

Kidney paired donation: benefit of this program on the transplant rate and graft survival

Donación renal pareada: beneficio de este programa en la tasa de trasplantes y sobrevida del injerto

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Abstract

Objective: To demonstrate the experience since the transplant program under paired kidney exchange donation implementation; program that increases the donation rate by 25-30% in hospitals with no inferior graft survival compared to directed living donor kidney transplantation. **Method:** Observational, analytical, longitudinal and prospective study from December 2018 to July 2021. All G5 KDIGO chronic kidney patients who were HLA or ABO incompatible with their original donors in the pretransplant protocol and who were transplanted under the paired kidney exchange donation program, were included. **Results:** 22 kidney transplants were performed under this program. Survival of the graft and the patient 1 year after transplantation was 100%. The post-transplant glomerular filtration rate was 72.5 ± 17 ml/min/1.73 m² body surface. 36.3% of hypersensitized patients were successfully transplanted. The in-hospital donation rate increased by 33.33%. **Conclusions:** Transplantation under the kidney paired donation program constitutes a real modality of successful transplantation when there is incompatibility with the original donor. The greater use and socialization of this program can increase the country kidney transplantation rate, reducing the waiting list. Our hospital represents the largest experience published in Mexico with this transplant program.

Keywords: Kidney paired donation. Kidney transplant. Exchange. Compatibility. HLA.

Resumen

Objetivo: Demostrar la experiencia adquirida desde la implementación del programa de donación renal pareada, el cual aumenta un 25-30% la tasa de donación en los centros hospitalarios sin inferioridad en la sobrevida del injerto comparado con el trasplante renal de donante vivo dirigido. **Método:** Estudio observacional, analítico, longitudinal y prospectivo de diciembre de 2018 a julio de 2021. Se incluyeron todos los enfermos renales crónicos G5 KDIGO que en el protocolo pretrasplante resultaron HLA o ABO incompatibles con sus donantes originales y que fueron trasplantados bajo el programa de donación renal pareada. **Resultados:** Se realizaron 22 trasplantes renales bajo este programa. La sobrevida del injerto y del paciente a 1 año postrasplante fue del 100%. La tasa de filtración glomerular postrasplante fue de 72.5 ± 17 ml/min/1.73 m² de superficie corporal. Fueron trasplantados exitosamente el 36.3% de pacientes hipersensibilizados. La tasa de donación intrahospitalaria aumentó un 33.33%. **Conclusiones:** El trasplante bajo programa de donación renal pareada constituye una modalidad real de trasplante exitoso cuando existe incompatibilidad con el donante original. La mayor utilización y la socialización de este programa pueden aumentar la tasa de trasplante renal nacional, disminuyendo la lista de espera. Nuestro hospital representa la mayor experiencia publicada en México con este programa de trasplante.

Palabras clave: Donación renal pareada. Trasplante renal. Cambio. Compatibilidad. HLA.

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Introduction

Compared to dialysis, renal transplantation is the most cost-effective renal replacement therapy modality capable of providing better survival and quality of life to patients, both adults and pediatric¹. According to data from the National Transplant Center (CENATRA), in 2019 and 2020, a total of 2986 and 914 renal patients were transplanted in Mexico, respectively. By the end of June 2021, 16,801 renal patients were waiting for their transplant. Our hospital transplanted 38, 14, and 14 renal recipients back in 2019, 2020, and the first half of 2021, respectively. Upon completing the transplant protocol, 30% to 40% of all couples will have ABO or HLA incompatibility². In 1986, Rapaport proposed that patients who cannot receive a kidney from their donor should be given the opportunity to exchange donors in such a way that each recipient receives a compatible kidney and donors can fulfill their wish for donation³.

The first actual exchange procedure took place in South Korea in 1991, followed by Europe in 1999, and the United States in 2000. The slow acceptance was mainly due to ethical and legal constraints³. In Mexico, the first cohort of renal transplant patients with donor exchange was published in 1998⁴, and subsequently, further reports would be published in 2017. Some transplant centers have performed this modality anecdotally. Our hospital formally initiated this program at the end of 2018. Currently, paired donation is an alternative authorized by CENATRA.

