Efficacy and Safety of Phenylephrine in the Management of Low Systolic Blood Pressure after Renal Transplantation

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BACKGROUND: Phenylephrine can be used to treat postoperative hypotension after renal transplantation. However, its effect on the renal allograft is unknown. We evaluated the safety and efficacy of this approach.

STUDY DESIGN: A retrospective cohort study of 307 renal transplant recipients between November 2005 and October 2011 was conducted, including 75 who required phenylephrine, 46 of whom were deceased donors renal transplant (DDRT) recipients and 29 who were living donor transplant (LDRT) recipients. These were compared with 75 controls matched by sex, age, type of transplant, and etiology of renal failure. The primary outcome was rate of delayed graft function (DGF). The following statistical tools were used: paired *t*-test for continuous data, McNemar's test for categorical data, and a nonlinear mixed decay model for change in serum creatinine (Cr).

RESULTS: Of 46 DDRT recipients who required phenylephrine, 17 developed DGF compared with 10 matched controls (relative risk [RR] 2.9, CI 1.4 to 6.0, $p = 0.0040$). Only one LDRT recipient required hemodialysis (DGF). No differences were noted in the number of hemodialysis treatments required (mean 2.7 in treatment group vs 3.4 in control). No significant differences were observed between phenylephrine and control groups in renal function on postoperative days 30, 90, and 365 Cr or graft survival. The immediate postoperative normalization of Cr was slower in the DDRT phenylephrine group compared with DDRT controls ($p < 0.0001$), but no difference in Cr was noted before discharge ($p = 0.49$).

CONCLUSIONS: Although there is a brief association between phenylephrine administration and a slower rate of transplanted kidney recovery, there is no clinically or statistically significant impaired outcome in the phenylephrine group at time of discharge. Administration of phenylephrine to support low blood pressure after renal transplant appears safe. (J Am Coll Surg 2014;218: 1207−1214. © 2014 by the American College of Surgeons)

Acute tubular necrosis (ATN) is a common phenomenon after kidney transplantation, resulting from perioperative tissue ischemia to the renal allograft. Acute tubular necrosis is responsible for the majority of delayed graft function (DGF)[1] and approximately 90% of post-transplant acute renal failure.[2] The long-term effects of post-transplant ATN include development of interstitial fibrosis,[3] impaired long-term graft function,[4-6] and possibly, inferior recipient survival.[1,7] Furthermore, once the allograft has developed ATN, the treatment is largely supportive, possibly requiring hemodialysis. Prevention of ischemia is therefore of utmost importance in the immediate postoperative renal transplant period.

A number of risk factors for graft ischemia arise from a combination of donor and recipient factors.[8] These include donor age and quality, the stress of brain death, organ preservation, cold storage and recipient hemodynamics including circulating volume, cardiac function, and systemic blood pressure. The transplanted kidney may be predisposed to "normotensive ATN," as ischemia/reperfusion injury and impaired vascular autoregulation lead to renal ischemia despite normal blood pressure.[9] The transplanted kidney is also subject to transient hypotension due to the effects of general anesthesia,[10] intraoperative fluid shifts,

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Abbreviations and Acronyms

ATN = acute tubular necrosis
Cr = serum creatinine
DDRT = deceased donor renal transplant
DGF = delayed graft function
LDRT = live donor renal transplantation
POD = postoperative day
SBP = systolic blood pressure

and impaired cardiac output. Prolonged cold ischemia time,[11,12] donor hypotension, intraoperative hypotension,[13] poor perioperative perfusion,[1,14] and even preoperative recipient low baseline blood pressure[15] are all risk factors for ATN, DGF, and primary allograft nonfunction.

Certain patient populations, such as recipients of deceased donor renal transplants (DDRT) compared with living donor renal transplants (LDRT),[16] elderly donors, elderly recipients,[17] or allografts meeting extended donor criteria[18] may be especially predisposed to development of ATN and its complications. Kidneys transplanted from donors after circulatory death are at particularly high risk for DGF.[8]

Various strategies to optimize blood flow to the newly transplanted kidney are used to counteract these risks, thereby preventing ATN and its sequelae. The approach to oliguria associated with low systolic blood pressure (SBP) varies greatly between centers and includes expectant management, further volume resuscitation, and administration of vasopressors or inotropic agents. Both the lack of published experience and the variety of approaches motivated us to further study the topic.

Treatment of the donor and recipients in the perioperative period to minimize ischemia has been attempted with aggressive hydration of donors and recipients,[19] harvesting kidneys from heart-beating cadavers, using neuraxial anesthesia,[10] hyperbaric oxygen,[20] and both normothermic[21] and hypothermic[22,23] organ preservation, with or without machine perfusion.[24,25] Dopamine infusions in the organ donor correlate with reduced incidence of DGF.[26] However, there are few studies on the effect of vasopressor agents on newly transplanted renal allografts.

The addition of vasopressor agents present an attractive alternative to isolated intravenous fluid resuscitation in the end-stage renal disease patient population, given a relatively high incidence of cardiovascular and pulmonary disease,[27] which predisposes these patients to adverse sequelae of fluid overload. Most previous research on the impact of vasopressor agents on kidney function has centered on dopamine receptor agonists, investigated extensively for acute renal failure prevention in critically ill patients.[28,29] Dopamine and other catecholamines have also been investigated for their specific role after renal transplantation, with varying reports on their efficacy.[29-31] Phenylephrine is a direct α-agonist, which has not similarly been investigated for its role in post-transplant kidney function.

We examined the routine use of phenylephrine for hypotension, defined as SBP less than 120 mmHg with oliguria or less than 110 mm Hg in the immediate post-transplant period. We hypothesized that increasing systemic blood pressure after renal transplantation with a phenylephrine infusion would improve renal perfusion and reduce ATN. We primarily studied the safety of this approach and its impact on the incidence of DGF, or the need for postoperative hemodialysis. Secondary endpoints included patient and allograft survival, and allograft function in the immediate postoperative period and up to 1 year after transplantation.

METHODS

This study was approved by the Rhode Island Hospital Institutional Review Board. This research was conducted in compliance with institutional standards of ethics. We conducted a retrospective, matched case-control study, sampled from all renal transplant recipients who received either LDRT or DDRT between November 2005 and October 2011 at a single tertiary care hospital. The patients included were routinely treated by a protocol that incorporates routine initiation of phenylephrine administration for SBP less than 120 mmHg with oliguria or less than 110 mmHg. We chose a higher SBP to optimize perfusion of the new renal allograft after having consistently observed oliguria in patients immediately after renal transplantation when the SBP is 90 to 110 mmHg, technically in the normal range, but apparently inadequate to perfuse the transplanted kidney (Fig. 1).

A treatment group of 75 patients who required phenylephrine was identified by cross-referencing our institution's pharmacy medication administration database with our departmental database of renal transplant recipients. A control group of 75 patients was then generated from this renal transplant database that best matched each phenylephrine group patient for sex, age at transplantation, etiology of end-stage renal disease, and type of transplantation (LDRT or DDRT) during this treatment period. Four patients who developed sepsis or cardiac complications and required administration of multiple vasopressor agents outside the phenylephrine protocol or admission to the ICU were excluded.

All patients received ABO-compatible renal transplants from crossmatch negative donors. Transplantation of a