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KIDNEY TRANSPLANTATION: A BRIEF REVIEW

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1. ABSTRACT

Since the first successful kidney transplant in 1954, results of these transplants have dramatically improved. Given refinements in surgical techniques and perioperative care, combined with superior immunosuppression, the procedure is now the treatment of choice for patients of all ages with ESRD. Acute rejection no longer represents a significant threat to graft loss, and the newer immunosuppressive drugs will likely diminish this problem further. Complications such as sepsis are fewer and more reliably managed with current therapies. Chronic rejection remains a major problem whose incidence has not been significantly altered. This along with a better understanding of the processes that may ultimately lead to graft tolerance will be the major challenges facing the field of renal transplantation as it enters the 21st century.

2. INTRODUCTION

In the last 35 years, few fields of medicine have undergone the rapid advances seen with renal transplantation. From the development of the surgical techniques necessary for transplantation at the beginning of the century (1) to the dawn of modern transplantation with the introduction of immunosuppressants in the late 1950s, to its current status as the treatment of choice for end-stage renal disease (ESRD), renal transplantation has enjoyed remarkable progress. This review will discuss several aspects of renal transplantation, including recent advances and areas where ongoing efforts are needed.

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3. HISTORY

The surgical techniques for organ transplantation, including methods of vascular anastomosis, were developed in animal models by Carrel and Guthrie (1, 2) in the early 1900s. The first clinical cadaver renal transplant was performed in 1933 by the Ukrainian surgeon Voronoy, with unsuccessful results secondary to the immunologic barrier (3). In the 1950's these obstacles were circumvented by performing the procedure between identical twins (4). The era of modern renal transplantation began with the introduction of azathioprine by Calne *et al*. (5) and Murray *et al*. (6) to suppress the human immune system. With the demonstration of the synergistic effect of glucocorticoids (7), renal transplantation was established as a viable option for the treatment of ESRD. This was followed soon by the development of polyclonal antilymphocyte agents such as ALG which contributed significantly to the treatment of acute rejection (AR)(8). Immunosuppression remained relatively constant for the next 15 years until the 80's, and the introduction of cyclosporine A (CyA)(9,10). At that time, it was the most specific immunosuppressive agent known. It resulted in significant improval in graft and patient survival rates, not only after kidney transplantation, but after all organ transplants, thus allowing for a dramatic increase in extrarenal transplants.

4. INDICATIONS AND PREOPERATIVE EVALUATION

For the majority of people with ESRD, transplantation results in superior survival, improved quality of life and lower costs as compared with chronic

dialysis (11,12). There are very few absolute contraindications and so most patients with ESRD should be considered as potential candidates. The surgery and general anesthesia, however, impose a significant cardiovascular stress. The subsequent lifelong chemical immunosuppression is also associated with considerable morbidity. Therefore, evaluation of a potential recipient must focus on identifying risk factors that could be minimized or may even contraindicate a transplant.

The preoperative evaluation can be divided into four phases: medical, surgical, immunologic, and psychosocial. The medical evaluation begins with a complete history and physical examination. Mortality after transplantation is just as likely to be due to underlying cardiovascular disease as to infectious and neoplastic complications of immunosuppression (13). Any history of congestive heart failure, angina, myocardial infarction or stroke should be elicited. Patients with symptoms suggestive of cardiovascular disease or significant risk factors (e.g. diabetes, age over 50, previous MI) should undergo further cardiac evaluation. This usually implies persantine thallium stress testing to identify areas of reversible ischemia, followed by coronary angiography if indicated. Echocardiography should be performed if patients have evidence of valvular disease or a history of congestive heart failure, to determine left ventricular ejection fraction. Any problems identified should be treated appropriately (medically or surgically); patients whose cardiovascular problems are too severe should not undergo transplantation. Patients with suspected cerebrovascular disease should undergo evaluation with carotid duplex Doppler studies.

