Vasopressin for Post-kidney Transplant Hypotension

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Introduction: Hypotension after deceased donor kidney transplant (DDKT) is a risk factor for delayed graft function (DGF) and poor graft survival (GS). We hypothesize that vasopressin use in hypotensive DDKT recipients (DDKTRs) to increase blood pressure (BP) reduces DGF rates and is safe without increasing mortality.

Methods: Group with vasopressin "study group" ($n = 45$) was defined as DDKTRs between 2012 and 2017 who required vasopressin for hypotension systolic BP (SBP) <120 mm Hg or diastolic BP (DBP) <60 mm Hg. DDKTRs with no-vasopressin "comparison group" ($n = 90$) were propensity score-matched DDKTRs between 2012 and 2017 without vasopressin use. Primary outcomes were GS, creatinine and allograft biopsy rate at 1 year, DGF rate, and death during transplant hospitalization.

Results: Vasopressin group had lower mean maximum and minimum SBP and DBP in the operating room (OR). Median vasopressin start time post-DDKT was 2 hours (interquartile range [IQR] 1–6), and duration of use was 42 hours (IQR 24–63). DGF, creatinine at 1 year, and allograft biopsy rates were comparable. No deaths occurred during transplant hospitalization. Multivariable analysis did not find an effect of vasopressin use on GS.

Conclusion: Treatment of hypotensive DDKTRs with vasopressin is safe and facilitated similar graft function and survival with that of nonhypotensive patients. In the absence of a randomized control trial, our study supports the safety of vasopressin therapy to prevent the adverse effects of hypotension.

Hypotension before, during, and after DDKT is associated with worse outcomes, increased rates of DGF, and poor GS.[1,2] Hypotension in people requiring dialysis can be multifactorial including owing to hypovolemia, autonomic neuropathy, vascular calcifications, arteriopathy, and from polypharmacy for management of hypertension. In the immediate perioperative period, this can result in several complications to the DDKTRs because of hypoperfusion and demand ischemia including cardiac hypoperfusion, arrhythmias, myocardial injury, stroke, and alteration of mental status.

From a transplant perspective, the most important effect of hypotension is graft hypoperfusion. This leads to DGF from ischemia and reperfusion injury and contributes to low urine output. Low urine output combined with significant shifts in fluids during and after surgery can lead to clinical complications related to intravascular volume overload. Traditionally, in clinical situations with low BP, such as septic shock, norepinephrine and vasopressin are used to improve clinical stability and improve or maintain perfusion. Similarly, in cardiogenic shock, dobutamine or dopamine is commonly used. However, these pressors have significant risks for arrhythmias compared with vasopressin.

The use of vasopressin postoperatively in DDKTRs with hypotension has become standard of care at many

centers, including ours, but there are no controlled studies. Given the significant effects of hypotension on the graft and recipient, our study aims to evaluate the effects of vasopressin on graft function among DDKTRs with hypotension. We hypothesize that vasopressin use to increase BP among DDKTRs results in improvement of renal function within the first year, reduces DGF rates, and is safe without increase in mortality.

METHODS

Study Design

A matched pairs study design was used, and all DDKTRs who required at least 6 hours of vasopressin for hypotension defined as SBP of <120 mm Hg or DBP of <60 mm Hg between January 1, 2012, and December 31, 2017, were included as "vasopressin group" (n = 45) referred to as "study group." In this group, vasopressin was used as the primary pressor of choice and dopamine or norepinephrine as the secondary pressor

of choice. Owing to patient's level of care at the time hypotension was noted (i.e., medical/surgical ward bed) and pressor administration protocols at our institute, secondary pressor, that is, dopamine, was administered first until the DDKT recipient could be transferred to the intensive care unit (ICU). In certain DDKTRs, both were ordered simultaneously with dopamine given first. In both these instances on transfer to the ICU, vasopressin was started and maximized first with weaning of dopamine. In those who remained hypotensive despite maximum vasopressin dose, dopamine was re-added to reach target BP. All patients who required vasopressin for septic, hemorrhagic, or cardiogenic shock were excluded. "No-vasopressin group" referred to as comparison group was matched DDKTRs between January 1, 2012, and December 31, 2017, who were normotensive and did not require vasopressin (Figure 1). Normotensive DDKTRs who were noted to have lower than expected urine output were administered dopamine only. Comparison group was selected by using propensity score
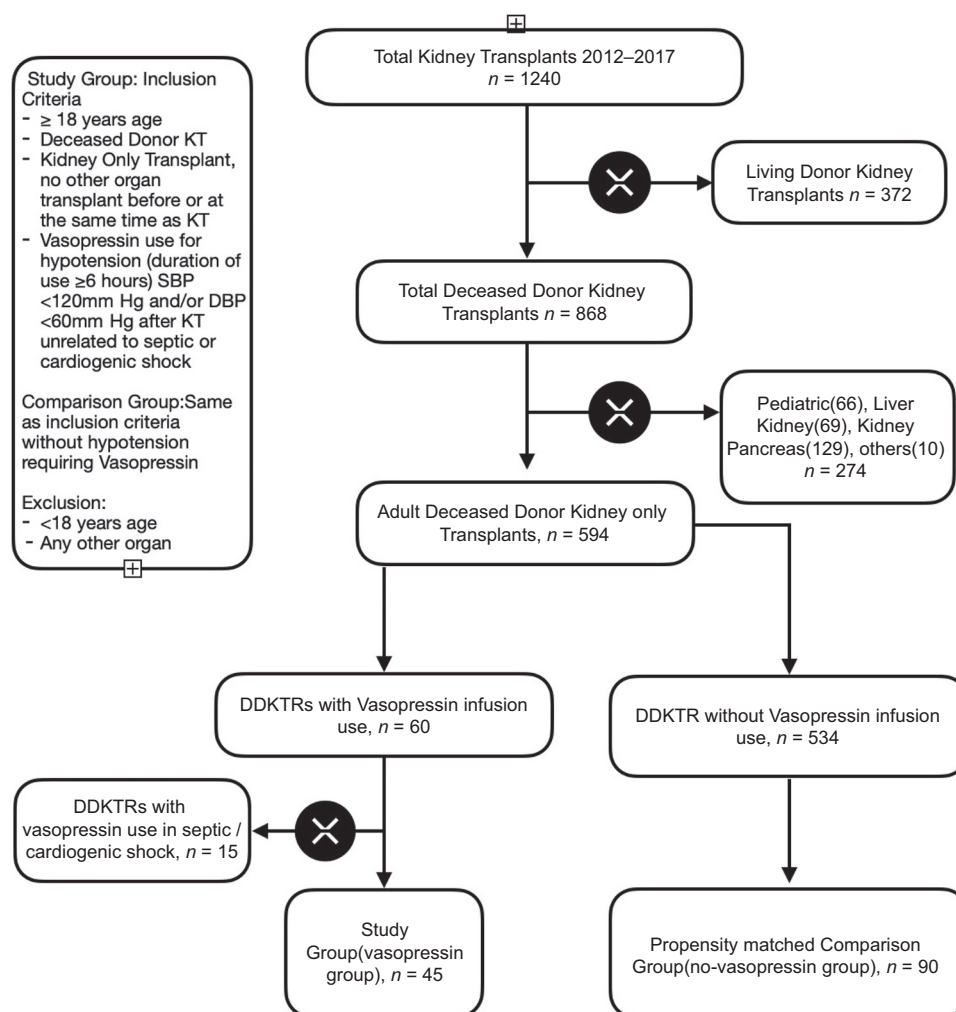
Figure 1. Study diagram, selection of study group, comparison group, inclusion and exclusion criteria. DBP, diastolic blood pressure; DDKTR, deceased donor kidney transplant recipient; KT, kidney transplantation; SBP, systolic blood pressure.

