

Practical Coagulation Management in Liver Transplantation Through Point-of-Care Analysis Using the TEG 6s Global Hemostasis System in Japan

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Liver transplantation (LT) is the standard treatment for end-stage liver disease. However, owing to a precarious balance between pro- and anticoagulation factors, patients undergoing LT are at high risk of massive bleeding and vascular thromboembolic complications. Thromboelastography (TEG) allows for the rapid, comprehensive, and accurate identification of coagulation monitoring undergoing LT. Newly released TEG 6s global hemostasis systems have been introduced, which we hypothesized could contribute to practical coagulation management in LT. TEG 6s was used for 15 patients undergoing LT at eight preset times during and after LT. Anesthesiologists and a surgical intensive care team managed coagulation during and after LT, based fully on TEG 6s findings. We focused on the citrated kaolin reaction time, citrated kaolin maximum amplitude, and functional fibrinogen maximum amplitude. TEG 6s was also used to determine transfusion principles with a focus on the details of cases with difficult to manage coagulation. Among 15 LT patients, six had massive bleeding-related complications and vascular thromboembolic complications. Case management and detailed TEG 6s results were reviewed. We recommend using the TEG 6s to obtain a comprehensive understanding of coagulation management as this global hemostasis system offers superior insights compared with standard laboratory tests.

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Introduction

Liver transplantation (LT) is the current standard treatment for end-stage liver disease (ESLD). However, owing to a precarious balance between pro- and anticoagulation factors, patients undergoing LT are at high risk of massive bleeding; thus, requiring massive transfusion. Moreover, some patients are also at high risk of vascular thromboembolic complications (Clevenger and Mallett 2014).

LT management and coagulation monitoring are challenging and are usually based on standard laboratory tests. However, Haas et al. (2015) reported that standard laboratory tests are only effective for some subsets of LT recipients. Tripodi et al. (2016) reported that prothrombin time (PT) and activated partial thromboplastin time (aPTT) prolongation in patients with ESLD did not reflect actual thrombin generation because of incomplete thrombin acti-

vation. Thromboelastography (TEG) was first reported by Hartert in 1948 (Hartert 1948). TEG allows for the rapid, comprehensive, and accurate identification of an individual's hemostatic condition in a point-of-care setting. In patients undergoing LT, TEG-based algorithms have been reported to reduce blood, fresh frozen plasma (FFP), and platelet transfusions (Kang et al. 1985; Sabate et al. 2016). Krzanicki et al. (2013) reported these algorithms to be superior in predicting hypercoagulability complications compared with standard laboratory tests. The TEG5000 (Haemonetics Corporation, Braintree, MA, USA) measures whole blood clotting through calculating the increasing torsion on a wire suspended in a small cup of clotting blood rotated backward and forward between 0° and 45° (Karon 2014). However, the TEG5000 system is limited in that it needs to be calibrated daily, trained and skilled personnel is required to perform the test, and the device needs to be

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placed in a low-vibration environment. As a new-generation TEG device, the newly released TEG 6s global hemostasis system (Haemonetics Corporation, Braintree, MA, USA, [hereafter referred to as the TEG 6s]) uses the resonant frequency of clotting blood samples to produce the same clotting measures as the TEG5000 device, but has the following advantages: less frequent calibration requirements, ease of use, and less sensitivity to movement.

We hypothesized that the TEG 6s could contribute to practical coagulation management in LT. Here, we report three cases of massive intra- and postoperative LT-related bleeding and three cases of intraoperative thrombotic complications. All cases were analyzed using the TEG 6s. This is the first observational pilot study conducted in Japan using this system.

Methods

This single-center prospective observational study was conducted at Tohoku University Hospital, Japan, a tertiary referral hospital performing 10-15 LTs annually. Following institutional review committee approval (No. 2021-1-658, approved on November 15th, 2021), the TEG 6s measurements started in August 2022. We performed 15 LTs between June 2022 and September 2023. Considering that the TEG 6s measurement is not covered by national insurance, written informed consent was obtained from all patients prior to the TEG 6s system measurement.

