

Clinical experience with artificial liver support systems

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PP Ting, AA Demetriou. Clinical experience with artificial liver support systems. *Can J Gastroenterol* 2000;14(Suppl D):79D-84D. Fulminant hepatic failure is a devastating disease that, despite recent therapeutic advances, continues to be associated with high morbidity and mortality. Orthotopic liver transplantation has emerged as the sole modality of treatment that significantly improves survival. However, the critical shortage of donors precludes timely transplantation for all patients. Consequently, almost half of all patients with fulminant hepatic failure die before a graft becomes available. This has generated interest in developing a system that would support patients until either native liver regeneration occurs or an optimal donor liver can be found. Investigators have used biological, artificial and bioartificial techniques in an attempt to improve survival in liver failure. This article reviews the history, the current state of the art and future directions of artificial liver support.

Key Words: *Bioartificial liver; Fulminant hepatic failure; Liver support*

L'expérience clinique menée avec des systèmes de support hépatique artificiels

RÉSUMÉ : L'insuffisance hépatique fulminante est une maladie dévastatrice qui, malgré les progrès thérapeutiques récents, continue d'être associée à de forts taux de morbidité et de mortalité. La transplantation hépatique orthotopique est devenue le seul mode de traitement qui améliore significativement la survie. Par contre, la pénurie grave de donneurs empêche une transplantation en temps opportun chez tous les patients. Par conséquent, près de la moitié des patients qui souffrent d'une hépatite fulminante meurent avant d'avoir accès à un foie. Cela a suscité l'intérêt à l'endroit d'un système qui permettrait aux patients de survivre jusqu'à la régénérescence de leur foie ou jusqu'à ce qu'un donneur puisse être trouvé. Des investigateurs ont utilisé des techniques biologiques, artificielles et bioartificielles pour tenter d'améliorer la survie dans l'insuffisance hépatique. Cet article passe en revue l'historique, l'état actuel des connaissances et l'avenir de ce mode de support hépatique artificiel.

Fulminant hepatic failure (FHF) is a devastating disease that, despite recent therapeutic advances, continues to be associated with high mortality rates, ranging from 70% to 90% depending on the etiology and the age of the patient (1). Cerebral edema, with increased intracranial pressure and subsequent brainstem herniation, is the most feared complication and is the usual cause of death (2). FHF is classically defined as "a potentially reversible condition, the consequence of severe liver injury, in which the onset of hepatic encephalopathy was within eight weeks of the first symptoms of illness, and in the absence of pre-existing liver disease" (3). Recently, a new classification has been proposed in which acute liver failure is subdivided into hyperacute, acute and subacute categories, based on the number of days from the onset of jaundice to the development of encephalopathy. This scheme has been shown to reflect better the dif-

ferent clinical patterns of illness and etiology, and to allow for more accurate prediction of prognosis (4). The causes of FHF may be divided into four broad categories: viral hepatitis, drug-induced hepatotoxicity, toxins and miscellaneous.

The emergence of liver transplantation as a treatment of FHF has reduced the mortality rate to 50% or even 20% after a more rigorous selection of patients (5). However, due to the severe shortage of liver donors, only 10% of FHF patients receive a transplant (6). Because of the emergent nature of FHF, centres are often forced to use suboptimal livers (steatotic, elderly donor or crosstype-unmatched livers) that have resulted in one- and five-year survival rates, significantly lower than those for other liver transplant recipients (1). Finally, the inability to identify patients who may recover with medical management alone has exacerbated the shortage of grafts (7). Because of these factors, up to 90% of patients with FHF

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develop irreversible neurological damage, multiple organ failure or sepsis while awaiting liver transplantation, and half of these patients will die before a graft becomes available (8). In addition, there is a significant subgroup of patients with FHF who would benefit from liver transplantation but who are disqualified due to medical or psychosocial contraindications, or are initially listed for transplantation but deteriorate to the point where they no longer meet transplant criteria while waiting for a graft.

The high morbidity and mortality of FHF, along with the lack of a viable, timely, easily accessible and available treatment modality, have stimulated interest in developing a method to support the liver in times of failure. This device would buy the patient precious time until a suitable graft can be found for transplantation. To be effective, it should be able to control cerebral edema and prevent the onset of multiorgan failure. In addition, it would offer a therapeutic modality to patients not deemed to be candidates for transplant, and it may also eliminate both unnecessary transplants and the need for lifelong immunosuppression in patients who have the potential for spontaneous recovery. Here, the history of artificial liver support development and the current state of the art in this field are reviewed.

