Sounding Board

TRANSPLANTATION OF LIVER GRAFTS FROM LIVING DONORS INTO ADULTS — TOO MUCH, TOO SOON

SINCE 1995, many liver-transplantation programs in the United States,[1,2] Europe,[3] and Asia[4,5] have performed adult-to-adult transplantation of liver grafts from living donors. Since 1997, more than 30 U.S. transplantation programs have performed more than 400 of these procedures. Although six of these programs have performed only 1 procedure each, one program has performed more than 100. Twenty-three centers are planning to start such programs.[6,7] Liver transplantation in adults with the use of grafts from living donors may initially have been regarded as a technical extension of the procedure for transplanting liver grafts from living donors into children. However, we are unaware of any formal analyses of whether it is ethical to perform the operation, even if donors and recipients provide informed consent.

In this article, we examine the ethical aspects of liver transplantation in adults with the use of grafts from living donors by comparing the procedure with liver transplants in children with the use of grafts from living donors and by considering a number of potential concerns.[8,9] Although we acknowledge the benefits of the procedure for selected adults when it is performed by competent surgical teams, we believe that it has been disseminated too quickly, that more programs than are required currently perform the surgery or plan to start doing so in the near future, and that inadequate data are being collected on outcomes for both recipients and donors. As a result, regulatory oversight may be required to protect the interests of all parties.

TRANSPLANTATION OF GRAFTS FROM LIVING DONORS INTO CHILDREN

During the 1980s, the leading U.S. liver-transplantation centers reported mortality rates of 20 to 30 percent among children on their waiting lists for transplants.[10] The high rates were due primarily to the lack of grafts of an appropriate size for children. By the late 1980s, innovative surgical techniques, including the use of reduced-size and split-liver cadaveric grafts, had reduced the number of deaths among infants and children on waiting lists but had not eliminated them.[10]

A successful transplantation of a liver from a living donor was performed in Australia in 1989 by Strong and colleagues.[11] Subsequently, the liver-transplantation team at our institution, which had had success with innovative liver surgery, designed a formal clinical trial that was approved by the institutional review board. Before the trial began, the clinical and ethical aspects of the new operation were analyzed.[12]

Only after the favorable results of this clinical trial had been published[13] did several leading liver-transplantation programs in the United States,[14,15] Europe,[16] and Asia[17,18] begin transplanting liver grafts from living donors into carefully selected children. Substantial technical modifications[19-21] have improved the procedure, which is now usually effective and safe for both the recipient[21] and the donor.[22,23] More than 1500 such surgeries have been performed throughout the world. Only two donors have died,[24] although it is possible that there have been unreported deaths among donors.

The basic operation (a left lateral segmentectomy) has predictable, demonstrated risks and benefits. Complications have been reported in less than 10 percent of donors; most of these complications have involved the biliary system.[23] The rate of graft survival at one year has increased from 74 percent to 94 percent, and mortality before transplantation has decreased significantly.[21] Liver transplantation in children with the use of grafts from living donors has been performed only by the most experienced liver-surgery programs in the world.

TRANSPLANTATION OF GRAFTS FROM LIVING DONORS INTO ADULTS

The first liver transplantation in an adult with the use of a graft from a living donor was performed at the University of Chicago in 1991 as an emergency procedure.[25] In recent years, we have obtained approval from our institutional review board for a prospective case study that extends our pediatric program of transplantation with the use of grafts from living donors (a procedure we have performed approximately 150 times) to include adult donors and recipients. As of April 2001, we have evaluated additional donors and recipients but have not transplanted another liver graft from a living donor into an adult. Several centers have reported their experience with this operation in adults.[1-3,5,19,26,27] Many key aspects of liver transplantation in adults with the use of grafts from living donors remain unclear; the same is not true of the procedure performed in children. First, there is a lack of agreement on the technique that is most effective and that provides the greatest safety for donor and recipient. Second, indications for the surgery have not been clearly defined or standardized. Third, the procedure has been developed with variable standards for approval by institutional review boards. The rapid proliferation of programs that perform transplantation in adults with the use of grafts from living donors (most of those in the United States have performed fewer than 10 procedures each) is alarming for an innovative, nonstandardized operation that places two people, one of whom is healthy, at risk.

