

# Paired kidney exchange transplantation: Maximizing the donor pool

P. K. Jha, S. Sethi, S. B. Bansal, M. Jain, R. Sharma, M. K. Phanish, R. Duggal<sup>1</sup>, R. Ahlawat<sup>2</sup>, V. Kher

Departments of Nephrology, <sup>1</sup>Lab Medicine and <sup>2</sup>Urology, Medanta Institute of Kidney and Urology, Medanta-The Medicity, Gurgaon, Haryana, India

## ABSTRACT

In the last decade, paired kidney exchange (PKE) transplantation has gained popularity worldwide as a viable alternative for end stage renal disease (ESRD) patients who have incompatible or sensitized donors. This study presents our experience with PKE transplantation and compares outcome between PKE and non-PKE renal transplant recipients. Between February 2010 and November 2013, 742 transplants were performed, of which 26 (3.5%) were PKE transplantations. All were two-way exchanges. PKE recipients were significantly older than non-PKE ( $46.73 \pm 9.71$  vs.  $40.08 \pm 13.36$  years;  $P = 0.012$ ) while donor ages were comparable. PKE patients had significantly higher number of HLA mismatches ( $5.03 \pm 1.14$  vs.  $3.49 \pm 1.57$ ;  $P < 0.0001$ ). After a median follow-up of 20 months (range: 3–47 months), there was no significant difference in patient survival (PKE 96.16% vs. non-PKE 96.65%;  $P = 0.596$ ) and death censored graft survival (PKE 96.16% vs. non-PKE 96.37%;  $P = 1$ ). Mean serum creatinine at 1 month and at last follow-up was lower in PKE versus non-PKE group ( $0.98 \pm 0.33$  vs.  $1.3 \pm 0.61$  mg/dl;  $P = 0.008$  and  $0.96 \pm 0.30$  vs.  $1.27 \pm 0.57$  mg/dl,  $P = 0.006$ , respectively). Biopsy proven acute rejection rate was 11.5% in PKE group and 16.89% in non-PKE patients ( $P = 0.6$ ). To conclude, paired kidney donation is an excellent way of increasing the donor pool and needs to be promoted to overcome the shortage of suitable kidney in our country.

**Key words:** Developing world, India, kidney transplant, paired kidney exchange

## Introduction

Kidney transplantation is the best form of renal replacement therapy (RRT) for end stage renal disease (ESRD) patients.<sup>[1]</sup> In India, of 175,000 new chronic kidney disease (CKD) patients developing ESRD annually, <10% receive any form of RRT and only 2% undergo renal transplant.<sup>[2]</sup> As per the first report of Indian CKD registry, of all the stage 5 CKD cases, 39% were on RRT out of which only 2% were being worked up for renal transplant.<sup>[3]</sup> Although deceased donation is popular in

western countries, it is still in its nascent stage here. Due to the uncertainty and long waiting time compounded with lack of awareness among general public, deceased donor transplantation is not a very popular treatment option yet for ESRD patients. Also, there are regional variations in deceased donor transplantation with majority happening in southern states of India and very few in northern states. Although outcomes of living donor transplantations are better than deceased donor transplants, there are very few living voluntary related donors who come forward for the noble cause. Many potential living donors get rejected due to ABO incompatibility or a positive cross-match with intended recipient. Options left in such a scenario are ABOi transplants and desensitization of sensitized recipient or paired kidney exchange (PKE) transplantation. Former is considerably more expensive and requires more immunosuppression while PKE is economically much better option, requires less immunosuppression compared to ABOi transplants and desensitization protocols, and is legally valid as well.

Indian experience in this field has been far and few.<sup>[4]</sup> We hereby present experience of PKE transplantation at our institution, a tertiary care center in north India.

