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An Update Overview on Paediatric Renal Transplantation

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Abstract Renal transplantation has developed to become the best renal replacement therapy for end-stage renal disease (ESRD) children. And in recent years, there are reports of good results even in infants. Currently, different programmes of enhancing cadaver kidney donation are conducted, and an alternative source comes from living donors of which parents are the main source. Cyclosporin has been used as the main immunosuppressant after transplant since the eighties, and in recent years, Mycophenolate Mofetil (MMF), and Tacrolimus (OKT3) are producing promising long term results. Anti-interleukin 2 receptor antibodies and sirolimus have also been shown to reduce early acute rejections. From the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS), graft survival of recipients below 1 year old have worst results, and those above 12 years also do not do well after a few years which might be related to drug non-compliance. Living grafts are having better results than cadaver. The main causes of graft loss are graft vascular thrombosis, rejections and recurrence of original disease. Chronic graft rejection or allograft nephropathy is the main reason for long term graft failure. The experience of paediatric kidney transplant at Princess Margaret Hospital is shared, and the good results are considered to be related to the small number of transplants that have been done in small children and infants.

Key words Complications; Donors; Immunosuppressants; Kidney Transplant; Outcome

Introduction

Since the first successful kidney transplant in 1954, renal transplantation has now developed and matured into the best treatment modality for managing end-stage renal disease (ESRD) patients even for the very young. There is a steady improvement in graft survival rate for both cadaver and living transplants with fewer rejections in recent years. In the late 80s, transplant surgeons were quite aggressive in transplanting young infants, and even kidneys from anencephaly newborns had been used as donor grafts. However, results were unsatisfactory and the outcome of transplanting such small infants was generally poor, which had led to a decrease in transplanting young infants in the early 90s. However, in recent years, with the improvement of the technique and avoidance of using small donor kidneys, there are increasing number of reports of successful results in transplanting young infants with promising outcome.[1-3] With the newer immunosuppressants, graft rejections are decreased and the overall long term graft survival is prolonged with fewer side-effects. Renal transplantation has become the best treatment option for ESRD children even at a young age in good hands.

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Kidney Source

Cadaver Donors

The main problem to kidney transplantation is shortage of donors. Much effort has been made to increase organ donation. For cadaver donation, the appointment of

coordinators to hospitals in Spain in 1989 resulted in an increase in the transplant rate to 33.6 per million population within 10 years, which was much higher than other countries during the same period.[4] In 1994, the NHS organ donor register was set up allowing individuals to register their wish to be considered as an organ donor. Worldwide, there are three acceptable systems of organ donation. One is by *Opting in (required consent)* which is a voluntary system in which the potential donor's next of kin is approached for consent of organ donation. People are encouraged to register as organ donors and to carry a donor card.[5] This is being practiced in UK. The second is by *Opting out (presumed consent)* by which potential organ donors are presumed to consent to organ donation, unless they have specifically registered not to. This is being practiced in Belgium, Germany, Italy and Singapore. The third is *Required request* in which doctors in charge of potential donors have to get someone to speak to the family about organ donation, and there is no expectation that donation will occur. This is being practiced in the United States. Statistics of rate of kidney donation and transplantation of different countries are shown for comparison (Table 1).

In Hong Kong, we are following the Opting in system of UK. Donation campaigns are conducted to increase public awareness, with a registry set up for consenting donors who are encouraged to carry donor cards. Transplant coordinators working in the transplant hospitals and clustered hospitals approach potential donors' relatives for consent. Since 2000, a scoring system for the allocation of kidneys has been introduced. The score is calculated basing on duration of waiting time, age of recipient and compatibility of HLA matching. Whenever there is a potential donor, several potential ABO compatible patients who score highest will have the HLA matched to see who should receive the kidneys. However, the number of cadaver transplant only comes up to an average of 50-60 per year in the past few years.[6] This can hardly meet the need of over three thousand patients on dialysis who are waiting for a transplant.

Table 1 Kidney transplantation activity rates (p.m.p)

	Cadaveric	Living
Spain	50	1
Austria	41	6
USA (UNOS)	35	16
France	31	1
Norway	28	18
Sweden	27	14
Netherlands	25	7
Germany	25	4
UK & Ireland	24	4
Italy	21	21
Denmark	20	7
Australia	19	8
Greece	9	8
Hong Kong	6	3

Source:- International figures on organ donation and transplantation activities 1998. Select committee of experts on the organisational aspects of cooperation in organ and tissue transplantation. Organs and Tissues 1999;3:141-146. Hong Kong data based on Renal Registry of Hospital Authority (2000)

Living Donors

Another kidney source is from living donors. Potential donors are mostly parents and siblings who are above 18 years old and able to give consent. Others include spouses, partners or relatives. Such mode of transplant is more common in children and according to the North America Pediatric Renal Transplant Cooperative Study (NAPRTCS), 49% of all paediatric transplant are from living donors, with 41% from parental origin.[7] Results of living transplantation generally fare better than that of cadaver transplant. This might be due to a better preparation of an elective nature of the operation having a shorter graft ischaemic time, and a better HLA matching since most of them are haploid in genetic constitution. As for long term sequelue for the donor, there are no evidences to show that donors have higher chance of proteinuria, hypertension, and renal failure.[8,9] However they need to be followed up for monitoring of complications. With the introduction of laparoscopic nephrectomy in recent years,[10,11] the operation becomes less painful to the donor who is left with a smaller scar. It may help enhance the willingness of donation. However the surgery is more demanding and possible damage to the donor kidney may be a factor for a balanced consideration.

