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COMPARISON OF STANDARD COAGULATION TESTS AND ROTATIONAL THROMBOELASTOMETRY FOR HEMOSTATIC SYSTEM MONITORING DURING ORTHOTOPIC LIVER TRANSPLANTATION - RESULTS FROM A PILOT STUDY

POREĐENJE STANDARDNIH KOAGULACIONIH TESTOVA I ROTACIONE TROMBOELASTOMETRIJE ZA PRAĆENJE HEMOSTAZNOG SISTEMA TOKOM ORTOTOPIČNE TRANSPLANTACIJE JETRE – REZULTATI PILOT-STUDIJE

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Summary

Introduction. During liver transplantation, continuous laboratory monitoring of complex changes of the hemostatic system is necessary. The aim of this study was to compare two methods of monitoring: standard coagulation tests and rotational thromboelastometry. **Material and Methods.** The study included 17 patients who had undergone orthotopic liver transplantation in the Clinical Centre of Vojvodina, Serbia in the period from June 2008 to October 2012. The coagulation parameters (platelet count, activated partial thromboplastin time, prothrombin time and fibrinogen level) were compared with the thromboelastometric parameters (coagulation time, clot formation time and maximal clot firmness). **Results.** The results showed a statistically significant correlation between the platelet count and maximum clot firmness of the intrinsically ($r=0.51$, $p<0.001$) and extrinsically activated thromboelastometric assays ($r=0.64$, $p<0.001$). The fibrinogen level and maximum clot firmness of the fibrinogen thromboelastometric test correlated significantly as well ($r=0.44$, $p=0.002$). No significant correlations were found among the activated partial thromboplastin time, prothrombin time, coagulation time and clot formation time. **Conclusion.** For an adequate perioperative monitoring of the dynamic intraoperative hemostatic changes and the optimal use of blood derivatives during liver transplantation, the combined application of standard coagulation tests and rotational thromboelastometry should be considered whenever possible.

Key words: Blood Coagulation Tests; Thromboelastography; Liver Transplantation; Hemostasis; Blood Chemical Analysis

Sažetak

Uvod. Tokom transplantacije jetre neophodno je kontinuirano laboratorijsko praćenje kompleksnih promena u hemostaznom sistemu. Cilj studije je poređenje dve metode praćenja: standardnih koagulacionih testova i rotacione tromboelastometrije. **Materijal i metode.** Ispitivanjem je obuhvaćeno 17 bolesnika kojima je urađena ortotopična transplantacija jetre u Kliničkom centru Vojvodine, Srbija, u periodu jun 2008−oktobar 2012. godine. Koagulacioni parametri: broj trombocita, aktivirano parcijalno tromboplastinsko vreme, protrombinsko vreme i nivo fibrinogena poređeni su sa tromboelastometrijskim parametrima: vreme koagulacije, vreme formiranja ugruška i maksimalna čvrstina ugruška. **Rezultati.** Rezultati ukazuju na postojanje statistički značajne korelacije između broja trombocita i maksimale čvrstine ugruška u testu unutrašnjeg ($r = 0,51$, $p < 0,001$) i spoljašnjeg puta koagulacije ($r = 0,64$, $p < 0,001$). Nivo fibrinogena i maksimalne čvrstine ugruška značajno koreliraju u fibrinogen-tromboelastometrijskom testu ($r = 0,44$, $p = 0,002$). Nije utvrđena značajna korelacija između aktiviranog parcijalnog tromboplastinskog vremena, protrombinskog vremena, vremena koagulacije i vremena formiranja ugruška. **Zaključak.** Za adekvatno perioperativno praćenje dinamičkih promena u hemostaznom sistemu i optimalnu primenu derivata krvi tokom transplantacije jetre treba razmotriti kombinovanu primenu standardnih koagulacionih testova i rotacione tromboelastometrije kad god je to moguće.

