



Review

Dialysis Access and Preemptive Kidney Transplantation

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Abstract: Sustainable vascular or peritoneal access for dialysis is very important for patients undergoing dialysis therapy, and access trouble is occasionally involved with unexpected occurrence of complications. Once access trouble occurs, dialysis therapy might be discontinued and be followed by a life-threatening state of patients with end-stage kidney disease. Bacterial infection, massive bleeding, and thrombosis in patients undergoing hemodialysis and acute infectious peritonitis and chronic encapsulating peritoneal sclerosis in patients undergoing peritoneal dialysis are important clinical issues. Preemptive kidney transplantation prior to dialysis has several advantages over transplantation after exposure to dialysis therapy. One of the notable advantages is the lack of necessity of dialysis access, which avoids access operations before transplantation. However, some transplant recipients may need short-term dialysis therapy due to the unexpected progression of chronic renal dysfunction. Dialysis access is required in a short preoperative period for preconditioning. The selection of renal replacement therapy without complications in a short-term dialysis before transplant surgery is important for the success of kidney transplantation. Appropriate preparation of short-term dialysis therapy and access is a key to success of preemptive kidney transplantation.

Keywords: vascular access; peritoneal access; renal replacement therapy; preemptive kidney transplantation



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1. Introduction

Preemptive kidney transplantation (PEKT) is defined as transplantation prior to dialysis therapy. Some transplant recipients need short-term dialysis therapy for preconditioning due to the unexpected progression of renal dysfunction. Such cases include the PEKT criteria and require dialysis access for hemodialysis (HD) or peritoneal dialysis (PD). The appropriate selection of short-term dialysis modality is important for preconditioning of PEKT with preventing dialysis access-related complications. In each therapy, stable and sustainable access is essential for improving dialysis treatment efficiency. In patients undergoing HD, vascular access (VA), such as arteriovenous fistula with native vessels, arteriovenous fistula with artificial graft, or catheter placement is needed for extracorporeal circulation; in patients undergoing PD, peritoneal catheter insertion is required. It has been reported that PEKT has better outcomes than non-PEKT due to no exposure to long-term dialysis therapy [1]. The frequency of PEKT had increased in nationwide study [2]. The selection of renal replacement therapy (RRT) is important because it avoids complications related to dialysis access. Immunosuppressive therapy is essential for kidney transplantation, and immediately before and after transplant potent immunosuppressants are administered, which may lead to infectious complications related to the presence of dialysis access.

Optimal modality selection of RRT is very important for improving life expectancy and maintaining good quality of life in patients with end-stage kidney disease (ESKD).

Matching patients to the most suitable modalities require that a number of factors be considered, including the patient's autonomy, medical and social factors, system-related issues, patient outcomes, and finances [3]. The paradigm of individual appropriate access for dialysis is changing as well as treatment policy of RRT with advancement of treatment methods. "Patient first: ESKD Life-Plan" is advocated by the most recent National Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [4]. The policy attains the "right access, in the right patient, at the right time, for the right reasons" [5]. Appropriate selection of dialysis access is one of the most important issues in the treatment of RRT.

In PEKT, preoperative management, including dialysis access, is important for the success of transplantation with the consideration of the influence of immunosuppressive therapy. We especially focus on the dialysis access related to PEKT in the optimal modality selection.

2. Epidemiology and Clinical Features of Preemptive Kidney Transplantation

PEKT has numerous advantages, because it avoids complications related to dialysis therapy. It has been commonly performed according to the nationwide survey based on large-scale registration data from the United Network of Organ Sharing (UNOS) or the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) registry. Recent studies have clearly demonstrated that PEKT is associated with better allograft and patient survival [1,2,6–9]. Improving the clinical outcomes of kidney transplantation in the national survey leads to the widespread use of PEKT. Moreover, improved clinical results have been shown in pediatric kidney transplantation, which has received great benefit for pediatric patients in terms of quality of life, mental health, and physical growth [6–8]. There is an interesting report demonstrating the ratio of PEKT in living-kidney transplantation in major countries. Norway has a high rate of PEKT, with 17.6% of all incidents in patients with ESKD receiving a transplant by day 91 after initiating RRT. However, more patients have initiated dialysis with ESKD, and the rate of PEKT for incident ESKD has stagnated even in the United States [10]. In many cases, kidney transplantation is performed after a certain period of dialysis treatment. It should be recognized that some cases have benefits of PEKT due to donor sources.