HISTORICAL PERSPECTIVES

Early attempts at developing an effective means of liver support focused on blood detoxification and the replacement of deficient essential factors (blood coagulation factors, albumin) manufactured by the liver. Whole blood exchange transfusions were rapidly replaced by the more effective and less risky technique of plasmapheresis, in which a patient's plasma is removed and replaced with plasma from normal donors. The results of early clinical trials with this technique were disappointing. Work by Sabin and Meritt (9), Lepore et al (10) and Freeman and Matthewsson (11) demonstrated that improvement (reduction in serum bilirubin and partial recovery from coma) was transient and seen predominantly in patients with drug-induced liver failure. Plasmapheresis continues to be widely used as a therapy for hepatic failure (12). However, in FHF, the overall survival rate remains below 50% (13). Significant complications of plasmapheresis include chemical toxicity, viral infections, and deaths from lung and brain complications (14). A recent study by Clemmesen et al (15) used high volume (15% of the body weight) repeated plasma exchange in 23 patients (14 with acute hepatic failure and nine with 'acute-on-chronic liver disease'). In the acute hepatic failure group, only one of eight patients who developed liver failure after paracetamol overdose died. However, only four of the eight patients fulfilled the King's College Hospital criteria of FHF (which has a predicted mortality of 90% without liver transplantation). In the acute-on-chronic liver disease group, only two of five survivors required transplantation. Despite the limitations and unproved efficacy, plasma exchange continues to be the most frequently used method of liver support in patients with acute liver failure.

Initial attempts at developing an artificial liver focused on blood detoxification, based on the assumption that the toxins

that cause comas in hepatic failure are small, dialyzable molecules. In 1958, Kiley et al (16) reported what is believed to be the first use of a mechanical device for the treatment of liver failure. He treated five patients having ammonia intoxication with hemodialysis. Four had symptomatic improvement of their neurological status, but none achieved long term survival. These results were confirmed 20 years later by Opolon et al (17), who demonstrated that FHF patients treated with dialysis showed statistically significant improvement in mental status but had no significant improvement in long term survival.

In 1959, Kimoto (18) reported the results of cross-hemodialysis between a healthy dog and a patient with metabolic encephalopathy due to acute liver failure. The patient demonstrated dramatic improvement and was awake 3 h after the procedure. Post-treatment ammonia levels were dramatically lower and antidog antibody levels were undetectable. However, the patient died seven days later of cardiac failure secondary to fluid overload. This isolated case report reinforces the notion that metabolic encephalopathy is associated with dialyzable substances and demonstrates that xenogeneic species may be used in humans without significant adverse immune response if the circulations are separated by a semipermeable membrane (19).

In 1965, Eiseman et al (20) reported their results in liver failure patients treated with extracorporeal pig liver perfusion. In 1966, extracorporeal perfusion using human cadaveric livers was reported (21). An interesting 1970 case report described a patient with liver failure who was treated with 16 extracorporeal liver perfusions from 10 pigs, three baboons, one calf, one monkey and one human during a 10-week period (22). In all of these attempts at extracorporeal liver perfusion, patients showed improvement in mental status, but again there were no long term survivors. These results confirm that it is possible to use xenogeneic grafts for repeated treatments if a semipermeable membrane separates the patients' blood from the foreign tissues.

In 1967, Burnell et al (23) used human-human cross-circulation to treat three patients with FHF. The first patient had demonstrated neurological improvement after the first treatment but died of recurrent gastrointestinal bleeding before the second treatment. The second patient showed no neurological improvement after four treatments. The third patient received 15 treatments and recovered completely. This patient is believed to be the first long term survivor after human-human cross-circulation for the treatment of FHF (19). Despite this success, severe transfusion reactions were observed in all of the treated patients, and the risk of disease transmission to the normal volunteer does not make this modality a viable treatment for FHF.

All of the early attempts at extracorporeal liver support resulted in the improved neurological status of FHF patients but no long term improvement in survival. However, two critical observations were made from this early work. First, the symptoms of hepatic encephalopathy can be improved through the removal of midsized molecules by dialysis; and second, liver failure is immunosuppressive and permits the use of allogeneic

or xenogeneic tissue without severe reactions if a semipermeable membrane separates the patient's blood from the foreign tissues. These observations have guided the thinking and development of the modes of modern liver support.

