Original Article

Deceased donor renal transplantation at army hospital research and referral: Our experience

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ABSTRACT

Context: In India, there are a large number of end-stage renal disease (ESRD) patients waiting for renal transplant. Deceased donor organ transplantation (DDOT) is the possible solution to bridge the disparity between organ supply and demand. The concept of expanded criteria donors (ECDs) was developed to combat the huge discrepancy between demand and organ availability. However, ECD kidneys have a higher propensity for delayed graft function (DGF), and therefore worse long-term survival. We present our experience of deceased donor renal transplantation.

Aims: We report single centre experience on DDOT including ECDs vis-à-vis patient/graft survival, graft function in terms of serum creatinine (SCr), rejection episodes, and delayed graft function in 44 DDOT

Materials and Methods: Between August 1998 and April 2011, 44 renal transplants from 35 deceased donors were performed, of which 37.2% were expanded criteria donors. Results were analyzed in terms of age of donor, terminal SCr, graft ischemia time, graft function, post-transplant complications, and graft and patient survival. All recipients received sequential triple drug immunosuppression and induction with rabbit antithymocyte globulin (rATG). The induction is commenced by giving first dose of rATG intraoperatively (dose 1.5 mg/kg) and subsequent rATG infusions were administered daily for a minimum of 5 and maximum of 7 doses depending on initial graft function.

Results: We have been able to achieve a mean cold ischemia time of 6.25 ± 2.55 h due to the coordinated team efforts. Delayed graft function occurred in 34% patients and 31.8% had prolonged drainage. There were no urinary leaks. Seven (16%) patients had biopsy-proven rejection episodes, all of which were reversed with treatment. Two patients underwent graft nephrectomy. One of these was due to hyperacute rejection and another due to anastomotic hemorrhage. One-year graft survival was 92.4% and the patient survival was 83.8%.

Conclusion: Deceased donor renal transplants have satisfactory graft function and patient survival despite the high incidence of delayed graft function. Retrieving kidneys from marginal donors can add to the donor pool.

Key words: Cold ischemia time, deceased donor, delayed graft function, end-stage renal disease

INTRODUCTION

In India, approximately 175,000 patients are added each year to the pool of end-stage renal disease (ESRD); however, only 10% of these receive renal replacement therapy and 2.4% patients receive renal transplant.[1,2]

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Limited number of live donor availability is one of the major reasons for this huge demand and supply gap. A deceased donor renal transplant program is the possible solution to the widening demand supply gap for kidney donors. Cadaver organ donation was accepted legally in 1994 by "The Transplantation of Human Organs Act". Establishment of NGOs like MOHAN foundation, Chennai, in 1994 has made a significant contribution in this direction.[3] However, only 2% of total kidneys for renal transplantation are procured from deceased renal donors due to various reasons.[4-6] Deceased donor transplant program in our hospital started in 1998. In this retrospective study, we highlight our experience in promotion of this program.

MATERIALS AND METHODS

A retrospective analysis of the records of 35 deceased donors and 44 renal transplant recipients from August 1998 to April 2011 was done. Of these only 7 DDOT were done

till 2005. Our DDOT program got accelerated from 2005 onward with cooptation of liver, cardiac, and corneal transplant program and a dedicated transplant coordinator in the team. Before 2010, one of the two retrieved kidneys was shared with another institute in the same city. After 2010, we are using both of the retrieved kidneys in our institute. All recipients were investigated for ESRD by the nephrologists in the Department of Nephrology and were then jointly evaluated by the integrated nephrology/urology team of the renal transplant program.

Our transplant program includes expanded criteria donors (ECDs) for renal transplantation. ECDs were defined as per the United Network for Organ Sharing (UNOS). All donors older than 60 years or donors between 50 and 59 years with any two of the following were included: Hypertension, cerebrovascular cause of brain death, or preretrieval serum creatinine (SCr) >1.5 mg/dl.[7-9]

All donors and recipients were ABO compatible, and all recipients had a negative donor T-cell cross-match. The donors were optimized in the ICU under the supervision of an intensivist. Organs were harvested on availability and preserved with cold histidine-tryptophan ketoglutarate (HTK) solution. Transplantation was carried out as per standard techniques. We routinely use DJ stent in our patients.

