

Treatment of fulminant hepatic failure – Is there light at the end of the tunnel?

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KDE KAITA. Treatment of fulminant hepatic failure – Is there light at the end of the tunnel? Can J Gastroenterol 1995;9(6):319-326. A lot of research has been done on fulminant hepatic failure (FHF), mainly because of the high mortality associated with it. Many centres continue to search actively for the ideal medical treatment for FHF because liver transplantation is often difficult in these very ill patients. The many forms of therapy that have been tried and reported in case reports, small clinical trials and the occasional randomized controlled trial are reviewed, as are the current data on bioartificial livers and isolated hepatocyte transplantation. The ideal treatment remains elusive, and more work needs to be done to find a highly effective form of therapy for these very ill FHF patients.

Key Words: *Fulminant hepatic failure, Treatment*

Traitement de l'insuffisance hépatique fulminante : y a-t-il de la lumière au bout du tunnel?

RÉSUMÉ : L'insuffisance hépatique fulminante (IHF) a fait l'objet d'abondantes recherches, surtout à cause du fort taux de mortalité qui lui est associé. De nombreux centres continuent de chercher activement le traitement idéal de l'IHF, compte tenu du fait que la transplantation hépatique est souvent difficile chez ces grands malades. Les nombreuses formes de traitement à l'essai qui ont fait l'objet de rapports de cas sont passées en revue, tout comme les données récentes sur les foies bio-artificiels et la transplantation d'hépatocytes isolés. Le traitement idéal n'a pas encore été trouvé et il faudra approfondir encore les recherches pour arriver à traiter efficacement ces très grands malades atteints d'IHF.

FULMINANT HEPATIC FAILURE (FHF) or acute liver failure is a condition defined as the development of encephalopathy within eight weeks of onset of the illness (1). Sub-FHF is defined as encephalopathy developing between two

and 12 weeks after illness onset (2) and late onset hepatic failure is encephalopathy developing between eight and 24 weeks after the illness (3). Although FHF is relatively uncommon, approximately 2000 cases are reported in the

United States annually (4), and it carries a mortality as high as 80 to 90% for stage 4 coma. As several excellent reviews have recently been written about the causes, pathophysiology and complications of FHF (4-11), this paper will review the therapeutic options that have been reported in the past, those being used now and possible therapeutic options for the future.

In brief, FHF is a life-threatening illness that results ultimately from the near complete destruction of the liver by various agents such as viruses, drugs, toxins, ischemia, genetic disorders or autoimmune disease. Survival for FHF patients has improved over the past two decades despite minimal advances in specific therapy, likely due to advances in intensive care medicine (12). Nonetheless, the search continues for treatment modalities other than liver transplantation which, although effective, has many problems associated with it. It requires a donor in an urgent situation who may not match ABO blood group or size, and life-long immunosuppression with all its associated complications (infection, tumours, renal dysfunction, hypertension, metabolic problems, etc). Liver transplantation is associated with a survival rate that, while improving, is still less than that of non-FHF liver failure (13,14). The only exception is in patients with grades 1 to 3 coma in whom survival can be as high as 80% (15). It is also important to note that if the FHF patient

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Received for publication October 11, 1994. Accepted March 10, 1995

survives without a liver transplant, he/she is left with a completely normal liver. Thus, it is imperative that more effective therapy for FHF be found.

STEROIDS

Two of the initial treatments reported for FHF were adrenalcorticotropic hormone (ACTH) and cortisone in the 1940s and early 1950s. There are several case reports of improvements in biochemistry, appetite, jaundice and survival in patients with grade 4 hepatic encephalopathy with such therapy (16-21). Perhaps the most cited article is that by Ducci and Katz (21). Their experience prior to steroids was that no patient in stage 4 coma survived FHF. In their study, six FHF patients were treated with cortisone, ACTH and antibiotics. However, only three of the six patients had true FHF; the other three had chronic hepatitis and cirrhosis. Of the three with FHF, two survived after being in stage 4 coma for more than 48 h. The third died 1 h after admission. The authors concluded that the treatment might have been effective by decreasing the extent of hepatic inflammation.

