5-1-1969

Treatment of hepatic coma by exchange blood transfusion

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The Treatment of Hepatic Coma by Exchange Blood Transfusion

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska
March 31, 1969
Omaha, Nebraska

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In the past ten years numerous articles have been written concerning the pathogenesis and management of hepatic coma. This condition has always been a severe challenge for the physician, especially when the coma is associated with acute hepatic failure.

The diagnosis of hepatic precoma and coma cannot be made by laboratory means alone; and many of the features of the condition--the organic dementia, the flapping tremor, the electroencephalographic changes, and the elevated blood ammonia levels--can be encountered, in whole or in part, in other disturbances such as uremia and congestive heart failure (1,2). Its recognition depends upon clinical acumen, laboratory findings, and some of the other features of condition such as: fetor hepaticus, jaundice and ascites. Hepatic coma can complicate liver disease of any type, but it is usually associated with Laennec's cirrhosis or acute viral hepatitis (1).

Since the clinical course is very fluctuant, a clinical system of grading the depth of coma is very useful. Such a simple grading system recommended by Sherlock (1, page1) is:

Grade 0--Normal.
Grade 1--Trivial apathy or euphoria, with or without neurologic signs.

Grade 2--Personality change with neurologic abnormalities.
Grade 3--Advanced confusion and disorientation.
Grade 4--Stuporous but responsive to stimuli.
Grade 5--Comatose.

Jones (3) has devised a more empirical system of grading based on electroencephalographic changes, and although this system is able to demonstrate smaller changes in the cerebral functioning of the patient, it is of limited use clinically.

ETIOLOGY

The fluctuations in hepatic coma and precoma, the seemingly diffuse involvement, and the essentially reversible nature of the cerebral disturbances suggest that the changes are metabolic (1,2). However, the condition is never present without some associated hepatocellular changes(1). The exact etiological agent or agents are not known (1,4,5), but many substances have been incriminated. The association of hepatic coma in patients with liver disease with the feeding of a high protein diet, ammonium chloride, urea, or choline suggests that the coma might be due to nitrogenous intoxicants (1,2). Many nitrogenous wastes, including ammonia, are produced in the gastro-

intestinal tract by the enzymatic action of bacteria on protein; and the failure of the liver to "filter out" these intoxicants, because of hepatocellular failure, might lead to hepatic coma(1,2). Complicating this hepatic failure is the extrahepatic portal-systemic collateral shunting which shunts blood around the liver into the systemic circulation as seen in cirrhosis (1). Other suggested factors have been the amines, potassium depletion, and respiratory alkalosis (1). Hypokalemia has been shown to induce clinical deterioration and an elevated blood ammonia level, irrespective of ammonia production from the gut. Ammonia salts appear to cross the blood-brain barrier to a higher degree in alkalotic states. Other factors might be hypoglycemia, disrupted intermediary metabolism, serotonin deficiency, or unconjugated bilirubin (1,2). Any factor decreasing cerebral or hepatic function such as hemorrhage, hypotension, shock, or infection; is likely to induce hepatic precoma in patients with cirrhosis or who have decreased hepatic reserve (5).

CONSERVATIVE MANAGEMENT

The present conservative management of hepatic

coma is based on the possible etiological factors which are known, and usually includes (1,2,4,6) : 1) Complete protein restriction or severe reduction. 2) Glucose feedings to supply a readily available source of energy. 3) Parenteral vitamin K and vitamin B complex. 4) The oral administration of poorly absorbed antibiotics--such as neomycin sulfate in a dose of 4-6 grams per day--to reduce the bacterial breakdown of protein in the gut. 5) Corticosteroids in large dosage in an attempt to minimize liver damage which might occur, and to support the patient through the initial insult. 6) Correction of aggravating factors such as gastrointestinal hemorrhage, electrolyte imbalances, and infection. Arginine and glutamic acid have been given in an attempt to "inactivate" or remove excess ammonia, but the results of such therapy have not been impressive (1).

The results of such conservative treatment depend upon the extent of liver damage, and are best in those patients with a chronic encephalopathy, who have cirrhosis with relatively good hepatic function (4). The results of such treatment in acute hepatic failure are almost universally poor (4,6). Burnell (7) in an extensive review of the available literature

from 1951 to1967, found only 36 survivors in a total of 207 patients with coma which was proven to be associated with acute hepatic failure.