Ključne reči: Koagulacioni testovi; Tromboelastografija; Transplantacija jetre; Hemostaza; Hemijske analize krvi

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Introduction

All components of the hemostatic system are altered in liver diseases due to impaired synthetic and excretory functions of the liver, decreased platelet count, and alterations in the hemostatic balance [1, 2]. These changes are proportional to the degree of impairment of liver function. In addition, portal

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Abbreviations
OLT – orthotopic liver transplantation
SCTs – standard coagulation tests
ROTEM® – rotational thromboelastometry
PLT – platelet count
aPTT – activated partial thromboplastin time
PT – prothrombin time
FBG – fibrinogen
CT – clotting time
CFT – clot formation time
MCF – maximum clot firmness
INTEM – intrinsically activated ROTEM® assays
EXTEM – extrinsically activated ROTEM® assays
FIBTEM – fibrinogen thromboelastometry test

hypertension that develops in hepatic insufficiency increases the risk of bleeding, whereas endothelial dysfunction and increased levels of the von Willebrand factor stimulate platelet adhesion [3], and increase the risk of thromboembolic complications. The changes in the physiological balance of hemostasis that increase the risk of bleeding include thrombocytopenia, platelet dysfunction, decreased levels of coagulation factors, plasmin inhibitors and thrombin-activatable fibrinolysis inhibitor**,** and increased levels of tissue plasminogen activator. The changes increasing the risk of thromboembolic complications, such as increased coagulation factor VIII levels, decreased activity of natural coagulation inhibitors and plasminogen levels occur at the same time [4].

Liver transplantation is an efficient treatment of patients with end-stage liver disease and irreversible impairment of liver function. During liver transplantation, most patients show multifactorial dysfunction of the hemostatic system [5] due to the drop in the levels of coagulation factors, natural coagulation inhibitors and antifibrinolytic factors [6], as well as quantitative and qualitative changes in procoagulation and anticoagulation factors and platelets [7, 8]. Orthotopic liver transplantation (OLT), during which the native liver is removed and replaced by the donor organ, is divided into the following phases: preanhepatic, anhepatic and postanhepatic. The preanhepatic phase reflects the preoperative condition of the diseased liver [9]. The anhepatic phase is characterized by a decrease in the levels of coagulation factors and dysfunction of the fibrinolytic system due to hyperfibrinolysis. During the postanhepatic phase, an increased fibrinolytic potential persists [10], as well as a thrombocytopenia and platelet dysfunction [11].

Continuous laboratory monitoring of changes in the function of the hemostatic system during OLT enables fast diagnosing of the dominant disorder at a given moment and administration of appropriate substitution therapy. There are two methods of monitoring the function of the hemostatic system during OLT: standard coagulation tests (SCTs) and rotational thromboelastometry (ROTEM®), and it is therefore necessary to analyze the correlation between the results obtained by these different methodologies. ROTEM® is routinely used in operating rooms, intensive care units and is also being introduced in the work of clinical laboratories.

The aim of the current study was to assess the correlation between coagulation and thromboelastometric parameters during OLT through monitoring the function of the hemostatic system using SCTs and ROTEM®.

Material and Methods

The study included 17 consecutive patients (5 women and 12 men), who had undergone OLT at the Clinical Centre of Vojvodina in Novi Sad, Serbia, in the period from June 2008 to October 2012. The most frequent etiology of liver insufficiency was viral hepatitis B and C, found in 10 patients. Both demographic and clinical characteristics of the patients are presented in table **(Table 1)**.

During the OLT, four to eight blood samples were analyzed for each patient, meaning at least one sample for each transplantation phase, depending on the patient's clinical status and laboratory findings as well. Blood samples were taken by cubital vein puncture; using the 3 ml tubes containing an-

Table 1. Demographic and clinical characteristics of the patients
Tabela 1. *Demografske i kliničke karakteristike pacijenata*

Mean age (years)/*Prosečna starost (godine)*	51.3
Mean follow-up (years)/*Prosečna dužina praćenja (godine)*	9
Diagnosis (pts)/*Dijagnoza (pacijent)*:	
hepatitis B/*hepatitis B*	6
hepatitis C/*hepatitis C*	4
– hepatocellular carcinoma/*hepatocelularni karcinom*	4
– autoimmune/*autoimuni*	3
Gender (pts)/*Pol (pacijent)*:	
– female/*ženski*	5
– male/*muški*	12
Variceal bleeding (pts)/*Varikozno krvarenje (pacijent)*	1
Thromboembolic events (pts)/*Tromboembolijske događaji (pacijent)*	1

Legend: pts - patients

Table 2. Intraoperative levels of coagulation parameters during phases of the transplantation
Tabela 2. *Intraoperativne vrednosti koagulacionih parametara tokom faza transplantacije*