Our perioperative management and surgical procedures for both cadaveric donor and living-donor LTs are briefly described. Patients were monitored using electrocardiography, pulse oximetry, invasive systemic blood pressure, a pulmonary Swan-Ganz catheter, and transesophageal echocardiography. General anesthesia was induced with propofol, fentanyl, and rocuronium, and maintained with propofol. After induction, a hepatectomy was performed using the piggyback technique. For both living-donor and cadaveric donor LTs, venous anastomosis was performed using a total clamp of the inferior vena cava. Portal vein anastomosis was performed in a standard continuous fashion. Arterial anastomosis of living-donor LT was performed using a micro-surgically interrupted technique, and cadaveric donor LT was performed continuously. Bile duct anastomosis was then performed using a duct or hepaticojejunostomy. When achieving hemostasis becomes challenging during surgery, we choose perihepatic gauze packing and second-look surgery for packing removal and fascial closure.

As previously described, the TEG 6s provides four

assays in one multichannel cartridge, with each assay measuring a specific component of the coagulation process (Gurbel et al. 2016; Lloyd-Donald et al. 2019). The first assay was citrated kaolin (CK), containing the coagulation activator, kaolin; providing clot reaction time (R time, the time from the start of analysis until thrombus amplitude reaches 2 mm); clot kinetics (K time, the time from thrombus amplitude reaching 2 mm until amplitude reaches 20 mm); the thrombus generation angle (alpha angle, the slope of a tangent line from the tracing at the midpoint between the R and the K time); thrombus maximum amplitude (MA), measuring absolute thrombus strength; and the percentage of fibrinolysis (LY30%). The second assay was the rapid-TEG assay (RT), which contains tissue factor and kaolin and provides rapid R time, K time, MA, and LY30%. The third assay was heparinase kaolin (HK), which contains kaolin and heparin-neutralizing enzymes, and provides R time, K time, alpha angle, and MA. The final assay was functional fibrinogen (FF), which provides the MA based on fibrinogen contribution to the thrombus and the functional fibrinogen level (an estimation of the plasma fibrinogen level, reference range). Although TEG 6s can assess many assays, as described in previous studies (De Pietri et al. 2016), in this study, we focused on the citrated kaolin reaction time (CK-R), citrated kaolin maximum amplitude (CK-MA), and functional fibrinogen maximum amplitude (FF-MA) to simplify our coagulation management and transfusion protocol. The manufacturers' reference ranges for CK-R, CK-MA, and FF-MA are 4.6-9.1 min, 52-69 mm, and 15-32 mm, respectively. We used control TEG6s data from six healthy Japanese living liver donors. The CK-R, CK-MA, and FF-MA results were 7.8 \pm 0.74 min, 54.5 \pm 5.44 mm, and 17.2 ± 2.85 mm, respectively (Table. 1).

A skilled anesthesiologist managed the coagulopathy during the surgery. The transfusion protocol during surgery was not entirely determined but was based on discretion and the TEG 6s findings. The TEG 6s made measurements at four preset times during surgery: at baseline (when the patient first entered the operating room), at the anhepatic phase (30 min after portal vein ligation), at reperfusion (30 min after arterial anastomosis), and postoperatively (when the patient entered the surgical intensive care unit [SICU]). A SICU team undertook the postoperative patient management based on the TEG 6s findings. The principles of transfusion were as follows: (i) FFP should be administered if the CK-R time is > 10 min, (ii) cryoprecipitate should be administered if the FF-MA level is < 15 mm, and (iii) platelets should be administered if the CK-MA level is < 40 mm.

Table 1	1. Reference ranges by the manufactures and healthy control group of CK-R, CK-MA and FF-MA.	
Variable	Reference ranges by the manufacturers	healthy control

The TEG 6s was measured at four preset times on postoperative day (POD)1, POD3, POD5, and POD7.

Erythrocyte concentrates were transfused to maintain hemoglobin levels at 8-9 g/dL. Albumin was administered during standard-volume resuscitation or in larger volumes if a patient experienced massive bleeding or ascites.

