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Personal Viewpoint

Equipoise: Ethical, Scientific, and Clinical Trial Design Considerations for Compatible Pair Participation in Kidney Exchange Programs

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Compatible living donor/recipient pair participation (CPP) in kidney exchange (KE) transplantation may substantially increase transplant volumes and significantly mitigate the O blood group donor shortage in KE. Initial ethical analysis did not support CPP for two primary reasons: (1) KE would be ''unbalanced,'' and (2) the possibility of undue influence experienced by the compatible pair living donor. Recent developments with CPP (modeling studies and small clinical experiences), have demonstrated substantial potential for increasing KE volumes. This encouraged us to reconsider initial ethical concerns, with a focus on the potential for a design of a prospective CPP clinical trial. This ethical reconsideration led us to conclude that the concept of unbalanced kidney exchanges (manifested primarily by differential benefit between compatible and incompatible pairs) is no longer as clear cut as originally conceived. In addition, application of two concepts substantially diminishes ethical concerns including: (1) ''quasi-compatible'' pairs, and (2) a priori definition of mitigating factors. We conclude that genuine uncertainty exists regarding whether kidney exchange is best performed with or without compatible pair participation and that a clinical trial is therefore warranted.

Abbreviations: CPP, compatible pair participation; DSA, donor specific antibodies; ESRD, end-stage renal disease; KE, kidney exchange

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Introduction

Living donor kidney transplantation is the optimal treatment for end-stage renal disease (ESRD) (1). However, many donor/recipient pairs are unable to undergo transplantation due to ABO-blood type incompatibility or the presence of recipient anti-HLA antibodies against the donor (termed donor-specific antibodies [DSA]) and therefore require desensitization and/or kidney exchange (KE) (2–4). Although desensitization yields acceptable outcomes, it is more expensive and incurs greater risks than KE (5–7).

After the initial description of the ethical and scientific principles for kidney exchange (8), the field has progressively expanded, with several nationally based kidney exchange programs established over the past several years, including the Dutch, Australian, Canadian, and British programs (9–11). A single US kidney exchange program, the National Kidney Registry, facilitated over 300 KE transplants in 2013. Despite the progressive expansion of KE, significant barriers remain that prevent full realization of KE potential (6). One barrier is the persistent dearth of O blood group donors, which persists despite participation of crossmatch incompatible donor/recipient pairs with blood group O donors. Compatible pair participation (CPP) presents another strategy that can address the O blood group donor shortage and also substantially increase KE volume.

Over the past several years, body of work has accumulated regarding ethical and scientific considerations regarding CPP. In addition, modeling studies have indicated substantial potential for CPP to increase KE volumes. These preclinical studies have subsequently been supported by early single center clinical experiences (12,13). Despite these advances, a clear ethical consensus for compatible pair participation on a large scale does not exist, and carefully designed clinical CPP trials have not been conducted. The purpose of this work is to determine whether equipoise (defined as a genuine uncertainty regarding whether KE is best conducted with or without CPP) exists for a clinical trial and to describe critical elements of a CPP clinical trial.

Nomenclature

The KE field does not have standard nomenclature, therefore definitions were required to develop a framework for ethical and scientific considerations of CPP.

Definitions

Donor/recipient pairs have been traditionally described as either ''compatible'' or ''incompatible'' based on (1) ABO compatibility and (2) DSA at levels high enough to generate a positive cytotoxic or flow cytometry crossmatch. However, this traditional dichotomous classification is inadequate for ethical and scientific considerations of KE programs. Therefore, an additional class of ''quasi-compatible'' donors is defined.

Compatible donor/recipient pair: Donor/recipient pair in which the recipient does not have ABO antibodies or DSA against the donor and is not at increased risk of acute rejection or reduced renal allograft function if transplanted with their original intended donor.

Incompatible donor/recipient pair: Recipient must meet each of two criteria: (1) recipient is at high risk of antibody mediated rejection and/or early allograft loss due to ABO- or HLA-incompatibility such that (2) desensitization treatment or kidney exchange would be required for transplantation to proceed.

Quasi-compatible donor/recipient pair: Recipient may proceed to transplantation without desensitization or kidney exchange; however, the recipient is at significantly increased risk for acute rejection and/or reduced renal allograft survival if transplanted with their original intended donor.

For the purposes of a clinical trial, ''significantly increased risk of acute rejection or reduced renal allograft function'' must be precisely defined by specific clinical scenarios a priori in the study protocol.

Risk mitigation: A predefined benefit for the compatible donor/recipient pair that is required for CPP in a KE.

Historical donor-specific antibody: An HLA antibody resulting from a distant HLA antigen exposure with a current level below the detection threshold of solid phase HLA single antigen bead microarray assay.

