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EVALUATION OF HEMOSTASIS PARAMETERS IN RECIPIENTS AFTER RELATED RIGHT LOBE LIVER TRANSPLANTATION

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Objective: to study the dynamics of hemostasis parameters in the early postoperative period and to identify the timing of restoration of the level of procoagulants and anticoagulants synthesized by the liver (received from a living related donor) in liver lobe recipients. **Materials and methods.** Under observation were 31 recipients and 31 related donors of liver lobe. They were treated at the Republican Specialized Scientific and Practical Medical Center for Surgery in Tashkent, Uzbekistan, from August 2022 to August 2023. Hemostasis parameters were determined in recipients, whose postoperative period was uneventful. **Results.** It was revealed that compensation in the hemostasis system occurs even at low levels of coagulation factors on day 10 after liver transplantation (LT). In recipients, a decrease in anticoagulants was more pronounced than that of procoagulants. In general, the hemostasis system was in an unstable equilibrium, which, under the influence of external and internal factors, can easily shift both towards hypercoagulable and hypocoagulable state. Activity of the fibrinolytic system and fibrinogen level are significant influencing factors. Gradual recovery of fibrinogen levels by the end of day 1 after surgery is the result of activation of the synthetic function of the liver. After LT, there were signs of endothelium activation, but not endothelial damage, which regress and normalize by postoperative day 10. At the same time, in the initial status, recipients had an increase in both the amount and activity of von Willebrand factor, which indicates endothelial damage and dysfunction. The low level of homocysteine in recipients is probably a protective factor against the development of thrombotic complications, and homocysteine dynamics reflects the gradual restoration of the functional activity of the liver, adaptation of the donor liver to functioning. **Conclusion.** Monitoring of hemostasis system in recipients after liver transplantation allows to prevent thrombohemorrhagic complications in time but also to assess the dynamic equilibrium of procoagulants and anticoagulants, the timing of restoration of the activity of the main hemostasis factors and, according to this, to vary the administration regimes of anticoagulants, antiplatelet medications, and fibrinolysis inhibitors, to carry out replacement therapy and to realize the concept of hemostasis management.

Keywords: liver transplantation, thrombohemorrhagic complications, endothelial dysfunction, coagulation factors, hemostasis.

INTRODUCTION

Thrombohemorrhagic complications in LT represent a major problem in the perioperative period [1–3]. Compromised initial status in patients with end-stage liver disease (ESLD), unbalanced hemostasis system, as well as the anatomical features of angioarchitecture of the donor liver, the direct technical peculiarities of all stages of LT, including processing of donor liver on the back table, create prerequisites for the development of these complications [4, 5]. Various reports have shown that the incidence of bleeding and thrombosis varies greatly, ranging from 0.02 to 25%, and it is impossible to predict the risk of thrombohemorrhagic complications solely based on preoperative hemostasiogram parameters [6, 7]. These difficulties are down to the fact that each patient has individual peculiarities of the reserve of compensatory capabilities of the hemostasis system, the degree of endothelial dysfunction and endotoxemia.

The initial metabolic status in ESLD patients is characterized by different degrees of dysproteinemia due the reduced protein-synthetic function of the liver (hypoalbuminemia on the background of hyperglobulinemia), manifestations of cholestasis and cytolysis syndrome, as well as hypocholesterolemia and hyperglycemia resulting from decreased glycogen and lipoprotein metabolism in the liver [8, 9]. Due to impaired synthetic function of hepatocytes, the production of protein coagulation factors and natural anticoagulants is also reduced, which is a prerequisite for the development of both thrombotic and hemorrhagic complications with a shift in the delicate dynamic balance of hemostasis factors [10]. It is known that almost all coagulation hemostasis factors (II, V, VII, IX, X, XI, XII, XIII), coagulation inhibitor factors (antithrombin, heparin cofactor II, protein C, protein S, tissue factor pathway inhibitor), fibrinolytic system components (plasminogen, alpha-2-antitrypsin, plasmin inhibitor) are synthesized in the liver [10, 11]. At the

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same time, such factors as urokinase-type plasminogen activator, thrombomodulin are synthesized outside the liver and their level depends on the degree of tissue and endothelial damage [12]. A significant aggravating factor in the development of thrombohemorrhagic complications is portal hypertension, varicose veins, hypertrophied diffuse collateral venous blood flow, which causes platelet sequestration in the spleen [11]. Portopulmonary hypertension is observed in 3–8% of cases and causes procoagulant shifts in the pulmonary endothelium, which may be the basis of the pathogenesis of this condition; intrapulmonary microthrombi at autopsy in patients with portopulmonary syndrome confirm this [13]. Borst et al. (2018) reported that bleeding and thrombotic events in LT developed in 20.7% and 25% of cases, respectively, and 50% of liver retransplantations were for thrombotic complications [14].