BIOARTIFICIAL LIVERS

The limited success of purely mechanical liver support that is based on toxin removal, along with the knowledge that the liver has complex synthetic and biotransformatory functions as well as waste removal functions, led to the concept that a biological component comprised of a mammalian liver tissue preparation of some kind is required to support FHF patients. The term 'artificial liver' was first introduced in 1956 by Sorrentino (24), who demonstrated that fresh liver tissue homogenates metabolized salicylic acid, barbituric acid and ketone bodies, and produces urea from ammonia. With the development of the portal vein collagenase perfusion technique for the isolation of liver cells, several authors used liver cells to construct liver assist systems, including Eiseman et al (20), Uchino et al (25) and Rozga et al (26). These experiments showed that bioartificial liver systems can, to some degree, replace a number of metabolic functions impaired or lost in FHF.

Matsumura et al (27) reported the first clinical use of a bioartificial liver in 1987. A patient with liver failure due to inoperable cholangiocarcinoma was dialyzed against cryopreserved rabbit hepatocytes. A significant decrease in total plasma bilirubin was noted, but there was no evidence that the treatment affected the patient's clinical course, and no follow-up studies were reported. In 1989, Margulis et al (28) treated 59 FHF patients with hemoperfusions through a 20 mL capsule that was filled with less than 0.5 g of isolated porcine hepatocytes mixed with charcoal particles. Although improved survival in the hepatocyte-treated group was reported, no evidence of physiological, biochemical and metabolic support was reported. This group has published no further studies.

Several biotechnological advances have facilitated the development of the bioartificial liver in the modern era. The realization of the importance of cell-cell and cell-matrix interactions in maintaining hepatocyte differentiation has led to the use of matrices or microcarriers. These give the isolated hepatocytes a surface on which to grow and the ability to maintain polarity. This has improved the level of differentiated function attainable with isolated hepatocytes. In addition, improvements in cell culture technology and techniques have increased the survival time and viability of hepatocytes *in vitro*. The use of hollow fibre cartridge technology in bioartificial liver design has been a significant advance. The semipermeable membrane increases the surface area for mass transfer while preventing the contact of the cellular components of the patient with xenogeneic hepatocytes.

CURRENT CLINICAL STATUS

The field of extracorporeal liver support has two major therapeutic approaches: nonbiological devices using charcoal hemoperfusion or hemofiltration, and biological devices

using extracorporeal whole liver perfusion or bioartificial livers with both mechanical and hepatocyte components.

The use of charcoal as an adsorbent of toxic substances from the circulation has been actively studied over the past 25 years. Well designed experiments conducted in animal models of liver failure demonstrated significant improvement in the survival of animals treated with charcoal hemoperfusion compared with controls (29-32). Initial clinical trials were conducted by Schechter et al (33), Yatzidis and Oreopoulos (34) and Chang (35). Follow-up studies confirmed that significant neurological improvement was observed, but long term survival was not improved (36). In a controlled trial by O'Grady et al (37), 137 patients with acute liver failure were divided into two groups based on their grade of encephalopathy at the time of enrollment. Patients with grade 3 encephalopathy were treated with either 5 or 10 h of charcoal hemoperfusion and compared with each other, but not with a control group. Patients in grade 4 encephalopathy were treated for 10 h and compared with standard medical management. No statistically significant improvement in survival was observed in any of the compared groups, although overall survival was high in patients with acetaminophen overdose and hepatitis A and B (37). Further statistical analysis of these data revealed that almost double the number of patients studied would have been required to demonstrate conclusively that charcoal hemoperfusion was of no benefit (36).

Recently, Ash et al (38) reported clinical results of the treatment of liver failure patients with hemodiadsorption using a suspension of powdered charcoal and a cation exchange resin. Patients were treated for 6 h daily for three to five days; control patients had similar treatment periods. Thirty-seven patients with acute or acute-on-chronic liver failure and encephalopathy were enrolled in four prospective, randomized, multicentre studies. Improvement was observed in the neurological status (defined as a decrease in Glasgow Coma Score by one point over three treatments) and the physiological status (defined as an increase in blood pressure during one treatment by 20%) of the patients, regardless of the etiology of hepatic failure. Improvement in outcome (defined as survival to discharge, transplantation or survival for five days) was observed in the group of patients having acute-on-chronic hepatic failure with stage 3 encephalopathy. Outcome was not improved in patients with FHF.