New Immunosuppressants

Prednisone, Cyclosporin and Azathioprine have been the mainstay of treatment since the 80s. In the 90s, Tacrolimus (OKT3) and Mycophenolate Mofetil (MMF) add to the choice of immunosuppressants in inducing and maintaining immunosuppression.[12-14] Side effects of these newer drugs are less compared with cycloporin with respect to hyper-

tricosis, gum hypertrophy, hypertension, hyperuricaemia, and nephrotoxicity. Steroid may even be spared.[15,16] Recent studies seem to show MMF may reduce the incidence of chronic allograft rejections and useful for long term maintenance.[17] Anti-interleukin 2 receptor antibodies (basiliximab and daclizumab)[18,19] and Sirolimus have produced impressive reduction in early acute rejections, though long term outcome results are awaited.[20] For rejections, pulses of prednisolone can be used with other immunosuppressants, like OKT3 or Antilymphocyte globulin therapy.

Graft Survival

According to the 12th Annual Report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) published in 2001, the overall one-, 3- and 5-year graft survival probabilities were 91%, 85%, and 80% for LD recipients, and 83%, 73%, and 65% for CD recipients respectively.[6] By breaking down into four age groups, 0-1 years, 2-5 years, 6-12 years, >12 years, it was noted that those below 1 year old fare worst, and the >12 years group though having good results in the first few years, dropped to a low range afterwards, possibly due to drug non-compliance. In recent years, there have been increasing reports from various centers on the successful results in transplanting infant.[1-3] Such encouraging results could be related to the maturation of the technique in highly specialised centers, and avoid using donor kidneys from small children. Without acute tubular necrosis, superior graft outcome can be achieved.

Reviewing specifically living transplant between 1988-1994 by The United Network for Organ Sharing (UNOS) Scientific registry (unlike NAPRTCS, UNOS is a mandatory transplant registry), initial graft survival rates were again poorer for infants compared with other age groups.[21] Over time the graft survival for adolescents steadily declined, whereas graft survival for infants remains stable. At 7 years, graft survival rates were markedly worse for adolescents (55%) compared with infants (71%), young children (78%), and older children (67%). The overall graft survival of all age groups at 6 years was 69%. As a strategy at the centers, unless graft thrombosis and technical losses in the infant and small child recipients can be eradicated, as well as long-term graft survival in adolescents could be improved, it will be difficult to subject a child's parent or sibling to donor nephrectomy.[22]

Complications

According to the annual report of NAPRTCS,[6] the main causes of graft loss were graft vascular thrombosis (12.1%), acute rejection (16.4%), chronic rejection (31.2%), and recurrence of original disease (5.7%), patient discontinued medication (3.6%). For vascular thrombosis, it is particularly more common in infant transplant. Chronic rejection or chronic allograft nephropathy was the most important cause for long term graft failure. The overall patient mortality was low and the 36 months post-transplant patient survival for LD and CD was 96.3% and 94.3% respectively. Other complications for these transplanted patients were infections and side-effects related to drugs.

The HK/PMH Experience

Renal transplant had started to be done in children in Hong Kong in late 80s and the early 90s. There were a total of 19 renal transplant <18 years old done in the past 5 years (1998-2002), with 3 <10 years old and 16 between 10 - <18 years old.[5] Because of the small number of ESRD children, it was decided by the Hospital Authority to have them concentrated at the Paediatric Nephrology Center at Princess Margaret Hospital (PMH) for management. By 2003, we have accumulated a total of 24 transplanted children having 25 allografts done in the past 10 years or so. There were 18 CD (72%) and 7 LD (28%), and the mean age at transplant was 15.7±5.1 years. The mean duration of follow up was 3.2±2.5 years. The mean waiting time for the local CD grafts was 4.4±2.4 years (range: 1.2-8.9 years). The acute rejection rate was low, with only 9 episodes in 6 grafts, and 19 grafts (76%) were free from rejections.[23] This compared favorably with that reported by NAPRTCS having 44 % free from rejections.[6] As for 1 & 3 years graft survival, we have 100 % and 100% for LD and 93.8% and 70.3% for CD respectively (cf. NAPRTCS – 1 & 3 years graft survival were 91% and 85% for LD, and 83% and 73% for CD recipients). However the number of our patients with more than three years post-transplant was only small (6 for LD and 6 for LD), though we had our first transplanted graft surviving for more than ten years. There were a total of 4 graft failure, including 2 due to recurrence of Focal Segmental glomerulosclerosis, 1 post-transplant lympho-proliferative disease, and 1 severe acute rejection. There were no cases of mortality with 100% patient survival. The good results that we have comparing

with those of NAPRTCS possibly relate to the fewer number of transplants done in small children, the youngest being 6.7 years old.

The Future

There has been much development in paediatric transplantation in recent years, especially in the improvement of results in infant transplants. With newer immunosuppressants better long term results can be achieved with fewer side-effects, and those unsightly features produced by cyclosporine and growth suppression by steroid may be avoided. The obstacles to long term success that need to overcome are chronic allograft nephropathy, recurrence of original diseases, and a small chance of malignancy. The shortage of donor kidney remains the main problem to be solved. It is hoped that by changing the society's attitude towards organ donation and instituting a system to facilitate its yield, organ donation can be enhanced. Before that, transplants from living donors remain the optimal solution for these unfortunate ESRD children.

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