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Antithrombin III in the prevention of thrombotic complications in high risk patients undergoing liver transplantation

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Introduction. *Recent studies have indicated an increased incidence of thrombotic vascular complications after liver transplantation. The reasons may be associated with surgical technique and "unbalanced" hemostasis in patients with diffuse liver diseases. The imbalance is determined by the deficiency of physiological procoagulants and anticoagulants due to a reduced protein-synthesis function of the liver in chronic hepatocyte injury. At the same time, 90% of all spontaneous antithrombin activity is associated with antithrombin III.*

Aim. *The aim of the study was to evaluate the efficacy of using antithrombin III concentrate in liver transplant patients.*

Material and methods. *A retrospective study included 46 patients undergoing liver transplantation who had non-occlusive thrombosis in the*

portal vein system prior to surgery and postoperative venous or arterial thrombosis.

Results. *The treatment results were compared between the group with antithrombin III concentrate and the control group in patients with portal vein thrombosis before surgery and postoperative venous or arterial thrombosis; the antithrombin III activity dynamics in the early postoperative period was assessed; the incidence of infectious, and vascular complications and the mortality rates were analyzed.*

Conclusion. *The antithrombin III concentrate administration during liver transplantation and in the postoperative period contributes to a rapid normalization of antithrombin III activity in blood, the decrease in mortality and in the incidence of infectious and thrombotic complication rates.*

Keywords: liver transplantation, portal vein thrombosis, hepatic arterial thrombosis, antithrombin III, anticoagulation therapy

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AT, antithrombin

FFP, fresh frozen plasma

LMWH, low molecular weight heparin

LT, liver transplantation

Introduction

Hemorrhagic complications in the early postoperative period have been the common problems after liver transplantation (LT). Studies conducted in recent years indicate an increased incidence of postoperative thrombotic complications, both in the portal vein system and in the veins of the lower extremities and pulmonary artery [1-3] that had previously been encountered in rare cases [4].

Hepatic artery thrombosis remains [6] the most serious LT postoperative thrombotic complication accounting for total from 2 to 9% [5] and potentially leading to liver failure, the graft loss and, consequently, the need for emergency retransplantation. The mechanism of developing thrombotic complications after LT is multifactorial and includes the factors associated with surgical techniques, on the one hand, [7, 8], and those non-associated with them, on the other hand [9, 10]. The latter factors include unstable, “imbalanced” hemostasis in patients with diffuse liver diseases. The imbalance is caused by the low activity of procoagulants, as well as of physiological anticoagulants due to the deficient synthesis of these proteins in chronic liver damage.

Maintaining blood in a liquid state and preventing blood clots is the main role of the anticoagulant system, which is represented in the body by physiological anticoagulants. The hemocoagulation process is under the strict control of proteins (inhibitors) that are present in the blood plasma. Antithrombin III (AT III, also known as heparin cofactor I) is one of the main inhibitors of coagulation factors. The scheme of blood antithrombin activity is currently considered in the form of "floating traps" that are focused on capturing thrombin. Meantime, AT III is constantly circulating in

the bloodstream, and its main function is the selective binding of thrombin (Fig. 1).

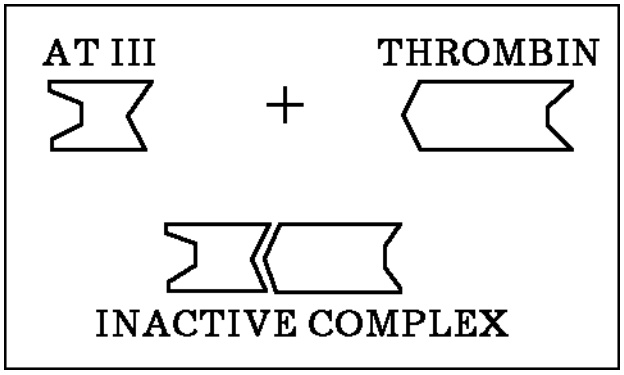

Fig. 1. The scheme of thrombin selective binding

The anticoagulant system is represented in the body by two groups of components: some are synthesized in the body as genetically determined ones (the primary anticoagulants); the others are formed only in the process of hemocoagulation and fibrinolysis (the secondary anticoagulants). The former are constantly circulating in the bloodstream, and their synthesis does not depend on the activation of the coagulation system at a current moment. They interact with active forms of coagulation factors and neutralize them.

