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MIXED ALLOGENEIC CHIMERISM AND TRANSPLANTATION TOLERANCE

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Transplantation tolerance in clinic has remained an elusive goal for transplanters since last five decades. Numerous experimental designs and conditioning regimes have been developed in rodent models where indefinite survival of vascularized allografts without immunosuppression has been reported. Relevance of these models in development of clinical tolerance induction protocol has remained very limited since these strategies fail to achieve similar results in humans. It has been suggested that it is relatively difficult to achieve transplantation tolerance in humans and large animals in comparison to inbred lab animals due to the presence of memory T-cell population in the later that are resistant to tolerance induction. It is quite possible that exposure to multiple microbial environment invokes memory T-cell system in humans and large animals as compared to inbred mice. Recently discovered costimulatory molecule ICOS is necessary to activate memory T-cell system. Blockade of this molecule could be the future agenda for tolerance.

More than 50 years ago Owen described naturally occurring "mixed chimerism" in fraternal bovine twins (sharing common placental circulation) who had two distinct types of erythrocytes long after their birth. Shortly after this Medawar et al showed that such chimeric twins were also tolerant to each other's skin grafts. Subsequently the same group also created neonatal mice model of chimeric tolerance where splenic and donor bone marrow stem cells from adult mice were infused in neonatal mice. The neonatal mice accepted skin grafts (for indefinite period) from adult donor mice. They demonstrated the link between chimerism and tolerance for the first time in the field of transplantation biology. It was clear from this data that stem cell transplantation can be used to create chimeric tolerance and be used effectively to create tolerance in solid organ transplantation. However this technique was not clinically acceptable to solid organ transplanters because of conditioning toxicity, graft versus host disease and failure of stem cell engraftment when MHC barriers were transgressed; as a result hematopoietic stem cell transplantation protocol could not be generated for routine practice in solid organ transplantation.

Transplanters were aware that mixed chimerism is superior strategy to full chimerism for tolerance induction where donor's and recipient's antigen presenting cells are coexisting providing full immune competence to third party antigens. In the recipient, thymic T-cells will continue to populate the peripheral system to interact with their own antigen presenting cells. Rats (not mice) and humans are prone to chronic rejection and mixed hematopoietic chimerism protects them from developing it.

This ideal concept has been our attainable (!) goal in living related renal transplantation program.

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PAEDIATRIC KIDNEY TRANSPLANTATION

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ABBREVIATIONS

ESRD	end stage renal disease
NAPRTCS	north american paediatric renal transplant cooperative study
UNOS	united network of organs sharing
MMF	mycophenolate mofetil

KEY WORDS

paediatric kidney transplantation; end stage renal disease.

Kidney transplantation is the preferred modality of treatment and the final goal of management of children with end stage renal disease (ESRD). In advanced countries paediatric kidney transplantation is well established with success rates equal to the transplantation in adults. The North American paediatric renal transplant cooperative study (NAPRTCS) established in 1987, publishes yearly reports notifying stable number of more than 500 kidney transplantations /year in USA, Canada and Mexico. The number of children reaching ESRD and requiring kidney transplantation is growing exponentially. The number of cadaver donor allografts available for transplantation has not increased in the last 20 years and the waiting period to receive cadaver kidney is longer now. Because of the special needs and problems of growth and development, paediatric patients have been given special consideration by United Network of Organs Sharing (UNOS) which is the regulatory agency responsible for organ allocation in the United States [1]. Recent data bases report cadaver transplantation in 49.9 % of paediatric age group, majority receive allograft between 6-17 years (73%) with 1 year survival in living related donor transplantation of 94 %, and in cadaver transplantation, of 93 %. Recent data from 12 European registries which analyzed 3184 children receiving renal replacement therapy (RRT) showed that graft survival has improved in allograft recipients from all age groups including the most difficult age group to treat i.e. those under 5 years from 1995 onwards [2]. Causes of allograft failure in both these series from USA and Europe are similar; chronic rejection (32.5 %); acute rejection (15 %); vascular thrombosis (in younger age group and in those who received peritoneal dialysis prior to transplantation (12 %) and recurrence of original disease (6.3 %). Mortality in 10% was due to infections, cardiovascular events, cerebrovascular accidents and rarely due to malignancy, mainly related to immunosuppression.

Growth, development and quality of life definitely improved over last 2 decades in paediatric allograft recipients in Western countries. It is now well recognized that paediatric patients require treatment in specialized paediatric centers and not by adult nephrologists because of the differences in immune

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responsiveness, drug metabolism and clearance, perfusion of transplanted allografts and special needs related to growth and development. Pre-transplant viral surveillance and immunization against chickenpox, hepatitis B, H. influenzae, are important in reducing morbidity and mortality in post-transplantation period. Improvement in growth is the major advantage of kidney transplantation in children. Children with significant growth retardation have greater catch-up growth following transplantation however, their growth is not sustained and normal adult height is seldom achieved. Attempts at reducing the dose of corticosteroids (which reduce growth hormone/ insulin like growth factor-1 axis) by giving alternate day oral prednisolone and use of growth hormone are successful in improving height in majority of children in initial post-transplantation period. Steroid-free immunosuppression is being tried by some centers for growth improvement. Thus the future of transplantation continues to be exciting with growing opportunities for reduced immunosuppressive regimes.

On the Indian scene the picture is not so rosy. Paediatric kidney transplantation is on slow tract. Expertise and experience in treatment of ESRD in children is improving. Trained paediatric nephrologists are involved in paediatric transplantation programmes in Ahmedabad, Bangalore, Lucknow, Chennai, Vellore, Mumbai and Delhi. Approximately 2-5 paediatric renal transplantations are performed per year at each center. A recent article depicts the current status from a single center that performed 39 paediatric living related donor kidney transplantations. The first year allograft survival was 89% and 3 year survival, 70%. The reason behind the decline in renal survival was stoppage of cyclosporin A due to financial constraints by 12 /34 patients 14-18 months post transplantation. Hypertension requiring 2-3 antihypertensive drugs; infections and complications related to immunosuppressive drugs were the main problems post transplantation[3].

Improved outcome in paediatric kidney transplantation is attributed to early diagnosis (or antenatal diagnosis by ultrasonography) of obstructive uropathy, congenital anomalies like hypoplasia / dysplasia or polycystic kidney disease; common potential causes of ESRD. Treatment of chronic kidney diseases by paediatric nephrologists in specialized paediatric centers to optimize the treatment by addressing the issues of growth, development, nutritional requirements, proper medication for hypertension, anemia, early treatment of bone disease etc. are inevitable components of dialytic treatment. Period of transition from chronic kidney disease to ESRD can be in months/ years. During this period regular follow up and parent counseling for renal replacement therapy helps in giving psychological support to the family preparing potential living related donor and for financial arrangements for transplantation. Dialytic period should be kept at minimum. Pre-emptive transplantation has definite advantage of lower morbidity and lesser expenses as compared to maintenance dialysis. Children with complications related to fluid/ electrolyte/ acid base balance need short term dialysis support prior to transplantation. Continuous ambulatory peritoneal dialysis though prohibitively expensive in India, is technically preferable to hemodialysis in children below 7-8 years of age. Parents are willing donors for their children, but cadaver donor allografts should be available at par with adults. Pre and post transplant care should preferably be delivered by the same paediatric nephrologist in the same center.

As regards financial aspect of kidney transplantation, with improvement in economic situation, initial expense of Rs. 100,000 -150,000/- for renal transplantation is within the reach of middle class families, but it is the expense required for immunosuppressive drugs like cyclosporine A/ tacrolimus, mycophenolate mofetil (MMF), polyclonal /monoclonal antibodies, intravenous methylprednisolone (used for treatment of rejections) and gancyclovir for cytomegaloviral infection which add to the total cost of post-transplantation care. Unless medical insurance becomes available, kidney transplantation will not be a viable therapeutic option for ESRD in children who belong to economically compromised class.

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ANESTHESIA IN PAEDIATRIC RENAL TRANSPLANTATION- AHMEDABAD EXPERIENCE

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ABSTRACT

Background: Advances in surgery, anaesthesia and immunosuppressive therapy have made renal transplantation a preferable alternative to chronic dialytic support in paediatric patients with ESRD. Properly selected anaesthesia and accurate monitoring will minimize the toxicity and perioperative complications in these patients. **Patients & Methods:** This was a retrospective, single center study on anaesthetic and perioperative management of 74 paediatric renal allograft recipients (<18 years of age) from January 1, 1994 to December 31, 2003. Majority of children maintained on hemodialysis had cardiovascular and metabolic complications. One child underwent preemptive transplantation. Forty six patients received balanced general anaesthesia with atracurium and isoflurane along with epidural anaesthesia; 28 patients were anaesthetized with combined spinal- epidural anaesthesia. Intraoperative finding of size of vessels was the deciding factor for anastomosis site. Haemodynamic stability was maintained by transfusion of 115.4 ± 10.6 ml/kg BW crystalloid, 4.5 ± 0.45 ml/ kg BW colloid and 1.6 units of blood. Mannitol, 20% (0.5-1 gm/ kg BW) and Furosemide (2-5 mg/kg BW) were used for diuresis resulting in 32.5 ± 4.6 ml/kg BW of urine output on table. Postoperative pain relief was provided by epidural narcotics in all patients.**Results:** Significant perioperative complications related to anesthesia were not observed in any patient. All recipients had early adequate allograft function. No morbidity/ mortality was observed in first 48 hours after surgery. **Conclusions:** Anticipating the potential problems of paediatric renal transplantation, mortality and morbidity can be controlled by accurate surgical, anaesthetic and postoperative management. In small children (<20 kg) receiving adult kidney, aggressive fluid management aimed at maximizing renal allograft perfusion is critical in optimizing early allograft function.

KEY WORDS

paediatric renal transplantation**;** anesthetic management

INTRODUCTION

Considerable progress has been achieved in organ transplantation to make it an acceptable therapeutic modality for patients suffering from end stage organ failure in adults as well as children. Improvements in immunosuppressive therapy, surgical techniques and organ preservation have facilitated increased patient and allograft survival.

Paediatric transplantation although relatively recent, has gained fairly rich experience with replacement of failing

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kidneys, liver and heart. Accumulated statistics over the last few years has proved that transplantation is the best option for children with end stage renal diseases (ESRD)[1, 2]. Transplantation is a superior alternative to dialytic support which can not address to problems of uremia related impaired growth and cognitive development as well as progressive cardiovascular complications [1-5]. Hence relative high mortality and poor quality of life associated with chronic dialysis in young children justify the risks of surgery and long-term immunosuppression [1,6,7]. In fact, the current recommendation is to "preemptively" transplant children with progressive renal insufficiency.

