L34

From: LIVER, NUTRITION, AND BILE ACIDS
Edited by G. Galli and E. Bosisio
(Plenum Publishing Corporation, 1985)

Gut for CV

LIVER TRANSPLANTATION: AFTER 20 YEARS OF EXPERIENCE THE PROCEDURE HAS COME OF AGE

David H. Van Thiel[1], Robert R. Schade[1], and Thomas E. Starzl[2]

Departments of Medicine[1] and Surgery[2], University of Pittsburgh School of Medicine, Pittsburgh,PA 15261

Abstract

The status of liver transplantation is reviewed with emphasis upon the current survival statistics and the quality of life to be expected in survivors. Present day indications and contra-indications for the procedure are reviewed.The operative procedure and the peri-operative problems which are to be expected following a successful transplant are discussed.

The first orthotopic liver transplant performed in a human was accomplished in March 1963[1]. Since that time, over 500 such procedures have been performed worldwide[2]. The vast majority, however, have been performed by a single surgical team headed by Thomas E. Starzl at the University of Colorado and since 1981 at the University of Pittsburgh. Moreover,since relocating at the University of Pittsburgh, the performance rate of the procedure has accelerated such that Dr. Starzl's entire experience prior to 1981 (extending over an 18-year period) has been duplicated in less than 3 years[2]. More important than the frequency of performance, both to the patient and referring physician however,is the recent dramatic improvement in survival figures achieved with liver transplantation[3]. Prior to 1980, the best survival figures ranged from 20-30% at 1 year. Since 1980, survival has approached 80% for all comers and averages between 80-90% for pediatric recipients and 50-70% for adult recipients. The ranges cited for the survival figures depend primarily upon the presence or absence of prior

surgery,co-existing hepatic or biliary sepsis,and disease severity as determined by the performance status of the patient at the time of the transplant surgery [2,4]. Specifically, those patients who are ICU bound prior to transplantation have the poorest prognosis with a 42% operating survival.In contrast,are patients who are ill with advanced to near fatal chronic liver disease but who are not hospital-bound (those who are admitted solely for the surgical procedure rather than necessary medical care and management of their hepatic disease prior to surgery) have a survival rate of 68% at 1 year. Those who do best, however, are those who are hospital-bound but not ICU-bound; they have a 1-year survival of 84%.

Equally important as survival, once it has been established that such heroic procedures can be performed with a reasonable chance of survival, is the quality of life which is to be expected after liver transplantation [5,6]. Pediatric recipients of a liver transplant would appear to be the most successfully rehabilitated patients.Thus,87.5% of pediatric survivors are fully rehabilitated and free of medical problems exclusive of those associated with routine postoperative follow-up care aimed at the recognition and control of the rejection process. Normal growth and physical as well as psychosocial development have occurred in most. Those who had demonstrated either growth or psychological developmental delays due to their liver disease prior to transplantation usually demonstrate a catch-up phenomenon following transplantation.

The quality of life data for adult liver transplant survivors are equally good with 85% of surviving adults returning to their pre-illness occupation on a full-time or regular basis following surgery.In addition,several younger adult recipients have returned to school, others have married,and two women have had three normal pregnancies between them since having been transplanted. Moreover, when careful evaluations of psychosocial and neuropsychiatric parameters have been performed pre- and post-transplantation, consistent improvement has been noted across a wide number of such variables in the adults so studied.

Now that this remarkable procedure can be shown to be accomplishable, and the quality of life experienced by survivors following the procedure has been shown to be considerably better than acceptable, the next question that arises is: who are the candidates

for the procedure? Regardless of the nature of the primary liver disease mandating the procedure, several generalizations can be made concerning this issue[2,6]. These are first, that acceptable candidates should be between 1 year and 50 years of age, older individuals are less able to survive the rigors of the procedure and the various cardiopulmonary challenges that accompany the procedure. In contrast, infants less than 1 year of age frequently provide a surgical challenge that is unacceptably great and as a result immmediate surgical complications are greatest in this group. Secondly, regardless of the age of the subject, acceptable candidates should be free of infection. Thus, to guarantee success, all pulmonary,urinary tract and hepatobiliary bacterial and fungal infections must be eradicated or have resolved prior to the performance of the procedure. Similarly, all viral illnesses should be eradicated prior to transplantation. In the absence of the ability to eradicate such infections, as occurs with patients with sclerosing cholangitis, secondary biliary cirrhosis, and hepatitis B antigenemia, 1 year survival rates of greater than 30-40% are not to be expected[7].