All recipients received sequential triple drug immunosuppression and induction with rabbit antithymocyte globulin (rATG). Calcineurin inhibitors were started on engraftment. Induction was commenced with steroid and rATG at a dose of 1.5 mg/kg. The first dose of rATG was given intraoperatively and subsequent rATG infusions were administered daily for a minimum of 5 and maximum of 7 doses depending on initial graft function. Maintenance immunosuppression consisted of tapering doses of steroids, mycophenolate mofetil (MMF), and tacrolimus (TAC). The administration of TAC was delayed until the patient had exhibited a brisk diuresis and a declining SCr level (<4.0 mg/dl). All patients received surgical site prophylaxis with a third-generation cephalosporin for 72 h, starting just before the induction of anesthesia.

Delayed graft function (DGF) was defined as a failure to decrease the SCr within 72 h or a requirement for dialysis within the first week after transplantation. Prolonged drainage was defined as more than 50 ml of drainage after postoperative day 7. Postoperative complications and rejection episodes were noted. The diagnosis of renal allograft rejection was suggested by a decline in renal function confirmed by ultrasound-guided percutaneous allograft biopsy as per the modified Banff classification.[10,11] Cellular rejections were treated with methyl prednisone (MP) 500 mg × 3-5 doses ± r-ATG 1.5 mg/kg single dose. Humoral rejections were treated with plasmapheresis (50 ml/kg per session × 4-8 sessions) + intravenous immunoglobulins (IVIG) 0.4 g/kg × 5-10 doses ± rituximab 375 mg/m^2 Body surface area BSA single dose or bortezomib (1.3 mg/m^2 BSA × 4 dosages). Post-transplant renal allograft function was evaluated by measuring SCr.

All patients were followed by the transplant program up to the point of graft loss or death. Results were analyzed in terms of age of donor, terminal SCr, graft ischemia time, graft function, post-transplant complications, and graft and patient survival. Patient survival was defined as time from transplantation to death. Graft survival was defined as time from transplant to requirement for hemodialysis.

RESULTS

A total of 44 renal transplants were done with organs retrieved from 35 deceased donors between August 1998 and April 2011. Of these, only seven were done between 1998 and 2005 and the remainder 37 from 2005 to April 2011. Thirty-three out of the 35 deceased donors were in-house, while 2 of the deceased kidneys were received from the other institute. Of the 35 donors, 37.2% (n = 13) patients were marginal donors (ECDs) due to one or more criteria.[7-9] Of these 13 deceased donors, 7 were hypertensive and died due to cerebrovascular cause, 2 hypertensive patients had SCr >1.5 mg%, while 5 patients were more than 60 years of age. Donor and recipient demographics are depicted in Tables 1 and 2, respectively.

Mean cold ischemia time (CIT) was 6.25 ± 2.55 h (1-16 h). Post-transplant, 15 patients (34%) had DGF [due to Acute

Table 1: Donor characteristics

	ECD (n=13)	SCD (n=22)
Mean age (years)	61±6.5	33±9
Mean serum creatinine (mg/dl)	1.18±0.4	1.12±0.5
Cerebrovascular cause of death (%)	53.8 (n=7)	27.2 (n=6)
History of hypertension (%)	69.2 (n=9)	22.7 (n=5)

ECD=Expanded criteria donors, SCD=Standard criteria donors

Table 2: Recipient and transplant characteristics

	Recipients of ECD (n=19)	Recipients of SCD (n=25)
Mean age (years)	38±12	43±11
Mean cold ischemia time (CIT in hours)	6.59±1.76	6.02±2.1
DGF, %	42.1 (n=8)	28 (n=7)
Prolonged drainage (lasting>7 days), %	31.58 (n=6)	32 (n=8)
Acute rejection episodes, %	15.8 (n=3)	16 (n=4)
Graft survival 12 months (%)	92	90
36 months (%)	73	89
Patient survival 12 months (%)	89	88.5
36 months (%)	62	60

ECD=Expanded criteria donors, SCD=Standard criteria donors, DGF=Delayed graft function, CIT=Cold ischemia time

Tubular Necrosis (ATN) in 7 patients, acute cellular rejection in 5, and antibody-mediated rejection in 2 patients] and all of these patients had full recovery of renal function with anti-rejection therapy. Fourteen patients (31.8%) had prolonged drainage with drainage lasting for more than 25 days in six of them. These six patients required treatment with 5% povidine-iodine solution instillation. None of our patients had urinary leak. Twelve (27.27%) patients developed chronic allograft nephropathy, and five (11.36%) patients developed post-transplant diabetes mellitus.

