
























International Kidney Paired Donation – The Experience of a Single Center

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ABSTRACT

Introduction: Kidney transplantation is the preferred treatment for end-stage renal disease, but organ scarcity can result in long waiting times. Living-donor kidney transplantation offers an alternative to deceased donation, but HLA or ABO incompatibility can pose a significant obstacle. This study aimed to show the results achieved by a Portuguese hospital since its integration into an international cross-over program, the South Alliance for Transplants (SAT). **Methods:** The SAT program was founded in 2017 and is composed of ten Spanish hospitals, three Italian hospitals and one Portuguese hospital. The program runs every 4 months and enrolled only pairs that were incompatible. Organ transportation is carried out in partnership with the Portuguese Air Force. **Results:** Three distinct cross-over kidney transplants were performed in partnership with three Spanish hospitals, culminating in the transplantation of three Portuguese patients out of a total of seven patients. The first swap was performed in March 2020, at the beginning of the COVID-19 pandemic, in partnership with two Portuguese and one Spanish hospital. It involved one donor/recipient pair from each country, with ABO incompatibility between the Portuguese donor and recipient, and no complications were reported. The second swap occurred in December 2021, with three donor/recipient pairs (one Portuguese, where the recipient presented anti-donor antibodies and positive crossmatch with the potential donor, and two from two Spanish hospitals). It was complicated by type-IB cellular rejection in the Portuguese recipient, one week after transplantation, which was treated with corticosteroid therapy. The third swap, also in December 2021, involved two donor/recipient pairs (one Portuguese and one Spanish). It was complicated by delayed renal function due to acute tubular necrosis (histological diagnosis) in the Portuguese recipient. At follow-up, the patients' serum creatinine levels were within normal limits, and no other unexpected outcomes were recorded. **Conclusion:** SAT program has allowed some successful cross-over kidney transplants, probably improving the outcomes of kidney transplantation in Portugal. The expansion of such programs may contribute to a more efficient use of the available resources, increasing the number of transplants performed and reducing waiting times.

Descriptors: Kidney Transplantation; Living Donors; International Cooperation.

Doação Renal Cruzada Internacional – A Experiência de um Único Centro

RESUMO

Introdução: O transplante renal é o tratamento preferencial da doença renal crônica terminal, porém, a escassez de órgãos pode resultar em longos tempos de espera. O transplante renal de doador vivo oferece uma alternativa ao doador cadáver, mas a incompatibilidade HLA ou ABO pode representar um obstáculo significativo. Este estudo teve como objetivo mostrar os resultados alcançados por um hospital português desde sua integração num programa internacional de doação cruzada, o *South Alliance for Transplants* (SAT). **Métodos:** O programa SAT foi fundado em 2017 e é composto por dez hospitais espanhóis, três hospitais italianos

e um hospital português. O programa ocorre a cada 4 meses e inscreve apenas pares que são incompatíveis. O transporte de órgãos é realizado em parceria com a Força Aérea Portuguesa. **Resultados:** Foram realizados três cruzamentos distintos em parceria com três hospitais espanhóis, culminando no transplante de três doentes portugueses de um total de sete doentes. O primeiro cruzamento foi realizado em março de 2020, no início da pandemia de COVID-19, com a parceria de dois hospitais portugueses e um hospital espanhol, envolvendo 1 par doador/receptor de cada país, em que o português apresentava incompatibilidade ABO e onde não se registraram complicações. O segundo ocorreu em dezembro de 2021 com 3 pares doador/receptor (1 português em que o receptor apresentava anticorpos anti-dador e crossmatch positivo com o potencial doador; e 2 de dois hospitais espanhóis), complicado com rejeição celular tipo-IB uma semana após o transplante no receptor português, tratada com corticoterapia. O terceiro cruzamento ocorreu também em dezembro de 2021 com 2 pares doador/receptor (1 português e 1 espanhol), complicado com atraso na função renal por necrose tubular aguda (diagnóstico histológico) na receptora portuguesa. Durante o *follow-up*, os níveis de creatinina sérica dos doentes mantiveram-se dentro dos limites normais, e não foram registradas outras intercorrências. **Conclusão:** O programa SAT permitiu a realização de alguns transplantes renais cruzados bem-sucedidos, provavelmente melhorando os resultados do transplante renal em Portugal. A expansão de programas semelhantes pode contribuir para um uso mais eficiente dos recursos disponíveis, aumentando o número de transplantes realizados e reduzindo os tempos de espera.

Descritores: Transplante Renal; Doadores Vivos; Cooperação Internacional.