We retrospectively collected patient characteristics, TEG 6s data that focused on citrated kaolin (CK) and functional fibrinogen (FF), and the amount of transfusion during and after LT. Red blood cell (RBC), FFP, platelets, and cryoprecipitate transfusion amounts were collected separately.

Case Reports

Cases 1-3: massive bleeding during and after LT

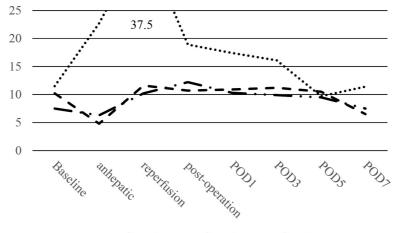
In Case 1, a 51-year-old female with primary biliary cholangitis and a model for end-stage liver disease (MELD) score of 23 underwent a cadaveric LT. The operative time and blood loss were 698 min and 7,715 mL, respectively. During the LT, she underwent the following transfusions: RBCs, 4760 mL; FFP, 6720 mL; platelets, 600 mL; and cryoprecipitate, 0 mL. The donor liver showed moderate macrosteatosis (66.6%). Massive bleeding occurred following liver reperfusion owing to hemodynamic instability and post-reperfusion syndrome. Due to postoperative bleeding, an exploratory laparotomy was performed on POD2. The transfusion amounts after liver transfusion in the SICU were as follows: RBCs, 3,080 mL; FFP, 1,920 mL; platelets, 500 mL; and cryoprecipitates, 0 mL. Her CK-R, CK-MA, and FF-MA findings are summarized in Figs. 1-4. Despite a massive transfusion, the patient experienced bleeding with an elongated CK-R time.

In Case 2, a 55-year-old male with cryptogenic cirrhosis and a MELD score of 27 underwent a cadaveric LT. The operative time and blood loss were 498 min and 11,590 mL, respectively. During the LT, he underwent the following transfusions: RBCs, 4,430 mL; FFP, 7,680 mL; platelets, 600 mL; and cryoprecipitate, 0 mL. During surgery, we observed that this patient had a cocoon abdomen due to his history of recurrent spontaneous bacterial peritonitis. Extensive adhesiolysis was required, which resulted in significant intraoperative bleeding. At eight hour postoperatively, the patient required a laparotomy owing to postoperative bleeding. The transfusion amounts after liver transfusion in the SICU were as follows: RBCs, 2,240 mL; FFP, 2,400 mL; platelets, 200 mL; and cryoprecipitate, 0 mL. His CK-R, CK-MA, and FF-MA findings are summarized in Figs. 1-3. Coagulation was relatively well controlled during surgery despite massive bleeding. However, the CK-R time postoperatively was 12.2 min, which was sufficient to induce postoperative bleeding.

In Case 3, a 39-year-old female with liver cirrhosis owing to biliary atresia and a MELD score of 40 underwent a cadaveric LT. The operative time and blood loss were 740 min and 32,273 mL, respectively. During the LT, she underwent the following transfusions: RBCs, 14,000 mL; FFP, 14,160 mL; platelets, 1,200 mL; and cryoprecipitate, 300 mL. The LT procedure became extremely challenging owing to severe preoperative coagulopathy and adhesions from a prior Kasai procedure. Optimal hemostasis during surgery was also challenging and gauze packing was used for hemostasis. On POD2, a laparotomy was performed to remove the gauze. The transfusion amounts after liver transfusion in the SICU were as follows: RBCs, 1,960 mL; FFP, 3,120 mL; platelets, 400 mL; and cryoprecipitate, 0 mL. Her CK-R, CK-MA, and FF-MA findings are summarized in Figs. 1-3. The CK-R times pre-LT through to POD5 were extended owing to severe coagulopathy, which led to massive bleeding. To achieve hemostasis, a more aggressive FFP transfusion was required.

