Association of Platelet Count and Platelet Transfusion With Serotonin Level During Living Donor Liver Transplantation: Possible Connection to Graft Regeneration

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ABSTRACT

Background. We recently showed that platelet counts and the amount of platelet transfusion during liver transplantation are positively associated with early graft regeneration. It was hypothesized that platelet-derived serotonin mediates liver regeneration.

Objectives. This study aimed to evaluate the association between intraoperative platelet count, platelet transfusion, and serum serotonin level.

Methods. Thirty-two recipients undergoing living-donor liver transplantation were enrolled into this prospective observational study. Serum platelet counts and serotonin levels were measured at the following times: anesthetic induction, start of the anhepatic phase, before graft reperfusion, 5 minutes/1 hour/3 hours/5 hours after graft reperfusion, and before/after platelet transfusion. Serotonin was measured by using a liquid chromatography tandem mass spectrometry.

Results. Serotonin level at the anesthetic induction was 24.5 μg/mL (interquartile range, 14.6 to 38.1 μg/mL). During surgery, serial changes in platelet counts and serotonin levels showed a similar trend: they decreased during the anhepatic phase, increased during the first hour after graft reperfusion, and thereafter gradually decreased. Serotonin level was positively correlated with platelet counts (correlation coefficient = 0.620, $P < .001$). Allogeneic platelet transfusion significantly increased platelet count from 22 (19–31) $\times 10^9$/L to 53 (50–81) $\times 10^9$/L ($P = .008$) and it also increased serum serotonin from 11.04 (6.41–15.34) μg/mL to 34.26 (25.86–41.94) μg/mL ($P = .008$).

Conclusions. Our findings indicate that allogeneic platelets could act as effector cells deriving serotonins. Also, our findings support the hypothesis that the association between platelets and post-transplantation graft regeneration is mediated by serotonin. Further studies are warranted regarding the respective role of serotonin and other platelet-derived molecules mediating liver regeneration.

THE REMARKABLE ability of the liver to regenerate has allowed living-donor liver transplantation (LDLT) to become a reality [1]. However, LDLT involves the potential risk of liver failure resulting from insufficient graft regeneration. Thus, liver regeneration has been a key element for the success of LDLT. Liver regeneration is orchestrated by the interplay of various cells and mediators. Among them, platelet-derived mediators are known to play important roles; specifically, a landmark study by Lesurtel et al. and studies that followed newly found that platelet-derived serotonin mediates liver regeneration [2–4]. The triggering signals for the regeneration pathways occur

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0041-1345/18
https://doi.org/10.1016/j.transproceed.2018.02.035

immediately after hepatic tissue injury, such as functional mass decrease or ischemia reperfusion injury. That is, regeneration of partial liver graft of reduced size is initiated immediately after graft reperfusion during LDLT; thus, the intraoperative postreperfusion period is considered highly critical [5]. In this regard, our recent research showed that intraoperative platelet counts during the postreperfusion phase and platelet transfusion were significantly associated with the degree of early graft regeneration after LDLT [5]. Taken together, we hypothesized that intraoperative platelet counts and platelet transfusion may affect graft regeneration in relation to serotonin pathway. In this study, we aimed to evaluate the association between intraoperative platelet counts and serum serotonin levels as well as the effect of intraoperative platelet transfusion on serum serotonin level in LDLT.

PATIENTS AND METHODS

After obtaining ethics committee approval (SMC 2015-02-065) and informed consent, 32 recipients undergoing a first elective adult-to-adult LDLT for treating chronic cirrhosis between March 2015 and January 2016 were enrolled into this prospective observational study. Anesthetic and surgical managements were performed according to our institutional standard protocols irrespective of the current study [5]. Serum platelet counts and serotonin levels were measured at the following determined times: immediately after anesthetic induction, at the start of the anhepatic phase, immediately before graft reperfusion, and 5 minutes, 1 hour, 3 hours, and 5 hours after graft reperfusion. Platelet counts and serotonin levels were additionally measured immediately before platelet transfusion and immediately after platelet transfusion when platelets were transfused. One unit of apheresis platelets, which contains 2.5–4.0 $\times$ 10^{11} platelets in 240–280 mL volume, were indicated when platelet count was $<30 \times 10^9$/L. All transfused platelets were leukoreduced and irradiated. The platelet storage duration was limited to 5 days or less.

