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Liver Replacement for Pediatric Patients

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ABSTRACT. Between March 1963 and January 1978, 74 patients 18 years of age or younger have had liver replacements at the University of Colorado Medical Center, Denver. The most common cause of native liver failure was biliary atresia (48/74, 65%); the second most common cause was chronic aggressive hepatitis (12/74, 16%). Twenty-nine patients (39%) lived for at least one year, and 16 are still alive one to nine years after transplantation. Technical surgical problems, rejection, and infection were the main causes of death. Improved immunosuppression is needed; nevertheless, the quality of life in the long-term survivors has encouraged continuation of this difficult work. *Pediatrics* 63:825–829, 1979, *pediatric, liver, transplantation, surgery.*

Two medical groups have accumulated a preponderance of the world experience in orthotopic liver transplantation (liver replacement), our own, at the University of Colorado Medical Center,[1,2] and the English team headed by Calne and Williams that works at Cambridge University and Kings College in London.[3] The British group has treated very few children because they rarely have had pediatric donors. In addition, they have been fearful of the growth limitation and cosmetic deformity inherent in long-term steroid therapy. Consequently, most of the world experience with pediatric liver transplantation has been from the University of Colorado series. In this report, the results will be given for 74 pediatric recipients (18 years old or younger) who had liver replacement between March 1963 and January 1978. Thus, a minimum potential one-year follow-up is available in every case.

METHODS

Case Material and Indications

The reasons for proceeding are given in Table I. All 74 patients had chronic liver disease. Biliary atresia was the most common diagnosis, accounting for almost twice as many cases as all other diseases combined (Table I). Chronic aggressive hepatitis was the next most common diagnosis. Eight patients had inborn errors of metabolism, including α_1-antitrypsin deficiency, Wilson's disease, tyrosinemia, and type IV glycogen storage disease. It has been established that the enzyme specificity and protein synthetic phenotypes of liver homografts remain permanently those of the donor.[1,3] Thus, any liver-based inborn error of metabolism is potentially curable with liver transplantation.

The appropriate time to recommend liver transplantation required judgment. The predictable and tragic course of victims of biliary atresia usually made it easy to proceed relatively early. However, this situation has been made more ambiguous with the increasing number of patients with successful or partly successful portoenterostomy. In such cases, it has been a technical advantage to have the potential recipient grow

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autopsy. The most common technique then used was cholecystoduodenostomy after ligation of the common duct. Even with seemingly satisfactory biliary drainage, the patients had an extraordinary incidence of bacteremia, which was probably caused by repeated contamination through the anastomosis between the gallbladder and duodenum. An important component of the reforms instituted several years ago was constant postoperative suspicion of the biliary reconstruction. Postoperative jaundice, fever, or abdominal pain has become a signal for cholangiography (T-tube or transhepatic), reexploration, or often both.

We abandoned cholecystoduodenostomy in 1974 and now do duct-to-duct anastomoses over a T-tube if this is feasible, which it never is if the diagnosis is biliary atresia. Reasonable options are cholecystojejunostomy and choledochojejunostomy anastomosing the gallbladder or common duct into an 18-in Roux limb. With cholecystojejunostomy, about one third of recipients develop obstruction of the cystic duct, but cholecystectomy and conversion to choledochoenterostomy has proved to be easy. It has seemed safer to secondarily anastomose such a dilated common duct to bowel than to attempt this initially with the tiny common duct of a normal infant liver. Formation of a Roux limb is hazardous in heavily immunosuppressed recipients. Eight patients in our combined adult-pediatric series of 141 have died from later perforations at the enteroenterostomy.[2] Four were infants or children.

Anomalies have been common in children with biliary atresia. The most serious was a combination of a preduodenal portal vein, a hepatic artery originating from the superior mesenteric artery, absent inferior vena cava, and malrotation of the gut.[1] We have seen this four times. We considered such cases to be untreatable until a success was obtained in a child who is now four years and four months postoperative. Other less ominous donor and recipient anomalies and their technical implications are described elsewhere.[1]

In many patients, splenectomy is advisable because of hypersplenism or massive splenomegaly. Failure to remove the spleen may lead to an inability to give the important drug azathioprine in the postoperative period because of persistent leukopenia.[1] However, splenectomy in infants is known to predispose pneumococcal and other kinds of bacteremia.

Postoperative Management

There are two fundamental guidelines. The first is to prevent or control rejection by combination drug therapy, which is begun on the day of operation and continued indefinitely. The second is to accurately diagnose postoperative hepatic dysfunction. Numerous technical surgical pitfalls were mentioned earlier, of which biliary tract problems were the most important and treatable. Besides ruling out biliary complications with cholangiography, frequent liver biopsies can strengthen the diagnosis of rejection, or they can point out other possibilities such as ischemic or drug injury and hepatitis. In short, the patient with postoperative hepatic malfunction should be approached unprejudicially as a diagnostic problem rather than assuming that rejection is the diagnosis.