### Address for correspondence:

Dr. Pranaw Kumar Jha,  
Department of Nephrology, Medanta Kidney and Urology Institute,  
Medanta-The Medicity, Gurgaon - 122 018, Haryana, India.  
E-mail: dr.pranaw@gmail.com

### Access this article online

#### Quick Response Code:



#### Website:

www.indianjnephrol.org

#### DOI:

10.4103/0971-4065.150721

## Materials and Methods

This is a retrospective analysis of consecutive renal transplants performed at our center between February 2010 and November 2013. Total 742 renal transplants were performed during the study period. All the patients who underwent renal transplant during this time period were included. Patients were divided into two groups-PKE group and other patients (i.e., non-PKE group). Medical records of these patients were reviewed extensively.

A paired kidney registry is being maintained at our center and various incompatible pairs were matched depending upon the availability of suitable donors and compatible recipients. Matching and donor allocation was done manually. As far as possible, donors were matched for age and glomerular filtration rate. Donor investigations were completed once the matching was done. When the pair was from state other than Haryana, necessary clearance was obtained from authorization committee of that state as well. Both the pairs were counseled in detail. It was also emphasized that occasionally one of the kidneys might not function as well as the other one in such PKE transplantation. Necessity of performing donor nephrectomies simultaneously in two different operation theaters to avoid renegeing was explained. Appropriate investigations, including various radiological, biochemical and serological tests were done as per standard protocol including diethylene triamine penta-acetic acid renogram and computed tomography renal angiogram of the donor. Necessary clearances were obtained. Donors and recipients were allowed to meet before renal transplant. Complement-dependent cytotoxicity (CDC) cross-match was done for all the patients while flow cytometry was done when indicated. All donors were operated by laparoscopic nephrectomy. Donor nephrectomies were performed simultaneously in different theatres.

Induction was offered to all the patients. Immunologically high-risk recipients (i.e., history of multiple blood transfusions pre-transplant, second or more renal transplant, multiple pregnancies, wife recipient) were offered thymoglobulin (1 mg/kg/day IV for 3 days) while others were offered basiliximab (20 mg intravenous on the day of transplant and repeated on postoperative day 4). Injection methyl prednisolone 500 mg IV was given intraoperatively to all the patients followed by 40 mg/day oral prednisolone on day 1, which was tapered to 20 mg by day 8. Maintenance immunosuppression consisted of a calcineurin inhibitor (tacrolimus or cyclosporine), mycophenolate sodium and prednisolone.

All the patients were followed up in OPD twice weekly for 1<sup>st</sup> month, once weekly for 2<sup>nd</sup> month, once in a

fortnight for 3<sup>rd</sup> month and thereafter monthly once for 12 months post-transplantation. Follow-up after 1<sup>st</sup> year was once in 2–3 months. Renal function tests, including serum creatinine and hemogram were done on every visit. Tacrolimus/cyclosporine level was done as per the need, decided by the treating physician. Tacrolimus level target was 8–12 ng/ml during first 3 months, 5–8 ng/ml from 3 to 6 months and <5 ng/ml thereafter. In patients on cyclosporine, C0 target level was 250–350 ng/ml during first 3 months, 100–250 ng/ml from 3 to 6 months and <100 ng/ml thereafter while C2 target level was 1000–1200 ng/ml during first 3 months and 600–1000 ng/ml thereafter. Both C0 and C2 levels were done for all the patients receiving cyclosporine. Prednisolone was tapered to 10 mg by the end of 3 months and 5 mg by the end of 6 months. Mycophenolate sodium was initiated at 720 mg twice daily initially and tapered to 360 mg twice daily by 6 months. Data were collected retrospectively from medical records, including demographic data, follow-up serum creatinine, biopsy proven acute rejections, graft, and patient loss and infections.

Statistical analysis was done using MedCalc for Windows, version 12.7.8 (MedCalc Software, Belgium). Data were reported as mean values  $\pm$  standard deviation. Continuous variables were compared using unpaired *t*-test while categorical values were compared using Chi-square test or Fisher's exact test. Kaplan–Meier method was used to generate survival curves. *P* < 0.05 was considered statistically significant.

