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1969

Treatment of hepatic coma by exchange blood transfusion

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Recommended Citation

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 disorien-
      tation.
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 sub-
stances 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 alka-
losis (1). Hypokalemia has been shown to induce clini-
cal 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 metabo-
lism, 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 ab-
sorbed antibiotics--such as neomycin sulfate in a dose
of 4-6 grams per day--to reduce the bacterial break-
down 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 im-
balances, 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 to 1967, 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 pro-
posed and tried clinically. Eisman (8) has used heterol-
ogous perfusion of the isolated pig liver in 8 mori-
bund 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 35.6 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 chil-
dren who died after receiving only one exchange, re-
gained 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 trans-
fusions 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 physi-
cians 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 hyper-
ventilation 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 signif-
icantly 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 quali-
ties 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 plas-
tic catheter and administered through a peripheral vein.
Berger (5) recommended the serial infusions and with-
drawals of aliquots of 500 ml. of blood in adults and
30-50 ml. aliquots in children, which were well toler-
ated clinically. Berger (5) has shown that rapid,
massive exchanges may be complicated by temporary
hypotension which might initiate disastrous conse-
quences 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 temper-
ature should be monitored continously. The time nec-
essary 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 plate-
lets), 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-dex-
trose blood for their exchanges. Krebs experienced
gastrointestinal hemorrhage midway in one of his ex-
changes, 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 cit-
rate intoxication, which is rare even in massive trans-
fusions.

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 com-
partment, 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 dif-
fusion of tissue bilirubin into the vascular compart-
ment. 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 prob-
ability 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 sub-
sequent 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 forma-
tion at the catheter site has been the only other com-
plication 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 re-
gained 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 re-
covery 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 di-
rectly 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) recom-
mends 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) rec-
ommend 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 ac-
cepted 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 in-
vestigation.

APPENDIX

TABLE 1

THE RESULTS OF TREATMENT BY EXCHANGE TRANSFUSION

Source	Case No.	Age	Sex	Etiology	Ex-changes	Re-sponse[a]	Out-come
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	23yr	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
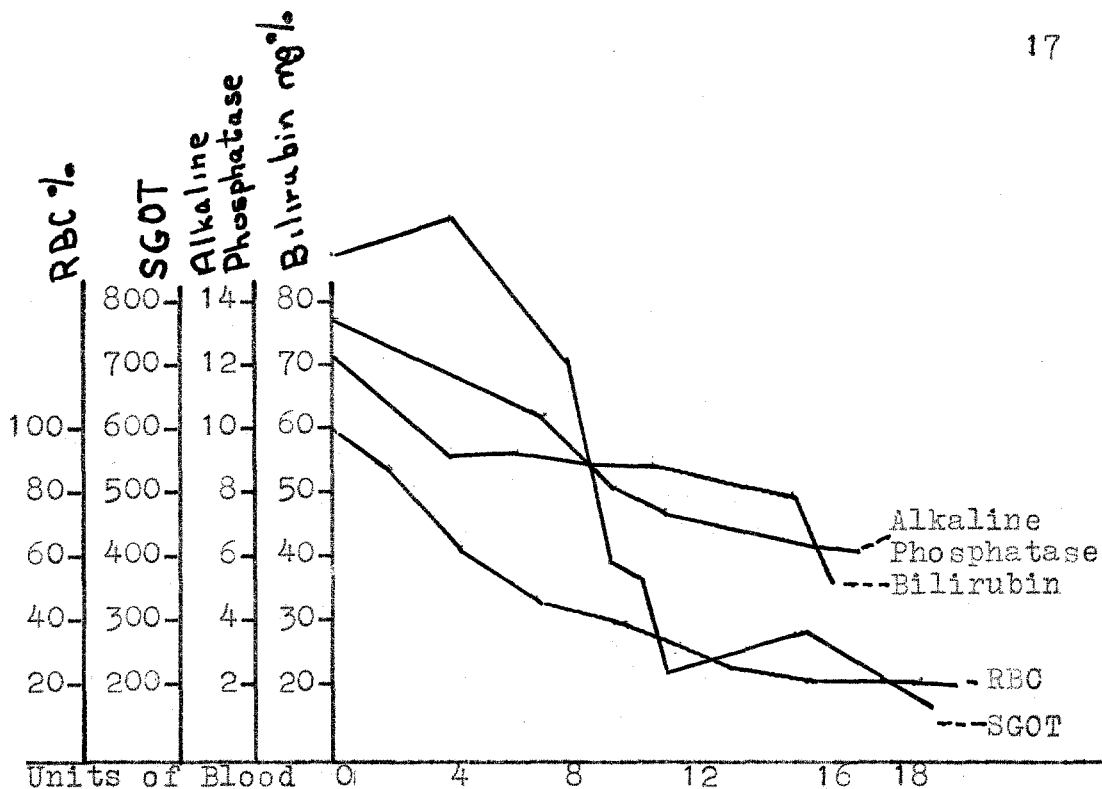
Figure 1--Measurable biochemical changes
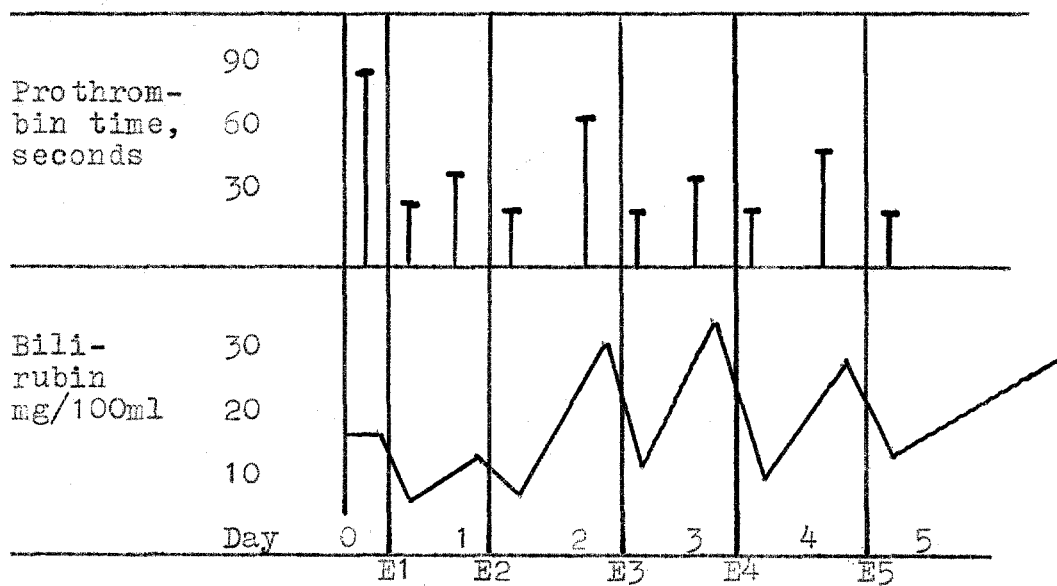affected by exchange transfusion. Berger (1, p272)

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

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