

Conquering immunological barrier- part 2: paired kidney exchange transplantation

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Abstract

ABO blood group or human leucocyte antigen (HLA) incompatibility remain major immunological barriers for organ transplantation. One strategic approach to conquer this barrier is desensitize the recipient yet it remains expensive, resource intensive with a higher risk of complications. Paired kidney exchange(PKE) is an alternative strategy, where an exchange of kidneys happens among pairs consisting of a recipient with a willing live donor, yet unmatched for the particular recipient, making transplant unfeasible. PKE has evolved in to many complex types since its introduction of concept in 1986. This review aims at discussing the types, global trends, challenges and ethical aspects of PKE transplantation.

Introduction

Kidney transplantation providing superior survival, better quality of life and lower costs remains the premier form of renal replacement therapy [1]. Yet, the gap between waitlisted patients for kidney transplantation and supply is ever mounting [2]. Therefore, novel innovative solutions are needed to meet the ever rising demand to increase the donor pool.

Living kidney donation compared to deceased donation provides better patient and graft survival, less delayed graft function and short stay in waiting list [3]. Even in the presence of a live donor, a predicted 30% of kidney recipients cannot be transplanted due to ABO blood group or human leucocyte antigen(HLA) incompatibility [4]. One strategic approach to conquer this immunological barrier is to employ desensitization of the potential recipient. Desensitization protocols targeting depletion of alloantibodies to HLA or ABO blood group antigens include plasmapheresis, intravenous immunoglobulin, pharmacological B lymphocyte depletion or splenectomy. Nonetheless,

desensitizing treatments are expensive, resource intensive, carries a higher risk complications associated with amplified immunosuppression [5].

Felix Rapaport in 1986, first introduced the concept of live donor exchange stating the need of anonymity between donor-recipient pairs, simultaneous surgeries in 2 institutions and transportation of donor kidney to recipient institute for implantation [6]. Yet, the first ever PKE transplants were carried out at a single center in South-Korea in 1991 [7]. Since then living donor paired kidney exchange(PKE) programs have developed and evolved in many countries.

PKE denotes to the exchange of kidneys among pairs consisting of a recipient with a willing live donor, yet HLA or ABO unmatched for the particular recipient, making transplant unfeasible. Hence the exchange will result in receipt of a better compatible kidney [8]. Over the years, PKE has evolved in to many forms. Two way exchanges comprises of two incompatible pairs with reciprocal incompatibilities swapping, while three-way exchanges add another incompatible pair. Saidman et al. depicted that 3 way paired exchange can enhance matching rate up to 66% and regarded the most appropriate length of PKE for a single center initiated program [9,10,11]. This addition of pairs will simultaneously increase the number of donations and the possibility of finding better matches although such exchanges face considerable logistical challenges. Nonetheless, PKE is a better strategy to conquer immunological barrier compared to desensitization as its medically simple, less expensive and reduced risk of infections because of lesser immunosuppressive burden [2].

In this review, we discuss about types, global trends, challenges and ethical aspects of PKE transplantation.

Types of PKE

1. Conventional balanced PKE

In this type, ABO blood group-incompatible two donor-recipient pairs, interchange donors to produce compatible transplants. Conventional paired donations are

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restricted to donors and recipients with blood groups A and B [12]. PKE can commence as a closed loop of 2-way kidney exchange but can be organized as 3-way, or multi-way exchanges[13].

2.Unconventional PKE

An unconventional paired donation is performed when donor–recipient pairs become incompatible as a result of a positive cross-match. This allows donors and recipients with blood type O and AB to participate in the exchange[12].

3.Live donor–deceased donor list exchange.

This PKE type permits the potential recipient of an otherwise incompatible pair to receive priority on the deceased donor waiting list by providing a kidney from his or her intended donor to a recipient in the list. One ethical concern of this type is that the blood group O recipients being potentially disadvantaged, as the most frequent exchange being non-blood type O donor kidneys for blood type O deceased donor kidneys resulting in O recipients to tolerate longer waiting times on the deceased donor waiting list [14].

Commencement of an exchange by an altruistic, non-directed donor can give rise to domino-paired exchange chains and non-simultaneous extended altruistic donor (NEAD) chains.