matching based on age, race, sex, cold ischemia time, warm ischemia time, donor type and whether the recipient had diabetes or not ($n = 90$). A logistic regression model was used for computing the propensity scores. Two-to-one optimal matching was done with 2 DDKTRs in the comparison group for every 1 DDKTR in the study group using the abovementioned variables. Standard maintenance immunosuppression protocol at our center was used for both groups consisting of tacrolimus titrated to a trough level of 8 to 10 ng/ml and mycophenolic acid without maintenance steroids. All biopsies performed were for-indication only, and no surveillance biopsies were performed as per practice at our center. All donor kidneys were machine perfused as per standard practice at our center. The primary outcome was death-censored GS at 1 year. Secondary outcomes of efficacy included creatinine at 1 year, need for allograft biopsy, and findings of rejection on biopsy, DGF rates, and death-censored GS at 3, 5, and 8 years. Secondary outcomes of safety were mortality, occurrence of hyponatremia, complication rates including infections, atrial fibrillation with rapid ventricular response, cardiovascular events, and length of stay in the hospital and ICU. Study design was approved by the Indiana University Institutional Review Board, and compliance was ensured with the Declaration of Helsinki regarding ethical standards as set forth for all transplants reviewed in the study.

Statistical Methods

Data collection was done with Statistical Package for Social Sciences version 27 (IBM Corporation, Armonk, NY). Data were exported to SAS version 9.4 (SAS Institute, Cary, NC) for analysis. Continuous variables were summarized using mean and SD or median and IQR depending on the variable distribution. Categorical variables were summarized using frequency and percentages. Group differences were assessed using t test or Wilcoxon rank sum test for continuous variables and χ^2 test or Fisher exact test for categorical variables. Overall GS was calculated from date of transplant to date of graft failure or date of death from any cause. Patients who remained alive and failure free were censored at their last known alive date. GS was also calculated with death as a censoring event (death-censored GS). GS probabilities were estimated using the Kaplan–Meier method. A Cox proportional hazards model was used to evaluate the association between risk factors and GS. The following risk factors were considered for the Cox model: recipient characteristics (age, gender, race, diabetes as cause of end-stage kidney disease [ESKD], whether patient was on dialysis before transplant, dialysis duration, and surgery duration), donor characteristics (cold ischemia time, warm ischemia time, donor type, and age), and transplant outcomes (DGF and rejection). Variables with $P < 0.10$ in the univariable analyses were included in a multivariable Cox regression model. Models were constructed for overall GS and death-censored GS. $P < 0.05$ was considered statistically significant.

RESULTS

Recipient Characteristics

Propensity score matching ensured that key variables were not statistically significant among the 2 groups Figure 2. The most common etiology for ESKD was hypertension. Median time on dialysis was 1717 days for the study group and 1685 days for the comparison group with no statistically significant difference. Cardiovascular comorbidities were comparable between the 2 groups. Mean cardiac ejection fraction was
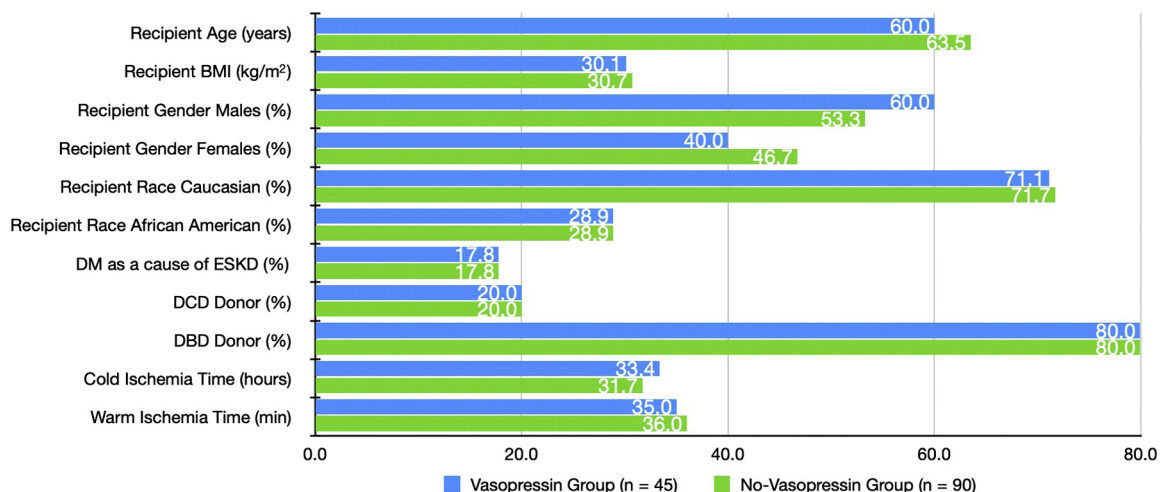
Figure 2. Comparison of vasopressin group (study group) and no-vasopressin group (comparison group): propensity-matched groups. BMI, body mass index; DBD, brain dead donor; DCD, donation after cardiac death; DM, diabetes mellitus; ESKD, end-stage kidney disease.

comparable among cases 60.2 ± 7.9% versus 62.5 ± 7.5% in controls ($P = 0.10$). Hemodialysis was the most common dialysis modality before DDKT (Table 1).

Donor and Transplant Characteristics

Median donor age was 41 years among the study group and 40.3 years in the comparison group. Furthermore, 20% of the donors in each group comprised donation after circulatory death. Most of the donors were male. Largest group of donors had blood type A followed by blood type O. Mean kidney donor profile index was 45.2 ± 22.9 in the study group versus 43 ± 22.5 among the comparison group. Cold and warm ischemia times were comparable owing to propensity score matching.

Antithymocyte globulin was used in 91% of the patients in each group which is the standard induction regimen at our center (Table 2).

Intraoperative and Post-transplant Characteristics

Median total OR time was 2.8 hours among the study group and 2.7 hours in the comparison group ($P = 0.69$). Any procedure other than transplant was considered additional. Frequency of additional procedures was similar in both groups. Mean maximum SBP during OR was 137.0 ± 20.4 mm Hg among the study group, whereas it was significantly higher at 166.9 ± 21.8 mm Hg in the comparison group ($P < 0.0001$). Mean lowest SBP in the OR was not significantly different between the study group (90.8 ± 15.2 mm Hg) and comparison group (95.6 ± 15.1 mm Hg). There was a statistically significant difference between these 2 groups for mean peak and lowest DBP in the OR (Table 3).

