

Paired Exchange: A New Innovation in Live Donor Kidney Transplantation

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Abstract

Barriers to traditional living-donor kidney transplantation include ABO incompatibility and positive cross-match. Paired exchange kidney transplantation (PEKT) is a viable and increasingly popular method to increase live donation. We discuss the pros and cons as well as the various ways to achieve PEKT along with a review of existing literature. To achieve the full potential of PEKT, the transplant community at large needs to work toward a national kidney paired donation program along with a centralized financial intermediary.

Keywords: Live donor kidney transplantation; Paired exchange; Kidney transport

Introduction

Kidney transplantation is the treatment of choice for patients with end stage renal disease. Living donor kidney transplantation is associated with fewer post-operative complications and higher graft survival compared to deceased donor kidney transplantation. However, ABO incompatibility and positive cross match are barriers to traditional living donor transplantation in roughly one third of instances [1]. Desensitization therapies have been used to enable successful transplantation across incompatible donor-recipient pairs, but these procedures are associated with higher costs, complications and inferior long-term outcomes [2]. Paired-exchange kidney transplantation (PEKT) is an innovative approach that can overcome these hurdles which is becoming popular in the United States. Computer simulation modeling has shown that PEKT can lower costs with improved outcomes compared to desensitization [3]. The idea of PEKT was first proposed by Felix Rapaport in 1986 though first PEKT was performed in the United States in 2000 [4]. Based on the SRTR data, PEKT transplants became more evenly distributed across centers from 2006 to 2008 and the trend remained unchanged from 2008 to 2011 (Gini coefficient 0.91 for 2006, 0.76 for 2008 and 0.77 for 2011) [5]. In subsequent years, many transplant centers started participating in PEKT. In the United States, paired kidney donation increased from around 200 in year 2008 to greater than 400 in 2011 [6]. While Canada has established a single national kidney paired donation registry, United States currently has seven active multicenter registries in addition to single center registries. Individual centers tend to refer only difficult-to-match pairs, hence limiting the maximal benefit to other recipients. A consensus conference was convened in March 2012 that addressed challenges of PEKT and strongly emphasized the need for developing a single well-functioning national registry for PEKT [7].

How PEKT Works

PEKT enables a recipient with willing but incompatible donor to find a potential match from a larger donor pool. With centralization of the donor/recipient pool, it has become easier to find compatible donors across the country. Details of patient's own HLA type as well as

the antigens to which they react strongly are uploaded to enable virtual cross-matching, similar to the process followed for deceased donor kidney allocation [8]. PEKT could involve one or more pairs as shown in Figure 1. It could be a simple two way exchange where each recipient accepts kidney from each other's willing donor (Figure 1a), a three-way exchange where donor of recipient A gives kidney to recipient B, donor of recipient B gives kidney to recipient C and donor of recipient C gives kidney to recipient A (Figure 1b) or the process can go on as a longer chain thus allowing multiple kidney transplants simultaneously.



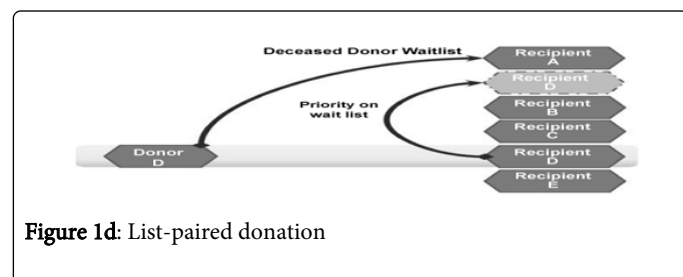
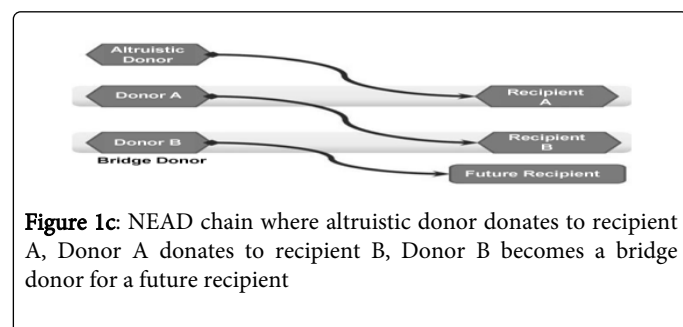
Figure 1a: Two-way PEKT exchange