Renal donor exchange is generally encompassed under the paired kidney exchange donation program, a program that has evolved over time. Initially, only the simplest modality was performed: pairwise exchange (simple swaps between 2 couples), later introducing exchanges among 3 couples and the concepts of renal donation chain, paired donation in domino, introduction of altruistic donors into the chains, non-simultaneous extended chains of altruistic donors⁵, use of bridge donors, initiation of chains with deceased donors, exchange of lists in chains⁶, (Figs. 1-3), and desensitization within the program. These variations arose to make sure donors could not withdraw after their paired recipient had received the kidney transplant⁷.

In addition to facilitating exchanges between incompatible pairs, paired kidney exchange donation programs now welcome compatible pairs, allowing recipients to receive kidneys from younger donors, with better anthropometric matching with their donor

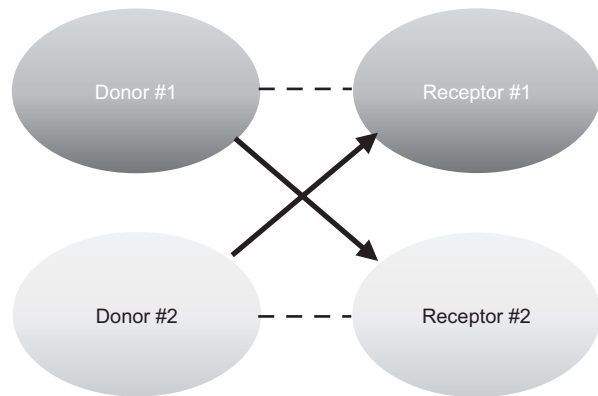


Figure 1. Closed-loop chain of 2 couples (adapted from Bahena CL, 2018⁶).

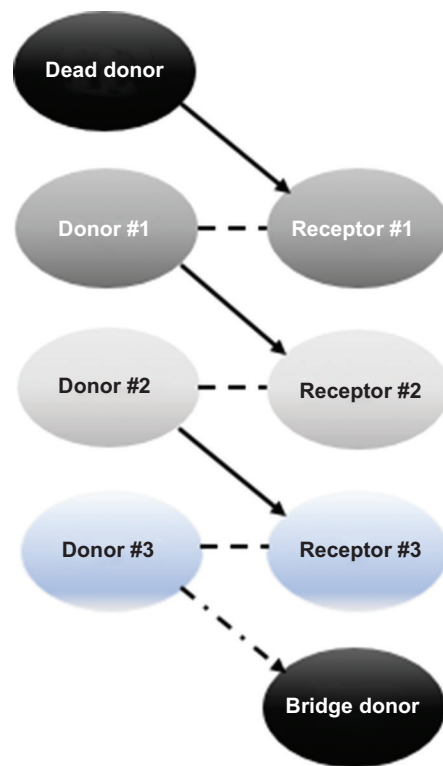


Figure 2. Deceased donor initiating the transplant chain with use of a bridge donor (adapted from Bahena CL, 2018⁶).

or better HLA compatibility. Adding compatible pairs to paired kidney exchange donation programs also increases the number of matches for incompatible pairs or hypersensitized patients, thereby improving the overall matching capabilities of the program^{8,9}.

To overcome the multiple challenges of selection within paired kidney exchange donation programs, manual mathematical calculations or highly efficient computer algorithms are used to select transplant

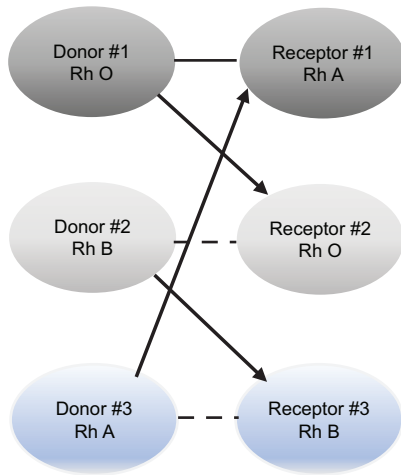


Figure 3. Introduction of an unbalanced compatible altruistic pair (adapted from Bahena CL, 2018⁶).

exchanges with n being the total number of incompatible donor-recipient pairs, the total number of combinations equals $(n^2 - n)/2^{10}$.