We carried out a retrospective study of 74 paediatric renal transplantations at the Institute of Transplantation Sciences, Ahmedabad. The aim of this study was to evaluate preoperative characteristics, intraoperative and postoperative management of paediatric renal allograft recipients with a special reference to anesthetic care.

PATIENTS

Children below 18 years of age who underwent renal transplantation from January 1st, 1994 to December 31st, 2003 were included in this study. Data analyzed were demographic characteristics, preoperative status, anaesthesia and surgical technique, intraoperative haemodynamic changes and postoperative complications.

DATA ANALYSIS

Table 1: Demographic characteristics

Characteristics	Mean ± SD
Age (Years)	15.2 ± 2.4
Sex (M: F)	69 / 5
Weight (Kg)	30.7 ± 5.46
Dialysis therapy (HD/PD)	61 /12
Duration of dialysis (Months)	8.4 ± 1.3
Source of donor (Live /Cadaver)	69 / 5

There were 69 male and 5 female recipients. Two patients were of 10 years of age and both of them weighed less than 10 kg. Eleven patients were between 10 to 14 years of age who weighed between 10 to 20 kg and rest of the patients were adolescents weighing more than 20 kg. There were 69 live and 4 cadaver donors who were adults. One girl aged 15 years weighing 22 kg received dual transplantation from a cadaver donor aged 3 years.

Sixty one patients were on maintenance hemodialysis out of which 41 were maintained on dialysis for more than 6 months while 20 were transplanted within first 6 months of dialysis therapy. Twelve patients were maintained on continuous ambulatory peritoneal dialysis before transplantation. One patient underwent preemptive transplantation.

Table 2: Etiology of ESRD

Primary cause of ESRD	Patients (n=74)
Chronic glomerulonephritis	34 (45.9 %)
Reflux uropathy	13 (18.6 %)
Membranoproliferative glomerulonephritis	8 (10.8 %)
IgA nephropathy	5 (6.8 %)
Alport syndrome	3 (4.1 %)
Focal segmental glomerulosclerosis	3 (4.1 %)
Renal stone disease	3 (4.1 %)
Membranous nephropathy	2 (2.7 %)
Rapidly progressive glomerulonephritis	2 (2.7 %)
Renal dystrophy	1 (1.4 %)

Chronic glomerulonephritis, reflux uropathy and IgA nephropathy were the most common causes of ESRD (table 2).

Table 3: Preoperative medical status

Preoperative medical finding	Patients (n=74)
Hypertension	63 (85.1 %)
ECG (LVH/ST-T wave changes/ BBB)	46/10/6
Cardiomegaly on X-Ray Chest	30 (40.6 %)
2-D Echocardiography (Reduced EF/ LV dysfunction)	10/4
Diabetes mellitus	4 (5.4 %)
Uraemic convulsions	4 (5.4 %)
Renal osteodystrophy	3 (4.1 %)

Sixty three (85.1 %) patients were hypertensive for more than 6 months before transplantation and were receiving antihypertensive drugs like clonidine, calcium channel blockers, β-blockers and ACE-inhibitors. Four patients were on insulin for diabetes mellitus. Three patients had features of renal osteodystrophy and could not walk on their own. All the patients were receiving calcium and vitamin D

supplements along with erythropoietin therapy (table 3). Bilateral nephrectomy was done for uncontrolled hypertension in 2 patients and for reflux uropathy in 1 patient before transplantation.

Table 4: Mean values of laboratory investigations on the day of surgery

Preoperative investigation	Mean ± SD
Hb (gm%)	9.04 ± 2.0
Hematocrit (%)	26.8 ± 7.3
Blood urea (mg%)	76.8 ± 14.4
Serum Creatinine (mg %)	4.97 ± 2.75
Serum Potassium (mmol /L)	3.56 ± 0.5
Serum Sodium (mmol/ L)	138 ± 4.96
Random Blood Sugar (mg %)	94.03 ± 16.8

All patients were mildly anaemic with lowest hemoglobin (Hb) of 7.4 gm% and highest hemoglobin of 13.2 gm%. Hematocrit ranged from 20 to 37 %. Six patients had elevated liver enzymes although their serum bilirubin was in normal range. Serum electrolytes and coagulation profile were within normal limits in all the patients (table 4).

ANAESTHESIA

Each patient was dialyzed within 24 hours preceding transplantation surgery. Immunosuppressive regime decided by the nephrologist was started day before surgery and anti-hypertensive medications were continued till morning of the surgery.

Table 5: Anaesthesia Technique

Technique of anaesthesia	Patients (n=74)
General anesthesia combined with epidural anaesthesia	46 (62.2 %)
Combined spinal and epidural anaesthesia	26 (35.1 %)
Combined spinal and epidural anaesthesia, but needed supplementation with general anaesthesia	2 (2.7 %)

Peripheral venous access was secured with 18/20 G IV cannula and IV Midazolam (0.05 mg/kg body weight-(BW) was given as premedication. Patients receiving general anaesthesia were induced with Inj. Fentanyl (2 ηg/kg BW) followed by Inj. Thiopentone sodium (5-7 mg/kg BW). Inj. Succinylcholine (1.5-2 mg/kg BW) was used to facilitate intubation and patients were maintained on N2O, O2, Isoflurane and Atracurium. Epidural catheter was placed in lateral position in L3-4 or L2-3 space in all the patients. In patients who received combined spinal and epidural anaesthesia, double space technique was utilized. Spinal anaesthesia was given with Bupivacaine, 0.5% (2.5 ml) and mixture of Bupivacaine, 0.5% and Xylocaine, 2% with adrenaline (1:200000) was used for epidural anaesthesia with dosage according to weight of the patient. Continuous effect was achieved with repeating one-third of the initial dose of local anaesthetic at regular intervals without waiting for the effect of the previous dose to wear off (table 5).

MONITORING

Standard monitoring consisted of electrocardiogram (ECG), noninvasive blood pressure (NIBP), pulse oxymetry, temperature and central venous pressure (CVP). Central venous catheter was introduced in all the patients through internal jugular route. In two patients weighing less than 10 kg, right radial artery was cannulated for both invasive blood pressure (BP) measurement and arterial blood gas analysis. Capnography was used in all patients who received general anaesthesia.

Table 6: Surgical technique

Site of anastomosis		Patients (n=74)
Extraperitoneal	External iliac vessels	61 (84.4 %)
	Common iliac vessels	10 (14.3 %)
	Common iliac artery + IVC	1 (1.4 %)
Intraperitoneal	Common iliac artery + IVC	1 (1.4 %)
	Aorta + IVC	1 (1.4 %)

External iliac vessels used for anastomosis in adults were used in 61 patients weighing more than 20 kg, In 11 patients weighing between 10-20 kg, common iliac vessels were chosen for anastomosis; and in one patient weighing less than 10 kg, anastomosis was done with common iliac artery and inferior vena cava (IVC) extraperitoneally. Two patients required intraperitoneal placement of kidney, with anastomosis to aorta and IVC in one; and to common iliac artery and IVC in another who underwent dual transplantation (table 6).

INTRAOPERATIVE HAEMODYNAMIC CHANGES

Thiopentone used for induction caused no significant fall in BP, however stress response to endotracheal intubation was observed in all patients who received general anaesthesia. Haemodynamic stability was better maintained in patients who received combined spinal epidural anaesthesia whereas five patients anaesthetized with general anaesthesia required Inj. Nitroglycerine for control of BP. Inj. Mannitol (0.5gm/kg BW) and Inj. Frusemide (2-5 mg/kg BW) were given intravenously prior to release of the clamp in all patients.

Table 7: Haemodynamic changes at the time of reperfusion

Haemodynamic factor	Before clamp release	After clamp release
Pulse (per min)	90.3 ± 6.7	100.3± 7.3
Systolic BP (mm Hg)	130.7 ± 10.03	116.7 ± 9.87
Diastolic BP(mm Hg)	94.3 ± 7.8	82.3 ± 7.1
CVP (cm H2O)	17.4 ± 2.1	14.5 ± 1.5

After release of the clamp, there was tachycardia and fall in both BP and CVP in all patients (table 7). In one patient who received intraperitoneal placement of graft, Inj. Heparin was given before clamping of aorta and IVC to prevent formation of microthrombi, resulting in to hypertension which was treated with Inj. Nitroglycerine. After release of the clamp, there was hypotension which was treated with fluid replacement and Inj. Dopamine (5-10 ηg/ kg BW /min). Inj. Sodium bicarbonate was administered to correct metabolic acidosis observed on arterial blood gas (ABG) analysis at that time, and effect of heparin was reversed with Protamine.

Table 8: Intraoperative fluid requirement

Intraoperative fluid	Mean ± SD
Crystalloids	115.4 ± 10.6 ml/kg
Colloids	4.5 ± 0.45 ml/kg
Blood / Packed Cells	1.6 units per patient

Immediate allograft function was established in all the patients and average urine output on table was 32.5 ± 4.6 ml /kg BW. The average duration of surgery was 270 ± 23 minutes and duration of anaesthesia was 294 ± 12 minutes. Average anastomosis time was 42 minutes while average warm and cold ischemia times were 45 seconds and 9 minutes respectively. All the patients who received general anaesthesia were adequately reversed with Neostigmine (0.05 mg/ kg BW) along with Atropine (0.02mg/ kg BW).

POSTOPERATIVE MANAGEMENT

All the patients were kept in intensive care unit for first 48 hours following surgery and their intra-operative monitoring was continued. Intravenous fluid replacement was done with combination of 0.9% Normal saline and 5% Dextrose with Sodabicarb (at the rate of previous hour's urine output + 50 ml). Serum electrolytes (Na^+, K^+, Ca^+, Mg^+) were measured at four hourly intervals and were replaced if indicated. Pain relief was provided through epidural catheter with Inj. Tramadol (2 mg/kg BW) or Inj. Buprenorphine (1.5-2 µg/ kg BW) every 8-12 hourly. None of the patients required postoperative ventilatory support.

Table 9: Postoperative complications

Complication	Patients (n=74)
Nausea, vomiting	12 (16.2 %)
Electrolyte disturbances	8 (10.8 %)
Convulsion	4 (5.4 %)
Hypertension	10 (14.3 %)
Hypotension	1 (1.4 %)
Fluid overload	1 (1.4 %)

Nausea and vomiting were the most common complications observed in patients who received general anaesthesia. Ten patients developed hypertension requiring treatment with Nitroglycerine. Eight patients showed electrolyte disturbances like hypocalcemia, hypomagnesaemia, hyponatremia, out of which 4 patients had convulsions. No morbidity/ mortality was observed in first 48 hours following surgery (table 9).

DISCUSSION

As with most organ transplantations, kidney transplantation was first pioneered in adults and only later applied to the paediatric patient population. With increasing experience in paediatric renal transplantation, remarkable improvements followed, in both patient and allograft survival. Although the basic pathophysiology of ESRD, organ preservation and immunology are same in children and adults, there are numerous aspects of renal transplantation that are unique to

the paediatric patients. These include etiology of ESRD, surgical technique and problems due to donor-recipient size discrepancy.