IS THERE A NEED FOR THE PROCEDURE IN ADULTS?

Subjecting a healthy donor to the risks of surgery can be justified only in clinical circumstances in which the potential recipient has a compelling need for a liver transplant from a living donor. According to current data obtained from the United Network for Organ Sharing, in 2000, a total of 10,887 patients in the United States were placed on a waiting list for a liver transplantation, 4934 liver transplantations were performed, and 853 of the patients placed on a waiting list that year died.[28] From 1998 to 1999, the number of liver transplantations performed in children with the use of grafts from living donors increased from 61 to 88, and the number of such procedures in adults increased from 25 to 131[28]; the total number of grafts from living donors increased further in 2000, to 355. Use of the procedure in adults has been justified by the disparity between the number of patients waiting for cadaveric organs and the number of organs that become available. Because of the disparity, the waiting period for a transplant can be long, and some patients die before an organ becomes available.

Whereas among children, use of liver transplants from living donors was justified by the significant effect of a prolonged waiting period,[10] waiting time alone does not appear to justify use of transplants from living donors in adults. Medical urgency and the severity of the underlying liver disease are better predictors of pretransplantation mortality than is the duration of the waiting period.[29] In fact, under the recently proposed Model for End-Stage Liver Disease system, organs would be allocated on the basis of the severity of a patient's liver disease, rather than on the basis of the time a patient has been on the waiting list.[30] Nonetheless, specific groups of adults may benefit from the availability of grafts from living donors, including patients with type A or O blood[31] and those with primary biliary cirrhosis,[32] small hepatocellular cancer,[33] or fulminant hepatic failure.[34]

RISKS AND BENEFITS FOR DONORS AND RECIPIENTS

Risks for Donors

The risks of liver donation are difficult to quantify. Procedures for evaluating donors are not uniform among transplantation programs. Some programs require a mesenteric angiogram[1-3,27] and liver biopsy,[1] whereas others do not.[5] There is also a lack of uniformity in the surgical technique used; some programs perform a right lobectomy,[1,5] removing approximately 60 percent of the hepatic mass, and others an extended right hepatectomy,[27] removing approximately 70 percent of the hepatic mass, including the middle hepatic vein. Different surgical teams perform each of these operations differently. The lack of standardization in the evaluation of donors and in the operative procedure, as well as variations in the experience and skill of surgical groups, makes it extremely difficult to assess the risks of complications and death to donors.

Morbidity attributable to surgical resection in donors of grafts for adult recipients has been reported to be as high as 50 percent, with complications including wound infection, injury to the nerves of the brachial plexus, and portal-vein thrombosis.[35] Furthermore, unlike a left lateral segmentectomy, a right lobectomy often results in postoperative hepatic insufficiency, although it has been reported to be reversible.[5] The rate and severity of complications are distinctly higher among donors of grafts for adults[35] than among donors of grafts for children.[23]

The most serious potential consequence of a right lobectomy or an extended right hepatectomy is death due to an intraoperative complication or postoperative liver failure. Although a right lobectomy performed in a healthy donor should carry a low risk of death, the mortality rate has not been clearly established. On the basis of discussions at professional meetings, as compared with reports in the literature, we are concerned that some centers may not be reporting deaths in a timely manner. In 1999, Strong stated that six persons had died as a result of liver donation[8] but did not specify whether the operations were performed to obtain grafts for children or adults.[36] We believe complications and deaths related to an innovative procedure — especially one involving living, healthy donors — should be reported in detail in a timely fashion in peer-reviewed journals and ideally to a registry.[36]

Benefits for Donors

For a donor, the benefit of donation is primarily psychological.[12] The outcome for the recipient notwithstanding, the donor usually has an elevated sense of self-esteem. A family member, spouse, or close friend may be strongly motivated to donate part of an organ, and such donors appear to benefit from knowing that they have done all they can to help, even if the recipient dies.