		Coagulation parameters/*Koagulacioni parametri*			
		PLTx10^9/L (N 140-400)	aPTT (R) (N 0.83-1.30)	PT (R) (N 0.83-1.30)	FBG (g/L) (N 2.2-4.96)
Phases of OLT *Faze OLT*	PAH	78 (50-129)	1.14 (1.08-1.50)	1.39 (1.21-1.74)	1.91 (1.45-2.82)
	AH	73 (54-106)	1.21 (1.08-1.39)	1.32 (1.22-1.56)	2.28 (1.97-2.75)
	POSTAH	94 (57-112)	1.51 (1.37-1.80)	1.46 (1.38-1.69)	2.02 (1.82-2.51)

Legend: PAH - preanhepatic phase; AH - anhepatic phase; POSTAH - postanhepatic phase
Legenda: OLT – ortotopična transplantacija jetre; PAH – preanhepatična faza; AH – anhepatična faza; POSTAH – postanhepatična faza; PLT – broj trombocita; aPTT – aktivirano parcijalno tromboplastinsko vreme; PT – protrombinsko vreme; FBG – nivo fibrinogena

ticoagulant 5.9 mg K2 EDTA (Terumo Europe N.V., Leuven, Belgium) for determining the platelet (PLT) count and 3.2% sodium citrate (Terumo Europe N.V., Leuven, Belgium) taken in 5 ml tubes for SCTs. Citrated plasma was separated after centrifugation at 4000G for 6 minutes. PLT count was determined on the automated hematology analyzers Beckman Coulter HmX (Mervue, Galway, Ireland Inc.) and Cell Dyn Sapphire (Abbott Diagnostic, USA). An automated coagulometer ACL 9000 (Instrumentation Laboratory, Milano, Italy) was used to determine the activated partial thromboplastin time (aPTT), prothrombin time (PT) and fibrinogen (FBG), using the reagents HemosIL APTT-SP Liquid, RecombiPlasTin 2G and HemosIL Fibrinogen-C XL (Instrumentation Laboratory, Milano, Italy). The results for aPTT and PT are expressed as ratios (R) of sample clotting time and clotting time of normal control plasma (Instrumentation Laboratory, Milano, Italy). SCTs were performed in the laboratory of the Department of Thrombosis, Hemostasis and Hematology Diagnostics of the Centre of Laboratory Medicine and in the laboratory of the Emergency Centre. The following coagulation parameters were measured: PLT count, aPTT, PT and FBG levels determined by the Clauss assay [12]. The following coagulation parameters were also tested during OLT: thrombin time, euglobulin clot lysis time, D-dimer and antithrombin. Thromboelastometry was performed in the operating room, on ROTEM® (Pentapharm GmbH, Munich, Germany) using reagents obtained from the same manufacturer. Whole blood samples for ROTEM® tests were taken in 3.5ml tubes with 3.2% sodium citrate-BD Vacutainer (Terumo Europe N.V., Leuven, Belgium). The samples for SCTs and ROTEM® were taken intraoperatively during all transplantation phases according to the following schedule: prior to the preanhepatic phase, 30 minutes after clamping blood vessels in the anhepatic phase, after graft reperfusion in the postanhepatic phase and at the end of the operation. The coagulation parameters: PLT, aPTT, PT and FBG were compared with the thromboelastometric parameters: coagulation time (CT), clot formation time (CFT) and maximal clot firmness (MCF) in the following ROTEM® tests [13]: intrinsically activated ROTEM® assay (INTEM), extrinsically activated ROTEM® assay (EXTEM), and fibrinogen activity, a modified EXTEM test with additional PLT inhibitor-cytohalazine D (FIBTEM). The PLT count was compared with the MCF of the INTEM and EXTEM assays; aPTT with CT and CFT of the INTEM assay; PT with CT and CFT of the EXTEM assay; FBG with MCF of the FIBTEM assay.

The results of non-parametric tests are presented in tables as medians and interquartile ranges. The patients' data in various phases of transplantations were compared using the Friedman test and the appropriate post hoc test (Wilcoxon) if the Friedman test showed a significant difference. Spearman's coefficient was used to correlate SCTs and ROTEM® parameters, $p<0.05$ being considered statistically significant. These statistically significant correlations are presented in the graphs. Statistical analysis was performed using Statistica 12.0 software (StatSoft Inc., Tulsa, OK, USA). Laboratory

Table 3. Intraoperative levels of thromboelastometry parameters during phases of the transplantation
Tabela 3. *Intraoperativne vrednosti tromboelastometrijskih parametara tokom faza transplantacije*

