Srp Arh Celok Lek. 2013 Sep-Oct;141(9-10):608-614
ОРИГИНАЛНИ РАД / ORIGINAL ARTICLE
DOI: 10.2298/SARH1310608N
UDC: 616-089.168-022.1

Laboratory Monitoring of the Haemostatic System Changes during Orthotopic Liver Transplantation

Sladjana Novaković-Anučin[1], Sanja Gnip[1], Višnja Čanak[1], Djurdjina Jurišić[1], Pavica Radović[1], Svetlana Erdeljan[2], Zoran Milošević[3,4], Gorana Mitić[1,4]

[1]Department of Thrombosis, Haemostasis and Haematology Diagnostics, Centre of Laboratory Medicine, Novi Sad, Clinical Centre of Vojvodina, Serbia;
[2]Clinic of Anesthesiology and Intensive Therapy, Clinical Centre of Vojvodina, Novi Sad, Serbia;
[3]Clinic of Abdominal, Endocrine and Transplantation Surgery, Clinical Centre of Vojvodina, Novi Sad, Serbia;
[4]Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

SUMMARY

Introduction In liver diseases, all components of the haemostatic system are changed and the degree of dysfunction is proportional to hepatocellular damage. During the liver transplantation, values of haemostatic parameters show substantial changes, while postoperatively there is a gradual normalisation of the haemostatic system function.

Objective The aim was to monitor the changes of the haemostatic system intraoperatively and postoperatively, including the dynamics at which physiological values of parameters are reached after transplantation.

Methods There were 17 cadaveric transplantations performed at the Clinical Centre of Vojvodina in the period from June 2008 to February 2012. The following parameters were tested: platelets, activated partial thromboplastin, prothrombin and thrombin time, fibrinogen, euglobulin clot lysis time, D-dimer, antithrombin and heparinemia. The results were presented intraoperatively in phases of transplantation, and postoperatively from day 1 to day 7, ending with postoperative day 14.

Results During transplantation, the most pronounced disorders among those observed are: thrombocytopenia (96±66.1×10^9/L), prolonged activated partial thromboplastin (1.80±0.8 R), prothrombin (1.59±0.4 R) and thrombin time (2.03±1.7 R), hypofibrinogenemia (2.13±0.5 g/L), hyperfibrinolysis (29±12.0 min), increase of D-dimer (1393±1220.4 ng/mL) and decrease of antithrombin (61±18.0%). Further monitoring after transplantation from postoperative day 1 revealed a gradual normalisation in the values, reaching physiological values for all parameters on postoperative day 14, except for the sustained high value of D-dimer (2606±1055.1 ng/mL). Heparinemia was within the prophylactic range (0.26±0 IU/mL).

Conclusion Thorough monitoring of the haemostatic system parameters in liver transplantations is of great importance, as it enables the use of optimal substitution therapy during and after transplantation, as well as an adequate postoperative thromboprophylaxis. Our study has shown normalisation of investigated laboratory parameters within 7-14 days after transplantation.

Keywords: haemostasis; haemostatic parameters; fibrinolysis; orthotopic liver transplantation

INTRODUCTION

In liver diseases, all components of the haemostatic system are changed as a result of decreased synthesis of the most of coagulation factors and impaired clearance. These changes correlate to the level of hepatocellular damage. The disorder of the liver's synthetic function is manifested by decreased levels of coagulation factors (F), which is one of the first indicators of liver disease. The drop of the FVII coagulation level primarily appears due to its short half-life [1, 2], while hypofibrinogenemia, decrease of FV level [3] and levels of other coagulation factors are indicators of a poor prognostic outcome since their level is decreased only in cases of severe liver damage, indicating the terminal stadium of the disease. In addition to decrease in synthesis, the structure of synthesized coagulation factors and inhibitors is altered. Moreover, there is a decrease in synthesis and an increase in catabolism of plasminogen and plasmin inhibitors. Impaired clearance of the activated coagulation factors and plasminogen activators contributes to further deterioration of haemostasis. Decreased number of platelets, which is a consequence of hypersplenism, is frequently accompanied by the impaired platelet function.

Liver diseases are characterised by derangement of physiological balance within the haemostatic system [3]. Some changes result in deterioration of its functions, increasing the risk of haemorrhagic complications, while, on the other hand, there are such changes that result in the increased activity of the haemostatic system, followed by the increased risk of thromboembolic complications. Haemostatic disorders in the chronic liver diseases which can result in bleeding include: thrombocytopenia, platelet dysfunction, reduced levels of most coagulation factors, hypofibrinogenemia and low levels of α_2-antiplasmin [4]. These changes are balanced by pro-haemostatic alterations like: reduced synthesis of natural coagulation inhibitors, decreased levels of plasminogen and increased levels of FVIII [5] and it might easily result either bleeding diathesis or thrombotic

Correspondence to:
Sladjana NOVAKOVIĆ-ANUČIN
Department of Thrombosis, Haemostasis and Haematology Diagnostics
Centre of Laboratory Medicine
Clinical Centre of Vojvodina
Hajduk Veljkova 1, 21000 Novi Sad
Serbia
sanucin@yahoo.com

events [6]. In patients with the cirrhosis and esophageal varices, the incidence of variceal bleeding ranges from 19-40% [7]. Portal vein thrombosis is a common complication with the prevalence of 10-25% [8, 9, 10]. Approximately 0.8% of all hospitalized patients with cirrhosis have had a non-portal venous thromboembolism, deep vein thrombosis and pulmonary embolism [11].