Common causes of ESRD in children are congenital or inherited anomalies of the genitourinary system like reflux uropathy, IgA nephropathy, Alport syndrome and renal dystrophy which accounted for 30% of cases in our series whereas this group represents more than 50% of cases in other series [1, 5, 8]. The mean patient age in our study was 15.2 ± 2.4 years, which might have contributed to this difference.

Although clinical manifestations of ESRD are fundamentally same in adults and children, abnormalities of calcium and phosphate metabolism have more serious consequences in growing children [9]. We observed renal osteodystrophy in 3 patients who required careful positioning during surgery to prevent pressure related injuries. There was significant number of patients (84 %) with "high renin hypertension" who required multiple drug therapy, in fact 2 patients required bilateral nephrectomy to achieve reasonable BP control. The knowledge of antihypertensive therapy is important as they have important interactions with anaesthesia like decrease in peripheral vascular resistance by calcium channel blockers, decreased myocardial contractility with beta-blockers and rebound hypertension with clonidine.

Sodium thiopental is well tolerated for induction in children with good cardiac function and suxamethonium is useful for intubation if serum potassium is < 5.5 mEq/ L due to its rapid onset of action. For maintenance of anaesthesia, atracurium is the muscle relaxant of choice, since its hydrolysis & Hoffman degradation are independent of renal function and its pattern of action remains unchanged [10]. Isoflurane is preferred as it has minimal toxicity and insignificant effect on cardiac output, allowing excellent blood flow during reperfusion of graft [11].

Use of regional anaesthesia for kidney transplantation is controversial but promising if coagulation parameters are within normal limits. It inhibits cardiovascular fluctuations during surgical stress as studied by Murakami et al in 33 paediatric renal transplantations [12]. It also provides early ambulation and excellent postoperative pain relief.

We have predominantly live related donor transplantation program having adult donors for paediatric recipients creating donor-recipient size discrepancy. Conventional adult surgical technique involves extraperitoneal pelvic placement of kidney with vascular anastomosis to external or internal iliac vessels; while in children vessel size is the deciding factor for anastomosis site. Smaller the child, higher is the site of anastomosis. Starzl et al devised a technique of transplanting adult kidneys intraperitoneally in children [13]. Two children in our series underwent transplantation with this technique so as to take the advantage of larger room in abdomen. Cross-clamping of major vessels as well as greater potential for third space and blood loss necessitated intra-arterial BP monitoring and sodium bicarbonate replacement to correct metabolic acidosis in these cases.

Apart from the haemodynamic changes induced by cross-clamping of major blood vessels, transplanting adult kidneys into children creates several other important problems. Acute volume shortage occurs during reperfusion after placing adult kidney with a vascular bed volume of 200-250 ml into a child. Aggressive plasma volume expansion (by raising CVP by 25 %) is necessary to prevent significant hypotension after unclamping the vascular supply to new kidney. Since the newly transplanted kidney requires adult levels of perfusion pressure to function properly, it is necessary to support BP by intentional hypervolaemia or low dose inotropes such as dopamine or dobutamine.

After reperfusion of kidneys, all allografts functioned immediately making adequate quantity of urine. This resulted in significant volume and electrolyte disturbances necessitating frequent evaluation of fluid and electrolyte balance with appropriate replacement. Postoperative analgesia by epidural route provided excellent pain relief in all patients.

SUMMARY

Although the principles of perioperative management of paediatric renal transplantation are similar to adult renal transplantation, small children (weight <20 kg) receiving adult kidney need special consideration. These include haemodynamic and metabolic changes induced by clamping of major blood vessels, acute volume shortage on reperfusion of transplanted kidney, the need to maintain adult levels of perfusion pressure in the immediate postoperative period and aggressive replacement of fluids and electrolytes to cope with large quantities of urine. The care of these complex patients can be greatly improved by sensitive assessment

and monitoring techniques resulting in lower morbidity and early adequate allograft function.

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HEMOPOETIC STEM CELL TRANSPLANTATION IN CHILDREN

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ABBREVIATIONS

ALL	:	Acute lymphatic leukemia	GVHD	:	Graft versus host disease
AML	:	Acute myeloid leukemia	MDS	:	Myelodysplastic syndrome
BMT	:	Bone marrow transplantation	MRD	:	Minimal residual disease
CY	:	Cyclosphosphamide	SCID	:	Subacute combined immune deficiency
HSCT	:	Hematopoietic stem cell transplantation			

KEY WORDS

bone marrow transplantation, immunologic deficiency syndromes, metabolic disease, hematologic malignancy, hemoglobinopathy, aplastic anaemia, autoimmune disorders.

Bone marrow transplantation (BMT) was attempted for the first time in 1939 in a patient with gold-induced aplasia and successfully performed in 1968 in a patient suffering from severe combined immunodeficiency (SCID). The field of transplantation has achieved a remarkable progress since then. Allogeneic hematopoietic stem cell transplantation (HSCT) is the preferred choice of therapy in many paediatric diseases like thalassaemia, subsets of sickle cell anaemia, metabolic diseases, hereditary immunodeficiency disorders, high risk acute/ relapsed leukemia and myelodysplastic syndrome (MDS). HSCT is also useful in autoimmune disorders and solid tumors. Non myeloablative/ non-ablative HSCT has less toxicity as compared to myeloablative transplantation. Hence it is useful in patients who can not tolerate conventional HSCT. Non myeloablative HSCT has demonstrated that tumor cells can be eradicated with immunotherapy and complete eradication of tumor cells with chemotherapy is not essential. The role of HSCT in common paediatric disorders is discussed below.

IMMUNODEFICIENCIES

SCID

Overall survival rate with histocompatible HSCT is 80% versus 60–70% in haploidentical transplantation. Repopulation with donor lymphocytes takes 3-4 months after

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transplantation with T-cell depleted marrow infusion as compared to 2–3 weeks in conventional HSCT. Preparatory regimen before transplantation leads to complete donor lymphohematopoietic engraftment[1]. This is in contrast to patients who need long term intravenous (IV) IgG and multiple transplants if pre-transplant chemotherapy is not used [2].

WISKOTT ALDRICH SYNDROME

Unlike SCID, Wiskott Aldrich Syndrome requires pre-transplant conditioning. Busulphan (BU) + cyclophosphamide(CY) is preferred over CY + irradiation to avoid long term toxicity associated with irradiation. Survival rate depends on the type of donors: 86% with histocompatible related donors; with unrelated matched donor, 83% in young patients (<5 years age) and 26% in old patients (>5 years age). To avoid disease related morbidity and mortality early HSCT is advisable.

OTHER IMMUNODEFICIENCY DISORDERS

HSCT is used for hyper-IgM syndrome, combined immune deficiency, common variable agammaglobulinemia and hereditary lymphohistiocytosis. CNS abnormalities may persist after HSCT in Chediak-Higashi syndrome.

ß THALASSAEMIA MAJOR

More than 5000 children suffering from this disorder have received HSCT so far. Lucarelli devised a classification for patients suffering from thalessemia wherein he divided them in to 3 classes; class I- adequate iron chelation, no hepatomegaly/ liver fibrosis; class II -1 or 2 of the previous criteria; class III- included all the above mentioned criteria. Lucarelli class I patients have 95% event-free survival, as compared to 61% in class III. Cyclosphosphamide reduction in conditioning regimen led to mixed chimerism instead of full chimerism [3]. This observation indicated that mini-transplantation (non-myeloablative HSCT) performed in leukemia could be adopted for thalassemia however multiple third party transfusions would predispose them to higher rejection rate. Experience with unrelated donors is limited, with event-free survival of 50 % [4]. Cord blood HSCT experience is also limited. Recent data suggest 2-year event-free survival of 79 % with cord blood. The use of Methotrexate for GVHD prophylaxis had greater risk of graft failure [5]. Conditioning with BU / CY was associated with a lower probability of engraftment as well as survival as compared to the combinations of BU, Thiotepa (TT), and CY / BU, TT, and fludarabine (FLU). Low incidence of GVHD has made HLA mismatched transplantation possible here.

SICKLE CELL ANAEMIA

An 8 year old sickle cell anemic child with acute myeloid leukemia (AML) when treated with HSCT was cured of sickle cell anemia also. Four year event- free survival of 73 % is reported by Walters et al [6]. At present, HSCT is offered for sickle cell anaemia with high morbidity or in advanced stage. Unfortunately no prognosticators are available as yet to define the need of HSCT for newly diagnosed cases. Experience with cord blood HSCT is limited. Recent data suggest 2-year event free survival of 90 %. There was higher risk of graft failure with the use of Methotrexate for GVHD prophylaxis [5]. Low incidence of GVHD makes HLA mismatched transplantation a viable option here. Stable mixed chimerism has been demonstrated in sickle cell disease [7]. Successful transplantation can yield a stable and better organ function.

APLASTIC ANAEMIA

Allogeneic HSCT and immunosuppressive therapy for aplastic anemia have similar outcome in children however immunosuppressive therapy has higher incidence of second malignancy making allogeneic HSCT as the preferred choice [8].

FANCONI ANAEMIA

These patients need low intensity conditioning regime compared to aplastic anaemia. They do well with low dose CY with or without total body irradiation (TBI). Chromosomal instability makes them prone to develop malignancies (in 40 %) after HSCT [9].

LYMPHOMA

Autologous HSCT increases survival rate in high-risk patients if applied in first clinical remission (CR) [10]. However it dose not improve survival in patients who have slow response to chemotherapy [11]. Allogeneic HSCT is superior to chemotherapy according to PARMA trial in relapsed cases of aggressive lymphoma [12]. Allogeneic HSCT is superior to autologous HSCT in recurrent lymphoblastic lymphoma [13].

MDS

This disease is very rare in children. Allogeneic HSCT results in long-term survival in otherwise incurable disease [14].

Autologous HSCT can be considered for patients who are in remission following chemotherapy.

ACUTE LYMPHATIC LEUKEMIA (ALL)

Allogeneic HSCT is advised in patients with Philadelphia chromosome, as they do not do well with chemotherapy alone. Related allogeneic HSCT gives 65% disease free survival while unrelated allogeneic HSCT gives about 50% disease free survival [15, 16]. Allogeneic HSCT is not better than chemotherapy alone in ALL with poor prognosis[17]. Allogeneic HSCT as a salvage therapy for patients with induction failure does not give good results in ALL compared to AML[18]. Allogeneic HSCT is superior to chemotherapy after first relapse with 40-65% survival [19]. However children with long first remission and favorable risk (like TEL-AML 1 gene rearrangement) may do well with second chemotherapy treatment alone. HSCT in this group has similar results after second and third remission also [20]. CY+TBI are better than CY+BU as a conditioning regimen in ALL[21]. Autologous HSCT in advanced disease after first CR gives moderate success [22]. The role of purging of autologous bone marrow is not established and there are no comparative trials of HSCT with purged marrow and with unpurged marrow. Minimum residual disease (MRD) detected by PCR predicts prognosis and chances of relapse. Knechtli CJ et al demonstrated poor prognosis of transplantation with increasing MRD detected by semiquantitative PCR before transplantation [23].

