

KIDNEY TRANSPLANTATION : STRATEGIES FOR EXPANDING DONOR POOL

AZFAR UDDIN SHAIKH¹, MD. WALIUL ISLAM², MD. ABUL HOSSAIN³, MOHAMMED MIZANUR RAHMAN¹, ZANNATUL FERDOUS²

¹Clinical Research Coordinator, New York Medical College, NY, USA, ²Dept. of Urology, National Institute of Kidney Diseases & Urology, Dhaka, Bangladesh, ³Dept. of Urology, Shaheed Suhrawardy Medical College Hospital, Dhaka, Bangladesh.

Abstract

Objective: To find out the appropriate strategies to increase the donor pool for kidney transplantation.

Methodology: The PubMed literature database was searched from 2015 to 20 years backward. Strategies to increase and improve live donor KT were suggested. In order to formulate some suggestions to reach that target, related experience and strategies published in journals of last 20 years both from developed and developing countries, were reviewed.

Results: Strategies to increase and improve live donor KT were suggested. Only Live donor KT can never fulfil the demand of KT. The most important step to boost up KT program is to start deceased Donor Organ Transplantation and by formulating a law and establishing infrastructure. Development of National Kidney Transplant Registry and coordination of KT at National level is also very important. Those patients who cannot afford expenditure for KT and post-transplant care, can be supported by raising fund at national and international level.

Conclusion: To increase living donor KT, techniques of increased graft survival, donor and recipient comfort, confidence and safety should be established. Inclusion of both brain death (BD) and Deceased Circulatory Death (DCD) in Deceased Donor pool will be good option for increasing donor pool.

Key words: Kidney transplantation, live donor, deceased donor.

Bangladesh J. Urol. 2015; 18(2): 88-93

Introduction

Since the first Kidney Transplantation (KT) in 1954, there has been a significant advancement of KT all over the world especially in the field of immunosuppression. Despite of that almost all countries are still far behind the demand. Main issue of KT is organ shortage. Kidney transplantation (KT) avoids the debilitating effects of long-term maintenance dialysis and the best treatment of end-stage renal disease (ESRD). This information should be circulated and awareness of organ donation should be nicely created through national media. A national

organ transplant registry is an indispensable requirement for patient care, research, mortality, morbidity and planning. Representative transplantation database systems are the 'Scientific Registry of Transplant Recipient' (SRTR) in USA. Asian countries also established transplantation database system such as Japan Renal Transplant registry, China Liver Transplant Registry, Thai Transplant Registry, Malaysia National Transplant Registry, Saudi Center for Organ Transplantation, Indian Transplant Registry, Korean Network for Organ Sharing etc[2]. Transplant should be coordinated at national level by National Transplant Coordinator and then Hospital/Institutional Coordinators. Fund collection, if needed, can be arranged at national

Correspondence: Azfar Shaikh, Clinical Research Coordinator & Clinical Rotation with NJ Center for Prostate Cancer & Urology, Hudson Valley Hemato-Oncology Group, New York Medical College, Valhalla, New York. E-mail: rimon3k@yahoo.com

level both by Govt. and NGOs. Campaign from national level to motivate people for organ donation and removal of any barrier for KT is appreciated. Fund collection, if needed, can be arranged at national level both by Govt. and NGOs. We appreciate a campaign from national level to motivate people for organ donation and removal of any barrier for KT.

Discussion

Transplant is coordinated in different way in different countries. In USA and Canada, majority KT are done from deceased donors. When an individual does not have a living donor but is an acceptable transplant candidate, he/she will be placed on a waiting list.