During the liver transplantation, most of the patients manifest multifactorial disorders in their haemostatic balance [12]. By convention, the surgical procedure is divided into the following phases of surgery: preanhepatic, anhepatic, reperfusion and postoperative phase. Preanhepatic phase is characterised by the hyperfibrinolysis and baseline hypocoagulable state which deteriorates mildly in the presence of surgical stress [6]. In anhepatic phase, there is a loss of coagulation factor synthesis and clearance, with dramatic changes in the activated partial thromboplastin time and prothrombin time [13]. The increased levels of tissue plasminogen activator (t-PA) secondary to release from the endothelial cells and decreased clearance in absence of liver can lead to hyperfibrinolysis with consequent afibrinogenaemia [14] and severe bleeding [15]. Profound coagulation abnormalities are related primarily to thrombocytopenia because of entrapment of platelets in the liver graft and the heparin-like effect of the donor liver dominated in the reperfusion phase [6] due to the release of heparin-like substances from the grafted liver. Increased clearance of t-PA and increased production of plasminogen activator inhibitors (PAI-1) lead to gradual dissolution of the hyperfibrinolysis [6]. Postoperative phase is characterised by thrombocytopenia and hypercoagulability [6].

Laboratory findings that are most frequently used in monitoring of haemostatic system in liver diseases are platelet count, prothrombin time, levels of individual coagulation factors and inhibitors, and euglobulin clot lysis time, where their values are successively worsening with the progression of disease.

OBJECTIVE

The objective of this study was to monitor the changes of haemostatic system activity intraoperatively, as well as postoperatively, and to estimate the time required for achieving physiological values of haemostatic parameters after orthotopic liver transplantation.

METHODS

The follow up was conducted on a cohort of 17 patients, 6 women and 11 men, who were subjected to cadaveric liver transplantation at the Clinical Centre of Vojvodina (KCV) in the period from June 2008 to February 2012. In the majority of cases, the aetiology of liver insufficiency was liver cirrhosis caused by viral hepatitis B and C, which was diagnosed in 12 patients in total. Demographic and clinical characteristics of the study population are presented in Table 1.

Laboratory testing was carried out at the laboratory of the Department of Thrombosis, Haemostasis and Haematology Diagnostics of the KCV Centre of Laboratory Medicine and the KCV Emergency Laboratory. Pre-, intra- and postoperative dosing of the substitution therapy and antifibrinolytics was based on the laboratory findings as well as clinical findings and it was given in order to achieve the optimal state of coagulation. Platelet concentrate was administered in case of severe thrombocytopenia, and fresh frozen plasma and cryoprecipitate for significant deficiency of coagulation factors. In order to achieve an optimal level of antithrombin, concentrate of antithrombin was given before, during and after the transplantations. Antifibrinolytic therapy with tranexamic acid was given during the transplantations in a small dose before reperfusion, then depending on the laboratory findings dose was adjusted in the reperfusion phase, or in preanhepatic phase if the patient had hypocoagulability. The following haemostatic parameters were tested: platelet count (PLT), activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FBG), euglobulin clot lysis time (ECLT), D-dimer, antithrombin (AT) and heparinemia (anti-Xa), and the tests were performed immediately after sampling blood for analysis. The test samples were taken intraoperatively in all phases of transplantation according to the following schedule: prior to preanhepatic phase, 30 minutes after clamping blood vessels in anhepatic phase, after graft reperfusion in postanhepatic phase and at the end of the operation, and postoperatively on a daily basis for 14 days, obtained by venepuncture of cubital vein, using the tubes containing anticoagulant K_2 EDTA for determining platelet count from blood sample, and 3.2% sodium citrate for haemostatic testing. Citrated plasma was separated after spinning at 2700 G for 6 minutes. Platelet count was determined by means of the automated haematology analysers Beckman Coulter HmX (Mervue, Galway, Ireland Inc.) at the Emergency Laboratory during transplantation, and on Cell Dyn Sapphire (Abbott Diagnostic, USA) from postoperative day 1. The haemostatic tests were performed on ACL units – automated coagulometers, manufactured by IL (Instrumentation Laboratory, Milano, Italy). Coagulometer ACL 9000 was used to determine aPTT, PT, TT, FBG, with reagents: HemosIL APTT-SP Liquid, RecombiPlasTin 2G, Thrombin

Table 1. Demographic and clinical characteristics of patients (N=17)

Characteristics		Value
Age (years)	Mean	51.6±7.3
	Range	38–61
Gender	Female	6
	Male	11
Diagnosis	Hepatitis B	7
	Hepatitis C	5
	Hepatocellular carcinoma	4
	Autoimmune	3
Follow-up (years)	Mean	8.6±7.7
	Range	1–27
Variceal bleeding		2
Thromboembolic events		1

The values are expressed as mean ± SD (range), and number of patients.