Arterial blood was drawn to measure serum serotonin via a radial arterial catheter into serum separating tubes containing citrate, theophylline, adenosine, and dipyridamole, and the arterial sample was immediately centrifuged at 1500 $\times$ g and 4°C for 15 minutes. The supernatant was stored at −80°C. The centrifugation device was nearby and we were able to transfer the arterial blood within 10 minutes after blood sampling and the serum preparation process of all blood samples was uniformly performed by S.H. Serotonin was measured using liquid chromatography tandem mass spectrometry (LC-MS/MS) [6]. Platelet count was measured immediately after arterial sampling in our central laboratory.

Data are analyzed using SPSS 19.0. (SPSS Inc, Chicago, Illinois, United States). Continuous variables are described as median (25th percentile, 75th percentile), and categorical variables are expressed as frequency (%). Correlation between continuous variables was performed using the Pearson's test. Comparison of paired datasets was performed using the Wilcoxon test. A P value $< .05$ was considered statistically significant.

RESULTS

Recipients' baseline characteristics are described in Table 1. A total of 224 datasets of platelet counts and serotonin levels were obtained. Platelet count was 54 (35–74) $\times$ 10^9/L after anesthetic induction (baseline value), being similar to the preoperative value measured 1 day before surgery (58 [36–87] $\times$ 10^9/L). Baseline serotonin level was 24.5 (14.6–38.1) μg/mL. During surgery, the movement of platelet counts and serotonin levels was similar (Figs 1A, B): they decreased during the anhepatic phase, increased during the first hour after graft reperfusion, and thereafter gradually decreased. As shown in Fig 1C, the serotonin level was positively correlated with platelet counts (correlation coefficient = 0.620, $P < .001$). Platelet transfusion was performed nine times for eight recipients: seven recipients received 1 platelet unit and another recipient received 2 platelet units. As shown in Figs 1D and 1E, transfusion of 1 single donor platelet unit significantly increased platelet count from 22 (19–31) $\times$ 10^9/L to 53 (50–81) $\times$ 10^9/L ($P = .008$) and it also increased serum serotonin from 11.04 (6.41–15.34) μg/mL to 34.26 (25.86–41.94) μg/mL ($P = .008$). This finding indicated that allogeneic platelets could act as effector cells that derive serotonins and mediate liver regeneration, similar to autologous platelets.

Table 1. Clinical Data From 32 Recipients Undergoing Living-donor Liver Transplantation

Variables	Descriptive Statistics
Graft factors	
Donor age (y)	31 (25–41)
Male donor	16 (50.0)
Macrosteatosis > 5%	16 (50.0)
Graft-to-recipient weight ratio	0.97 (0.91–1.17)
ABO blood-type incompatible donor	8 (25.0)
Cold ischemia time (min)	86 (81–112)
Warm ischemia time (min)	35 (24–50)
Pringle maneuver (rounds) during procurement	
0	16 (50.0)
1–2	13 (40.6)
≥3	3 (9.4)
Recipient factors	
Age (y)	54 (50–59)
Male	26 (81.3)
Body mass index (kg/m^2)	24.2 (21.4–26.7)
Non-viral cirrhosis	7 (21.9)
Hepatocellular carcinoma	
None	9 (28.1)
Within the Milan criteria	15 (46.9)
Beyond the Milan criteria	8 (25.0)
MELD score	12 (9–17)
Neutrophil-to-lymphocyte ratio	2.3 (1.1–3.4)
Refractory ascites	5 (15.6)
Operative time (min)	510 (447–570)
Salvaged RBC during surgery (mL)	803 (588–1248)
Allogeneic RBC transfusion during surgery (units)	0 (0–1)

Data are presented as the median (25th percentile–75th percentile) or frequency (%) values.
Abbreviations: MELD, model for end-stage liver disease; RBC, red blood cells.

DISCUSSION

This is the first work to describe the intraoperative changes of serum serotonin during LDLT. Serum serotonin was measured by using a LC-MS/MS, a highly reliable method.