Risks for Recipients

The risks for the recipient can be divided into the risks associated with liver transplantation in general, such as hemorrhage, infection, primary nonfunctioning of the graft, and death, and those specific to the receipt of a right-lobe graft. For a right-lobe graft, the risks include those due to the cut surface, which include bile leaks and infections, and those due to the provision of insufficient hepatic mass.[37] Refinements in surgical techniques have reduced some of these risks.[38] Transplantation of grafts from living donors is associated with high rates of graft loss and death among recipients who are in poor condition before transplantation,[5] those with clinically significant portal hypertension at the time of surgery,[39] and those who receive

a graft that is small for their body size.[40] The risks of graft loss and death are inversely related to the experience of the surgical team.[4]

Benefits for Recipients

To justify the use of a liver graft from a living donor, it is necessary to show that such a graft has a measurable, incremental benefit for the intended recipient, as compared with a full-size or split cadaveric graft. We are unaware of data demonstrating such a benefit. Although the survival advantage among children who receive liver grafts from living donors has been shown to be associated with the superior quality of the graft and the shorter period of ischemia before transplantation,[20] such studies have not been performed for liver transplantation in adults with the use of grafts from living donors.

Equipoise for Donors and Recipients

When standard therapy is compared with an innovative procedure, equipoise is required.[41] Equipoise is an initial balance between risks and benefits in the two study groups. In conventional clinical trials, the benefits and risks apply only to the patients in the study groups, but in trials of transplantation involving living donors, both the recipients and the donors have a stake in the outcome. The potential benefit for recipients varies according to their clinical status at the time of transplantation and their specific liver disease. For this operation, there is a double equipoise, which reflects a balance between potential benefits and risks for both the recipients and the donors. In certain situations, the use of a graft from a living donor cannot be justified ethically. For example, it would be unethical to transplant a graft from a living donor into a patient with end-stage liver disease and widely metastatic carcinoma who had severe multisystem organ failure and was in an intensive care unit, even if both the donor and the recipient were willing to proceed.

INFORMED CONSENT

The two informed-consent documents needed for an experimental surgical procedure involving a living donor and a recipient are related. The risks and benefits may be difficult to specify. Moreover, they are likely to vary among institutions according to the skill and experience of the team performing the surgery.

Because of the special circumstances of liver transplantation in adults with the use of grafts from living donors, informed consent should be obtained in three steps. First, the recipient should provide informed consent to the planned transplantation in general and to the additional risk of receiving a right-lobe graft from a living donor. Second, the donor should provide informed consent — this process must be as free from coercion as possible, and since the donor and the recipient usually know each other, the donor must be offered an opportunity to decline. Third, the recipient should accept or decline the proposed gift from the donor. Both the recipient and the donor must be informed of the risks and benefits of transplanting a graft from a living donor and those of transplanting a graft from a cadaveric donor, as well as the risks and benefits of the lobectomy performed to obtain the graft from the donor. Ultimately, the potential recipient must have the right to decline a donation from a living donor.

In our view, the surgeon performing each operation must ultimately be responsible for obtaining informed consent. To protect both the recipient and the donor from the surgeon's enthusiasm for the procedure, which might be perceived as a conflict of interest, we recommend that a consultant in internal medicine who is uninvolved with the surgical team be designated as the "consent advocate" for both the donor and the recipient.

FIELD STRENGTH AND INSTITUTIONAL CLIMATE

The term "field strength" refers to the capacity of a surgical team to meet the technical demands of an innovative procedure.[9] Broelsch recently stated that a team planning to perform liver transplantation in adults with the use of grafts from living donors should have proven success, with validation of good outcomes, in performing transplantation with the use of reduced-size cadaveric grafts, transplantation of in situ and ex vivo split cadaveric grafts, transplantation in children, and complex biliary reconstructions and liver resections.[42] We agree. Although it is difficult to quantify the field strength of surgical teams, it is troubling that the performance of liver transplantation in adults with the use of grafts from living donors has not been restricted to high-volume transplantation centers that have track records in all facets of hepatobiliary and liver surgery. Centers that perform fewer than 20 transplantations involving cadaveric grafts per year have lower rates of survival among recipients than centers that perform 20 or more such procedures each year.[43] Brown recently reported that 22 of 54 programs responding to a survey had performed liver transplantation in adults with the use of grafts from living donors but that only 7 of these 22 programs had performed more than 10 such procedures.[7] We are concerned that many of the programs that currently perform liver transplantation in adults with the use of grafts from living donors or that plan to do so in the next year[7] may not have adequate field strength or the established record of success that is required to undertake this complex and dangerous operation.

