Dialysis for acute hepatic failure

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This is a translation of version 1 published on April 28, 2000.
The latest version of this report is not available in English.

Published Aug 14, 2000
Version 1

Findings by Alert

To date, dialysis for acute hepatic failure has been tested on only a small number of patients in the world. Various dialysis methods for hepatic failure are intended to be used as a life supporting intervention while waiting for access to a liver suitable for transplantation. Without treatment, the patient would die within a few days. Currently there are three ways to perform liver dialysis. With albumin hemodiafiltration, the patient's blood is filtered through a membrane which captures proteins but releases water-soluble substances and protein-bound toxins. In the second method, the patient's blood is circulated through an animal liver located outside of the patient's body. The third method involves filtering the patient's blood through artificial columns containing liver cells from animals.

Currently, no* scientific evidence is available concerning patient benefit from dialysis in acute hepatic failure, neither in the short nor the long term. The potential risk for spreading infection via the use of cells or organs from animals has not been determined. Likewise, there is no scientific evidence regarding cost effectiveness. If this method is adopted in Sweden, the economic impact on the health services is expected to be minor since the target group for treatment is small.

The most promising method is albumin hemodiafiltration. The method is being studied in patients with chronic hepatic failure awaiting liver transplantation.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see “Grading of evidence”.

Alert is a joint effort by the Swedish Council on Technology Assessment in Health Care (SBU), the Medical Products Agency, the National Board of Health and Welfare, and the Federation of Swedish County Councils.

Technology

In acute hepatic failure, blood can be purified from certain substances by circulating the patient's blood (perfusion) through an animal liver placed in a sterile container outside of the body. This can be used as a life support measure while awaiting a suitable liver for transplantation. The first attempt was made in the 1960s, however, with poor results [1,5].

Organs from animals have been used with varying results. Initially, apes were viewed as a suitable animal donor due to their immunological similarity to humans, but ethical considerations speak strongly against using these animals. Harvesting organs from pigs has also been discussed. A basic problem is that human blood contains antibodies against pig tissue. However, science has produced transgenic pigs, ie, pigs that received a human gene in their DNA, for transplantation purposes. This creates a lower risk for hyperacute rejection following transplantation [12]. With these new research results, it may be possible to use pig livers for perfusion to patients with acute hepatic failure.

The influence on, eg, thrombocytes and peripheral blood profiles that has been observed in trials, leads, eg, to thrombocytepenia (reduced number of platelets in the blood), with a risk for coagulation problems and clots in the small vessels [3]. Furthermore, in longer-term perfusion it is necessary to maintain other liver functions, eg, production of coagulation factors. It is not known whether proteins produced in a perfused animal liver are as functional in humans as proteins from the human liver. However, the perfused animal liver is shown to have the capacity to eliminate bile salt from the bloodstream and concentrate it in excreted bile [6]. Recently, liver dialysis has received greater attention since more patients have survived after liver transplantation following liver dialysis. [4].

Another method of liver dialysis is to filter the patient's blood through isolated liver cells from animals. Several attempts to develop artificial columns with liver cells from pigs have been described. These columns are produced by culturing the cells (hepatocytes) on a glass or plastic surface [9]. One study showed an effect on reduced cerebral edema and some improvement in the patients liver test [8]. A problem with dialysis involving liver cells is to obtain a sufficiently large volume of cells so that the liver cell function can be maintained for several days, up to 1 week.

The most promising method currently is albumin hemodiafiltration based on MARS (Molecular Adsorbent Recycling System) [13]. This system uses a membrane similar to that used in hemodialysis for kidney failure, and which is nearly impermeable for proteins but allows water-soluble substances and protein-bound toxins to pass through. The method is being tested in trials on patients with acute and chronic hepatic failure who are awaiting liver transplantation.

Target group

Patients affected by acute hepatic failure due to liver necrosis (cell death in liver cells) generally have a short survival time. The cause behind rapid onset may be a viral infection or side effects from drugs. Liver transplantation is currently the only treatment available. A severely limitation is the number of the available organs. The number of liver transplantations in Sweden is currently 80 to 90 per year, ie, 9 to 10 transplantations per million inhabitants. The need can be expected to increase to 20 transplantations per million inhabitants, ie, approximately 150 or 160 per year. Sweden has a relatively low transplantation rate in relation to other European countries and the United States. One reason is the lower number of liver cirrhosis cases caused by hepatitis C or excessive use of alcohol. These disease groups will probably increase in size.