MATERIAL AND METHODS

There were 31 recipients and 31 related donors of liver lobe treated at the Republican Specialized Scientific and Practical Medical Center for Surgery in Tashkent, from August 2022 to August 2023. This group of recipients was selected at the second stage of mastering the LT technique at our Center, i.e. 4 years after the first LT in 2018.

The recipients were predominantly male (22 *vs.* 9 females); mean age was 40.15 (95% CI: 38.7–45.6) years, the etiology of cirrhosis was dominated by chronic hepatitis B and delta in 26 (83.9%) cases; mean score on the Model of End-Stage Liver Disease (MELD) scale was 14.4 (95% CI: 12.8–15.9); fibroscan was 33.6 (95% CI: 29.1–38.0). The baseline risk of thrombohemorrhagic complications according to the Wells probability scale was high, as 28 (90.3%) had varicose veins (2.8 (95% CI: 2.61–3.14) trunk) and a history of bleeding in 10 (32.2%) patients (1 to 5 episodes). All recipients had an uncomplicated postoperative period.

Hemostatic factors were studied on an automatic coagulometer ACL-TOP (USA) using standard kits: activated partial thromboplastin time (aPTT), thrombin time (TT), prothrombin complex including prothrombin time (PT) and international normalized ratio (INR), antithrombin III (AT III) were determined, plasminogen, D-dimer (highly sensitive by immunoturbidimetric method), von Willebrand factor (vWF), vWF activity, homocysteine, natural plasma anticoagulants – protein C and protein S. The parameters were evaluated preoperatively, immediately postoperatively (p/o), 12 hours, 24 hours after LT, as well as on days 5–7 and day 10 of the postoperative period.

RESULTS

The average graft weight in our study was 627.2 ± 45.8 grams. Both at baseline and at all follow-up periods, the parameters of prothrombin complex – PT, INR – characterizing the level of factor II, were significantly lower than in donors, they were also below the lower limit of the reference interval. Within 1 day (p/o, 12h and 24h after LT), PT was prolonged 1.6–1.63 times ($p < 0.05$), INR increased 1.6–1.65 times ($p < 0.05$), and a gradual increase in factor II synthesis during the first week after LT still did not lead to achievement of target values. On days 5–7, PT and INR had positive dynamics, but were lower than in donors by 1.35 and 1.3 times ($p < 0.05$), respectively, remaining at this level until day 10 of follow-up. On day 10 of follow-up, INR was 1.3 times lower than donors' values, PT was 1.33 times prolonged ($p < 0.05$) (Fig. 1). The peak of PT prolongation and INR increase occurred at the end of day 1 after surgery, indicating a deficiency of coagulation factors in this period.

Partial restoration of prothrombin levels by day 10 was sufficient for balance in the hemostatic system, which is reflected by TT and aPTT levels. On day 10, TT and aPTT were within the reference interval. It should be noted that the peak of TT and aPTT prolongation occurred in the period immediately after the end of the