Figure 1b: Three way PEKT exchange

If a chain is initiated by an altruistic or non-directed donor, it could lead to multiple donations ending with a donor who is yet to donate, designated as a bridge donor (Figure 1c). This concept was introduced as Never Ending Altruistic Donor (NEAD) chains [9]. These transplants do not necessarily undergo simultaneously because of logistic issues and time involved in finding next compatible recipient. Sometimes, a bridge donor can end up donating to a patient on deceased donor waiting list, in a process called closed chain domino transplantation that can have a favorable impact for remaining wait listed patients hoping to receive deceased kidney transplant. Another type of PEKT is list-paired donation where willing but incompatible living donor donates kidney directly to a patient on deceased donor

list and in return for this, that donor's incompatible recipient receives a high priority on deceased donor wait list (Figure 1d) [1,10].



Concern for prolonged cold ischemia with donor kidney transport

The traditional in-center kidney transplantation (ICKT) in which donor and recipient undergo surgery in the same transplant center has the potential advantage of minimizing cold ischemia time (CIT). In PEKT involving multiple transplant centers, donor kidneys are transported after procurement to the intended recipient's transplant center to make it more convenient for the donor who may prefer not to travel long distances in the peri-operative period. There have been concerns about this approach in terms of possible adverse graft outcomes from the associated prolonged CIT including delayed graft function (DGF) and risks of unforeseen delay in transportation of the organ.

Simpkins et al. [11] analyzed united network of organ sharing database and found no adverse effects of CIT up to eight hours on one year kidney allograft function, rates of acute rejection or long-term graft survival in 38,467 living donor kidney recipients despite a slightly increased risk for developing DGF. On the contrary, analysis of United States renal data system showed association between prolonged CIT and risk of developing DGF, AR, prolonged hospital stay and reduced graft survival in deceased donor kidney transplant recipients [12]. The difference in the implications of prolonged CIT on living versus deceased donor kidneys could partly be explained by the susceptibility of deceased donor kidneys to injury associated with brain death, effect of inflammatory milieu, stress hormones and prolonged warm ischemia time that is exacerbated by prolonged CIT. Immediate graft function and better allograft survival with living donor kidney transplantation could be attributed to the controlled environment at the time of procurement of a high quality kidney from a living donor under anesthesia which makes the impact of modest increase in CIT minimal. Segev et al. [13] reported no DGF and excellent immediate graft function despite a median CIT of 7.2 hours in 56 live donor transplants where kidneys were transported to the intended recipient. In our single center experience, CIT for the

transported kidneys was 13.1 ± 6.6 hours without any adverse outcomes in patients undergoing PEKT [14]. Others have also reported CIT ranging from 8 to 14 hours with no appreciable adverse effects on the transported organs [15].

Disadvantage for blood group O recipients

Since candidates with blood group O are universal donors, these kidneys are compatible for other blood group recipients as long as cross-match is negative, resulting in scarcity of blood group O donors in PEKT for blood group O recipients. Gentry et al proposed to encourage compatible pairs to enter in PEKT to expand the donor pool and circumvent this issue. If compatible pairs are included in PEKT, blood group imbalance can be corrected. Only 30% of incompatible pairs have O donors, 61% of incompatible pairs have O recipients. Amongst compatible pairs, 67% have O donors and one third of these donate to non-O recipients. The recipients of compatible pair might also benefit from participating in PEKT by finding a younger donor or by avoiding a high immunologic risk donor/recipient combination such as child to mother or husband to wife [16].

Outcomes of ICKT versus PEKT

One-year graft and patient survival as well as allograft function, AR rates and incidence of proteinuria were similar between PEKT and ICKT groups in our single center experience [14]. This was despite a significantly longer CIT and higher PRA in the PEKT group. Similar results were reported on two year follow up with respect to death-censored graft survival (97.1% versus 97.6%, $p=ns$), patient survival (97.1% versus 94.8%, $p=ns$) and rejection rates (8.7% versus 9.9%) in PEKT versus living related kidney transplantation [17,18]. Five and ten year allograft survival rates (86.3% versus 82.3%, $p=ns$) were similar in exchange versus non exchange groups undergoing living kidney donation [19].