In acute hepatic failure, the course is often rapid. Despite a well-developed collaboration within the Nordic countries, it is difficult to acquire organs that meet the needs of the individual patient. The patients who are candidates for liver dialysis are those with rapid onset of hepatic failure where, due to time factors, it is necessary to find a liver for transplantation within a few days. With dialysis, the patient can survive somewhat longer. This increases the chances of finding a suitable liver for transplantation. In Sweden, the method could be used by approximately 15 patients per year.

Relation to other technology

In patients with acute liver disease, treatment can be provided via different types of transplantations, eg, both a whole liver from a deceased human and part of a liver from a living donor. It is also possible for two patients to share a donated liver. Currently, the latter method is uncommon since in only a few cases has it been possible for a liver to function in two adults. Within the next year, this method will enter clinical practice in Sweden.

Some attempts have been made to transplant animal livers to humans. A few cases are described in the literature. The first case of transplantation of a chimpanzee liver to a human was done as early as the 1960s [2]. Baboon livers have also been transplanted to humans, for the first time in 1993 [11]. Results from a trial were published in 1995 describing transplantation of a baboon liver to a human with B hepatitis and HIV infection. The results of these trials, however, showed that patients survived only a short time. In recent trials, pig livers have been transplanted to a patient with acute hepatic failure and a rapid disease course. Even in this case, the patient survived only a short time [7].

Recently, it has been reported that high volume plasmapheresis has been used for acute hepatic failure. The method is being tested in a controlled trial involving hospitals in Copenhagen, Helsinki, and London.

An attempt has also been made to remove a liver in a patient with total hepatic failure (hepatic necrosis) to reduce leakage of toxic substances (toxic metabolites) into the bloodstream. Liver transplantation must, however, take place within 2 to 3 days.

Risks and side effects

Several studies are underway to survey the risks of transmitting infection from animals to humans, which may be the case in two of the dialysis methods described. In particular, the risks are related to endogenic retrovirus. It has been shown that an endogenic retrovirus from pigs can infect the human cells in tissue samples, but researchers have yet to find any signs of endogenic pig virus in patients who have been exposed to living pig tissue [10]. We cannot yet exclude the risk that infection could be transmitted between humans and initiate an epidemic.

Patient benefits

No scientific studies are available to show the patient benefits of liver dialysis.

Costs and cost-effectiveness

No information is available on costs and cost effectiveness.

Structure and organization of health services

The use of pig livers as a life support measure in acute hepatic failure means that resources must be obtained for raising and purchasing transgenic pigs. It is not realistic to create such an organization before it is possible to transplant kidneys from animals, where potentially large humanitarian and economic benefits can be achieved through xenotransplantation. However, it is possible to foresee some increased need for inpatient beds if liver dialysis using pig livers becomes reality. The need for intensive care will increase for the patients in question. The total economic impact on health care is expected to be minor since the target group is small.

Ethical aspects

Treatment of acute liver failure is life saving, which means that patients who are candidates are presumably prepared to accept a high risk and substantial side effects from treatment. The most important ethical problem concerns the methods that involve animal organs. The ethical aspects related to perfusion of animal livers do not differ in principle from those that apply to xenotransplantation

generally (see Alert document Xenotransplantation, examples involving kidney transplantation). As mentioned earlier, apes are not considered as donors since humans find it easy to identify with a not-so-distant species. The same problem is not as likely to appear with pigs because of the large volume of pigs that are raised and butchered for food each year. Nevertheless, unanswered questions remain concerning the risks of using organs and cells from transgenic animals. These and other questions are addressed in a paper from the xenotransplantation committee but should be debated further [14]. Similar studies have already been conducted in other countries, eg, the United States and Great Britain, and are also underway in the Council of Europe, EU, OECD, and WHO.

Diffusion in Sweden

To date, pig livers have not been used in perfusions conducted in Sweden. However, two patients with kidney failure are attached to blood circulation in pigs at Sahlgrenska University Hospital in Göteborg. These trials have allowed researchers to make important immunologic observations [3].

Early in year 2000, albumin hemodiafiltration based on the MARS method was used for the first time in Sweden (Göteborg) on a patient with a very rapid course of acute hepatic failure. The patient could be discharged from the hospital without requiring liver transplantation.

Current evaluation research

Randomized controlled trials of the albumin hemodiafiltration method are currently under way. The results from these trials are expected in 1 to 2 years at the earliest.

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