Post-DDKT serial laboratory values for serum sodium, blood urea nitrogen, and creatinine were recorded to assess for trends. There was no significant clinical or statistical difference between median serum

Table 1. Recipient characteristics

Variable	Vasopressin group ($n = 45$)	No-vasopressin group ($n = 90$)	P value
Recipient age (yr)	60 (52–69)	63 (53–68)	0.90
Recipient BMI (kg/m^2)	30.1 ± 6.2	30.7 ± 5.7	0.53
Number of HTN meds	1 (0–2)	2 (1–3)	0.05
Time on dialysis (d)	1717 (876–2967)	1685 (1121–2373)	0.82
Recipient gender, n (%)			0.71
Female	23 (51.5)	50 (55.6)	
Male	22 (48.9)	40 (44.4)	
Recipient race, n (%)			1.00
Caucasian	32 (71.1)	64 (71.1)	
African American	13 (28.9)	26 (28.9)	
Etiology of ESKD, n (%)			0.59
HTN	13 (28.9)	31 (34.4)	
GN	15 (33.3)	16 (17.8)	
DM	8 (17.8)	16 (17.8)	
PKD	3 (6.7)	11 (12.2)	
Vasculitis	1 (2.2)	2 (2.2)	
Congenital	1 (2.2)	3 (3.3)	
Others	4 (8.9)	11 (12.2)	
Previous transplant	9 (20)	12 (13.3)	0.31
Midodrine pretransplant	10 (22.2)	5 (5.6)	0.0037
Atrial fibrillation	6 (13.3)	3 (3.3)	0.06
Diastolic heart failure	14 (31.1)	23 (26.1)	0.54
Pulmonary HTN	10 (22.2)	19 (21.6)	0.93
Ejection fraction (%)	60.2 ± 7.9	62.5 ± 7.5	0.10
Dialysis modality, n (%)			0.25
HD	33 (73.3)	65 (72.2)	
PD	9 (20)	10 (11.1)	
PD then HD	1 (2.2)	1 (1.1)	
HD then PD	0 (0)	2 (2.2)	
Not on dialysis	2 (4.4)	12 (13.3)	
Recipient and donor CMV status, n (%)			1.00
CMV donor + to recipient neg	9 (20.0)	17 (18.9)	
Other combinations	36 (80.0)	73 (81.1)	
Recipient blood group, n (%)			0.67
A	22 (48.9)	37 (41.1)	
O	17 (37.8)	40 (44.4)	
B	4 (8.9)	11 (12.2)	
AB	2 (4.4)	2 (2.2)	

BMI, body mass index; CMV, cytomegalovirus; DM, diabetes mellitus; ESKD, end-stage kidney disease; GN, glomerulonephritis; HD, hemodialysis; HTN, hypertension; PD, peritoneal dialysis; PKD, polycystic kidney disease.

Table 2. Donor and transplant characteristics

Variable	Vasopressin group ($n = 45$)	No-vasopressin group ($n = 90$)	P value
Donor type, n (%)			1.00
Brain dead donor	36 (80.0)	72 (80.0)	
DCD donor	9 (20.0)	18 (20.0)	
Donor age (yr)	41 (27–53.8)	40.3 (25–52.1)	0.74
Donor gender, n (%)			0.46
Female	18 (40.0)	42 (46.7)	
Male	27 (60.0)	48 (53.3)	
Donor KDPI	45.2 ± 22.9	43.0 ± 22.5	0.66
Laterality of transplanted kidney, n (%)			0.81
Right	23 (51.1)	48 (53.3)	
Left	22 (48.9)	42 (46.7)	
Donor terminal creatinine (mg/dl)	0.9 (0.7–1.3)	0.7 (0.6–1.2)	0.45
Donor blood group, n (%)			0.79
A	22 (48.9)	38 (42.2)	
O	18 (40.0)	40 (44.4)	
B	3 (6.7)	9 (10.0)	
AB	2 (4.4)	3 (3.3)	
Warm ischemia time (min)	35 (32–40)	36 (32–41)	0.34
Cold ischemia time (h)	33.4 ± 11.9	31.7 ± 12.2	0.44
HLA mismatch	4 (3–5)	4 (3–5)	0.26
PRA class I	0 (0–10.5)	0 (0–0)	0.06
PRA class II	0 (0–5)	0 (0–0)	0.56
Induction immunosuppression, n (%)			1.00
ATG	41 (91.1)	82 (91.1)	
ATG + rituximab	4 (8.9)	8 (8.9)	
Plasmapheresis			1.00
PLEX required	2 (4.4)	3 (2.5)	

ATG, antithymocyte globulin; DCD, donation after circulatory death; HLA, human leukocyte antigen; KDPI, kidney donor profile index; PLEX, plasma exchange; PRA, panel-reactive antibody.

Table 3. Intraoperative and postoperative characteristics

Variable	Vasopressin group (n = 45)	No-vasopressin group (n = 90)	P value
Total surgery time (h)	2.8 (2.4–3.2)	2.7 (2.3–3.3)	0.69
Additional procedure done, n (%)	10 (22.2)	25 (27.8)	0.49
Additional procedure type, n (%)			0.24
Native nephrectomy	5 (50)	11 (44)	
Arterial reconstruction	3 (30)	4 (16)	
Hernia repair	0 (0)	7 (28)	
Arterial reconstruction + hernia repair	0 (0)	1 (4)	
Native nephrectomy + arterial reconstruction + other	1 (10)	0 (0)	
Native nephrectomy + other, n (%)	0 (0)	1 (4)	
Other	1 (10)	1 (4)	
OR max SBP (mm Hg)	137.0 ± 20.4	166.9 ± 21.8	<0.0001
OR min SBP (mm Hg)	90.8 ± 15.2	95.6 ± 15.1	0.09
OR max DBP (mm Hg)	71.1 ± 14.9	89.5 ± 14.9	<0.0001
OR min DBP (mm Hg)	41.4 ± 9.3	48.1 ± 9.2	0.0001
Sodium 36/48 h post-transplant (mmol/l)	138.8 ± 3.5	139.0 ± 3.0	0.67
BUN 24 h post-transplant (mg/dl)	52.7 ± 16.0	46.3 ± 17.2	0.0387
Creatinine (mg/dl)			
12 h post-transplant	7.2 ± 2.8	6.3 ± 2.9	0.11
24 h post-transplant	6.9 ± 3.0	5.4 ± 2.9	0.0088
Urine output (ml)			
12 h post-transplant (ml)	560.0 (262–1245)	2347.5 (1290–3650)	<0.0001
24 h post-transplant (ml)	2305.0 (939–3471)	4642.5 (2845–6800)	<0.0001
Total fluid in 24 h post-transplant (ml)	6767.9 ± 2729.4	8479.1 ± 3268.9	0.0030
Net fluid status 24 h post-transplant (ml)	4283.0 ± 2531.7	3853.5 ± 2588.5	0.36
Time to start vasopressin post-transplant (h)	2 (1–6)	N/A	-
Starting vasopressin dose (units/h)	2 (2–3)	N/A	-
Maximum vasopressin dose (units/h)	4 (2–5)	N/A	-
Duration of vasopressin use (h)	42 (24–63)	N/A	-
Dopamine for low UOP, n (%)	N/A	14 (100)	
Time to start dopamine for low UOP (h)	N/A	2.8 (1–19)	-
Total duration of dopamine use (h)	N/A	39.5 ± 14.6	-
Starting dose of dopamine (mcg/kg/min)	N/A	3 (3–3)	-
Max dose of dopamine (mcg/kg/min)	N/A	3 (3–3)	-
Secondary pressor required, n (%)	22 (48.9)	N/A	-
Name of secondary pressor, n (%)		N/A	-
Dopamine	18 (81.8)		
Nor epi	4 (18.2)		
Time to start secondary pressor post-transplant	1 (1–6)	N/A	-
Starting dose of secondary pressor (mcg/kg/min)	5 (3–5)	N/A	-
Duration of secondary pressor use (h)	75.5 (7–144)	N/A	-
Need to use additional pressor, n (%)	4 (8.9)	N/A	-
Furosemide infusion, n (%)	20 (44.4)	10 (11.1)	<0.0001