		Thromboelastometry parameters/*Parametri tromboelastometrije*						
		CT (sec) INTEM (N 100-240)	CFT (sec) INTEM (N 30-110)	MCF (mm) INTEM (N 50-72)	CT (sec) EXTEM (N 38-79)	CFT (sec) EXTEM (N 34-159)	MCF (mm) EXTEM (N 50-72)	MCF (mm) FIBTEM (N 9-25)
Phases of OLT/*Faze OLT*	PAH	169 (149-179)	111 (98-187)	50 (43-60)	64 (55-71)	149 (104-211)	50 (42-60)	11 (8-17)
	AH	167 (146-185)	163 (127-181)	48 (41-55)	59 (50-69)	167 (76-203)	45 (42-59)	11 (7-16)
	POSTAH	214 (193-234)	164 (117-193)	49 (44-53)	57 (49-63)	153 (121-190)	49 (47-57)	11 (9-14)

Legend: PAH - preanhepatic phase; AH - anhepatic phase; POSTAH - postanhepatic phase
Legenda: OLT – ortotopična transplantacija jetre; PAH – preanhepatična faza; AH – anhepatična faza; POSTAH – postanhepatična faza; INTEM – ROTEM®testovi unutrašnjeg puta koagulacije; EXTEM - ROTEM®testovi spoljašnjeg puta koagulacije; FIBTEM – fibrinogen-tromboelastometrijski test; CT – vreme koagulacije; CFT – vreme formiranja ugruška; MCF – maksimalna čvrstina ugruška

parameters were correlated throughout the entire procedure and for each separate phase of OLT as well. The correlation for the entire OLT was analyzed for all values of each laboratory parameter obtained with both methods, SCTs and ROTEM®.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with the approval of the Ethical Board of Clinical Centre of Vojvodina for conducting the research.

Results

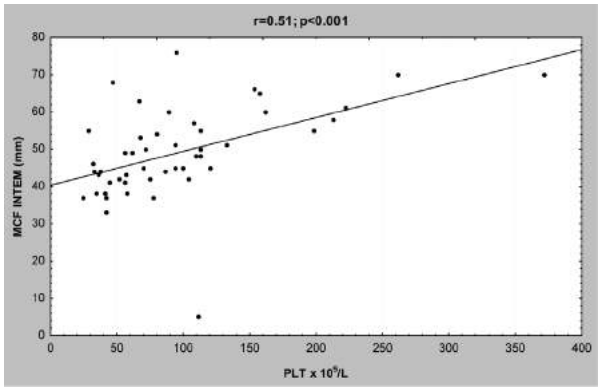
Alterations in the coagulation and thromboelastometric parameters across the different intraoperative phases of liver transplantations are shown in **tables 2 and 3**. The results of correlation of coagulation and thromboelastometry parameters are presented in **Table 4**.

The PLT count showed statistically significant correlations with MCF INTEM and MCF EXTEM in the preanhepatic phase; with MCF EXTEM in the anhepatic phase and the postanhepatic phase. The correlation was not statistically significant in the INTEM assay in either anhepatic or postanhepatic phase. During the entire procedure there was a highly statistically significant correlation between the PLT count and the MCF in both ROTEM® tests, INTEM **(Graph 1)** and EXTEM.

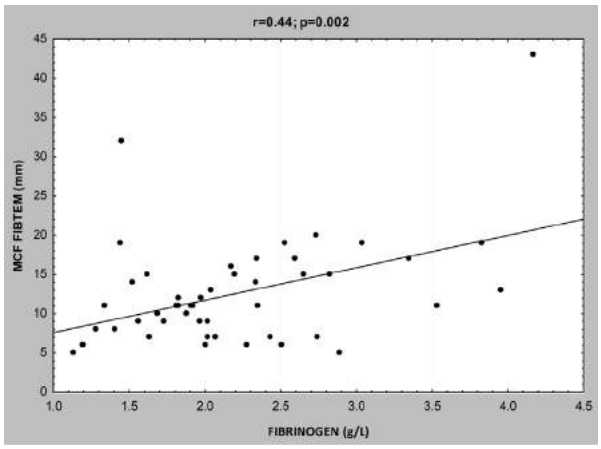
Table 4. Corellations between coagulation and thromboelastometry parameters in preanhepatic, anhepatic, postanhepatic phase and during the entire OLT
Tabela 4. *Korelacija između koagulacionih i tromboelastometrijskih parametara u preanhepatičnoj, anhepatičnoj, postanhepatičnoj fazi i tokom čitave OLT*