Mathematical algorithms based on the blood type of donors and recipients, sensitization status, and the size of the pool of incompatible pairs can determine the highest probabilities of successful matching within the program, optimizing the successful pairing of donors and recipients¹¹ based on the principles of fairness, utility, and justice¹².

Regardless of the immunological complexity and search for a compatible donor in the donor pool of a chain, there are also logistical challenges. Firstly, the creation of chains takes time and is often done electively in such a way that donor and recipient operations can be performed sequentially and within a reasonably short period of time. On the other hand, transplants from deceased donors are semi-urgent, and chains starting with deceased donors need to be mobilized urgently and non-electively¹³.

Method

This study aims to demonstrate the experience gained since the implementation of the renal transplantation program under paired kidney donation, a modality that can increase the donation rate by 25% to 30% in the hospital without inferiority regarding graft survival compared to directed living donor renal transplantation.

This study was an observational, analytical, longitudinal, and prospective study of patients transplanted under the paired kidney exchange donation program

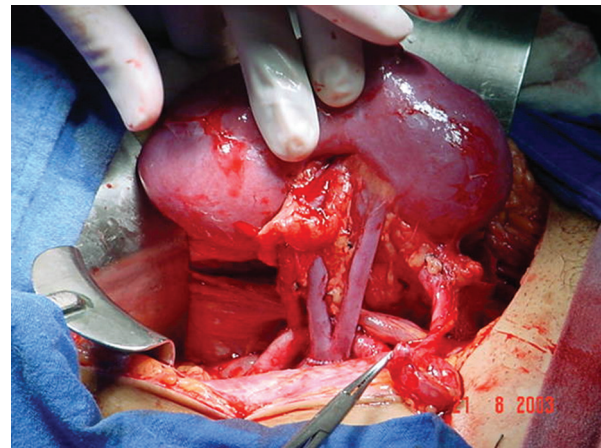


Figure 4. Paired kidney transplant program. Implantation of the graft with end-to-side vascular anastomosis from renal vein to external iliac vein and from renal artery to external iliac artery.

at our hospital from December 2018 through July 2021. All the couples that accessed the program completed the pre-transplant protocol and were evaluated and authorized by the internal transplant committee. The donation risk was estimated for each donor, and the probability of matching-compatibility was estimated for each recipient and crossing¹⁴. The Alvin Roth algorithm was used to perform the pairings in the transplant chains. Each recipient's notarial contract deed was requested, and simultaneous or sequential nephrectomies of the donors were performed in adjacent operating rooms. Nephrectomies were performed using a conventional technique through open or laparoscopic nephrectomy, and the kidneys were perfused ex vivo with a preservation solution prior to implantation that was performed in the right iliac fossa and contralateral to the kidney obtained, with end-to-side vascular anastomosis from renal vein to external iliac vein and from renal artery to external iliac artery (Fig. 4) using 6-0 Prolene vascular sutures. Neoureterocystoanastomosis was performed using the Leich-Gregor technique with 6-0 PDS sutures and a ferule mounted over a 6-Fr double-J ureteral catheter.

The induction of immunosuppression was performed based on the baseline immunological risk, using basiliximab or thymoglobulin. Maintenance was completed with mycophenolic acid, tacrolimus, and prednisone. No renal patient was desensitized before or after transplantation. The baseline demographic, clinical, and biochemical characteristics of this group of patients were determined, along with post-transplant assessments in compliance with the hospital internal protocol. Renal allograft biopsy was performed between months 3 and 9,

and these were evaluated using Banff criteria (2017). Glomerular filtration rate (GFR) and graft survival 1 year after transplantation were determined, along with the GFR of each donor in the post-transplant period.

