

REVIEW ARTICLE

RECENT ADVANCES IN KIDNEY TRANSPLANTATION

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INTRODUCTION

Kidney transplantation is the treatment of choice for patients with end-stage renal failure (ESRF). Since the first kidney transplant was performed between identical twins in 1954¹, significant advances in the scientific and clinical aspects of transplantation have led to a consistent improvement in outcomes. Kidney transplantation therefore confers significant survival benefit to patients when compared to dialysis². We explore some of the developments in kidney transplantation that have led to refinement in technique and improvement in outcomes over the years.

Expansion of the donor pool and outcomes

Since the turn of the century, the number of cadaveric donors has increased significantly in the developed world. Concerted and focused initiatives at improving awareness and streamlining logistics has resulted in a significant improvement in donor numbers and organ utilisation. In addition to an increase in the number of standard criteria donors (SCD), the numbers of extended criteria donors (ECD) and kidneys transplanted from donors after cardiac (DCD) has also increased significantly. The increase in the number of DCD donors has seen the most marked rise in the recent past³. Despite an increase in overall transplants, living donor transplants have remained relatively stable since 2004. Patient survival following renal transplantation remains excellent, with one-year unadjusted survival rates ranging from 95% to 98% for recipients of deceased donor and living donor transplants, respectively³.

Recipients of kidneys from living donors have better five-year patient survival (90%) when compared to recipients of non-ECD (83%) or ECD (69%) deceased donor kidneys³.

Immunological advances

The combination of calcineurin inhibitors (CNI) and anti-metabolite with or without corticosteroids (CS) remains the most common maintenance immunosuppression regimen². Since the turn of the century tacrolimus (TAC) has replaced cyclosporine (CYA) as the CNI of choice. This switch is mainly due to evidence from a variety of trials demonstrating less acute rejection (AR), improved blood pressure control and graft function with TAC at the expense of increased risk of new-onset diabetes, neurologic and gastro-intestinal side effects⁴. Based on the evidence from three large multicenter trials, Mycophenolate Mofetil (MMF) replaced Azathioprine (AZA) as the anti-metabolite of choice due to reduction in the rate of acute rejection (AR)⁵. However, more recently there appears to be a resurgence in the use of AZA in low immunological risk groups and living donor recipients due to follow up data from the trials not demonstrating any significant long-term difference in graft or patient survival between AZA and MMF use⁶. The use of CS at the time of discharge has decreased from 97% to 68%⁴. The use of induction therapy has also significantly increased over the last decade. The current Kidney disease improving global outcomes guidelines (KDIGO) recommend IL-2 receptor antagonist (IL-2RA) as first line induction agents and use lymphocyte depleting agents for patients at high

immunological risk⁷. Prospective randomized trials have demonstrated reduced AR rates although higher incidence of adverse events in patients undergoing anti-Thymocyte globulin induction when compared to IL-2RA induction in high immunological risk groups⁸. Recently Alemtuzumab has shown efficacy in reduction of AR and short-term safety as an induction agent in high risk groups. However, more prospective long-term studies are necessary to establish long term safety and outcomes with Alemtuzumab use.

In recent years, there has been a significant increase in the HLA and ABO- incompatible transplantation⁹. Successful incompatible transplant protocols are varied but include plasmapheresis or immunoadsorption to remove anti-HLA or –ABO group antibodies followed by infusion of low-dose IVIG for immunomodulatory effects¹⁰. Rituximab (anti-CD20 antibody) has also been used for sensitized patients at highest risk for severe AMR and has replaced splenectomy in most ABO-incompatible protocols. Induction therapy is either with a lymphocyte depleting agent or IL-2RA, followed by maintenance immunosuppression with TAC/MMF/CS⁴. Short-term outcomes following ABO incompatible transplants are comparable to compatible live donor transplants¹¹. The safest and most cost-effective avenue for living donor transplantation in incompatible patients is through Living Donor Exchange programmes. These have been shown to be especially effective in the United Kingdom, Europe and the USA. In India, there have been several reports of two and three way paired exchanges at single centres¹³. However, a robust national or regional registry facilitating this process is still in its infancy.

