Postoperative Management

The immunosuppression protocol consisted of tacrolimus and low-dose steroids according to our previous research [14]. The target

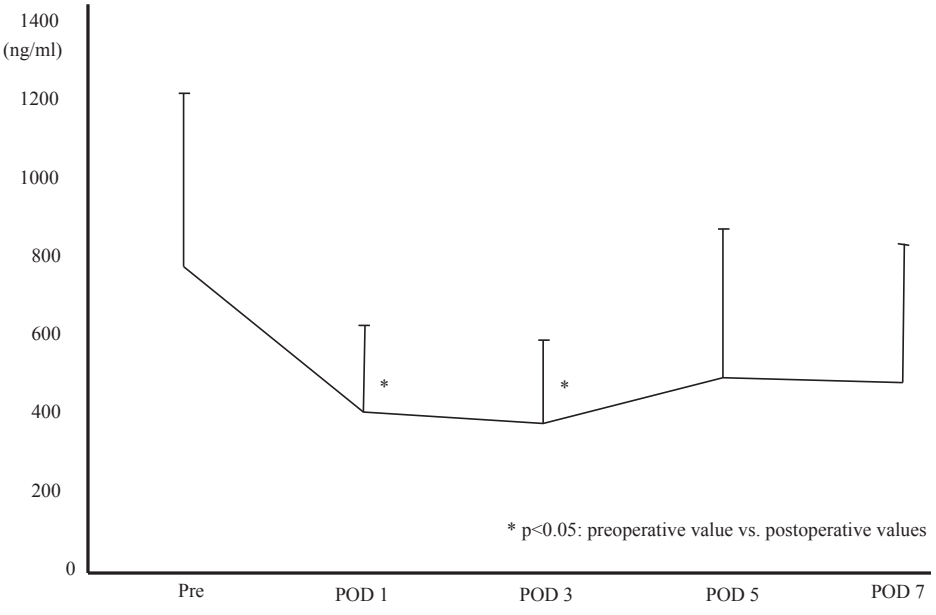

Fig 1. Perioperative changes in serum hyaluronic acid (HA) levels in living donor liver transplantation recipients (study I). Serum HA levels decreased after living donor liver transplantation, and HA levels on postoperative days (PODs) 1 and 3 were significantly lower than that of pretransplant levels ($P = .034$ on POD 1, $P = .028$ on POD 3).