Financial and ethical considerations

PEKT is more cost effective as compared to continuing dialysis or implementing desensitization protocols for highly sensitized patients. If a national kidney paired exchange program is established in USA, it would save \$750 million annually [3,20]. Insurance companies and private payers are reluctant to pay for evaluation of a potential donor unless eventual transplantation to the "given" recipient could be guaranteed. If a financial intermediary for PEKT is established similar to organ procurement organization for deceased donors, financial pressures currently limiting adoption of national program could be overcome [21]. In order to pay for evaluation of potential donors, donor travel or kidney transport, donor nephrectomy, professional fees, donor complications, follow up, and administrative fees for running PEKT program, it was proposed to develop a national kidney paired donation standard acquisition charge (KPD-SAC). SAC would represent average cost of a realized donor and would be paid by each recipient center to the donor center [7]. This model is preferred by several commercial insurance payers [22].

Many programs participating in PEKT believe that kidneys from living donors are of comparable quality. Chan et al. showed that with the exception of recipients aged 18-39 years, who had the best outcomes with donors aged 18-39 years, living donors aged between 18-64 years has minimal effect on allograft survival [23]. Some programs have implemented limits such that they would not match

donors to a recipient more than 20 years younger than the candidate's incompatible donor [24].

There have been ethical concerns with PEKT. One of the biggest benefits to the donor is emotional satisfaction in helping out a loved one, which is theoretically lessened if kidney is given to an unrelated, anonymous recipient. Also, the quality of donor kidney and the transplant outcomes might be totally different in two different recipients that could cause frustration and anger in living donors and might negatively impact the decision to participate in exchange programs.

Other potential concern with NEAD chains is donor renegeing when bridge donor backs out and refuses to donate when the incompatible recipient has already received transplant from another pair [25]. There have also been concerns about coercion with PEKT where the donors are unable to use 'incompatibility' as an excuse to avoid donation and cannot withdraw at a later date especially when their incompatible recipients have already received transplant via PEKT [26-28]. It has been proposed to institute "time limits" to prevent donor renegeing, limit open chain PEKT and encourage bridge donors to donate to patients on deceased donor wait list [28].

Conclusion

PEKT seems to be a very practical and cost effective approach of dealing with problems of organ shortage and donor-recipient incompatibility for patients with end stage renal disease. Transplant program should be encouraged to participate in PEKT to expand the donor pool. Transplant community should actively work towards the goal of establishing a national kidney paired donation program overcoming the financial and logistic barriers.

