Treatment of Hepatic Coma by Exchange Transfusion

A Report of Three Cases

by

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The results of conservative treatment of coma due to acute viral hepatitis is poor 1-3. During a period of 12 months, ending October 1966, this condition has been fatal in almost all of our patients (Table 1). Within this period we have had 26 cases of coma in a series of 175 patients admitted because of viral hepatitis.

Little is known about the basic disturbances that underlie hepatic coma. An increase of blood ammonia has been implicated in its pathogenesis, but most investigators regard hepatic coma as a metabolic encephalopathy which is not due to any single agent.

As it is seen in Fig. 1, the food protein is a source of blood nitrogenous substances. In massive hepatic necrosis hemorrhage and the presence of blood proteins in the gastrointestinal tract adds to this. The inability of liver cells to metabolize nitrogenous and other injurious substances, which are called "lethal substances", results in metabolic encephalopathy and death.

Considering the above facts and capacity of the liver for regeneration after acute necrosis, the routine management of hepatic coma includes the administration of intestinal nonabsorbable antibiotics, special amino acids

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(such as arginine), and massive doses of glucocorticosteroids. To date there is no evidence confirming the efficiency of the latter.

Recently, other forms of management, such as human cross circulation, heterologous liver perfusion, and hemodialysis, have been used, but the results have been disappointing. An interesting point is that hemodialysis, despite the lowering of blood ammonia levels, has no therapeutic effect. It appears that the injurious substances are at least in part protein-bound, and can not be withdrawn by hemodialysis.

Because of the above mentioned reasons, efforts have been made to lower temporarily the level of lethal substances by means of the exchange transfusion, providing an opportunity for liver cells to regenerate.

METHODS

Homologous citrated blood was administered through a polyethylene catheter introduced into the femoral vein through a cutdown. In the first case, the blood was withdrawn from the same vein, but in the other cases it was withdrawn by arterial puncture from the femoral artery. Two ml. of 10 per cent calcium gluconate solution was infused after the administration of each 100 ml. of citrated blood to neutralize the effect of the citrate. In some cases hypotension and shock occured during the procedure. This was treated with glucocorticosteroids, mephenesin, and anthistamines. Puls rate, blood pressure, breath rate, and body temperature were recorded throughout the exchange transfusion, and 2.4 million units of penicillin was administered intravenously. Whenever the patient developed irritability and agitation, calcium gluconate and promethazine were used. After each exchange transfusion, the patients received intravenous perfusion of 5% dextrose solution together with penicillin, and were kept warm. During the next few days water and electrolyte balance, body temperature, and mental state were recorded. The 2nd exchange transfusion of the 3rd case was started with heparinized blood, but coagulative difficulties arose during the procedure. These difficulties, which appeared to be due to an insufficient amount of heparin, forced us to continue the procedure with citrated blood.

CASE REPORTS

Case 1. Fever, anorexia, abdominal pain and vomiting developed abruptly in a 16-year-old boy who had no history of any previous injections. After 6 days, the symptoms abated but jaundice appeared and increased gradually. The patient's general condition worsened and prostration forced him to go to bed. By the 20th day after the onset of symptoms, mental confusion, vomiting and tremor occurred. On the same day (October 12, 1966) the patient was admitted to the Pahlavi Hospital delirious and disoriented. He was deeply jaundiced and had some hyperreflexia. There was no neck stiffness, the liver edge was not palpable. The temperature was normal. Biochemical findings included the following: thymol test 18 units, cephalin-cholesterol flocculation test 4+, SGOT 580 units, SGPT 620 units, direct serum bilirubin 19.5 mg. per 100 ml., indirect serum bilirubin 2.5 mg. per 100 ml. and serum ammonia 566 µg. per 100 ml.

Treatment with intravenous infusion of glucose and parenterally administered glucocorticosteroid and tetracycline was started a few hours after admission.

During the next few days the patient's clinical condition deteriorated. On the 4th hospital day direct serum bilirubin rose 22 mg. per 100 ml. and indirect serum bilirubin rose to 3 mg. per 100 ml.

The 1st exchange transfusion of citrated blood (not possible to obtain fresh heparinized blood readily) was performed that evening. Forty minutes after the beginning of the procedure, and after 540 ml. of blood was exchanged, the patients blood pressure fell to 50 mm. Hg., the ex-
termitities became cold and exterme moisture was noted on the face and neck. The blood pressure rose to normal after the injection of 15 mg. of mephenesin and infusion of 350 ml. of additional blood. The exchange transfusion was then continued and there was a significant fall in the temperature of coma after approximately 4000 ml. of blood had been exchanged. All total 5970 ml. of blood was infused and 5380 ml. was drained in a period of four and half hours.