Moore used the term "institutional climate" in discussing the motivation of a surgeon, surgical team, or institution to perform an innovative procedure.[9] Such a procedure can increase the prestige of individual surgeons and of the institution. For surgeons, the benefits may include scholarly publication, career

advancement, increased status within the medical community, and monetary rewards. The possible benefits for the institution are greater market exposure and an increase in referrals — both for the particular procedure and for other services. We should consider whether the needs of patients or those of surgeons and institutions are the driving force behind programs of liver transplantation in adults with the use of grafts from living donors.

CONCLUSIONS

We recommend that all adults who are candidates for a liver graft from a living donor meet the criteria of the United Network for Organ Sharing for placement on the waiting list for a cadaveric graft[44] and that they be placed on the list. One reason for this recommendation is that patients who have graft loss (primary nonfunctioning of the graft or hepatic-artery thrombosis) within seven days after transplantation automatically qualify as a Status I candidate (one needing a transplant with the greatest urgency)[44] for a cadaveric liver graft. Patients who otherwise would not initially qualify for a cadaveric liver graft but who would qualify if a graft from a living donor failed should not place at a disadvantage those patients who do qualify and are awaiting a cadaveric graft.

The safety of both the donor and the recipient must be ensured through a process that balances the risks and benefits for each. This involves a three-step procedure for obtaining informed consent that provides protection for the donor–recipient pair and makes it clear that the recipient has the right to decline a donation from a living donor.

We believe it is unreasonable to expect that the surgeons and transplantation programs already performing liver transplantation in adults with the use of grafts from living donors, and those planning to do so, will regulate themselves. Surgical-specialty societies could have taken an earlier and more active role in self-regulation of the field by permitting only programs that met criteria such as those suggested by Broelsch[42] to perform the surgery. Realistically, however, specialty societies may not have enough clout to regulate the actions of surgeons and transplantation programs. In the absence of professional self-regulation, private health insurers and government agencies, such as the Health Care Financing Administration (HCFA), should provide oversight.

Private and public health insurance plans provide coverage for liver transplantation in adults with the use of grafts from living donors on a case-by-case basis. Insurers can be expected to collect data at least on short-term outcomes (i.e., survival rates among donors and recipients and costs), and they will eventually decide, retrospectively, which programs they will continue to cover. The transplantation community should work with insurance companies to identify centers of excellence by establishing a registry to which transplantation programs must report data on short- and long-term outcomes for donors and recipients.

HCFA has a list of criteria for determining whether a transplantation program is eligible for Medicare reimbursement. These criteria define minimally acceptable standards for the performance and outcomes of liver transplantation with the use of cadaveric grafts. Transplantation programs that are already accepted as Medicare providers should be required to apply for special certification to perform liver transplantation with grafts from living donors. Specialty societies should assist HCFA in establishing the minimal criteria for certification and the clinical indications for the procedure. We suspect that fewer than 15 high-volume programs in the United States with surgical expertise and field strength will initially meet the criteria for certification to perform liver transplantation in adults with the use of grafts from living donors.

We hesitate to propose changes in a tradition that has permitted the surgical community, through professional self-regulation, to be the sole arbiter in determining when an innovative surgical approach is introduced into practice. Unfortunately, in the case of this procedure, the surgical and transplantation communities in the United States have not established criteria for selecting donors and recipients or standards of surgical technique and have not required the certification of programs. This lack of self-regulation has resulted in the use by many liver-transplantation programs of liver grafts from living donors in adults. Therefore, we believe that this internal, professional control should be supplemented by an external mechanism for prospective regulation, which may include government intervention. Unless professional self-regulation for other innovative surgical procedures improves, government regulation may not be restricted to innovative liver transplantation.

DAVID C. CRONIN II, M.D., PH.D.
J. MICHAEL MILLIS, M.D.
MARK SIEGLER, M.D.
University of Chicago
Chicago, IL 60637

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