## Results

During the study period, total 79 patients got registered for PKE. Of this two were HLA incompatible while the remaining 77 got registered due to blood group incompatibility. No blood group compatible pair got registered for PKE. Of the registered patients, 26 underwent PKE. This constituted 3.5% of total renal transplants (*n* = 742) performed during the study period. Reason for exchange was ABO incompatibility in all of them. All were two-way donations. Median waiting time for getting suitable donor after registration was 3 months. There were 13 recipients each of blood group A and B. Median follow-up duration was 20 months (range: 3–47 months). Out of the 26 PKE patients, 22 were from other states. Median time from getting a suitable pair to transplant was 2 months, including authorization committee clearance. Of the remaining 53 patients who got registered but could not undergo PKE, 7 patients got transplanted outside, 24 were still waiting for transplant, 18 patients were lost to follow-up, 2 underwent ABO incompatible renal transplant while 2 patients expired.

Table 1 shows the patients' demographic data. Mean recipient age was significantly higher in PKE group (46.73 ± 9.71 years) versus non-PKE group (40.08 ± 13.36 years) (*P* = 0.012). Donor age was comparable between the two groups (46.53 ± 9.74 years in PKE vs. 48.10 ± 11.22 years in others; *P* = 0.481). Among PKE recipients, 88.46% (*n* = 23) were male while 81.14% (*n* = 582) of patients in non-PKE group were male (*P* = 0.448). Dialysis vintage was 4.90 ± 2.77 months in PKE versus 4.88 ± 7.49 months in non-PKE group (*P* = 0.989). Significantly more patients in PKE group had diabetic CKD as cause of ESRD (50% vs. 24.72%, *P* = 0.009), while there were significantly more patients with chronic glomerulonephritis in non-PKE group (0% vs. 14.39%, *P* = 0.038). Significantly more patients in PKE group had pre-transplant hepatitis B (11.54%, vs. 2.51%) (*P* = 0.033). Distribution of hepatitis C was similar between the groups (7.69% in PKE vs. 3.07% in non-PKE; *P* = 0.203). Twenty-four patients undergoing PKE received basiliximab induction followed by tacrolimus, mycophenolate mofetil and prednisolone as maintenance immunosuppression while the remaining two received thymoglobulin induction followed by tacrolimus and mycophenolate maintenance immunosuppression.

Table 2 shows blood group distribution among the pair registered for PKE. It also shows the blood group distribution and recipient donor relationship of PKE recipients.

Table 3 shows the immunosuppression and surgical details of PKE group patients.

Table 4 shows study outcomes. Mean serum creatinine at one month was significantly better in PKE (0.98 ± 0.33 mg/dl)

**Table 1: Demographic characteristics and clinical profile of patients**

	PKE <i>n</i> =26 (%)	Non-PKE <i>n</i> =716 (%)	<i>P</i>
Mean recipient age (years)	46.73±9.71	40.08±13.36	0.012
Mean donor age (years)	46.53±9.74	48.10±11.22	0.481
Recipient gender (male)	23 (88.46)	582 (81.14)	0.448
Donor gender (male)	2 (7.69)	202 (28.21)	0.023
HLA mismatch	5.03±1.14	3.49±1.57	<0.0001
Dialysis vintage (months)	4.9±2.77	4.88±7.49	0.989
Native kidney disease			
Diabetes mellitus	13 (50)	177 (24.72)	0.009
Hypertension	6 (23.07)	225 (31.42)	0.517
CGN	0	103 (14.39)	0.038
CIN	1 (3.85)	99 (13.82)	0.237
ADPKD	3 (11.54)	30 (4.19)	0.103
Others	3 (11.54)	82 (11.45)	1.000
Pre transplant hepatitis C	2 (7.69)	22 (3.07)	0.203
Pre transplant hepatitis B	3 (11.54)	18 (2.51)	0.033