The next day the general condition was improved, the tendon reflexes were normal, and the patient was oriented and thirsty. Biochemical findings were: direct serum bilirubin of 14.0 mg. per 100 ml, indirect serum bilirubin of 2.0 mg. per 100 ml, SGOT of 80 units, SGPT of 120 units, serum Potassium of 7 m Eq. per l. and serum Sodium of 126 m Eq. per l.

On the next day, the patient was mentally clear and looked a little tiered. During the next night the 2nd exchange transfusion was carried out with 3 liters of citrated blood. The direct serum bilirubin fell to 13.0 mg. per 100 ml; the thymol test was 12 units and the cephalin-cholesterol flocculation test 2+.

During the succeeding days the patient remained mentally alert and jaundice gradually disappeared.

On the 21st hospital day some infection appeared at the site of the femoral vein cutdown, which was used during the 1st exchange transfusion. There was also some leg swelling. This was treated successfully with penicillin.

The patient was discharged from the hospital on November 23, 1966 with direct serum bilirubin of 0.7 mg. per 100 ml, indirect serum bilirubin of 0.7 mg. per 100 ml, SGOT of 44 units, SGPT of 25 units blood fibrin of 3 gr. per l.

Case 2. A 5-year old girl was admitted to the Pahlavi Hospital on November 10, 1966, with a history of fluctuating jaundice over the previous 20 days. There was a history of previous injections. Growth and development had been normal.

Physical examination showed jaundice, swelling of both feet, purpuric rashes, tachycardia, and irritability. The liver edge was not palpable. The blood hemoglobin was 65%, the red cell count 4,100,000, and the total white count 18,000. Biochemical findings included the following: thymol test 10 units, cephalin-cholesterol flocculation test 3+; SGOT 250 units, SGPT 230 units, direct serum bilirubin 5.0 mg, indirect serum bilirubin 2.6 mg, and serum ammonia 35 g. per 100 ml. Therapy included intravenously infused fluids, and orally administered neomycin, tetracyclins and glucocorticosteroids.

On the 9th hospital day the clinical state deteriorated, the jaundice increases, and coma developed. Exchange transfusion was begun. A total of 2300 ml. of blood was infused and 2170 ml. was withdrawn. Improvement in consciousness was noted after exchange of 1000 ml. of blood, and by the end of the procedure she was speaking, but was still in a delirious state. A 2nd exchange transfusion was carried out the next day with an exchange of 1000 ml. of blood. Severe tachycardia and generalized seizures occurred during the procedure, which was treated with cefazid and promethazine. At the end of the exchange transfusion the patient was vomiting and developed disrhythmie tachycardia. The SGOT fell to 55 units, SGPT to 34 units, direct serum bilirubin to 0.8 mg. per 100 ml, and indirect serum bilirubin to 1.0 mg. per 100 ml. The thymol test was 12 units and the cephalin-cholesterol flocculation test 3+. The next day the patient died in a state of dyspnea, cyanosis, and arrhythmia.

At autopy, there was a shrunken nodulated liver. Diffused foci of hepatization were found at the base of the lungs. Microscopical section showed massive necrosis of the hepatocytes.

Case 3. A 25-year old male was admitted to Pahlavi Hospital on December 6, 1966, because of mialaise, abdominal pain, and jaundice of 7 days' duration. He had lost consciousness on the night before admission. On examination, he was noted to be deeply stuporous, and responded sluggishly to painful stimuli. The pupils were equal and reacted to light. The level of consciousness was fluctuating and a few hours after admission there was extrane disorientation and violent behavior. The blood hemoglobin was 60%, and the total white cell count 16,800. The thymol test was 16 units, and the cephalin-cholesterol flocculation test 4+. The SGOT was 860 units and the SGPT 1200 units. The direct serum bilirubin was 12.0 mg. and the indirect serum bilirubin 2.5 mg. per 100 ml.

The 1st exchange transfusion was carried out with 5 liters of citrated blood. There was no significant improvement in general condition until the next morning, when mental clarity improved somewhat. A further exchange of 5 liters was carried out on the 2nd hospital day. At
the end of the procedure the mental state had improved so that he could answer simple questions. A few hours later he was mentally alert and asking for water. The SGOT fell to 420 units, and the SGPT to 580 units. The thymol test was 25 units, the cephalin-cholesterol flocculation test 3+, the serum direct bilirubin 100 mg. per 100 ml., and the serum indirect bilirubin 2.5 mg. per 100 ml.