ACUTE MYELOID LEUKEMIA (AML)

Zitttoun RA demonstrated increased disease free survival with allogeneic HSCT in first CR [24]. GVHD, infection and interstitial pneumonia were responsible for graft failure rather than disease relapse. Good prognosis group AML patients [t (15:17), t (8:21), inv (16)] should be transplanted in first relapse. Patients with primary induction failure have only 21% chance of 3-year survival following HSCT [25]. Autologous HSCT is done in relapse when donor is not available. There is 30% long-term survival with autologous HSCT performed during first relapse [26]. Purging of marrow with 4-hydroxy-cyclosphophamide/ mafosfamide in autologous HSCT increases survival [27]. Autologous HSCT has higher disease free survival as compared to chemotherapy in first CR, but overall survival is not different; since they are salvageable with transplantation in case of relapse following chemotherapy [24]. Autologous BMT is not superior to chemotherapy alone in children with first relapse, due to higher mortality associated with it [28]. Non-myeloablative stem cell transplantation with donor lymphocyte infusion has several advantages over conventional transplantation including better chances of eradicating leukemia and less toxicity/ hospital stay/ cost / GVHD. It is a new modality of treatment demonstrated to be useful in animal trials and human studies [29, 30]. However many questions have to be answered before it can replace the conventional HSCT like optimum conditioning regimens, period of GVHD immuno-prophylaxis, role of T-cell depletion, and role and timings of donor lymphocyte infusion.

HODGKIN'S LYMPHOMA

Autologous HSCT is recommended for induction failure, relapsed cases and high risk patients in first CR [31, 32, 33].

SOLID TUMORS

Autologous HSCT is useful in advanced stage neuroblastoma. There are several methods adopted for purging infiltrated marrow to improve the outcome [34].

METABOLIC DISORDERS

Osteopetrosis: Slow turn over of osteoclasts delays clinical improvement, usually noted by 4 months after successful HSCT.

Osteogenesis imperfecta: Horwitz et al. demonstrated clinical improvement with HSCT [35]. This proves that mesenchymal stem cells are grafted to develop in to osteoblasts. This observation opens up possibility of treating all genetic mesenchymal disorders with HSCT.

Gaucher's disease (deficiency of glucocerebrosidase) can be cured with HSCT but due to slow turnover of macrophages, clinical improvement may take 6 months. Unlike enzyme replacement therapy, HSCT can improve CNS abnormalities also.

Hurler's syndrome (deficiency of α-hyaluronidase) shows late improvement (up to 6 months) like Gaucher's disease and osteopetrosis. CNS abnormalities also improve unless developmental quotient is less than 70 at the time of HSCT.

HSCT has been tried in mucopolysaccharidosis type VI (Maroteaux-Lamy syndrome), type III (San Filippo syndrome) and type IV (Morquio syndrome), but has shown no improvement in type IV and type III and hence not recommended.

HSCT is helpful in rare metabolic disorders like globoid leukodystrophy and adrenoleukodystrophy (in early stages). However unrelated HSCT is not very useful since GVHD accelerates disease progression. In metachromatic leukodystrophy peripheral neurological abnormalities do not recover.

AUTOIMMUNE DISORDERS

Animal models have proved the usefulness of HSCT in autoimmune disorders [36, 37]. At present autologous/ allogeneic HSCT is offered to the patients with autoimmune disorders with significant morbidity/ mortality, resistant to / not tolerating conventional treatment. So far more than 400 HSCTs have been performed. Autologous HSCT is safe, but relapse which is common can be reduced with T-cell depletion. European BMT group results show 40-50 % improvement in various autoimmune disorders.

The use of HSCT is becoming popular and safer with progress in intensive care services.

Non-myeloablative HSCT can be performed on out-patient basis due to less intensive conditioning involved with it; however being a new modality of treatment it is premature to predict whether it can replace conventional HSCT. Non-hematological donor cells have been demonstrated in patients who received HSCT for hematological disorders indicating stem cell plasticity/ transdifferentiation. This has encouraged the use of HSCT for treatment of non-hematological disorders: myocardial infarction, ischemic vascular disease, stroke etc [38]. HSCT is also helpful in inducing immune tolerance in solid organ transplantation [39]. HSCT in this situation should be able to create stable mixed chimerism so that there is no host versus graft disease (to eliminate the need of life long immunosuppression) / GVHD.

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IMMUNOPATHOLOGY OF CYCLOSPORIN INDUCED TISSUE INJURY IN RENAL ALLOGRAFTS–AHMEDABAD EXPERIENCE

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ABSTRACT

Introduction: Cyclosporin (CsA), a potent immunosuppressant is known to prevent rejections across MHC barriers in animals by calcineurin inhibition. Although it effectively improves renal allograft survival, CsA nephrotoxicity is paradoxically responsible for chronic allograft dysfunction. **Material and methods:** We report a single center, retrospective study of 159 renal allograft biopsies of 2 groups of patients; who willingly underwent hematopoietic stem cell transplantation (HSCT) pre-transplantation and those who underwent renal transplantation directly. Biopsies were sub-classified in 2 groups; first group of 127 biopsies including 64 HSCT protocol patients and 63 controls performed within 180 days post-transplantation. Second group of 32 biopsies had 26 HSCT protocols and 6 controls performed after 180 days post-transplantation. CsA was administered to all the patients with an intention to maintain trough levels, 160 ± 20 ng / mL up to 3 months post-transplantation and 100 ± 20 ng / mL subsequently. **Results:** CsA toxicity was observed in 82.9 % HSCT protocol biopsies vs 40.6 % of controls. **Conclusion:** Our patients have higher incidence of CsA nephrotoxicity and HSCT protocol in particular, has CsA sparing effect.

ABBREVIATIONS

BM	:	Bone marrow	IL	:	Interleukin
CsA	:	Cyclosporine	LCM	:	Lymphocytotoxicity cross match
G-CSF	:	Granulocyte colony stimulating factor	LRD	:	Living related donor
GM-CSF	:	Granulocyte macrophage colony stimulating factor	PBSC	:	Peripheral blood stem cells
HSCT	:	Hematopoietic stem cell transplantation	SCr	:	Serum creatinine
HUS	:	Hemolytic uremic syndrome			

KEY WORDS

cyclosporine toxicity, hematopoietic stem cell transplantation, mixed hematopoietic chimerism, renal transplantation.

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INTRODUCTION

Cyclosporin (CsA), a very potent immunosuppressive drug was identified by J. Borel. It is a lipophilic undecapeptide with 11 amino acids isolated from soil fungus (Tolypocladium inflatum Gams) and has molecular weight of 1200 kd. [1, 2]. It was found to prevent rejections across MHC barriers in most of the animal models. However the effect has been observed to be time and dose dependent. The generation of cytotoxic lymphocytes in mixed lymphocyte reaction is prevented by CsA, but once generated CsA has no effect on cytotoxic activity. It inhibits interleukin (IL) 2 production significantly [3, 4]. CsA predominantly acts against CD 4+ (T- helper) lymphocyte generation. It controls T-cell dependent B-cell activity although in general, it has not been thought to inhibit B lymphocyte function. Murine models have shown inhibition of generation of T- cell independent B lymphocytes by CsA[5]. It also has inhibitory effect on IL1 production by macrophages, and IL 2/ IL 3 / IL 4/ inteferon ã production by T lymphocytes. It does not influence inflammatory granulation response in vivo[6]. Studies of binding of CsA to various cells suggests that although a large amount of cell- associated drug is located in cytosol, there may be different binding to different cells, with splenocytes and thymocytes showing particularly high activity [7]. Cyclosporin-immunophilin complex binds to calcineurin and blocks dephosphorylation of nuclear factor of activated T-cells and its translocation in to the nucleus, preventing the transcription of IL 2 gene [8]. CsA promotes enhanced transforming growth factor- â production, consequently causing fibrosis, a characteristic feature of chronic rejection.

CLINICAL EXPERIENCE

When CsA was introduced in 1981, multicentric trial proved actuarial survival at 1 year, of 72 % in CsA group versus 52 % in controls on steroids and Azathioprine. After 5 years, graft survival was 55 % in CsA group and 40 % in controls [9]. However CsA nephrotoxicity is more likely to occur in kidneys that have incurred ischemia reperfusion injury. Steroids were not able to protect the allografts from CsA nephrotoxicity which was confirmed by performing renal allograft biopsies 1 year after transplantation.

Side effects of CsA with reference to kidneys

Three types of clinical nephrotoxicity are observed with CsA. The first type occurs immediately after transplantation usually in kidneys damaged by acute ischemia and is more often seen with the use of intravenous CsA. The second type is acute toxicity seen any time after 2-3 weeks and is always associated with deteriorating renal function, usually but not always associated with high blood levels of CsA. The third type usually presents as hemolytic uremic syndrome (HUS) like picture in the first two weeks after transplantation; however it can also occur in 1 to 5 months after transplantation with gradual loss of allograft function.

The florid signs of acute rejection previously seen with prednisone and azathioprine like fever, graft tenderness and swelling, oliguria and rapidly rising serum creatinine levels are much less evident in patients treated with CsA. Pathophysiology of CsA nephrotoxicity is decrease in renal blood flow with an increased renal vascular resistance at the level of afferent arteriole of the glomerulus and a decreased glomerular filtration rate [10]. CsA inhibits production of prostaglandin metabolites but may increase the production of thromboxane, a potent vasoconstrictor [11]. This effect of CsA on the arachidonic acid metabolic pathway within the kidney may be responsible for the functional and morphological changes of its nephrotoxicity. Acute CsA nephrotoxicity is rapidly reversed after cessation of CsA administration.

In HUS like nephrotoxicity, patients present with acute renal failure, thrombocytopenia, microangiopathic hemolytic anemia, elevated lactic dehydrogenase and hyper-bilirubinemia. Encephalopathy may also result. These changes have been found to be reversed with the discontinuation of its administration or using heparin/ streptokinase [12].

Late toxicity is a chronic condition with slow, steady deterioration of renal function and histology revealing severe interstitial fibrosis. In vitro studies showed that human mesangial cells and renal fibroblasts produced more collagen III on exposure to CsA [13].

Other less common features include hyperkalemia, hyperchloremia, metabolic acidosis, hypomagnesemia and hyperuricemia. Gingival hyperplasia, hypertrichosis, liver dysfunction and tremors are the most common non-renal manifestations.