Table 2. Intraoperative and postoperative levels of haemostatic parameters (mean±SD and range)

Phases and days of liver transplantation		Haemostatic parameters with normal values								
		PLT ($\times 10^9$/L)	aPTT (R)	PT (R)	TT (R)	FBG (g/L)	ECTL (min.)	D-dimer (ng/mL)	AT (%)	aXa (IU/mL)
		140–400	0.83–1.30	0.93–1.30	0.85–1.30	2.20–4.96	>120	<230	75–122	0.10–0.40
PAH	Mean±SD	116±89.2	1.19±0.2	1.42±0.3	1.87±1.6	2.28±0.9	59±42.3	1229±1206.6	61±18.0	/
	Range	29–372	0.98–1.70	1.10–2.13	1.15–7.70	1.13–3.83	6–120	292–4950	39–111	
AH	Mean±SD	96±66.1	1.43±0.5	1.38±0.3	2.03±1.7	2.41±0.8	29±12.0	1110±1383.1	71±16.0	/
	Range	25–262	0.87–2.85	1.12–2.20	1.15–7.70	1.19–4.17	5–50	346–6250	35–105	
PR	Mean±SD	100±54.1	1.80±0.8	1.59±0.4	2.01±1.5	2.13±0.5	55±31.1	1393±1220.4	72±16.7	/
	Range	32–213	1.28–4.27	1.26–3.11	1.02–7.70	1.28–2.89	20–120	399–5490	45–117	
POP	Mean±SD	91±58.0	1.41±0.3	1.52±0.2	2.16±1.7	2.64±0.6	>120	1194±1184.7	82±10.0	/
	Range	33–206	1.10–2.13	1.31–2.03	1.00–7.70	1.93–3.71		335–5077	62–92	
1	Mean±SD	75±54.3	1.25±0.2	1.48±0.2	1.28±0.2	3.46±0.7	>120	1027±795.8	80±10.0	0.20±0.2
	Range	15–199	0.96–1.69	1.14–1.95	1.05–1.76	1.96–4.54		258–2733	61–99	0.01–0.46
2	Mean±SD	74±54.4	1.15±0.4	1.36±0.2	1.64±1.6	3.44±0.7	>120	1049±696.8	87±10.5	0.32±0.3
	Range	16–215	0.80–2.67	1.07–1.74	1.02–7.70	2.11–4.81		352–2768	73–108	0.17–0.83
3	Mean±SD	70±53.1	1.05±0.2	1.33±0.3	1.24±0.1	3.30±0.7	>120	1184±1053.3	88±11.1	0.23±0.1
	Range	13–199	0.77–1.83	0.92–1.64	1.06–1.49	2.10–4.97		344–3935	63–107	0.10–0.33
4	Mean±SD	72±60.3	0.96±0.1	1.31±0.2	1.24±0.1	3.10±0.8	>120	1676±1157.5	88±10.6	0.25±0.1
	Range	13–242	0.74–1.08	0.96–1.60	1.01–1.48	1.75–5.04		454–4393	73–110	0.13–0.44
5	Mean±SD	66±55.6	0.93±0.1	1.31±0.2	1.19±0.1	3.20±0.5	>120	2156±1354.4	84±8.2	0.25±0.1
	Range	17–190	0.73–1.21	0.98–1.54	1.00–1.45	2.36–4.17		765–4655	74–99	0.16–0.39
6	Mean±SD	77±67.4	0.96±0.1	1.33±0.4	1.19±0.1	3.34±0.8	>120	2246±1313.9	82±7.9	0.25±0.1
	Range	11–240	0.74–1.34	1.03–2.55	1.02–1.39	2.29–4.85		695–4753	72–98	0.20–0.33
7	Mean±SD	94±74.1	0.94±0.1	1.27±0.3	1.17±0.1	3.45±0.9	>120	2089±991.7	83±10.2	0.24±0.2
	Range	4–252	0.73–1.22	1.01–2.13	0.93–1.43	2.25–5.23		866–4267	60–100	0.07–0.51
14	Mean±SD	147±107.3	0.98±0.1	1.17±0.2	1.19±0.2	3.66±1.3	>120	2606±1055.1	85±16.3	0.35±0.2
	Range	15–390	0.81–1.21	0.86–1.56	0.88–1.59	1.64–5.63		953–4740	62–122	0.14–0.64

PAH – preanhepatic phase; AH – anhepatic phase; RP – reperfusion phase; POP – postoperative; SD – standard deviation; PLT – platelet; aPTT – activated partial thromboplastin time; R – ratio of sample clotting time and clotting time of normal control plasma; PT – prothrombin time; TT – thrombin time; FBG – fibrinogen; ECLT – euglobulin clot lysis time; AT – antithrombin; aXa – anti-factor Xa activity

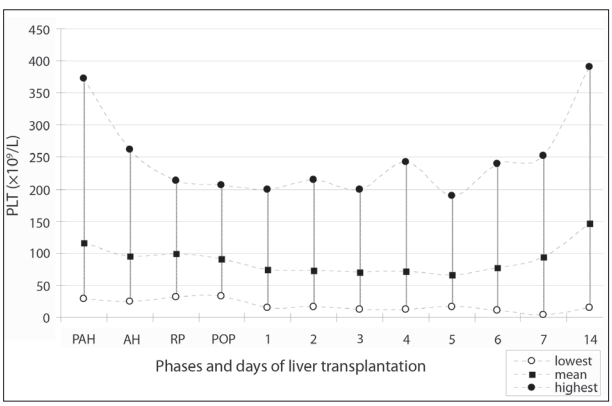
Time IL, HemosIL Fibrinogen-C XL according to Clauss method. Determination of ECLT was performed manually, with incubation in water bath at 37°C. Coagulometer ACL 7000 was used for determining D-dimer and the level of AT activity, with the reagents: HemosIL D-Dimer and HemosIL Antithrombin. Heparin level in plasma was measured with coagulometer ACL 200, with HemosIL Heparin reagents. All reagents were produced by IL (Instrumentation Laboratory, Milano, Italy).