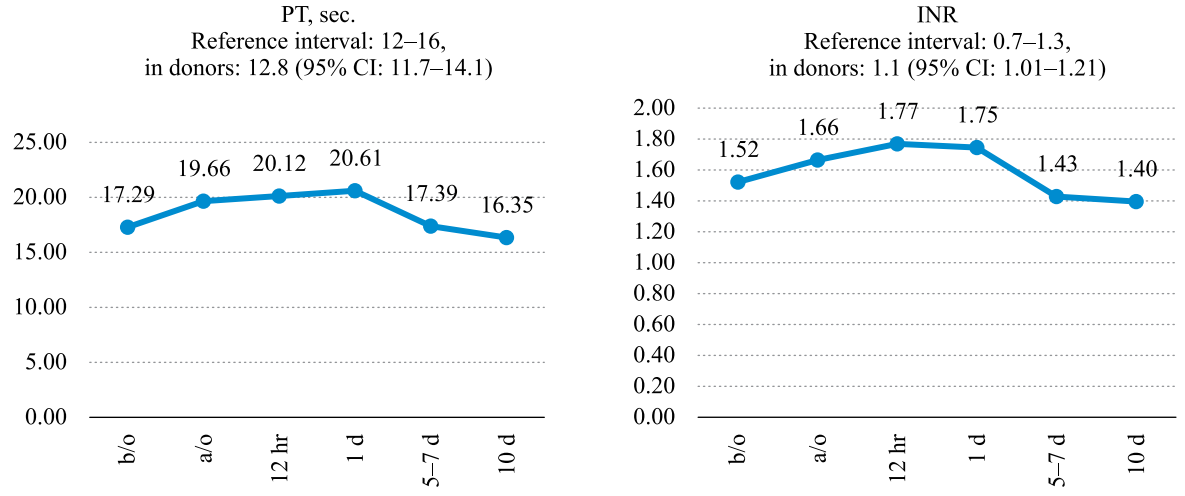

Fig. 1. Dynamics of Prothrombin Time and International Normalized Ratio in liver lobe recipients

operation, which is connected with the peculiarities of back-table preparation of the donor liver, application of washing and preserving solutions, as well as management of the graft reperfusion period during its implantation. Back-table preparation of the liver lasted for 93.3 ± 17.6 min. In the period from 12 hours to 5 days after LT, the TT parameter was at a steady-state level and prolonged relative to donors by 1.3–1.35 times, and aPTT had a second peak of lengthening to 59.8 seconds (95% CI: 29.5–77.6) by the end of day 1 of follow-up (Fig. 2).

The wide variability of aPTT was remarkable, which was due to individual characteristics of each recipient, heparin dose and AT III levels, since aPTT is an indicator of heparin therapy efficacy. On days 5–7, aPTT was at the target level of 41.1 seconds (95% CI: 33.7–52.6), and by day 10, it was 33.7 seconds (95% CI: 20.5–47.6), which is within the reference interval. At the same time, there was a deficiency of AT III, as well as natural anticoagulants synthesized by the liver – proteins C and S.

AT III levels in liver recipients remained low up to day 10 of the postoperative period, although the level tended to increase gradually starting from day 5 (Fig. 3).

We emphasize that low AT III levels reduces the ineffectiveness of heparin therapy, because heparin is not active in the absence of its cofactor, which is AT III. AT III levels in healthy donors is 100.3% with a reference interval of 83–128%, and in liver recipients it was reduced relative to this level by 3.2; 3.0; 3.6; 2.3 and 1.7 times during the observation stages ($p < 0.05$). The peak of AT III decrease occurred on day 1 after the operation, after that AT III tended to increase; by day 5, it increased 1.6 times relative to the previous period and increased in dynamics by day 10, but still remained below the reference interval and 1.7 times lower than in donors. The low level of AT III during anticoagulant therapy may serve as an indicator in favor of choosing alternative anticoagulants (Xa inhibitors, etc.) up to day 5 after surgery due to the possible ineffectiveness of unfractionated heparin under AT III deficiency.

The level of proteins C and S, which were initially reduced relative to the level of healthy donors by 1.9 ($p < 0.05$) and 1.1 ($p > 0.05$) times, respectively, were partially restored on day 10 of follow-up. By day 10 of follow-up, protein C was restored only to 57%, which is 1.5 times lower than the target level ($p < 0.05$), and protein S was restored to 52.9%, which is 1.6 ($p < 0.05$) times lower than the target level. Moreover, the peak of protein C and S decrease was 12 hours after LT, when protein C was reduced 2.8-fold and protein S was reduced 2.3-fold relative to donor levels ($p < 0.05$) (Fig. 4).