Statistical analysis

The variables analyzed were age, sex, etiology of chronic kidney disease, blood type and Rh, panel of reactive antibodies, type of induction to immunosuppression, type and level of maintenance immunosuppression, body mass index, hemoglobin and serum creatinine levels, GFR in mL/min/1.73 m² of body surface area, complications, and graft status at the time. Histological variables from renal allograft biopsy were obtained according to Banff classification (2017)¹⁵. The Student t test was used to compare the means of the GFR and the graft survival of patients transplanted under the paired kidney exchange donation program and in a cohort of patients with directed related/unrelated living donors in our hospital. Mean values with standard deviation and the percentages of the variables were calculated using SPSS 25.

Results

A total of 22 patients were transplanted using the following modalities: 1 chain of 5 couples, 1 chain of 4 couples, 3 chains of 3 couples, and 2 crossings of 2 couples. Among these, 4 renal recipients were transplanted through chains that started with a deceased donor. In the 5-couple chain (the last one performed), an important milestone was achieved in Mexico with the first inter-center transplantation (donor exchange between 2 hospitals).

A total of 63.6% of the patients included in the study were women (Table 1). Preemptive transplantation was performed in 9.1% of the patients. Both the PRA (panel of reactive antibodies) level and type of induction immunosuppression used are shown on table 2. The most common etiology of chronic kidney disease was not established in 31.8% of cases, followed by systemic arterial hypertension in 27.3% of cases. In 18.1% of cases there was list exchange (the chain started with a deceased donor). The mean post-transplant proteinuria levels were 150.38 mg/day. A total of 90.1% of the patients were on the reference immunosuppression scheme (FK: tacrolimus/MMF: mycophenolate mofetil/PDN: prednisone), and 9.1% on a minimized scheme. All grafts remain

Table 1. Clinical and biochemical characteristics of recipients and donors under the paired kidney exchange donation program

Variable	Mean (± SD)
Receptor	
Age (years)	35.27 (± 12.45)
Sex	
Men	8 (36.4%)
Women	14 (63.6%)
Body mass index (kg/m ²)	24.77 (± 3.30)
Panel of reactive antibodies	
Class I	25.18%
Class II	28.68%
Donor	
Age (years)	42.22 (± 10.52)
Post-donation creatinine levels (mg/dL)	1.18 (± 0.29)
Post-donation GFR ratio (mL/min/1.73 m ²)*	75.04 (± 15.98)

GFR: glomerular filtration rate; SD: standard deviation.

*Estimated using the CKD-EPI formula.

functional, including hypersensitized recipients, with a median post-transplant follow-up of 18.0 months. The mean GFR was 72.5 ± 17 mL/min/1.73 m², and the mean waiting time since accessing the cross-matching program until transplantation, 4.8 months.

The study included a total of 2 sensitized patients (9.1%) with PRA levels ≥ 25% and 6 highly sensitized patients (27.27%) with PRA levels ≥ 80%.

Two surgical complications and 1 medical complication were reported, all of which resolved promptly, with fully functional grafts (Table 3).

In our hospital, during the study period, a total of 66 patients underwent transplantation, 40 of whom were from directed living related/unrelated donors, 4 from deceased donors, and 22 from the paired kidney exchange donation program, which represents a 33.33% increase in the rate of transplantation with the use of this novel program (Fig. 5)¹⁶.

Discussion

According to CENATRA data from 2017 through 2020 in Mexico, the mean waiting time to receive a kidney from a deceased and a living donor was 30.2¹⁷ and, 3.38 months, respectively¹⁸. In our cohort of patients transplanted under the paired kidney exchange donation program, the mean waiting time was 4.9 months, shorter than the waiting time for a deceased donor kidney.

