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The effect of norepinephrine versus dopamine in renal transplant recipients on postoperative graft function

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ABSTRACT

Background: Finding the ideal vasopressor for use during the crucial phase of graft anastomosis is still an ongoing search to improve graft function in recipients of renal transplants. This study aimed to compare the effect of norepinephrine versus dopamine on renal graft function and postoperative serum creatinine.

Methods: A randomized single-blind clinical trial of 44 patients was divided into two equal groups. Group N: norepinephrine infusion was used at a starting dose of $0.05\mu g/kg/min$ with dose range: $0.05-0.15 \mu/kg/min$ and group D; dopamine infusion was used at a starting dose of $5\mu g/kg/min$ with dose range: $5-15 \mu/kg/min$. Postoperative serum creatinine and renal doppler resistive index, were compared between the two groups.

Results: There were significant differences within and between both groups over time regarding postoperative serum creatinine levels (group D, P-value < 0.001, group N, P-value < 0.001 and between both groups, P-value=0.013). Regarding the hemodynamics, after perfusion of the new renal graft, at 30 min the norepinephrine group had lower HR than dopamine group (P-value=0.031), at 20 and 30 min the norepinephrine group had higher CVP than dopamine group (P-value=0.015 and 0.022 respectively), at immediate time of perfusion (0 time) and 20 min post perfusion, the dopamine group had higher UOP than norepinephrine group (P-value=0.012 and 0.001 respectively), while there was no significant difference in the postoperative hemodynamic data.

Conclusions: Norepinephrine and dopamine have comparable effects on graft function in the renal recipient patients.

1. Introduction

For patients with end-stage renal illness and chronic renal failure, kidney transplantation is currently acknowledged as the preferred course of treatment. Improved quality of life, a better costbenefit ratio, and potentially longer survival are linked to renal transplants [1]. Urine output and blood creatinine levels are typically used to gauge the transplanted kidney's success in the initial days. Reduced transplant survival and more recipient problems have been linked to early graft dysfunction. These characteristics led us to investigate the fluid dynamics during the surgery in relation to the early graft function (biochemical parameters and urine production) [2]. Maintaining an appropriate intravascular volume and perfusion pressure is the most crucial intraoperative step to enhance immediate transplant performance [3,4]. Hypotension is commonly encountered, especially

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after the fascia is dissected and might be further exacerbated after reperfusion of the graft [5].

Norepinephrine is an adrenergic agonist with a potent α -adrenergic receptor agonistic action; it is a relatively weak agonist at β -adrenergic receptors. Norepinephrine is an effective vasopressor for maintaining blood pressure with less tendency to decrease heart rate and cardiac output [6]. Dopamine is a commonly used vasoactive drug that acts on a stepwise manner on dopaminergic and adrenergic (α and β) receptors [7].

We undertook this study to investigate the effect of two types of vasopressors: norepinephrine versus dopamine in renal transplant recipients and their influence on the postoperative primary outcome regarding postoperative serum creatinine level. The secondary outcomes were postoperative blood urea level, postoperative urine output, postoperative renal artery Doppler resistive index.

CONTACT Omar M Soliman Soliman Soliman Soliman Soliman (Network) Clinical trial registration number: The Clinical Trials.gov (NCT03107858).

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2. Materials and methods

2.1. Ethical considerations

This was a randomized, single-blind, clinical trial, approved by the University's Institutional Review Board (IRB17200154). The methodology of this study followed the Declaration of Helsinki (revised DOH 2013). A written informed consent was taken from the patients or their relatives. The trial was registered before patient enrollment in The Clinical Trials.gov (NCT03107858), and carried out in Assiut University Hospital, Renal Transplantation Unit.

2.2. Participants

Patients scheduled for a living donor kidney transplantation were included in the study. Patients less than 18 years old, and who refused consenting for enrolment in the study, were excluded.