Untreated malignancy and active infection are absolute contraindications to transplantation because of the requisite lifelong immunosuppression. Following curative treatment of malignancy, an interval of 2 to 5 years is recommended prior to transplantation (14). This recommendation is influenced by the type of malignancy, with longer observation periods for neoplasms such as melanoma or breast cancer and shorter periods for carcinoma in situ or low grade malignancies such as basal cell carcinoma of the skin. Chronic infections such as osteomyelitis or endocarditis must be fully treated. Other areas of the medical evaluation should concentrate on gastrointestinal problems such as peptic ulcer disease, symptomatic cholelithiasis, and hepatitis. Patients with ulcers should receive appropriate treatment followed by endoscopic evaluation to document resolution. Cholelithiasis should be treated by cholecystectomy prior to the transplant. Patients who are hepatitis C positive, but have no evidence of active hepatic inflammation, are acceptable transplant candidates. Whether patients with hepatitis B should be transplanted is controversial. There is an increased risk in these patients of developing chronic active hepatitis and cirrhosis after receiving immunosuppression (15), but many have excellent long-term survival rates and improved quality of life compared with those on chronic dialysis. Therefore, many centers feel that chronic hepatitis B infection, in the absence of cirrhosis or active viral replication, is not a contraindication to transplantation (16).

The surgical evaluation should concentrate on identifying vascular or urologic abnormalities that may affect transplantation. Evidence of vascular disease that is revealed by the history (claudication or rest pain) or the physical examination (diminished or absent pulse, bruit) should be evaluated further by Doppler studies or angiography. Severe aortoiliac disease may make transplantation technically impossible; one option in these patients is a revascularization procedure such as an aorto-bifemoral graft prior to the tranplant. Areas of significant stenosis proximal to the planned site of implantation may need preoperative balloon angioplasty. Urologic evaluation should rule out chronic infection in the native kidney, which may require nephrectomy pretransplant. Other indications for nephrectomy include huge polycystic kidneys, significant reflux, or uncontrollable renal vascular hypertension. Children especially require a complete GU tract examination to evaluate reflux and bladder outlet obstruction.

An assessment of the patient's immunologic status involves determining blood type, tissue type (HLA A,B,DR antigens), and presence of any cytotoxic antibodies against HLA antigens (because of prior transplants, blood transfusions, or pregnancies).

A psychosocial evaluation is necessary to ensure that patients understand the nature of the transplant procedure, with its attendant risk. They must be capable of following the medical regimen following the transplant. Patients who have not been compliant with their medical regimen in the past must demonstrate a willingness and capability to do so, before they undergo the transplant.

Finally, it is important to remember that patients may be on the cadaver organ waiting list for prolonged periods. Regular reevaluation is necessary to search for any progression of underlying or new disease that may require attention or may contraindicate transplantation.

5. DONOR EVALUATION

Living donors are preferred over cadaver donors. Recipients of living donor organs enjoy improved long-term success, avoid a prolonged wait and are able to plan the timing of their transplant in advance. Moreover, they have a significantly decreased incidence of ATN, increased potential for HLA matching and the opportunity to initiate and optimize immunosuppression therapy preoperatively. All of these advantages contribute to a lower incidence of early acute rejection and to improved graft and patient survival rates. While there is significant benefit for the recipient, there is no physical benefit for the living donor, only potential for harm. Therefore, it is paramount that the risks of donation are acceptably low, that the donor is fully aware of the potential risks, and has

freely given informed consent. Laboratory evaluation of the donor should include basic blood tests (e.g. CBC, electrolytes, glucose, viral serology), assessment of renal function (serum creatinine, creatinine clearance, urinalysis) and an anatomic evaluation of the kidneys (IVP, angiogram). With appropriate preoperative screening, the risk of a lethal complication as a result of donation is estimated to be less than 0.05% (17). The incidence of postoperative complications was roughly 8% in one large series (18); most of these were relatively minor. Living unrelated donors are being used with increasing frequency, with excellent results, comparable to living related (non-HLA identical) donors (19).

In the absence of living donors, transplant candidates are placed on the cadaver organ waiting list. Determining the appropriateness of a given cadaver donor depends on that donor's medical history (e.g. age, diabetes, increased blood pressure, any known kidney abnormality or previous malignancy) and pre-donation renal function. The serum creatinine is the most useful measurement of renal function. It is important to determine the admission creatinine, its trend over the duration of hospitalization, as well as the reversibility of any elevation with appropriate measures such as hydration. With marginal renal donors (e.g. those with hypertension or diabetes, or those over age 65 but with normal serum creatinine), the kidneys should be biopsied at the time of procurement. As long as less than 10% of examined glomeruli are sclerotic, long-term success rates are good (20).

6. OPERATIVE PROCEDURE

The surgical technique for renal transplantation has changed very little from the original pelvic operation described in 1951 by Kuss *et al*. (21). The most common approach today is the standard pelvic operation, with retroperitoneal placement of the kidney allowing easy access for percutaneous renal biopsy. Usually, the right iliac fossa is chosen because of the more superficial location of the iliac vein on this side. However, the left iliac fossa should be used if the patient may be a candidate for a future pancreas transplant, if it is a second transplant, or if there is significant arterial disease on the right side.

