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RENAL TRANSPLANTATION DURING THE TWENTIETH CENTURY: A REVIEW

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ABSTRACT

Objectives: To provide an overview of the various advancements and problems associated with both live and cadaver donor renal allograft transplantation during the twentieth century.

Data source: Major published reviews on renal transplantation during the the last five decades of the twentieth century were reviewed using Medline internet search and the Index Medicus. The developments in immunosuppressive therapy associated with renal transplantation, the problem of the shortage of both live and cadaveric organ donors and post-transplant complications were examined. The future of renal transplantation including cross species transplantation (xenotransplantation) is discussed.

Conclusion: Renal transplantation has evolved over the years to become a very successful and routine procedure. However, the transplant waiting lists have remained long due to a continuously shrinking kidney donor pool which is due to improved results of neurosurgical procedures, better emergency and intensive care services and the failure to adequately prevent and treat post transplant chronic renal failure.

INTRODUCTION

The improvements in renal transplantation over the last four decades have been one of the great success stories in modern medicine. Renal transplantation has become the gold standard therapy for most patients with end stage renal disease. This is because patient mortality and morbidity have progressively been reduced over the years. This has been made possible due to improvement in pre-operative donor evaluation and surgery, kidney preservation, recipient selection and surgery, histocompatibility techniques and advances in immunosuppression coupled with better and successful management of various complications. The shortage of organs continues to be a significant problem and must be urgently addressed. The development of specific therapies that can be altered according to various patient comorbidities, the prevention of chronic rejection, the reduction of toxicity, the various immunosuppressive agents and the improvement of the various national donor organ networks must be addressed in the next decade for a safer complication free procedure.

HISTORICAL PERSPECTIVES OF RENAL TRANSPLANTATION

History of modern organ transplantation has many milestones(1). The kidneys were the preferred organ of experimental transplantation because they are paired and have a simple blood supply and the flow of urine through the ureter acts as an instant indicator for the of successful function of the transplanted kidney(2). The history of

renal transplantation illustrates successful combination of the fields of surgery, medicine, immunology and government. Significantly, Carrel developed the modern method of vascular suturing at the turn of twentieth century which was an important step towards the future of renal transplantation(3). In 1933, the first human renal transplant was performed by Voronoy in the Ukranian part of the then Soviet Union(4). The recipient was a 26-year old female who had attempted suicide with mercuric chloride while the donor was a 66 year old male whose kidney was harvested six hours after death. Under local anaesthesia, the renal vessels were anastomosed to the femoral vessels and a cutaneous ureterostomy was performed. The transplanted kidney made a small amount of blood stained urine but the patient died only forty eight hours after the operation.

In December 1954, at the Peter Bent Brigham hospital in Boston, USA, Murray and Merrill performed the first successful human renal transplantation when a kidney from one twin was transplanted into the other twin with end stage renal disease(5). It was, however, not until 1958 when the first histocompatibility antigen was discovered during which period radiation was extensively used for immunosuppression. Glucocorticoids and azathioprine became part of immunosuppressive regimen in 1962(6). The direct crossmatch between donor lymphocytes and recipient serum was introduced in 1966, and heterologous anti lymphocyte serum was used as an immunosuppressant in human renal transplantation. At about the same time the preservation of the donated kidney for over twenty four hours was made possible(7). Donor specific blood transfusions also became part of standardised pre-transplant

immunological protocol for living donor transplantation(8). The first clinical trials of cyclosporine were reported in 1978 by Calne *et al*(9) and followed three years later by the successful use of monoclonal antibody for the treatment of renal allograft rejection. Over the years the multidisciplinary improvement and the development of the understanding of immunology and tissue matching, immunosuppression, donor and recipient management and transplantation techniques have made renal transplantation a routine procedure in many parts of the world.

Renal transplantation is still not readily available in most of the African countries as it is expensive and difficult to sustain due to insufficient allocation of funds by the various governments. There are, however, several renal transplant programmes in Africa and include South Africa(10), Egypt(11), Morocco(12), Kenya(13) and more recently Nigeria.

DONOR SELECTION

The two types of kidney donors are the living donor or the brain-dead cadaver donor. The declaration of brain death in a cadaver donor is the responsibility of the potential cadaver organ donors physician. The aim of the transplant surgeon is to preserve the renal vessels, preserve ureteral blood supply, and to minimise warm ischaemia time. Living donor transplantation is known to be superior to cadaveric transplantation(14). The one year graft survival rate after renal transplantation is 90% for recipients of living donor kidneys and 77% for cadaver donor kidneys(15).