2.3. Randomization

Forty-four patients were randomly allocated (using computer generated table) into one of two groups (22 patients in each), Norepinephrine group (N); nor-epinephrine infusion was used at a starting dose of $0.05\mu g/kg/min$ with dose range: $0.05-0.15 \mu/kg/min$ and Dopamine group (D); dopamine infusion was used at a starting dose of $5\mu g/kg/min$ with dose range: $5-15 \mu/kg/min$.

2.4. Study protocol

All patients were anesthetized according to our institute's protocol. Immunosuppressive therapy was started the day before surgery. Maintenance fluid therapy in the form of ringer's acetate was provided with the start of preoperative fasting. Patients were premedicated with H2 blockers (50 mg ranitidine), prokinetics (10 mg metoclopramide) and no sedatives. Patients on antihypertensive drug therapy received their morning dose two hours before induction of anesthesia. Standard ASA monitoring was commenced prior to induction of anesthesia. Central venous pressure, invasive blood pressure monitoring and urine output (through a silicon Foley's catheter) were commenced after induction of anesthesia. General anesthesia with endotracheal intubation and mechanical ventilation was used with fentanyl (1µg/kg), propofol (1-2 mg/ kg), cis-atracurium (0.15 mg/kg). Anesthesia was maintained with 2-4% MAC sevoflurane in 50:50 oxygen-air mixture. Maintenance fluid therapy was continued throughout surgery. Additional fluid therapy in the form of 0.9% normal saline was used to maintain a central venous pressure of 10-15 mmHg. Irradiated packed RBCs was used in case of the need of blood transfusion. Mannitol 20% 0.5ml/kg was started 15 min

before arterial de-clamping. Sodium bicarbonate 8.4% 50 ml was infused with arterial de-clamping over an hour. First dose methylprednisolone 500 mg 12 h preoperatively, second dose methylprednisolone 500 mg was given with the renal artery clamp release. Hemodynamic drug support was typically started with arterial de-clamping; after ensuring a central venous pressure of 10–15 mmHg. The infusion rate of the study drug was adjusted to a hemodynamic goal of MAP of 100–110 mmHg. After emergence, all patients were transferred to the isolation booth in the intensive care unit where the infusions were continued as described.

All patients were prescribed intravenous acetaminophen 1 g every 6 h, with fentanyl infusion at a rate of 0.5µg/kg/h. Hemodynamic goals were CVP 10-15 mmHg and MAP of 100-110 mmHg were continued with postoperative hemodynamic monitoring. Preoperative data were duration of chronic renal failure, duration of dialysis etiology of chronic renal failure, and type of dialysis. Intraoperative data were surgical and anesthetic times, administered fluids, intraoperative blood loss heart rate and mean arterial blood pressure were documented every 5 min, while central venous pressure and urine output were documented hourly. Intraoperative complications were documented and treated, such as hypotension was treated with 30 ml/kg normal saline 0.9%, hypertension was treated with small boluses 50-100 ug of phenylephrine, bradycardia was treated with 10-20 ug/kg atropine, and tachycardia was treated with esmolol 0.5 mg/ kg. Postoperative data were heart rate, mean arterial blood pressure, and central venous pressure were documented hourly, total UOP was calculated and documented in 24 h, while renal artery doppler resistive index was documented every 4 h. Renal Artery Doppler, measurements were obtained in the interlobar arteries of the renal cortex. The ultrasound examination was considered technically adequate if the following criteria were met: (a) a clear two-dimensional longitudinal scan with definition of renal parenchyma, (b) a good color Doppler image with representation of the intrarenal vascular blood flow, and (c) at least three consecutive Doppler time-velocity spectra for each renal area (upper, middle, and lower regions). Waveforms were recorded and renal Doppler resistive index was calculated according to Planiol and Pourcelot protocol [8], to reduce sampling error, three Doppler measurements were obtained for each of the three renal regions. The mean values were then averaged to create an index for the entire organ. The wall filter was adjusted to a low frequency (100 MHz) and the pulsed wave Doppler spectrum was expanded by utilizing the lowest frequency shift range that did not result in aliasing. Renal Doppler resistive index