BUN, blood urea nitrogen; DBP, diastolic blood pressure; max, maximum; min, minimum; N/A, not applicable; OR, operating room; SBP, systolic blood pressure; UOP, urine output.

sodium in both groups. Trends of creatinine and donation after circulatory death clearance in the first 12 and 24 hours showed lower creatinine and donation after circulatory death in the comparison group compared with the study group. Difference in mean creatinine (6.9 ± 3.0 vs. 5.4 ± 2.9, $P = 0.0088$) and donation after circulatory death (52.7 ± 16 vs. 46.3 ± 17.2, $P = 0.0387$) levels at 24 hours post-DDKT were statistically significant between the groups. Median urine output at 12 and 24 hour was 560 ml in the study group and 2347.5 ml in the comparison group ($P < 0.0001$) and 2305 ml in the study group and 4642.5 ml in the comparison group ($P < 0.0001$), respectively.

Vasopressin Use, Dose, and Duration

Median time to start vasopressin post-DDKT was 2 (IQR 1–6) hours. Starting vasopressin dose was 2 (IQR 2–3) units/h, and median maximum dose used was 4 units/h. Median duration of vasopressin use was 42 (IQR 24–63) hours. When maximum dose of vasopressin was used and patients' BP was still below target SBP of 120 mm Hg or DBP of 60 mm Hg consistently, infusion of a secondary pressor was added to vasopressin. This was required in 48.9% of the cases ($n = 22$). Among these, 82% had dopamine whereas 18% had norepinephrine. Median time to start secondary pressor was 1 (IQR 1–6) hour

post-transplant, and median duration of use was 75.5 (IQR 7–144) hours. A third pressor was used in 8.9% of patients to meet BP goal. Vasopressin and norepinephrine infusions were only administered in the ICU setting whereas dopamine infusion could be infused at a fixed rate in the non-ICU setting. DDKTRs among the comparison group who had lower urine output had infusion of dopamine. Only 15.6% of such DDKTRs in the comparison group required this and was started at a median time of 2.8 hours with mean duration of 39.5 ± 14.6 hours. None among the comparison group required an additional pressor (Table 4).

Outcomes and Survival Comparison

DGF rate, defined as need for dialysis during transplant hospitalization, was comparable between the study (6.7%) and comparison (5.6%) groups. Similar to creatinine levels at 24 hours, difference in creatinine was noted at discharge (1.9 vs. 1.5, $P = 0.0433$). Despite these early changes, creatinine at 12 months was not statistically different (1.3 vs. 1.2, $P = 0.45$). Comparable rates of allograft biopsies were performed. The median follow-up time from transplant to last visit was 3.9 years in the study group and 5.3 years in the comparison group ($P = 0.16$). No patient died in either group during transplant hospitalization. Overall, 1-year GS was 95.5% among the vasopressin group versus 98.9% in the no-vasopressin group ($P = 0.30$), and 5-year GS was 73.6% in the vasopressin group versus 79.6% in the no-vasopressin group ($P = 0.50$). Death-censored GS at 1 year was not different: 100% among study group versus 98.9% in comparison group ($P = 0.31$). Kaplan–Meier survival curves are shown in Figures 3-5 and 5 (Table 5).

Univariable and Multivariable Analyses for GS

Univariable analysis (Table 5) of GS showed male sex, diabetes as a cause of ESKD, and surgery duration as independent risk factors for poor GS. Multivariable model (Table 6) showed that DDKTRs with diabetes as the cause of ESKD had an increased hazard of kidney graft failure compared with nondiabetic DDKTRs (hazard ratio [HR] = 3.03, 95% CI = 1.46–6.29, $P = 0.0030$), but it has no effect on graft failure in the study group versus comparison group (HR = 1.43, 95% CI = 0.71–2.89, $P = 0.32$).

Death-censored GS univariable analysis showed race and rejection during the first year as significant factors. These risk factors persisted in multivariable analyses where, similar to overall GS, the study group did not experience a significantly different hazard of kidney graft failure compared with the comparison group

(HR = 0.57, 95% CI = 0.16–1.99, $P = 0.38$) (Tables 7 and 8).

DISCUSSION

Our study demonstrated equivalence in terms of our primary end point of GS and safety in the use of vasopressin post-DDKT. Given that hypotension is a major risk factor for DGF, this equivalence translates to efficacy of the approach. Previously studies have looked at pressor support among donors,[3,4] but studies on pressor use among DDKTRs are limited. Most of these were done on intraoperative pressor use, whereas few studies[5–7] looked at the use of dopamine or phenylephrine to raise SBP in the immediate post-transplant period. To our knowledge, there are no reported studies on the use of vasopressin post-DDKT, GS, and safety.

We found a consistent difference in the pretransplant midodrine and antihypertensive medication use. Our study shows that DDKTRs in the study group were on lower median BP medications compared with the comparison group (1 vs. 2) and higher percentage of DDKTRs among the study group were on midodrine. A review of US transplant registry, pharmacy, and Medicare claims data of >16,000 kidney transplant recipients showed that 1.9% of them had used midodrine before transplant.[8] This study showed higher rates of DGF, hypotension, graft failure, and death in this group compared with kidney transplant recipients who did not receive midodrine. Our study showed that those with midodrine use and lower number of antihypertensive medications also had lower intraoperative SBP and DBP and lower urine output in the first 24 hours after DDKT. BP changes persisted after DDKT. A study from Dolla et al.[1] looking at pretransplant hypotension showed that the odds of DGF were 4.5 times higher with mean BP <80 mm Hg. Further analysis of 18 paired grafts in different recipients (hypotensive vs. nonhypotensive) showed that the odds of DGF were 7 times higher compared with normotensive pairs. Pretransplant hypotension was also shown to be associated with perioperative hypotension and perioperative fluid administration of >3 L.[1] In our study, the vasopressin group received significantly less net fluid compared with no-vasopressin groups but ended up with a nonsignificant higher net positive fluid status in the first 24 hours post-DDKT owing to significantly less urine output (2.3 L vs. 4.6 L, $P < 0.0001$).