It was not until 22 years later that Ware et al (22) published the results of the first prospective, randomized controlled trial of steroids in FHF. In this trial of 15 patients, all with viral hepatitis, 11 were randomized to placebo and four to steroids. There were seven survivors in the placebo group and no survivors in the treatment group. Since the completion of this trial there have been three larger, prospective, randomized controlled trials published (23-25). All three studies concluded that steroids should no longer be used for patients suffering from FHF and may be associated with a higher mortality than the control patients. In summary, although steroids at first looked extremely promising, the results of controlled trials were not supportive. Thus, steroids have no role in the treatment of FHF except perhaps for the rare instance of FHF due to autoimmune hepatitis.

It was soon thereafter that a variety of treatment modalities were reported to be effective in isolated case reports,

small uncontrolled clinical trials or both. Examples included hyperbaric oxygen, coenzymes, hemodialysis and peritoneal dialysis, exchange blood transfusions, extracorporeal whole liver perfusion and cross-circulation (26). Most promising was a trial by Trey et al (27) wherein five of seven FHF patients treated with exchange transfusions survived. Once again, however, when a prospective, randomized controlled trial was subsequently performed by Redeker and Yamahiro (28) the results were discouraging. No survival advantage was found in the 21 patients enrolled in their trial with exchange transfusions; in fact, there was a higher mortality in the treatment group.

Plasmapheresis has also been studied in several case reports. In 1970 Lepore and Martel (29) published the results of this therapy in five patients. No survivors were reported, rendering plasmapheresis much like exchange transfusion.

EXTRACORPOREAL WHOLE LIVER PERFUSION

Extracorporeal whole liver perfusion and cross-circulation are theoretically appealing because they afford time for hepatic regeneration to occur. However, case reports using porcine livers, and less frequently human livers, for extracorporeal whole liver perfusion have not been too successful in improving survival (26). The technique has recently been looked at again by Chari and co-workers (30). They treated four patients, two with FHF due to hepatitis B virus (HBV), one with FHF due to ischemia and one with primary nonfunctional postliver transplant, with ex vivo pig liver perfusions. All had temporary neurological and biochemical improvements but only one survived long enough to be transplanted. There are the additional problems of technical difficulties, immune reactions and ethical issues. Indeed, cross-circulation has been associated with death (31) and could result in cross-infection of the healthy participant. Therefore, as with steroid therapy, time and further experience with these therapeutic options have proven

them to be ineffective and/or inappropriate for treatment of FHF in humans.

CHARCOAL HEMOPERFUSION

The next putative advance in FHF management came with charcoal hemoperfusion. In the early 1970s, several investigators reported that charcoal hemoperfusion provided survival rates of 40 to 45% in FHF (32-36). Biocompatibility problems between the charcoal cartridges and platelets led Gazzard et al (36), at Kings College in London, to refine the treatment by adding prostacyclin (a prostaglandin analogue) to prevent platelet activation and subsequent hypotension. With this intervention, survival rates increased to 65% in patients with grade 3 coma (37,38). Based on these results, a two-part prospective, randomized controlled trial was performed by the investigators from the same location (39). The trial involved 137 patients over three years. It was divided into trial A, patients with grade three coma who received either 5 or 10 h of hemoperfusion per day, and trial B, patients with grade 4 coma who received either no perfusion or 10 h per day. The results of the trial led to the conclusion that enhanced survival was most likely the result of improvements in intensive care management rather than charcoal hemoperfusion. This was further illustrated by the fact that the survival rate in the acetaminophen group was the same in both trial A and the no perfusion group of trial B (42.9 to 58.3% versus 55.6%). Earlier work at the Kings College suggested that cerebral edema developed less often in patients treated earlier in grade 3 coma compared with patients started in grade 4 coma (49% versus 78%, $P < 0.05$) (38). However, their more recent work in a controlled setting was not able to confirm these results (39). In this trial, cerebral edema developed in 68.4 to 77.3% of patients in grade 3 coma. This result is not different from the 78% documented in their earlier work. Thus, there appears to be little role for charcoal hemoperfusion alone in patients with FHF.

