Renal Transplantation in Children

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Renal failure in children is a severe debilitating disorder as it not only causes uremic syndrome but is associated also with severe growth retardation. In infants it can result in central nervous system complications which include progressive encephalopathy, developmental delay and seizures [36]. Approximately 7 children per 1,000,000 total population aged less than 16 years, have renal failure [42]. It has been shown that early treatment of renal insufficiency results in improved growth and neurological development [21,22,34].

The medical management of renal insufficiency consists of correction of electrolyte imbalance, treatment of hypertension and urinary tract infection and provision of intensive nutritional support. At end stage renal disease (ESRD) dialysis is commenced and renal transplantation should be considered as it offers the best prospects of a normal life style with improved growth and development in the child and adolescent [13]. The treatment is carried out by a team of specialists which include nephrologist, urologist, specialist nurses, dieticians and psychologists. Parents are also actively involved in the child's treatment, ensuring that medication is given regularly and in many cases performing peritoneal dialysis in the home environment.

Medical therapy - advances

Early treatment of renal insufficiency in children is mandatory to maintain normal development [13, 22]. Advances include the use of human recombinant erythropoietin which can correct the anemia of chronic renal failure. Controlled studies of its affect on growth and cognitive development are being performed [25,28]. Also recombinant growth hormone has been shown to restore growth rate in the short term [3,26]. It is hoped that the addition of these two drugs to the established form of medical treatment will improve the development of the child, however the long term affect of this therapy is as yet unknown.

Dialysis

Indications for dialysis are fluid overload in the oligo-anuric patient, single or multiple electrolyte abnormalities, no response to medical treatment or progressive uremia. Peritoneal dialysis is most commonly used in infants and children and is considered as an interim treatment while the patient awaits a renal transplant. Dialysis can be commenced in the neonate if required [40]. Peritoneal dialysis is carried out by insertion of a silastic tube with single or double Dacron cuffs into the peritoneal cavity under local or general anaesthetic. Dialysis is performed intermittently or continuously overnight and once the technique has been established, it can be carried out by the parents in the home environment. Complications of dialysis include mechanical outflow obstruction, intra-abdominal bleeding, internal organ injury and tube site infection. Late complications are peritonitis, cuff erosion, hernia formation, flow obstruction with omentum or fibrin deposits. Acute pancreatitis is a rare but life threatening event.

The peritoneal catheter has a limited period of function and in a large series of patients [40] there was a survival rate of 94 % in the first year and 34 % in the second year. Hemodialysis with placement of a double lumen silastic catheter into the right atrium via the internal jugular vein is reserved for emergency treatment or if peritoneal dialysis has been unsuccessful. Hemodialysis is less suitable for young children as they do not tolerate exchange of large volumes of blood and treatment is performed in a hospital [40]. Renal transplantation with its promise of a return to a normal physiological state is the goal of most ESRD programmes.

Pre-transplant evaluation

The risk of recurrent primary disease and the affect of lower urinary tract abnormalities are the specific factors to be considered in pre-transplant evaluation of the child. Recurrent primary disease in the transplant kidney may account for up to 5 % of graft failure in children [6,18]. Poor results are noted in primary oxaluria if liver transplantation has not been performed concurrently or previously. Many forms of nephritis may show histological recurrence in the graft but no clinical manifestation or only mild disease is noted in the kidney transplant. However, focal segmental glomerulosclerosis and mesangiocapillary glomerulonephritis occur with sufficient frequency and severity to deter the use of living related donors unless there is no alternative. The same applies to hemolytic uremic syndromes. A rare antiglomerulo-basement membrane nephritis affecting some patients with Alport's syndrome usually results in graft failure.

There are significant lower urinary tract abnormalities in 20 % of children who undergo renal transplantation [37]. These include posterior urethral valves, neuropathic bladder, vesicoureteric reflux with abnormal bladder function and bladder exstrophy. Unfavourable results of renal transplantation have been reported in patients with posterior urethral valves [7,35]. The cause of the poor outcome was a possible reduction of bladder compliance which may transmit increased pressure to the transplant kidney and lead to decreased blood flow with reduced glomerular filtration; however urodynamic data on bladder function was not submitted to support this hypothesis.

A prospective study of bladder function before transplantation in boys with posterior urethral valves is being undertaken [9]. Abnormal bladder function may have a serious affect on renal transplants and the lower urinary tract in the "at risk" patients must be very carefully assessed.

Characteristics of a suitable bladder to receive a kidney transplant, are a good volume (for recipient size), low end-fill pressure (less than 30 cms of water) and good flow rate with absence of gross detrusor instability [5]. Abnormal bladders may be reconstructed with ileum, colon or stomach [28] or an enlarged ureter which can be incorporated into the bladder in a "clam-type" ureterocystoplasty [11,23]. These containers may be emptied by intermittent catheterisation per urethra or a Mitrofanoff channel. Intermittent catheterisation to maintain bladder emptying and prevent infection is not a contraindication to renal transplantation [2]. It is recommended that reconstruction should be performed 6 months before the transplant, however, problems may occur with mucus, stone formation and infection during the interval between reconstruction and transplantation if the urine output decreases.

Hematuria and cystitis are a specific consequence of a high acid output in the gastrocystoplasty if it is associated with oliguria [29]. Transplantation into urinary diversions, e.g. ileal or colonic conduits or ureterostomies have been described [5,33] and are of equal success to those transplanted into reconstructed bladders. Pre-transplant nephrectomy is performed for gross proteinuria, hypertension or recurrent urinary tract infections.