Table 2. Demographic characteristics of patients transplanted under the paired kidney exchange donation program

Receptor	Sex	Age (years)	Etiology CKD	Type of dialysis	BT and Rh D/R	PRA class I/II	DSA	CMT	HLAmm	CMV	Induction
1	M	11	Valvas	HD	O+/O+	98/100%	No	Negative FC	1A/1B/1DR	D+/R+	ATG (4 mg/kg/d)
2	W	60	SAH	PD	O+/O+	7/9%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab
3	M	29	ND	HD	O+/O+	5/8%	No	Negative FC	2A/1B/1DR	D-/R+	Basiliximab
4	W	46	ND	PD	O+/O+	68/44%	No	Negative FC	1A/1B/1DR	D+/R+	ATG (1 mg/kg/d)
5	W	44	ND	<i>Preemptive</i>	O+/O+	6/0%	No	Negative FC	1A/1B/2DR	D+/R+	Basiliximab
6	M	28	ND	HD	O+/O+	10/5%	No	Negative FC	1A/1B/2DR	D+/R+	Basiliximab
7	W	37	IgA	HD	O+/O+	6/2%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab
8	M	28	ND	HD	A+/A+	8/14%	No	Negative FC	2A/1B/1DR	D+/R+	ATG (3.5 mg/kg/d)
9	W	24	ND	<i>Preemptive</i>	O+/O+	8/5%	No	Negative FC	1A/1B/1DR	D+/R+	ATG (4 mg/kg/d)
10	W	41	SAH	HD	O+/O+	45/84%	No	Negative FC	1A/1B/1DR	D+/R+	ATG (4.5 mg/kg/d)
11	M	31	SAH	HD	O+/O+	7/10%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab
12	W	49	SAH	HD	O+/O+	4/24%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab
13	W	39	SAH	HD	A+/A+	30/16%	No	Negative FC	1A/1B/0DR	D+/R+	ATG (3 mg/kg/d)
14	W	46	SAH	HD	O+/O+	100/99%	No	Negative FC	1A/0B/0DR	D+/R+	ATG (5.5 mg/kg/d)
15	M	42	MN	HD	O+/O+	68/82%	No	Negative FC	1A/2B/1DR	D+/R+	ATG (4 mg/kg/d)
16	M	32	CGN	PD	O+/O+	5/8%	No	Negative FC	2A/2B/1DR	D+/R+	Basiliximab
17	W	40	CGN	HD	O+/O+	52/88%	No	Negative FC	2A/B/1DR	D+/R+	ATG (4.5 mg/kg/d)
18	W	46	DM2	PD	O+/O+	2/7%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab
19	W	30	SLE	PD	O+/O+	9/11%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab
20	W	15	ND	HD	A+/A+	7/5%	No	Negative FC	0A/1B/0DR	D+/R+	Basiliximab
21	M	13	AHUS	HD	A+/A+	4/7%	No	Negative FC	2A/2B/1DR	D+/R+	Basiliximab
22	M	45	ADPKD	HD	O+/O+	5/3%	No	Negative FC	1A/1B/1DR	D+/R+	Basiliximab

ADPKD: autosomal dominant polycystic kidney disease; AHUS: atypical hemolytic uremic syndrome; ATG: anti-thymocyte globulin; BT: blood type; CGN: chronic glomerulonephritis; CKD: chronic kidney disease; CMT: crossmatch testing; CMV: cytomegalovirus; D: donor; DM2: type 2 diabetes mellitus; DSA: donor specific antibodies; FC: flow cytometry; HD: hemodialysis; HLAmm: human leukocyte antigen mismatch; IgA: IgA-induced nephropathy; M: man; MN: membranous nephropathy; ND: not determined; PD: peritoneal dialysis; PRA: panel of reactive antibodies; R: receptor; SAH: systemic arterial hypertension; SLE: systemic lupus erythematosus; W: woman.

Although our experience with the paired kidney exchange donation program is limited to only 22 renal transplant patients, according to Massie et al.¹⁹, our hospital qualifies as a center with very high utilization of the paired kidney exchange donation program.