NEW FORMS OF MANAGEMENT

In an attempt to improve upon the survival rates associated with hepatic coma from acute hepatic failure, several new forms of therapy have been proposed and tried clinically. Eisman (8) has used heterologous perfusion of the isolated pig liver in 8 moribund patients. His results varied from "dramatic " improvement to "minimal neurological changes." There were no long term survivors. Burnell (7) has reported using cross-circulation with a human volunteer in 4 cases, with 1 survivor and "dramatic" improvement in the coma of the other 3. Hemodialysis has been used by Sherlock (1), with a lowering in the blood ammonia level, but without clinical improvement. Bosman (9) has successfully used cross-circulation between man and a baboon (Papio ursinus ursinus), whose blood had been replaced with compatible human blood. Sabin (10) has used plasmapheresis and plasma infusion on 3 alcoholics with refractory coma--there was clearing of the coma following each exchange. Although these

forms of therapy have shown some initial promise and there were no reported complications, there has been little follow-up work done in these areas, and they are not without their obvious dangers of infection and immunological complications.(4).

EXCHANGE BLOOD TRANSFUSIONS

Another new form of therapy for hepatic coma, which has received a great deal of attention in recent years, is the use of exchange blood transfusions. Although exchange transfusions have been used since 1916 for such things as carbon monoxide poisoning, burns in children, septicemia, drug poisonings, malignant scarlet fever, and hemolytic disease of the newborn; it was not until 1958 that the technique was successfully used in the treatment of hepatic coma (4,11).

Lee and Tink (11), faced with the problem of a 13 year old boy with clinically typical infectious hepatitis, who was deteriorating rapidly and was deeply comatose despite the usual conservative treatment, decided to try an exchange blood transfusion. On the third day of hospitalization an exchange was carried out using 3260 ml. of fresh blood. After this his

serum bilirubin dropped from 33.6 mg. per 100 ml. to 17.4 mg. per 100 ml.; however, his clinical condition remained unchanged. The following day a second exchange was carried out using 3140 ml. of blood. His serum bilirubin dropped from 24 to 9.9 mg. per 100 ml., without clinical improvement. By 24 hours after his second exchange he was responding to commands, and by 36 hours he was alert and cooperative. His subsequent recovery was uneventful.

This technique was not used again until 1963 when Trey began using it; unaware of the earlier work by Lee and Tink(4). The work reported by Trey (4) in 1966 consisted of 12 patients who had coma--grade 4-5 (1)--associated with acute hepatic failure. He treated 7 children, ages 13 months to 8 years, and 5 adults. Four of the children and 2 of the adults recovered. All of the patients, except 2 of the children who died after receiving only one exchange, regained consciousness.

In the same issue of The New England Journal of Medicine in which Trey reported his work, Berger (12) published his results of using blood exchange transfusions on a 25 year old, deeply comatose physician with serum hepatitis. Exchange transfusions were used

in this case, as by Trey, as a last resort in a patient who was thought to be moribund (4,12). The patient was deteriorating rapidly; he exhibited decerebrate posture, frequent seizures, hyperventilation, a blood urea nitrogen of 1 mg. per 100 ml., a prothrombin time greater than 60 seconds; and none of his physicians had ever seen a patient survive with similar findings. The first exchange transfusion was carried out using 11 units of fresh heparinized blood. The clinical condition did not improve or deteriorate; however, there was a significant drop in his serum bilirubin and prothrombin time. Twelve hours later a second exchange transfusion was carried out using 10 units of similar blood. Immediately the hyperventilation and decerebrate posture ceased, and in general he appeared better. Within 48 hours there was unmistakable clinical improvement, the patient became responsive, and he quickly recovered.

Since the original reports by Trey and Berger, numerous reports have been published by people using the technique on patients with unresponsive hepatic coma associated with infectious hepatitis (3,4,5,11-16), serum hepatitis (4,14,17), halothane anesthesia (3,5,7), antituberculosis drug therapy (18), and the use of

monamine oxidase inhibitors (3). A summary of these studies is shown in Table 1 of the Appendix. There were 42 patients treated by exchange blood transfusions with 14 survivors and definite clinical improvement in 17 of the patients who died. These results are significantly better than those reported by Burnell (7), where only 12per cent of the patients survived as compared to a 33per cent survival in the group treated by exchange transfusions.

Although no etiology for hepatic coma has been firmly established (1,4,5), exchange transfusions have been used with the rationale that by exchanging the patient's blood for "fresh blood," certain unknown toxic substances could be "washed out" or diluted, or certain essential factors which are produced by the liver are supplied (4,5,12). The therapeutic objective is to maintain life during the critical period of virtual hepatic standstill until the regenerating liver cells can resume their activity (3,4,5).