Yoshida et al (39) also had initial clinical success using plasma separation and hemodiafiltration to treat patients with FHF. Their system used a high performance membrane with large pores that allowed efficient removal of midsized molecular toxic substances of 1500 to 5000 Da from the plasma. In 93% of the 67 treated patients, the FHF was caused by viral hepatitis. A high rate of recovery from initial grades 1 to 4 coma was observed in the treated patients. The greatest therapeutic gains were observed in patients with hepatitis A or hepatitis B infection. In hepatitis B carriers and patients with non-A, non-B hepatitis, the results were less impressive. The overall survival rate was 55%, a rate similar to that after liver transplantation. This is of particular relevance because while orthotopic liver transplantation is the

gold standard of treatment for FHF in Western countries, it has only just become an option in Japan due to recent revisions in the legal definitions of brain death in that country. Thus, although purely artificial liver support systems without a biological component have fallen out of favour because of the failure to improve survival, the results reported by Ash et al (38) and Yoshida et al (39) suggest that there may be a role for their use in specific situations in specific subpopulations of patients with acute hepatic failure.

Several groups have recently revived interest in extracorporeal whole liver perfusion, where the patient is connected to either a human or nonhuman liver outside of their body. Fox et al (40) recently used this modality to treat three patients using donor livers deemed unsuitable for transplantation. Two of three patients were successfully supported, and 'bridged' to orthotopic liver transplantation and survival. The third patient died of multisystem organ failure and was never transplanted. Chari et al (41) treated four patients with extracorporeal liver support using porcine livers. One patient was successfully supported to successful liver transplantation, but the other three died of sepsis, cerebral edema and multisystem failure, respectively. Fair et al (42) presented a case report of a single patient treated briefly (4 h) with extracorporeal support through a porcine liver. This patient was successfully transplanted 8 h later. Some clinical success has been enjoyed using whole liver extracorporeal perfusion. Only one of the four deaths reported in these isolated cases has been directly attributed to the technique of extracorporeal liver support. However, several issues remain. The choice of species is perhaps the main one. Using a 'good', high quality human liver would likely improve the results of extracorporeal support. However, ethical issues would then arise over why such livers are not used for transplantation. Several extracorporeal whole liver perfusion studies are being carried out with porcine livers. However, the direct contact of patient human blood or plasma with foreign tissue raises important immunological issues as well as concern about the risk of cross-species pathogen transmission. Finally, pig livers have been shown to maintain good function only for approximately 6 h. An FHF patient would require daily treatments (at the minimum) for extended periods of time. This would require the maintenance of large pig colonies and daily donor hepatectomies at treatment sites. This approach is probably not practical.

Most groups interested in extracorporeal liver support use a mechanical system with a biological component. They use a bioreactor or an interface between the biological components and the blood or plasma perfusion circuit. The main differences among research groups lay in the type of cells used, the matrix used to carry the cells and whether whole blood or plasma perfusion is used.

Mammalian hepatocytes are by necessity the biological component of choice. Attempts at producing an artificial cell, which duplicates the myriad number of functions of hepatocytes, have been unsuccessful. Normal human hepatocytes would be the ideal tissue to use, but as mentioned earlier, cadaveric organs are already in critically short supply.

A human hepatoblastoma cell line (C3A) has been developed and was used clinically by Sussman et al (43). Short term safety was documented in an uncontrolled phase I study, which used this cell line in an extracorporeal liver assist device (ELAD) to treat patients with FHF and stage 3 or 4 hepatic encephalopathy. Of the 11 patients treated, six died, four were bridged to liver transplantation and one patient recovered spontaneously. Five of the six deaths were due to cerebral edema, and liver support was discontinued prematurely in four of these patients (44). A controlled trial using the ELAD was conducted. Twenty-four patients were classified into two groups: those believed to have a significant chance of spontaneous survival, and those who fulfilled criteria for transplantation. Patients in the two groups were then randomly placed into control and ELAD treatment groups. No improvement in survival was noted in the ELAD-treated groups compared with controls (45). In addition to these discouraging initial results, long term safety issues with these malignant cell-derived lines need to be addressed.