If other factors are ruled out, the patient's survival (short of retransplantation) depends upon control of rejection. As much azathioprine is given as is possible without causing bone marrow depression and leukopenia. The dose-maneuverable agent to meet crises is thus prednisone. Most patients are also given a two- or three-week course of intravenous antilymphocyte globulin (ALG).[1,2] Although these double- or triple-agent regimens usually can prevent or reverse rejection, the price of prolonged high-dose steroid therapy is all too frequently an inexorable decline of the patient's health, capped in the end by a fatal infection.[2]

RESULTS

The outcome in 74 pediatric patients treated one to almost 16 years ago is given in Table I. Twenty-nine (39%) of the 74 recipients lived for at least one year after operation and 16 (22%) still survive, all but four with follow-ups of more than two years. Ten of the 16 long-term survivors have follow-ups of at least four years, with a maximum of nine years. The 13 late deaths occurred from one to six years postoperatively (times of death are given in a footnote to Table I). It has been documented that many of the patients who died after one year were already in trouble at the 12-month convalescence mark,[2] and thus might have been saved by earlier consideration of retransplantation. The commonest cause of death after one year was chronic rejection.[2]

Although the results have slowly improved over the years, the overall percentage of one-year survival of pediatric recipients from 1963 to the summer of 1976 was only 35%. By this time the technical and management improvements described earlier had been completed. From then until December 1977, the one-year survival rate in pediatric recipients was 62%.

Pooling the total pediatric experience from 1963 to 1977, we found that the results in patients

less steroids, we have in the last year used thoracic duct drainage as a lymphoid-depleting immunosuppressive adjunct, usually starting on the day of transplantation, and continuing for one to three months.[2] It is too early to judge the value of this procedure or to preclude the possibility that its greatest effectiveness will be for pretreatment of transplantation. What is clear is that the next major improvement in survival will depend on some kind of improvement on the double- and triple-drug programs that have been so dangerous in the past.

With end-stage liver disease, nothing short of new hepatic tissue will permit survival. Thus, the only alternative to liver replacement is auxiliary liver transplantation involving the placement of an extra liver in some ectopic site, such as the right paravertebral gutter, pelvis, or splenic fossa. Fortner et al[5] recently compiled a total of 43 clinical trials contributed from many centers, including four from the University of Colorado and seven from their own institution. There had been only one unqualified success, that being the 5½-year postoperative survival of a child with biliary atresia. In this case, the auxiliary liver was still functioning well in September 1978. All of the other patients died within a few weeks or months after the operation. The division between pediatric and adult recipients is not clear in these collected cases.

Many of the failures after auxiliary liver transplantation have resulted from the need for awkward or tenuous revascularization procedures and from the placement of an extra organ in an abdomen that may already be overcrowded. For ideal revascularization, blood returning from the splanchnic viscera should pass preferentially through the homograft,[6] a condition that may be technically difficult to achieve.

In the future, the most important use of auxiliary liver transplantation may be to tide patients over a bout of fulminant hepatic failure, allowing time for the acutely damaged native liver to regenerate. The concept has been validated in controlled animal experiments and even in partially successful clinical trials at our institution, but long-term survival of such patients has not yet been accomplished.

IMPLICATIONS

Each year children die from liver failure due to uncorrectable biliary atresia, chronic aggressive hepatitis, or inborn errors of metabolism, in spite of good medical management. For these children the only opportunity for survival is liver transplantation. At present, liver replacement is more successful than auxiliary liver transplantation. In children with chronic survival after liver replacement, the quality of life and the degree of rehabilitation suggest that this difficult treatment will be increasingly used, particularly if survival continues to improve.

So far, liver transplants have been performed only in clinical research centers, thereby shielding parents from hospitalization and physician expenses. The grant costs in this research setting have been comparable to those for renal recipients in the developmental phases of kidney transplantation some years ago, allowing for an inflation factor.

SUMMARY

Orthotopic liver transplantation was performed on 74 pediatric patients between March 1963 and January 1978. The most common indications for operation were biliary atresia (48 examples) and chronic aggressive hepatitis (12 examples). Twenty-nine recipients (39%) lived for at least one year and 16 are alive now with follow-ups of one to nine years. The results improved slowly for the first 13 years, and more rapidly since 1976, when the one-year survival has been 62%. Technical surgical complications, systemic side effects of immunosuppression, and incompletely controlled rejection accounted for most of the early, as well as the late deaths.

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