Proc. Eur. Biol. Transpl. Assoc
1971, 8, 198-202

Extracorporeal Porcine Liver Perfusion for Hepatic Coma in Acute Viral Hepatitis

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Five patients with hepatic coma complicating acute viral hepatitis have been treated in our department with extracorporeal porcine liver perfusion. Two of them regained consciousness soon after the second perfusion, recovered within several weeks, and were discharged from the hospital. Three others died with symptoms of progressive liver insufficiency.

In the following report clinical, biochemical, and haematological data obtained in 10 perfusions have been summarised.

CASE HISTORIES

The age of the patients ranged between 21 and 37 years. In all patients there was biochemical and clinical evidence of viral hepatitis and massive hepatic necrosis. No antecedent history of chronic liver disease could be documented in any. Coma developed between the 16th and 36th day of the clinical hepatitis. Patients were admitted to the Liver Perfusion Unit for extracorporeal perfusion usually in the 2nd or 3rd day of the coma. Neurological examination revealed in all patients the presence of grade IV coma. They were unconscious, spastic, with decerebrate posturing, did not respond to voice, and responded slowly to pain. Biochemical investigation revealed serum bilirubin levels of 14.5-28.3 mg/100 ml, and serum SGOT activity of 270-5360 units/ml. The intensity of biochemical changes did not correspond to the clinical status of the patients.

Criteria for selection of patients for treatment with heterologous liver perfusion were based mostly on neurological findings corresponding to grade IV coma, then on biochemical evidence of massive liver tissue necrosis, with absence of complications like azotaemia, ascites, respiratory insufficiency and major coagulation disorders with mucosal bleeding.

PERFUSION TECHNIQUES

Two perfusions were performed in each patient on consecutive days, lasting from 3 to 6 hours.

Pig livers were washed out in situ with 12 l buffered Ringer's solution at

4°C then removed, placed in a specially designed container, and connected to the patients' blood vessels.

The superficial femoral artery and vein of the patient were exposed and cannulated. Blood flowed from the femoral artery to the hepatic artery and portal vein of the pig's liver. Pressures in both vessels were continuously monitored, that in the portal vein being adjusted to 15-20 mmHg. The outflow line led from the hepatic veins, by gravity, to the femoral vein. No pump or oxygenator was used. The temperature in the container was maintained at 37°C the liver being totally immersed in isotonic electrolyte solution. The common bile duct was also cannulated and bile collected.

For clinical evaluation of liver perfusion the following studies were performed in the patient: blood pressure, pulse and respiration rate, and urine output continuously, acid-base balance serum electrolytes, blood glucose, haematocrit, serum proteins hourly, SGOT, SGPT, LDH, alkaline phosphatase, blood ammonia and serum bilirubin also hourly, fibrinogen concentration, platelet count and euglobulin lysis time every hour.

To evaluate the heterologous liver function hepatic artery and portal vein pressures, liver blood flow, and oxygen consumption were measured every 30 minutes. The amount of excreted bile was estimated at hourly intervals, and its bilirubin concentration was measured.

Ascitic fluid was transuded continuously through the liver capsule. Its amount, bilirubin concentration, protein level and SGOT and SGPT activity were measured.

To avoid blood clotting in the perfusion system heparin was given to the patient in high doses. The initial dose was 100 mg, followed by additional doses of 50 mg, depending on the result of thrombin time estimations. The lower limits for thrombin time were estimated at 5 minutes, values below that limit necessitated rapid administration of heparin.

RESULTS

I. CLINICAL COURSE OF PERFUSION

Systemic blood pressure remained in all patients at normal levels, and there was no tendency toward hypotension. Urine output was normal.

A. Acid-base balance

Two patients demonstrated typical signs of respiratory alkalosis with hyperpnoea, arterial blood pH up to 7.72, and Pco_2 30-32 mmHg. In one patient there was evident metabolic acidosis with blood pH 7.29, Pco_2 35 mmHg, and HCO'_3 18-20 mEq/l. In two others acid-base equilibrium remained within normal limits. These two patients recovered, whereas the three others with acid-base disorders died.

B. Blood glucose

There was a constant tendency toward hypoglycaemia. This was controlled with continuous intravenous drip of 5% dextrose. Major fluctuations in glucose level were observed despite the constant glucose infusion.

C. Serum electrolytes

In 3 out of 10 perfusions considerable drop in potassium level was observed. This was caused by substantial loss of potassium to the ascitic fluid, and required intravenous replacement of that ion.