HORMONES

During the late 1970s insulin and glucagon therapy was studied. Earlier work with mice by Farivar et al (40) revealed that insulin and glucagon given immediately after inoculation with murine hepatitis virus resulted in a dramatic increase in survival. It was felt that this was the result of increased hepatic regeneration because previous trials had shown increased markers of hepatic regeneration in partially hepatectomized rats treated with insulin and glucagon (41). Moreover, Farivar and colleagues also documented increased DNA synthesis in treated rats compared with controls. Similar results were found in rats but not rabbits treated with chemical toxins known to induce FHF (42,43). Based on these findings and retrospective reviews showing a survival advantage compared with historical controls (44,45), two major prospective, randomized controlled trials were performed (46,47). Once again, the results were discouraging. The two trials included 56 FHF patients in at least stage II encephalopathy. They found no differences in mortality between the hormone-treated and control groups. While a beta error due to the small sample sizes could not be excluded, the larger of the two trials found that mortality was higher in the treatment group (67% versus 82%), which renders this argument less relevant. Presently, insulin and glucagon cannot be considered useful in the treatment of FHF.

PROSTAGLANDINS

Prostaglandin therapy has recently received much attention. Positive findings have been reported with various types of prostaglandins in several models of FHF, including galactosamine and murine hepatitis virus-3 (48-59). The exact mechanism of this protective effect has not been determined. There is evidence that prostaglandins are cytoprotective (51-55), responsible for preservation of hepatic microcirculation (56), antiviral (58,59), immunosuppressive (62-65), and able to preserve the blood brain barrier (66) and enhance hepatic regeneration (67,68).

The first human studies with prostaglandins were reported by Sinclair et al (69,70) who administered prostaglandin E₁ (PGE₁) to 17 FHF patients with various viral etiologies. This uncontrolled trial found survival to be 100% in patients presenting with grades 1 to 3 coma and 45% in patients presenting with grade 4 coma. Overall survival was 71%, significantly better than historical controls (4-11). However, these promising results were not supported by two subsequent uncontrolled trials from France (71,72). The French investigators found that PGE₁ was ineffective in increasing the spontaneous survival rate for FHF due to either hepatitis B or drugs, or undetermined etiologies. The only randomized controlled trial to date was also unable to find an overall benefit to prostaglandin therapy (73). This trial, which involved PGE₂, took place over three years and enrolled 41 patients. The survival rate in the treated group was 40% versus 38% in the placebo group. On subgroup analysis, the study revealed that PGE₂ may be more effective if started within 10 days of FHF onset, particularly in patients suffering from FHF due to drugs or toxins. Obviously further controlled trials with larger numbers of patients are required to determine whether prostaglandin therapy has any role in the treatment of FHF in humans.

INTERFERON

Work has been done looking at the role of interferon in patients with FHF due to acute viral hepatitis. Patients with fulminant viral hepatitis have absent or grossly deficient amounts of interferon alpha and gamma (74). Based on these findings, Levin et al (75) treated 32 patients with FHF due to viral causes with interferon alpha (3 MU intramuscularly for seven to 14 days). The overall survival rate in this uncontrolled trial was 50%. Nine of 22 patients (41%) with grade 3 to 4 coma survived. However, the study population included 17 patients with hepatitis A virus (HAV) of whom nine survived, which mirrors the approximate survival rate for untreated HAV (4,7). Therefore, the 50% overall survival in the study by Levin and colleagues may

reflect a patient population with a better prognosis rather than the effects of interferon per se. A trial similar to that of Levin et al was recently carried out by Sanchez-Tapias et al (76). They enrolled 12 patients with viral FHF mostly due to HBV/hepatitis delta virus or HBV alone. Only one patient had HAV. Ten of the 12 patients died despite the absence of grade 4 coma at the start of therapy (76). Poor results were also reported by Milazzo et al (77) in 16 patients treated with interferon beta intravenously. Thus, the use of interferon for viral-induced FHF can not be advocated.