Other conditions which mitigate against successful liver transplantation in patients with chronic liver disease are active drug or alcohol abuse, uncontrolled psychiatric disorder, primary extrahepatic or metastatic hepatobiliary malignancy, advanced mental retardation, portal vein thrombosis, and disabling cardiopulmonary or renal failure[6].These latter two situations,however,particularly the last, are only relative contraindications as multiple organ transplants are becoming a reasonable therapeutic option and may in the future be applied more broadly as success with individual organ transplantation continues to improve.

Acute fulminant hepatic failure has not been an important condition which has been treated to date with liver transplantation[2,6,7]. This apparently paradoxical situation obtains because such patients rapidly deteriorate and consideration of transplantation as a therapeutic option usually is initiated only after advanced coma has occurred. In such case, brain edema leading to herniation usually occurs before an appropriate donor can be identified and transplantation can be accomplished. Moreover, the likelihood of recurrent infection in cases of fulminant viral hepatitis would seem to be great and therefore not warrant the procedure.

The conditions for which hepatic transplantation has been applied differ in pediatric and adult cases and are shown in Tables 1 and 2. 50% of the pediatric cases have been transplanted for biliary atresia.The majority of the other pediatric recipients have been transplanted for alpha 1 antitrypsin deficiency or chronic liver disease of unknown ethiology. In contrast, the leading conditions for which hepatic transplantation has been applied in adult recipients are postnecrotic cirrhosis, primary biliary cirrhosis and primary hepatic malignancy.

Table 1. INDICATIONS FOR TRANSPLANTATION IN PEDIATRIC PATIENTS (< 18 YEARS)

Liver Pathology	**%**
Biliary atresia *	50%
Alpha-1-antitrypsin deficiency	15%
Chronic aggressive hepatitis	8%
Byler's disease	8%
Secondary biliary cirrhosis	2%
Budd-Chiari syndrome	2%
Neonatal hepatitis	2%
Subacute Wilson's disease	2%
Tyrosinemia	2%
Type 1 glycogen storage disease	2%
Sea-blue histiocyte syndrome	2%
Cellular inflammatory pseudotumor	2%

* Two had Alagille's syndrome

Table 2. INDICATIONS FOR TRANSPLANTATION IN ADULT PATIENTS (> 19 YEARS)

Liver Pathology	**%**
Postnecrotic cirrhosis	30%
Primary biliary cirrhosis	20%
Primary liver malignancy	18%
Sclerosing cholangitis	12%
Secondary biliary cirrhosis	7%
Budd-Chiari syndrome	5%
Alpha-1-antitrypsin deficiency	3%
Alcoholic cirrhosis	3%
Adenomatosis	1%

After the three main disease conditions described above, a wide variety of metabolic liver diseases make up the majority of the other conditions for which liver transplantation has been performed in pediatric patients[8]. In contrast, acquired liver diseases make up the majority of the other conditions for which liver transplantation has been applied in adult cases[2,6,7].

Factors that make surgery more difficult and as a consequence, extract a toll in terms of early survival are previous surgical procedures, particularly those in the right upper quadrant, such as prior attempts at biliary tract, reconstruction and portal caval shunting[7,9]. Such procedures make identification and dissection of the hilar structures more difficult and may have altered the anatomy further complicating the surgical dissection. Moreover, in attempts to take down a pre-existing portal caval shunt, the portal vein can be damaged, at times back to the confluence of the inferior mesenteric and splenic veins making the reestablishment of portal continuity difficult, if not impossible following graft insertion even with the use of an iliac vein graft.