PKE: Paired kidney exchange, HLA: Human leukocyte antigen, CGN: Chronic glomerulonephritis, CIN: Chronic interstitial nephritis, ADPKD: Autosomal dominant polycystic kidney disease

versus other group (1.3 ± 0.61 mg/dl) (*P* = 0.008). Same was the case with mean serum creatinine of the two groups at last follow-up (0.96 ± 0.30 mg/dl in PKE vs. 1.27 ± 0.57 mg/dl in non-PKE; *P* = 0.006). Patient survival was 96.16% in PKE versus 96.65% in non-PKE group (*P* = 0.596). One patient in PKE group died due to cardiac event 11 months post-transplant. He had past history of coronary artery disease for which coronary artery bypass graft was done before transplantation. Overall graft survival and death censored graft survival rate was 92.31% and 96.16% in PKE while it was 94.27%

**Table 2: Blood group distribution and donor relation**

Variables	<i>n</i> =79
Blood group distribution of donor and recipient pair registered	
A recipient; B donor	36
B recipient; A donor	41
B recipient; AB donor	2
Blood group distribution of PKE transplant recipients	
A recipient; B donor	13
B recipient; A donor	13
Donor relation of PKE transplant recipients	
Spouse	21
Parent	2
Sibling	1
Others	2

PKE: Paired kidney exchange

**Table 3: Immunosuppression and surgical details of PKE group**

Variables	<i>n</i> =26
Immunosuppression	
Induction	
Basiliximab	24
Thymoglobulin	2
Maintenance	
Tacrolimus/MMF/prednisolone	24
Tacrolimus/MMF	2
Surgical details	
Warm ischemia time (s)	145.17±41.72
Total ischemia time (min)	61.41±27.81
Donor arteries	
Single	22
Double	4
Donor veins	
Single	26

PKE: Paired kidney exchange, MMF: Mycophenolate mofetil

**Table 4: Recipient outcome**

	PKE <i>n</i> =26 (%)	Non-PKE <i>n</i> =716 (%)	<i>P</i>
Mean serum creatinine at one month (mg/dl)	0.98±0.33	1.3±0.61	0.008
Mean serum creatinine at last follow up (mg/dl)	0.96±0.30	1.27±0.57	0.006
Patient survival	25 (96.16)	692 (96.65)	0.596
Graft survival	24 (92.31)	675 (94.27)	0.658
Graft survival (death censored)	25 (96.16)	690 (96.37)	1.000
Biopsy proven acute rejection	3 (11.5)	121 (16.89)	0.600
Infection	3 (11.5)	63 (8.8)	0.497

PKE: Paired kidney exchange

and 96.37% in other group, respectively ( $P = 0.658$  and 1, respectively). Biopsy proven acute rejection was seen in 11.5% in PKE and 16.89% in non-PKE group patients ( $P = 0.6$ ). Infection rate was 11.5% in PKE and 8.8% in non-PKE ( $P = 0.497$ ).

Figures 1 and 2 show Kaplan–Meier curves comparing patient survival and death censored graft survival between the study groups, respectively.

## Discussion

In the current study, donor age was  $46.53 \pm 9.74$  years, which was comparable to that of other paired kidney donation studies by Tuncer *et al.* (45 years)<sup>[5]</sup> and Gumber *et al.* (45 years).<sup>[6]</sup> Mean recipient age was  $46.73 \pm 9.71$  years, which was relatively higher compared to above two studies (40.9 years and 36 years, respectively). Mean waiting time on dialysis was  $4.9 \pm 2.77$  months. Patient survival was 96.16% in our study. In the study by Montgomery *et al.* and Tuncer *et al.* it was 100%.<sup>[7,5]</sup> Similarly, excellent patient survival rate was seen in other studies by Waigankar *et al.* (100%)<sup>[8]</sup> and Kute *et al.* (94.64%)<sup>[9]</sup> Death-censored graft survival rate was 96.16%, which was similar to excellent graft survival noted in other studies by Montgomery *et al.* (95.5%),<sup>[7]</sup> Gumber *et al.* (94.4%),<sup>[6]</sup> Pahwa *et al.* (100%)<sup>[10]</sup> and Kute *et al.* (97.5%)<sup>[9]</sup> Acute rejection rate was 11.5%. This was better than acute rejection rate of 18% reported by Montgomery *et al.*,<sup>[7]</sup> 30% by Fuller *et al.*<sup>[11]</sup> and 22.8% by Tuncer *et al.*<sup>[5]</sup> In studies by Kute *et al.* and Pahwa *et al.*, acute rejection rate was 16% and 15.9%, respectively.<sup>[9,10]</sup>