With the standard approach, the dissection is extraperitoneal. The iliac vessels are identified and assessed for suitability for anastomosis. The internal iliac artery can be used as the inflow vessel, with an end-to-end anastomosis, or the external iliac artery can be used with an end-to-side anastomosis. To minimize the risk of lymphocele formation, only a modest length of artery is dissected free and lymphatics overlying the artery are ligated. The donor renal vein is anastomosed end-to-side to the external iliac vein.

After the vascular anastomosis is completed and the kidney perfused, urinary continuity can be restored by a number of methods. The most common techniques are a posterior Leadbetter-Politano, anterior multi-stitch (Litch) or an anterior single-stitch (22). Results with the three methods are similar (23). Regardless of the technique used, the anastomosis must be tension-free and protected by at least a 1 centimeter submucosal tunnel to provide protection against reflux during voiding.

7. POSTOPERATIVE COURSE

The initial postoperative care is not unlike that of other surgical patients. Fluid and electrolyte status, vital signs, CVP, and urine output are carefully monitored. Special issues include immunosuppression and monitoring for transplant-related surgical and medical complications unique to these patients.

7.1 Surgical complications

As with other surgical cases, postoperative hemorrhage, wound infection and seroma may be seen. Unique complications can be categorized as vascular, urologic or lymphatic.

Vascular complications can involve the donor vessels (renal artery thrombosis, renal vein thrombosis), the recipient vessels (iliac artery thrombosis, psuedo aneurysms, deep venous thrombosis) or both. Renal artery thrombosis usually occurs early posttransplant, often resulting in graft loss. Most commonly, it occurs secondary to a technical problem such as intimal dissection, kinking or torsion of the vessels. Other causes include hyperacute rejection, unresponsive acute rejection, and a hyper-coaguable state. Presentation is with a sudden cessation of urine output. Diagnosis is easily made with color flow Doppler studies. While urgent thrombectomy is indicated, the majority of grafts are non-salvageable and require removal. Stenosis of the renal artery, a late complication, presents with evidence of graft dysfunction or hypertension. Doppler studies constitute a good screening exam with high sensitivity (87.5%) and specificity (100%) (24,25). First-line treatment is with interventional radiologic techniques, while surgery is reserved for those not responding.

Arterial complications that affect the recipient vessels are much less common, but can be equally devastating. Early events such as iliac artery thrombosis can be limb threatening, while late complications such as pseudoaneurysms or fistula can lead to significant hemorrhage. In our series of 1833 kidney recipients, an acutely ischemic extremity posttransplant was noted in 8 (incidence=0.075%) (26). Predisposing risk factors were underlying peripheral vascular disease and insulin-dependent diabetes (IDDM). Prompt surgical exploration with balloon thrombectomy is essential to salvage the limb and prevent long-term sequelae.

Renal vein thrombosis is not as common as its arterial counterpart, but again graft loss is the usual end result. Causes include angulation or kinking of the vein, compression by hematoma or lymphocele, anastomotic stenosis and extension of an underlying DVT. Doppler studies are again the best diagnostic test. Urgent thrombectomy is rarely successful and nephrectomy is usually required.

Venous thromboembolic complications that affect the recipient vessels (DVT and PE) are not uncommon. In our series of 1833 renal recipients, the incidence of DVT was 6% and PE was 1% (27). Identified risk factors included age over 40, IDDM, and a history of DVT. Prophylaxis with low-dose heparin was recommended for patients with these risk factors.

Urinary tract complications, manifesting as leakage or obstruction, generally occur in 2% to 10% of cases (28). The underlying cause is often related to poor blood supply and ischemia of the transplant ureter. Leakage most commonly occurs from the anastomotic site. Causes other than ischemia include undue tension created by a short ureter or direct surgical injury. Presentation is usually early (before the 5th posttransplant week); symptoms include fever, pain, swelling at the graft site, increased creatinine level, decreased urine output, and cutaneous urinary drainage. Diagnosis can be confirmed with hippurate renal scan. Early surgical exploration with ureteral re-implantation is usually indicated, though small leaks may be managed by percutaneous nephrostomy and stent placement with good results.