During the next few days the jaundice at first increased slightly, gradually decreased and disappeared. The patient was discharged from the hospital on January 4, 1967, in a good general condition.

**DISCUSSION**

Indications for exchange transfusion in hepatic coma are still not clear. Tery et al. have graded the level of consciousness of their patients according to the criteria proposed by Adams and Foley, and have considered a Grade 3 or Grade 4 disturbance of consciousness as an indication for exchange transfusion. As there is no direct correlation between the levels of serum glutamin oxalacetic transaminase on one hand, and the severity of the underlying disorder on the other, these biochemical criteria are not reliable as an indication for exchange transfusion. Repeated measurement of cerebrospinal-fluid glutamin proves impractical, and therefore cannot be used as an indication for exchange transfusion. Some investigators believe that exchange transfusion should be carried out if after 24-48 hours of standard treatment there is no improvement in the clinical condition.

The high mortality rate of hepatic coma among our patients, and our experience, although limited, on the management of these patients with exchange transfusion shows that:

A. Exchange transfusion should be carried out in all patients who are admitted in coma due to viral hepatitis.

B. It should be carried out in all patients who are initially in a good mental state but begin to show signs of mental deterioration.

C. Although the use of citrate as an anticoagulant raises the ammonia content of blood, and theoretically there is a danger of aggravating the encephalopathy, exchange transfusion should not be avoided when heparinized blood is not available.

### Table 1. Survival in Coma Due to Acute Viral Hepatitis

<table>
<thead>
<tr>
<th>Source of Data</th>
<th>Date</th>
<th>Total No. of Cases</th>
<th>No. of deaths</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katz et al.</td>
<td>1962</td>
<td>23</td>
<td>14</td>
<td>Glucocor; Antibiotics</td>
</tr>
<tr>
<td>Mc Donald et al.</td>
<td>1963</td>
<td>13</td>
<td>9</td>
<td>Protein withdrawal; antibiotics; some patients received glucocor.</td>
</tr>
<tr>
<td>Sherlock</td>
<td>1963</td>
<td>11</td>
<td>8</td>
<td>Protein withdrawal; antibiotics.</td>
</tr>
</tbody>
</table>

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**Summary**

Three cases of hepatic coma due to acute hepatitis were treated by exchange transfusion with citrated blood. This was performed in the first 2 cases (patients No 1 and No 2) after failing to respond to other forms of treatment, and in the last patient, who was admitted to hospital in coma, a few hours after admission. (Patient No 3) Two of the 3 patients, patients 1 and 3 recovered, 1 died, (patient No 2) although 2 successive exchange transfusions alleviated coma to some degree.

**Resumé**

Nous avons traité 3 cas de coma hépatique (par suite d'hépatite virale aigue) par la transfusion éxanguine avec du sang citraté. Parmi ces cas 2 avaient failli de reproche aux traitements le troisième a été apporté à l'hôpital à l'état de coma.

Le premier et le dernier malades sont gueri mais le deuxième succomba quoique 2 exanguine transfusion successives avaient bien l'état a certain degree.
A Test For Impending Thrombo-embolism Conditions.

Preliminary report.

The incidence of human intravascular thrombosis has been long attributed to the process of hemostasis, that is platelet aggregation, blood clotting and vasoconstriction. The present in vitro study of blood drawn from normal controls and patients with acute myocardial infarction suggested the diagnostic value of this test. Samples of whole blood were obtained from control and thrombotic patients. Blood samples were treated with heparin, EDTA and followed by administration of strontium chloride in different molar concentration (i.e., 0.005 - 0.50M). Blood smears were made and stained with Wright’s stain routinely. Microscopic observation of blood smears prepared from thrombotic patients showed an affinity of platelets and leucocytes to form specific aggregates. The degree and pattern of aggregation revealed mild and/or severe thrombotic episodes. Normal control smears showed fewer aggregates of different and specific cytocomposition. Squamous epithelial and cornified cells were found in smears of patients with acute myocardial infarctions whose blood was drawn from either vena punctures and/or taken from subclavus canulae. These findings suggest that physiologic change in blood vessels may lead to certain acute thrombotic conditions eventually through the involvement of other hemostatic mechanisms.

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