Despite significantly higher HLA mismatches and older recipients, outcome of PKE recipients in terms of graft function, patient survival and death censored graft

survival as well as biopsy proven acute rejection rates were similar to live renal transplant recipients in non-PKE group in our study. Although, the short-term follow-up is an important limiting factor. In a similar study by Kute *et al.*, the outcomes were comparable between PKE and non-PKE group. Here, once again, the follow-up was short term.<sup>[12]</sup>

There is a huge demand and supply mismatch for living-related donors. Many of the voluntary living related donors get rejected because of ABO incompatibility or positive cross-match. It has been shown that such incompatibilities can account for rejection of 35% of otherwise suitable donors.<sup>[13]</sup> To circumvent this problem, various alternatives have been devised such as ABOi transplants and desensitization protocols for patients with a positive cross-match. Patients undergoing desensitization or ABOi transplants require plasmapheresis sessions, which expose them to higher chances of blood-borne infections. Also, net immunosuppression is considerably higher in such transplants due to requirement of rituximab, thymoglobulin, etc., over and above regular maintenance immunosuppression. Finally, these options are significantly more expensive compared to conventional transplants. There has been an increasing enthusiasm to promote PKE program as an alternative, which also reflects in the latest amendment of Transplantation of Human Organs (THO) Act 2011. PKE is cheaper and requires less immunosuppression compared to ABOi transplants or desensitization protocols. There is a need of national level PKE program with a national PKE registry to promote better matching and increase number of patients benefiting from it.<sup>[14]</sup>

Historically, first PKE transplant was performed in South Korea in 1991<sup>[15]</sup> although it was first proposed

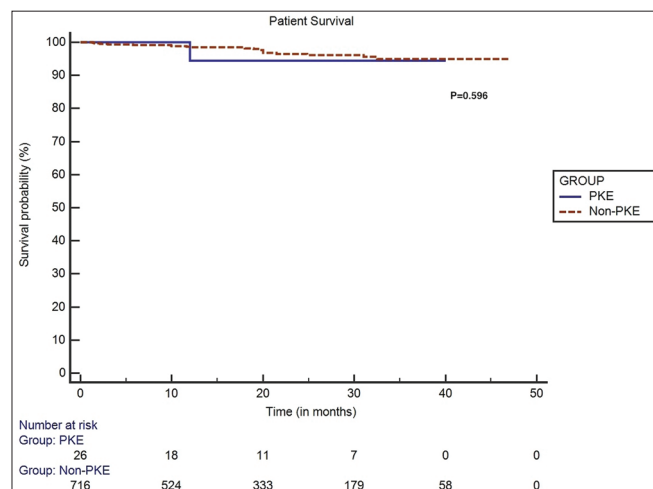


Figure 1: Kaplan-Meier graph comparing patient survival between PKE group and non-PKE group patients