Cases 4-6: intraoperative thrombotic complications during LT

In Case 4, a 23-year-old male with primary sclerosing



– – Case 1 **––** •Case 2 •••••• Case 3

Fig. 1. CK-R results concerning massive bleeding during and after liver transplantation. The CK-R results of massive bleeding cases are relatively higher compared to the results of intraoperative thrombotic cases.

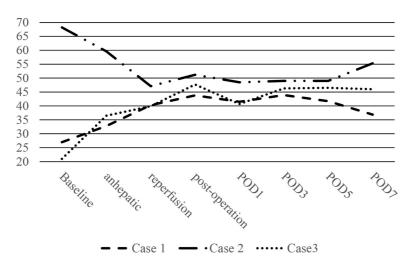


Fig. 2. CK-MA results concerning massive bleeding during and after liver transplantation. The CK-MA results of massive bleeding cases are relatively lower compared to the results of intraoperative thrombotic cases.

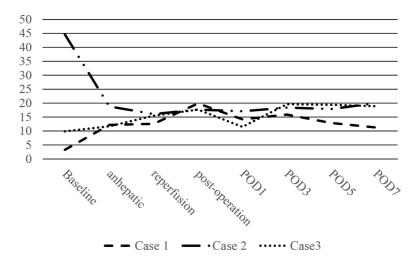


Fig. 3. FF-MA results concerning massive bleeding during and after liver transplantation. The FF-MA results of massive bleeding cases are relatively lower compared to the results of intraoperative thrombotic cases.

cholangitis and a MELD score of 10 underwent a livingdonor LT. His coagulation factor level was maintained as the indication for LT was recurrent cholangitis. The operative time and blood loss were 765 min and 2,009 mL, respectively. The anesthesiologist did not administer any blood products during the LT. His LT was complicated with intraoperative portal vein thrombosis immediately following reperfusion, leading to reanastomosis. Immediately upon admission to the SICU, we initiated an intravenous administration of 5,000 U of unfractionated heparin daily in recognition of his hypercoagulable state. No blood products were administered in the SICU. His CK-R, CK-MA, and FF-MA findings are summarized in Figs. 4-6. Analysis of the CK-R, CK-MA, and FF-MA findings from baseline to POD7 revealed a hypercoagulable state in the patient, which contributed to the intraoperative thrombotic complications. Consideration could have been given to perioperative heparinization, which may have mitigated these risks during implantation.

In Case 5, a 51-year-old male with alcoholic cirrhosis and a MELD score of 8 underwent a living-donor LT. The indication for LT was hepatic encephalopathy leading to recurrent episodes of coma, and his coagulation factor level was still maintained. The operative time and blood loss were 913 min and 5,204 mL, respectively. During the LT, he underwent the following transfusions: RBCs, 3,080 mL; FFP, 2,640 mL; platelets, 0 mL; and cryoprecipitate, 50 mL. His LT was complicated with a common hepatic artery thrombosis occurring prior to arterial anastomosis, necessitating arterial thrombectomy using a 4-Fr Fogarty catheter. No blood products were administered in the SICU. His CK-R, CK-MA, and FF-MA findings are summarized in Figs. 4-6. We initiated administration of 5,000 U of unfractionated heparin daily on POD7. His CK-R time remained within the normal range throughout the procedure, whereas his FF-MA level remained consistently very low. In such

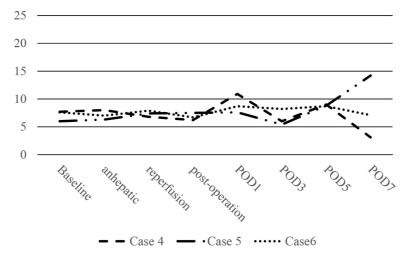


Fig. 4. CK-R intraoperative thrombotic complications during liver transplantation. The CK-R results of intraoperative thrombotic cases are relatively lower compared to the results of massive bleeding cases.