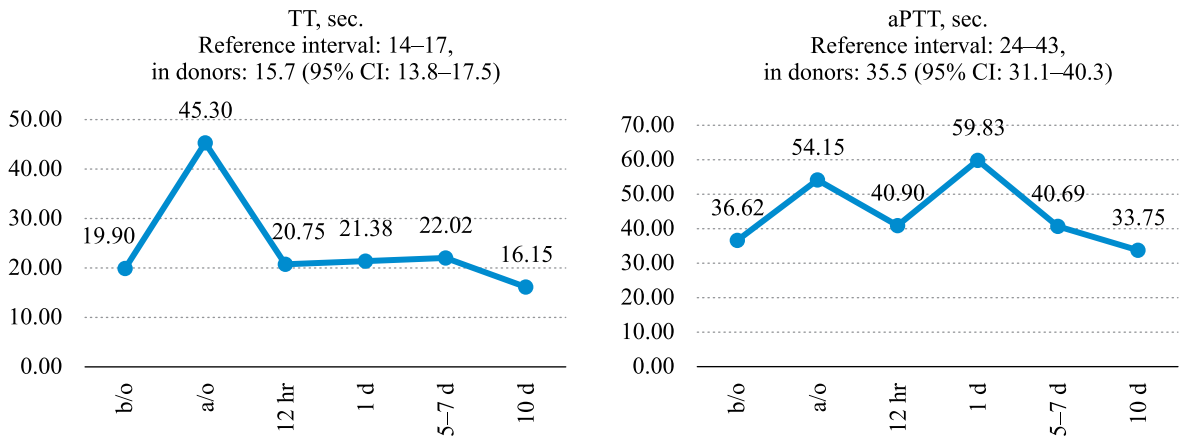

Fig. 2. Dynamics of Thrombin Time and Activated Partial Thromboplastin Time in liver lobe recipients

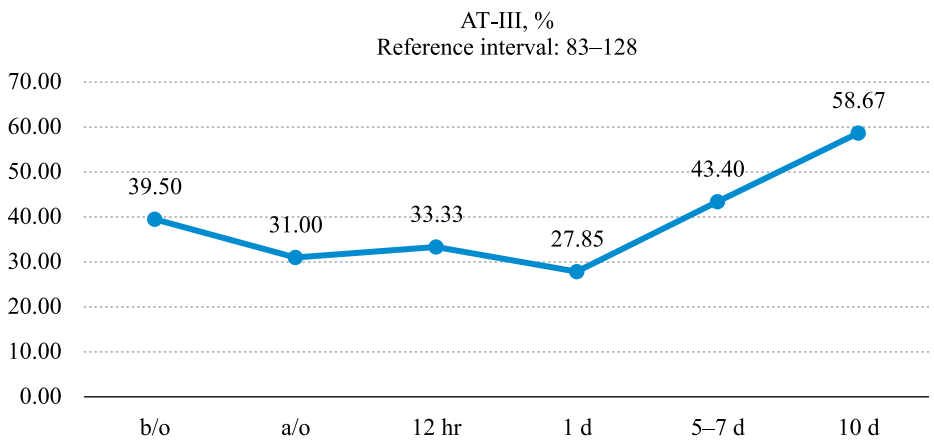

Fig. 3. Dynamics of antithrombin III in liver lobe recipients

Thus, the results show that compensation in the hemostatic system occurs even at low levels of coagulation factors on day 10 of LT, when TT and aPTT are within the reference interval, while INR is prolonged 1.3 times, AT III is reduced 1.7 times, protein C and S are reduced 1.5 and 1.6 times relative to donors, respectively.

As can be seen, the decrease in anticoagulants is more pronounced than in procoagulants, and in general the hemostatic system is in unstable equilibrium, which, under the influence of external and internal factors, can easily shift both towards a hyper- and hypocoagulable state. A significant influencing factor in this case is fibrinolytic activity and fibrinogen levels (Fig. 5).

Thus, plasminogen activity was reduced during the first week after LT, being 2.2 and 2.5 times lower ($p < 0.05$) relative to donors 12 hours and 24 hours after LT. By day 5, plasminogen activity slightly increased, and by day 10 it was within the reference interval, exceeding that of donors by 1.2 times. Fibrinogen levels were decreased to a greater extent immediately after LT and gradually increased over 1 week, reaching the reference-interval level on day 10 after LT.

Assessment of vWF amount and vWF activity showed that both parameters decreased in the recipients by day 10 after LT (Fig. 6).

Immediately after the end of the operation, there was increased vWF activity (vWF Act) without an increase in vWF amount (vWF Ag), and subsequently there was a clear tendency to a decrease in vWF amount, but without a decrease in its activity up to day 5 of follow-up. On day 10, the quantitative content of vWF Ag normalized and vWF Ag activity decreased to the level of the reference interval, but both indices were higher than in donors by 2.1 and 1.5 times for vWF Act and vWF Ag, respectively ($p < 0.05$).