Transplantation

The surgical technique of kidney transplantation in adults and children is similar. Selection of the site of anastomosis of donor artery and vein to recipient is influenced by previous abdominal surgery or transplants, relative size of donor kidney and the need for simultaneous surgery, e.g. recipient nephrectomy. If the kidney size permits, the approach should be through a "hockey-stick" incision, extraperitoneally to preserve the peritoneal cavity for dialysis at a later date. However, a large adult kidney can be inserted into a 10-20 kg infant via a midline incision intraperitoneally with end-to-side anastomosis of the renal vessels to the aorta and inferior vena cava. Vascular end-to-side anastomosis is usually performed with 6/0 prolene, 4 quadrant sutures [37]. A ureteric anastomosis can be performed in the traditional Leadbetter-Politano fashion or a more simple Lich-Gregoir approach. A ureteric stent to ensure safe drainage during the 3 to 4 day postoperative period when there is a massive diuresis is of benefit. Early graft function is expected.

Perioperative management is important and protocols vary with each unit. Basic principles of a typical regime [16] include administration of perioperative antibiotics (third generation cephalosporins) at the time of premedication. A central venous pressure (CVP) line and arterial line are in-

serted in the operating theatre, after the induction of anaesthesia.

High circulating fluid volume is maintained and the central venous pressure during reperfusion of the graft should be 15-18 cms of water. Plasma and red blood cells are continuously perfused and Manitol (0.5 g/kg) is given before the clamps are released. Postoperative care should be in a high dependency unit with meticulous control of perfusion and electrolyte balance.

Immunosuppression

There is no consensus of how to achieve optimum immunosuppression but triple or quadruple therapy with cortical steroids, Azathioprine, Cyclosporin and a polyclonal antibody is standard practice. Maximal immunosuppression with minimal toxicity is obtained using several drugs simultaneously or sequentially [6,22,32,42]. Prednisolone blocks the activation of the T-cells while Cyclosporin blocks Interleukin II, which maintains the activity of T-cells. Azathioprine is an anti-metabolite which blocks DNA and RNA synthesis and thus proliferaton of lymphocytes. These three drugs are relatively ineffective in suppressing acute rejection and polyclonal antibody such as anti-thymocyte globulin is incorporated in anti-rejection therapy in many centres.

Surgical complications

Early vascular thrombosis particularly of the renal vein is peculiar to pediatric renal transplantation. Other surgical complications are ureteric fistulae or obstruction, lymphocele, reflux or late onset of renal artery stenosis. The high incidence of vascular complications is related to vessel size and possibly to poor blood flow through the kidney secondary to a low cardiac output in a small recipient [7]. The European Dialysis Transplant Association (EDTA), on assessing graft loss in children (1983-1986), found that 20 % were associated with venous thrombosis. Grafts from older children and with good HLA DR-matched donors had a better outcome [4].

The Toronto Group found that 10 of 38 graft failures in recipients under 6 years were associated with venous thrombosis [7]. The incidence of transplant renal artery stenosis varies from 4 % to 15 % [10,18,41]. A recent study from Los Angeles [27] looking specifically at transplant renal artery stenosis reported an incidence of 8 % (31 to 400 cadaveric grafts) and the complication occurred approximately 12±6.1 years after the transplant. In a large transplant series ureteric complications occurred in 14 % of cases [31,34]. Transient ureteric leak in the early post-operative period occurs with the abnormally high urine output. Persistent leak may require open surgical intervention or a ureteric stent. Breakdown of ureterovesical anastomosis may be related to ischemic necrosis secondary to a period of acute rejection. Late onset ureteric stenosis is probably secondary to ischemia of the ureter.

Results

The overall success of renal transplantation is good but varies considerably between units with a one year graft survival of between 57 % and 96 % [32]. Since the introduction of Cyclosporin there has been a significant improvement in both graft and patient survival in the pediatric age group [8]. Generally cadaveric transplants in infants and young children fare less well than from living related donors. Also cadaveric donors less than 6 years old are associated with relatively poor outcome particularly when the recipient is also young. Early studies of children under 5 years of age from North America reported actuarial cadaveric survival rates of 28 %-58 % [1,42].

More recently the EDTA reported actuarial graft survival rates of 65 % at one year for children 0-5 years, 78 % for the group aged 5-15 years [4]. The 1989 Report of the North American Pediatric Renal Transplant Co-operative Society [20] had similar results with the youngest recipients having the lowest graft survival rates, 51 % 0-1 year. A recent report from Spain [19] reviewing 10 years experience of renal transplantation in children found a 1 year survival rate for first cadaveric grafts of 67 % in the 1-5 year group.

More encouraging results have recently been reported by the Minnesota Group [32] who have equal graft survival in all age groups. Their study includes a predominance of living related donors (80 %). Since 1983 their graft survival at 1 and 5 years is 96 % and 82 % respectively. In all age groups living related donor kidneys continue to be the most im-

portant predictor of long-term renal allograft function. However, improved results with cadaveric transplantation in children under 6 years of age have recently been reported by the Los Angeles Group using quadruple immunosuppression with the addition of anti-lymphocyte globulin to Cyclosporin, Azathioprine and Prednisolone [15]. The one year actuarial graft survival improved from 33 % to 90 % with no change in patient survival. This experience was mirrored by the Minnesota Group [32] when cadaveric recipients received a two-week course of Minnesota anti-lymphocyte globulin in conjunction with standard triple immunosuppression.

Results of renal transplantation in children will continue to improve. Reconstruction of the abnormal bladder before transplantation should contribute to better long-term kidney function. Intensive perioperative management with meticulous surgical technique should provide primary function at the time of kidney insertion. Manipulation of immunosuppression will continue to increase graft and patient survival. Renal transplantation in children and in infants remains the optimum treatment of end stage renal disease.

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