Pathologic changes in CsA nephrotoxicity

Pathologic diagnosis of CsA toxicity was made in 61% of

early series and 38 % of biopsies almost a decade later [14, 15]. Acute nephrotoxicity could be functional and no morphological damage may be recorded or it can be observed as toxic tubulopathy wherein isometric vacuolization is noted in proximal tubules which occurs due to dilatation of endoplasmic reticulum, and appear empty on electron microscopy [16]. Tubular microcalcification is sine que non of CsA toxicity. The microcalcifications scattered throughout the nephron are believed to arise as dystrophic calcification of degenerated tubular cells [17]. HLA- DR expression on tubular cells is less common in CsA toxicity than in acute rejections [18]. In interstitium there is predominant CD4 + T – cell population with CsA nephrotoxicity in contrast to mononuclear cellular infiltration with predominant CD 8+ cells with rejection [19]. In CsA toxicity, the mononuclear cells have a tendency to remain in peritubular capillaries [20].

CsA causes acute arteriolopathy wherein apoptosis of arteriolar smooth muscle cells leads to subintimal segmental hyalinosis. The pioneering work of Mihatsch defined CsA arteriolopathy [21]. This could also be accompanied by thrombosis. In glomeruli, if capillary thrombi are noted without any evidence of rejection, these may be indicative of CsA toxicity. In arterioles CsA toxicity leads to replacement of necrotic/ apoptotic smooth muscle cells by rounded, “lumpy” protein deposits leading to the beginning of hyalinosis of chronic lesion. The arteriolar endothelial cells are hypertrophied, giving a `constricted’ appearance to the arterioles. These cells have prominent vacuoles with glycogen accumulation in cytoplasm. Microthrombi and fibrinoid necrosis follow mucoid thickening of intima eventually mimicking HUS. Vascular intimal hyperplasia is the most prominent lesion noted in small vessels.

HUS

The glomeruli appear swollen, capillaries may be bloodless with scattered fibrin/ platelet thrombi especially at hilum, the so called “pouch lesion”. GBM may be focally reduplicated with variable mesangial expansion and sclerosis. Variable necrosis may also occur. Tubules may show necrosis in addition to tubulopathy. Interstitium has no particular damage.

Chronic CsA toxicity

Most studies have shown that after 1 year of transplantation, glomeruli show increased global and segmental sclerosis and periglomerular fibrosis. Focal tubular atrophy and interstitial fibrosis are also accompanying lesions.

Measurement of CsA

Estimation of CsA has to be standardized by each center. Generally optimal trough levels in whole blood in the first three months after transplantation are considered to be 150 to 250 ng/ ml and after the first three months it is desirable to maintain lower range of 100 to 200 ng /ml [22].

AHMEDABAD EXPERIENCE

This was a retrospective study carried out at the Institute of Transplantation Sciences, Ahmedabad, India, of 159 renal allograft biopsies performed between January 1, 2003 and December 31, 2003. These biopsies belonged to two groups of patients with living related donors (LRD); those who willingly underwent hematopoietic stem cell transplantation (HSCT) before renal transplantation with an attempt to create donor-specific hyporesponsiveness and the other group of control transplant recipients who did not opt for the tolerizing protocol. These were further classified in two groups; the first one included 127 biopsies performed before 180 days post-transplantation and the second one included 32 biopsies performed 180 days post-transplantation. These were arbitrarily classified to differentiate between early acute and late rejections. The indication for performing biopsies was unexplained and sustained rise in serum creatinine (SCr) of more than 10 % of baseline levels. The demographic profile of both groups was fairly balanced in early graft dysfunction period. Sixty four protocol biopsies belonging to 54 males and 10 females with the mean age group of 33.5 years were performed at mean post-transplantation period of 29.9 days. Sixty three control biopsies were performed on 51 males and 12 females with the mean age group of 36.4 years and mean post-transplantation period of 26.5 days. (table 1 A).

TABLE 1A : Patient Demographics of Biopsies Performed Within 180 days Post-Transplantation

Biopsy	Gender (M:F)	Age (Yrs)	Bx Period (days)
Tolerance Protocol (n=64)	54:10	33.5 (15-58)	29.9 (0-126)
Control (n=63)	51:12	36.4 (16-54)	26.5 (0-176)

In second group biopsies performed 180 days post-transplantation, 26 (22 males and 4 females) belonged to HSCT protocol group and 6 biopsies belonged to controls (with all males). Demographics are mentioned in table 1B. In the HSCT protocol patients who were biopsied 180 days after transplantation, 1 patient transplanted in March 1999 and 4 patients transplanted in year 2000 underwent protocol without thymic inoculation. The remaining patients had undergone the same HSCT protocol as that of patients who underwent HSCT protocol mentioned above. (table 1B)

TABLE 1B: Patiend Demographics of Biopsies Performed After 180 days Post-Transplation

Biopsy	Gender (M:F)	Age (Yrs)	Bx Period (days)
Tolerance Protocol (n=26)	22 : 4	35 (14-55)	614 (210-1580)
Control (n=6)	6 : 0	24.3 (15-39)	537 (304-1100)

Tolerance Induction Protocol

Intrathymic renal tissue transplantation

The patients in HSCT tolerance protocol group received donor-renal tissue following negative lymphocytotoxicity cross matching (LCM) test. The mean weight of renal tissue was 600 micrograms and mean total glomeruli were 12. It was procured with standard kidney biopsy procedure under local anesthesia and inoculated into recipient thymus, for which a 4 cm long incision was made in to the right second intercostal space under general anesthesia. After cutting all the muscles, mediastinal fascia was opened and thymus was identified in the retrosternal space. Then minced renal tissue was inoculated with 20 gauze needle. Hemostasis was checked and wound closed.

Cyto-ablataion - reduction technique

We subjected these patients to cyto-ablative conditioning of 400 rads of total lymphoid irradiation (TLI) administered over four alternate days followed by cytoreduction regimen of Rapamycin, 2 mg/day for 7 days.

HSC mobilization, collection, infusion and inoculation techniques

Donors received Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF), 10 *u*g /kg BW /day subcutaneously for two days. Bone marrow (BM) aspiration was performed under sedation and local anesthesia from their posterior superior iliac crest. From 500 ml of aspirated unfractionated BM, 100 mL was inoculated into sternal BM of the recipient and 200 mL each, was infused into portal and peripheral circulation under general anesthesia after cytoreduction . Subsequently Granulocyte Colony Stimulating factor (G-CSF), 10 *u*g/ kg BW/ day, was added to GM-CSF to stimulate and mobilize the stem cells. Donors were then subjected to leucophoresis twice on stem cell separator (Hemonetics, MCS 3p, USA) and peripheral blood stem cells (PBSC) were collected and immediately infused in unmodified form in to the periphery of recipients. Their CD 34+ and total cell counts were performed. Average BM CD 34^+ cell count was 1.2 % and average total cell yield was 1.2 x 10^8 cells/kg BW. The average total PBSC (CD 34^+: 0.9%) yield was 24.2 x 10^8 cells/ kg BW.

Transplantation surgery was carried out 6 days after the last PBSC infusion following negative lymphocytotoxicity cross match (LCM) results.

HLA typing and cross-matching by LCM

HLA typing and LCM were performed at the beginning and end of tolerance induction protocol using conventional serological techniques (one- Lambda pre-dot trays were used for HLA- A, B, DR typing), using auto cross-match, dithiothretol and standard cytotoxicity methods with mixed-cell population. T and B lymphocytes were each separately utilized for cross-matching and donor-specific positivity was found with mixed-cell population.

Recipient immunosuppression

CsA was the principal immunosuppressant for all the patients. The doses were adjusted with an intention to maintain trough blood levels of 160 ± 20 ng / mL up to 3 months post-transplantation and 100 ± 20 ng / mL subsequently. Prednisolone, 0.5 mg/kg BW /day was administered for the first month post-transplantation followed by 0.2 mg/kg BW/ day subsequently. Azathioprine, 2 mg/kg BW/ day was added as a third drug following acute rejection (AR) episodes.

Azathioprine was replaced by mycophenolate mofetil whenever toxicity was observed.

Histopathology examination

The biopsies were performed on 3 ìm thick paraffin sections and were stained with hematoxylin and eosin, periodic acid Schiff, Gomori's trichrome and Jone's silver methaneamine stains. Rejection was diagnosed as per modified Banff classification [23].

OBSERVATIONS

We observed an overwhelming effect of CsA toxicity in our patients. In biopsies performed within 180 days post-transplantation in protocol group, 32 (50 %) biopsies revealed acute CsA toxicity with changes of toxic tubulopathy showing isometric vacuolization in majority of proximal tubules and arteriolopathy with segmental subintimal hyalinosis in all of them (figure 1A, B).

Tubular microcalcification was seen in only two biopsies. The incidence of acute CsA toxicity was less in controls; with 26 (41.3 %) biopsies showing similar changes. The other pathological changes were acute tubular necrosis, acute tubulo-interstitial rejection (that was borderline or mild in protocol group as compared to moderate to severe in controls), acute vascular rejection and recurrent or de novo glomerulopathy (table 2A).

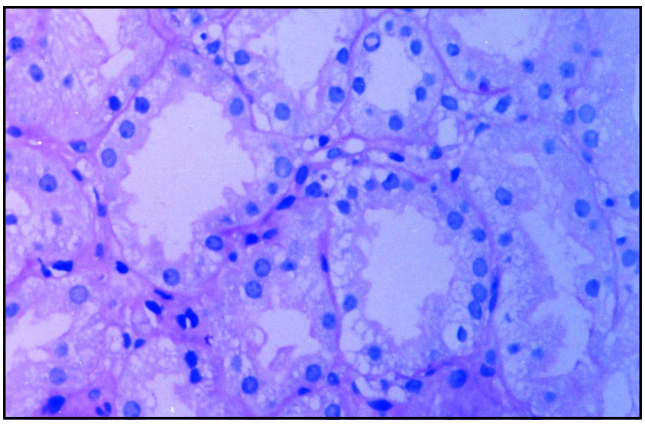

Figure 1A : CsA induced toxic tubulopathy. H & E stain, showing isometric vacuolization in tubules, x 400

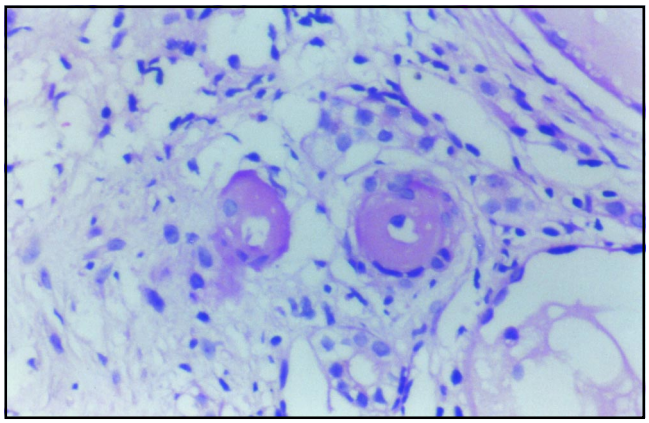

Figure 1B : CsA induced toxic arterioloapthy. H& E stain, showing marked subintimal arteriolar hyalinosis, x 400