Platelet count in recipients decreased 4.6 times relative to the donor level on day 1 and remained at this level until day 5 after LT, and by day 10 increased 2.1 times relative to the previous period, although it did not reach the level of the lower limit of the reference interval and the donor level (Fig. 7). It should be noted that on day 1 after LT, thrombocytopenia is probably compensated by an increase in their aggregation properties under increased vWF activity, and by day 5, vWF activity synchronously decreases and platelet count increases, providing the balance of anti- and pro-aggregation properties. At the same time, platelet aggregation did not increase and there was no initiation of the blood coagulation cascade with the development of thrombotic (both arterial and venous) complications. D-dimer levels were elevated

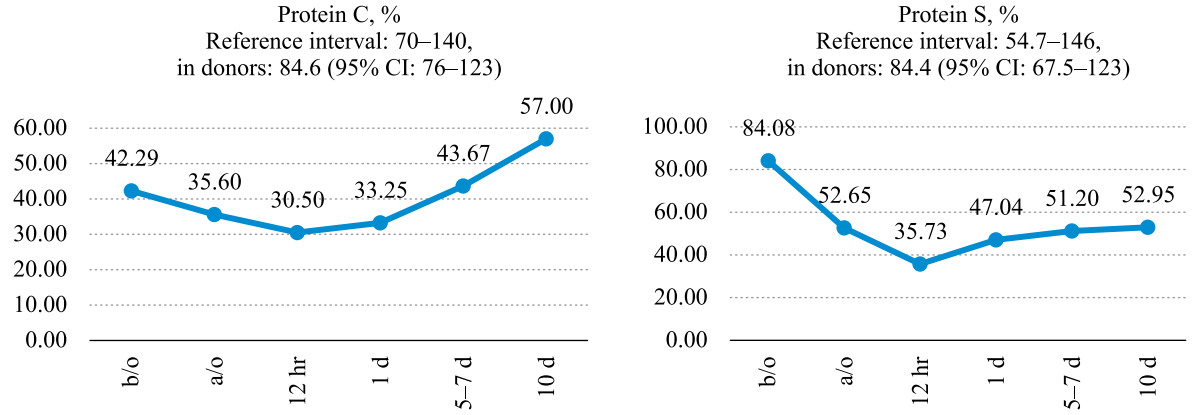

Fig. 4. Dynamics of proteins C and S in liver lobe recipients

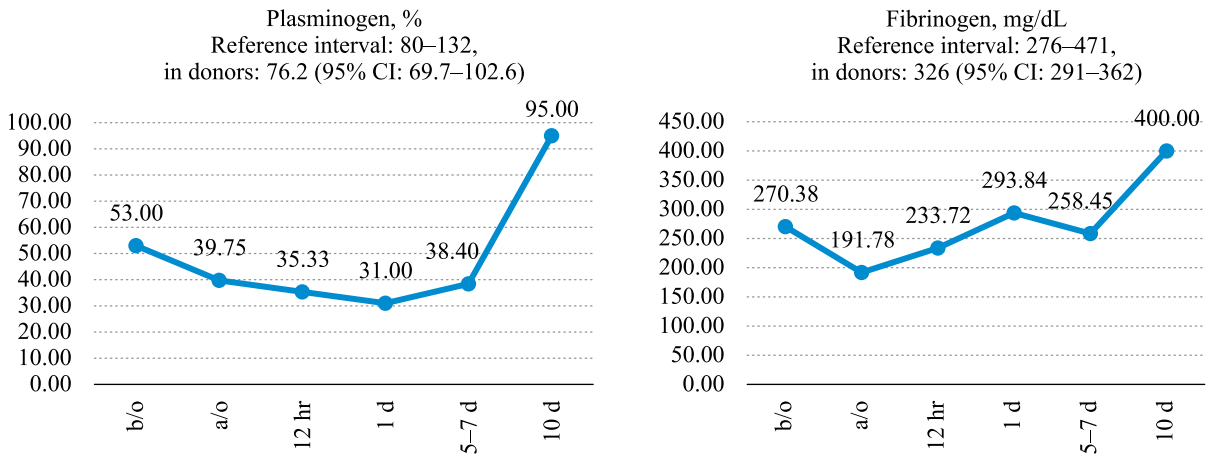

Fig. 5. Dynamics of plasminogen and fibrinogen levels in liver lobe recipients

in all periods, averaging 962–3869 ng/mL, reflecting multidirectional shifts in this index.