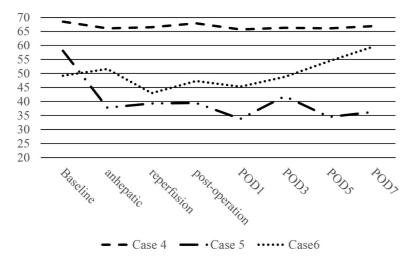


Fig. 5. CK-MA intraoperative thrombotic complications during liver transplantation. The CK-MA results of intraoperative thrombotic cases are relatively higher compared to the results of massive bleeding cases.

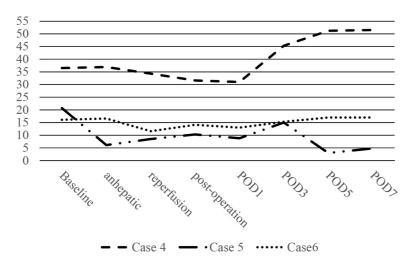


Fig. 6. The result of FF-MA of intraoperative thrombotic complications during liver transplantation. The FF-MA results of intraoperative thrombotic cases are relatively higher compared to the results of massive bleeding cases.

cases, close attention should be paid to the risk of intraoperative thrombotic complications.

In Case 6, a 59-year-old female with primary biliary cholangitis and a MELD score of 12 underwent a livingdonor LT. The operative time and blood loss were 582 min and 541 mL, respectively. The transfusion amounts during LT were: RBC, 560 mL; FFP, 1,920 mL; platelets, 0 mL, and cryoprecipitate, 0 mL. LT was complicated by right posterior portal vein thrombosis immediately following reperfusion, necessitating thrombectomy with temporary portal vein clamping. No blood products were administered in the SICU. Her CK-R, CK-MA, and FF-MA findings are summarized in Figs. 4-6. We conducted a case review with an anesthesiologist and concluded that an excessive administration of FFP occurred despite the CK-R time being within the normal range during the anhepatic phase. This contributed to the development of intraoperative thrombotic complications.

Discussion

This study provides an initial description of TEG 6s findings in relation to six LTs performed in Japan. Historically, in Japan, coagulation management during LT has depended on standard laboratory tests as the TEG 6s is not covered under Japan's national insurance scheme. Our case series illustrates three cases of significant bleeding and three cases of intraoperative thrombotic complications, providing highly beneficial information.

In the early years of LT, patients frequently underwent massive transfusions to treat severe coagulopathy (Cleland et al. 2016). With advancements in surgical techniques and perioperative care, the median blood loss associated with this procedure has significantly decreased. However, there remains a subset of patients for whom substantial intraoperative transfusion is still necessary (Chow et al. 2018). Emerging evidence suggests that thrombotic complications are common in patients undergoing LT (Krzanicki et al. 2013). This paradoxical phenomenon arises from rebalanced hemostasis, which was proposed based on the finding that overall thrombin generation is preserved in LT recipients (Tripodi et al. 2005). In both hypo- and hypercoagulable states, standard coagulation tests solely evaluate plasma events in hemostasis, ignoring the role of platelets and thereby providing an inadequate and potentially misleading assessment of bleeding and thrombotic risks for LT recipients (Stravitz 2012). Therefore, achieving an accurate assessment of hemostasis requires a whole-blood assay to measure the net effect of the interactions between cellular and soluble factors. From this standpoint, the description of standard laboratory tests (PT, aPTT, platelets and fibrinogen) in this case series may be potentially confounding, so we intentionally do not discuss them.

TEG is a point-of-care monitoring system that provides quantitative data on the speed, strength, and stability of the overall coagulation process. TEG was first introduced for the clinical management of LT by Kang et al. in

1985. Since then, the clinical utility of this point-of-care device has been supported in prospective randomized clinical trials in relation to cardiac surgery and liver transplant surgery, as well as in a recent systematic review (Kang et al. 1985; Shore-Lesserson et al. 1999; Wikkelsoe et al. 2011). The TEG5000 has been marketed since 2000, but issues concerning ease-of-use and labor- and time-intensive operations have limited its widespread use in practice. The TEG 6s has been available since 2010, and substantial evidence has emerged validating its performance compared with the TEG5000 (Gurbel et al. 2016; Lloyd-Donald et al. 2019; Robson et al. 2019; Neal et al. 2020). The TEG 6s has gradually been applied in Japanese clinical practice, particularly in the field of cardiac surgery (Yamamoto et al. 2022; Sato et al. 2023; Tamura et al. 2024). However, no studies have reported on the use of the TEG 6s in patients with LT in Japan.