TABLE 2A : Histopathology Profile of Biopsies Performed Within 180 days of Post-Transplatation

	Protocol (n=64)	**Control (n=63)**
Acute CsA toxicity	32 (50 %)	26 (41.3 %)
Acute tubular necrosis	22 (34.4 %)	20 (31.8 %)
Acute tubulointerstitial rejection	19 (29.7 %)	41 (65.1 %)
Acute vascular rejection	4 (6.3 %)	21 (33.3 %)
Chronic CsA toxicity	4 (6.3 %)	2 (3.2 %)
Recurrent/De novo glomerulopathy	3 (4.7 %)	2 (3.2 %)

We compared CsA levels in both groups and found that there was no significant difference between their trough levels (performed by EMIT assay using Syva, Behring, USA). Changes of chronic CsA toxicity observed in the form of tubular atrophy, periglomerular fibrosis and focal interstitial fibrosis were also observed in this period. Four (6.3 %) protocol biopsies and 2 (3.2 %) control biopsies showed these changes. There was also CsA induced HUS in 2 (2.7 %) protocol and 1 (1.6 %) control biopsies (figure 2).

In biopsies studied after 180 days of transplantation, acute CsA toxicity was noted in 16 protocol (61.5 %) biopsies, including 2 biopsies showing CsA induced HUS; 2 (7.7 %) protocol biopsies showed acute tubular necrosis, 5 (19.2 %) protocol and 4(66.6 %) controls revealed mild acute tubulointerstitial rejection with underlying chronic cellular rejection with chronic transplant glomerulopathy; acute

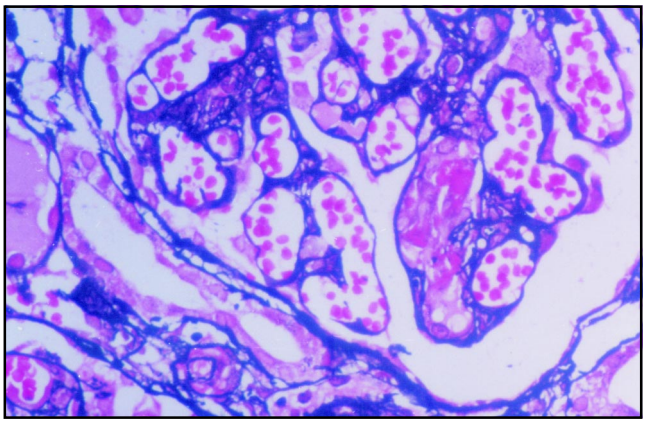

Figure 2: CsA induced HUS. Jone's silver methaneamine stain, showing mesangiolysis, ectatically dilated capillaries filled with fresh RBCs and hyaline thrombi, x 400.

tubulointerstitial rejection, type IA, was noted in 6 (23.1 %) protocol biopsies; and changes of chronic CsA toxicity in 6 (23.1 %) protocol biopsies and 2 (33.4 %) control biopsies and recurrent glomerulopathy (pauci-immune crescentic glomerulonephritis) in 1 (13.9 %) protocol biopsy. (table 2B).

TABLE 2B: Histopathology Profile of Biopsies Performed After 180 days of Post-Transplatation

Histopathology	Protocol (n=26)	Control (n=6)
Acute CsA toxicity	16 (61.5 %)	0
Acute tubular necrosis	2 (7.7 %)	0
Acute on chronic rejection + chronic transplant glomerulopathy	5 (19.2 %)	6 (100 %)
Acute tubulointerstitial rejection	6 (23.1 %)	0
Chronic CsA toxicity	6 (23.1 %)	2 (33.3 %)
Recurrent/De novo glomerulopathy	1(3.9 %)	0

In protocol group biopsies performed within 180 days, mean SCr of 2.52 mg % at the time of biopsy dropped significantly to 1.88 mg% (p=0.0003), and in controls, mean SCr of 2.78 mg% at the time of biopsy dropped to 2.19 mg%; one month after tapering off CsA (p=0.02). In the protocol group biopsies performed 180 days after transplantation, mean SCr of 2.49 mg% dropped to 2.23 mg% and in controls, mean SCr of 4.01 mg% dropped to 2.81 mg% one month after tapering off CsA (statistically not significant in both groups). Overall incidence of CsA toxicity was observed in 58 (82.9 %) protocol biopsies out of 70 and it was observed in 28 (40.6 %) out of 69 control biopsies.

Trough CsA levels of 300 ± 20 ng/ml were attained at the dose of 3 mg/kg BW/ day in protocol recipients as compared to 5 mg/kg BW/ day CsA dose in controls throughout the post-transplantation period.

We have observed that in early post-transplantation period, HSCT along with limited cyto-ablation-reduction cause apoptotic deletion of host T-cell population in thymus, liver, bone marrow and lymph nodes along with low grade mixed hematopoietic chimerism. We suspect that in our mixed chimeric model the total T-cell repertoire is depleted thereby making free CsA available to tissues. This could be the possible explanation of enhanced CsA toxicity in our HSCT –protocol recipients.

CONCLUSION

Our experience with CsA shows that CsA induced toxicity is much higher in our patient population. There is no correlation between trough blood levels and tissue changes. The hematopoietic stem cell transplantation protocol has a CsA sparing effect as compared to controls.

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PEDIATRIC RENAL TRANSPLANTATION FROM A SURGEON'S PERSPECTIVE

Khemchandani S. I.

ABBREVIATION

NAPRTCS	:	North American paediatric renal transplant cooperative study	CISC	:	Clean intermittent self-catherization
VCUG	:	Voiding cystourethrography	IVC	:	Inferior vana cava
UDS	:	Urodynamic study	ESRD	:	End stage renal disease

KEY WORD

Paediatric Transplantation; Transplantation Surgery

INTRODUCTION

The principal reasons for the excellent outcome after paediatric renal transplantation are improvement in organ preservation, surgical technique, immunosuppressive regimes and close long-term follow up.

Renal transplantation is less common in children than in adults and is performed for different reasons. Other major differences from adult renal transplantation include; recipient donor organ size discrepancy, higher incidence of urological abnormalities and higher requirement of immunosuppression. Transplants in very small children are more technically demanding than transplants in adults. A well functioning renal allograft is the best treatment for a child with end stage renal disease (ESRD), perhaps even more so than in an adult [1]. We have performed 74 paediatric renal transplantations from September 1994 to December 2003 at the Institute of Transplantation Sciences, Ahmedabad.

ETIOLOGY OF ESRD

The causes of ESRD are quite different in children compared with adults. Of 96% of children who had ESRD in report of the North American Paediatric Renal Transplant Cooperative Study (NAPRTCS) nearly 34% had renal hypoplasia, dysplasia, obstructive uropathy, prune belly syndrome or pyelonephritis[2]. In our series, only 5% with obstructive uropathy with ESRD were transplanted. In NAPRTCS series,

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6% children had reflux nephropathy, as compared to 17% in our series.

Causes of Esrd	Its	Naprtcs
Obstructive Uropathy	4 (5%)	34%
Reflux Nephropathy	13 (17%)	6%
Chronic Glomerulonephritis	51 (70%)	45%
Others	6 (8%)	15%

THE RECIPIENT

A general principle in recipient selection is that patients should be free of infections and anatomic anomalies that predispose to infection. Chronic or recurrent infections such as peritonitis associated with chronic ambulatory peritoneal dialysis catheters, hemodialysis shunt infections and chronic pyelonephritis require management before transplantation. Abdominal wall stomas (urinary conduits, ureterostomies, ileostomies and colostomies) should whenever possible, be removed.

AGE OF PATIENT

Accumulating experience shows that young age and low weight are no longer contraindications to transplantation. Certainly complications of hemodialysis and chronic renal failure including growth failure are indication for consideration of early transplantation.

Age in years	Patients (n=74)
0-5	**Nil**
6-10	**6** (8.1 %)
11-15	**16** (21.6 %)
16-18	**52** (70.3 %)

Children below 18 years age who underwent renal transplantation from September 1994 to December 2003 were included in our series. Majority of children were between 16-18 years of age.

EVALUATION

A complete evaluation is needed in children with history of genitourinary anomalies: as posterior urethral valves, vesicoureteric reflux, neurovesical dysfunction, imperforate anus, Hinmann-Allen syndrome, exstrophy-epispadias complex, incontinence, urinary diversion, recurrent urinary tract infections or renal failure of unknown etiology.

Microbiology should include urine culture; at least one culture should be done after voiding cystourethrography (VCUG). VCUG should be done in all children with history of genitourinary anomalies. Special investigation like urodynamic study (UDS) is required in children with history of posterior urethral valves, voiding dysfunction, neurogenic dysfunction etc.

PRETRANSPLANT NEPHRECTOMY

Preservation of kidneys in children with chronic renal failure offers substantial advantages. Even in presence of poor clearance; continued urine output facilities dialysis management, some Vitamin D and erythropoietin effects will be maintained. These effects will be beneficial during the patient's wait for transplantation or if the renal allograft incurs permanent or even temporary dysfunction. In addition, preserved ureters allow for greater reconstructive flexibility for any ureteral complications of the allograft [3].

Nephrectomy before transplantation is no longer considered a routine. Nephrectomy should be reserved for specific indications such as persistent pyelonephritis; renin mediated hypertension, severe symptomatic proteinuria, severe vesico-ureteral reflux and severe polyuria. Kidneys with some functional potential may be preserved by procedures like pyeloplasty, ureteral reimplantation and urinary undiversion. Low grade primary reflux (grade 1, 2) without a history of urinary tract infection may require no treatment. High grade reflux (grade 3, 4) without marked ureteral tortuosity or upper tract stasis may best be managed by ureteroneocystostomy before transplantation [4]. Nephrectomy or nephroureterectomy may be appropriate for patients with huge refluxing megaureters and poorly functioning kidneys.

Many children may have urinary diversion and defunctionalized bladders without even having their original pathological condition corrected (e.g. posterior urethral valves). Ideally in these cases, there should be continence, adequate volume capacity, the ability to empty to completion and the absence of bladder outlet obstruction. Hence all patients should undergo voiding cystourethrography and cystourethroscopy if needed. Neurogenic bladder should be investigated and function stabilized. An undiverted, non-

intubated system is preferable and occasionally bladder augmentation may be necessary. If this is not possible clean intermittent self-catherization (CISC) is preferable to urinary stoma. Post transplant urologic monitoring is necessary to maintain upper tract stability.