	PLT	aPTT	PT	FBG
MCF INTEM		/	/	/
PAH	r=0.74 p=0.001*			
AH	r=0.43 p=0.061			
POSTAH	r=0.28 p=0.271			
INTRAOP	r=0.51 p<0.001*			
MCF EXTEM		/	/	/
PAH	r=0.72 p=0.001*			
AH	r=0.63 p=0.009*			
POSTAH	r=0.59 p=0.012*			
INTRAOP	r=0.64 p<0.001*			
CT INTEM	/		/	/
PAH		r=0.30 p=0.242		
AH		r=0.16 p=0.546		
POSTAH		r=0.11 p=0.451		
INTRAOP		r=0.13 p=0.389		
CFT INTEM	/		/	/
PAH		r=0.23 p=0.375		
AH		r=0.39 p=0.121		
POSTAH		r=0.26 p=0.309		
INTRAOP		r=0.35 p=0.354		
CT EXTEM	/	/		/
PAH			r=0.20 p=0.444	
AH			r=0.14 p=0.582	
POSTAH			r=0.73 p<0.001*	
INTRAOP			r=0.20 p=0.172	
CFT EXTEM	/	/		/
PAH			r=0.52 p=0.031*	
AH			r=0.42 p=0.093	
POSTAH			r=0.12 p=0.633	
INTRAOP			r=0.23 p=0.121	
MCF FIBTEM	/	/	/	
PAH				r=0.21 p=0.424
AH				r=0.69 p=0.002*
POSTAH				r=0.01 p=0.997
INTRAOP				r=0.44 p=0.002*

Legend: PAH - preanhepatic phase; AH - anhepatic phase; POSTAH - postanhepatic phase; * - statistically significant correlation
*Legenda: OLT – ortotopična transplantacija jetre; PAH – preanhepatična faza; AH – anhepatična faza; POSTAH – postanhepatična faza; INTEM - ROTEM® testovi unutrašnjeg puta koagulacije; EXTEM - ROTEM® testovi spoljašnjeg puta koagulacije; FIBTEM – fibrinogen- tromboelastometrijski test; MCF – maksimalna čvrstina ugruška; CT – vreme koagulacije; CFT – vreme formiranja ugruška; PLT − broj trombocita; aPTT – aktivirano parcijalno tromboplastinsko vreme; PT – protrombinsko vreme; FBG – nivo fibrinogena; * − statistički signifikantna korelacija*



Graph 1. Corellation between platelet count and maximum clot firmness of intrinsically activated thromboelastometry test during transplantation
Grafikon 1. *Korelacija između broja trombocita i maksimalne čvrstine ugruška u testu unutrašnjeg puta koagulacije tokom transplantacije*



Graph 2. Corellation between fibrinogen level and maximum clot firmness of fibrinogen thromboelastometry test during transplantation
Grafikon 2. *Korelacija između nivoa fibrinogena i maksimalne čvrstine ugruška u fibrinogen-tromboelastometrijskom testu tokom transplantacije*

The correlation was not significant between aPTT and CT INTEM in the preanhepatic, anhepatic and postanhepatic phases, nor between aPTT and CFT INTEM in any of the transplantation phases, preanhepatic, anhepatic and postanhepatic phase. No significant links were found either between aPTT and CT INTEM or between aPTT and CFT INTEM during the entire procedure.

A significant correlation between PT and CFT EXTEM was observed in the preanhepatic phase, and an even more significant one between PT and CT EXTEM in the postanhepatic phase. PT was not significantly correlated with CT EXTEM in either preanhepatic or anhepatic phase, nor was PT correlated with CFT EXTEM in the anhepatic and postanhepatic phases. Throughout the entire procedure there were no significant correlations between PT and CT EXTEM, nor between PT and CFT EXTEM.

FBG showed a significant correlation with MCF FIBTEM in the anhepatic phase and no significant ones with MCF FIBTEM in the preanhepatic and postanhepatic phases. During the entire procedure a significant correlation between FBG and MCF FIBTEM was observed **(Graph 2)**.

Discussion

This is the first study conducted in our country that compares two methodologies of laboratory monitoring of the hemostatic system during liver transplantation. It is also the first study that has analyzed laboratory parameters of hemostasis separately for each transplantation phase.