In 1984, Congress passed the National Organ Transplant Act in USA. This act prohibited the sale of human organs and mandated a national Organ Procurement and Transplantation Network (OPTN) to oversee organ recovery and placement and equitable organ distribution policies. The United Network for Organ Sharing (UNOS) is an independent, non-profit organization. It was awarded the national OPTN contract in 1986. It is the only organization ever to operate the OPTN. Organ Procurement Organizations (OPO) are non-profit agencies operating in designated service areas covering whole states or just parts of a state. OPOs are responsible for: approaching families about the option of donation, evaluating suitability of potential donors, coordinating the recovery and transportation of donated organs and educating the public about the need for organ donation. Most deceased donor kidneys are transplanted to recipients in the same service area as the deceased donor. Although there are recommended guidelines for organ allocation, each OPO may request a "variance" to fit the special needs to the patients waiting for kidney transplantation in their service area. Whenever a donor is identified within an OPO the HLA tissue typing results are entered into the UNOS national computer system. UNOS has the HLA tissue typing information of all patients awaiting kidney transplantation in the United States. If a waiting list patient has the identical HLA tissue type as the donor the kidney will be given to him/her regardless of the geography. Unfortunately, many more patients are medically suitable for transplants than organs available. The waiting times are many years and growing longer. Matched Recipient may stay in a different State where organ is send via helicopter. Transplant Surgeon in Recipient's hospital harvest organ. Sometimes Transplant Surgeon (for Recipient) travel with his/her team to procure organ from deceased donor.

When I was working with transplant team at Westchester Medical Center, I traveled with our team by helicopter to procure Kidney and liver from a deceased donor, victim of road traffic accident.

Singapore, a small country, developed a different system. Transplant Coordinator makes a monthly roster from enlisted transplant surgeons and also select hospital for transplantation for every day. If donor kidney is available, surgeon and hospital assigned for that day carry out organ transplantation. They have a good national registry for all patients. Singapore model may be more useful for Bangladesh. Transplant surgeons should be dedicated to transplant only; he/she might come from Urology or from General Surgery but well trained in transplantation. Full time involvement in transplant is very much essential for a Transplant Surgeon. It is the time to develop multiorgan transplantation like kidney, liver, pancreas in Bangladesh. Post-graduation course (MS/FCPS) in Transplant Surgery is the demand of time now.

Living donor kidney transplants are the best option for many patients for several reasons - Better long-term results, no need to wait on the transplant waiting list for a kidney from a deceased donor, surgery can be planned at a time convenient for both the donor and recipient, lower risks of complications or rejection, and better early function of the transplanted kidney. Living Donor Transplant is still the principal method of renal transplantation in Bangladesh. Main problem is organ scarcity. So, strategies to increase living donor pool is an important way to increase our KT.

Strategies for Expanding The Living Donor Pool: Traditionally, over 50% of potential living donors otherwise suitable for donation did not proceed because immunologic screening of the recipient revealed circulating donor-specific ABO antibodies (up to 30% of donors) or human leucocyte antigen (HLA) antibodies[3]. In the new millennium, major advances have overcome these barriers. ABO-incompatible (ABOi) living donor kidney transplantation (LDKT) programs have been successfully established in achieving patient and graft survival rates comparable to those of ABO-compatible KT[4]. The main disadvantage of ABOi-LDKT is its cost, which might be considered as prohibitive in low-income countries like Bangladesh. Nonetheless, compared with dialysis expenses, ABOi-LDKT remains cost effective in many developed countries[5,6]. Alternatively, these patients can also be included in a paired-donor exchange program which is described below.

Starting in 1998, **HLA-incompatible (HLAi) LDKT programs** [i.e. renal transplantation in a recipient with a positive complement-dependent cytotoxic (CDC)- or flow cytometric-crossmatch against the donor] have been developed mostly in the USA using protocols similar to those used for ABOi-LDKT[7]. The long-term results showed that US patients who received HLAi-LDKT had a significant survival benefit compared with HLA sensitized patients, who remained on the transplant waiting list[7]. However, compared with standard HLA compatible LDKT, HLAi-LDKT carries an increased risk of acute antibody-mediated rejection, transplant glomerulopathy and graft failure^{8,9} jeopardizing the long-term success of transplantation. Alternate is paired-door exchange program discussed below.

