EDITORIAL

Bioartificial liver support system: a “bridge” too far?

Despite improvement in supportive medical care, acute liver failure (ALF) remains a devastating illness with over 60% mortality with conventional treatment. Orthotopic liver transplantation (OLT) is currently the only treatment known to improve chances of survival in ALF. All patients with ALF unfortunately do not receive OLT due to scarcity of donor livers and the uncertainty of its availability in the time window when it is really required. The problem of organ shortage is compounded by difficulty in predicting the outcome of liver failure. The King’s College prognostic criteria, adopted by most centers, have failed to accurately identify patients at low risk of dying. In India, OLT is still in its infancy, with the largest reported single-center experience being of only 16 cases. The cost of liver transplant appears to be out of the reach of a majority of our patients. Moreover, lack of awareness amongst the public makes cadaver donors rare, and ignorance amongst physicians makes them poorly managed prior to donation, as is suggested by a high incidence of primary non-function.

Therefore, not surprisingly, the focus now is on development of alternative strategies. Surgeons have already come up with auxiliary liver transplantation and the use of live-related transplants to overcome some of the limitations of OLT in the setting of ALF. The concept of providing liver support as a “bridge” till the time a donor liver becomes available (or till the native liver regenerates) has led to several innovative ideas.

Earlier attempts to detoxify blood by using hemodialysis, hemoperfusion over charcoal and resins or immobilized enzymes, plasmapheresis and plasma exchange have not been very rewarding. The newer molecular adsorbent recirculating system (MARS) enables albumin-bound toxins to be removed by dialysis, along with other dialyzable toxins, as it uses a double-sided, albumin-impregnated polysulfone or hollow-fiber dialysis membrane or a molecular adsorbent in a close-loop dialysis circuit.

However, organ support can expect to be a success if the organ involved has a single defined function. For example, hearts are pumps, kidneys are filters, lungs are membranes; in that sort of language, what is a liver? These non-biological systems cannot provide the multitude of functions such as metabolism, synthesis, biotransformation, excretion and detoxification, that the liver normally performs and that are essential to maintain life. Liver support is likely to succeed only if it is provided by another liver or hepatocytes. Ex vivo perfusion through human liver, though technically feasible, has not been extensively explored in recent years probably for the pragmatic reason that the proven efficacy of transplantation dictates usage of available organs. The main biological approaches being investigated include isolated cell transplantation, tissue engineering of implantable constructs, transgenic xenotransplantation, and extracorporeal bioartificial liver devices (BAL).

BAL incorporates a mechanical circuit (bioreactor) that brings together the patient’s blood or plasma and “foreign” functioning hepatocytes. While clinical trials with some designs are already underway, the ideal BAL is yet to be invented. The issues that require to be addressed include the choice of cellular components (including its carriers), the bioreactor designs, the safety and the efficacy of the system. A major advantage of using hepatocytes in BAL over traditional hepatocyte transplantation and older support techniques, such as cross-circulation and extracorporeal liver perfusion, is that BAL can be constructed from semipermeable materials that provide a barrier between the hepatocytes and the host’s immune system. The limitations of bioartificial liver systems could include the material and membrane interactions that are seen with other medical devices.

The various types of hepatocytes used for BAL so far are mature human hepatocytes, cultured human fetal hepatocytes, tumor-derived cells from hepatoblastoma, immortalized cells (C3-B, HepZ, OUMS-29, NKNT-3, etc.), stem cells and xenogenic hepatocytes (porcine, rabbit, canine). Each of the cell types has its own inherent advantages and limitations. Tumor-derived cells have an obvious concern that potentially oncogenic material may find its way into the patient’s blood. Reversibly immortalized human hepatocytes as a possible “eternal fountain of liver support” have been explored in studies on rats. The ideal choice of cells would be human hepatocytes but they survive unchanged in culture only for short periods and are in short supply. This situation makes xenogenic hepatocytes an attractive choice, even though their use is restricted in some countries by regulatory authorities.