AT III is the primary physiological anticoagulant and represents α_2–globulin that belongs to serpins (***SER***ine ***P***rotease ***In***hibitors) [11].

The main site of AT III synthesis is the liver parenchymal cells, while its small amount is synthesized by the endothelium of the blood vessels. A significant AT III portion is deposited in tissues. There is an assumption that the deposited AT III plays the role of a buffer that maintains stable AT III plasma level. In addition, AT III plays the role of the main plasma heparin cofactor and, under the heparin effect, is transformed from a progressive anticoagulant into an immediate inhibitor, antithrombin II. AT III is the main inhibitor of the thrombin and active forms of many other plasma factors (Xa, IXa, XIa, XIIa), except for factor VII (Fig. 2).

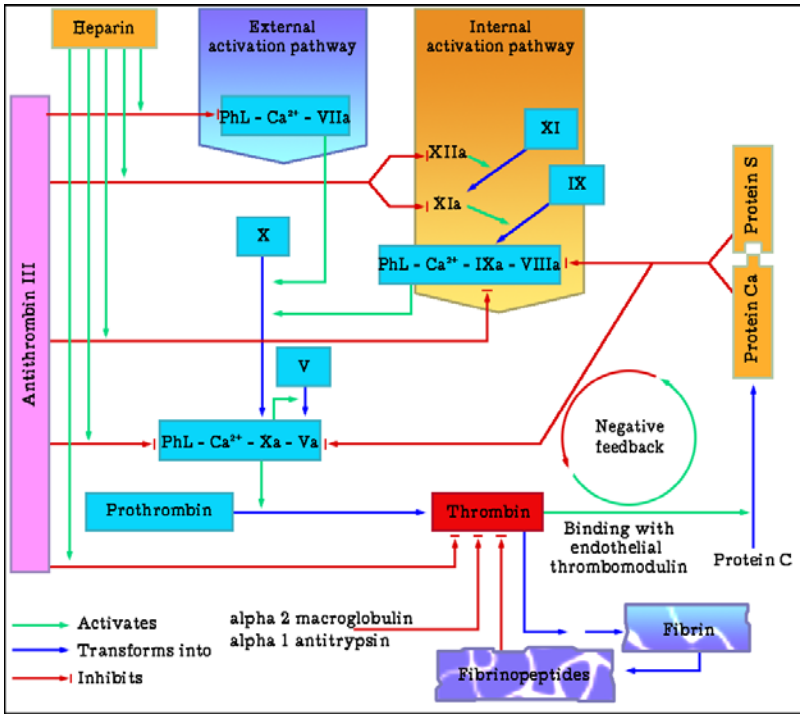

Fig. 2. The inhibitory effect of antithrombin III

AT III neutralizes, besides thrombin, other serine proteases. Moreover, in the absence of heparin, the neutralization rate is insignificant, while the formation of the antithrombin–heparin complex significantly (1000–100,000 times) increases the anticoagulant effect of AT III.

The AT III content in blood of healthy people is in the range from 80 to 140%. Quantitatively, about 750 mg of AT III are detected in plasma of a healthy person. Meanwhile, almost 90% of all spontaneous antithrombin activity of the blood is believed to be associated with AT III. The AT III half-life is 3 days. The value of AT III as the main modulator of hemostasis may be judged by the tendency to thrombosis typically occurring in individuals with congenital or acquired AT III deficiency. AT III deficiency is a serious risk factor for venous and arterial thrombosis. The coagulation slow-down and the inactivation of thrombin and other heparin coagulation factors directly depend on the blood level of AT III: the lower is the plasma level of AT III, the lower is the heparin effect. The effect of heparin can be

provided to the full only if the blood level of AT III is at least 60%. A number of authors consider the insufficient activity of this physiological anticoagulant to be the leading cause of heparin resistance [12].