ROTEM® is a whole blood *point-of-care* test, intended for the study of visco-elastic properties of the coagulum [14] and diagnosis and differentiation of hemostatic disorders. It enables monitoring of all coagulation phases and provides information not only on the clotting time, but also on the dynamics of clot formation, the mechanical clot stability and its lysis over time [15], as well as the degree of heparinization [16]. The disadvantages of ROTEM® are the inability to detect activity of natural coagulation inhibitors and assess thrombin activity. ROTEM® does not detect all hemostatic disorders; therefore, it is important to perform simultaneous SCTs during liver transplantation [17]. SCTs provide thorough information about the function of the extrinsic and intrinsic pathways of the hemostatic system, antithrombin levels and the degree of increase in thrombin activity [18]. However, since the tests use plasma without blood cells, which requires previous centrifugation of the blood sample and plasma separation, the time required to obtain results is longer than the test time of ROTEM®, which is about 10 minutes. Another limitation of SCTs is that FBG levels may be falsely increased due to the presence of heparin and colloid and the inability to determine mechanical stability of the clot [17].

Our results showed a highly significant correlation between PLT count and MCF INTEM and MCF EXTEM during OLT, which is similar to the results of previous studies [19, 20]. The PLT count correlated with MCF INTEM significantly in the preanhepatic phase and with MCF EXTEM in all the transplantation phases as shown in the study of Stanchev et al. [20].

The study results did not show a correlation between aPTT and CT INTEM, nor between aPTT and CFT INTEM during the entire procedure, which has been reported by other authors as well [19, 21, 22]. No statistically significant correlation was found between aPTT and CT INTEM, and aPTT and CFT INTEM in any of the transplantation phases. However, some authors showed a strong correlation between aPTT and CT INTEM during the transplantation [19].

Comparisons between PT and CT EXTEM, and PT and CFT EXTEM did not show statistically significant correlations, which is in agreement with the literature data [19–22]. PT correlated significantly with CT EXTEM in the postanhepatic phase. Tripodi et al. reported an important correlation between PT and CFT EXTEM during transplantation [7], which was found only in the preanhepatic phase, that being similar with the findings of Stanchev et al. [20].

FBG showed a significant correlation with MCF FIBTEM during transplantation, which is consistent with several previous studies [19–21]. The correlation was significant even in the anhepatic phase, as shown in the study of Stancev et al. [20].

The poor correlation found between certain coagulation and thromboelastometry parameters could be explained by the fact that different methodologies of the tests and the presence of blood cells, endothelial cells and platelets were applied during thromboelastometric testing [21].

Some studies have demonstrated the efficiency of ROTEM® in reducing transfusions of blood products [23, 24]. ROTEM® may be a useful guide for perioperative transfusion; however, it cannot be used as a substitute for aPTT and PT [21]. Substitution depends on the patient's laboratory findings and clinical condition, involving a PLT concentrate, fresh frozen plasma, cryoprecipitate, antithrombin concentrate, packed red blood cells, and antifibrinolytic therapy. ROTEM® is an appropriate method for estimation of PLT count and FBG level based on the MCF, particularly useful in afibrinogenemia, hypofibrinogenemia and dysfibrinogenemia [25]. Although certain coagulation parameters did not correlate with thromboelastometric parameters, perioperative monitoring with both SCTs and ROTEM® provides better comprehension of the complexity of rapid intraoperative changes in the hemostatic system. These changes may occur due to hemodilution [20], severe intraoperative blood loss [20], complexity of the surgical procedure [4] or pronounced fibrinolysis [20]. Timely diagnosis of this disorder enables optimal substitution therapy.

The limitation of this study is the small number of patients due to the small number of liver transplantations performed in our country. Similar studies which analyzed the correlations of SCTs and ROTEM® parameters during OLT also consisted of a relatively small number of patients (20-30), and our results correspond to the results of these studies. On the other hand, this study provides valuable information about the laboratory monitoring of patients undergoing OLT and it would be useful to continue further research by analyzing a larger number of patients.

Conclusion

Our results showed significant correlations of platelet count with maximum clot firmness of intrinsically activated rotational thromboelastometry assays and maximum clot firmness of extrinsically activated rotational thromboelastometry assays and of fibrinogen level with maximum clot firmness of fibrinogen thromboelastometry test. The results obtained indicate that maximum clot firmness may be used with a great degree of certainty to assess the function of platelet count and fibrinogen levels. No significant correlations were found between the coagulation parameters (activated partial thromboplastin time and prothrombin time) and the thromboelastometric parameters (clotting time and clot formation time of the intrinsically activated rotational thromboblastometry and extrinsically activated rotational thromboblastometry assays). A combination of standard coagulation tests and rotational thromboelastometry enables the best perioperative laboratory monitoring of the hemostatic system and the optimalal blood product substitution during liver transplantation.

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