One- and 3-year graft and patient survival in ECDs and standard criteria donors (SCDs) groups are given in Table 2. Overall graft and patient survival at 1 and 3 years in our cadaver transplant program is 92.4% and 83.8%, and 79.3% and 61.2%, respectively [Figures 1 and 2]. Two patients had graft nephrectomy, one due to hyperacute rejection and the other due to dehiscence of arterial anastomosis on 14th postoperative day. A total of eight renal transplant recipients have been lost due to death from various causes. Five patients died due to septicemia following disseminated bacterial or fungal infection, two due to cardiovascular causes, and in one case the cause was not known.

DISCUSSION

Deceased donor renal transplant (DDOT) with "marginal donors" or ECD is increasing in number. In the United States, 15-20% of donors were ECD in 2002.[12] Currently, deceased donation rate in India is 0.08 per million population per year.[1,13] The current donation rate, if pushed to 1 from 0.08 per million donations, would take care of the requirement of all the livers, heart, and lungs in the country and, to some extent, the kidney shortage.[14] In India, where DDOT accounts for less than 4% of the total transplants, discarding the marginal kidneys would hamper the program. In our study, ECD comprised 37.2% (n = 13) of DDOT. In the circumstances of organ shortage, DDOT with ECD is a feasible option.

In India, very few centers have a viable deceased donor renal transplant program. In our center also, the deceased donor renal transplants were initially scarce from 1998 to 2005. However, this program got accelerated from 2005 onward with cooptation of liver, cardiac, and corneal transplant program and a dedicated transplant coordinator in the team. This resulted in a 55% successful conversion of potential donors to voluntarily donate organs which is amongst the best in available literature.[15,16]

We harvested the organs immediately on availability and used HTK solution for cold preservation. Cold preservation of kidneys is vital for graft function and has a critical role in the success of deceased donor kidney transplantation. A reduction in CIT can be associated with better renal allograft outcomes.[17,18] Increasing ischemia up to 18 h has not been found to be detrimental for graft outcome. The risk of graft failure rises with ischemia time of 19-24 h to relative risk (RR) 1.09, 25-36 h to RR 1.16, and > 36 h to RR 1.30 (P < 0.001). CIT is strongly associated with DGF, with a 23% increase in the risk of DGF for every 6 h of cold ischemia.[19]

We could achieve a reasonably good CIT of 6.25 ± 2.55 h.[20-22] We achieved it with coordinated and concerted team efforts and by operating to transplant the retrieved kidneys as soon as possible irrespective of the time of day/night. The moment somebody is declared brain dead in ICU, 6-8 recipients (average 3-4 per kidney) are called for by the nephrology team and their cross-match is sent and dialysis started. Urology team is divided into retrieval and transplant teams. The retrieval team remains in touch with transplant co-coordinator and other retrieval teams. As soon as the consent is obtained, donor is prepared for retrieval and, after heart and liver retrieval by Gastrointestinal and Cardio-vascular surgery teams, our team retrieves both kidneys which are perfused and transplanted into two best suitable cross-match recipients as soon as the cross-matches are received. This has resulted in an acceptable rate of DGF (34%) in our cases.[5,11,12,21-24] DGF is an independent