In the Canadian registry, the mean number of days elapsed since a candidate participates in a compatibility

cycle under the paired kidney exchange donation program until transplantation was actually performed was 182 days (range, 47-1741; mean $\pm$ SD, 275 $\pm$ 17)²⁰, while, at the Mayo Clinic (United States), the median waiting time since program enrollment until transplantation was 330 days (range, 178-539)²¹. Our hospital has an average of 147 days from admission to transplantation

Table 3. Biochemical and histological evolution of patients after kidney transplant under paired kidney exchange donation

Receptor	BMI	Hb	Proteinuria (mg/day)	Cr (mg/dL)	GFR (mL/min)	FK (ng/mL)	IS	Histological criteria Banff (2017)	Complications	Graft status
1	21.3	12.9	122	1.12	75	5.3	FK/MMF/PDN	g1, cg0, ci0, ta0, i1, t0, ptc0, ah1, v0	None	Functional
2	23.3	16.6	100	1.40	40	3.9	FK/mTORi/PDN	g1, cg0, ci2, ct2, i1, t0, ptc1, ah1, v0	VK	Functional
3	27.4	19.8	199	1.2	93	6.4	FK/MMF/PDN	g0, cg0, ci0, ta0, i0, t0, ptc0, ah0, v0	None	Functional
4	19.4	17.8	177	1.1	59	2.7	FK/mTORi/PDN	g2, cg0, if1, ta1, i1, t0, ptc3, ah1, v0	None	Functional
5	24.7	13.6	150	1.0	61	5.6	FK/MMF/PDN	g1, cg0, if1, ta1, i0, t0, ptc0, ah0, v0	None	Functional
6	23.5	16.6	167	1.3	77	5.3	FK/MMF/PDN	g1, cg0, if1, ta1, i1, t0, ptc1, ah2, v0	None	Functional
7	25.8	14.7	248	1.1	60	4.5	FK/MMF/PDN	g1, cg0, if1, ta1, i0, t0, ptc0, ah1, v0	None	Functional
8	24.2	20.6	139	1.5	60	6.3	FK/MMF/PDN	g2, cg0, if1, ta1, i1, t0, ptc3, ah0, v0	None	Functional
9	29.6	16.6	136	0.9	91	8.2	FK/MMF/PDN	g0, cg0, if1, ta1, i0, t0, ptc0, ah0, v0	None	Functional
10	23.6	19.3	229	0.8	73	7.2	FK/MMF/PDN	g1, cg0, ci0, ta0, i0, t0, ptc0, ah0, v0	None	Functional
11	27	15	102	1.2	84	8	FK/MMF/PDN	g1, cg0, ci2, ct2, i1, t0, ptc1, ah0, v0	None	Functional
12	25.2	13.4	262	0.8	89	5.6	FK/MMF/PDN		None	Functional
13	25.4	10	116	1.3	50	4.1	FK/MMF/PDN		Ureteral ischemia	Functional
14	27.1	13.9	232	0.9	73	8.1	FK/MMF/PDN		None	Functional
15	26.4	15.4	186	1.7	54	12.6	FK/MMF/PDN	g1, cg0, if1, ta1, i0, t0, ptc1, ah0, v0	None	Functional
16	24.4	16	192	1.33	73	4.8	FK/MMF/PDN	g0, cg0, if1, ta1, i0, t0, ptc0, ah1, v0	None	Functional
17	32.4	15.6	77	1.28	56	5.3	FK/MMF/PDN	g2, cg0, ci0, ta0, i0, t0, ptc3, ah0, v0	None	Functional
18	20.4	12.3	134	0.7	102	9	FK/MMF/PDN		None	Functional
19	20.1	12.3	165	1	64	7.7	FK/MMF/PDN		None	Functional
20	23.3	11	120	1	65	5.3	FK/MMF/PDN		None	Functional
21	21	12.8	126	0.7	101	5.1	FK/MMF/PDN		None	Functional
22	29.5	13.2	200	1.2	95	9.5	FK/MMF/PDN		Lymphocele	Functional

Ah: arteriolar hyalinosis; BMI: body mass index; cg: chronic glomerulitis; Cr: creatinine; FK: tacrolimus; g: glomerulitis; GFR: glomerular filtration rate; Hb: hemoglobin; I: interstitial inflammation; if: interstitial fibrosis; IS: immunosuppression; MMF: micophenolate mofetil; mTORi: mTOR inhibitor; PDN: prednisone; ptc: peritubular capillaritis; t: tubulitis; ta: tubular atrophy; v: intimal arteritis; VK: poliovirus.

under this program, which is lower than the period reported in the medical literature.