Paired kidney donation (PKD) is when two or more living kidney donor/recipient pairs, who are not compatible with each other because the recipient has circulating HLA- and/or ABO antibodies against his/her own donor, exchange the kidneys in such a way that recipients receive compatible kidneys. PKD avoids the costs and complications of desensitization therapies for ABOi- and HLAi-LDKT. There are several ways in which a PKD program can be organized. The simplest one is to perform two-way paired donation between two or three incompatible pairs. To avoid the possibility that after one donor has given a kidney to the other pair's recipient, that recipient's co-registered donor may refuse to donate in return, paired donor transplant operations should be performed simultaneously[10]. This might be a good option for Bangladesh. In the USA, as well as single-center independent PKD programs, there are also competitive non-profit registries such as National Kidney Registry or The Alliance for Paired Donation.

Strategies for the Sensitized Patient With No Living Donor Available: Patients who develop antibodies against a large variety of HLA antigens (highly sensitized patients), because of pregnancy, blood transfusion and previous transplantation, have limited opportunity of having a compatible living donor or of receiving a crossmatch-negative organ from a deceased donor using standard allocation algorithms. For them options are, 'The Eurotransplant Acceptable Mismatched Program', 'Overnight' desensitization in deceased-donation (with a CDC-positive crossmatch by treating 9 L of plasma with immunoabsorption immediately before transplantation) and intravenous immunoglobulin/rituximab while on dialysis to increase deceased-donor transplantation rates[10].

Strategies for Expanding The Deceased-Donor Pool: Even for patients who are not sensitized, access to transplantation is limited by the increasing disparity between organ supply and demand. In an attempt to counter this trend and to manage the increasing proportion of older donors and donors with comorbidities, as well as the increasing number of elderly recipients, selection criteria for organ donors have been widened, leading to the use of donors that would have previously been deemed unsuitable. In a study, it was found that there was no difference of graft survival in **Extended-Criteria Donors (ECD)** compared with control group of standard criteria donors[11]. ECDs are defined as -1) donors aged 50-59 years with ≥ 2 of the following risk factors – a history of hypertension, diabetes, death by cerebrovascular accident, impaired renal function (Final preprocurement $SCr > 1.5$ mg/dl); or 2) donors aged ≥ 60 years, independently from the presence or absence of risk factors¹¹.

Donation After Circulatory Death (DCD) - After approval of DCD by the World Health Organization in 2011, DCD became more and more accepted, and allocation of DCD organs is now routine practice in 10 of the 27 European Union countries as well as North America, some countries in South America, Australia and Japan[12]. A precise pathway on organ donation including DCD was published recently. Currently, there are five categories of DCD donors in the 2003 modified Maastricht classification[12]. The first two categories refer to donors who died unexpectedly, death being declared on arrival at the hospital or after unsuccessful resuscitation. These donors are predominantly used in France and Spain [46]. However, most countries use the remaining three categories of donors that refer to instances when death is anticipated, and donation occurs soon afterwards. This condition, called 'controlled' circulatory death, may take place in an intensive care unit or a special care unit[12]. In controlled donation, the techniques for organ reperfusion are easier, whereas in uncontrolled circulatory death the procedures are more demanding[13]. Various factors explain the different DCD practices across different countries. Among the most important factors are different legislations concerning consent for organ donation (presumed versus explicit consent), and different attitudes and regulations concerning the withdrawal of futile life-sustaining treatments. Furthermore, different national legislations exist concerning the length of the 'no touch' period after declaration of death and initiation of organ retrieval (e.g. 20 min in Italy versus 2–5 min in many other countries).

In the USA, the proportion of DCD donors is roughly 10%, but there is large international variability. In the UK, where controlled DCD donors represent 40% of the deceased donor pool, the waiting list has shown a small decline, despite a plateauing of brain-death donors and living donors and a constant rate of newly wait-listed patients¹⁴. In Bangladesh, we can include DCD while making Organ Act for Deceased Donor.

In USA, Canada number of Deceased donor is doubled than of living donor; in European countries most of the KT from deceased donor. Deceased donor transplant is the major organ supply for KT all over the world. Bangladesh needs an organ procurement act for deceased donor transplant. Along with brain death donors if circulatory death donor (DCD) pool is added during construction of Organ Act for Deceased Donor in Bangladesh, the number of organ from deceased donor pool will be increased to boost up transplantation. We have to develop Transplant team and technique for multi organ transplantation to utilize deceased organs fully. Most of the patients of ESRD are from DM. In that case, simultaneous kidney and pancreas transplant might be a good option for us also.