The study of homocysteine levels in the recipients showed that it decreased 2.5 times relative to the donor level immediately after surgery, increased 2 times from this level after 12 hours p/o, a plateau up to 24 hours p/o and gradually increased to the level of donors and reference interval, which was noted already on day 5 after LT (Fig. 8).

This indicates the restoration of amino acid metabolism reactions in the liver, in particular transmethylation reactions involving methionine and homocysteine,

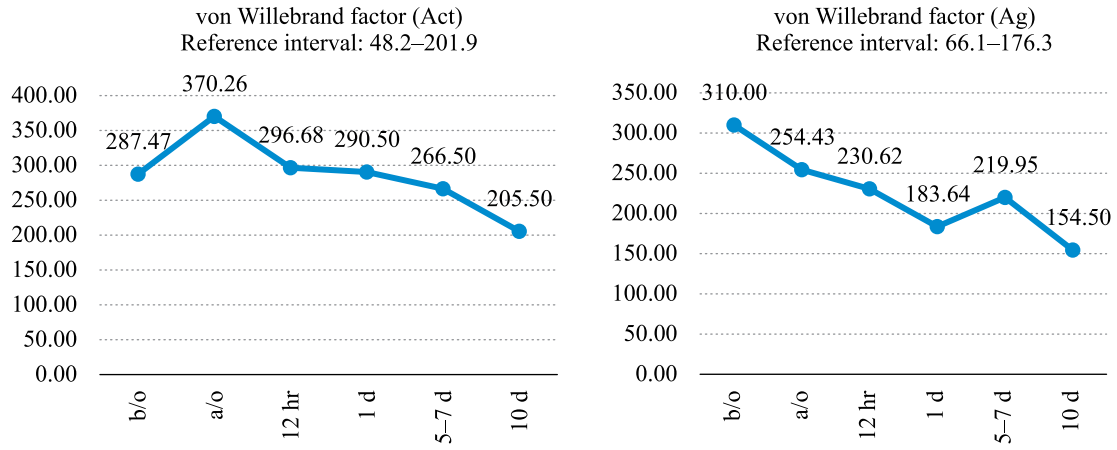

Fig. 6. Dynamics of Willebrand factor levels in liver lobe recipients

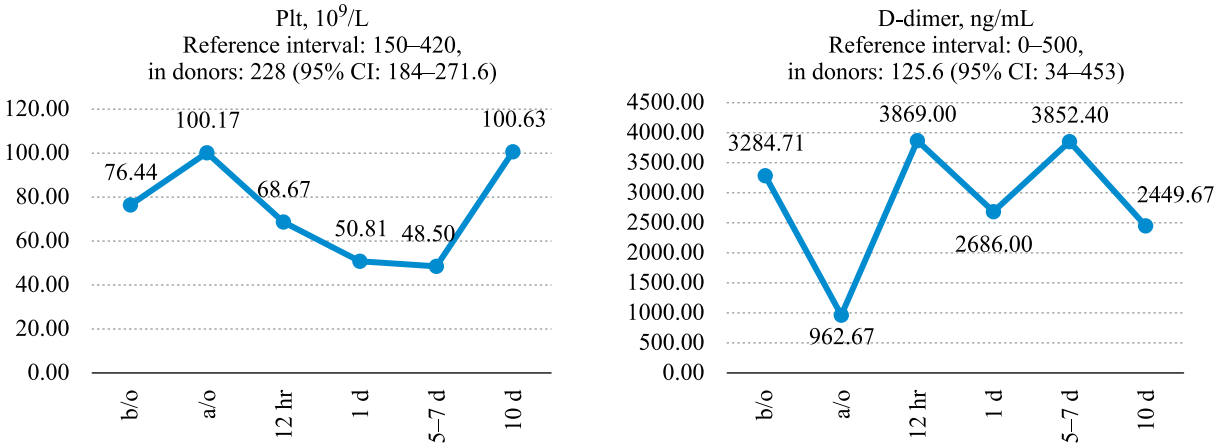

Fig. 7. Dynamics of platelet (Plt) and D-dimer levels in liver lobe recipients

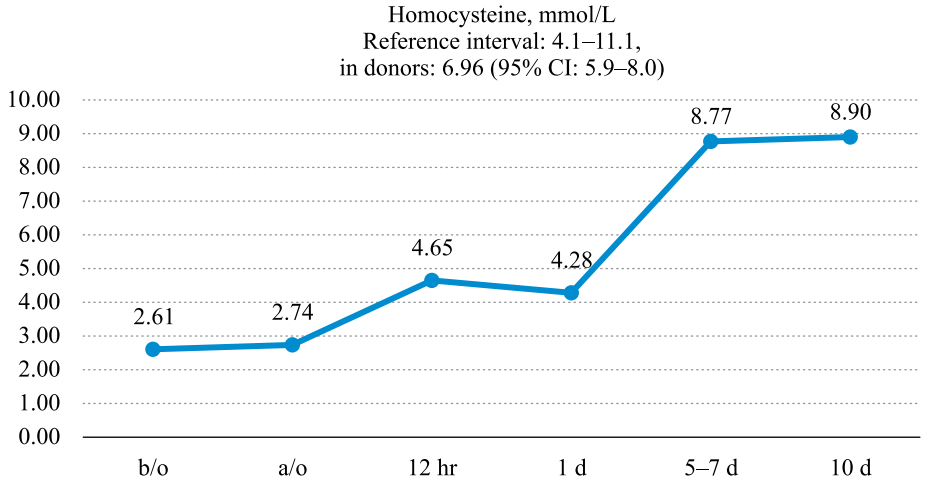

Fig. 8. Dynamics of homocysteine levels in liver lobe recipients

as well as the general amino acid catabolic pathways through transamination, decarboxylation and deamination. Note that homocysteine, when its level is elevated, is an independent factor in the development of stroke and thrombosis, and is also associated with the development of brain disorders (depression, Alzheimer's disease, chronic fatigue syndrome), and osteoporosis. Low level of homocysteine in liver recipients is probably a protective factor against the development of thrombotic complications, and homocysteine dynamics reflects the gradual recovery of the functional activity of the liver, and adaptation of the donor liver to function in the recipient's body.

DISCUSSION

LT from a living related donor differs from LT from a deceased donor in that the recipient does not receive the whole organ, but only a part of it. Consequently, the timing of liver function restoration will be different, which is related to the amount of functioning liver parenchyma. According to reports, in recipients of whole liver from a cadaveric donor, recovery of synthetic liver function and normalization of hemostasis factors occur on days 1–2 [8, 11]. We found that the