Obstruction may present early or late. Early postoperative obstruction may be due to edema, blood clots, hematoma or kinking. Late obstruction is generally due to scarring and fibrosis from chronic ischemia. Initial treatment with percutaneous transluminal dilatation (PTD), followed by placement of an internal or external stent, has yielded good results. In a series of 39 patients with ureteral stenosis, PTD was successful in 30 (70%), with a recurrence rate of less than 10% (29).

Lymphoceles (fluid collections comprising lymph that generally result from cut lymphatics in the recipient) occur in 0.6 to 18% of patients(30). These usually do not present until at least 2 weeks posttransplant. Symptoms are generally related to the mass effect and compression of nearby structures (e.g. ureter, iliac vein). Ultrasound will confirm a fluid collection, though percutaneous aspiration may be necessary to rule out other collections such as urinoma, hematoma, or abscess. The standard surgical treatment is creation of a peritoneal window to allow for drainage of the lymphatic fluid into the peritoneal cavity, where it can be absorbed. This can be accomplished by either a laparoscopic or an open approach. Percutaneous insertion of a drainage catheter, with or without sclerotherapy is another option; however, it is associated with a high rate of recurrence and risk of infection (31).

7.2. Medical complications

Medical problems unique to transplant recipients are related to infections and graft dysfunction secondary to rejection or drug toxicity.

There are four types of clinical rejection: hyperacute, accelerated, acute, and chronic. Only the first three are seen in the early posttransplant period; the last (CR) remains the most frequent cause of graft failure. Hyperacute and accelerated rejection occur very early posttransplant and reflect host anti-donor presensitization; with current crossmatch techniques, these events are relatively rare. Acute rejection, however, is not uncommon, affecting at least one-third of recipients on standard CyA-based immunosuppression. It is most prevalent in the first few months posttransplant, and is unusual after the first year.

With current immunosuppression, symptoms such as fever, graft tenderness, malaise, and oliguria are unusual with acute rejection. The most common manifestation is an asymptomatic rise in the serum creatinine. The previously discussed technical problems, as well as medical causes such as dehydration, infection and CyA induced nephrotoxicity, must be ruled out. Physical examination, routine biochemistry tests, CyA blood level determination and a Doppler ultrasound will usually rule in or out these possibilities. The diagnosis of AR is ultimately best established with a renal biopsy. Treatment is then initiated based on the severity of rejection, degree of dysfunction, and previously administered immunosuppression. Options include a course of high-dose steroids or antilymphocyte preparations (ATG or OKT3).

8. IMMUNOSUPPRESSION

Induction and maintenance immunosuppression varies from center to center. Existing regimens are likely to change in the near future with the completion of phase III trials of newer immunosuppressive drugs. At the present time, most transplant centers use a combination of CyA, prednisone and azathioprine (AZA) for maintenance, with or without a polyclonal (ATG) or monoclonal (OKT3) antilymphocyte agent for induction therapy.

The introduction and widespread use of CyA in the early 1980s substantially improved transplant outcome. Over the ensuing decade, there was very little change in terms of immunosuppressive therapy. There are however now a number of new drugs that have been approved for clinical use including microemulsion CyA, tacrolimus, sirolimus and mycophenolate mofetil.

Microemulsion cyclosporine (CyA-ME, Neoral) is actually not a new drug, but rather an old drug in a new package. The active drug remains cyclosporine A. The newer formulation has superior oral bioavailability, compared with the older formulation (CyA, Sandimmun) (32), especially in patients who were poor absorbers of

CyA (33). Whether or not this improved pharmacokinetic profile correlates with an improved clinical outcome is currently being studied. The European multicenter study did demonstrate a decrease in the incidence of AR at 3 months in the CyA-ME group versus the CyA group (34). A longer follow-up is necessary to substantiate the benefit.

Tacrolimus, (FK506) a metabolite of a soil fungus found in Japan, works in a similar manner to CyA, but is much more potent on a molar basis. Extensively studied in liver transplant recipients, it is currently undergoing phase III trials in renal recipients. It is being evaluated both in the setting of refractory AR as well as primary therapy. In a multicenter trial of tacrolimus for refractory AR, early results were encouraging (35). Of 73 patients who started tacrolimus for steroid-resistant rejection, improvement was seen in 78%, stabilization in 11%, and progressive deterioration in 11%. Only 10 patients had a recurrent episode of AR after switching to tacrolimus. In the U.S. multicenter study (19 centers) of tacrolimus versus CyA for primary therapy after cadaver kidney transplant, no significant difference was seen after 1 year with respect to graft or patient survival (36). Biopsy-proven AR was lower in the tacrolimus group (30.7% versus 46.4%, $p<0.01$), as was the incidence of steroid-resistant rejection. Adverse effects were similar in both groups, except for the incidence of IDDM, which was significantly higher in the tacrolimus group (20% versus 4%, $p<0.001$).