At the same time, we should note that the anticoagulation system is depleted much faster than the coagulation system, the production rates of physiological anticoagulants in pathologic conditions lags far behind the rate of their consumption, which dictates the need to fill their deficit in such conditions. One should emphasize that the physiological role of the anticoagulant system is to maintain the blood in a liquid state and limit the process of blood clotting. The launch of the anticoagulant system occurs in parallel with the activation of the coagulation system, i.e. almost from the moment of the first active Hageman factor (XIIa) portions appearing. Anticoagulants block only active forms of blood plasma coagulation factors. The self-retardation of the hemostasis system is observed at all stages of coagulation. And AT III, being a heparin cofactor, provides the anticoagulant activity of the latter.

At early stage of LT development, the low level of AT III was considered in a number of studies [13, 14] as a risk factor for thrombotic complications after LT. Hashikura et al. advocated the inclusion of AT III in the protocol of anticoagulation therapy after LT in children [14].

In their study Kauffmann et al. reported on the AT III threshold level that determined the thrombosis development: 8 of 11 patients with AT III levels below 70% developed thrombosis, whereas with AT III levels higher 70%, only 1 of 37 patients developed thrombosis [15].

Francis et al. also claim that the AT III level of at least 60% is required for the manifestation of an adequate anticoagulant effect of heparin [16].

The AT III level is known to drop after LT and to remain low for 14 days [17]. Its replenishment by AT III concentrate transfusion provides an adequate anticoagulant effect [18].

At the same time, a consensus on the use of AT III concentrates after LT has not been reached yet.

The purpose of this study was to assess the efficacy of using AT III concentrate in patients undergoing LT.

Material and methods

The retrospective study included 46 patients with non-occlusive thrombosis in the portal vein system diagnosed at Doppler sonography before the LT surgery, and postoperative venous or arterial thrombosis who underwent LT in the Moscow City Liver Transplantation Center of N.V. Sklifosovsky Research Institute for Emergency Medicine in the period from 2006 to 2018.

All patients suffered from decompensated liver cirrhosis of various etiologies. The predominant cause of cirrhosis in 39 patients (85%) was the viral hepatitis C and B. In the others, the cause of cirrhosis was toxic or cholestatic damage of the liver. There were 25 men and 21 women. The mean age of the patients was 51 (38; 54) years old.

Anticoagulant therapy with heparin or low molecular weight heparins (LMWH) was administered to all patients at the stage of arterial reperfusion or on the 1st day after LT surgery. The transfusion of allogeneic fresh frozen plasma (FFP) was undertaken intraoperatively in most cases. The patients were divided into two groups depending on administering the therapy with AT III concentrate or not: the 1st group (n = 23) did not receive AT III

concentrate, the 2nd group (n = 23) received the AT III therapy. Both groups were comparable by the patient gender and age.

The AT III concentrate was administered during surgery and on day 1 after LT in the calculated dose: AT III (IU) = (target concentration of AT III (80%) - patient's AT III activity (%)) x patient's body weight (kg) x 0.5.

Within the study framework, after obtaining a screening coagulogram in all patients, the AT III activity in the blood plasma was studied on the 1st, 3rd, and 5th day after LT. The test was made on a Sysmex 1500 automatic coagulometer (Japan), using reagents from Siemens (USA).

The reference values of AT III activity in blood plasma ranged from 75-125%.

For statistical processing, the median (Me) and quartiles (25%; 75%) were calculated. The Mann—Whitney U-test and the Wilcoxon W-test were used to assess the differences. The differences between the values were considered statistically significant at a significance level of over 95% ($p < 0.05$).

Study results and discussion

The 1st group of patients (n = 23) included 12 men and 11 women aged 46 (36; 53) years old. Before surgery, non-occlusive thrombosis in the portal vein system was recorded in 10 patients (43.5%) of the 1st Group. There were no other thrombotic complications before surgery. The patients did not receive anticoagulant therapy before surgery.