liver function to synthesize enough coagulation factors and anticoagulants in liver lobe recipients recovered slowly, because the target values were partially reached only on day 5–7. The synthesis of natural anticoagulants lagged behind the synthesis of coagulation factors, and fibrinolytic activity depended on the course of the postoperative period. It is known that plasminogen activation level depends on the degree of tissue damage with the release of tissue factors (plasminogen activators, PAI-1 plasminogen activator inhibitors, the degree of endotoxemia, the severity of endothelial dysfunction and the intensity of deactivation of bioactive molecules, including liver involvement) [11]. Progression of a decrease in natural plasma anticoagulants 12 hours after LT, which we identified, may be a risk factor for thrombotic complications during this period, especially under AT III deficiency, and requires mandatory monitoring every 12 hours during the first 3 days after LT.

Low levels of protein C with normal levels of protein S, its cofactor, also indicates a predisposition to thrombotic complications. It is known that protein C deficiency leads to impaired inactivation of Y and YII factors, which increases the procoagulant potential of blood plasma, because active thrombin (IIa) not only catalyzes fibrinogen conversion into fibrin, but also activates the anti-clotting mechanism through protein C activation. When protein C is sufficient, the following cascade is triggered: IIa interacts with thrombomodulin, calcium, prothrombin, and further this complex activates protein C, and it interacts with cofactor S and calcium ions, and the complex consisting of protein C, protein S, and calcium destroys active factors V and VII, thus inhibiting coagulation hemostasis through both intrinsic and extrinsic pathways [11, 13]. The deficiency of natural anticoagulants synthesized by the liver is partially balanced by the deficiency of procoagulants; however, this dynamic equilibrium is unstable.

