Effect of Treatment With Tranexamic Acid on ComplementActivationandIschemiaReperfusionInLiverTransplantation in Pigs

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COMPLEMENT is gradually being considered in ischemia-reperfusion, especially in xenotransplantation.^{1–5} Reperfusion injury is characterized by deposition of C3 and C5b-9.¹ Complement inhibitors are used in amelioration of warm ischemia^{1,2} and rejection episodes.³ Tranexamic acid (Amca), a synthetic antifibrinolytic agent, has proven to be effective in acquired angioedema (a deficiency of the C1 inhibitor [Ci-inh]).⁶ Because of the increased risk of severe fibrinolysis, Amca is often used during orthotopic liver transplantation (OLT).⁷ Although no report of the use of Amca was found in the treatment of ischemia-reperfusion injury, the anticomplement effect of Amca has been demonstrated.⁸

Our aim was to study the complement activation and the effect of Amca on complement and ischemia-reperfusion injury in a liver allograft with donor warm ischemia.

MATERIALS AND METHODS

Twenty-one liver transplants were performed on Large White pigs. In all donors, the hepatic blood supply was occluded for 30 minutes before the extraction. The animals were divided into two groups, according to the treatment received by the recipients: the control group (n = 11) did not receive Amca and the Amca group (n = 10) received a single intravenous (IV) dose of 500 mg of Amca at the beginning of the OLT.

Total complement activity (CH100) and C1-inh were measured at the beginning of OLT, in the preanhepatic phase, 1 minute prerevascularization, and 5, 15, and 30 minutes postrevascularization. Blood samples were extracted from the jugular vein during the OLT and the following 3 days and also from the portal vein (only for CH100) during the OLT. Blood was extracted for liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], total bilirubin, lactate dehydrogenase [LDH], alkaline phosphatase) and coagulation studies (prothrombin time, partial thromboplastin time, thrombin time, and fibrinogen) at the beginning of OLT, at the end, at 6 hours post-OLT, at 24 hours, and thereafter daily. We determined malondialdehyde (MDA) concentrations in the hepatic tissue at the beginning in the donor (initial), at the end of OLT (postreperfusion), and on the third day. Statistical analysis was performed with SPSS statistical software (SPSS Inc, Chicago, III).

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RESULTS

Complement

We observed a significant decrease in CH100 (46.4%) in the Amca group (378.5 in the Amca group vs 455.8 in the control group, P = .012) during the preanhepatic phase. CH100 declined further significantly with reperfusion to a near minimal level at reperfusion (P < .05). The values were maintained in both groups during 6 hours postreperfusion. The Amca group started with a lower CH100 and showed no significant recovery during the reperfusion period of 72 hours. A 50.4% inhibition of CH100 in the preanhepatic phase of the Amca group was also observed in the portal circulation (P = .0038).

A 13% increase in C1-inh was observed in the Amca group at the preanhepatic phase (P = .027). C1-inh was reduced by 59% in the Amca group and by 62.5% in the control group (P = .2). The evolution of C1-inh was similar to CH100 during the first 30 minutes of reperfusion but concentrations increased in both groups from 6 hours postreperfusion, contrary to what was observed in CH100 activity.

Liver Function

The pattern of change of AST was similar in the two groups, increasing with reperfusion and peaking at 24 hours. The peak level in the Amca group (371.1 IU/L) was less than one half of the control group (812.3 UI/L). The difference between them was significant from the third day (151.2 UI/L in the Amca vs 492.3 UI/L in the control group, P = .021).

A significant difference was observed in prothrombin time at the end of OLT (83.4% in the Amca group vs 73.4% in the control group, P = .05) and at 6 hours (81.8% in the Amca group vs 59.8% in the control group, P = 0.003). We did not find any differences in other liver function tests and coagulation studies.

The increase in MDA concentration during reperfusion in the Amca group was significantly lower than in the control group (P = .007). The mean survival time in the Amca group was 103.8 ± 39.2 hours and 59.2 ± 19.8 hours in the control group (P = .24).

DISCUSSION

This study concerns the effect of complement on ischemiareperfusion injury and the consequences of its inhibition.

Complement activation was observed during reperfusion in our study, as demonstrated by other authors.⁵ Depletion or inhibition of complement activation would attenuate the oxidant stress and liver injury during the reperfusion.¹ Inhibition of complement activation is effective in prolongation of survival in xenotransplantation. This is being studied in xenografts by creating transgenic lines of pigs expressing human complement regulatory proteins.⁴ We opted for Amca, a drug with a considerable anticomplement activity.⁸ In our study, the decline of the total complement activity (CH100) showed that Amca can significantly inhibit complement activation in vivo. There was a significant improvement in graft function and a lipoperoxidation reduction in the animals that received Amca.

REFERENCES

- 1. Jaeschke H, Farhood A, Bautista AP, et al: Am J Physiol 264:G801, 1993
- 2. Weisman HF, Bartow T, Leppo MK, et al: Science 249:146, 1990
- 3. Pruitt SK, Kirk AD, Bollinger RR, et al: Transplantation 57:363, 1994
- 4. Rosengard AM, Cary NRB, Langford GA, et al: Transplantation 59:1325, 1995
- 5. Tomasdottir H, Henrinkson BA, Bengston JP, et al: Transplantation 55:799, 1994
- 6. Cugno M, Cicardi M, Agostini A: J Allergy Clin Immunol 93:870, 1994
- 7. Boylan JF, Klinck JR, Sandler AN, et al: Anesthesiology 85:1043, 1996
- 8. Takada A, Takada Y: Thromb Res 13:193, 1978