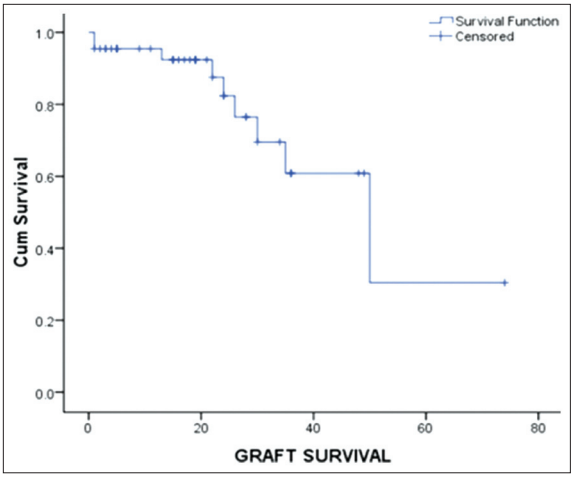

Figure 1: Kaplan Meier graft survival curve

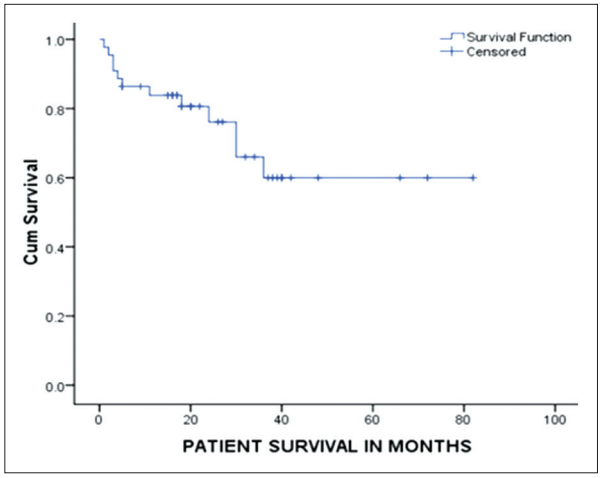

Figure 2: Kaplan Meier patient survival curve

predictor of poor graft survival in cadaveric renal transplant recipients.[22]

In India, individual centers have reported their outcomes. The 1-year allograft and patient survivals of 100 DDOT from four major centers in Chennai were 82% and 86%, respectively, with their 2-year allograft and patient survivals of 74% and 80%, respectively.[25]

In a study by Mani, 1-year and 4-year graft survivals of 88 DDOT in Chennai were 72% and 63%, respectively, and patient survival was hardly different from graft survival.[26] Five-year patient and graft survivals of 68 DDOT in Chennai were 61.7% and 58.8%, respectively, with biopsy-proven acute rejection in 26.4%, DGF in 50%, and CIT of 5.6 ± 3.2 h.[11]

In our study, over a mean follow-up of 21.84 ± 16.39 months, 1-year graft and patient survival rates were 95.4% and 83.8%, respectively, with a high 1-year post-transplantation mortality. Most of these deaths were caused by sepsis. It is possible that long duration of hemodialysis HD before transplant, ECD, increased DGF, triple immunosuppressive regimens with ATG induction, a delayed presentation and diagnosis, and tropical climate and socioeconomic factors may have contributed to high infection rate leading to a higher 1-year post-transplantation mortality, with most of these deaths caused by sepsis.[26-31] As brought out by Samhan *et al*., the recipients of renal allograft in developing countries may be more prone to infections, which are the most common cause of post-transplant mortality.[32]

There are data to suggest that these kidneys have a higher rate of primary nonfunction, DGF, and rejection, and a greater susceptibility to preservation injury, drug toxicity, and the effects of post-transplant hypertension.[33-39] Moreover, the longevity of an ECD kidney is believed to be much shorter, with the half-life estimated to be 4-6 years compared with 8-12 years with an SCD kidney from a deceased donor.[33-37]

In our series, the ECDs were characterized by older donor age (mean 61 ± 6.5 years for ECD vs. 33 ± 9 years for SCD), a higher terminal SCr (mean 1.18 ± 0.4 mg% for ECD vs. 1.12 ± 0.5 mg% for SCD), and a higher cerebrovascular cause of death (53.8% vs. 27.2%) [Table 1]. One-year graft and patient survival in recipients of ECDs and SCDs were comparable; however, 3-year graft survival in ECD was less (73% vs. 89%). Our results highlight the importance and role of utilizing organs from marginal donors with expanded criteria as a feasible option for deceased donor renal transplant.

CONCLUSION

The rate of cadaver kidney transplantation in India is low, and under these circumstances, retrieving kidneys from marginal donors can add to donor pool. The role of the transplant coordinator in proper counseling of the family of deceased donor is vital in ensuring a greater conversion rate for making larger number of organs available for transplantation. A sustained effort at minimizing CIT is helpful in achieving good graft function. Ischemia time may be significantly reduced with proper co-ordination between different organ retrieval and transplant teams. The success of this program depends to a considerable extent on a coordinated team effort willing to go that extra mile for the sake of the patient.

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