

## Retrospective Study

**International kidney paired donation transplantations to increase kidney transplant of O group and highly sensitized patient: First report from India**

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**Abstract****AIM**

To report the first international living related two way kidney paired donation (KPD) transplantation from India which occurred on 17<sup>th</sup> February 2015 after legal permission from authorization committee.

**METHODS**

Donor recipient pairs were from Portugal and India who were highly sensitized and ABO incompatible with their spouse respectively. The two donor recipient pairs had negative lymphocyte cross-matching, flow cross-match

and donor specific antibody in two way kidney exchange with the intended KPD donor. Local KPD options were fully explored for Indian patient prior to embarking on international KPD.

### RESULTS

Both pairs underwent simultaneous uneventful kidney transplant surgeries and creatinine was 1 mg/dL on tacrolimus based immunosuppression at 11 mo follow up. The uniqueness of these transplantations was that they are first international KPD transplantations in our center.

### CONCLUSION

International KPD will increase quality and quantity of living donor kidney transplantation. This could be an important step to solving the kidney shortage with additional benefit of reduced costs, improved quality and increased access for difficult to match incompatible pairs like O blood group patient with non-O donor and sensitized patient. To the best of our knowledge this is first international KPD transplantation from India.

**Key words:** Kidney paired donation; International kidney paired donation; Living donor kidney transplantation

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**Core tip:** Kidney paired donation (KPD) has rapidly increased the access to living donor kidney transplantation (LDKT) in the last decade. The participation in the international kidney exchange registries will expand the donor pool for kidney transplantation. We report first Indian international living related KPD transplantation which occurred on 17<sup>th</sup> February 2015 after legal permission from authorization committee between a pair from Portugal and India who were highly sensitized and ABO incompatible with their spouse respectively. International KPD will increase quality and quantity of LDKT. This could be an important step to solving the kidney shortage with additional benefit of reduced costs, improved quality and increased access for difficult to match incompatible pairs like O blood group patient with non-O donor and sensitized patient.

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## INTRODUCTION

There is growing incidence of chronic kidney disease in India and worldwide<sup>[1,2]</sup>. There is imbalance between

organ supply and demand. Indian chronic kidney disease registry reported in 2010 that only 2% of end stage renal disease patients received kidney transplantation. The majority (61%) of patients did not afford renal replacement therapy<sup>[2]</sup>. There is lack of compliance to maintenance dialysis therapy (32% on hemodialysis and 5% on peritoneal dialysis) due to poverty and lack of uniform access to renal replacement therapy resulting in higher morbidity and mortality<sup>[1,2]</sup>. It is difficult to expand deceased donor kidney transplantation in India due to various problems including lack of awareness. The ABO compatible living donor kidney transplantation (LDKT) is the cost effective way for Indian end stage renal disease patients<sup>[3-5]</sup>.

Kidney paired donation (KPD) has rapidly increased the access to LDKT in the last decade<sup>[3-11]</sup>. KPD avoids the cost and complications of desensitization therapies for ABO incompatible and human leukocyte antigen (HLA) incompatible LDKT with best long term outcome. Currently, national KPD program exist in many countries including South Korea, The Netherlands, United States, Canada, Australia, United Kingdom, and Spain<sup>[6,11]</sup>. Twenty percent increase in KPD transplants can be achieved with domino paired donation. ABO blood type O group patients and highly sensitized patients have less chance to get LDKT in kidney exchange program<sup>[11]</sup>. The large donor pool could increase transplant rate for such patients. The participation in the international kidney exchange registries will expand the donor pool for LDKT<sup>[12,13]</sup>.

## MATERIALS AND METHODS

We report international two way KPD transplantations which occurred on 17<sup>th</sup> February 2015 after legal permission from authorization committee between a donor recipient pair from Portugal and India who were highly sensitized and ABO incompatible with their spouse respectively. Authorization committee permission was obtained for this overseas donor from Government of Portugal, authorization committee of our hospital and the state authorization committee of Government of Gujarat, India. The lymphocyte cross-matching (LCM), T and B cell flow cytometry crossmatch (FCM) and donor-specific antibodies (DSA) titers were performed for immunological compatibility. Lymphocyte cross-matching > 20%, T cell and B cell FCM above 50 and 100 median channel shift (MCS) and donor-specific antibody > 1000 mean fluorescent intensity (MFI) were considered positive and contraindication for transplantation in our transplant center. The patient from Portugal had lymphocyte cross-matching of 90% positive, T and B cell FCM were 186, 231 MCS respectively with his wife as donor. The class 1 donor-specific antibody was 11600 MFI (Table 1).