The basic principle is to preserve the native kidney if possible, remove potential anatomic source of infection and refunctionalize the diverted bladder. Every effort should be made to stabilize urinary tract through CISC / surgery/ drugs.

In our series, bilateral nephrectomy was done in 4 patients before transplantation; in 1 for uncontrolled hypertension and in 3 for reflux nephropathy. Bilateral ureteral reimplantation was done in 2 patients of posterior urethral valves with high grade reflux.

THE DONOR

Transplantation in very small children is more technically demanding than transplantation in adults. These patients tend to have additional congenital problems that worsen their overall prognosis hence a good option for the small recipients is a kidney from a living relative, usually a parent. In NAPRTCS series also results are better with living related donors.

In our series all living and cadaver donors were adults except one cadaver donor who was 3 years old. One female child aged 15 years and weighing only 22 kg received dual transplantation from this child.

Donor Source

Donor	Patient (n=74)
Living related	52 (70.27 %)
Extended family	17 (22.97 %)
Cadaver	5 (6.75 %)

PREEMPTIVE TRANSPLANTATION

Over the past decade, an increasing number of children have undergone transplantation prior to going on dialysis (preemptive transplantation). In NAPRTCS series, one third of living related and 13% of cadaveric donor transplantation were preemptive. In India also awareness is increasing for preemptive transplants. In our series, one child was transplanted preemptively before dialysis was ensued.

TECHNICAL ASPECTS OF TRANSPLANTATION

The surgical technique for paediatric transplantation represents simple variation of those used in adults. However, physiological disturbances created are significantly different and require careful management. Paediatric patients with body weight over 20 kg can be treated surgically as adults using the standard pelvic retroperitoneal approach with the vascular anastomosis performed at the level of external iliac vessels. In children who weigh 10-20 kg the vascular anastomosis is usually performed at the level of the inferior vena cava (IVC) or common iliac vessels. For children less than 10 kg, an anastomosis at the level of IVC and aorta is required. In our patients site of anastomosis was as follows:

Patients (n=74)	Weight	Site of anastomosis
61 (82.4 %)	>20 kg	External iliac vessels
10 (13.5 %)	10-20 kg	Common iliac vessels
2 (2.7 %)	<10 kg	Common iliac vessels
1 (1.4 %)	<10 kg	IVC & Aorta

Ureteroneocystostomy is performed by extravesical technique but the length of suburothelial tunnel should be four to five times the ureteral diameter to ensure no reflux. Post-operatively attention to the volume and composition of intravenous fluid is essential to ensure good renal function.

COMPLICATIONS

Most urologic complications occur due to ischemic damage to the urinary tract leading to urinary extravasation, obstruction and ultimately graft loss. In our series, there has not been any major urological problem. Haematoma are generally self-limiting but symptomatic lymphocoele usually require drainage. Vascular complications of renal transplantation include thrombosis, renovascular hypertension, pseudoaneurysm and peripheral thromboembolic disease.

In our series, we have not seen any thrombotic graft loss or renovascular hypertension from renal artery stenosis. We have lost two grafts due to pseudoaneurysm; both children had infective focus.

DISCUSSION

The principle reason for excellent results after paediatric renal transplantation is increasing experience in organ

preservation, surgical technique and immunosuppressive regimes. The most common causes of ESRD are congenital and inherited anomalies in NAPRTCS data while in our series, only 5% children with obstructive uropathy were transplanted. In NAPRTCS data, 6% children had reflux nephropathy, while 17% children with reflux nephropathy were transplanted in our series. Probably our children with reflux are not being diagnosed and managed early. High grade reflux was managed by nephroureterectomy in 3 patients and ureteroneocystostomy in 2 patients.

Since majority of donors were adults, there was recipient donor organ size discrepancy leading to technically demanding anastomosis especially when IVC and aorta were used. In our series, we lost 2 grafts due to mycotic pseudo-aneurysms, which could have been prevented with vigorous control of infection.

Hence, in spite of all these complications, in an uncomplicated case; recovery is rapid, rejection is non-existent or easily treated and results are gratifying with excellent patient and graft survival. Restoration of normal health, growth, development, sexual maturation and reintroduction of the paediatric recipient as a productive member of society is also critical. These children should never be discharged from follow up.

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OUR EXPERIENCE OF TOLERANCE INDUCTION IN PAEDIATRIC RENAL ALLOGRAFT RECIPIENTS WITH LIVING RELATED DONORS

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ABBREVIATIONS

CyA	:	Cyclosporin A	LRD	:	Living related donor
HSCT	:	Hematopoietic stem cell transplantation	PBSC	:	Peripheral blood stem cells
LCM	:	Lymphocytotoxicity cross matching	SCr	:	Serum creatinine

KEY WORDS

Paediatric transplantation, tolerance, chimerism, hematopoietic stem cell transplantation.

It was mid July 1992 when we moved in to the new premises of the institute and reorganized the renal transplantation program. The first paediatric renal transplantation of the state of Gujarat was performed on these premises on 22nd September, 1994 on a 13 years old boy (BB) suffering from chronic glomerulonephritis, with his mother's kidney. In those days cyclosporine (CsA) was not easily available to us. He was supported with two principal drugs; azathioprine and prednisone. He had stable and adequate allograft function for 2 years. We performed 16 more living related donor (LRD) renal transplantations with these immunosuppressants till December 1998. One year allograft survival in this group of patients was 68.8 %, at par with other centers then. The longest surviving allograft out of this group of patients belongs to a 21 years man (DT) transplanted at the age of 13 years with his father's kidney on 10th April, 1996. Now his serum creatinine (SCr) has started increasing (2.86 mg %). The first paediatric transplantation with cadaver donor was performed on 7th May, 1998 in a 16 years old boy (VS) with HCV infection. He has stable allograft function since then, with present SCr of 1.2 mg%. He is maintained on azathioprine and prednisone.

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On 15th August, 1998 we launched one of the most ambitious clinical research projects in which we wanted to validify Medawarian concept of donor-specific tolerance induction in our renal transplantation programme, with donor specific allogeneic hematopoietic stem cell transplantation (HSCT) as an adjuvant [1,2]. We wanted to make it safe hence there was no conditioning with cytoablation/ reduction initially [3]. This protocol was implemented till February 2001. We aimed at stem cell dose of $15 \pm 5 \times 10^8$ cells/ kg body weight [4]. We were desirous of achieving the benefits of activation induced cell death leading to depletion of potentially rejecting T-cell repertoire utilizing Zinkernagel's concept of MHC restriction [5]. We transplanted only one paediatric recipient; a 10 years old boy (ND) in this group of 27 patients. His present SCr is 1.3 mg%.

We implemented portal infusion technique in October 1998. Gorczynski's demonstration of persistent donor specific tolerance in mouse model with portal infusion of allogeneic stem cells instead of conventional systemic route encouraged us to implement this strategy in our patients [6]. Donor stem cells when infused in portal circulation get trapped in hepatic microcirculation and initiate a series of events leading to peripheral tolerance. This form of tolerance is attributable to clonal anergy of CD 8^+ T-cells [7]. The first paediatric recipient (PG) of this group was a ten years old boy who received his mother's kidney on 18th March, 1999. He has maintained stable allograft function; with present SCr of 1.4 mg %. He was initially supported with CsA and prednisone, and switched over to azathioprine at the end of 1 year post-transplantation. We transplanted 23 children under this protocol till 5th September, 2002. There was 100% 1 year allograft survival with acute rejection in 1 patient. (table). However not all patients were doing well. We achieved prope tolerance (which may be defined as early stable allograft function with <10 % allografts showing single episode of acute cellular rejection that responded to the standard anti-rejection therapy) in this group, but we were not able to prevent smouldering rejections and recurrence of glomerulopathies.

We came across Remuzzi's work on rodent models wherein he inoculated donor antigenic tissue in to thymus to create classical central tolerance [8]. Hence we further modified our protocol at the end of January 1999. We decided to invade the thymus at this juncture with donor bone marrow derived stem cell inoculum and transplanted 6 children under this modified protocol out of which 5 children are doing well, with stable allograft function (table). This protocol was used till March 2002.

The incidence and intensity of acute rejection episodes became significantly less, easily and effectively treatable; and the allograft function remained stable and better with minimum incidence of viral/ bacterial infections. However the goal of achieving drug-free allograft survival without chronic rejection eluded us. This brought us to a point of improvising upon our protocol by replacing donor derived stem cells with donor derived kidney tissue for thymic inoculation. This was implemented after reviewing Posselt's work [9]. We aimed at exposing donor endothelial cells rich in MHC II expression to the developing thymocytes [10]. We implemented this protocol from 13th March 2002 to 5th February, 2004. Four children were transplanted under this modified version of the protocol. All these recipients attained stable allograft function earlier and are maintaining SCr of 1.0 mg %.

So far we were not able to demonstrate presence of chimerism in all patients. At this juncture, we decided to be aggressive in our approach of conditioning. We added two doses of donor-specific transfusions to stimulate proliferation of donor–specific T-cell clones followed by limited target-specific irradiation to create space. This was followed by administration of anti-T-cell antibody, cyclophosphamide and CsA to delete the stimulated T-cell clones. Within 24 hours of achieving target of less than 10 % recipient CD 4^+ cell count, donor bone marrow stem cells in unmodified form were infused. This number was supplemented by additional 1 or 2 cytokine stimulated peripherally mobilized stem cells at intervals of 2 to 3 days. Renal transplantation was performed about 1 week after the last hematopoietic stem cell infusion following negative lymphocytotoxicity cross matching (LCM). All patients who developed donor-specific cytotoxic antibodies were treated with CsA and cyclophosphamide. In case of high crossmatch positivity intravenous gamma globulins and plasmapheresis were also used. Transplantation was followed as soon as negativity was achieved. We have performed renal transplantation in 3 children so far under this protocol since 16th October, 2003. All of them have achieved stable early allograft function, with demonstrable hemato-lymphopoietic chimerism (table).

It appears that we have created the model of chimeric tolerance in clinic which is safe and cost effective.