Dual Kidney Transplant: One strategy in overcoming the imbalance between the limited nephron mass (supplied from older donors/ECD) and the metabolic request of the recipient is dual kidney transplant (DKT)[15]. The first DKT was performed in the United States in 1996 by Johnson and associates[16]. Donor estimated glomerular filtration rate (eGFR) is a criterion used for decision making in DKTs. Centers participating in dual kidney groups perform DKT with kidneys from donors with eGFR under 1.2 mL/s and > 55 years of age that have been refused for single organ transplant by local centers[17]. Kidney grafts were recovered using the standard multiorgan retrieval technique. Grafts were preserved separately under hypothermic conditions or using a hypothermic machine perfusion system. After bench surgery, 2 kidney grafts were implanted sequentially either bilaterally, using separate incisions, or unilaterally. A urethral stent was not used routinely, and it was left for the transplant surgeon's consideration[15]. Review of articles revealed that dual transplant procedure may help improve results of kidney transplants from expanded criteria donors and extend the donor pool by using kidneys that would be discarded otherwise[18-20]. In Bangladesh, we can consider it also.

Live Donor to Deceased Donor Waiting List

Exchange: This program is a way for a living donor to benefit a loved one, even if their blood or tissue types do not match. The donor gives a kidney to another patient who has a compatible blood type and is at the top of the kidney waiting list for a "deceased donor" kidney. In exchange, that donor's relative or friend would move to a higher position on the deceased donor waiting list, a position equal to that of the patient who received the donor's kidney.

Spanish Model: Spain is the example in the world of continuous improvement in cadaveric organ donation. Their concept is Organ shortage is not due to a lack of potential donors, but rather to a failure to turn many potentials into actual donors. A proactive donor detection program performed by well-trained transplant coordinators, the introduction of systematic death audits in hospitals and the combination of a positive social atmosphere with adequate economic reimbursement for the hospitals have accounted for this success. This model can be partially or totally translated to other countries if basic conditions are satisfied[21].

Pediatric Transplant: Although the number of children with end-stage renal disease (ESRD) in need for renal transplantation is small compared with adults, the problem associated with renal transplant in children are numerous, varied, and often peculiar. Pre-emptive transplantation has recently been growing in popularity as it avoids many of the associated long-term complications of ESRD and dialysis. Changes in immunosuppression to more potent agents over the years will have affected transplant outcome. Transplantation is currently the best option for children with ESRD[22]. This is the time for development pediatric transplant in Bangladesh.

WHAT'S NEW?: **New drugs** are constantly introduced in the market for immunosuppression like Eculizumab[23] (the humanized anti C5 antibody), proteasome inhibitor Bortezomib[24], complement inhibition by C1-esterase inhibitors, Sirolimus, Alemtuzumab (Campath), Anti-interleukin-2 Receptor Antibody (Zenapax® or Simulect®), Belatacept[25](a fusion receptor protein that blocks the co-stimulation pathway CD80/CD86/CD28, was recently approved for the prevention of acute rejection in KT), Humanized anti CD40 antibodies[26] etc. **Bioartificial Kidney** - Early work has shown promise by developing functional kidney tissue and even prolonging survival following transplantation in animals[27]. Human studies have

shown that a cell bioreactor can improve patient's mortality in acute kidney injury. Despite these early successes, there are obstacles to overcome before a bioartificial kidney will become standard of care. A major issue for the field is cell sourcing. There are ethical concerns over using human embryos and fetal cells for organ development. Finally, the field will need to move beyond rodents and demonstrate the feasibility of their techniques in larger animals and eventually humans. There is also promising result of hematopoietic stem cell infusion/transfusion for the induction of allograft tolerance[28].

Organ Trade: In some developing countries, people sell their kidney mostly because of grave poverty. After some incidences in past in Bangladesh[29], we are now strict and we have strong Organ Donation Act. To prevent transplant tourism, we must develop our KT program.