The results were statistically processed by descriptive statistical method, and the descriptive statistical data were presented in tables and illustrated by graphs, as the highest, mean and lowest values of the tested haemostatic parameters, and standard deviation thereof as a variability measure, starting from the intraoperative findings in phases of transplantation, followed by postoperative daily checks from day 1 to day 7, ending with the liver transplantation postoperative day 14.

RESULTS

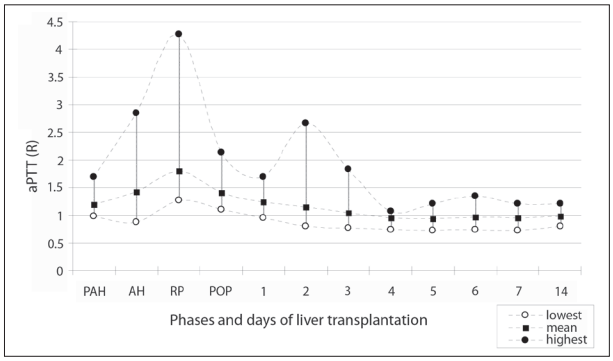
During the liver transplantation, the laboratory values of haemostatic parameters showed substantial changes, while postoperatively there was a gradual normalisation in the function of the haemostatic system which was apparent as early as the first week, reaching physiological values for all tested parameters on postoperative day 14, except for the sustained high value of D-dimer (Table 2).

The majority of patients had mild thrombocytopenia ($116\pm89.2\times10^9$/L) at the beginning of transplantation. During transplantation, PLT count was decreased, more pronouncedly in the anhepatic phase ($96\pm66.1\times10^9$/L), while from postoperative day 6 there was a gradual increase in PLT count values, reaching the normal PLT values ($147\pm107.3\times10^9$/L) on postoperative day 14 (Table 2 and Graph 1).

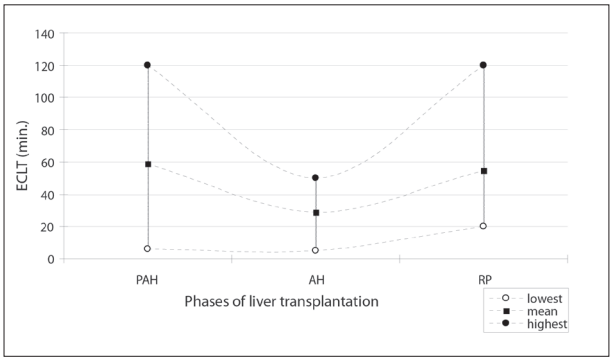


Graph 1. Changes in platelet count (PLT) during and after the liver transplantation

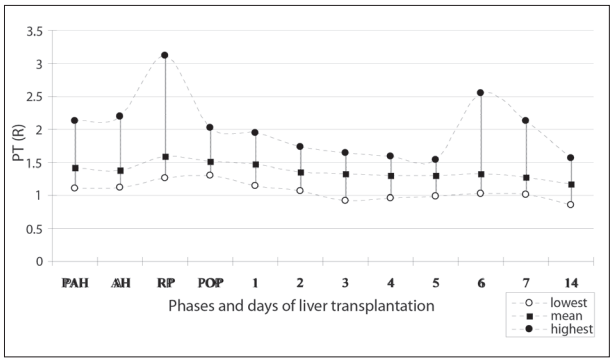
PAH – preanhepatic phase; AH – anhepatic phase; RP – reperfusion phase; POP – postoperative; 1–7, 14 – days



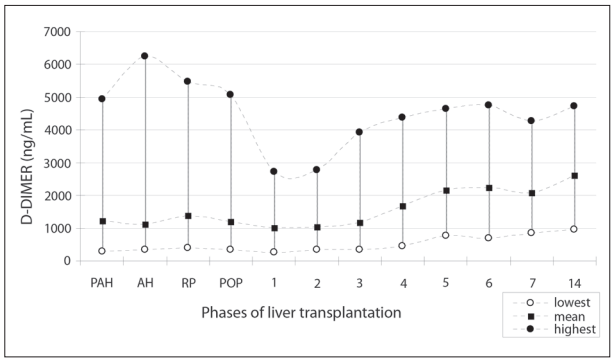
Graph 2. Changes in activated partial thromboplastin time (aPTT) during and after the liver transplantation



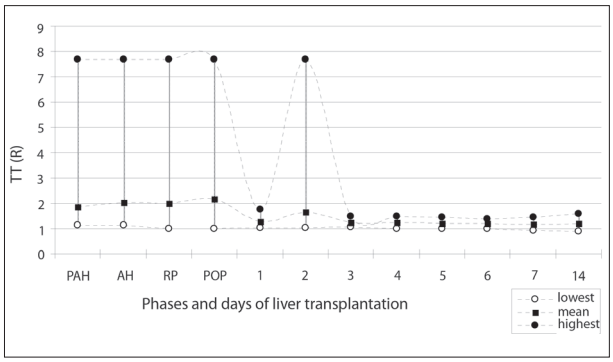
Graph 6. Changes in euglobulin clot lysis time (ECLT) during the liver transplantation