The live donor must be assured by the surgeon of normal renal function and normal life after unilateral nephrectomy. The donor is usually left with the better of the two kidneys and is considered to be unsuitable when there is significant mental dysfunction; high risk peri-operative morbidity and mortality; significant renal disease; active infection; transmissible malignant disease; ABO incompatibility; or positive crossmatch between donor lymphocytes and recipient serum. The success of living renal donor transplantation is contingent upon a reliable pre-operative assessment of the live donor candidate(16). Serologic screening is performed for human immunodeficiency virus (HIV), human T-lymphoproliferative virus type 1 (HTLV-1), syphilis, hepatitis B and Epstein Barr virus(17). Abdominal ultrasonography can be performed to exclude significant renal and intrabdominal abnormalities. Accurate delineation of renal vascular anatomy is an important integral component in the evaluation of the living renal donors. Individual variations in renal arterial anatomy are common occurring in 32% of donors(18). Routine evaluation of potential live renal donors has relied upon conventional renal arteriography, digital subtraction angiography and magnetic resonance imaging in mapping the renal arterial vasculature(19). More recently helical computed tomography of the kidney with a three

dimensional arteriography emerged as a less invasive method used to evaluate potential living renal donors(20). In an attempt to promote live donation of kidneys, some surgeons have used laparoscopic techniques for the donor hoping that the appropriate potential live donors will be keener as their resultant scars and discomfort would be reduced(21).

The selection criteria for a potential cadaver kidney donor is from the age of eighteen months(22), to fifty five years(23). The cadaver organ donor must not be a diabetic or hypertensive, have normal renal function, no transmissible malignancy and generalised bacterial or viral infection. There should also be negative assays for syphilis, hepatitis, HIV and HTLV-1. Tissue typing and cross matching can be performed on peripheral blood samples or inguinal lymph nodes before kidney retrieval. Currently, most cadaver donors are multiple organ donors and are usually physiologically maintained in the operating theatres by anaesthesiologists to ensure adequate ventilation and circulatory support so that the administration of drugs such as diuretics, heparin, and alpha blocking agents, among others, can be effected as the situation demands prior to organ harvesting(24). The shortage of donor organs remains a stumbling block to renal transplantation. Structurally anomalous kidneys were previously considered unsuitable for transplantation, but horseshoe kidneys are now transplantable either *en block* into one recipient or can be separated and transplanted into two recipients with good results(25). Paediatric donors who were previously discarded are now fully utilised(26), and the use of double renal transplant from an adult donor who is considered to have some form of partial renal impairment is now being encouraged(27). In some African countries the absence of legislation concerning organ harvesting from brain dead potential cadaveric donors has favoured renal transplantation from living donors(28). But even in countries where such legislations exist like in the United States of America, a shortage of cadaveric donor kidneys has created long waiting lists for patients on chronic dialysis while awaiting renal transplantation(29)

RECIPIENT SURGERY

In 1991, eleven thousand kidneys were transplanted in Europe alone, making the procedure one of the commonest operations(30). The most important development in the surgical technique of renal transplantation was described by Carrel and Guthrie at the beginning of the twentieth century(31). Since then, ureteric stents have been introduced, but Carrel's technique has remained largely unchanged. Modifications have been effected for paediatric renal transplantation involving the use of the aorta and inferior vena cava instead of iliac vessels(32). Pancreatic transplantation to protect the kidney graft of a diabetic patient and the use of ileal conduits and augmented bladders for ureteric drainage are some of the other recent developments(33,34).

COMPLICATIONS OF RENAL TRANSPLANTATION

Complications following renal transplantation can be categorised as urological and those as a result of immunosuppressive therapy.

Urological complications: The urological complications following renal transplantation include significant haematuria, ureteric obstruction and necrosis and urine leak and lymphocoele formation and cause significant morbidity with the potential to cause early renal allograft failure(35). Immediate vascular complications include the kinking of the graft artery or vein, suture line stenosis and thrombosis. The incidence of major urological complications has been reported as 3.7-12.5%(36). The successful formation of vesico-ureteric anastomosis for which several techniques are described is important in preventing these complications and in securing a functional transplant(37, 38). The two major factors that affect success of vesico-ureteric anastomosis are vascularity of the donor ureter which is potentially at risk during the donor nephrectomy and handling during transplantation, and the surgical technique used during the operation. Extravesical techniques(38) are more effective and simple to perform compared to the Leadbetter-Politano technique(37) and in particular they avoid a separate cystostomy associated with urine leaks and allow the use of shorter ureters(39).

Complications related to immunosuppressive therapy: The importance of acute rejection in the early post-operative period is today not as relevant as it once was due to the introduction of cyclosporine, tacrolimus, rapamycin and more recently, lymphocyte specific mycophenolate. Antilymphocyte preparations are effective immunosuppressive agents for the treatment of post transplant rejection in renal transplantation. Polyclonal preparations have been used for more than 20 years and recently monoclonal antibodies like Orthoclone OKT3 and anti-IL-2 receptor have become readily available and regularly employed. These agents prevent acute rejection when used prophylactically soon after renal transplantation and they also effectively treat acute rejection episodes(40). Chronic rejection is now the most important cause of returning to dialysis after failure of renal transplantation. The chronic allograft nephropathy refers to the progressive decline in renal function seen in renal transplant recipients in association with alloantigen dependent and alloantigen independent factors(41).