Most researchers use a hollow fibre cartridge system for their bioreactors. Usually, cells are inoculated into the extrafibre space while blood or plasma passes through the fibre lumen. Nyberg et al (46) suspended hepatocytes in a collagen gel, which is injected into the lumen of the hollow fibres. The gel contracts after 24 h, creating a third space within the fibres. Medium is then pumped down the fibre lumen while whole blood or plasma is passed through the extrafibre space. The rationale is to keep hepatocytes nourished during treatment, but the system has several limitations. Only a small number of cells can be placed in each bioreactor, which may be insufficient to treat large animals or patients. In addition, the entrapment of cells within the gel limits mass transport to passive diffusion.

An important issue in bioartificial liver support is whether whole blood or plasma should be used to perfuse the bioreactor. Proponents of whole blood perfusion argue that plasma separation complicates liver support treatment, increases extracorporeal priming space and elevates cost. However, the use of modern plasma separation technology (single venous access, continuous high yield plasma collection and low extracorporeal volume) offers many advantages over the use of whole blood. Systemic heparinization is avoided in coagulopathic patients. The use of plasma eliminates direct cell-cell interaction between human blood and xenogeneic liver cells, and the hemolysis and platelet depletion associated with whole blood perfusion are avoided. Safety features, such as particle or fibrin detectors and microporous cell filters, can be incorporated into the system. Finally, high flow recirculation of plasma improves bidirectional solute transport and oxygen delivery, because at high flow rates, fluid convection, not diffusion, drives the flow of solutes across the fibres.

We have developed a bioartificial liver consisting of a plasma separator and a high flow plasma recirculation system. The bioartificial liver loop consists of a hollow fibre bioreactor filled with 5×10^9 to 7×10^9 cryopreserved porcine primary hepatocytes attached to collagen-coated microcarriers. Additionally, a charcoal column is placed before the bioreactor to enhance the detoxifying capability of the

bioartificial liver and to protect the hepatocytes from the toxic effects of hepatic failure plasma. Plasma that has passed through the bioreactor returns to the plasma separator, is reconstituted with blood cells and is returned as whole blood to the patient via a standard superficial femoral vein dialysis catheter. Treatments last 6 h each and are conducted on a daily basis, or at more frequent intervals if needed, until a patient receives a transplant or recovers spontaneously. A phase I clinical trial has been completed (47). All patients fulfilled the diagnostic criteria of FHF, were failing maximum medical management and were candidates for urgent liver transplantation. All treated patients remained hemodynamically stable. A significant improvement in putative liver function tests was observed. Most remarkable was a significant improvement in neurological status with decreased intracranial pressure and stable cerebral perfusion pressure. The Comprehensive Level of Consciousness Score (48), which includes the assessment of brainstem function, improved significantly. Five patients recovered without transplant, and the remaining 21 patients, except two, were successfully bridged to transplantation; all were discharged from the hospital in good condition and neurologically intact. No adverse effects were noted during or after any of the treatments. These preliminary results are encouraging and led to the initiation of a controlled, multi-centre phase II to III study, which is still ongoing.

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FUTURE DIRECTIONS

The ultimate goal of investigators in this field is to develop a bioartificial liver that can provide enough support to sustain patients long enough to allow their native livers to regenerate and recover normal function, thereby avoiding liver transplantation. To achieve this, an effective liver support system must arrest and/or reverse the rapid development of intracranial hypertension, which leads to brainstem herniation and death. In our series, five of 23 FHF patients were successfully 'bridged' to recovery without transplantation. The potential risk of transmission of pathogens (ie, pig endogenous retrovirus) (49) from porcine tissues to humans needs to be determined. To avoid the possible risks of disease transmission, the use of a human hepatocyte cell line expressing liver-specific functions is desirable. The optimal mass of hepatocytes needed to provide adequate support remains to be determined. Also, improvement of hepatocyte cryopreservation technology, development of more efficient cell bioreactor systems and standardization of treatment protocols would facilitate the wider use of bioartificial liver technology. Finally, the establishment of dedicated, multi-disciplinary liver support units with expertise in the care and management of this complex disease is just as important as new technology in the successful treatment of acute liver failure.

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