INTRODUCTION

Kidney transplantation (KT) is the best treatment for end-stage renal disease.^{1,2} However, wait times can be long due to organ scarcity.^{2,3} At the end of 2021, there were 1944 patients on the waiting list for kidney transplantation in Portugal, and only 451 transplants were performed during the year.⁴

Living-donor KT, in addition to being associated with a shorter delay in function and higher patient and graft survival compared to deceased donation, is an alternative to overcome organ scarcity.² However, finding a suitable organ donor can be a significant challenge due to the limited availability of organs and the high demand for them. For many donor-recipient pairs, the presence of HLA or ABO incompatibility can pose a significant obstacle. One possible solution to overcome this hurdle, is the implementation of desensitization or ABO-incompatible programs.^{1,5} Kidney paired donation programs also emerge as a way to address the aforementioned problems, with increased likelihood of a better match, but expanding the pool of donor pair remains a challenge.^{2,3,5}

The concept of kidney paired exchange was first described in 1986 by Dr. Felix Rapaport⁶ and first performed in 1991 in South Korea.⁷ In Portugal, the national kidney exchange program was created in 2010, administered by Instituto Português do Sangue e da Transplantação, and the first swap was performed three years later.⁸ Since 2017, Portugal has also participated with one hospital, Centro Hospitalar Universitário do Santo António (CHUdSA), in an international cross-over program, the *South Alliance for Transplants* (SAT). Furthermore, through this program, CHUdSA also facilitates the transplantation of incompatible pairs from other Portuguese hospitals. With this study, we aim to show the results achieved by CHUdSA since its integration into this program.

METHODS

Program creation

Portugal has a National Kidney Paired Donation Program (PNDR) established through National Ordinance 802/2010 on August 23rd. The first paired exchange took place in Portugal in 2013. Pair selection occurs four times a year or as needed. The algorithm is applied whenever a new pair joins the program to assess potential cross-matching possibilities. The solutions determined are discussed in the PNDR expert committee meeting. Isogroup allocation is preferred in the matching process, with the general principle being to prioritize transplanting the recipient who is the most challenging to match.

In 2017, Portugal integrate an international kidney paired donation program, the *South Alliance for Transplants*, joining Spain and Italy. In order to be eligible to participate, centers were required to perform a minimum of 10 kidney transplants per year and obtain accreditation from the European Foundation of Immunogenetics for their human leukocyte antigen laboratory. Currently, it consists of ten Spanish hospitals, three Italian hospitals, and one Portuguese hospital, Centro Hospitalar Universitário de Santo António, which joined the program in 2018.

Patient selection and allocation model

The international program enrolled only pairs that were ABO or HLA incompatible. To ensure a coordinated and efficient process, a specially designed checklist was implemented.

In Portugal, the selection of pairs is carried out in partnership with the Instituto Português do Sangue e da Transplantação and any donor-recipient pair enrolled in the PNDRC can be included in the international program, provided there is no suitable pair in the national database and the kidney transplant will be performed at CHUdSA.

The PRA calculations were performed using the Eurotransplant calculator, encompassing the entire allo-sensitization history.

The international program's requirements were incorporated into the Spanish KEP software, which includes a registry of pairs and a matching algorithm. The pair selection takes place every four months and the coordination of the initiative was overseen by the Organización Nacional de Trasplantes (ONT) in Spain.

Transplant Procedure

The donor nephrectomies are simultaneous at the hospital where the pair is being followed or at a national hospital with agreement with SAT for that. It is always the kidney that travels, with the transport being carried out by air if necessary. In the case of Portugal, this transport is carried out with the collaboration of the Portuguese Air Force. The transplant surgeries are performed as soon as the organs are available to improve outcomes.

RESULTS

The Portuguese participation resulted in the realization of three distinct cross-over (designated TR1, TR2, and TR3) in partnership with three Spanish hospitals (Fundació Puigvert, Hospital Clinic i Provincial, and Hospital Universitari Bellvitge), culminating in the kidney transplantation of three Portuguese patients, out of a total of seven patients.

The demographic data of the three portuguese pairs involved in these crossmatches are shown in Table 1.

Table 1. Demographic data

	Pair 1, TR1		Pair 2, TR2		Pair 3, TR3	
	Recipient	Donor	Recipient	Donor	Recipient	Donor
Gender/Age	Male/54y	Female/51y	Male/54y	Male/57y	Female/43y	Male/46y
Blood type, ABO Rh	A, Rh+	B, Rh+	0	0	0	B
Etiology of CKD	Hypertensive nephrosclerosis	N/A	Unknown	N/A	Lupus-like nephropathy	N/A
Previous KRT	PD	N/A	HD	N/A	HD	N/A
KRT time, months	4	N/A	302	N/A	72	N/A
Previous KT, n	0	N/A	2	N/A	0	N/A
cPRA	0%	N/A	99.77%	N/A	0%	N/A
Relationship	Conjugal		Brother		Conjugal	
Incompatibility	ABO incompatibility		HLA incompatibility		ABO incompatibility	

CKD – Chronic Kidney Disease; cPRA – calculated Panel Reactive Antibody; HD – Hemodialysis; PD – Peritoneal Dialysis; KRT – Kidney Replacement Therapy; KT – Kidney Transplant; N/A - Non-applicable. Source: Elaborated by the authors.