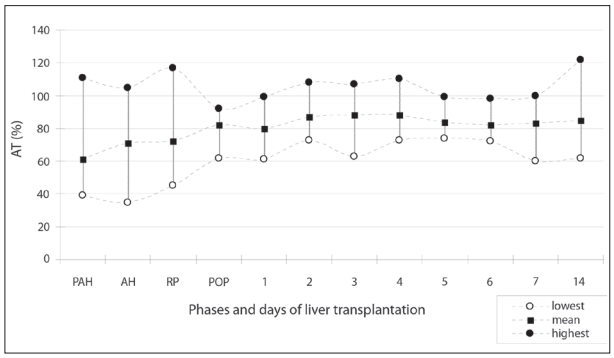
Graph 3. Changes in prothrombin time (PT) during and after the liver transplantation



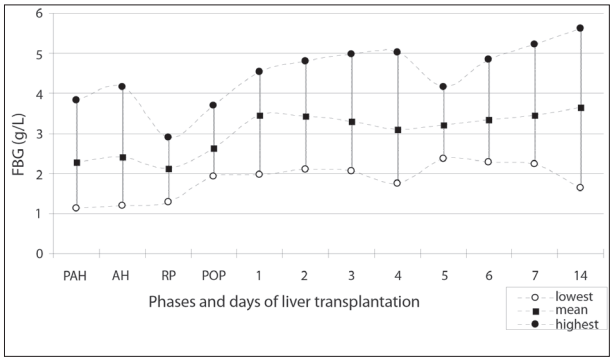
Graph 7. Changes in D-dimer during and after the liver transplantation



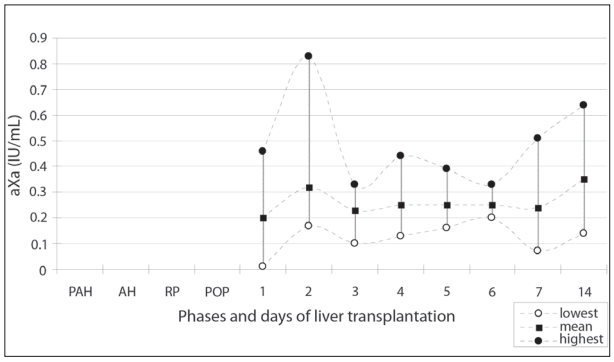
Graph 4. Changes in thrombin time (TT) during and after the liver transplantation



Graph 8. Changes in antithrombin (AT) during and after the liver transplantation



Graph 5. Changes in fibrinogen (FBG) during and after liver transplantation



Graph 9. Changes in anti-Factor Xa activity (aXa) after the liver transplantation

Prolonged aPTT in anhepatic phase of transplantation resulted from the loss of coagulation factor synthesis in the absence of liver (1.43±0.5 R), while in reperfusion phase it was due to transplant's heparin release (1.80±0.8 R). Postoperatively, aPTT was normalised from postoperative day 1 (1.25±0.2 R) (Table 2 and Graph 2).

Slightly prolonged PT (1.42±0.3 R) was evident in the majority of patients in preanhepatic phase, which was more pronounced during transplantation in reperfusion phase (1.59±0.4 R). PT normalised (1.27±0.3 R) on postoperative day 7, which was consistent with the gradual normalisation of the coagulation factor levels (Table 2 and Graph 3).

Prolonged TT during transplantation in preanhepatic phase (1.87±1.6 R), anhepatic (2.03±1.7 R) and reperfusion phases (2.01±1.5 R) occurred due to hyperfibrinolysis, and as a result of heparin release from the grafted liver in reperfusion phase. First 2 days after transplantation, slightly prolonged TT was a laboratory effect of the intravenous unfractionated heparin. Normal TT value (1.24±0.1 R) was recorded on postoperative day 3 (Table 2 and Graph 4).

Intraoperatively, there was an observed drop in the FBG level (2.13±0.5 g/L) in reperfusion phase of transplantation due to hyperfibrinolysis, while postoperative FBG values remained within the limits (Table 2 and Graph 5).

ECLT was presented intraoperatively, since the function of the fibrinolytic system was normalised postoperatively by antifibrinolytic therapy. Intraoperatively, hyperfibrinolysis dominated in the anhepatic phase of transplantation (29±12.0 min) due to increased t-PA levels, but it was also present in both preanhepatic (59±42.3 min) and reperfusion phases (55±33.1 min) (Table 2 and Graph 6).

D-dimer values were significantly increased in the majority of patients at the very beginning of transplantation (1229±1206.6 ng/mL), which was consistent with the presence of extravascular fibrinolysis. Intraoperative increase of values in reperfusion phase (1393±1220.4 ng/mL) was consistent with the accelerated fibrinolysis, while postoperative successive increase was due to coagulation system activation, showing significantly higher D-dimer values (2606±1055.1 ng/mL) on postoperative day 14 (Table 2 and Graph 7).

In the majority of patients the level of AT activity was lower (61±18.0%) at the beginning of transplantation than it was during transplantation in the anhepatic phase (71±16.0%), with normalisation after the surgery (82±10.0%), which was constantly maintained at physiological level with an adequate substitution by AT concentrate (Table 2 and Graph 8).

Postoperatively, laboratory effects of the parenteral anticoagulant therapy were monitored by determination of the anti-Xa activity, the level of which was within prophylactic range (0.26±0 IU/mL) (Table 2 and Graph 9).