We have already performed renal transplants with chains of 4 and 5 couples, although a Dutch study

recommends that the maximum length of an optimal chain for all practical purposes is 3 couples, especially for newly initiated exchange programs, because several simultaneous surgeries can limit the technical

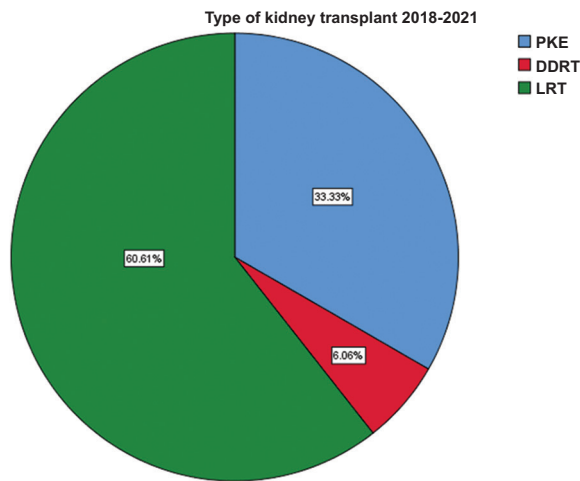


Figure 5. Types of renal transplants performed at our hospital from December 2018 through July 2021. PKE: kidney paired exchange donation; DDRT: deceased donor renal transplant; LRT: directed living related/unrelated donor renal transplant (adapted from Bahena et al., 2022¹⁶).

capabilities and resource of multiple centers, as significant coordination is required¹¹.

When the GFR of patients transplanted under the donor exchange program was compared, we saw that such GFR was 72.5 mL/min/1.73 m², higher than the GFR found in a cohort of 44 patients transplanted at our hospital throughout the same study period but from directed related/non-related living donors (66.56 mL/min/1.73 m²; $p = 0.123$).

When we analyzed the GFR and graft survival free from rejection of our pediatric recipients under the donor exchange program, we saw that both values are similar to those reported by Sypek et al.²² in the Australian registry of the pediatric paired renal exchange program.

The rate of graft survival in our center at follow-up was 100% in patients transplanted under the paired renal donation program, compared to 97.7% in directed living donors ($p = 0.489$). These data are similar to those reported by Kute et al.²³ who demonstrated that graft survival is similar when using related donation compared to donation under the paired program. Additionally, in the Canadian registry of paired kidney donation of 135 renal recipients followed for 1 year, the patients' and the allograft survival rates were 99% and 96%, respectively. In the same Canadian cohort, biopsy confirmed an acute rejection rate of 8%²⁰, compared to 9.1% in our patients from the paired program (all of these were subclinical rejections).

The 1-year adjusted graft survival after the transplant was 97.3%, 98.1%, and 97.7% for sensitized recipients

with PRA levels of 0-79%, > 80%, and > 99.9% groups, respectively²⁴. The overall graft survival rate in our cohort was 100% at 1-year follow-up.

The donors' dropout rate in our cohort was 0% because only in 13.6% of cases bridge donors were used, and they were advised in advance on the maximum waiting time of 3 weeks to donate their organs, as recommended by Kher and Kumar²⁵.

Conclusions

Renal transplantation under the paired kidney exchange donation program is an additional option to increase the rate of renal transplantation. However, it must be kept under strict in-hospital medical-ethical protocols and national legal regulations and consistent with the Declaration of Istanbul²⁶. Transplantation groups should be encouraged to promote this modality to integrate regional or national donor exchange programs to reduce the national waiting list for renal patients and, consequently, increase the rate of renal transplants in Mexico.

Funding

None whatsoever.

Conflicts of interest

None reported.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this study.

Patients' data protection. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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