

Overview of Renal Transplantation in the United States

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Abstract

Renal transplants have been performed in US since 1954. Survival rates have improved with new techniques and immunosuppressants. The 5 year survival rate of cadaveric and living related is 66% and 78% respectively. Renal transplant offers a cost effective and better quality of life. Since 2001 the number of live kidney donors has surpassed cadaveric donors in United States. As a society we need to encourage organ donation via education and outreach programs.

Keywords: Renal transplants; Immunosuppressants; Live kidney donors; Cadaveric donors; Organ donation; Education and outreach programs

Background

Joseph Murray performed the first renal transplant in the United States in 1954 [1]. Although the donated kidney was rejected soon after the procedure, this breakthrough opened many doors in the field of transplant surgery [2]. Soon after, a group of surgeons from Boston successfully transplanted a kidney in identical twins, to eliminate a potential immune response [3]. This attempt proved to be visionary as the kidney lasted a full 8 years after the transplant.

Although pioneering surgeons faced great challenges in their initial attempts, these procedures laid the groundwork for modern day advances. The changes in surgical technique, improved tissue typing, and the advent of immunosuppressive medications have allowed renal transplants to become the gold standard for patients with end stage renal disease in the United States. Such transplants not only offer a cost effective alternative to long-term dialysis [4], but also lead to a better quality of life [5].

Forty six years after the first successful kidney transplant was performed, more than 200,000 kidney transplants have been reported at transplant centers throughout the United States [6]. The trend towards increased utilization of kidney transplant should continue as survival rates improve. Compared with the 5 year cadaveric and living donor graft survival rates reported for kidney transplants 25 years ago, today's results of 66% and 78% are encouraging [6]. Notably, since 2001, the number of live kidney donors has surpassed the number of cadaveric donors in the United States [7].

Procedure

Surgical approaches to renal transplantation in the United States are straightforward. After the donor kidney is harvested, the vessels are trimmed to the appropriate size to allow correct anastomosis. Next, an incision is made to expose the iliac vessels. The renal vein and artery are then anastomosed to the external iliac vein and artery respectively [8]. Finally, the kidney is placed in the iliac fossa in order to allow for simple biopsy in the case of rejection [8]. In athletes, the kidney is

often placed deeper within the abdomen to protect it from trauma associated with contact injuries. Most often, the diseased kidneys are left within the abdomen to avoid additional complications [9]. However, in the case of polycystic kidney disease and uncontrolled hypertension, native kidneys may be removed.

Donor safety must be a priority in living donor kidney transplantation. A thorough medical evaluation is needed to ensure adequate donor health pre and post surgery. Additionally, renal function must be observed over time. Prior to surgery, donors are screened for any absolute contraindications including uncontrolled hypertension, diabetes, BMI greater than 35, and nephrolithiasis with high likelihood of recurrence [10]. In hereditary renal disease, genetic studies must also be analyzed in order to minimize the risk of recurrence.

If the donor's health and kidney function are adequate, nephrectomy can be performed using several different techniques. Open, laparoscopic and robot-assisted techniques are currently available for donor nephrectomy. Minimally invasive laparoscopic and robotic techniques have become more prevalent. They minimize the drawbacks of open donor nephrectomy, making it more appealing to prospective donors [11]. These methods tend to reduce hospital stay, have shorter operative times, and longer warm ischemia times, thus allowing the donor a quicker return to work without compromising graft function [12].

Immunosuppression

Since the 1950's, physicians have recognized the need for immunosuppression in renal transplants [2]. Since then, various techniques and medications have been used to encourage successful acceptance of donor kidneys. However, these techniques have come at the expense of transplant tolerance. Transplant tolerance is a state in which there is a lack of a destructive immune response by the recipient toward the donor organ, in the absence of maintenance immunosuppression, and with a fully intact immune system [13].

To this point, the medical field has not been able to achieve "true tolerance" as immunosuppression regimens have expanded in order to accommodate changing protocols. Exact treatment protocols differ throughout transplant centers within the field. However, the primary

goal of therapy is to control the CD4+ T-cell reaction believed to be responsible for initiating the rejection response in transplant procedures [14]. Current regimens most often use a "triple therapy" consisting of a glucocorticoid, a calcineurin inhibitor (CNI), and an antiproliferative agent. Doing so allows for adequate immunosuppression while limiting toxicity associated with high-doses of a single agent [15]. Interestingly, some centers have dropped corticosteroid use entirely due to increased risk of infection, increased frequency of hypertension, hyperlipidemia and glucose intolerance [16].