Surgical Advances

Since it was first described in the early 1990s, Laparoscopic donor nephrectomy has replaced open donor nephrectomy due to significantly reduced donor morbidity and hospital stay¹³. Various approaches to laparoscopic donor nephrectomy have been used which include laparoscopic intraperitoneal, laparoscopic retroperitoneal and Laparoscopic hand assisted approaches. The technique used is down to the expertise of the centre and all approaches seem to have equivalent safety and efficacy. Recently there have been reports of Laparoscopic single port donor nephrectomy through either a small peri-umbilical or flank incision with good results¹³. Over the last decade, robotic assisted donor nephrectomy has also been described with reduced post-operative hospital

stay when compared to the laparoscopic hand-assisted technique¹⁴. However, the cost of a robotic procedure is a mitigating factor in its widespread use. Over the last two decades, minimally invasive donor surgery has had a significant impact in increasing the number of living donors and altruistic donors due to the minimal donor morbidity and reduced hospital stay.

The open approach is still the most widely used for the recipient of a kidney transplant. Over the decade last there have been case series reported of laparoscopic and robotic kidney transplantation. However, the disadvantages of laparoscopic and robotic approaches to kidney transplantation seem to be a longer duration of warm ischaemia due to longer anastomosis times with resultant lower rate of creatinine clearance in the immediate post-operative period and lack of haptic feedback. The robotic approach has the further disadvantage of higher cost^{15,16,17}. The laparoscopic approach requires intraperitoneal placement of the kidney with fixing of the kidney in an extra-peritoneal pouch to prevent torsion¹⁷. Despite the slower reduction in creatinine and higher rate of delayed graft function the graft and patient outcomes after 6 months are similar between both open and minimally invasive approaches to kidney transplantation. However, in morbidly obese recipients, the minimally invasive approach may be beneficial by reducing morbidity from surgical site infections (SSIs) and reducing hospital stay¹⁵.

With the increased acceptance of organs from ECD donors there has been an increase in the number of dual kidney transplant over the last couple of decades. While histologic and GFR based criteria for selection of donors as suitable for dual transplants exist, they are flawed and not completely reliable. Further studies are therefore needed to identify the best allocation criteria to ascertain similar outcomes in recipients of single and dual ECD kidneys¹⁸. Recently, a single centre from the UK, has reported enbloc-kidney transplantation from neonatal donors into adult recipients with successful outcomes¹⁹. This highlights that neonatal donors are an underutilised resource which can help improve access for patients to a kidney transplant.

Discussion

With the improvement in immunosuppressive drugs and better understanding in the management of transplant recipients, graft and patient outcomes have steadily improved, further reinforcing renal transplantation as the treatment of choice for patients with ESRF.

Expansion in the deceased donor pool with increased acceptance of marginal donors, extended criteria donors and use of dual transplantation has further increased the access to transplantation for patients on the kidney transplant waiting list. From an Indian perspective, while living donation is thriving and forms the major source of organs for transplantation, cadaveric donation is still not as well developed when compared to the western world. Recent progress in cadaveric donation in isolated regions in India, especially Tamil Nadu, is a promising prospect for the future of cadaveric donation in India. Increasing awareness about donation, improving the logistics and, replicating and improving existing regional cadaveric donation models nationally will further help in improving the numbers of cadaveric donors in India. Despite the high number of living donors, paired exchanges for incompatible donors can be improved by having a robust national or regional

registry. With respect to surgical technique, India is already on par if not ahead of several countries in embracing laparoscopic and robotic techniques. In future, India might be able to provide vital experience and training for future surgeons worldwide in these novel and advanced techniques. Furthermore, given the burden of diabetes and renal failure, and the relative infancy of the pancreas transplant program in India, there is abundant scope for increasing the number of pancreas and kidney transplants. This group of patients may be particularly suitable for pancreas after kidney transplant given the relative scarcity of cadaveric donors to ensure equitable access of cadaveric kidneys to all patients on the waiting list. In conclusion, there seems to be abundant scope for development in the field of renal transplantation in India and the next couple of decades will be interesting and may generate vital experience to aid future practice.

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