There have been several methods developed for carrying out the exchanges, but the desirable qualities of any such method are efficiency and safety. Berger (5) threads a large bore catheter from a peripheral vein into one of the vena cavae. Removal

of blood is facilitated by gravity drainage, while infusion is aided by a pressure bag. Sabin (10) and Berger (4) recommended that the blood be withdrawn from the brachial or femoral arteries by way of a plastic catheter and administered through a peripheral vein. Berger (5) recommended the serial infusions and withdrawals of aliquots of 500 ml. of blood in adults and 30-50 ml. aliquots in children, which were well tolerated clinically. Berger (5) has shown that rapid, massive exchanges may be complicated by temporary hypotension which might initiate disastrous consequences in a gravely ill patient. Berger (5) also found that to maintain an adequate circulatory volume with a sufficient safety margin, it was necessary to infuse an excess of 500-1000 ml. of whole blood in most exchanges. Pulse rate, blood pressure and temperature should be monitored continously. The time necessary for an exchange took 1 to 4 hours (4,5).

In the vast majority of exchanges performed to date, fresh blood treated with heparin sodium has been used. The rationale for using heparinized blood is that this blood supplies certain missing clotting factors (factor V, antihemophilic factor, and platelets), avoids citrate intoxication and has a lower

ammonia content than banked blood (5). The problem of bleeding with the administration of heparin can be easily controlled by the administration of 0.5 mg. to 0.75 mg. of protamine sulfate for each 1 mg. of heparin given after each 4 units exchanged (5). The problem of citrate intoxication has been studied by Krebs (13) and Lederman (18) who used banked acid-citrate-dextrose blood for their exchanges. Krebs experienced gastrointestinal hemorrhage midway in one of his exchanges, but this was controlled by the administration of two units of fresh blood. Krebs (13) gave calcium gluconate (10 ml. of a 10per cent solution after each 6 units exchanged) to prevent the possibility of citrate intoxication, which is rare even in massive transfusions.

The magnitude of the exchange, as most other parameters of exchange transfusions, has not been firmly established. Berger (12) determined that if the lethal factors were limited to the vascular compartment, an exchange of 12 units in a 70 kg. man--which would replace about 80per cent of the initial blood volume--would be sufficient. It is more likely, however, that the offending substance exists both in circulating and tissue bound forms (4,12). The extent

of blood stream detoxification, therefore, does not parallel erythrocyte exchange, but also depends upon the speed of toxin diffusion from the tissues into the vascular compartment. For this reason, the usual volume exchanged approximates 2 blood volumes (5).

The number of daily exchanges to which one is committed once this form of therapy has been undertaken is unclear in the literature. Trey (4), Berger (5), and Lederman (18) advocate daily exchanges until clinical improvement, unavailability of blood, or mechanical problems force discontinuance. Jones (3), however, suggests that if the patient's condition does not improve after several exchanges, especially if he is oliguric, the underlying disease may be of such severity that further exchanges are unlikely to be beneficial. Only one of the survivors to date has required more than 3 exchanges (4).

The measurable biochemical changes brought about by exchange transfusions consist of decreases in the levels of serum bilirubin, transaminase, alkaline phosphatase, ammonia, and improvement in the prothrombin time (4,5,13). These changes do not correlate well with clinical improvement (4,5,17,13); they merely indicate the extent of washout of toxic metabolites(5).

The serum bilirubin value tends to rise rapidly after completion of the exchange which indicates the diffusion of tissue bilirubin into the vascular compartment. Typical biochemical changes associated with the exchange are shown Figures 1 and 2 of the Appendix.

Exchange transfusion appears to be a relatively safe procedure and the dangers are minimal. The probability of serum hepatitis developing after each 10 units exchanged is 4per cent (5). There is always the risk of sepsis but Krebs (4) was the only one with this complication. Progressive thrombocytopenia with subsequent bleeding tendencies was encountered by Jones (3). He postulated that the thrombocytopenia might be due to the dilution of platelets by exchanged blood, the effect of heparin on the platelets, or possibly the development of platelet antibodies. Hematoma formation at the catheter site has been the only other complication reported (4).

The clinical improvement which is associated with exchange transfusions is difficult to relate in time to the procedure in some cases, but easily related in others. There have been patients treated who regained consciousness within hours of the exchange (4). There have been those in which the exchange appears to

halt the progression of the coma immediately with recovery of consciousness 24 to 72 hours later (3, 13). Some with multiple exchanges have shown definite clinical improvement with each exchange. Because of the severity of coma in the cases reported, most of the authors believed that the clinical improvement was directly related to the exchange procedure even though they admitted that spontaneous recovery has been known to occur after 24 hours of hepatic coma (3,4,5).