Equipoise: Represents the point at which ethical concerns in a prospective clinical trial are justified by the known risks and anticipated potential of the new modality being evaluated.

CPP historical perspectives

Ethical concerns in KE as first proposed by Ross and Woodle outlined included informed consent, privacy and confidentiality, commercialization, and exploitation (8). As additional KE variations emerged that required ethical consideration, Ross and Woodle introduced the concept of CPP in unbalanced kidney exchanges (14), which has been supported by others (12,15). Subsequently, additional ethical considerations and clinical experience with CPP have emerged along with modeling data demonstrating the ability of CPP to increase KE volumes. Given these new ethical and clinical considerations, we felt it appropriate to reevaluate CPP in KE.

Initial ethical concerns: Unbalanced kidney exchanges

As originally described in unbalanced KE, a compatible donor/recipient pair participates in a KE to facilitate transplantation for an incompatible donor/recipient pair (12,15). We considered such exchanges as unbalanced because the compatible donor/recipient pair did not have to participate in a kidney exchange to achieve transplantation, whereas the incompatible donor/recipient pair had to participate in kidney exchange to achieve transplantation. Therefore a benefit was assured for the incompatible pair as compared to the compatible pair (14).

Early ethical considerations expressed concerns regarding the potential for undue influence in CPP (14). Whereas a compatible donor could directly donate to the intended recipient, once committed to a KE, a compatible donor may feel pressure to participate in KE even though there is no formal obligation. This perceived pressure is often silent.

Although these two ethical concerns (unbalanced kidney exchanges and undue influence) were reasonable in the early KE considerations, new perspectives have been provided by more recent publications regarding: (1) CPP modeling data, (2) surveys of donors and recipient attitudes toward CPP, (3) early clinical CPP experiences, and (4) newer ethical issues.

CPP modeling data

Segev and colleagues provided the first modeling of CPP in KE (5,16). In their study, they modeled two types of mitigating factors for CPP reduction in donor age and avoidance of paternal antigen. They also modeled varying degrees of CPP and effects on single center and large multicenter programs. The studies revealed that CPP increased match rates from 28.2% to 64.5% for a single center program and from 37.4% to 75.4% for a national program (5).

An important aspect of CPP includes assuring that the compatible donor/recipient pair receives benefit (usually by receiving a better quality kidney or a better matched kidney), which we term risk mitigation. Importantly, modeling data indicates that the requirement for risk mitigation does not substantially reduce match rates (6). Segev and colleagues considered a 10-year reduction in kidney donor age as an acceptable benefit (6).

Donor and recipient attitudes toward CPP

In the Dutch national KE program, only one-third of the donors and recipients were willing to consider CPP (17). More thorough studies of donor and recipient attitudes

towards CPP have demonstrated ambivalence towards CPP (12). Recipients were more likely to agree to CPP if it provided a better match, if the recipient was a relative, and if the donor strongly supported participation. Donors were more likely to accept CPP if it provided an advantage for the recipient, such as a younger donor or a better match, or if the donor knew the other recipient, or if the other recipient was a child (12).

The impact of delays in transplantation on willingness to consider CPP revealed that donors and recipients were willing to participate if the delay on transplantation was 1 month. Delays of 1–6 months decreased donor and recipient willingness to agree to CPP (12).

Ratner and colleagues demonstrated that CPP places pressure on donors and recipients to participate in KE, as 38% of potential recipients and 46% of potential donors responded that CPP would place unwanted pressure on them (15). Ethical considerations considered in this study also included donor equity, donor/recipient age matching, discrepancy in donor/recipient attitudes, and anonymity between donor/recipient pairs.

CPP clinical experiences: Clinical experiences with CPP have recently accumulated (12,15,18,19). In a single center KE program (San Antonio), compatible donor/recipients pairs (where the donor was over 45 years of age and was not HLA identical) were approached for CPP (18,19). In this experience, 17 compatible pairs were included in KE procedures that provided 134 transplants. Although the effect of CPP on match and transplant rates in KE was not rigorously examined, CPP was felt to be responsible at least in part for an increase in the total live donor kidney transplants. Additional smaller case series have also suggested that CPP facilitates transplantation in KE (12,15).

Concept of quasi-compatible pairs

A limitation of prior ethical considerations of CPP has been the dichotomous classification of donor/recipient pairs as compatible or incompatible. Such a classification is restrictive, and does not reflect reality; therefore we have defined a third group that we term ''quasi-compatible'' (see definitions under nomenclature).

From a clinical perspective, quasi-compatible pairs (like incompatible pairs) will benefit from KE, whereas compatible pairs do not have a clear benefit from KE participation *a priori*. Conceptually, the degree of clinical benefit between incompatible and quasi-compatible pairs represents a continuum, however, since both experience significant benefits from CPP neither would require risk mitigation.