The decrease in fibrinogen immediately after LT is probably due to the fact that fibrinogen is the factor that first responds to hemodilution and massive blood loss. The mean volume of blood loss in our study was 1388.9 ± 198.9 mL for the entire period of surgery, which lasted, on average, 596.7 ± 29.0 min. Gradual recovery of fibrinogen levels by the end of day 1 is the result of the inclusion of the synthetic function of the liver.

Von Willebrand factor is an informative marker of the endothelium state. Our results show that recipients after LT have signs of endothelial activation, but not endothelial damage, which regress and normalize by day 10 after LT. At the same time, in the initial status, recipients have an increase in both vWF amount and vWF activity, which indicates endothelial damage and endothelial dysfunction.

D-dimer levels in recipients was elevated in all follow-up periods, which was expected given the end stage of the liver disease at baseline and surgical trauma resulting from LT. Taking into account the low specificity of D-dimer for prognosis of thrombotic complications in the postoperative period, D-dimer elevation should be considered as typical, and monitoring of the dynamics of this index should be performed as indicated, if clinically necessary. We also note that all recipients received anticoagulant therapy, we did not observe arterial and venous thromboembolic complications in any case. The low level of homocysteine, which we observed in our patients, may be protective against these formidable complications.

Taking into account the above mentioned, monitoring the hemostatic system in liver lobe recipients allows not only to timely diagnose thrombohemorrhagic complications, but also to ascertain the dynamic balance of pro- and anticoagulants, the timing of restoration of the activity of the main factors of the hemostatic system and, according to this, to vary the regimes of anticoagulants, antiplatelet agents, fibrinolysis inhibitors administration and to carry out replacement therapy, i.e. to implement the concept of hemostasis management.

CONCLUSION

The results we obtained have allowed us to draw the following conclusions.

1. In liver lobe recipients in the initial status, there is a balanced decrease in coagulation factors (IIa), as well as anticoagulants (proteins C, S, AT III) against the background of significantly ($p < 0.05$) increased vWF Ag and vWF Act relative to donors.
2. During the first day after LT, INR was reduced by 1.6–1.63 times; TT was prolonged 1.3 times, AAT III was decreased 3.0–3.6 times, protein C 2.8–2.5 times; protein S 2.3–1.4 times, plasminogen 2.2–2.5 times, while there is a clear tendency of prolongation of TT and PT, and decrease in proteins C and S by 12 hours

of the postoperative period against the background of sharply reduced AT III level. This allows us to consider this period as a critical one, when the synthetic and elimination function of the liver is insufficient.

3. By day 5–7 after LT, there is no complete recovery of the level of hemostatic factors, although INR, AT III, protein C, and plasminogen levels were significantly higher relative to day 1 of follow-up, however, lower than the donor level by 1.3, 2.3, 1.9 times ($p < 0.05$), respectively.
4. Compensation in the hemostatic system occurs even at low level of coagulation factors on day 10 of LT, when TT and aPTT are within the reference interval, and INR is prolonged 1.3 times, AT III is reduced 1.7 times, protein C and S are reduced 1.5 and 1.6 times relative to donors, respectively ($p < 0.05$).
5. Immediately after the end of the operation, there was increased vWF activity (vWF Act) without increased vWF amount (vWF Ag), and subsequently there was a clear tendency to a decrease in vWF quantitatively, but without a decrease in vWF activity up to 5 days of follow-up; on day 10, the quantitative content of vWF Ag normalized and its activity decreased to the reference interval level. However, both indices were higher than in donors by 2.1 and 1.5 times for vWF Act and vWF Ag, respectively ($p < 0.05$), reflecting first endothelial activation and then its regression.
6. The synthesis of natural anticoagulants lags behind the synthesis of coagulation factors, and fibrinolytic activity depends on the course of the postoperative period; in recipients after LT there are signs of endothelial activation, but not endothelial damage, as evidenced by the level of vWF Ag, vWF Act, when vWF Ag decreases while vWF Act remains high, and subsequently there is a tendency towards normalization of these indices to the reference interval level by day 10 after LT.
7. Low level of homocysteine in liver recipients is probably a protective factor against the development of thrombotic complications, and the dynamics in the increase in homocysteine levels by day 10 after LT reflects the gradual recovery of the functional activity of the liver, adaptation of the donor liver to function in the recipient's body.

The authors declare no conflict of interest.

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