D. Aminotransferase activity

SGOT and SGPT activity increased slightly in 4 out of 10 perfusions, remaining at initial levels in all others. Experimental experience suggests that this increase in aminotrasnferase activity might be accounted for by the release of enzymes from the porcine liver to the patient's circulation.

E. Serum bilirubin

There was a substantial decrease in serum bilirubin concentration following the perfusion in all patients. The mean initial values were 19.59 mg/100ml (range 28.3-12.4), decreasing to 7.77 mg/100 ml (range 14.5-4.92) by the end of the procedure. There was a rapid return of serum bilirubin level within a few hours of the perfusion to the initial values. No correlation between the fall of bilirubin concentration and clinical improvement was observed.

F. Coagulation and fibrinolysis

Slight thrombocytopaenia was noted in all patients before the perfusion. Further decrease in platelet count was observed during the perfusion, from 180,000-67,000 to 90,000-14,000/mm^3. Electronmicroscopic and isotope studies revealed trapping of platelets in the heterologous liver, a phenomenon which might be explained on immunological grounds. Heparin consumption in the perfusion system was high, possibly due to platelet disintegration and release of platelet factor 4. Fibrinogen concentration fell during the perfusion to values 120-90 mg/100 ml. Substantial shortening of euglobulin lysis time was noted.

II. THE HETEROLOGOUS LIVER

A. Blood flow

Mean liver blood flow was 0.54 ml/g of liver/min, with range 0.125 to 0.79 ml. Flows above 0.5 ml were considered as normal or nearly normal. Two major haemodynamic changes occurred in the course of each perfusion. ^{133}Xe wash-out studies revealed uneven distribution of blood in the liver with

high flow areas in the middle portion of the organ, the peripheral parts being relatively underperfused.

There was a rapid drop in blood flow rate usually occuring in the 3rd and 4th hour of perfusion.

B. Bile production

The heterologous liver produced bile at a rate of 0.08 to 1.59 ml/100 g of liver/hour, with the bilirubin concentration 124 to 410 mg/100 ml. The average bilirubin excretion with bile was 74 mg (range 6-193). Bilirubin was also eliminated with the ascitic fluid. The average amount excreted by this route was 115 mg with the range 6-401 mg. Thus the mean total amount of excreted bilirubin was 236 mg (range 28-428), equivalent to the daily amount of bilirubin produced by a normal man.

C. Ascitic fluid

The amount of fluid produced was variable and ranged from 160 ml in one patient to as much as 1700 ml. The bilirubin concentration in the fluid ranged from 0.1 to 6.8 mg/100 ml, protein level from 0.52 to 2.6 g/100 ml, and SGOT activity from 100 to 396 units/ml. Total protein loss to the ascitic fluid amounted to 93.5 g (31.2 - 174.2) during a 6 hour perfusion.

CONCLUSIONS

1. Five patients with hepatic coma complicating acute viral hepatitis were treated with extracorporeal liver perfusion and two of them recovered.
2. There was no correlation between biochemical and clinical improvement.
3. Liver blood flow and coagulation disorders created major problems during the perfusion. They may be caused by the immunological processes taking place in the temporary liver xenograft.

OPEN DISCUSSION

COLOMBI (Basle): I would be very interested to hear the levels of the blood clotting factors II, V and VII prior to treatment. Secondly, in our series of 35 patients in Basle, Switzerland, we have a considerable number with hepatic coma and acidosis. I wonder whether you have made any blood lactate determinations?

OLSZEWSKI: Before we started the perfusions we found a decrease in the level of all the coagulation factors; I don't have the figures here with me, but there were also disorders of the fibrinolytic system. In answer to the second question, there was an increase in LDH activity in the serum of the patients, and also a slight increase in blood lactate levels.

V PARSONS (London): I'm really reporting for Dr Roger Williams in the Liver Unit at King's, where they have done liver perfusions in exactly the same way as you have. They also found that they had to give very large doses of heparin to keep the pig liver going for six hours. After 24 patients had been treated in this way, they stopped using the liver and just gave the patients heparin. After 24 consecutive deaths they have now had four survivors, just by using heparin alone in patients with grade 4 coma. I wonder what you think about this? Is your liver perfusion just giving the patient heparin?

OLSZEWSKI: Well, we of course didn't give heparin alone!