DISCUSSION

The course of orthotopic liver transplantation is characterized by severe impairment of the haemostatic system. Preanheptic, explantation phase involves removal of recipient's liver and reflects the preoperative state of the damaged liver [16]. Bleeding in this phase is mainly surgical and can be significant, due to portal hypertension, parenchyma vulnerability and possible existence of adhesions from previous surgical interventions [17]. Anhepatic phase involves clamping of large liver blood vessels, portal vein and the inferior vena cava. It is characterised by the absence of the liver and hepatic clearance [18]. This stage is dominated by the fibrinolytic system's disorder, caused by the increased level of t-PA, which is released from the endothelium of large blood vessels, while it cannot be eliminated through liver due to absence of hepatic clearance or inactivated by PAI-1 [18, 19, 20]. Bleeding is nonsurgical, since the large blood vessels are clamped, so it is a direct consequence of haemostatic disorder due to hyperfibrinolysis [15], the use of heparin if applicable during the surgical techniques or negative effect of hypothermia, while the appearance of dilutional coagulopathy is also possible [21]. Deterioration of the fibrinolytic system function depends on the duration of anhepatic phase – the longer the anhepatic phase, the more pronounced hyperfibrinolysis is [22]. The postanhepatic, reperfusion phase involves reperfusion of donor liver after revascularisation by clamp removal, and haemostatic disorders depend on the quality of the liver transplant. In this phase, bleeding is a result of hyperfibrinolysis [15], heparin release from the transplant, liver ischemia and hypothermia [21], dilution effect of cold preservation solution residue in the liver after rinsing, which inhibits platelet aggregability [23], or the dilution effect due to massive transfusion [21], as well as thrombocytopenia due to platelet sequestration in the transplant and platelet dysfunction caused by the loss of platelet granules [24, 25]. The damaged cells of the liver sinusoids are adhered to by platelets, which release mediators that may cause intravascular coagulation [26].

Our study results show preoperative presence of complex haemostatic system disorders in the sample group, the dominant being fibrinolytic system impairment, elevated D-dimer value, prolonged PT and AT deficiency. Significant dysfunction of the fibrinolytic system during liver transplantation was also observed by other authors [14, 27].

During the liver transplantation, in its various phases, there are evident changes of laboratory haemostatic parameters which correspond to data presented in literature [22]. The most pronounced haemostatic disorder during transplantation was observed in the anhepatic phase, predominantly hyperfibrinolysis, prolonged TT and drop of the PLT count. In reperfusion phase, there are complex haemostatic disorders: high fibrinolytic activity, increase of D-dimer values, hypofibrinogenemia, prolonged TT, aPTT, PT, and decrease of AT activity. Similar results during liver transplantation, particularly in the reperfusion phase, were presented in other studies, primarily in the values of FBG, prolonged aPTT, TT, decrease in the level of AT, and the highest values of D-dimer [27].

Further monitoring after liver transplantation from postoperative day 1 revealed a gradual normalisation in

doi: 10.2298/SARH1310608N

the values of the monitored laboratory parameters of the haemostatic system in the first week, and our results show no significant differences in comparison to the research of other authors [22]. The first to normalise were aPTT, FBG, AT, normal TT value was recorded on postoperative day 3, and from postoperative day 7, PT also restored to normal. Moderate thrombocytopenia was evident during the first week, reaching the physiological platelet count on postoperative day 14, which is in accordance with the literature data [28, 29]. D-dimer value showed gradual increase, remaining in the significantly high range even after two weeks.

Substitution therapy during liver transplantation is necessary because of significant intraoperative bleeding due to complexity of the surgical procedure itself and co-occurring serious haemostatic changes [13, 30, 31]. Substitution is highly dependent on clinical bleeding and laboratory findings as well. It includes fresh frozen plasma, cryoprecipitate, PLT concentrate, blood derivatives and AT concentrate. A continuous antifibrinolytic therapy is also necessary.

After transplantation, the liver function usually improves after postoperative day 3 [32]. During early postoperative period, there is an increase of the coagulation factor levels [33]. Thrombocytopenia persists for several days due to hypersplenism, influence of HLA cytotoxic antibodies [22] and immunosuppressive therapy. Hypercoagulability follows in later postoperative period, with a threat of thromboembolic complications due to different recovery rates of factors and inhibitors of coagulation, namely, faster normalisation of coagulation factors [33]. Moreover, immunosuppressive therapy leads to increased levels of FBG, FVIII and PAI-1 [34]. Possible complications include thrombosis of the anastomosed blood vessels, hepatic artery or portal vein, with possible development of pulmonary thromboembolism. During the first five days, the liver rejection often happens as a consequence of the hepatic artery thrombosis [35]. Extensive studies involving sample groups of 700-1200 transplanted patients state that thrombosis develops in the hepatic artery in 2.0-2.7% of cases and that it can cause liver graft dysfunction [36, 37, 38]; therefore, thromboprophylaxis with unfractionated or low-molecular-weight heparin is recommended in postoperative period. In our cohort, thromboprophylaxis was implemented from the postoperative day 1 with the unfractionated heparin in the first 48 hours, followed by low molecular weight heparin. The dose was adjusted according to the findings of the anti-Xa activity and the levels maintained within the prophylactic range.

A continuous monitoring of the haemostatic system laboratory parameters is mandatory during the liver transplantation in order to optimise substitution and antifibrinolytic therapy during and after transplantation, as well as to apply adequate measures to prevent thromboembolic complications, depending on patient's clinical status and the estimated risk of haemorrhagic and thromboembolic complications.