Finally, portal hypertension, a common accompaniment of advanced chronic liver disease, results in the formation of fragile, but at times, massive venous collaterals within adhesions which have formed from prior surgical procedures. Such adhesions can lead to major problems in terms of obtaining hemostasis throughout the procedure from the point of host organ removal through attempts at obtaining hemostasis prior to closure following engraftment and completion of all of the vascular and biliary anastomoses necessitated as a result of the transplant procedure.

Each phase is associated with its own particular difficulties and technical procedures have been developed for each. The most recent surgical advances would seem to have been made during phase 3, when the patient is ahepatic and consists of the creation of femoral and portal venous bypasses to either the internal jugular or more commonly the axillary veins using a heparin-free system which has eliminated the need for systemic heparinization. This technical advance has markedly reduced the rate and severity of postoperative bleeding while allowing that fraction of the cardiac output delivered to the lower body below the diaphram during the procedure to be returned to the heart during the performance of the ahepatic phase of the operation. As a result, the organ engraftment can be accomplished in a careful determined way without the time restraints necessitated by systemic hypo-

tension due to a declining central venous return and resultant reduction in cardiac output. Moreover, the immediate postoperative period also has been made more easy as a result of this advance. Specifically, as the volume of blood and colloid administered during the ahepatic phase of the procedure in an effort to maintain the cardiac output, has been reduced by this advance, the postengraftment volume overload experienced in terms of pulmonary edema has not been seen or has been reduced considerably. As a result, postoperative Intensive Care Unit time, problems with oxygenization and respiration usage have all been reduced.

Postoperatively, three different phases of potential graft failure can be identifiable. They are: 1) early (day 1 to 5) technical failures due to a vascular thrombosis or biliary anastomatic leak; 2) sepsis which occurs between day 3 through day 14; and 3) rejection which is a late cause of graft failure usually seen during the third and fourth weeks postoperatively. The presenting signs of each of these three postoperative problems are remarkably similar and include development of a large firm and tender liver, increasing jaundice and fever, with or without an accompanying leucocytosis. Early presentation of any of these signs necessitates evaluation of the grafts vascular and biliary anastomosis. After an initial period of little or no difficulty, a later change in the transplant patient's condition mandates a search for infection in or around the liver and biliary structures and finally consideration of rejection. Sonography and cholangiography should be attempted early when the patient's postoperative progress either halts or deteriorates.Early intervention directed at resolving the various differential possibilities that might exist in a given case are to be pursued actively[7,9]. Such procedures not only establish a specific diagnosis but also guide attempts at subsequent therapy such as surgical repair or drainage, antibiotic administration, or enhanced immunosuppression.

The infections that most plague patients postoperatively are those due to gram negative organisms and fungi that presumably leak into the surgical wound from the gut during the surgical procedure[10]. Acute CMV viral infection or its reactivation appear to occur universally in such patients also and can be demonstrated by buffy coat isolation or identification of the characteristic changes present in urinary sediment and liver tissue obtained by biopsy.

Infection with the herpes family of viruses also occurs commonly postoperatively and is usually manifested as either nasal labial genital or zoster-like lesions[11]. Rarely, herpetic hepatitis occurs and can be identified by isolation of the virus from hepatic tissue obtained at biopsy or by using specific immunohistologic techniques.Candida infection of the esophagus, stomach, and wound are seen less often. Finally, aspergillosis and mucor infections also occur and may necessitate treatment with Amphotericin.

As with all life extending advances in medicine ad surgery, new problems develop in patients so treated which are unique to either the procedure or the medical care necessitated by it. Thus, problems of chronic low grade rejection and the late development of recurrent hepatic failure in the transplanted organ and the need for a second transplant procedure should be kept in mind. To date, a single patient has been retransplanted late (after 5 years of survivorship with their original grafted organ). Similarly, problems occurring as a consequence of the necessary lifelong need for immunosuppression should be expected. These include those dependent upon cyclosporine administration such as nephrotoxicity, hepatotoxicity, tremor, hypertension, seizures, gingival hypertrophy, increased body hair and the various other problems shown in Table 3.