The indications for exchange transfusion are difficult to establish at this time. Trey (4) recommends using exchanges on patients who have a grade 4-5 coma (1), and who continue to deteriorate despite the usual forms of therapy. Jones (3) and Berger (5) recommend that exchanges be used only on those patients suffering from acute reversible hepatic necrosis. None of the authors have suggested that exchange transfusions should be used as a substitute for the presently accepted forms of therapy; and most believe that, until the effectiveness of the procedure has been proven more conclusively, it be used only on patients where the outcome with conventional therapy probably would be fatal. The results with exchange transfusions, however, are sufficiently encouraging to warrant continued investigation.

APPENDIX

TABLE 1

THE RESULTS OF TREATMENT BY EXCHANGE TRANSFUSION

Source	Case No.	Age	Sex	Etiology	Exchanges	Response[a]	Outcome
Trey	1	6yr	F	Infectious	1	Yes	Living
	2	7yr	M	Infectious	1	Yes	Living
	3	8yr	M	Infectious	1	Yes	Living
	4	13mo	M	Unknown	1	Yes	Died
	5	18mo	F	Infectious	1	Yes	Living
	6	34yr	M	Serum	7	Yes	Living
	7	68yr	M	Infectious	2	Yes	Died
	8	<10yr	-	Infectious	1	No	Died
	9	<10yr	-	Infectious	1	No	Died
	10	>20yr	-	Infectious	3	Yes	Living
	11	>20yr	-	Infectious	3	Yes	Died
	12	>20yr	-	Unknown	3	Yes	Died
Berger	13	25yr	M	Infectious	2	Yes	Living
	14	24yr	M	Unknown	2	No	Died
	15	23yr	M	Infectious	3	No	Died
	16	39yr	F	Infectious	1	Yes	Living
	17	22yr	F	Unknown	5	Yes	Died
	18	51yr	F	Unknown	5	Yes	Died
	19	41yr	F	Halothane	4	Yes	Died
Lee	20	13yr	M	Infectious	2	Yes	Living
Krebs	21	17yr	M	Unknown	1	Yes	Living
Jones	22	5yr	M	Infectious	5	Yes	Died
	23	42yr	F	M.A.O.I.	8	Yes	Died
	24	59yr	F	Infectious	6	Yes	Died
	25	68yr	F	Halothane	6	Yes	Died
	26	23yrs	F	Infectious	2	No	Died
	27	66yr	M	Halothane	15	Yes	Died
	28	51yr	M	Infectious	5	No	Died

[a] A clinical response of at least one grade as defined by Sherlock (1).

TABLE 1--Continued.

Source	Case No.	Age	Sex	Etiology	Ex-changes	Re-sponse	Out-come
Lederman	29	23yr	F	Drugs	2	Yes	Living
	30	23yr	F	Drugs	2	Yes	Living
Davis	31	25yr	F	Infectious	3	No	Died
	32	30yr	F	Serum	2	No	Died
	33	39yr	F	Infectious	3	No	Died
Burnell	34	61yr	F	Halothane	6	No	Died
	35	11yr	M	Infectious	13	Yes	Died
Gelfand	36	25yr	F	Serum	3	Yes	Living
McKechnie	37	18yr	F	Infectious	1	Yes	Living
	38	37yr	F	Infectious	1	Yes	Died
	39	55yr	F	Infectious	1	No	Died
Zacarias	40	17mo	F	Infectious	1	Yes	Died
	41	23mo	M	Infectious	1	Yes	Died
	42	22mo	F	Infectious	1	Yes	Died
Total	42	. .	.	. . . . .	.	31	14