PUTRESCINE

Putrescine is essential for hepatic regeneration (78-80). It is the product of the enzyme ornithine decarboxylase which is commonly used as a marker of hepatic regenerative activity (78). Nishiguchi et al (81) were able to demonstrate a marked improvement in hepatic DNA synthesis and a marked survival benefit (88% versus 40%, $P < 0.01$) in D-galactosamine induced acute liver failure in rats treated with putrescine compared with untreated controls. Although putrescine may seem ideal to study in humans, it is not without concerns. Systemically administered putrescine may enhance cerebral edema (82) and may have an antidiuretic and nephrotoxic effect (83). Therefore, the search for the ideal agent continues.

N-ACETYLCYSTEINE

When administered within 10 h, N-acetylcysteine is the treatment of choice for acute acetaminophen overdose (84-87). Its use beyond 15 h after the overdose was discouraged by Prescott et al (84,88) who found that despite its safety, late administration (given up to 24 h after an overdose [89]), does not prevent hepatic necrosis. However, these findings were not supported by Harrison et al (90); their retrospective analysis of 100 patients treated with N-acetylcysteine between 10 and 36 h after ingestion found that mortality (37% versus 58%) and progression to grade 3 to 4 coma (51% versus 75%) were improved in the

treatment group. Keays and associates (91), in a prospective, randomized trial of 29 patients, also found that N-acetylcysteine given late after the overdose (36 h or more) was associated with a marked improvement in survival (64% versus 20%). Finally, the most recent prospective, randomized controlled trial using N-acetylcysteine in established FHF due to acetaminophen (mean 53 to 56 h postingestion) revealed that N-acetylcysteine was effective in improving survival (48% versus 20%), reducing the incidence of cerebral edema (40% versus 68%) and reducing the incidence of hypotension requiring inotropic support (48% versus 80%) (92). However, in many of the late treatment trials, tests of hepatic function, in particular the prothrombin time, were similar in both groups at the end of treatment, and rates of improvement were also similar. This finding led the group at Kings College (92) to suggest that it is not the glutathione repleting properties of N-acetylcysteine that improve survival but rather its effects on oxygen delivery and consumption.

Based on the premise that FHF is associated with covert tissue hypoxia (93), Harrison et al (94) studied the role of N-acetylcysteine on the hemodynamics and oxygen transport in patients with acetaminophen- and nonacetaminophen-induced FHF. This trial revealed that N-acetylcysteine in established FHF improves oxygen delivery, cardiac index and oxygen consumption in all forms of FHF and may be related to improvements in the microcirculation as a result of increased endothelium-derived relaxing factor (nitric oxide). Furthermore, N-acetylcysteine improves cerebral bloodflow and cerebral metabolic rate for oxygen which, in turn, may account for the reduced incidence of cerebral edema in patients suffering from FHF treated with late N-acetylcysteine (95). In summary, N-acetylcysteine appears to have a lot of promise for the treatment of FHF due to acetaminophen and perhaps all causes of FHF. Again, it must be stressed that more controlled trials are needed to confirm these initial promising studies. However, the relative safety of this agent, its posi-

tive effects on oxygen delivery and consumption, and its proven effectiveness in acetaminophen-induced FHF make N-acetylcysteine a worthwhile therapeutic option in the management of FHF patients regardless of the cause.