There is consensus among transplant centers through controlled randomized trials and meta-analysis that induction therapy with biologic antibodies helps in reducing rejection and failure [17,18]. Recently, the costimulation blocker belatacept, which inactivates a receptor on T cells, has shown promise as a potential alternative to more traditional "triple therapy" [19].

Still other techniques for controlling graft rejection include the use of mesenchymal stromal cells (MSC). Such cells display the ability to inhibit the proliferation of alloactivated recipient T-cells and protect against ischemia/reperfusion injury [20-22]. Further development of MSC technology, could provide patients with treatment options similar to a "true" immunological transplant tolerance.

Despite progress in controlling the cell-mediated immune response, antibody mediated rejection (AMR) poses a significant challenge to short and long-term graft survival in kidney transplantation [23]. Specifically, growing populations of sensitized patients present great challenges in avoiding humoral transplant rejection. Although treatments such as monoclonal antibodies, intravenous immunoglobulin (IVIG) and plasmapheresis (PP) have been developed for this problem, AMR remains a difficult issue to address.

Though formidable challenges still exist, these advancements represent the significant progress made in immunosuppressive techniques over the past 50 years of transplant surgery (Table 1).

Immunosuppressive Agent	Year Introduced	Category
Predisone	1955	Glucocorticoid
Azathioprine	1968	Antiproliferative
Cyclosporine	1983	Calcineurin Inhibitor
Tacrolimus	1994	Calcineurin Inhibitor
Mycophenolate mofetil (MMF)	1995	Antiproliferative
Basiliximab	1998	IL-2 Receptor Antibody
Sirolimus	1999	Antiproliferative
Belatacept	2011	Costimulation blocker

Table 1: Immunosuppressive treatment

Survival Rates of Graft (Living vs. Cadaveric Comparisons)

Renal transplant has long been associated with less mortality than patients on dialysis awaiting transplantation [24]. However, due to limited donor organs, cadaveric and living donors are both used

regularly in the United States. A shortage of cadaver kidneys relative to increasing demand has led to a remarkable rise in transplantation from living donors [25].

This trend may be beneficial, as living-related donor (LRD) renal allografts have been recognized to have a higher overall graft survival than cadaver donor transplants [26-28]. Proposed mechanisms for this disparity include inflammatory injury around the time of brain death [27] and delayed graft function associated with cadaveric kidneys [29]. For these reasons, living-donor transplantation is encouraged as the first option for children with end-stage renal disease [30].

Further advantages to live donor transplantation include the need for less immunosuppression [31], and desensitization techniques that can overcome complications such as HLA disparity and ABO or cross-match incompatibility [32]. Additionally, modern imaging modalities may be used on living donors to achieve greater long-term success. In particular, CTA and MRI are being utilized to assess the renal vasculature of living related donor kidneys [33,34]. Also important, live donation can allow transplantation to occur before initiation of renal replacement therapy.

While live kidney donation has proven to be superior in many ways, there is still a place for cadaveric donations. It seems improved harvesting techniques and early grafting of the cadaveric kidneys could allow similar results to living kidney transplant [35]. More research must be done to create practice guidelines that will improve cadaveric transplants in the future.

Discussion on Donation

Often live donors are unable to donate to the intended recipient because of difficulty in immunocompatibility [28]. Recently, kidney exchange, in which incompatible patient donor pairs are matched, has facilitated transplantation of kidneys from living donors [29]. However, problems still arise when trying to obtain adequate numbers of cadaveric kidneys, as there is an upper limit to the number of such kidneys available for transplantation [35]. To become a deceased donor an individual must have registered with the department of motor vehicles or had his/her organs donated by the next of kin after death.

For years, researchers have been studying methods that will yield greater organ donor participation rates. To alleviate this problem, economists have produced numerous theoretical organ-sale markets. However due to ethical concerns, it is unlikely that any of these will be approved for use in the United States. Another interesting approach to raise organ donor rates involves the "reciprocity policy." Under this policy, those who have donated organs would be granted preference in the event that they later required a transplant [36].

Another possible solution is a move towards presumed consent. In the United States, we currently employ a system of expressed consent, essentially forbidding organ transplant unless expressed directly in advance. However, other nations (notably Belgium), have improved donor rates using a presumed consent approach [37]. In this system, patients are presumed to be organ donors unless otherwise noted. In this way, patient autonomy is still respected, but the number of organs available for donation is increased.

As a society, it seems that we are headed in the direction of increased organ donation. However, more must be done to increase participation in donor registries. Greater efforts should be put forth towards giving potential donors more opportunities to register.

Further, the lack education surrounding live donation must be addressed before rates improve significantly. Outreach campaigns, particularly amongst minority populations may prove to be useful in improving donation rates [36]. In taking these steps we can provide additional chances for potential donors to consider donating an organ that may one day, save a life.

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