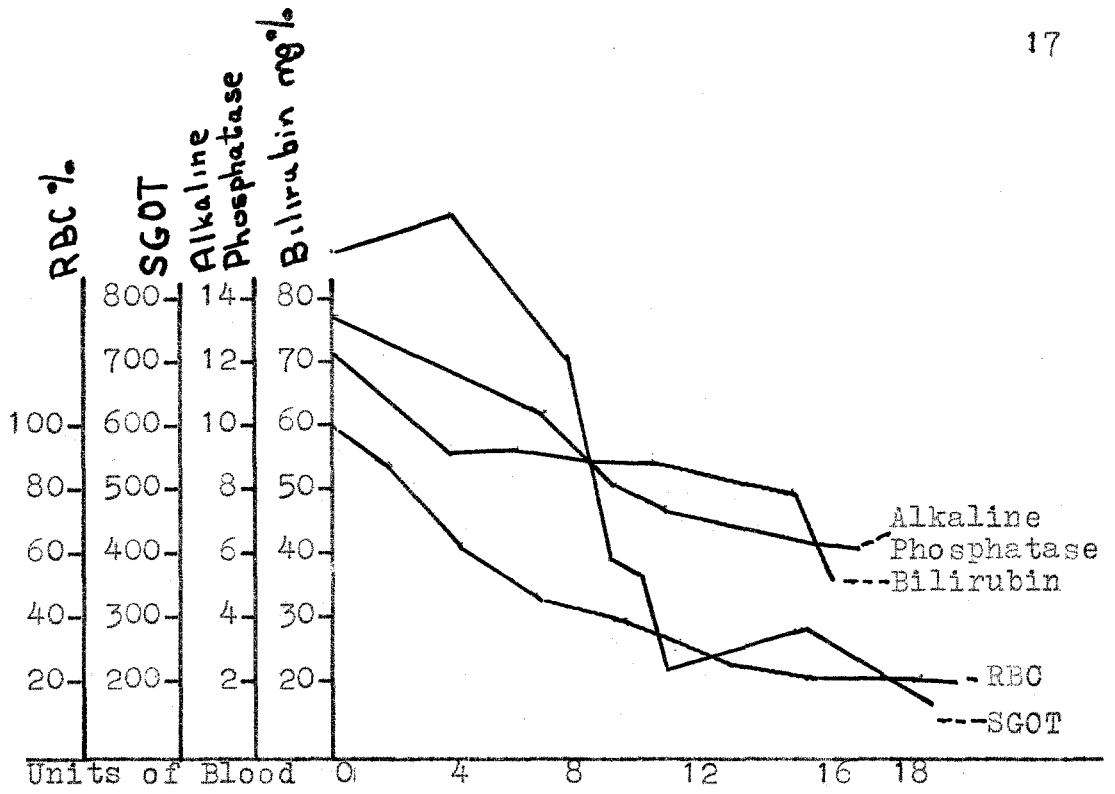

Figure 1--Measurable biochemical changes affected by exchange transfusion. Berger (1, p272)

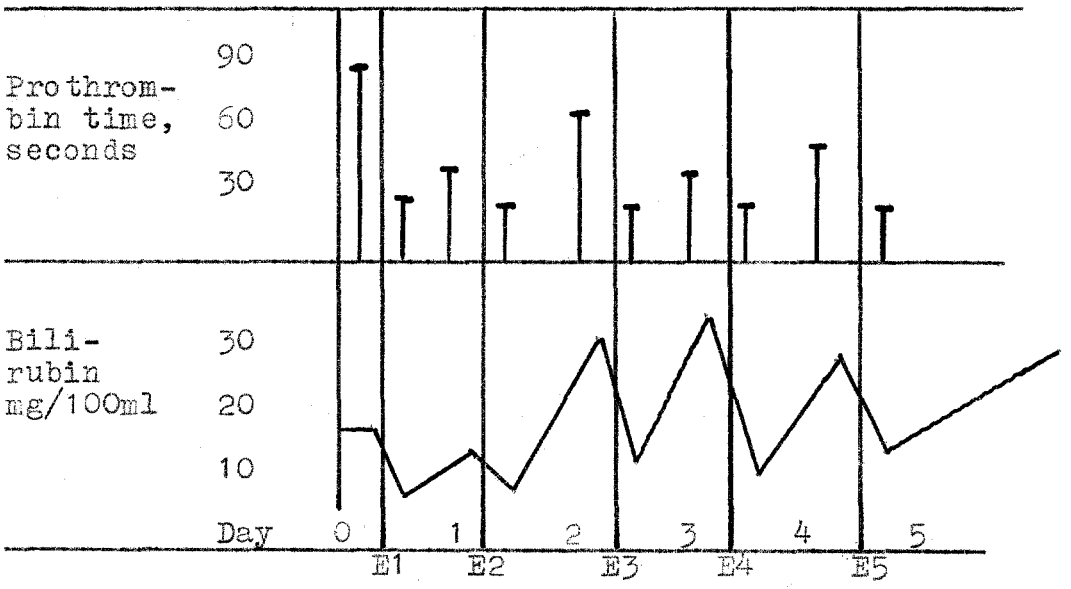

Figure 2--Changes in serum bilirubin and prothrombin time seen with multiple exchanges. Berger (1,p273)

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