Current Advances in Liver Support Systems

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In this issue of the journal, Sorkine et al. [1] review current developments in liver support systems, a most exciting topic that has generated renewed interest and research efforts in recent years.

Despite improved outcomes in patients with fulminant hepatic failure following the introduction of liver transplantation in the early 1980s, mortality among these patients remained high. Organ shortages, which make it difficult or impossible to perform transplantation in a timely manner, may explain the relative high mortality of 40–50% among these patients [2]. Complications and side effects associated with immunosuppression also play a role in the outcome of liver transplantation for FHF. Ethical issues, such as the question of whether to offer transplantation to patients after a suicide attempt, are another factor that can sometimes make liver transplantation a less than ideal therapeutic measure for patients with FHF. Finally, current scoring systems for identifying the need for liver transplantation in patients with FHF, such as the Kings College criteria [3], cannot always precisely predict outcome. While some patients require urgent transplant, others may recover spontaneously.

A liver support system, on the other hand, may either provide temporary support until an organ becomes available, or ideally replace the failing liver until it can regenerate. Experience with auxilliary liver transplantation, in which a liver segment is implanted near the diseased liver, has shown that in most patients with FHF, if given enough time, the native liver regenerates [4]. The period required for regeneration, however, may vary from a few days to several months. Theoretically, the support device should be able to replace liver function for the duration of that interval.

Unlike hemodialysis, which has long been used as a replacement therapy for patients with renal failure, and despite major advances in biotechnology and molecular biology, the development of an artificial liver is only in the initial phase. A major hurdle is the fact that the complex biochemical and excretory functions of the liver cannot be replaced by a device that supplies only the excretory function, as in the case of hemodialysis for renal failure.

FHF = fulminant hepatic failure

Initial attempts to improve the outcomes of FHF patients with use of plasma exchange or plasmapheresis, before the era of liver transplantation, were unsuccessful [5,6]. Later, when charcoal and anion exchange resins were added to the hemoperfusion circuit to remove protein-bound toxins, improved metabolic profiles as well as temporary recovery of conciousness were described in several clinical reports [3], but no survival benefit could be demonstrated.

Sorkin and colleagues describe a new generation of blood purification systems that combine hemodialysis and adsorption to charcoal, resins or albumin. Compared to charcoal hemoperfusion alone, these new systems provide enhanced removal of tightly protein-bound compounds as well as reduction in ammonia levels and maintenance of acid-base and electrolyte balance [7]. The use of an albumin-impregnated hollow fiber dialysis membrane in the molecular adsorbent recirculating system is based on the principle that albumin molecules with free binding sites compete for toxins bound to carrier proteins in the perfused blood. The adsorbed toxins are moved in turn from the membrane to the dialysate, which is based on the use of 5% human albumin. Although initial reports on these new systems in patients with FHF are promising [8], further experience in randomized controlled studies is required before the treatment can be employed on a routine basis. Furthermore, because they offer only limited metabolic support, these systems may provide only a bridge to a transplant, or in the best scenario, to spontaneous recovery.

A more appealing approach, which would render liver transplantation obsolete, is the development of a biological liver support system. Such a system would provide not only hemopurification but also other metabolic liver functions, such as protein synthesis, detoxification, and enzymatic activities (i.e., cytochrome p-450). During the last decade a vast amount of research focused on the development of a biological liver support system. Advances in hepatocyte isolation and culture techniques, improved understanding of hepatocyte-matrix interaction, and innovative biomaterial technology have resulted in the development of a new generation of liver support systems. The new generation of devices includes bioreactors that incorporate viable liver cells in a culture [9]. In the devices tested so far, the cellular component, cell mass and bioreactor specifications differed widely.

Three different cell types have been tested: porcine hepatocytes, primary human hepatocytes, and replicating human hepatocyte cell lines. While the main advantage of porcine hepatocytes is their ready availability and lower cost, questions regarding their antigenicity and the risk of transmission of infections might limit their long-term use. Primary human hepatocytes are a limited option because of the lack of normal liver tissue.

While transformed human hepatoma or hepatoblastoma cell lines lose their differentiated liver function, human hepatocytes transfected with a retrovirus vector carrying oncogene (SV 40 large-T) can proliferate and maintain differentiated function in a culture for more than 6 months [10]. However, the applicability of such cell lines for a clinical setting is unclear, due to reports of development of hepatocellular carcinoma in experimental animals expressing this oncogene. Another strategy utilizes immortalized human hepatocyte lines without oncogenes or carcinogenes [11]. These cells maintain protein synthesis (albumin, prothrombin, fibrinogen and -1 antitrypsin) for 3 weeks at levels similar to those of freshly isolated primary hepatocytes. They do, however, lose some degree of liver-specific enzyme activities (glucose-6-phosphatase and cytochrome p-450 isoforms).

Culture conditions and cellular interactions are important factors. Because hepatocytes survive only a few hours in a simple suspension culture, new techniques to maintain hepatocyte viability and differentiated function have been developed. These technologies are based on induction of cellular polarity, as occurs in a normal liver *in vivo* by immobilization of cells in a collagen gel, the addition of extracellular matrix, and promotion of 3-dimensional cell-cell adhesion [12].

Bioreactors must provide adequate hepatocyte perfusion and removal of the waste products of cellular metabolism. Oxygenation is important to maintain cell function and hepatocyte attachment. Therefore, in systems using plasma rather than whole blood, an oxygenator is added. The two systems that have been clinically tested so far are the bioartificial liver, which contains cryopreserved, microcarrier-attached porcine hepatocytes [13], and the extracorporeal liver assist device, which contains a transformed human hepatoma cell line (C3A) [14]. Each system consists of hollow fiber membranes, with anticoagulated plasma or blood perfused through the hollow fiber lumen and cultured hepatocytes in the extra-fiber space. An improved design of the biomaterial and membranes in the bioartificial liver system, which facilitates perfusion and diffusion gradients within the device, has recently been developed and tested in animal models [15]. The largest experience using bioartificial support system is with this device. Almost all patients treated with the bioartificial liver showed significant improvements in neurological status, reduced intracranial pressure, and reductions in ammonia and aromatic amino acid levels [13]. All transplant candidates were successfully bridged to transplant. Clinical studies using this system are ongoing, but the advanced design bioreactors have not yet been tested in humans.

An alternative treatment approach in FHF that might be valuable in the near future is the use of allogeneic hepatocyte transplantation. These cells are injected via the portal system and reside within the liver. The need for adequate cell mass and the requirement for systemic immunosuppression are the main drawbacks of this new technology. Preliminary clinical experience in patients with FHF demonstrated hepatocyte engraftment and function 24–72 hours after injection [16]. No long-term function could be demonstrated however, because all the patients either died or underwent whole-organ transplantation within a short time after hepatocyte transplant.

In summary, seminal progress has been made in the development of liver support systems for treatment of patients with acute liver failure. The new generation of artificial systems provides improved purification of blood toxins but are limited by their lack of full metabolic support and therefore are expected to be useful only as a bridge to transplant. The biological reactors, although providing metabolic support in addition to blood purification, demonstrated only a temporary improvement of metabolic and clinical parameters of patients with acute liver failure. Further improvements, including provision of sufficient cell mass, long-term maintenance of hepatocyte function along with improved bioreactor design to enhance mass transfer between the blood and the immobilized hepatocytes, are needed for biological liver support systems to become a definitive treatment for acute liver failure.

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