OTHER AGENTS

Other agents that have been tested recently in the treatment of FHF include hepatic stimulatory substance, antithrombin III (AT III) and anti-endotoxin monoclonal antibodies. Hepatic stimulatory substance alone and with other presumed enhancers of hepatic regeneration (insulin, transforming growth factor-alpha and insulin-like growth factor II) was ineffective in altering the survival rates of 62 dogs with FHF (96). AT III infusions in rats with FHF due to dimethylnitrosamine improved serum bilirubin levels, prothrombin time, alanine aminotransferase levels, and reduced the degree of histological damage at 24 h (97). However, in an uncontrolled trial of 26 humans with FHF due to various causes, a 27% survival rate was reported using AT III, not an improvement over historical controls (98). A randomized controlled trial with AT III remains to be performed. In one case report, Manthous et al (99) described the results of monoclonal anti-endotoxin antibody treatment in a patient with acute hepatitis A. The trial was based on previous data from patients with cirrhosis and acute liver failure where hemodynamic parameters similar to septic shock and increased endotoxin levels were reported (100-102). The patient described in the report from Manthous and co-workers showed a significant improvement in hemodynamic parameters following anti-endotoxin antibody administration. Unfortunately, the patient died 10 days later from intractable status epilepticus. Before his death he had remained hemodynamically stable and off all inotropes. Obviously, more data on anti-endotoxin antibody are required.

ARTIFICIAL SUPPORT SYSTEMS

Because of the early failures associated with artificial support systems,

much work has recently addressed the development of a bioartificial liver support system and hepatocyte transplantation as either bridges to transplantation or interventions that will allow time for spontaneous recovery from FHF. As presently designed, these devices offer more than other treatment modalities. Specifically, they have the ability to both clear and metabolize toxic compounds as well as synthesize products that are essential for the recovery process. Intact hepatocytes have been stressed as being essential in liver support systems (103-106). Extracorporeal devices come in various forms. Some implement primary hepatocytes of nonhuman species (106,107), while others employ cultured human hepatoblastoma cells (108,109). Some devices consist of hollow fibre cartridges with hepatocytes lining the capillary tubing (106-109), while others are suspensions of encapsulated hepatocytes (110). Despite the various designs being studied, the bioartificial liver is essentially made of the same components. These components are live hepatocytes, a barrier to separate the patient's blood cells from the hepatocytes, and a mechanism for perfusion of the patient's whole blood or plasma over the cells (111). These devices are just now being tried in humans with FHF. While the results are encouraging, they are still confined to limited case reports. Therefore, randomized trials will be required to assess their role in FHF definitively.

ISOLATED HEPATOCYTE TRANSPLANTATION

Isolated hepatocyte transplantation for FHF is by no means a new therapeutic modality. It has been shown in animal models of FHF to improve survival regardless of whether the cells are allogeneic or xenogeneic (112-118). The process usually involves intraperitoneal implantation of free hepatocytes, coated microcarrier beads, spheroid hepatocyte aggregates, hepatocytes immobilized on porous, biodegradable polymeric substrates or microencapsulated gel droplets. Immunosuppression is required to maintain viability by preventing rejection of the cells.

The microencapsulation technique may provide a means of transplanting hepatocytes in the absence of immunosuppression because the cells are sequestered from the host immune system. The technique has yet to be reported in humans. Much work remains to be done in this area of research.

CONCLUSIONS

Most of the treatment modalities, short of transplantation, have been fraught with initial success in case reports and uncontrolled trials, only to be proven ineffective in larger randomized control studies. However, for the most part, even the large controlled studies

do not contain sufficient patient numbers to exclude a beta error. Multi-centre or multinational trials may represent the only solution to this problem; ideally, such trials would also allow for stratification of patients based on etiology, coma grade, age and time interval from onset to encephalopathy.

What does the future hold? Most certainly research will continue with the more promising agents including N-acetylcysteine and perhaps prostaglandins. The results of ongoing studies with bioartificial livers and hepatocyte transplantation are eagerly awaited. More effort is needed to identify agents that enhance and inhibit hepatic re-

generative activity. Finally, a combination of some of the above therapeutic modalities may be what is required to improve survival rates further in FHF patients. In the interim, good supportive management and possibly N-acetylcysteine administration with early transfer to liver transplant units must remain the treatment of choice for patients suffering from FHF.

ACKNOWLEDGEMENTS: Dr Kaita is the recipient of a Roche Canada/University of Manitoba Hepatology Fellowship Award.

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