Vasopressin is preferred over other pressors, such as norepinephrine and phenylephrine, owing to its relatively safer cardiovascular profile with less risks of arrhythmias and kidney-specific actions. Vasopressin is a 9-amino acid-long derivative of antidiuretic hormone with activity on smooth muscle cells of blood vessels and kidneys.[9] Clinically, vasopressin is used to treat

Table 4. Outcomes and survival comparison

Variable	Vasopressin group (n = 45)	No-vasopressin group (n = 90)	P value
Total hospital days	10.0 (7.0–15.0)	7.0 (6.0–9.0)	<0.0001
Total ICU days	4.0 (3.0–5.0)	0.0 (0.0–0.0)	<0.0001
DGF (need for RRT post-transplant), n (%)	3 (6.7)	5 (5.6)	1.00
Atrial fibrillation post-transplant, n (%)	2 (4.4)	4 (4.4)	1.00
Creatinine			
At discharge (mg/dl)	1.9 (1.3–3.1)	1.5 (1.1–2.0)	0.0433
At 7 d (mg/dl)	2.1 (1.3–4.6)	1.5 (1.1–2.4)	0.0112
At 3 mo (mg/dl)	1.3 (1.1–1.9)	1.3 (1.0–1.5)	0.33
At 6 mo (mg/dl)	1.3 (1.1–1.7)	1.2 (1.1–1.5)	0.22
At 12 mo (mg/dl)	1.3 (1.1–1.6)	1.2 (1.0–1.6)	0.45
Need for biopsy within first year, n (%)	16 (35.6)	30 (33.3)	0.80
Rejection, n (%)			0.89
AMR/ACR	0 (0)	1 (1.1)	
ACR	11 (24.4)	24 (26.7)	
No rejection	34 (75.6)	65 (72.2)	
Severity of rejection, n (%)			0.85
Borderline	6 (54.5)	11 (44.0)	
IA	1 (9.1)	5 (20.0)	
IB	4 (36.4)	7 (28.0)	
II	0 (0)	2 (8.0)	
Follow-up time transplant to last visit (yr), median (95% CI)	3.9 (3.4–4.5)	5.3 (4.5–6.0)	0.16
Complications, n (%)			<0.0001
C diff colitis	0 (0)	2 (2.2)	
GI bleed 2/2 to ulcer	0 (0)	1 (1.1)	
HTN emergency	0 (0)	1 (1.1)	
NSTEMI	14 (31.1)	2 (2.2)	
Respiratory failure	0 (0)	1 (1.1)	
Stress-induced cardiomyopathy	0 (0)	1 (1.1)	
TTP	1 (2.2)	0 (0)	
None	30 (66.7)	82 (91.1)	
Cause of death, n (%)			0.58
COVID-19	1 (9.1)	0 (0)	
Cancer	3 (27.3)	3 (33.3)	
Cardiovascular/MI/arrest	1 (9.1)	2 (22.2)	
Cirrhosis	0 (0)	1 (11.1)	
Exsanguinating from AVF	1 (9.1)	0 (0)	
Fall	1 (9.1)	0 (0)	
Respiratory failure	1 (9.1)	2 (22.2)	
Sepsis	0 (0)	1 (11.1)	
Unknown	3 (27.3)	0 (0)	
Patient survival,[a] n (%)			
1 yr	42 (95.5)	88 (100.0)	0.15
3 yr	39 (91.0)	81 (97.8)	0.15
5 yr	13 (77.6)	50 (93.4)	0.05
8 yr	5 (65.1)	13 (83.3)	0.12
Kidney graft survival, death censored,[a] n (%)			
1 yr	42 (100)	87 (98.9)	0.31
3 yr	38 (95)	78 (94.3)	0.86
5 yr	13 (95)	48 (85.5)	0.08
8 yr	5 (83.1)	13 (78.7)	0.73
Kidney graft survival, death as an event,[a] n (%)			
1 yr	42 (95.5)	87 (98.9)	0.30
3 yr	38 (86.4)	78 (92.0)	0.35

(Continued)

Table 4. (Continued) Outcomes and survival comparison

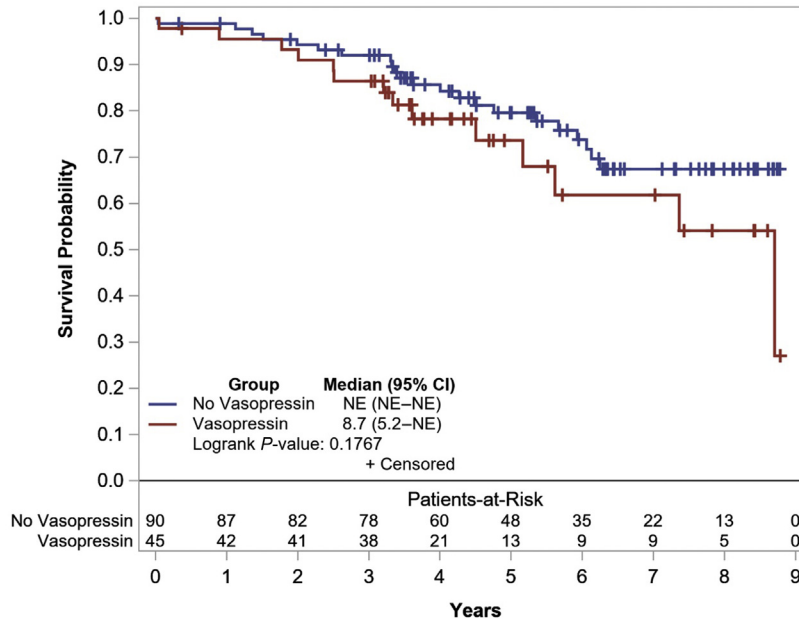| Variable	Vasopressin group (n = 45)	No-vasopressin group (n = 90)	P value
5 yr	13 (73.6)	48 (79.6)	0.50
8 yr	5 (54.1)	13 (67.4)	0.30

ACR, acute cellular rejection; AMR, antibody mediated rejection; AVF, arteriovenous fistula; C diff, *Clostridioides difficile*; DGF, delayed graft function; GI, gastrointestinal; HTN, hypertension; ICU, intensive care unit; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; RRT, renal replacement therapy; TTP, thrombotic throcytopenic purpura.
[a]Percentages were calculated using the Kaplan–Meier method which account for censoring.

hypotension related to shock, in postcardiac surgery care, cardiac resuscitation protocols, and intraoperative management of hypotension. In the kidney, medullary interstitial cells, vasa recta, and epithelial cells of the collecting duct contain vasopressin receptors.[10] Vasopressin selectively contracts efferent arterioles through vasopressin receptors but not afferent arterioles,[11] and can potentially increase glomerular filtration rate, probably leading to increase in urine output as well. It has quick onset of action with a half-life of 10 to 35 minutes, down-regulated by vasopressinases.[12] One significant factor to consider is that it is only administered in the ICU setting, potentially prolonging the length of stay in the ICU and overall in the hospital.