Table 3. RECOGNIZED CYCLOSPORINE TOXICITY

1. excessive immunosuppression
2. neuropathy
3. hypertension
4. hirsutism
5. gingival hypertrophy
6. tremor
7. cholestasis/hepatotoxicity
8. lymphoma (?pseudolymphoma)
9. pseudotumor cerebri
10. drug-drug interactions

The specific mechanisms responsible for the cyclosporine-associated postoperative problems are only slowly being identified. Thus the hypertension can be shown to be due, at least in part, to an enhanced activation of the renin angiotension aldosterone system as well as an apparent angiotension independent enhancement of systemic vascular resistance[12]. Similarly, the lymphomas that have been reported to occur with cyclosporine use would appear to be new or reactivated Epstein Barr virus infections that are associated with cyclosporine use and appear to be dose-dependent[13]. Thus their prevalence is greater in heart and renal transplantation situations which require greater immunosuppression than it is in liver transplant recipients. Moreover, on at least two occasions, the tumor has resolved when the cyclosporine dose has been reduced dramatically or replaced with Azathiaprine. It is clear that with advances in virology, hypertension, and tumor research which are to be expected in the future, these unique problems associated with cyclosporine use will become less and less of a problem for the transplant surgeon, his medical colleagues and their patients. Moreover, with steady refinements in surgical procedures, donor organ preservation and pretransplant assessment, immunotherapy and application of the procedure per se, success with orthotopic liver transplantation should improve even more. Even in the absence of such expected refinements it is clear that hepatic transplantation is here to stay, and that it has indeed, come of age.

REFERENCES

1. T.E. Starzl, T.L. Marchioro, K.N. Von Kaulla et al., Homotransplantation of the liver in humans, Surg.Gynecol.Obstet., 117:659-679 (1963).
2. T.E. Starzl, S. Iwatsuki, D.H. Van Thiel, et al., Evaluation of liver transplantation, Hepatology, 2:614-636 (1982).
3. T.E. Starzl, G.B.G. Klintmalm; R. Weil III, et al., Liver transplantation with the use of cyclosporin A and prednisone, N. Eng. J. Med., 305:266-269 (1981).
4. T.E. Starzl, S. Iwatsuki, B.W. Shaw, Jr. et al., Consensus conference report on liver transplantation,Hepatology,in press.
5. D.H. Van Thiel, R.R. Schade, T.E. Starzl, After 20 years, liver transplantation comes of age, Ann. Int. Med., in press.

6. D.H. Van Thiel, R.R. Schade, J.S. Gavaler et al., Medical aspects of liver transplantation, Hepatology, in press.
7. S. Iwatsuki, B.W. Shaw Jr, T.E. Starzl, Current status of hepatic transplantation, Semin. Liver Dis., 3:173-180 (1983).
8. B.J. Zitelli, J.J. Malatack, J.C. Gartner, B.W. Shaw, S. Iwatsuki, T.E. Starzl, Orthotopic liver transplantation in children with hepatic based metabolic disease, Transplant. Proc., in press.
9. R.R. Schade, B.W. Shaw Jr, Liver transplantations:1984. Viewpoints in Digestive Diseases, in press.
10. M. Ho, C.P. Wajszczak, A. Hardy, J.S. Drummer, T.E. Starzl, T.R. Hakala, H.T. Bahnson, Infections in kidney, heart, and liver transplant recipients on cyclosporine, Transplant. Proc., in press.
11. D.H. Van Thiel, R.R. Schade, T.E. Starzl, et al., Liver transplantation in adults, Hepatology, 2:637-640 (1982).
12. M.E. Thompson, E.H. Ginchereou, R.A. Reeves, J.M. Itzkoff, A.P. Shapiro, R. McDonald Jr, B.P. Griffith, H.T. Bahnson, Hypertension following cardiac transplantation. First International Congress on Cyclosporine, Houston TX, May 16-19, 1983 (abstract).
13. Unpublished data in preparation.