Patient 1 and 2 were registered with our KPD registry due to sensitization and ABO incompatibility respectively. The manual allocation was performed by a Nephrologist under supervision of authorization committee to ensure proper allocation. Sensitized patients, O group patients

**Table 1** Human leukocyte antigen data of patient and donor

	A		B		Bw	Cw		DR B1		DR B3, 4, 5		DQ B1		
Patient 1	1	24	15	37	4	6	6	8	10	12	52	-	5	7
Donor 2	1	11	40	-	6	-	15	-	8	11	52	-	7	4
Patient 2	2	33	15	51	6	-	1	12	4	8	53	-	7	8
Donor 1	1	68	15	55	6	-	7	0	7	14	52	53	2	6

Patient 1: Donor specific antibody in mean fluorescence intensity with donor 1, A68 = 9870; B55 = 7736; CW7 = 11600 and no donor specific antibody with donor 2; Patient 2: No donor specific antibody with donor 1 and 2.

with non-O donor, HLA match, dialysis time, donor age and waiting time were considered in this allocation. We demonstrated absence of DSA in the each recipient using data of blood groups, HLA antibody profile of recipients and HLA report of donor and recipient. All the three immunologic tests (LCM, FCM, and DSA) were negative and acceptable with intended KPD donor for both the recipients. Thus virtual cross-match approach has maximized the matching in sensitized patients in KPD program.

The donor-recipient pairs have negative LCM, FCM and DSA in two way kidney exchange with the intended KPD donors. There was no DSA even at low titer prior to transplant. Both the donors were of similar age group with similar creatinine, glomerular filtration rate and renal vessel anatomy (Table 2). Each pair underwent uniform pre-transplant evaluation of patient and donor by transplant team costing 1000 USD and  $\leq$  2 wk time. The total cost of kidney transplantation in our hospital is 5000 USD. Both the donors and patients underwent simultaneous donor nephrectomy and the transplantation surgery in our single center.

### Immunosuppression

Induction immunosuppressive regimen included rabbit thymoglobulin (1.5 mg/kg single dose) and methyl prednisolone (500 mg/d  $\times$  3 d) and prednisolone, tacrolimus, and mycophenolate sodium (360 mg four times per day) were immunosuppressive agents in maintenance regimen. Tacrolimus trough level was 8-10 ng/mL during first 3 mo after transplantation and 4-8 ng/mL thereafter. Prednisolone dose was  $\leq$  20 mg/d during first 3 mo after transplantation and 5-10 mg/d thereafter. Patients were started on prophylaxis for pneumocystis jirovecii pneumonia (trimethoprim-sulfamethoxazole for 12 mo), fungal infections (fluconazole 100 mg/d for 3 mo) and cytomegalovirus infection (valganciclovir 450 mg/d for 3 mo).

## RESULTS

Table 2 showed the demographics and outcome of two-way kidney exchange. Table 1 showed HLA data of patient and donor. Both pairs underwent uneventful kidney transplant surgeries and at 11 mo of follow up serum creatinine is 1 mg/dL on tacrolimus based immunosuppression. After transplantation monthly DSA for 3 mo

and at 6, 9 mo were negative in sensitized patient.

## DISCUSSION

The key feature of our case report is that this was the first international KPD transplantations in our center. The Portuguese patient came to our transplant center for directed kidney transplantation with his wife as kidney donor. He came to our transplant unit with the information about our transplant center from the social media website and one of his friends was working in our hospital. On the initial pre-transplant evaluation, he was found to be sensitized with his wife as kidney donor. They were not registered in Portuguese kidney sharing scheme. The mis-matched antigens against which sensitized Portuguese recipient had DSA were avoided. The anti-A antibody titer in blood group O Indian recipient with husband as donor was 1:256. ABO incompatible kidney transplantation was not considered due to patients was having pulmonary tuberculosis, higher cost and risk of infections. The single center KPD program which is commonly practiced in India has inherent limitations to expand the donor pool. Each state, region and the entire country of India needs a more robust, organized kidney sharing scheme and efforts should be made to establish a national/regional pool of kidney sharing registry as is the case with the European, North American and other developed countries. There is no national KPD program in India. Local and regional kidney sharing options were fully explored for the Indian patient prior to embarking on international kidney sharing.