TR1

The first crossmatch was a 2-way exchange between recipient 1 and a donor from Fundació Puigvert, which took place on March 12, 2020. The donor was male, 40 years old, and had blood type A Rh-. They had 8/8 HLA ABCDR mismatches with negative complement-dependent cytotoxic crossmatch (CDC) and flow cytometry crossmatch (FC). The induction immunosuppressive therapy was carried out with basiliximab, mycophenolate mofetil (MMF), tacrolimus (TAC), and methylprednisolone (MP). The surgery was performed without any complications, and the patient showed immediate diuresis. The cold ischemia time was approximately 5 hours. After 8 days of hospitalization, the patient was discharged with a serum creatinine (SCr) of 1.4 mg/dL, without unexpected outcomes during that period. About 24 months later, the patient has an SCr of 1.2 mg/dL and any adverse events occurred during this period. The kidney harvest surgery from the Portuguese donor, as well as the hospitalization and subsequent follow-up, also occurred without any recorded complications.

TR2

This crossmatch involved recipient 2 and donor 2 and was a 3-way exchange with Hospital Clinic i Provincial and Hospital Univeritari Bellvitge. It took place on December 14, 2021. The donor 2 was a 56-year-old male with blood type 0 Rh+. Recipient 2 was a candidate for their third kidney transplant and had multiple class I and II anti-HLA antibodies, and the donor had 4/8 mismatches in the HLA

ABCDR loci. A CDC and FC crossmatches were negative. They received induction therapy with anti-thymocyte globulin (ATG), MMF, TAC, and MP, and immunomodulatory therapy with intravenous immunoglobulin (IGIV). The surgery was performed with the renal graft placed intra-peritoneally, and no intercorrences were recorded. The kidney experienced a cold ischemia time of 5.1 hours. The patient had immediate diuresis and was discharged on the 8th postoperative day with SCr of 1.0 mg/dL. On the 15th day post-transplant, the patient was readmitted due to acute kidney injury (SCr 1.8 mg/dl) with no apparent trigger. A renal biopsy was performed, which documented T-cell-mediated rejection with a Banff IB score. The patient received three days of methylprednisolone bolus therapy, and the acute kidney injury resolved. Twelve months after the transplant, the patient had SCr of 1.1 mg/dl, and no other complications were recorded. Donor 2 donated the kidney to Hospital Clinic i Provincial, and no complications were recorded with the donor.

TR₃

Another 2-way exchange took place on December 16, 2021, with the Hospital Clinic i Provincial. The Spanish donor was 58 years old and had blood type 0. Receptor 3 had 6/8 HLA ABCDR mismatches. No anti-HLA antibodies were identified in the histocompatibility study and the CDC or FC crossmatch was negative. The patient received induction therapy with basiliximab, MMF, TAC, and MP. The kidney underwent a cold ischemia time of 8.9 hours. During the surgery, there was a need for anastomotic interposition of the superior gastric vein, and at the end of the procedure, a cyanotic appearance of the renal graft was observed, which prompted therapy with bolus unfractionated heparin (HNF) in the operating room and HNF perfusion during the first 5 days. Due to delayed graft function, an angio-CT was performed on the third day, which revealed hypoperfusion in the middle third of the kidney, and a percutaneous renal biopsy was performed on the 11th day, which only showed acute tubular necrosis. Recovery of renal function was observed on the 15th day, and the patient was discharged on the 20th day post-transplantation with an SCr of 2.3 mg/dl. During the following 12 months, there were no readmissions or other complications, and the patient had an SCr of 1.3 mg/dl. The surgery of donor 3 also proceeded without complications, as did the 12-month follow-up in the outpatient clinic.

DISCUSSION

Although we registered an episode of T-cell-mediated acute rejection in recipient 2 and delayed graft function in recipient 3, the achieved results remain positive. This is not only due to the absence of complications for at least the following 12 months, but also because these were patients who were unable to receive the kidney directly from their donor and potentially faced a prolonged wait for a renal transplant.