Conclusion:

To increase living donor KT, we have to develop techniques of increased graft survival, donor and recipient comfort, confidence and safety. We need to increase public awareness and coordination of transplant work from National Level. Laparoscopic Donor Nephrectomy might increase comfort to donor, quick recovery and can motivate people for donation³⁰⁻³¹. Creation of National Transplant Registry and Coordination of KT from National level is highly demanding. Strategies to increase living donor pool especially paired donation that was discussed earlier might be helpful. Development of dedicated Transplant Surgeons for multi organ transplantation is also important. Inclusion of both brain death (BD) and Deceased Circulatory Death(DCD) in Deceased Donor pool will be good option while formulating a deceased organ donation act. Consideration of extended criteria donor (ECD) and focus on pediatric transplantation is necessary. It is very much essential to follow up all transplant patients and provide them support through a fund. Many a countries raise fund through National level programs with involvement of national celebrities. Everyone will be interested if approached properly. Newer immunosuppressant/ immunomodulatory drugs are really expensive and selected patients might get help from the fund. Poverty is an important barrier for expansion of transplantation program. Many of the patients can't go for KT because they are unable to afford that. fund/support system with the help of Govt. and NGOs to boost up transplant program should be developed. Implimentation of knowledge based on experience of developed and

developing countries, might help to progress KT program on the right tract.

Conflict of Interest: None declared

References:

1. H.U Rashid, A Khanam, S Islam, M.A Wahab, K.M Iqbal. Experience with living donor kidney transplantation in Bangladesh. *Transplantation Proceedings*. 1999, 31(8); 3112.
2. C. Ahn, T.Y. Koo, J.C. Jeong, M.Kim, J. Yang et al. Initial Report of the Korean organ Transplant Registry: The first report of National Kidney Transplantation Data. *Transplantation Proceedings* 2014, 46; 425-430.
3. Karpinski M, Knoll G, Cohn A, et al. The impact of accepting living kidney donors with mild hypertension or proteinuria on transplantation rates. *Am J Kidney Dis*. 2006; 47:317–323.
4. Takahashi K, Saito K, Takahara S, et al. Excellent long-term outcome of ABO-incompatible living donor kidney transplantation in Japan. *Am J Transplant*. 2004; 4:1089–1096.
5. Genberg H, Kumlien G, Wennberg L et al. ABO-incompatible kidney transplantation using antigen-specific immunoadsorption and rituximab: a 3-year follow-up. *Transplantation*. 2008; 85:1745–1754.
6. Schnitzler M, Machnicki G. ABO-incompatible living donor transplantation: is it economically "compatible"? *Transplantation*. 2006; 82:168–169.
7. Montgomery RA, Lonze BE, King KE, et al. Desensitization in HLA-incompatible kidney recipients and survival. *N Engl J Med*. 2011; 365:318–326.
8. Sharif A, Kraus ES, Zachary AA, et al. Histologic phenotype on 1-year post transplantation biopsy and allograft survival in HLA-incompatible kidney transplants. *Transplantation*. 2014; 97:541–547.
9. Bentall A, Cornell LD, Gloor JM, et al. Five-year outcomes in living donor kidney transplants with a positive crossmatch. *Am J Transplant*. 2013; 13: 76–85.
10. Umberto Maggiore, Rainer Oberbauer, Julio Pascual, Ondrej Viklicky, Chris Dudley et al. Strategies to increase the donor pool and access to kidney transplantation: an international perspective. *Nephrol Dial Transplant*. 2015 Feb; 30(2): 217–222.