### The ethical challenges

As per transplant human organ act 2014 (India), authorization committee of hospital or district or state can approve legal permission of KPD transplantation when the kidney donors are near relatives of the swap recipients. In our report both the donors are near relatives (spouses).

The authorization committee permission was obtained for an overseas donor from Government of Portugal, hospital and the state authorization committee of Government of Gujarat. All the steps were taken to ensure adherence to transplant human organ act and the Declaration of Istanbul principles with the exchange of equivalent kidneys in size, function, anatomy, immunology and donor age. This allowed exchange of equivalent kidney between donor-recipient pairs with positive cross-

**Table 2** Demographics and outcome of two way kidney exchange

	Patient 1	Patient 2	Donor 1	Donor 2
<b>Patient data</b>				
Age (yr)	40	30		
Gender	Male	Female		
Original disease - ESRD	Hypertension	Hypertension		
ABO blood group	A	O		
Dialysis duration (mo)	12	12		
Weight (kg)	68	40		
Original donor relation	Wife	Husband		
Reason for Joining KPD	Sensitized	ABO incompatible		
Time from KPD registration to find KPD donor (wk)	2	36		
Time from KPD donor to transplant	4 wk	4 wk		
Desensitization	No	No		
State	Portugal	Rajasthan, India		
<b>Donor data</b>				
Age (yr)			36	33
Gender			Female	Male
Weight (kg)			60	60
ABO blood group			O	A
Glomerular filtration rate (right/left)			56/54	54/54
Creatinine (mg/ dL)			0.6	0.7
Renal vessel (right/left)			1 artery and vein on each side	1 artery and vein on each side
Laparoscopic donor nephrectomy			Left	Left
<b>Surgical details and outcome</b>				
Warm ischemia time (s)			150	117
Cold ischemia time (min)			60	90
Anastomosis time (min)			43	35
Intraoperative urine (mL)			1800	500
Kidney transplant date			17 Feb 2015	17 Feb 2015
Creatinine (mg/dL)			1	1
Follow- up (mo)			11	11

KPD: Kidney paired donation.

match barrier to transplantation in Portugese pair and ABO incompatibility barrier to transplantation in Indian pair. Thus both the pairs get the reciprocal sharing of benefit. The health and well-being of Portugese living donor and patient was monitored at regular interval for early diagnosis of any medical or surgical problems due to donation and transplantation. This was performed by sharing of medical reports performed at local laboratory by email communication and in person at regular interval. The administration of such a program should be ensured with support of all transplantations centers and transplant societies using computer software, uniform allocation algorithm, central and dedicated coordination and team work. All should act today with team work for better tomorrow. International kidney paired exchange is usually done in the context of reciprocal sharing agreements - which does not exist in this case. However this is one step close to start such program between 2 or more countries to pool their respective KPD cohorts.

There are encouraging reports of international KPD transplantation all over the world<sup>[6,8]</sup>. It will increase the LDKT opportunity for sensitized and O group patients by direct benefit of increase in donor pool and benefit from differences in heterogeneity of blood types in the population, antigens and antibodies profile. Garonzik-Wang *et al*<sup>[14]</sup> reported international kidney exchange

between the United States and Canada in a 10-way domino chain transplantation which were performed between September 2009 and July 2010. KPD sharing between United States and Canada was logistically possible due to close geographic location, similar language and culture. Three international KPD transplantations between May 2013, and March 2014 were reported in Turkey where national KPD program increased LDKT by 5%<sup>[15]</sup>. The international organ exchange from deceased donors substantially contributed (7.2% of deceased donor transplantations) to the Swiss transplant activity during the period 2009-2013<sup>[16]</sup>. The cold ischemia time < 8 h does not significantly affect long term graft survival. Therefore transport of living donor kidney can be preferred over donor travel in multicenter simultaneous KPD program where cold ischemia time < 8 h<sup>[17,18]</sup>. Despite prolonged cold ischemia time for interstate exchanges, the Australian kidney exchange program preferred to transport kidney over the travel of living kidney donor<sup>[19]</sup>.