4.Domino Paired Exchange (DPE)

DPE was initially described by Johns Hopkins Medical School with the objective of maximizing the benefit of altruistic donation [15]. A potential recipient with a willing but incompatible living donor is matched with a compatible altruistic donor. The kidney from the recipient's donor is then matched to the next compatible potential recipient in a deceased donor waiting list. Alternatively, it can be used to add another incompatible pair to the chain.

5.Non-simultaneous Extended Altruistic Donor (NEAD) chains

A NEAD chain modifies the DPE chain structure as the transplants are not executed simultaneously. This differs from the standard PKE practice of performing exchanges concurrently, in order to eliminate risks of defaulting by the donor. In a NEAD chain, the chain progresses similar to a DPE chain, but the last donor becomes a “bridge donor.” The bridge donor waits to enter another PKE when the matches are done, lengthening the chain further. Yet, the potential disadvantages would be ending up with a difficult to match bridge donor waiting longer times for an acceptable match and propensity of donor to default [16].

6.PKE with compatible pair participation

Participation of ABO and HLA compatible pairs can further increase the number of successful paired exchanges. The advantage for the compatible pair linking with the PKE may be to receive a better HLA and size-matched kidney or a younger donor [17].

7.PKE with desensitization

Desensitization has been utilized successfully to transplant ABO and HLA incompatible pairs. The highly sensitized recipients may find a more appropriate donor against whom they have a lower level of sensitization by merging PKE program with desensitization protocols. Montgomery et al. has used this modality successfully at John Hopkins Institute, USA [18].

Figure 1: Conventional balanced PKE

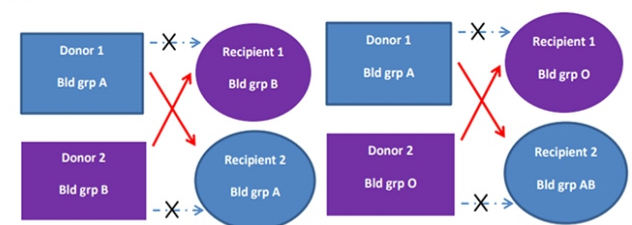


Figure 2: Unconventional PKE

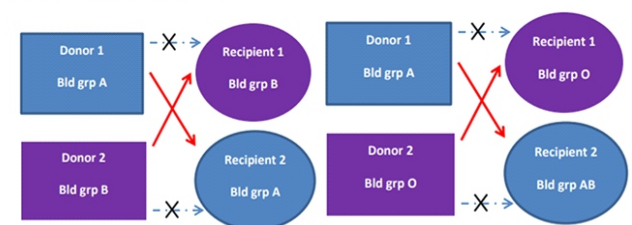


Figure 3: List exchange

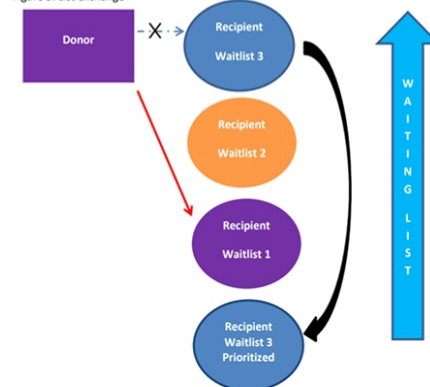


Figure 4 : DOMINO PKE

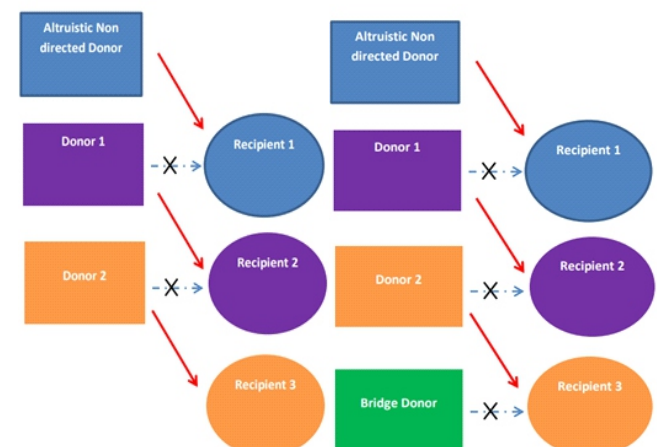


Figure 5 :NEAD PKE

Ethics aspects and challenges of PKD

1. Accumulation of O group recipients

In a PKE program, blood group O recipients tend to accumulate, mainly due to comparative shortage of blood group O deceased donors, blood group incompatibility in living donors and granted priority to HLA matching over ABO blood group matching in PKE allocation algorithms [19,20]. Unconventional PKE can mitigate the issue to a certain extent permitting some exchanges to the benefit of group O recipient [21]. Yet, conventional and list exchange programs disadvantage blood group O recipients. Majority of incompatible recipients being blood group O and their intended non-O donor provides a kidney to the deceased donor pool shortening non-O waiting times. In contrast, it prolongs O waiting times.