Major concerns regarding the use of xenogenic donors are the risk of transmission of zoonoses and immunogenicity. Porcine endogenous retrovirus (PERV) has been shown to infect human tissue in vitro. Transmission of PERV-like viruses is a possible though unproven risk of using porcine hepatocytes for BAL. The problem of immunogenicity of xenogenic hepatocytes can be overcome to some extent by immunosuppression by encapsulation, which may also provide protection to the hepatocytes during cryopreservation. Attempts have been made to “humanize” the xenogenic hepatocytes by immunomodulation by UV-B (280-320 nm) irradiation.

Since the liver synthesizes proteins and enzymes, which

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are species-specific, another possible concern is metabolic incompatibilities when xenogenic hepatocytes are used for human patients.25

The bioreactor design must provide for adequate nutrient perfusion and waste product removal from cellular components, apart from facilitating viability and function of hepatocytes. When plasma rather than whole blood is used for perfusion, the design must also include an integrated oxygenator.26 Commonly used designs include hollow fiber, flat plate, monolayer perfused beds or scaffolds and beds with encapsulated or suspended cells.7 The semipermeable membrane chosen should selectively block the xenogenic substances from entering into the circulation. The extracellular matrix should promote stabilization of the primary hepatocyte phenotype as the hepatocytes are anchorage-dependant and rapidly lose differentiatated functions.

At least five such systems are undergoing trials,21 HepatAssist (Circe Biomedical, Massachusetts), LIVER2000 (Algenix, Minneapolis), BLSS (Bioartificial Liver Support System; Excorp Medical, Minneapolis), and MELS (Modular Extracorporeal Liver Support; Charité Virchow Clinic-Berlin, Berlin) have been tested in series of patients with acute or acute-on-chronic liver failure.29-32 It is only the extracorporeal liver assist device (ELAD, Vitagen, California) that has been tested in a randomized and controlled study with promising results.31 However, the data are still preliminary and are confounded by the unpredictable withdrawal of patients from BAL support upon availability of donor liver for OLT. The ethical concern of withholding a potentially beneficial treatment from any group of patients is real; however, randomization is best performed between a bioartificial liver treatment group and a similar group of patients receiving only standard medical therapy.32 Although some authors recommend that controlled studies should be performed only in liver transplant centers,33 the situation in developing countries is vastly different as facilities for liver transplantation are usually not available. The ultimate test for bioartificial livers would be improvement in survival, which can only be assessed at a place where liver transplantation is not available. The promise that these devices may prove to be a useful bridge to transplantation, and in the developing world where liver transplantation is not available, as a bridge to spontaneous recovery, keeps interest alive. Despite this, surprisingly, very little work is being done in this field in our country, where it seems to be the need of the hour.

In this background, the paper in the current issue of the Journal,28 though based on a preliminary study, is welcome and is likely to attract a lot of attention. The authors have presented a series of in-vitro experiments with alginate poly-L-lysine-encapsulated goat hepatocytes, with the ultimate goal of developing an ideal BAL device. They have reconfirmed the immuno-isolation provided by encapsulation of hepatocytes and have also evaluated a hollow fiber bioreactor module using these encapsulated hepatocytes and shown its ability to detoxify ammonia to urea. While all ongoing trials on BAL using xenogenic hepatocytes have opted for porcine hepatocytes, the authors have chosen to break new ground by using goat hepatocytes. Positive aspects of this move include unlimited availability from the slaughterhouse, and if the authors' findings are confirmed, more immune-compatibility with human serum. However, it also raises several new questions: Will the use of goat hepatocytes throw up a scar of prion or ruminant virus infection similar to that of PERV? How compatible will goat hepatocyte functions be with human metabolism?25 How do goat hepatocytes compare with porcine hepatocytes during actual use?

We still have miles to go, but a step in a new direction is always full of possibilities. This may well prove to be the answer we are waiting for – the Indian goat trick for a “bridge” considered too far.

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References


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