In Japan, most PEKT cases involve living-donor kidney transplantation due to small numbers of deceased-donor kidney transplantations. The ratio of PEKT in living-kidney transplantation has increased annually since the 1990s. Currently, PEKT accounts for 30–40% of living-donor kidney transplantation. The annual report from the Japanese renal transplant registry showed that a total of 2057 kidney transplants, including 1827 from living donors and 230 from deceased donors, were performed in 2019 in Japan. In the survey, the reported 1428 living-donor kidney transplantation consisted of 835 (58.5%) kidney transplantation for chronic maintenance dialysis cases, 433 (30.3%) PEKT without pre-transplant dialysis, and 160 (11.2%) PEKT with preoperative dialysis for preconditioning. A significant number of patients scheduled PEKT undergo short-term dialysis therapy before transplant, and the choice of dialysis modality and access is a critical issue in the cases.

It is occasionally difficult to decide the timing of initiation of PEKT, because earlier PEKT may lead to unnecessary prolongation of renal replacement therapy, requiring immunosuppressive therapy. However, later timing of PEKT requires a certain period of dialysis therapy with VA or peritoneal access. Fissell et al. reported that a better renal function at the time of listing for transplant is associated with a greater likelihood of PEKT [11]. However, kidney transplant surgery is associated with mortality in the perioperative stage due to the necessity of invasive surgical procedures and intense immunosuppression; therefore, early PEKT, which requires unnecessary immunosuppressive therapy, should be avoided in the timing of higher residual renal function.

Appropriate decision making for the preparation and timing of PEKT is very important, which may lead to good clinical outcomes.

3. Preemptive Kidney Transplantation, Advantage and Disadvantage

It is well known that dialysis duration affects the clinical outcome of kidney transplantation. Patients undergoing a longer period of dialysis therapy tend to have a higher incidence of complications and a significantly poorer prognosis compared to kidney transplant recipients [7–9,12,13]. Patients undergoing long-term dialysis have a high incidence rate of cardiovascular disease, arteriosclerosis obliterans, mineral bone disorder, abnormal calcification, amyloidosis, and sarcopenia, which might lead to operative complications associated with transplant surgery and management [14–21]. PEKT can avoid various organ disorders originating from exposure to long-term dialysis therapy. Moreover, some investigators speculated that the lower rate of delayed graft function associated with PEKT might be explained by the benefits of residential renal function, which allows the avoidance of perioperative complications [1,7]. End-stage renal failure causes weakened immune potential, which is followed by less resistance to opportunistic infections [22]. In PEKT, unnecessary dialysis therapy prevents operations of dialysis access, such as arteriovenous fistula and peritoneal catheter insertion. Conditions without dialysis access protect from cardiac vascular disease by cardiac output syndrome and peritoneal infection related via the peri-catheter.

However, PEKT has several disadvantages in clinical issues. Patients who underwent PEKT had a tendency to non-adherence (NA), which is likely to cause acute rejection. This is because they have not experienced dialysis therapy and have not recognized the importance of immunosuppressive therapy for continuous RRT. It has been reported that 28% of transplant recipients have experience with NA, which is one of the reasons for graft dysfunction [23]. The risk of graft loss in patients with NA is seven times higher than in patients with good adherence [24]. The survey revealed that 69% of nephrologists in the US cited NA as a factor to hesitate PEKT. The experience of dialysis therapy would lead to a desire for no return to dialysis. The advantages and disadvantages that should be acknowledged when performing PEKT are summarized in Table 1.

Table 1. Advantages and disadvantages of PEKT.