One strategy is to register more O donors with incompatible recipients. The other, is to recruit O donors to participate in a PKE despite having a ABO and HLA compatible intended recipient expecting a better allograft for the recipient [17]. Yet, in spite of an early disadvantage for group O recipients, they will eventually benefit through a shorter waiting time once national programs become established, permitting vast numbers of A and B recipients to be removed from the waiting list [20].

2. Coercion of the donor

The potential kidney donor can refute donation due to medical reasons like ABO or HLA incompatibility. Yet, PKE could add pressure on the donor as alternative options to donate are opened. Therefore, a thorough psychological evaluation is needed to make sure that donor is motivated without undue pressure or coercion [20].

3. Discrepancy of quality in PKE organs

PKE may result in inequities to recipient- donor pairs. For example, one donor may offer a better-quality kidney by being younger or by presenting a better HLA match hence, one party getting a greater benefit. However, it could be argued that it's a better comprise for parties as the recipients can avoid ongoing dialysis or an unknown waiting time on the deceased donor waiting list [22,23].

4. Simultaneous donor nephrectomy requirements

Rapaport et al. suggested that the PKE operations should be performed simultaneously with the notion that both procedures could be terminated if a complication happened in

one surgery [6]. Understandably, division of the renal vessels would be the the point of no return. This approach would provide the best opportunity for both couples of an impartial and unbiased exchange of organs.

Yet the practicality of simultaneous operations is questioned due to limitations in the human resources, infrastructure, travel, cold storage of organs etc. NEAD is an option yet; the long chain could break if donor defaults or recipient becomes medically unfit [24]. Further, there is no consensus within national PKE programs regarding when to halt the synchronous procedures in case of a donor complication or how to allocate the non-transplant organ in a recipient complication precluding transplant [20].

5. Balkanization of Patient Pools

Another challenge to PKE's triumph is the balkanization of patient pools. Potential matches that could exist between patient pools are prevented when transplant centers and pairing organizations operate independently of one another. The obvious solution is to amalgamate regional and national pairing organizations. Segev et al. projected a single national program would produce more transplants, better HLA matching, superior allograft survival rates, a decrease in the number of pairs necessary to travel, and robust benefits to highly sensitized patients [25]. The other strategy is to add a compatible pairs to the PKE. Gentry et al. demonstrated that expanding the patient pool by incorporating compatible pairs approximately doubles the pool's match rate in either in a single-center program or a national program [26].

Another strategy is to expand the PKE beyond country's border by making international collaborations. A 10-way exchange was originated in 2009 by a non directed donor with inclusion of a patient-donor couple from Canada [27]. Increasing the length of PKE was also discussed as a solution. Ashlagi and colleagues in 2012 demonstrated that the in-cooperation of longer chains (mainly NEAD chains) significantly increase the match rates, especially among highly sensitized patients [28]. Yet increasing length adds significant logistical complexities.

6. Positive Cross Match Complications

The most frequent interference to a KPD exchange remains positive cross matches [29]. Historically, a positive cross match has barred a donation within an exchange disrupting the entire chain.

One option is to employ desensitization protocols to reduce the number of highly sensitized patients. Merging

desensitization with PKE permits a recipient to find a better matched donor needing lesser desensitization relative to the intended donor.

Inclusion of high definition virtual cross matches into matching algorithm has ensued high match rates, even in small patient pools [30]. Further, having a single reference HLA laboratory or laboratories with uniform standards rather than multiple conflicting standards has shown to reduce number of positive cross matches [31].