DGF has been shown to be a key factor in kidney function at 1 year and long-term GS.[13] The rate of DGF in the United States among DDKTRs was 29.1% in 2019.[14] This was higher among DCD-KTRs with DGF reported in 45% to 55% in 1 center's review.[15] A number of factors are implicated in the causation of DGF, including cold ischemia time, warm ischemia time, reperfusion injury, use of calcineurin inhibitors, and increased renin-angiotensin. One important cause of DGF is hypotension in the postoperative period. SBP and especially DBP have been shown to correlate with perfusion of the kidney allograft. Furthermore, the intraoperative target of SBP >120 mm Hg holds true in the postoperative time frame as well.[16] Hypotension is a risk factor for DGF, and it can be hypothesized that correcting hypotension with vasopressin should reduce DGF rates. DGF was mostly observed in DDKTRs. However, no significant difference was found in the DGF rates between the 2 groups, which may represent efficacy from raised BP among the vasopressin group making them comparable with the no-vasopressin group. Another factor is machine perfusion for kidney allografts before transplant. Kidneys in both groups were machine perfused, a standard protocol at our institute, which may have contributed to the overall decreased rates of DGF seen in our study. Previously, Cannon et al.[17] analyzed a cohort of machine-perfused kidneys against propensity-matched cold

Kidney Graft Survival (KGS) Kaplan-Meier (KM) Curve with Death as an Event
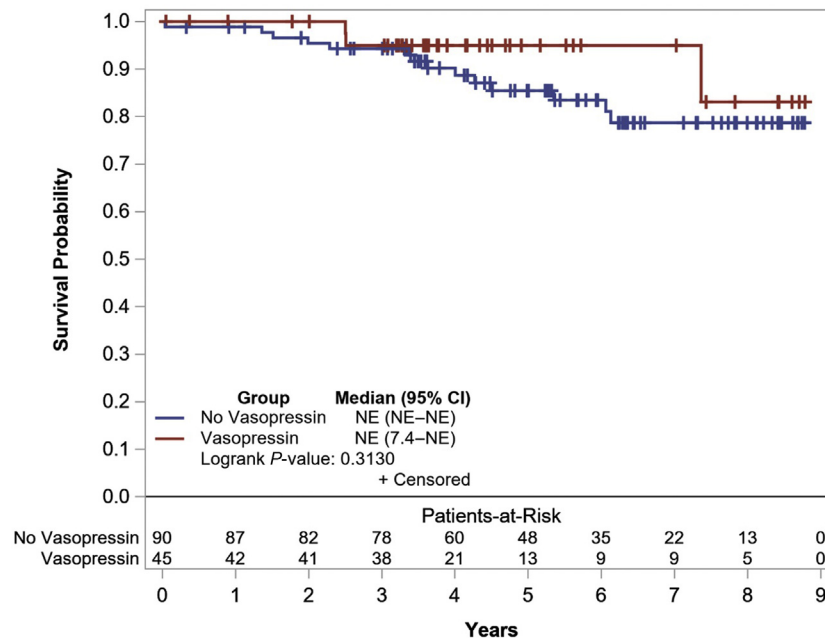

Figure 3. Comparison of overall graft survival between vasopressin group versus no-vasopressin group. KGS, kidney graft survival; KM, Kaplan-Meier; NE, not estimable (the survival curve did not cross 0.5).

storage kidneys. In addition, they also compared a cohort of paired kidneys where 1 kidney was machine perfused and the other used cold storage. Decreased incidence of DGF was seen among machine perfused kidneys compared with those using cold storage (21.1% vs. 29.1%, $P < 0.001$). A similar trend was reflected in paired kidney analysis, with rates of DGF (19.7% of the machine perfused vs. 27.5% in cold storage, $P < 0.001$).

Other known risk factors for poor GS were confirmed in our study,[18,19] and propensity matching of DGF risk factors allowed a comparison between the 2 groups to the extent possible in a retrospective study.

KGS KM Curve with Death Censored

Figure 4. Comparison of death-censored kidney graft survival between vasopressin group versus no-vasopressin group. KGS, kidney graft survival; KM, Kaplan-Meier; NE, not estimable (the survival curve did not cross 0.5).

Overall Survival KM Curve
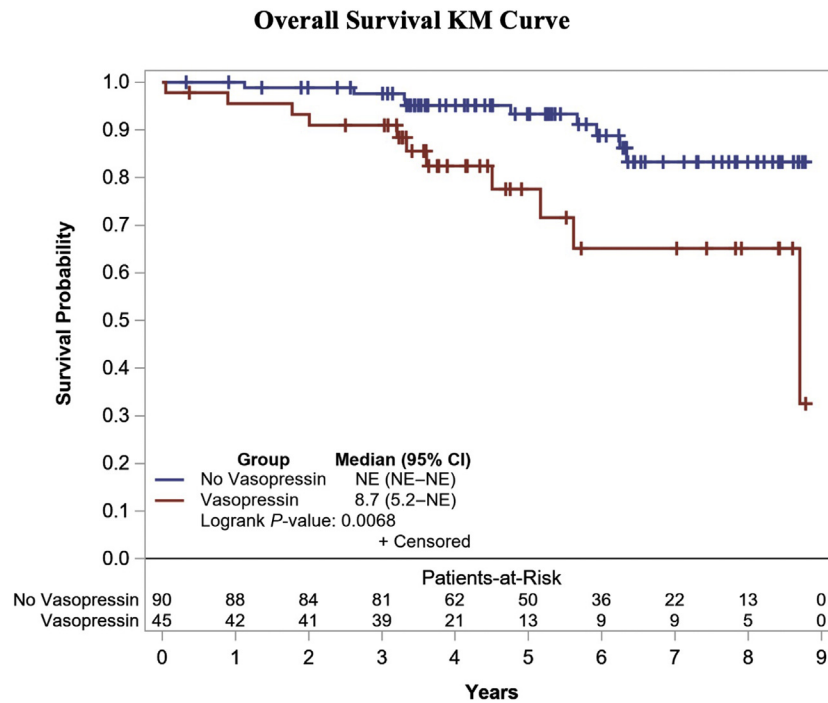
Figure 5. Comparison of overall patient survival between vasopressin group versus no-vasopressin group. KM, Kaplan-Meier; NE, not estimable (the survival curve did not cross 0.5).