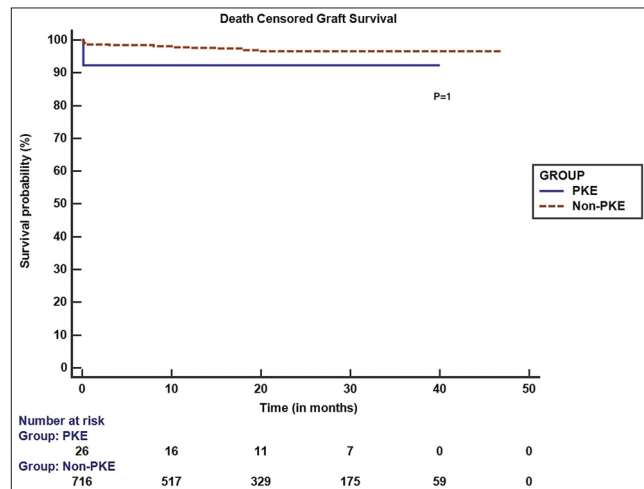


Figure 2: Kaplan-Meier graph comparing death censored graft survival between PKE group and non-PKE group patients

by Felix Rappaport way back in 1986.<sup>[16]</sup> Switzerland and USA performed their first PKE in 1999 and 2000, respectively.<sup>[17,18]</sup> Since then, it has gained popularity across the globe.

Although PKE is an attractive option, there are few ethical issues that need to be addressed. It is difficult to maintain anonymity, which can give rise to coercion and money laundering practices.<sup>[19]</sup> Financial conflict of interest can arise in case of different socioeconomic status of pairs. Also, there is always a concern among the pairs regarding age difference between the donors and 'quality' of the kidney. Hence, both the parties should be counseled in detail and adequately informed to allay any unnecessary fear and misconceptions. Operations should be performed simultaneously to prevent the problem of renegeing by either donor after nephrectomy of the other.<sup>[20]</sup>

There are some limitations to current study. We did 26 successful PKE transplants, but could not match remaining pairs registered for paired exchange. Matching was done manually. Also, the final number of patients in PKE group for analysis was small. As the number of pairs registered under such program increases, so does the chance of getting a successful match. Hence it is important to promote the program at state and national levels, so that different centers can share the pairs for the benefit of maximum number of recipients. One important hindrance here is that if both the donor nephrectomies are performed at one center, it may not be acceptable to the other center sharing the pair. An alternative is to transfer the kidneys across the centers after nephrectomy. It has been shown that risk of delayed graft function does not increase during such transfer.<sup>[21]</sup>

Another important limitation is that O blood group recipients are at disadvantage in PKE transplantation because of excess of registered O group recipients compared to very few O group donors. Compatible pairs with O donors should be educated that donation by them is going to help needy O group recipients and increase chances of matching. This has been stressed upon in previous studies as well.<sup>[22]</sup> A non-directed donation or a deceased organ donation can also help in such a scenario by initiating a domino. Participation by pairs with AB blood group recipients is another way to increase matching.

Although there are few limitations as mentioned above, there is an increasing interest in PKE. There is a growing need to maintain a state and nationwide registry to promote PKE across different centers. This will benefit many patients, expand the donor pool, and avert the need for expensive desensitization protocols and ABO incompatible transplants.