11. S. Martinez-Vaquera, M.D. Navarro Cabello, M. Lopez-Andreu, J.M. Duenas Jurado, C. Rodelo Haad et al. Outcomes in Renal Transplantation with Expanded-Criteria Donors. *Transplantation Proceedings*, 2013; 45, 3595-3598.
12. Morrissey PE, Monaco AP. Donation after circulatory death: current practices, ongoing challenges, and potential improvements. *Transplantation*. 2014; 97:258–264
13. Neyrinck A, Van Raemdonck D, Monbaliu D. Donation after circulatory death: current status. *Curr Opin Anaesthesiol*. 2013; 26:382–390.
14. Johnson RJ, Bradbury LL, Martin K, et al. Organ donation and transplantation in the UK—the last decade: a report from the UK national transplant registry. *Transplantation*. 2014;97(Suppl 1): S1–S27.
15. Peter Balaz, Slavomir Rokosny, Peter Wohlfahrt, Mariana Wohlfahrtova, Milos Adamec et al. Dual Kidney Transplant: A Single-Center Experience and Review of the Literature. *Experimental and Clinical Transplantation*. 2013; 11(5); 388- 395.
16. Johnson LB, Kuo PC, Dafoe DC, et al. The use of bilateral adult renal allografts - a method to optimize function from donor kidneys with suboptimal nephron mass. *Transplantation*. 1996;61(8):1261-1263.
17. Lu AD, Carter JT, Weinstein RJ, et al. Outcome in recipients of dual kidney transplants: an analysis of the dual registry patients. *Transplantation*. 2000;69(2):281-285.
18. Dafoe DC, Alfrey EJ. Dual renal grafts: expansion of the donor pool from an overlooked source. *Transpl Int*. 1998;11(3):164-168.
19. Gill J, Cho YW, Danovitch GM, et al. Outcomes of dual adult kidney transplants in the United States: an analysis of the OPTN/UNOS database. *Transplantation*. 2008;85(1):6268.
20. Cruzado JM, Fernandez L, Riera L, et al. Revisiting double kidney transplantation: two kidneys provide better graft survival than one. *Transplant Proc*. 2011;43(6):2165-2167.
21. Matesanz R, Miranda B. *J Nephrol*. A decade of continuous improvement in cadaveric organ donation: The Spanish model. 2002 Jan-Feb;15(1):22-8.
22. B. Saeed. Pediatric Renal Transplantation. *Int J Organ Transplant Med*. 2012; 3(2): 62–73.
23. A service of the U. S. National Institutes of Health. Cited: 2013-06-03. Available from: <http://www.clinicaltrials.gov/>
24. Fehr T, Gaspert A. Antibody-mediated kidney allograft rejection: therapeutic options and their experimental rationale. *Transpl Int*. 2012; 25:623–632.
25. Charpentier B, Medina Pestana JO, Del C Rial M, Rostaing L, Grinyó J, Vanrenterghem Y, Matas A, Zhang R, Mühlbacher F, Pupim L, et al. Long-term exposure to belatacept in recipients of extended criteria donor kidneys. *Am J Transplant*. 2013;13: 2884–2891
26. Goldwater R, Keirns J, Blahunka P, First R, Sawamoto T, Zhang W, Kowalski D, Kaibara A, Holman J. A phase 1, randomized ascending single-dose study of antagonist anti-human CD40 ASKP1240 in healthy subjects. *Am J Transplant*. 2013; 13:1040–1046.
27. Steven Kim, William H. Fissell, H. David Humes, and Shuvo Roy. *Current Strategies and Challenges in Engineering a Bioartificial Kidney*. *Front Biosci (Elite Ed)*. 2015; 7: 215–228
28. Granados JM, Benichou G, Kawai T. Hematopoietic stem cell infusion/transplantation for induction of allograft tolerance. *Curr Opin Organ Transplant*. 2015 Feb; 20(1):49-56.
29. Moniruzzaman M. “Living cadavers” in Bangladesh: bioviolence in the human organ bazaar. *Med Anthropol*. 2012 Mar; 26(1):6991.
30. Shaikh A. Laparoscopic Live Donor Nephrectomy: Is this the right choice? *Bangladesh Journal of Urology* 2009; 12(1): 24-28.
31. Shokeir AA. Open versus laparoscopic live donor nephrectomy: a focus on the safety of donors and the need for a donor registry. *J Urol*. 2007 Nov;178(5):1860-6

Abbreviation:

DCD : Deceased Circulatory death
 ESRD : End state Renal Disease
 KT : Kidney Transplantation