With comparable death-censored GS at 1 year and potentially beyond, we hypothesize that this is related to improvement in BP and hemodynamics resulting in reduction in DGF rates. A major limitation of our study is significant confounding by indication as vasopressin was used among patients who were hypotensive, which by itself is a risk factor for DGF, cardiovascular events, and other end-organ hypoperfusion complications. *Post hoc* analysis of the folic acid for vascular outcome reduction in transplantation trial participants, who were kidney transplant recipients, found that 10 mm Hg decrease in baseline diastolic BP <70 mm Hg was associated with 31% higher relative risk of cardiovascular disease (HR = 1.31) and mortality (HR = 1.31) in a 4-year time period.[20] This reflects the adverse impact of post-DDKT hypotension and the potential improvement in outcomes with increasing blood periods in the post-DDKT period. It is plausible that hypotensive patients have impaired kidney allograft perfusion pressure that negatively affects function. Some studies reviewing the ischemia-reperfusion injury model have shown that impaired perfusion leads to poor oxygenation, and development of an environment leading to cellular injury.[21]

In our study, patients either persistently had lower BP in the OR or developed post-DDKT hypotension soon after surgery with most getting started on vasopressin within 2 hours. Moreover, the hypotension recurred once vasopressin was stopped or decreased with the median duration of vasopressin use being 42

hours. Day *et al.*[7] looked at phenylephrine requirement for post-KT hypotension and DGF. They found a higher rate of DGF and slower improvement of renal function among DDKTRs who received phenylephrine compared with controls, which became comparable by the time of discharge.[7] Management of post-DDKT hypotension is a complex and challenging problem without an established uniform approach. Most of the recipients are volume expanded owing to intraoperative volume resuscitation, being off dialysis schedule, and reduced urine output. This makes volume resuscitation less favorable. Other strategies used in this time frame include avoidance of hemodialysis or close time-limited hemodynamic monitoring. When hypotension persists despite these measures, a key intervention is the use of vasopressor agents. Data on safety and risk of arrhythmias from vasopressors have mainly been studied in septic shock because of their use indicated by default. Extrapolation of that data from a meta-analysis to compare vasopressin against dopamine shows that vasopressin is significantly less likely to cause arrhythmias compared with dopamine.[22] In our study, no difference in the rates of atrial fibrillation was seen among the 2 groups, highlighting the safety profile of vasopressin.

We show that those who received vasopressin were able to achieve renal function on par with those who did not receive vasopressin at the 1-year time frame. Serum creatinine levels were significantly different at the time of discharge (1.9 mg/dl in vasopressin group

Table 5. Univariable analysis of overall kidney graft survival

Variables	n	HR	95% CI	P value
Group, vasopressin vs. no-vasopressin	135	1.59	0.81–3.13	0.18
Recipient age, 1-yr increase	135	1.02	0.99–1.05	0.30
Recipient gender, male vs. female	135	2.36	1.19–4.70	0.0140
Recipient race, African American vs. White	135	1.67	0.84–3.32	0.14
Cold ischemia time, 1-h increase	135	0.99	0.97–1.02	0.70
Warm ischemia time, 1-min increase	135	1.00	0.96–1.03	0.80
Donor type, BD vs. DCD	135	1.19	0.50–2.88	0.69
Diabetes as cause of ESKD, yes vs. no	135	2.30	1.15–4.60	0.0189
Delayed graft function, yes vs. no	134	1.73	0.61–4.90	0.31
Donor age, 1-yr increase	135	1.01	0.99–1.03	0.52
Dialysis duration, 1-yr increase	135	1.07	0.99–1.16	0.10
Dialysis before transplant, yes vs. no	135	1.30	0.40–4.24	0.67
Surgery duration, 1-h increase	135	1.57	1.20–2.06	0.0010
Rejection, yes vs. no	135	1.86	0.95–3.66	0.07

BD, brain death; DCD, donation after circulatory death; ESKD, end-stage kidney disease; HR, hazard ratio.

Table 7. Univariable analysis of death-censored kidney graft survival

Variables	n	HR	95% CI	P value
Group, vasopressin vs. no-vasopressin	135	0.53	0.15–1.86	0.32
Recipient age, 1-yr increase	135	0.99	0.96–1.03	0.68
Recipient gender, male vs. female	135	2.01	0.77–5.30	0.16
Recipient race, African American vs. White	135	3.18	1.22–8.26	0.0178
Cold ischemia time, 1-h increase	135	1.00	0.96–1.04	0.83
Warm ischemia time, 1-min increase	135	0.97	0.92–1.03	0.38
Donor type, BD vs. DCD	135	0.82	0.27–2.53	0.73
Diabetes as cause of ESKD, yes vs. no	135	1.43	0.47–4.41	0.53
Delayed graft function, yes vs. no	134	2.85	0.82–9.95	0.10
Donor age, 1-yr increase	135	1.00	0.97–1.04	0.90
Dialysis duration, 1-yr increase	135	1.07	0.95–1.20	0.27
Dialysis before transplant, yes vs. no	135	0.56	0.16–1.96	0.37
Surgery duration, 1-h increase	135	1.14	0.62–2.10	0.68
Rejection, yes vs. no	135	3.32	1.28–8.64	0.0139

BD, brain death; DCD, donation after circulatory death; ESKD, end-stage kidney disease; HR, hazard ratio.

vs. 1.5 mg/dl in the comparison group, $P = 0.0433$); however, over time, the creatinine levels became comparable, and no significant difference was observed at 1 year (1.3 mg/dl vs. 1.2 mg/dl, $P = 0.45$). We observed a similar need for kidney allograft biopsy (35.6% in the vasopressin group vs. 33.3% in the no-vasopressin group) and similar percentage of rejection (Banff borderline to II). Given these findings, it appears that the probable reduction in DGF rates by improved hemodynamics potentially led to comparable GS at 1 year. Studies have shown that DGF has been associated with higher incidence of rejection episodes within the first year of transplant (HR = 1.71).[23]

Secondary Safety Outcomes/Rates of Complications

No deaths occurred in either group during transplant hospitalization admission. There were 2 deaths occurring at home within 12 months of DDKT unrelated to kidney transplant (exsanguination from arteriovenous fistula and second with unknown cause of death). Overall higher mortality was observed among DDKTRs in the vasopressin group for the duration of the study follow-up; however, no specific cause of death was more often observed between these 2 groups. Second, most of the deaths among the cases occurred owing to malignancy >12 months after their transplant. Overall

patient survival at 1 year was comparable for the no-vasopressin group (100%) compared with the vasopressin group (95.5%). Subgroup analyses were also performed for overall kidney GS and death-censored kidney GS, between vasopressin-only versus no pressor of any kind. Adjusted for other risk factors selected from univariable analyses, the vasopressin-only group did not appear as a significant risk factor for both GS (HR = 1.96, 95% CI = 0.89–4.30, $P = 0.09$) and death-censored kidney GS (HR = 1.03, 95% CI = 0.27–3.93, $P = 0.9699$) at a significance level of $\alpha = 0.05$ (Supplementary Tables S1–S4, S5A, S5B, S6A, and S6B). However, a potential limitation with this analysis is led by the small sample sizes ($n = 23$ for the vasopressin-only group and $n = 76$ for the no pressor of any kind group), and therefore, future studies with larger subgroups would be important to further clarify this.