## References

1. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, *et al.* Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999;341:1725-30.
2. Chugh KS. Five decades of Indian nephrology: A personal journey. *Am J Kidney Dis* 2009;54:753-63.
3. Rajapurkar MM, John GT, Kirpalani AL, Abraham G, Agarwal SK, Almeida AF, *et al.* What do we know about chronic kidney disease in India: First report of the Indian CKD registry. *BMC Nephrol* 2012;13:10.
4. Modi P, Rizvi SJ, Pal B, Baradwaj R, Gupta S, Shah V, *et al.* Living donor paired-kidney exchange transplantation: A single institution experience. *Indian J Urol* 2010;26:511-4.
5. Tuncer M, Tekin S, Yüccetin L, Sengül A, Demirbas A. Comparison of paired exchange kidney transplantations with living related kidney transplantations. *Transplant Proc* 2012;44:1626-7.
6. Gumber MR, Kute VB, Goplani KR, Shah PR, Patel HV, Vanikar AV, *et al.* Transplantation with kidney paired donation to increase the donor pool: A single-center experience. *Transplant Proc* 2011;43:1412-4.
7. Montgomery RA, Zachary AA, Ratner LE, Segev DL, Hiller JM, Houp J, *et al.* Clinical results from transplanting incompatible live kidney donor/recipient pairs using kidney paired donation. *JAMA* 2005;294:1655-63.
8. Waigankar SS, Kamat MH, Joshi S, Gandhi BV, Bahadur M, Deshpande RV. Living donor transplant options in end-stage renal disease patients with ABO incompatibility. *Indian J Urol* 2013;29:114-8.
9. Kute VB, Shah PS, Vanikar AV, Gumber MR, Patel HV, Engineer DP, *et al.* Increasing access to renal transplantation in India through our single-center kidney paired donation program: A model for the developing world to prevent commercial transplantation. *Transpl Int* 2014;27:1015-21.
10. Pahwa M, Saifee Y, Tyagi V, Chadha S, Jauhari H. Paired exchange kidney donation in India: A five-year single-center experience. *Int Urol Nephrol* 2012;44:1101-5.
11. Fuller TF, Feng S, Brennan TV, Tomianovich S, Bostrom A, Freise CE, *et al.* Increased rejection in living unrelated versus living related kidney transplants does not affect short-term function and survival. *Transplantation* 2004;78:1030-5.
12. Kute VB, Gumber MR, Vanikar AV, Shah PR, Patel HV, Engineer DP, *et al.* Comparison of kidney paired donation transplantations with living related donor kidney transplantation: Implications for national kidney paired donation program. *Ren Fail* 2013;35:504-8.
13. Segev DL, Gentry SE, Warren DS, Reeb B, Montgomery RA. Kidney paired donation and optimizing the use of live donor organs. *JAMA* 2005;293:1883-90.
14. Kute VB, Vanikar AV, Shah PR, Gumber MR, Patel HV, Modi PR, *et al.* Facilitators to national kidney paired donation program. *Transpl Int* 2013;26:e38-9.
15. Kwak JY, Kwon OJ, Lee KS, Kang CM, Park HY, Kim JH. Exchange-donor program in renal transplantation: A single-center experience. *Transplant Proc* 1999;31:344-5.
16. Rapaport FT. The case for a living emotionally related international kidney donor exchange registry. *Transplant Proc* 1986;18:5-9.
17. Thiel G, Vogelbach P, Gürke L, Gasser T, Lehmann K, Voegelé T, *et al.* Crossover renal transplantation: Hurdles to be cleared! *Transplant Proc* 2001;33:811-6.
18. Zarsadias P, Monaco AP, Morrissey PE. A pioneering paired kidney exchange. *Stud Br Med J* 2010;18:c1562.
19. Lucan M. Five years of single-center experience with paired kidney exchange transplantation. *Transplant Proc* 2007;39:1371-5.

20. Chkhotua A. Paired kidney donation: Outcomes, limitations, and future perspectives. *Transplant Proc* 2012;44:1790-2.
21. Segev DL, Veale JL, Berger JC, Hiller JM, Hanto RL, Leiser DB, *et al.* Transporting live donor kidneys for kidney paired donation: Initial national results. *Am J Transplant* 2011;11:356-60.
22. Kute VB, Vanikar AV, Gumber MR, Shah PR, Patel HV, Engineer DP, *et al.* Successful three-way kidney paired donation with compatible pairs to increase donor pool. *Ren Fail* 2014;36:447-50.

**How to cite this article:** Jha PK, Sethi S, Bansal SB, Jain M, Sharma R, Phanish MK, *et al.* Paired kidney exchange transplantation: Maximizing the donor pool. *Indian J Nephrol* 2015;25:349-54.

**Source of Support:** Nil, **Conflict of Interest:** None declared.