References

- Chkhotua A (2012) Paired kidney donation: outcomes, limitations, and future perspectives. *Transplant Proc* 44: 1790-1792.
- Gloor J, Stegall MD (2010) Sensitized renal transplant recipients: current protocols and future directions. *Nat Rev Nephrol* 6: 297-306.
- Segev DL, Gentry SE, Warren DS, Reeb B, Montgomery RA (2005) Kidney paired donation and optimizing the use of live donor organs. *JAMA* 293: 1883-1890.
- Rapaport FT (1986) The case for a living emotionally related international kidney donor exchange registry. *Transplant Proc* 18 Suppl.
- Massie AB, Gentry SE, Montgomery RA, Bingaman AA, Segev DL (2013) Center-level utilization of kidney paired donation. *Am J Transplant* 13: 1317-1322.
- OPTN/SRTR 2011 annual data report, accessed March 30, 2014
- Melcher ML, Blosser CD, Baxter-Lowe LA, Delmonico FL, Gentry SE, et al. (2013) Dynamic challenges inhibiting optimal adoption of kidney paired donation: findings of a consensus conference. *Am J Transplant* 13: 851-860.
- Amico P, Hönger G, Steiger J, Schaub S (2009) Utility of the virtual crossmatch in solid organ transplantation. *Curr Opin Organ Transplant* 14: 656-661.
- Rees MA, Kopke JE, Pelletier RP, Segev DL, Rutter ME, et al. (2009) A nonsimultaneous, extended, altruistic-donor chain. *N Engl J Med* 360: 1096-1101.
- Delmonico FL, Morrissey PE, Lipkowitz GS, Stoff JS, Himmelfarb J, et al. (2004) Donor kidney exchanges. *Am J Transplant* 4: 1628-1634.
- Simpkins CE, Montgomery RA, Hawxby AM, Locke JE, Gentry SE, et al. (2007) Cold ischemia time and allograft outcomes in live donor renal transplantation: is live donor organ transport feasible? *Am J Transplant* 7: 99-107.
- Ojo AO, Wolfe RA, Held PJ, Port FK, Schumouder RL (1997) Delayed graft function: risk factors and implications for renal allograft survival. *Transplantation* 63: 968-974.
- Segev DL, Veale JL, Berger JC, Hiller JM, Hanto RL, et al. (2011) Transplant live donor kidneys for kidney paired donation: initial national results. *Am J Transplant* 11: 356-360.
- Bhargava A, Arora S, Marcus RJ, Sureshkumar KK: Outcomes of paired exchange live donor kidney transplantation: A Single Center experience (Submitted to Transplantation Proceedings in Feb 2014)
- Butt FK, Gritsch HA, Schulam P, Danovitch GM, Wilkinson A, et al. (2009) Asynchronous, out-of-sequence, transcontinental chain kidney transplantation: a novel concept. *Am J Transplant* 9: 2180-2185.
- Gentry SE, Segev DL, Simmerling M, Montgomery RA (2007) Expanding kidney paired donation through participation by compatible pairs. *Am J Transplant* 7: 2361-2370.
- Kute VB, Gumber MR, Vanikar AV, Shah PR et. al (2013) Comparison of kidney paired donation transplantations with living related donor kidney transplantation: implications for national kidney paired donation program. *Ren Fail.* 35(4):504-8.
- Tuncer M, Tekin S, Yılmaz L, Ağazade A, Demirbas A (2012) Comparison of paired exchange kidney transplantations with living related kidney transplantations. *Transplant Proc* 44: 1626-1627.
- Huh KH, Kim MS, Ju MK, Chang HK, Ahn HJ, et al. (2008) Exchange living-donor kidney transplantation: merits and limitations. *Transplantation* 86: 430-435.
- Wallis CB, Samy KP, Roth AE, Rees MA (2011) Kidney paired donation. *Nephrol Dial Transplant* 26: 2091-2099.
- Rees MA, Bargnesi D, Samy K, Reece L (2009) Altruistic donation through the Alliance for Paired Donation. *ClinTranspl.*
- Irwin FD, Bonagura AF, Crawford SW, Foote M (2012) Kidney paired donation: a payer perspective. *Am J Transplant* 12: 1388-1391.
- Chang P, Gill J, Dong J, Rose C, Yan H, et al. (2012) Living donor age and kidney allograft half-life: implications for living donor paired exchange programs. *Clin J Am Soc Nephrol* 7: 835-841.
- Akkina SK, Muster H, Steffens E, Kim SJ, Kasiske BL, et al. (2011) Donor exchange programs in kidney transplantation: rationale and operational details from the north central donor exchange cooperative. *Am J Kidney Dis* 57: 152-158.
- Serur D, Charlton M (2011) Kidney paired donation 2011. *Prog Transplant* 21: 215-218.
- Thiel G, Vogelbach P, Gürke L, Gasser T, Lehmann K, et al. (2001) Crossover renal transplantation: hurdles to be cleared! *Transplant Proc* 33: 811-816.
- Ross LF, Rubin DT, Siegler M, Josephson MA, Thistlethwaite JR Jr, et al. (1997) Ethics of a paired-kidney-exchange program. *N Engl J Med* 336: 1752-1755.
- Woodle ES, Daller JA, Aeder M, Shapiro R, Sandholm T, et al. (2010) Ethical considerations for participation of nondirected living donors in kidney exchange programs. *Am J Transplant* 10: 1460-1467.