Global experience of PKE

PKE programs have emerged in many countries, since the world's first PKE program was organized at Yonsei University College of Medicine in Seoul, South Korea [32]. It's becoming popular in developed as well as developing countries due to the admirable outcomes compared to deceased donation alone [2]. The successful programs are well established in Netherlands (2004), United Kingdom (2006), Australia (2007), Spain (2009), Canada (2009), India (2000) and United states (2010). Yet, the design and developments of PKE programs show significant variation across the world. The differences are usually generated due to the country specific challenges and differences in legislations. Further, international paired kidney exchanges are emerging in number of countries [27]. European Network for Collaboration on Kidney Exchange Programs (ENCKEP) is such a program started in 2016 which is operational in European countries [33]. The geography, close collaboration, language similarity and philosophical understandings have helped to build international PKE programs.

Application of PKE developing world

PKE is ideal to conquer the hurdle of immunologically incompatible transplants in developing countries due to multiple reasons. Firstly, it reduces the waiting time for transplantation as well as the individual and national costs associated with maintenance haemodialysis [34]. Secondly, it is an ideal strategy to increase the donor pool in countries where deceased donor program and ABO incompatible transplants are not well established [19]. Moreover, KPE transplants require lesser immunosuppression, fewer infective complications and reduced costs coupled with greater patient and graft survival compared to transplantation after desensitization, making it ideal to low income countries [35]. Further, it will be a partial solution for organ trafficking seen in these countries [36].

Shrestha et al reported excellent results of Nepal's PKE

program from 2016 to 2021 comparable to live donor program, demonstrating the feasibility of such a program in a developing country [35]. The Dutch experience highlighted the importance an independent organization for fair and impartial allocation and matching of kidneys, a good relationship and trust between different transplant teams and a central histocompatibility laboratory in establishing a national PKE program [10]. Kute et al. from India suggested that for a PKE program to be successful, it entails strong mixture of mathematical modeling, enthusiasm, patience and team work [13]. A PKE program can be formed in a developing country based on lessons learnt from the established centers, yet could be merged with the individual ethical and infrastructure concerns of their transplant community.

Newer trends in PKE

1. Trans-organ paired exchange

This novel concept describes a donor who is barred to donate one organ due to certain reason, is allowed to another organ for exchange. For example, a donor from pair one who's unable to donate kidney, donates liver to the recipient of pair two needing a liver. Donor of pair two donates kidney to recipient in pair one who needs a kidney [37]. However, there is a concern regarding the huge discrepancy of mortality risk in donating different organs. Hence, trans-organ paired exchange is an attractive yet a difficult proposition. Further, it will be an additional pressure on donor to engage in transplantation [2].

2. The advanced donation program (ADP)

ADP is a new initiative to overcome "chronological incompatibility" of organ donation. A donor opts to donate his kidney at his convenience, as he or she won't be available for the scheduled date for synchronous transplantation with other pairs. Consequently, his recipient receives the kidney from the intended donor after activating the chain in the due date.

Another modification is the voucher system. Here, a donor provides his organ in a non-directed manner, activating a PKE chain. His or her coupled recipient gets a voucher to be used in future as the recipient doesn't need a kidney transplant at present. A classic example is a grandfather donating a kidney to get a voucher for his granddaughter with chronic kidney disease potentially needing a transplant in the future. National kidney registry, USA introduced a family voucher program in 2019 [2].

3. Global kidney exchange (GKE)

GKE is another new strategy proposed to increase number of transplants through PKE. It encompasses PKE between pair resident in a high-income (HIC) country with another pair from low- and middle-income country (LMIC). The pair from LMIC being immunologically compatible is financially incompatible as a result of deprived socioeconomic status. The pair from HIC is immunologically incompatible. The cost of dialysis saved for patient from HIC is used to fund the transplant related expense of the pair from LMIC. The first experience of GKE was reported by Rees et al. in 2017, where a pair from Philippines initiated the PKE chain in USA [38]. Although appealing, the ethical dilemmas such as higher financial gain by HIC by getting more transplants, non-assurance of continued transplant care for the pair from LMIC and the negative impact on national PKE program in LMIC has been highlighted [2].

Conclusion

PKE is an excellent strategy to expand the donor pool for patients with end stage renal disease awaiting transplantation. It's a better strategy to conquer immunologically incompatible transplants compared to desensitization. Although appealing, PKE is allied with numerous ethical dilemmas and challenges needing innovation. Finally, global utilization of PKE has grown steadily and evolved exponentially proving to be an ideal strategy to developing world to put emphasis on.

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