CONCLUSION

Laboratory monitoring of the haemostatic system changes in liver transplantations in our study has shown gradual improvement of all investigated laboratory parameters of the haemostatic system after the first day after transplantation, with normalisation within 7-14 days.

ACKNOWLEDGEMENT

We thank Prof. Dr. Milotka Fabri, infectious disease specialist, who has contributed to the paper analysis and statistical reseach.

REFERENCES

1. Osterud B. Factor VII and haemostasis. Blood Coagul Fibrinolysis. 1990; 1(2):175-81.
2. Cordova C, Violi F, Alessandri C. Prekallikrein and factor VII as prognostic index of liver failure. Am J Clin Pathol. 1986; 85:579-82.
3. Joist J. Hemostasis abnormalities in liver disease. In: Colman R, Hirsh J, Marder V, Salzman E, editors. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. Philadelphia: JB Lippincott Company; 1994. p.906-15.
4. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011; 365:147-56.
5. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood. 2010; 116:878-85.
6. Agarwal A, Sharma N, Vij V. Point-of-care coagulation monitoring during liver transplantation. Trends in Anaesthesia and Critical Care. 2013; 3:42-48.
7. Bosch J, Garcia-Pagan JC. Complications of cirrhosis. I. Portal hypertension. J Hepatol. 2000; 32(1 Suppl):141-56.
8. Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut. 2005; 54:691-7.
9. Fimognari FL, De SA, Piccheri C, Moscatelli R, Gigliotti F, Vestri A, et al. Evaluation of D-dimer and factor VIII in cirrhotic patients with asymptomatic portal venous thrombosis. J Lab Clin Med. 2005; 146:238-43.
10. Tsochatzis EA, Senzolo M, Germani G, Gatt A, Burroughs AK. Systematic review: portal vein thrombosis in cirrhosis. Aliment Pharmacol Ther. 2010; 31:366-74.
11. García-Fuster MJ, Abdilla N, Fabiá MJ, Fernández C, Oliver V, Forner MJ. Venous thromboembolism and liver cirrhosis. Rev Esp Enferm Dig. 2008; 100:259-62.
12. Scharrer I. Leberzirrhose und Gerinnungsstörungen. Hämostaseologie. 2005; 25:205-8.
13. Lewis JH, Bontempo FA, Awad SA, Kang YG, Kiss JE, Ragni MV, et al. Liver transplantation: intraoperative changes in coagulation factors in 100 first transplants. Hepatology. 1989; 9:710-4.
14. Goerlinger K. Coagulation management during liver transplantation. Hämostaseologie. 2006; 26:64-75.
15. Porte RJ. Coagulation and fibrinolysis in orthotopic liver transplantation: current views and insights. Semin Thromb Haemost. 1993; 19:191-6.
16. Csete M. Operative hemostasis changes and their treatment. In: Busuttil R, Klintmalm G, editors. Transplantation of the Liver. Philadelphia, London, Toronto: WB Saunders Company; 1996. p.449-57.
17. Vuković M, Milošević Z, Moljević N. Transplantacija jetre. Novi Sad: Medicinski fakultet; 2010.

18. Elezović I. Fibrinoliza i fibrinogenoliza u akutnoj leukemiji [doktorska disertacija]. Beograd: Medicinski fakultet; 1993.
19. Porte R, Bontempo F, Knot E, Lewis J, Kang Y, Starzl T. Tissue-type-plasminogen activator-associated fibrinolysis in orthotopic liver transplantation. Transplant Proc. 1989; 21:3542.
20. Dzik W, Arkin C, Jenkins R, Stump D. Fibrinolysis during liver transplantation in humans: Role of tissue-type plasminogen activator. Blood. 1988; 71:1090-5.
21. Kang Y. Blood coagulation during liver, kidney, and pancreas transplantation. In: Lake C, Moore R, editors. Blood: Hemostasis, Transfusion, and Alternatives in the Perioperative Period. New York: Raven Press Ltd; 1995. p.529-37.
22. Vavić N. Hemostaza u transplantaciji jetre. Beograd: Zadužbina Andrejević; 2001.
23. Himmelreich G, Riess H. In vitro inhibition of platelet aggregation by the liver with UW solution as the preservation fluid. Transplantation. 1991; 52:30-3.
24. Himmelreich G, Hundt K, Isenberg C, Benchstein W, Neuhaus P, Riess H. Thrombocytopenia and platelet dysfunction in orthotopic liver transplantation. Semin Thromb Hemost. 1993; 29(3):209-12.
25. Porte R, Blauw E, Knot E, de Maat M, de Ruiter C, Minka-Bakker C. Role of the donor liver in the origin of platelet disorders and hyperfibrinolysis in liver transplantation. J Hepatol. 1994; 21(4):592-600.
26. Palareti G, De Rosa V, Fortunato G, Grauso F, Legnani C, Maccaferri M, et al. Control of hemostasis during orthotopic liver transplantation. Fibrinolysis. 1988; 2(Suppl 3):61.
27. Llamas P, Cabrera R, Gomez-Arnau J, Fernandez MN. Hemostasis and blood requirements in orthotopic liver transplantation with and without high-dose aprotinin. Haematol. 1998; 83(4):338-46.
28. Faeh M, Hauser SP, Nydegger UE. Transient thrombopoietin peak after liver transplantation for end-stage liver disease. Br J Haematol. 2001; 112:493-8.
29. Mehta AB, Burroughs AK. Thrombopoietin concentration after orthotopic liver transplantation. Br J Haematol. 2001; 114(4):960-1.
30. Lewis J, Bontempo F, Cornell F, Kiss JE, Larson P, Ragni MV, et al. Blood use in liver transplantation. Transfusion. 1987; 27:222-5.
31. Cabrera R, Rios E, Briz M, et al. Behavior of the coagulation and fibrinolysis during liver transplantation for liver cirrhosis. Transplantology. 1992; 3:87-95.
32. Grande L, Rimola A, Garcia-Valdecasas J. Recovery of liver graft after initial poor function. Transplantation. 1992; 53:228-30.
33. Velasco F, Villabla R, Fernandez M. Diminished anticoagulant and fibrinolytic activity following liver transplantation. Transplantation. 1992; 53:1256-61.
34. Kang Y. Coagulation and liver transplantation. Transplant Proc. 1993; 25(2):2001-5.
35. Jennings I, Calne R, Baglin T. Predictive value of von Willebrand factor to ristocetin cofactor ratio and thrombin-antithrombin complex levels for hepatic vessel thrombosis and graft rejection after liver transplantation. Transplantation. 1994; 57:1046-51.
36. Stange B, Glanemann M, Nuessler N, Settmacher U, Steinmüller T, Neuhaus P. Hepatic artery thrombosis after liver transplantation. Liver Transpl. 2003; 9(6):612-20.
37. Settmacher U, Stange B, Haase R, Heise M, Steinmüller T, Bechstein WO, et al. Arterial complications after liver transplantations. Transpl Int. 2000; 13(5):372-8.
38. Proposito D, Loinaz Sequrola C, Garcia Garcia I, Jimènez C, Gonzalez Pinto I, Gomez Sanz R, et al. Assessment of risk factors in the incidence of hepatic artery thrombosis in a consecutive series of 687 liver transplantation. Ann Ital Chir. 2001; 72(2):187-205.