Advantages	<ul style="list-style-type: none"> ● Good allograft and patient survival compared to non-PEKT ● Avoidance of complications related to long-term dialysis ● Needless of vascular or peritoneal access operation ● Good socio-economic performance
Disadvantages	<ul style="list-style-type: none"> ● Difficulty in timing decision ● Possibility of non-adherence ● Preoperative hypodynamic state compared to patients undergoing dialysis ● Preoperative Electrolyte and acid-base abnormalities without correction by dialysis

PEKT, preemptive kidney transplantation.

It is occasionally difficult to decide the timing of PEKT, because earlier PEKT may lead to unnecessary prolongation of renal replacement therapy requiring immunosuppressive therapy. However, later timing of PEKT will require short-term dialysis therapy with dialysis access, such as vascular or peritoneal access. Appropriate cooperation and planning for the initiation of PEKT might be important for transplant physicians and surgeons.

As mentioned above, it is reported that PEKT has better clinical outcome. However, the earlier events of transplantation may lead to better clinical results. The fact needs to be carefully examined by more scientific and precise approaches.

4. Dialysis Access for each Renal Replacement Therapy

4.1. Decision Making of Renal Replacement Therapy

The selection of RRT, including PEKT, is important because it affects patient survival, quality of life, and social activities such as occupation for adults and school life for non-adults. The patient needs to receive dialysis access for HD or PD, if the PEKT is impossible for ESKD. The most valuable advantage of PEKT is unnecessary of dialysis access, except

in some cases that have unscheduled progress. The appropriate choice and timing of initiation of RRT to avoid complications related to dialysis access are important for stable and sustainable RRT.

4.2. Vascular Access for Hemodialysis

In patients undergoing HD, VA is essential for the efficient dialysis therapy. The blood flow volume in HD is directly related to therapeutic efficiency. It is well known that a lower efficiency leads to a lower survival in patients undergoing HD, so stable dialysis access is an essential tool for clinical outcome. In HD, several series of dialysis access are available, such as arteriovenous fistula with native vessels (AVF), arteriovenous fistula with artificial graft (AVG), and catheter insertion. A tunneled cuffed catheter (TCC) is usually used in the patients undergoing long-term catheter dialysis. TCC use is associated with a greater risk of infection with sepsis than AVF or AVG, which affects hospitalization and mortality [25–28]. The type of VA used in patients undergoing HD is known to have a significant influence on patient survival. In patients using TCC, access-related complications were responsible for 43% of all deaths, and infection was a single cause of death [29]. The policy of dialysis access differs across countries and areas in the world. The merits and demerits of each VA should be well known by the responsible staff and the findings should be used for appropriate shared decision making of RRT. The famous nationwide survey of the Dialysis Outcomes and Practice Patterns Study (DOPPS) showed international trends in VA use from 1996 to 2007 [30]. In Japan, more than 90% of patients undergoing HD use AVF, which is higher than that in other countries. The frequent use of AVF in Japan may lead to good clinical survival compared to other countries.

4.3. Peritoneal Access for PD

In patients undergoing PD, appropriate peritoneal catheter insertion and stable catheter function, including both filling and draining dialysate are essential for efficient dialysis. Catheter functioning failure originating from obstruction or abnormal positioning by fibrin or peritoneal organs, such as omentum, mesentery, and fallopian tubes, has a significant effect on dialysis efficiency. Long-term PD may cause encapsulating peritoneal sclerosis, which may cause PD interruption and be occasionally lethal due to bowel dysfunction with nutritional disorders [31–34]. One of the typical features of PD is the impossibility of long-term therapy over several years. Thus, PD may play a role as a bridge connection to PEKT for short-term dialysis therapy. Temporary peritoneal catheter insertion may be useful for preconditioning of PEKT.

4.4. Comparison in each Access for Dialysis Therapy

The incidence rates of hospitalization due to septic bacteremia are higher in patients undergoing HD than in patients undergoing PD due to the characteristics of methods with extracorporeal circulation. The choice of HD compared to PD as an initial modality doubles the risk of hospitalization due to sepsis [35]. It was reported that examination of hospitalization for bacterial endocarditis in 327,993 patients showed a relative risk (RR) of 17.86 (95% CI 6.62 to 48.90) in patients undergoing HD and a RR of 10.54 (95% CI 0.71 to 158.13) compared with the general population [36]. PD has an advantage in avoiding septic infection, because VA has a high risk of blood flow infection.