Indian society of organ transplantation in collaboration with international mentorship should take the lead role in expansion of KPD as it will increase LDKT > 25%. There should be a formal agreement between 2 or more countries to pool their respective KPD cohorts. Together transplant community can make a significant difference in the lives of kidney patients around the

globe. International KPD will be better than national exchange which will be better than regional exchanges or single center kidney exchanges to expand the donor pool. The large donor pool will increase the transplant rate in kidney exchange. It allows an optimized donor-recipient match, due to an expansion of the donor and recipient pool. It will further optimize potential of this modality to increase transplantation of O group patients and sensitized patients.

In international KPD, there are several potential sources of increasing the donor pool by assembling a database of incompatible pairs, including more two-way exchanges, longer domino chains instead of short chains (2-way or 3-way pairs), integrating list exchange and non-directed donors with exchange among incompatible patient-donor pairs and lastly in near future integrating compatible pairs. Living donor KPD transplant also reduces the waiting list in deceased donor kidney transplantation for those who have no living donor available.

### Global kidney exchange

In 2010 Indian chronic kidney disease registry reported that 61% of stage 5 end stage renal disease population did not receive dialysis or kidney transplant mainly due to poverty and lack of access<sup>[2]</sup>. Poor compatible donor-recipient pairs (A blood group patient and O blood group donor) in developing world could not undergo kidney transplantation due to poverty and lack of health insurance care despite having healthy willing kidney donor. Many donor-recipient pairs in developed world (O blood group patient and A blood group donor) could not undergo kidney transplantation due to immunological barriers despite availability of health insurance care. These two pairs could exchange kidney with each other after legal permission in global kidney exchange to overcome financial and immunological barriers to transplantation. The cost of both kidney transplantations is paid by the health insurance payer of the developed country. Legal and logistical problems should be addressed for the implementation of global kidney exchange. This provides gift of life for the poor patients who would otherwise die due to lack of kidney transplant despite having kidney donor. The advantages of global kidney exchange are reduced costs, increased access to kidney transplantation and improved quality of match<sup>[20,21]</sup>. More studies are required to address willingness of patients, health care professionals to participate in global kidney exchange. To ensure success, an effort is required to standardize transplant principals, practice, policies and legislation among various countries.

International KPD will increase quality and quantity of LDKT. It would best balance the principles of utility and justice. Our study showed that international KPD could be an important step to solving the kidney shortage with additional benefit of reduced costs, improved quality and increased access for difficult to match donor recipient pair like O blood group patient with non-O donor and sensitized patient. To the best of our knowledge this is

first international KPD transplantation from India.

## COMMENTS

### Background

Kidney paired donation (KPD) has rapidly increased the access to living donor kidney transplantation (LDKT) in the last decade. KPD avoids the cost and complications of desensitization therapies for ABO incompatible and human leukocyte antigen incompatible LDKT with best long term outcome.

### Research frontiers

The participation in the international kidney exchange registries will expand the donor pool for kidney transplantation.

### Innovations and breakthroughs

Here the authors reported first international 2-way KPD transplantations from India.

### Applications

International KPD will increase quality and quantity of LDKT. It would best balance the principles of utility and justice. The study showed that international KPD could be an important step to solving the kidney shortage with additional benefit of reduced costs, improved quality and increased access for difficult to match donor recipient pair like O blood group patient with non-O donor and sensitized patient. To ensure success, an effort is required to standardize transplant principals, practice, policies and legislation among various countries.

### Terminology

LDKT: Living donor kidney transplantation; KPD: Kidney paired donation; DDKT: Deceased donor kidney transplantation; DSA: Donor specific antibody.

### Peer-review

An important positive step in attempting to increase the number of acceptable kidney donor-recipient pairs using two collaborating countries. What might be added to the brief text is some assessment of the time and expense of conducting the pretransplant typing and evaluations required to select willing donor-recipient pairs.

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