Лабораторијско испитивање промена хемостазног система током ортотопичне трансплантације јетре

Слађана Новаковић-Анучин[1], Сања Гнип[1], Вишња Чанак[1], Ђурђина Јуришић[1], Павица Радовић[1], Светлана Ердељан[2], Зоран Милошевић[3,4], Горана Митић[1,4]

[1]Одељење за тромбозу, хемостазу и хематолошку дијагностику, Центар за лабораторијску медицину, Клинички центар Војводине, Нови Сад, Србија;
[2]Клиника за анестезију и интензивну терапију, Клинички центар Војводине, Нови Сад, Србија;
[3]Клиника за абдоминалну, ендокрину и трансплантациону хирургију, Клинички центар Војводине, Нови Сад, Србија;
[4]Медицински факултет, Универзитет у Новом Саду, Нови Сад, Србија

КРАТАК САДРЖАЈ

Увод Код обољења јетре све компоненте хемостазног система су измењене, а поремећај функционалности овог система сразмеран је хепатоцелуларном оштећењу. Током трансплантације јетре вредности параметара хемостазе значајно се мењају, да би се постоперационо забележила постепена нормализација функционалности хемостазног система.

Циљ рада Циљ истраживања били су посматрање и бележење промена хемостазног система током и после операције, те утврђивање динамике постизања физиолошких вредности параметара након трансплантације јетре.

Методе рада Од јуна 2008. до фебруара 2012. године у Клиничком центру Војводине урађено је 17 кадаверичних трансплантација јетре. Испитивани су следећи параметри: тромбоцити, активисано парцијално тромбопластинско време, протромбинско и тромбинско време, фибриноген, еуглобулинско време лизе коагулума, *D*-димер, антитромбин и хепаринемија. Резултати су бележени интраоперационо, по фазама трансплантације, и од првог до седмог дана после операције, а потом 14. дана.

Резултати Најизраженији поремећаји уочени током трансплантације јетре били су: тромбоцитопенија (96±66,1×10^9/*l*), продужено активисано парцијално тромбопластинско (1,80±0,8 *R*), протромбинско (1,59±0,4 *R*) и тромбинско време (2,03±1,7 *R*), хипофибриногенемија (2,13±0,5 *g/l*), хиперфибринолиза (29±12,0 мин.), пораст *D*-димера (1393±1220,4 *ng/ml*) и пад антитромбина (61±18,0%). Даљим праћењем након трансплантације, од првог постоперационог дана, бележи се постепена нормализација вредности параметара, а физиолошке вредности свих параметара постигнуте су 14. дана, сем одржавања повишених вредности *D*-димера (2606±1055,1 *ng/ml*). Ниво хепаринемије био је у превентивном опсегу (0,26±0 *IU/ml*).

Закључак Континуирано испитивање параметара хемостазног система код трансплантације јетре од изузетног је значаја јер омогућава оптималну примену супституционе терапије током и након операције и одговарајуће постоперационе тромбопрофилаксе. Резултати лабораторијског испитивања указују на нормализовање вредности хемостазних параметара током 7–14 дана након трансплантације јетре.

Кључне речи: хемостаза; хемостазни параметри; фибринолиза; ортотопична трансплантација јетре

Примљен • Received: 02/04/2012 **Прихваћен • Accepted:** 20/02/2013

doi: 10.2298/SARH1310608N