The advantages and disadvantages of each type of dialysis access are presented in Table 2.

Table 2. Advantages and disadvantages of each access for dialysis therapy.

Accesses	Advantages	Disadvantages
Vascular access for hemodialysis	AVF <ul style="list-style-type: none"> • Good patency • Relatively resistant to local infection • Economical superiority without medical materials 	<ul style="list-style-type: none"> • Essential for superficial vein • Effect on cardiac function
	AVG <ul style="list-style-type: none"> • Possibility without superficial vein • Sustainability of large blood flow volume 	<ul style="list-style-type: none"> • Easy to local infection • Necessity of artificial materials • Slightly difficulty in operation
	TCC <ul style="list-style-type: none"> • Relatively easy operative procedure • Available for emergent dialysis therapy 	<ul style="list-style-type: none"> • Easy to systemic infection • Necessity of artificial materials • Possibility of thrombosis
Peritoneal access for peritoneal dialysis	<ul style="list-style-type: none"> • Unnecessity of extracorporeal circulation • Mild effect on residual renal function • Less impact on cardiac function 	<ul style="list-style-type: none"> • Worsen body image • No tolerance of long-term dialysis therapy

AVF, arteriovenous fistula with native vessels; AVG, arteriovenous fistula with graft; TCC, tunneled cuffed catheter.

5. Dialysis Access and Preemptive Kidney Transplantation

Preoperative dialysis therapy is commonly unnecessary in cases in which PEKT is planned. However, some patients require preoperative dialysis therapy due to the unexpected progression of chronic renal disorder or wrong-going preoperative management. The choice of RRT before PEKT is difficult in some cases. Preoperative RRT should be carefully prepared without interference with the initiation of PEKT. In particular, the occurrence of complications of infectious disease related to dialysis access should be avoided. Before PEKT, immunosuppressive therapy is induced for protection from the occurrence of acute rejection as preconditioning. If ABO-incompatible or HLA mismatch kidney transplantation is planned, relatively potent immunosuppressive therapy will be performed before the operation to protect against acute humoral rejection caused by accelerated production of donor-specific antibodies. Preoperative immunosuppression may lead to infection related to dialysis access, which prevents the performance of scheduled PEKT. In consideration of short-term dialysis before PEKT, the appropriate selection of therapy and access that is advantageous for short-term dialysis is important. A tunneled cuffed catheter (TCC) is available for the preoperative condition. In TCC insertion, operation procedure is easier and less invasive than that of arteriovenous fistula (AVF) and PD catheter insertion. AVF may affect cardiac function according to AVF blood volume, and PD catheter operation may require general anesthesia. Both dialysis accesses cannot be used for dialysis therapy immediately after the access operation, and the access removal operation has a greater burden compared to the removal of TCC. TCC could be one of the options to be selected as dialysis access for patients in pre-PEKT condition.

Furthermore, recent advancement in medical equipment including ultrasonography have made it easier to approach blood vessels. Direct puncture of the central vein has been applied to cases requiring emergent dialysis or short-term dialysis. The puncture method using advanced ultrasonography can be one of the useful tools as dialysis access for patients in pre-PEKT condition.

6. Preemptive Kidney Transplantation and Dialysis Access for Pediatric Patients

Kidney transplantation is preferred for pediatric patients with ESKD. PEKT should be the first choice of RRT for pediatric patients with chronic renal failure. Both VA and peritoneal access are barriers for pediatric patients. PD is often selected when PEKT is difficult to choose for various reasons, such as transplant donor source or physical reasons. However, PD in pediatric patients sometimes causes complications related to peritoneal access, such as abnormal catheter positioning, due to the narrow abdominal cavity. Moreover, PD has no tolerance for long-term treatment, forcing RRT to change