Examples of quasi-compatible pairs

Quasi-compatible pairs may be defined based on immunologic criteria or nonimmunologic criteria.

Immunologic quasi-compatible pairs: A frequently encountered example of a quasi-compatible pair includes female recipients who are re-exposed to paternal antigen by kidney transplantation and therefore incur an increased risk for antibody-mediated rejection. Immunologic quasi-compatible pairs may also include patients with low-level DSA that does not cause a positive flow cytometry crossmatch. Although these pairs may undergo transplantation without KE, they are at increased risk for AMR and potentially, reduced renal allograft survival. Similarly, patients with higher DSA levels and a low level positive flow cytometry crossmatch, can also undergo transplantation, yet are at even higher AMR risk and lower renal allograft survival (2).

Additional examples of quasi-compatible donor/recipient pairs include blood group A_2 donors with O or B blood group recipients (and A_2B blood group donors with blood group B recipients) if the anti-A blood group antibodies are at 1:4 titer or less with minimal risk of AMR. Recipients with anti-A blood group antibodies with titers are above 1:8 are considered incompatible, as transplantation must be performed only with multiple plasmapheresis treatments. Table 1 presents examples of incompatible and quasi-compatible pairs.

Nonimmunologic quasi-compatible donor/recipient pairs

Nephron mass/GFR: A substantial size discrepancy between donor and recipient wherein the recipient would

Table 1: Quasi-compatible and incompatible donor/recipient pairs

Quasi-compatible pairs
Immunologic examples
Female recipients of a kidney from husband or child with potential
reexposure to paternal antigen
Re exposure to HLA antigen from a previously rejected kidney transplant
Recipient with DSA but negative flow cytometry crossmatch
Recipient with DSA with low level flow cytometry crossmatch
A_2 blood group donor to O or B blood group recipient
A_2B blood group donor to B blood group recipient
Non-immunologic examples
Substantial difference in donor/recipient GFR
Substantial donor/recipient age differences
Donor Infection Transmission Risk
CMV seropositive donor to seronegative recipient
EBV seropositive donor to seronegative recipient
Hepatitis B core positive donor to seronegative recipient
Hepatitis C antibody positive/viral load negative donor to Hepatitis C
seronegative recipient
Incompatible donor/recipient pairs
ABO incompatible
Recipient with DSA and positive cytotoxic crossmatch to donor
Recipient with DSA to donor and strongly positive flow cytometry
crossmatch to donor

be receiving an estimated nephron mass that is less than optimal are considered quasi-compatible. As an example, a large male receiving a kidney from a substantially smaller female with a measured or estimated glomerular filtration rate (GFR) less than what one might consider optimal. Clearly, in these scenarios, the transplant may proceed, however, a KE may provide a more desirable (or optimal) kidney with an expected improvement in long-term allograft survival compared to the original donor kidney.

Donor/recipient age difference: Donor/recipient pairs with marked discrepancies in donor/recipient age are considered quasi-compatible. As an example, a recipient in their 20s may have as their only potential donor someone in their 60s, or alternatively, a recipient in their 60s may have as their only donor someone in their 20s. Some authors state age has not been demonstrated to affect renal allograft outcomes, except in recipients aged 18–39; however, living donor age in kidney exchange is controversial and should not be dismissed (20,21).

Donor infection transmission: Donor/recipient pairs with increased potential for virally mediated disease are also considered quasi-compatible, as seronegative donors will provide a clinically significant reduction in posttransplant infectious risk, but are not absolutely required for transplantation. Examples may include hepatitis B core antibody positive donors with hepatitis B surface antibody negative recipients, CMV seropositive donors with CMV seronegative recipients and EBV seropositive donors with EBV seronegative recipients.

Mechanisms for mitigating risk for CPP

One approach for mitigating risk in CPP is to provide a donor kidney for the compatible pair recipient that has advantages over that of their original donor (Table 2). Potential approaches may include a kidney with enhanced HLA matching, particularly for Class II antigens. For the purposes of a clinical trial, we would recommend that if improved HLA matching is the chosen mitigating factor for allowing CPP, that an increase of at least one additional DR antigen match or at least two additional HLA A or B matches should be required. A second approach may include providing a kidney from a younger donor. For clinical implementation, we would propose that a reduction in donor age of at least 15 years, which has been demonstrated to decrease age related risk of renal allograft failure across various recipient groups (21). A third potential approach for mitigating risk would include providing a kidney with a higher GFR. Since transplant kidneys GFR decreases by about 1–2 mL/min/year, a 10 mL/min higher GFR would be expected to add 5–10 years of additional graft survival.