Table: Our Experience with HSCT Protocols in Peadiatric Allograft Recipients

Protocol	Control	PBSC	PBSC+ Portal Admin.	PBSC+HSC in Thymus	PBSC, Portal, Thymic Tissue in Oculation	T Protocol
Period	1.9.94-1.12.98	1.9.98-13.2.01	2.10.98 - 5.9.02	27.1.99-13.5.02	13.3.02 - 5.2.04	16.10.03 Onwards
Patients	16	1	23	6	4	3
FN. Grafts At Present (%)	6 (37.5%)	1	19 (82.6 %)	5 (83.3 %)	4 (100%)	3 (100 %)
AR (%)	9 (56.3 %)	0	1 (4.3 %)	5 (83.3 %)	0	0
Res. DS (%)	2 (12.5 %)	0	3 (13 %)	0	0	0
CR (%)	10 (62.5%)	0	1 (4.3 %)	1 (16.7 %)	0	0
SCr (mean) (mg%)	1.7	1.3	1.4	1.55	1.07	0.93
CMV INF.(%)	5 (31.3%)	0	1 (4.3 %)	0	0	0
GFtloss (%)	10 (62.5%)	0	1 (4.3 %)	1(16.7 %)	0	0
Pt Loss (%)	10 (62.5%)	0	3 (13 %)	1 (16.7 %)	0	0
LCM +ve	0	0	9 (39.1 %)	5 (83.3 %)	4 (100 %)	3 (100 %)
1 Yr Gft Survival (%)	11 (68.8%)	1 (100 %)	23 (100%)	6 (100 %)	1 (100%)	NA

Key to table

HSC: Hematopoietic stem cells, PBSC: Peripheral blood stem cells, T protocol: Includes 2 donor specific blood transfusions, limited target irradiation, donor specific T-cell depletion with anti-T-cell antibody, cyclophosphamide and cyclosporine before renal transplantation

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SUCCESSFUL PRIMARY USE OF POLYPROPYLENE MESH FOR WOUND CLOSURE IN PEDIATRIC RENAL TRANSPLANTATION SURGERY - A CASE REPORT

Modi P. R[1], John P. J.[1], Khemchandani S. I.[2]

ABSTRACT

We report a case of 13 years old child who developed acute allograft dysfunction during wound closure in renal transplantation surgery; achieved by using polypropylene mesh; no incisional hernia has been observed in 26 months of follow-up.

ABBREVIATION

LRD : Living related donor

KEY WORDS

Polypropylene; wound, renal transplantation

CASE REPORT

A 13 year old boy, weighing 23 kg, measuring 120 cms in height, with end stage renal disease underwent living related donor renal transplantation (LRD) at the Institute of Transplantation Sciences, on 11/4/'02. The size of adult donor kidney was 10.5 x 4 x 3 cm^3. Vascular anastomosis was carried out using right common iliac vessels since his small caliber internal/external iliac arteries were unsuitable. Brisk diuresis was established immediately on release of clamp. Stented ureteric reimplantation was done by Lich's method. Wound had to be reopened due to sudden drop in urine output during closure. The hypoperfused soft kidney regained its perfusion on reopening of the wound and urine output was re-established. Intraoperative colour Doppler study revealed normal donor and recipient vessels. Kinking of renal artery due to malpositioning of kidney during closure was suspected and bolsters of Surgicel^R were kept for its prevention. However,

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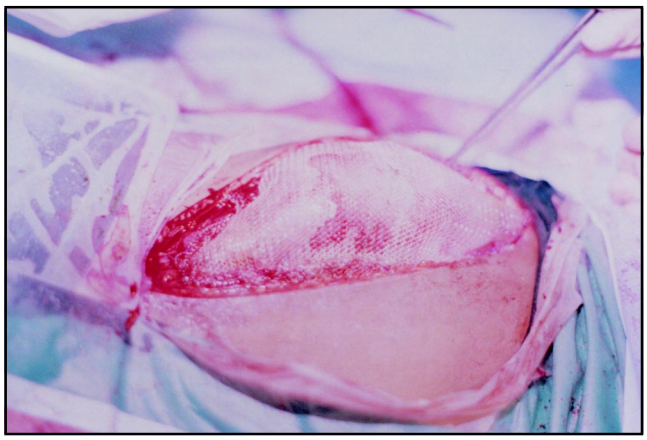
the same problem recurred on reattempting wound closure. Eventually wound closure was carried out by enlarging the surface area for wound closure with polypropylene mesh



Mesh margins were cut to 1 cm. in excess to wound size and sutured to the external oblique aponeurosis by 4/0 polypropylene sutures. In post operative period patient had oliguric acute tubular necrosis for a period of one week. He is on triple drug immunosuppression (Cyclosporine A, Prednisolone, Mycofenolate mofetil). Prophylactic antibiotics were given for 7 days following surgery. Wound healing was uneventful and no complications were observed during 26 months of follow up.

COMMENT

Adult donor renal allograft is usually kept extraperitoneally in children weighing more than 20 kg[1]. Wound closure is usually not a problem. However, kinking of renal artery/ vein occurs rarely, due to malpositioning of the kidney during wound closure[2]. Such malposition is more common with right renal allograft where renal vein is short but arterial length is long; this may result in to arterial kinking and usually is accompanied by anuria/ oliguria. An ischemic, anuric renal allograft in immediate postoperative period needs urgent re-exploration. Intraoperative colour doppler study for donor and recipient vessels and renal allograft should be done to rule out thrombosis or hyperacute rejection. Even though urine output may be established immediately after wound re-exploration, ischemia-reperfusion injury could occur. Dismembering vascular anastomosis, reduction of length of artery, reperfusion and re-anastomosis may inflict ischemic injury to the allograft resulting in to immediate and long term adverse effect on allograft function.

Polypropylene mesh has been used successfully for incisional hernia repair in patients who have undergone transplantation or are on immunosuppressants[3]. Wound infection, however, is a potential problem and hence prophylactic use of antibiotics is suggested.

In our patient, donor's left kidney was transplanted on right side. We achieved wound closure without changing the position of allograft and its vessels.

CONCLUSION:

This was a rare and difficult situation where allograft malposition was prevented by successful use of polypropylene mesh for wound closure in LRD pediatric renal transplantation.

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SUCCESSFUL DUAL EN BLOC RENAL TRANSPLANTATION FROM PAEDIATRIC CADAVERIC DONOR TO A PEDIATRIC RECIPIENT- A CASE REPORT

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ABBREVATION

Bone marrow	:	B M
End Stage Renal Disease	:	ESRD

KEY WORDS

Cadaveric dual renal transplantation, end stage renal disease

CASE REPORT

A 3-year old female child had viper snake bite resulting in to brain stem death on 27/09/2000. The family decided to donate her organs to a needy paediatric recipient at the Institute of Transplantation Sciences, Ahmedabad, India. All her renal and liver function parameters were with in normal limits. After procuring permission from the parents, in situ perfusion and en bloc harvesting of kidneys along with aorta and vena cava was carried out and 250 ml. bone marrow (BM) was aspirated from her anterior superior iliac crests. Spleen was also removed.

Bench surgery was performed to close one end of inferior vena cava and aorta, and branches and tributaries of both great vessels were sutured and closed. The dual renal allograft was transplanted extraperitoneally en block in a 14 years old female child suffering from end stage renal disease. The donor aorta and vena cava were anastomosed with recipient's right common iliac artery and inferior vena cava respectively in end to side fashion. Stented ureteric reimplantation was

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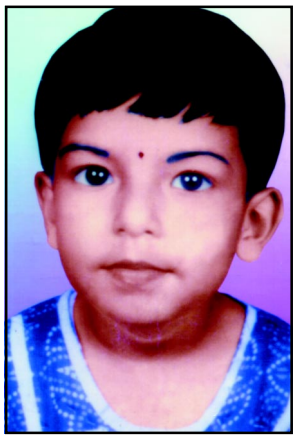
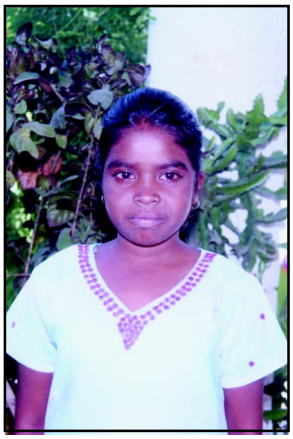
carried out by Lich's method. We infused 205 ml. unmodified BM containing 2.2 x 10^8 cells/kg BW and 4 x 10^8 splenic cells mixed in 100 ml. normal saline in to portal circulation as soon as urine output was established from both kidneys. We infused 50 ml. unmodified BM in her peripheral circulation after the surgery was completed.

She had one episode of acute tubulo-interstitial rejection in the early post transplantation period. At present, she is on cyclosporine and mycophenolet mofetil and is maintaining serum creatinine around 1. 94 mg%. She has also undergone reconstructive bone surgery for her bilateral genu valgum.



Bulbul



TINA

On Left is Bulbul, Tina (Recipient) on
Right & The Equipment below which has mad
Bulbul Live in the form of Tina

COMMENT

Renal transplantation is the treatment of choice for patients with ESRD. Kidneys from very young children (0-6 years) showed less one and five year graft survival than kidneys from older children[1]. Better survival was observed with en bloc compared with solitary kidney transplants from pediatric donors to pediatric recipients[2]. The first reported successful en bloc kidney transplantion was performed in 1969. Improved surgical technique for en bloc kidneys introduced by Nghiem in 1991[3]. The use of this technique minimized thrombosis and other surgical complications and improved success after such transplantation.

To our knowledge this is the first reported case of pediatric dual renal transplantation with adjuvant hematopoietic stem cell transplantation and splenic cell infusion from a cadaveric pediatric donor in India.

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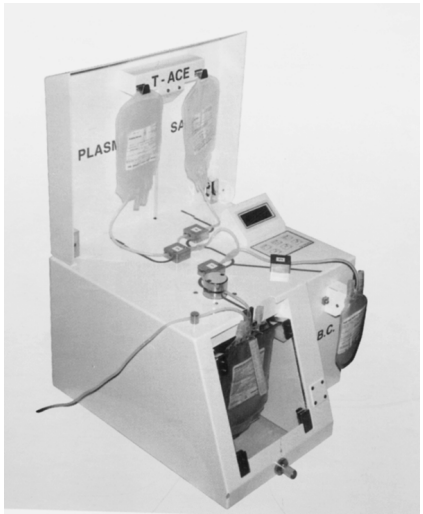
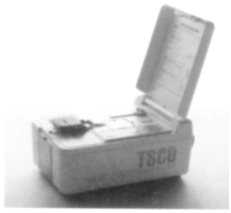
Blood depends Life on it.



Blood defines life and death. Reason why the shortage of blood is a serious issue for each one of us to consider. Did you know that the blood deficit in almost all states, nationwide, ranges between 20% to 50% ? That is a frightening shortage indeed !



The answer to this emergency-like situation is Component Separation. It involves the separation of blood into its 4 components, namely RBCs, Platelets, Plasma and Cryoprecipitate. By doing so you can save 3 lives. Not just one. Food for thought, isn't it ? Don't you agree that this is a sure bet against the shortage of blood and of wastage us well ?

In this context, wouldn't Component Separation increase the safety of blood as well ? The choice is ours. Let's make it the safe one.

BLOOD Component Separation SAVE 3 LIVES - NOT JUST 1

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