Coagulation monitoring using the TEG 6s can reduce the overall transfusion requirements as empirical therapy is eliminated and specific management of coagulation defects is instituted at an early stage (Trzebicki et al. 2010). Bezinover et al. (2018) reviewed the current evidence on coagulation management in LT and concluded that the TEG5000 is a valuable assay. However, experiences using the TEG 6s have not been well documented. In Case 1, the CK-R time after reperfusion was 11.6 min, which was suboptimal for achieving effective hemostasis. Additionally, the CK-R times between POD1 and POD5 remained consistently prolonged, exceeding 10 min. The extended CK-R time observed in this case was attributed to severe coagulopathy resulting from ischemic reperfusion injury, specifically in the context of using the liver from a donor with moderate macrosteatosis. Croome et al. (2019) reported a significant increase in the transfusion requirements for LT using grafts with moderate macrosteatosis. In Case 2, the patient experienced massive bleeding, which was attributed to extensive adhesiolysis. Surgical bleeding and coagulopathy after reperfusion contribute to substantial intraoperative and postoperative bleeding. The CK-MA level during and after LT consistently exceeded 40 mm, which is typically sufficient to achieve effective hemostasis. However, in cases involving surgical bleeding, elevated CK-MA levels have proved insufficient to achieve effective hemostasis, as CK-R times should be shortened. In Case 3, the LT for a recipient with a history of Kasai procedure, commonly referred to as carry-over, proved challenging owing to a history of recurrent cholangitis, severe adhesions, and hepatic portal regional inflammation. These factors have been shown to result in substantial bleeding during the transplantation procedure, rendering such cases notably challenging (Miyagi et al. 2022).

Our patient exhibited severe coagulopathy and thrombocytopenia prior to transplantation, as evidenced by a notably challenging hepatectomy. Following reperfusion, the CK-R time extended to 37.5 min, and the CK-MA level was undetectable, representing coagulopathy of unprecedented severity in our experience. Experts have issued recommendations for coagulation management during LT. FFP is recommended when the CK-R time is < 14 min, cryoprecipitate is advised when the FF-MA level is < 8 mm, and platelets should be administered when the CK-MA level is < 40 mm (Coakley et al. 2006; Wang et al. 2012; De Pietri et al. 2016; Bezinover et al. 2018). These recommendations were initially derived from data obtained using the TEG5000; however, Gurbel et al. (2016) reported that the reference ranges of both the TEG5000 and the TEG 6s are closely aligned and highly validated. Therefore, these recommendations can be applied directly to the TEG 6s. Based on our experience, we consider that a CK-R time of < 10 min is advisable during episodes of surgical bleeding. However, in cases of nonsurgical bleeding, achieving hemostasis may be feasible with a CK-R time < 14 min.

As shown in Case 3, where the CK-R time was > 14 min and the CK-MA level was < 40 mm, achieving hemostasis proved to be notably challenging, necessitating massive transfusion (Lawson et al. 2017).

To date, this is preliminary data; however, we managed 15 LT recipients using TEG 6s based coagulation management. We compared the amount of intraoperative bleeding and blood transfusion after LT in 15 recipients managed using TEG 6s-based coagulation management with those managed using standard laboratory test-based coagulation management. The amount of intraoperative bleeding, the amount of transfusion including RBC, FFP, and platelets after LT for patients managed using TEG 6s-based coagulation management versus standard laboratory tests, were $8,133 \pm 7,577$ ml and $11,150 \pm 11,792$ ml (P = 0.20), 4.2 ± 7.2 and 5.5 ± 10.5 (P = 0.35), 7.0 ± 9.2 and 12.4 ± 16.1 (P = 0.13), and 11.0 ± 18.9 and 21.4 ± 23.1 (P = 0.09), respectively.