Twenty patients (87%) received donor FFP in the intraoperative and early postoperative period. The FFP volume was 1275 (910; 2600) ml.

In the early postoperative period, an anticoagulant therapy was administered in several options to 20 patients (87%): 6 patients (26%)

received heparin at a dose of 8,000–12,000 U/day in a continuous infusion from day 1 after LT; 14 patients (61%) received LMWH in a therapeutic dose starting from day 2 (provided no hypocoagulation signs were seen in the coagulogram). Three patients (13%) did not receive anticoagulant therapy due to a high risk of hypocoagulation bleeding.

The 2nd group of patients (n = 23) included 13 men and 10 women aged 52 (41; 57) years old. Non-occlusive thrombosis in the portal vein system was diagnosed before LT in 16 patients (69.5%). No other thrombotic complications were seen.

Fifteen patients (65%) received a donor FFP transfusion in the amount of 600 (562; 880) ml that was significantly (p=0.001) lower than that the 1st Group. The AT III concentrate in the calculated dose was administered to all patients intraoperatively, and 2 patients receive it additionally on the 1st day of the postoperative period. The mean concentrate dose was 1000 (1000; 1750) U. All the patients received the anticoagulant therapy in the early postoperative period in the form of a continuous infusion of either heparin up to 10,000–15,000 U/day from day 1 after LT (11 patients; 47.8%), or LMWH in a therapeutic dose under coagulogram monitoring (12 patients; 52.2%).

The baseline values of AT III activity in patients were not statistically different between the two groups (p=0.108): 80 (47; 95)% and 67 (45; 90)% for the 1st group and the 2nd group, respectively. On day 1 day post-surgery, the AT III activity was not significantly different between the groups either: AT III was 55.6 (48.4; 64.8)% in the patients of the 1st Group, 56.3 (39.3; 90.5)% in those of the 2nd group. However, by day 3rd, a statistically significant (p = 0.002) increase in the AT III activity in the 2nd group had been recorded reaching 79.4 (59; 106)% compared to 52.3 (49.1; 68.3)% in

the 1st group. By day 5, the level of AT III activity had reached the normal value 89.5 (78.2; 116)% in the 2nd group patients, and remained low 54.9 (50.3; 65.1) in the 1st group (p = 0.009).

The comparative analysis of the AT III activity depending on anticoagulant therapy scheme showed the following results: in the patients of the 1st group receiving heparin, the AT III activity dynamics, starting from day 3 after LT, was significantly different from that in the patients of the 2nd group who also received heparin. The AT III activity in the 1st group on day 3 and day 5 after LT was significantly lower than that in the patients of the 2nd group (Table 1).

Table 1. Comparison of antithrombin III activity dynamics in the patients who received heparin

Day after surgery	AT III (%) in the 1st group (n=6) Me (25%; 75%)	AT III (%) in the 2nd group (n=11) Me (25%; 75%)	p
1	58.1 (53; 69.2)	54.8 (51; 90.5)	0.09
3	50.8 (48.6; 62)	72.1 (69.8; 106)	0.005
5	50.6 (49.4; 65.1)	83.6 (76.8; 112)	0.003

A similar trend in the dynamics of AT III activity was recorded in the patients of the 1st and 2nd groups who were on anticoagulant therapy with LMWH (Table 2).

Table 2. Comparison of antithrombin III activity dynamics in the patients who received low molecular weight heparins

Day after	AT III (%) in the 1st group	AT III (%) in the 2nd group	p

surgery	(n=14) Me (25%; 75%)	(n=12) Me (25%; 75%)	
1	50.9 (49.1; 66)	68.5 (61; 84.8)	0.014
3	50.4 (49; 63.8)	86 (79.6; 110)	0.006
5	53.2 (50.6; 62.3)	96.2 (82; 118)	0.002

There was a statistically significant increase in the activity of AT III in the patients of the 2nd group on day 1, day 3, and day 5 compared to those of the 1st group (Table 2).