Table 2: Mitigating factors

Reduction in donor age – lower by at least 15 years
Increase number of HLA DR matches by at least one match
Increase number of HLA A or B matching by at least two matches
Increase GFR in donor kidney by at least 10 mL/min

Ethical protections for CPP

The potential risk of undue influence in compatible pair donors is an ethical concern for CPP in KE. One approach for addressing this issue is to assure that neither the donor nor recipient in a compatible pair are aware of details regarding the number of potential pairs in the KE until after the KE is completed. Other standard ethical protections as previously described (8,22) should be followed to protect donor/recipient pairs in CPP.

A maximal waiting time for transplantation should be established with the compatible pair at the time of consent to participate in KE. The amount of time a compatible pair should wait should be short, ideally 3 months. Exploitation of compatible pairs by media stories focused on their participation should be avoided so as to assure appropriate motivation. Privacy and confidentiality should be assured for CPP as originally described in general for KE participants (8) and for nondirected donors (22).

Education and consent for CPP in KE

Education for compatible donors and compatible recipients in CPP should be standardized across participating centers in a CPP trial. Potential risks and benefits should be clearly outlined (Table 3), as well as protective measures to minimize undue influence. Compatible donor/recipient pairs should determine *a priori* how long they would be willing to wait before proceeding to transplantation without CPP. In addition, transplant nephrologists and transplant surgeons caring for compatible donor/recipient pairs should provide an unbiased opinion of what length of time would be reasonable to wait before abandoning CPP. Mitigating factors and their expected effects should be clearly explained, and donor/recipient pairs should be able to decide *a priori* which mitigating factors they are willing to accept. A standardized consent form detailing risks and procedures should be employed with required signatures of compatible donor/recipient pair.

Equipoise consideration

As originally defined by Freedman (23), equipoise exists when genuine uncertainty exists regarding the comparative therapeutic merits of two different therapeutic approaches with respect to a comparative clinical trial. In the present paper, we hold that uncertainty exists regarding whether kidney exchange is best performed with or without CPP. Previously, we had rejected compatible pair participation as an unbalanced kidney exchange. However, as we have presented in this work, the emergence of published clinical experiences and modeling studies of compatible pair participation, has diminished these early ethical concerns such that a genuine uncertainty now exists regarding

Table 3: Benefits/risk summary based on degree of donor/recipient compatibility

	Incompatible pairs	Quasi-compatible pairs	Compatible pairs
Potential benefits[1]			
Better immunological match	+++	++	+/−
Better kidney quality (GFR, donor age)	+/−	+/−	++
Avoidance of desensitization	+++	++	N/A
Potential risks[1]			
Longer wait for transplantation	N/A	+/−	+++
Increased cold ischemic time of donor kidney	+/−	+/−	+++

[1]Greatest effect expressed by +++, followed by ++, followed by +.

Table 4: Psychological and ethical endpoints in CPP clinical trial

Undue influence
Effect of additional waiting time on compatible pairs
Perceptions of quality of kidney received
Perceptions regarding medical right to knowledge
Privacy/confidentiality
Informed consent regarding kidney exchange
Impact of CPP on donor/recipient relationship

whether kidney exchange is best performed with or without CPP.

Clinical trial proposal

A CPP clinical trial should test the effects of CPP on ethical and psychosocial issues affecting compatible pair donors and recipients. The impact of CPP on KE match rates and transplantation rates should also be studied. Ethical issues to be evaluated by questionnaires, participant observation, and/or indepth interviews should be specifically designed to assess previous ethical issues including (but not limited to) undue influence, privacy, confidentiality, right to withdraw consent, commercialization, exploitation, and perceptions of fairness (8). It is important that an expert in the field of ethics and qualitative research be involved in the trial since analysis can be difficult to interpret. Ethical and psychosocial issues would be evaluated for incompatible pairs, quasi-compatible pairs, and compatible pairs (Table 4). Risk mitigation would be carefully defined in the study protocol. Observed KE transplantation and match rates in the study will be evaluated by: (1) performance of match runs with and without CPP, (2) comparison of KE match rates and transplantation rates to historical match rates and transplantation rates in the KE program in the year preceding the KE trial, and (3) modeling studies previously published using actual CPP and KE patient data. Transplant rates will be individually assessed for specific recipient ABO blood groups, and also within defined tiers of HLA sensitization (e.g. cPRA $<$25, 26–50, 51–75, 75–95, 96–98, and 99–100).

Conclusions

In the fourteen years since the publication of a paper analyzing ethical considerations regarding CPP, much has been learned about the clinical and ethical issues related to CPP. This combination of new clinical information and the evolution of ethical perspectives now suggest that a multicenter clinical trial of CPP in KE is warranted.

Author Contributions

Initial conceptualization: Woodle and Ratner.
Manuscript preparation: Cuffy and Woodle.
Manuscript editing and additional concept development: Cuffy, Ratner, Siegler, and Woodle.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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