Mycophenolate mofetil (MMF) was approved by the FDA for the prevention of acute renal rejection in May 1995. It is a semi-synthetic derivative of mycophenolate acid (MPA), the active immunosuppressive compound. MPA is a reversible inhibitor of an enzyme that is crucial for the de-novo synthesis of purines. The net result is a selective and reversible antiproliferative effect on T and B lymphocytes. MMF has recently undergone extensive evaluation in large multicenter studies. For treatment of refractory AR, MMF was found to be more effective than standard high-dose intravenous(IV) steroids for controlling the refractory episode and preventing subsequent rejection episodes (37). After 1 year of follow-up, 31.5% of patients in the IV steroid arm had lost their graft or died, compared to 18.2% in the MMF arm ($p=0.04$). Another multicenter trial involving 21 centers over 3 continents examined MMF versus azathioprine (AZA) for primary therapy in cadaver renal transplants, and reported similar encouraging results (38). After 6 months of follow-up, treatment failure (defined by biopsy-proven graft rejection, graft loss, death, or discontinuation of the drug) was significantly higher in the AZA group (50.0%) versus both MMF groups (34.8% for 3 gm/day and 38.2% for 2 gm/day, $p<0.05$). AR was more frequent in the AZA group (35.5% versus 15.9% for MMF 3 gm/day and 19.7% for 2 gm/day, $p<0.05$). After 1 year of follow-up, graft survival in the MMF group was marginally superior, though not statistically significant. Whether or not this decrease in early AR will translate into improved long-term graft survival remains unknown. Results from the tri-continental study after 3 years of follow-up show a marginal improvement in graft survival in the MMF groups (84.8% for MMF 3 gm/day and 81.9% for 2 gm/day) vs. the AZA group (80.2%, p=ns). Rejection as a cause of graft loss was lower in the MMF groups (3.0% for MMF 3 gm/day and 5.3% for 2 gm/day) vs. the AZA group (9.8%, p=ns) (39).

Sirolimus, a macrolid antibiotic, is structurally similar to tacrolimus. It is 50 times more potent than, and synergistic with, CyA. Currently, it is undergoing phase II clinical trials in renal recipients. Early results from these multicenter studies indicate that sirolimus may allow CyA dose reduction or early corticosteriod withdrawal (40). In a study of cadaver renal recipients, six different cohorts received placebo or sirolimus (at 3 or 5 $mg/m^2/day$) plus a full or half dose of CyA. Results after 6 months of follow-up show that the incidence of AR was decreased roughly 4 fold in all recipients on sirolimus and full-dose CyA, compared with the control group (41). Non-black recipients on sirolimus and half-dose CyA had a similar reduction in AR.

9. RESULTS

Outcome after kidney transplantation has steadily improved over the past three decades, thanks to improvement in immunosuppression, antirejection therapy, organ retrieval techniques, perioperative care, and treatment of posttransplant infectious complications. Over the last 10 years, use of CyA has been a primary factor, especially in patients traditionally considered high-risk: diabetics, children, and those over age 60.

Most centers now report patient survival rates exceeding 95% during the first posttransplant year for all recipients. Living donors have a clear advantage over cadaver donors; reported 5-year patient survival rates after living and cadaver transplants are approximately 90% and 80%, respectively. Compared with dialysis, the survival advantage after a transplant is probably greatest for diabetics. Without a transplant, overall survival in this group is 26% at 5 years (11). Our 1991 data indicates that after a transplant, the 5-year patient survival rate is about 85% in nondiabetics and 80% in diabetics (42). The major cause of death in all our recipients was cardiovascular (MI, CVA); sepsis accounted for less than 3%, while malignancy accounted for 2%.

While graft survival has improved significantly in the early posttransplant years, there remains a steady decline in the subsequent years, reflecting the continued problem of CR. Combined data from the UNOS registry for 1993 reported 2-year graft survival rates of 87% with living donors and 73% with cadaver donors (43). Our 1991 data shows a 5-year graft survival rate of 73%. The main causes of graft loss in this group were death with a functioning graft and CR. The technical graft failure rate was 2%; acute rejection caused only 1.7% of graft losses. Thus, as a result of refinements in surgical techniques and

immunosuppression, most recipients who lose their grafts will do so either because of death or CR.

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