We should note that an additional investigation of AT III activity in the patients of the 2nd group with regard to the anticoagulant therapy being conducted showed that the patients who received the AT III concentrate in combination with LMWH (n = 12) had a significantly higher AT III level after surgery than did the patients who received heparin (n = 11) (Table. 3).

Table 3. Comparison of antithrombin III activity dynamics in the 2nd group between the patients who received heparin or low molecular weight heparins

Day after surgery	AT III (%) in the 2nd group with heparin (n=11) Me (25%; 75%)	AT III (%) in the 2nd group with LMWH (n=12) Me (25%; 75%)	p
1	59 (52; 90.5)	68.5 (61; 84.8)	0.037
3	72.1 (69.8; 106)	86 (79.6; 110)	0.016
5	83.6 (76.8; 112)	96.2 (82; 118)	0.013

The analysis of LT outcomes in the 1st and 2nd groups showed that there was a statistically significant difference between the groups in infectious complication rates in the early postoperative period (p = 0.048). Infectious complications developed in 6 patients (26%) of the 1st group and in 1 patient (4.3%) of the 2nd group.

Mortality was 39.2% (9 deaths of 23 patients) in the 1st group, and 17.4% (4 deaths of 23 patients) in the 2nd group (p = 0.18).

Thrombotic complications after LT occurred in 15 patients (65%) of the 1st group and in 11 patients (47.8%) of the 2nd group (p = 0.30). Meanwhile, among the patients of the 1st group who received anticoagulant therapy with heparin, postoperative thrombotic complications occurred in 6 (26%). The same number of cases with developed thrombotic complications (n=6; 26%) was recorded in the 1st group among those who received LMWH therapy. Three patients (13%) of the 1st group who did not receive anticoagulant therapy due to hypocoagulation, also developed thrombotic complications. In the 2nd group, post-LT thrombosis was registered mainly in the patients who received heparin (n= 10; 43.5%) versus 1 case (4.3%) in a patient who received LMWH (p = 0.0001).

As for the types of vascular thrombosis, the prevailing ones were the hepatic artery thrombosis in 7 patients (30%) of the 1st group and in 5 (22%) of the 2nd group, and also the portal vein thrombosis in 7 patients (30%) of the 1st group and in 4 (17.4%) of the 2nd group. In one patient of the 1st group, the portal vein thrombosis was associated with mesenteric thrombosis, and in another patient, a combination of hepatic artery thrombosis and splenic artery thrombosis was recorded. Both those patients had received heparin anticoagulant therapy. In the 2nd group, one patient developed thrombosis of the internal jugular and subclavian veins on the right and another patient was diagnosed with pulmonary embolism. Both patients had also received heparin.

Among total of 26 patients (in both groups) with preoperative portal vein thrombosis, 6 patients (23%) developed thrombotic vascular complications in the early period after LT.

An adequate anticoagulant effect of heparin is determined by a sufficient level of AT III. The problem of AT III deficiency in patients

undergoing LT can be solved by the infusion of the AT III concentrate. In conditions of low AT III activity, the agents of choice for anticoagulation therapy might be LMWHs providing a more selective antithrombotic effect. A combination of LMWH with AT III concentrate seems to be optimal for the prevention of vascular thrombotic complications in LT.

Conclusions

Thus, thrombotic complications in patients undergoing liver transplantation have been the subject of many studies in recent years. An effective prevention of thrombosis in the early postoperative period can play a key role in improving the results of this surgical intervention.

1. A low activity of physiological anticoagulants, in particular antithrombin III, preoperatively, and its further decrease in the early postoperative period increases the risk of thrombosis and reduces the efficacy of anticoagulant therapy with heparin.

2. The comparative analysis of the treatment with antithrombin III concentrate showed that the administration of antithrombin III concentrate during surgery and in the early postoperative period contributed to a rapid normalization of AT III activity. The patients treated with antithrombin III concentrate had lower mortality in the early postoperative period and developed fewer infectious and thrombotic complications. In addition, the antithrombin III concentrate therapy in combination with low molecular weight heparins could significantly reduce the risk of thrombosis after liver transplantation.

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