Other reports of international donation have emerged, involving programs from around the world.⁹⁻¹² The USA and Canada reported a domino exchange that began with a deceased donor and was implemented between September 2009 and August 2010.⁹ In Asia, specifically in India, the first international KPD was reported in 2018, involving an Indian pair and a Portuguese pair, although the Portuguese patient was not registered on the Portuguese waiting list.¹⁰ In Europe, the first report of a similar case was reported in 2016 between the Czech Republic and Austria.¹¹ Since then, other international programs have been created, including the SAT, which recorded its first result in July 2018 after the first matching run was conducted in May 2018, which was a 2-way exchange between Spain and Italy.¹²

The advantages of programs like these have been discussed extensively, with a particular emphasis on the increased number of available donors, which improves the likelihood of finding a match by increasing genetic diversity - a factor that is particularly important for sensitized patients. Additionally, these programs increase the likelihood of a better match between pairs, resulting in greater HLA compatibility and potentially reducing the incidence of rejection episodes.^{9,10} For this reason, several national and international cross-donation programs have been formed as a primary attempt to increase transplantability, such as Eurotransplant or Scandinaviantransplant in Europe, or United Network for Organ Sharing (UNOS) Paired Kidney Exchange Program in the United States.

There are various strategies for carrying out KPD, with the two most common being the two-way and three-way exchange. In a two-way exchange, two pairs of incompatible donors and recipients are matched and their kidneys are exchanged. In a three-way exchange, three pairs of donors and recipients are matched, and their kidneys are exchanged in a circular fashion. However, there are also more complex strategies, such as the „chain“ donation, which involves more than two pairs of donors and recipients in a sequential fashion.^{1,5} This approach requires careful coordination and can present challenges, such as the possibility of non-compliance of a donor who needs to continue the chain.^{1,5,13}

International kidney paired donation programs face another challenge, as they often involve long distances between the hospitals involved, which can lead to longer cold ischemia times and associated complications. Based on our own experience, the cold ischemia time is shortened by the use of airforce transport instead of commercial flights. Our cold ischemia times

have ranged between 5.0 and 8.9 hours. In a 2017 study by Gill et al.¹⁴ that evaluated the impact of cold ischemia times of up to 16.0 hours, a significant increase in delayed graft function was reported for cold ischemia times between 8.1 and 16.0 hours, but no association was found between graft loss and ischemia times up to 16 hours. Another study evaluated 2,363 living donor kidney transplants conducted between 2008 and 2018 and found no association between extended ischemia time (≥ 16 hours) and an increased risk of delayed graft function or death-censored graft failure.¹⁵ Taken together, these findings suggest that cold ischemia time should not be a barrier to the expansion and implementation of KPD programs.

A Global Kidney Exchange Program (GKEP), an idea initiated by Rees et al.,¹⁶ which involves kidney paired donation between high-income and low-income and medium-income countries (LMICs). Beyond the potential benefits associated with this type of transplantation, similar to those already addressed for international programs, there are concerns about the ethical implications of such programs. They may perpetuate existing inequalities between high and low-income countries, which has motivated a statement from the Declaration of Istanbul Custodian Group.¹⁷ Some critics argue that the practices of most PRMBs lack transparency, leaving room for exploitation and corruption,¹⁸ or raise ethical concerns regarding the commodification of organs.¹⁹ On the other hand, proponents of the idea argue that a GKEP could help address the global shortage of donor organs and provide lifesaving opportunities for patients in need. They also note that such programs could foster collaboration and information-sharing between countries and institutions, potentially leading to improvements in transplant practices worldwide.^{16,20} Despite the controversy surrounding the proposal, the idea of a GKEP remains an intriguing possibility for advancing kidney transplantation on a global scale.

CONCLUSION

Our experience and that of other locations show that programs like these offer numerous benefits, such as expanding the pool of available donors, improving compatibility between donors and recipients, and avoiding the costs and risks associated with desensitization therapies for ABO or HLA incompatible transplantations. These programs represent a valuable option for individuals who require a kidney transplant and can be an effective means of increasing transplant success rates and improving quality of life for patients. However, the success of these programs depends on the number of pairs enrolled. To ensure the success of these programs, there is a need for greater awareness, education, and promotion of their benefits and outcomes among the public, healthcare providers, and policymakers alike.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR'S CONTRIBUTION

Contribuições científicas e intelectuais substantivas para o estudo: Francisco JT, Carvalho R, Freitas J, Coimbra MT, Vilela S, Almeida M, Tafulo S, Pereira RC, Bolotinha C, Ivo M, Sampaio S, Ribeiro C, Silvano JL, Malheiro J, Pedroso S, Dias L, Martins LS; **Concepção e desenho:** Francisco JT, Almeida M; **Análise e interpretação de dados:** Almeida M, Tafulo S; **Redação do artigo:** Francisco JT, Almeida M; **Revisão crítica:** Almeida M; **Aprovação final:** Almeida M.

DATA AVAILABILITY STATEMENT

All data were generated or analyzed in this study.

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