Emerging evidence indicates that thrombotic complications are prevalent in patients undergoing LT. Compared with bleeding complications, the estimated incidence of thrombotic complications is low; however, these complications, including intraoperative pulmonary embolism, intracardiac thrombosis, portal vein thrombosis, and hepatic artery thrombosis, pose a potentially fatal risk and are, thus, of significant clinical relevance (Warnaar et al. 2008; Zahr Eldeen et al. 2016). A hypercoagulable state can easily be overlooked when relying solely on standard laboratory tests. While TEG has been proposed as an easily applicable test to assess hypercoagulability (Ben-Ari et al. 1997; Ramsay et al. 2004), there is variability in the definition of hypercoagulability in LT. Krzanicki et al. defined hypercoagulability using TEG as having a high G value (G > 7,100 $dyne/cm^{-2}$, G = 5,000 × CK-MA / [100 – CK-MA]) and a shortened CK-R time (CK-R < 12 min) (Krzanicki et al. 2013). Zahr et al. (2016) defined hypercoagulability as a G value > 7,100 dyne/cm⁻² and suggested that this criterion could reliably identify recipient groups at an elevated risk of early hepatic artery thrombosis. We present three cases of LT with intraoperative thrombotic complications, each of

which offers highly insightful clinical scenarios. In Case 4, portal vein thrombosis occurred immediately after reperfusion, prompting us to perform thrombectomy and reanastomosis. LT for cholestatic liver disease is generally associated with a heightened risk of hypercoagulability (Ben-Ari et al. 1997). The G value consistently exceeded 7,100 dynes/cm⁻², and the CK-R time remained at < 12 min throughout the entire LT period, indicating a high risk of intraoperative thrombotic complications. In Case 5, hepatic artery thrombosis occurred prior to arterial anastomosis, which was likely attributable to a relatively prolonged anesthetic phase (115 min). Alcoholic cirrhosis typically does not correlate with hypercoagulability as detected using TEG (Krzanicki et al. 2013). However, in this case, coagulation factors were maintained due to the patient's indication for LT, which was a recurrent episode of hepatic encephalopathy, as observed with a shortened CK-R time throughout the procedure. In Case 6, portal vein thrombosis occurred immediately after reperfusion, necessitating thrombectomy. The risk factor for intraoperative thrombotic complications in this case was a shortened CK-R time, and the indication for LT was cholestatic liver disease (Ben-Ari et al. 1997). Therefore, more attention should be paid to FFP transfusions throughout such procedures. In Cases 4 and 6, heparin was administered following LT. Continuous infusion of heparin for prophylaxis against thrombotic complications is a common clinical practice, despite the lack of scientific data (Li et al. 2024). Based on our experience, if there is no surgical bleeding and the CK-R time is < 10 min or the G-value is > 7,100 dyne/cm⁻², heparin infusion should commence at the onset of the anhepatic phase. Continuous heparin infusion should be considered in patients at high risk of thrombotic complications.

In conclusion, we present three cases of massive bleeding and three cases of intraoperative thrombotic complications during LT, with the aim of advocating for the proactive consideration of coagulation management strategies. Coagulation management during LT directly affects patient survival outcomes, highlighting its critical importance. We recommend using the TEG 6s to gain a comprehensive understanding of coagulation management during LT surgery, as this device offers superior insights compared with standard laboratory tests. We described massive bleeding and intraoperative thrombotic complications during LT, raising the question of whether TEG-based coagulation management is necessary for all low-risk LT patients. Therefore, it is imperative to establish relevant principles in relation to coagulation management strategies during LT using the TEG 6s in a large patient cohort.

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Author Contributions

Muneyuki Matsumura participated in the research design, the performance of the research, and the writing of the paper. Kengo Sasaki, Kazuaki Tokodai, Koji Miyazawa, Atsushi Fujio, Hiroyuki Ogasawara, Michiaki Unno, and Takashi Kamei participated in the performance of the research.

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Conflict of Interest

The authors declare no conflict of interest.

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