Combination immunosuppression is the most popular approach for the long term management with cyclosporine or tacrolimus, azathioprine or mycophenolate and steroids. To date, no specific agent has eliminated chronic rejection so that no real progress has been made in long-term renal allograft survival of over ten years achieved since the azathioprine and steroid combinations of the 1960s. Major complications of bacterial and fungal sepsis have become significantly less of a problem today. This is because with improved immunosuppressive agents available the

previously high doses of steroids and anti-lymphocyte globulins are now avoided. Although bacterial urinary tract infections are still common, currently the more significant and specific problems of infection after renal transplantation remain with viral infections. These include cytomegalovirus which carries implications for long-term graft survival and acute renal allograft rejection in the immediate post transplant periods and herpes simplex virus which has been implicated as a cause of genitourinary carcinoma and Kaposi's sarcoma(42). Epstein Barr virus has been implicated as a cause of post transplant lymphoproliferative disease, and myogenic tumours involving bone(43,44). Adenovirus types 11 and 35 are associated with haemorrhagic cystitis in renal transplant recipients. The incidence of squamous and basal cell cancers of the skin have been reported to increase significantly after transplantation but no viral causal relationship has been established(45). Demineralisation of bone through long-term steroid administration leads to osteopaenia and pathological fractures. New diabetes mellitus occurs in a small percentage of kidney transplant recipients due to the diabetogenic effect of the glucocorticoids and cyclosporine. Hypertension after renal transplantation is common and may result from medications such as glucocorticoids, cyclosporine and tacrolimus and from allograft rejection. Metabolic complications like dyslipidaemia and cardiovascular complications such as ischaemic heart disease can also complicate renal transplantation as a result of immunosuppressive therapy. Erectile dysfunction in patients after renal transplantation is not uncommon but can be due multiple factors including immunosuppressive therapy(46).

SURVIVAL IN RENAL ALLOGRAFT TRANSPLANTS

A successful renal transplant from a living related donor currently remains the most effective replacement therapy for both adults and children with end stage renal disease, resulting in decreased time on dialysis, increased graft survival and better function compared to cadaver donor transplants. Predictors of graft survival in children who receive live related renal transplants include age at transplantation, time on dialysis and race, with adolescents and black recipients having the lowest survival rates(47). For cadaveric renal transplants, one and five-year graft survival rates are reported as 92% and 78% respectively(48). Donor age and the cause of death, the type of graft perfusion and cold ischaemia time and the type and length of dialysis treatment are known to be significant factors in determining the onset of graft function or failure.

For the long-term survival of renal allograft transplants, it has been reported that HLA identical twins have a half life of 25 years, parental donors a half life of 13 years and for cadaver donors a half life of eight to eleven years. HLA, A, B, DR matching are known to exert the greatest effect on the half life with Caucasian recipients having a

longer half life than black recipients(49). Renal biopsy is important and recommended for the long-term renal transplant survivors. This is because any histological changes noticed on biopsy may help to further predict graft prognosis in the long- term(50).

FUTURE OF RENAL TRANSPLANTATION

The single most important problem of renal transplantation today remains the shortage of both live and cadaver organ donors. This is because of the improved success in transplantation surgery over the years and the more efficient and successful measures taken to treat the critically injured patients from road traffic accidents resulting in reduced deaths, and the successful performance of more neurosurgical operations. Consequently, transplant co-ordinators worldwide are pursuing a continuously shrinking donor population. Future advancement of renal transplantation therefore depends on several factors. These include the reduction of the number of patients on the various waiting lists by addressing successfully the wasteful problem of chronic allograft rejection resulting in fewer recipients being returned back to the waiting lists. This can be effected through the successful future developments in immunosuppressive therapy. The number of live organ donors can also be expanded by encouraging the pre-dialysis transplantation of live donors who are not necessarily related to the recipient(51). Non heart beating donors have also become increasingly an additional source for cadaver kidney donation. The accident and emergency rooms, the intensive care units and the streets are the three sources of these kind of donors(52). In addition, those developing and African countries without legislations concerning the harvesting of organs from potential brain dead cadaver donors should be encouraged to enact them urgently in order to expand the cadaver donor pools.

There also now exists more interest, laboratory investigations and speculations relating to cross species transplantation (xenotransplantation) than ever before for various organs including the kidney. Substantial progress in xenotransplantation research is currently progressing along two avenues. One level of research focusses on the immediate application of xenotransplantation using concordant sub-human primate donors. The other level is designed to achieve a much broader application utilising discordant porcine donors(53). The major barrier to discordant xenogeneic organ transplantation is the phenomenon of hyper-acute rejection which results from the deposition of a high titre of preformed antibodies that activate serum complement on the luminal surface of the vascular endothelium leading to vascular occlusion and graft failure within minutes to hours(54). Significant research is currently being focussed on the strategy to overcome hyper-acute rejection using the pig to primate transplant models. It is hoped that when the hyper-acute rejection is overcome by newer methods of prophylaxis and treatment xenogeneic kidney transplant would be possible in the near future.

Finally, the approach of a polyglycan skeleton with cellular seeding as performed for the growth of an ear, phalanx or length of a trachea though still a very long way from the complexities of the kidney, may possibly be utilisable in the future(51).

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