after a certain period of the first RRT. If immediate induction of dialysis therapy is needed, TCC can be easily used and operated for the pediatric patients. AVF or AVG for pediatric patients is a barrier for several reasons. One of the reasons is that narrowing of vessels causes difficulty in surgical procedures and affects hemodynamics in small circulation. In a large national sample of pediatric patients with ESKD, significant graft and patient survival benefits were demonstrated in both living and deceased donors of PEKT. Among 7527 pediatric recipients over a 13 year study period, compared with children who underwent PEKT, those undergoing dialysis before transplantation experienced much higher rates of graft failure (HR 1.32, 95% CI: 1.10–1.56) and death (HR 1.69, 95% CI: 1.22–2.33) [37]. Various clinical studies have documented equivalent outcomes and modest survival benefits for pediatric PEKT recipients [6–8,38,39]. Considering the particular physical and mental condition of pediatric patients, PEKT is the best choice for RRT.

7. Apheresis Therapy for Preconditioning of PEKT

Pre-existing alloantibodies directed against donor human leukocyte antigens (HLA) and blood group antigens are widely prevalent in the subpopulation and affect clinical outcomes of kidney transplantation [40–42]. The appropriate desensitization protocol is essential for the success of kidney transplantation in patients with preformed donor specific antibody (DSA), such as anti-ABO-blood-group-antibody and anti-HLA-antibody. Acute antibody-mediated rejection (AMR) due to preformed DSA sometimes occurs in recipients of ABO-incompatible kidney transplantation and patients with donor-specific HLA antibody in the absence of proper desensitization. AMR may cause graft loss by excess antibody production and complement activation in the early stage after kidney transplantation. The desensitization protocol varies at each transplant center, and several desensitization protocols have been used to prevent AMR. These protocols have increased the success rate in sensitized recipients [41,43,44]. The common desensitization protocol includes pretransplant apheresis, induction therapy with anti-CD20 antibody and intravenous immunoglobulin, and maintenance therapy with immunosuppressive drugs [45–48]. Therapeutic apheresis is essential for prevention of AMR, and is commonly performed as plasmapheresis, double filtration plasmapheresis, or immune absorption [48–50].

The purpose of apheresis is removal of preformed DSA with extracorporeal circulation. Temporary VA is essential for pretransplant apheresis therapy. Patients undergoing dialysis therapy have permanent vascular access such as AVF, AVG or TCC. On the other hand, patients scheduled for PEKT have no permanent VA and require temporary VA for apheresis therapy. Temporary catheter insertion in the central vein is the common method for apheresis therapy for desensitization. TCC can be selected for performing apheresis as preconditioning, because it has the advantage of protection from general infection due to the presence of subcutaneous tunnel and cuff. Potent immunosuppressive therapy is performed for sensitized patients, which can be followed by conditions prone to systemic infection. The occurrence of sepsis following VA infection may lead to the discontinuation or postponement of transplantation.

When TCC is inserted for apheresis therapy as preconditioning, it needs to be removed after successful sensitized transplantation. However, TCC should not be removed just after transplantation because of the high incidence rate of acute AMR within two weeks post operation in the case of ABO-incompatible kidney transplantation [51]. Considering that catheter placement is required for a few weeks, TCC may be one of the options for VA for PEKT in an ABO-incompatible recipient. Moreover, the direct puncture of central vein under echo guidance is also useful method for the rescue treatment of AMR. The latest centrifugal plasma exchange method needs minimal circulation blood volume and can be safely performed by peripheral intravenous route, such as elbow vein. The appropriate vascular access for apheresis therapy should be selected from several options for patients scheduled ABO-incompatible kidney transplantation.

8. Conclusions

PEKT may be the best option for RRT in suitable patients with ESKD. However, in some cases, dialysis access might be required before PEKT. The management of protection from complications caused by immunosuppressants in the preoperative and perioperative periods is important in these cases. The best sequential RRT should be considered a lifelong treatment for each patient with ESKD, and PEKT may be the best initial treatment option. The correct selection of access, whether VA or peritoneal access, may lead to a successful goal of RRT, including PEKT.

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