Both groups were at par with national 1 year patient survival for DDKT of 96.3%.[24] At 3 years, both groups had excellent patient survival having no significant difference (91% vs. 97.8%) and was comparable to national data (91.3%).[24] There are a number of variables that affect patient survival, including transplant related, for example, degree of immunosuppression and rate of infections, and general health factors, for example, cardiovascular, making it difficult to determine specific factors. Longer follow-up time increases

Table 6. Multivariable analysis of overall kidney graft survival

Variables	HR	95% CI	P value
Group, vasopressin vs. no-vasopressin	1.43	0.71–2.89	0.32
Recipient gender, male vs. female	2.89	1.39–6.01	0.0046
Diabetes as cause of ESKD, yes vs. no	3.03	1.46–6.29	0.0030
Dialysis duration, 1-yr increase	1.05	0.96–1.15	0.28
Surgery duration, 1-h increase	1.53	1.16–2.03	0.0027
Rejection, yes vs. no	2.10	1.04–4.23	0.0376

HR, hazard ratio; ESKD, end-stage kidney disease.

Table 8. Multivariable analysis of death-censored kidney graft survival

Variables	HR	95% CI	P value
Group, vasopressin vs. no-vasopressin	0.57	0.16–1.99	0.38
Recipient race, African American vs. White	2.87	1.10–7.54	0.0318
Rejection, yes vs. no	3.05	1.16–8.02	0.0236

HR, hazard ratio.

the likelihood of these factors affecting survival. We also reviewed incidence of infections, hypertensive episodes, respiratory failure, and cardiovascular complications, including atrial fibrillation and acute coronary syndrome (ST elevation myocardial infarction [STEMI]/non-STEMI). Significant difference was observed in the incidence of non-STEMI (31.1% in the vasopressin group vs. 2.2% in the no-vasopressin group). Data for vasopressin-related adverse effects are derived from studies in vasodilatory shock, post-cardiac surgery, critical care, and high-dose vasopressin use in patients with variceal complications. No studies have been done on vasopressin use outside of these indications; hence, we compare the adverse effect profiles with these studies. Some of these used very high vasopressin dose up to 20 units/h and injected into the mesenteric arteries, which lead to systemic vasoconstrictive effects and ischemic complications.[25] In our study, we used low-dose vasopressin with a median starting dose of 2 units/h and a maximum median dose of 4 units/h. This is similar to doses used clinically in vasodilatory shock. Yao et al.[26] found no association between vasopressin use and overall incidence of adverse events or arrhythmias. Higher incidence of digital ischemia was shown in their meta-analysis which may be reflective of patients in those studies having shock, concomitant catecholamine use, or vasopressin. No occurrence of digital ischemia was noted in our study. The vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery trial looking at vasopressin use versus norepinephrine postcardiac surgery found significantly less incidence of atrial fibrillation and no difference in occurrence of digital and mesenteric ischemia, STEMI, or hyponatremia.[27] A meta-analysis reviewing risks of arrhythmias among patients treated with vasopressin for septic shock showed a decreased incidence of atrial fibrillation among the vasopressin group compared with the catecholamine group.[28] Patient who required vasopressin were by indication hypotensive, and hypotension is a risk factor for non-STEMI owing to demand ischemia. Moreover, none of the patients among those who received vasopressin had STEMI or any other cardiovascular complication from the non-STEMI. Therefore, the significance of this observation is unclear.

Previous studies on vasopressin use among patients with septic shock, critically ill but hemodynamically stable patients and those with cirrhosis have shown occurrence of significant hyponatremia with vasopressin use.[29–33] No such occurrence was seen in our study, and serum sodium measurements at 6, 12, 24, and 48 hours remained within the normal range with no significant difference in both

groups. This may be explained by allograft kidneys having acute tubular necrosis owing to ischemia and reperfusion injury in the setting of donation and transplant and lack of responsiveness of renal tubules to vasopressin.

Our study has important implications for transplant programs who manage DDKTRs with post-transplant hypotension. It shows that vasopressin can be safely used to optimize BPs post-DDKT. Further studies with larger cohorts potentially across different centers can help identify factors that may predict the occurrence of post-transplant hypotension. Larger data sets can also help in development of an algorithm where BP and urine output targets can be added and candidates with hypotension can be identified earlier and started on vasopressin. Those studies will also further clarify the safety profile of vasopressin in this setting.

Strength and Limitations

To best of our knowledge, this is the first study to report the use of vasopressin and its impact on DDKT survival. Currently, there are a significant number of patients with ESKD with longer waitlist time and the fact that the current Kidney Allocation System (2014) is geared toward prioritizing these patients, transplant programs are likely to encounter more recipients who are hypotensive, require midodrine pretransplant, or suffer from interdialytic hypotension. This means that the number of people requiring pressors to maintain perfusion of allograft is expected to increase. Our study informs transplant teams that such KTRs may continue to remain hypotensive after transplant and how vasopressin can be used to safely raise BP. Our study also reflects on the need to include the presence of hypotension pretransplant or on dialysis as a significant risk factor for post-transplant hypotension and need for vasopressin.

Our study had several limitations. First, the need for vasopressin because of hypotension led to confounding by indication, as hypotensive patients were more likely to have effects from hypoperfusion, including demand ischemia, lower urine output, and high net positive volume status, and that was not possible to separate from effects of vasopressin. Second, even though key factors affecting GS were matched in both groups, there are several other factors that may have affected GS in the subsequent months, for example, adherence to medications. Third, no control group was ethically possible to compare hypotensive DDKTRs who did not receive vasopressin. Fourth, our study was not powered to detect associations among subset of categories within a group, for example, among cases who required

midodrine pretransplant versus those who did not or those who received vasopressin alone versus those who required vasopressin and dopamine. Last, owing to patient's level of care at the time hypotension was noted, some DDKTRs with hypotension were initially started on a dopamine for a brief time as vasopressin cannot be administered outside of the ICU setting. These DDKTRs were then weaned off dopamine and started on vasopressin once in the ICU.

In conclusion, vasopressin appeared to protect against hypotension-induced DGF among DDKTRs. The results suggest that preemptive treatment of hypotensive DDKTRs with vasopressin is safe and can bring death-censored GS at 1 year and potentially beyond on par with nonhypotensive DDKTRs, albeit with increased LOS as vasopressin is administered in the ICU setting only. In the absence of a randomized control trial, our study supports that vasopressin therapy may be safe as a treatment to prevent the adverse effects of hypotension. Future studies, including prospective trials, are needed to compare vasopressin use against other vasopressors and establish its unique role in post-DDKT care.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

Supplementary File (Word)
Table S1. Recipient characteristics.
Table S2. Donor and transplant characteristics.
Table S3. Intraoperative and postoperative characteristics.
Table S4. Outcomes and survival comparison.
Table S5A. Univariable analysis of overall kidney graft survival (n = 99).
Table S5B. Multivariable analysis of overall kidney graft survival.
Table S6A. Univariable analysis of death-censored kidney graft survival (n = 99).
Table S6B. Multivariable analysis of death-censored kidney graft survival.

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