normal values range from 0.48 to 0.68, whereas values more than 0.70 were deemed abnormal. All complications (fever, pneumonia, acute rejection, and perirenal hematoma) were recorded. Laboratory parameters: Renal Function Tests (baseline, 4, 12 and 24-h postoperative), hemoglobin, hematocrit, platelet Count, white blood cell count, albumin, and liver function tests at 24-h postoperative. The Primary outcome was postoperative serum creatinine level. The secondary outcomes were postoperative blood urea level, postoperative urine output, postoperative renal artery Doppler resistive index.

2.5. Sample size

A sample size of 22 patients per group is required to detect a minimal effective difference of 0.4 in the postoperative serum creatinine level (mg/dl) between the two studied groups considering an alpha error of 0.05. This will yield a power of the study of 80%.

2.6. Statistical analysis

Data was analyzed using the Statistical Package for Social Science (SPSS), version 26.0 for Windows.

Quantitative data tested for normality by Shapiro– Wilk test while data and expressed as mean \pm SD or median (range). Independent Sample T-test/Mann Whitney U-test was used to compare quantitative data between nor epinephrine and dopamine groups at each time point separately, one-way repeated measures ANOVA test was used to identify changes over time in within each group separately and Two-way repeated measures ANOVA Test was used to identify changes in the measurement within the two group over time. Chi square and fisher Exact test was used to compare proportions between groups. The level of significance was considered at *p* value < 0.05.

3. Results

Among the 50 patients who were screened for eligibility, 6 patients were excluded as they did not sign for consent. Forty-four patients were finally analyzed between the two study groups, as shown in the flow chart of the studied groups (Figure 1). The socio-demographic data of the enrolled patients showed no significant differences between the two study groups (Table 1). There were significant differences within and between both groups over all times regarding postoperative serum creatinine levels (group D, *P*-value< 0.001,

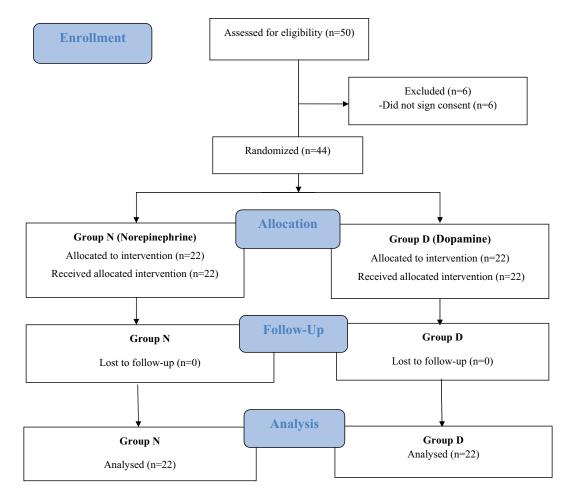


Figure 1. CONSORT flow chart between the study group.

Table 1. Sociodemographic and clinical characteristics of the patients in the study groups.

Variables	Norepinephrine (n=22)	Dopamine (n=22)	P-value
Age (years)	34.09 ± 9.10	37.82 ± 11.44	0.239*
Gender			
• Male	17 (77.3%)	16 (72.7%)	0.728***
Female	5 (22.7%)	6 (27.3%)	
Anthropometric measures			
 Weight (kg) 	71.27 ± 10.56	73.05 ± 14.63	0.647*
• Height (cm)	169.50 ± 9.03	166.41 ± 7.64	0.228*
• BMI	25.08 ± 5.13	26.32 ± 4.68	0.405*
Duration of chronic RF (months)	11.0 (3–40)	13.50 (0–73)	0.581**
Duration of dialysis (months)	10.50 (3-38)	12.0 (0-72)	0.564**
Anesthesia time (min)	290.05 ± 43.04	312.86 ± 41.61	0.081*
Operation time (min)	256.50 ± 40.28	271.05 ± 22.70	0.148*
Need blood transfusion	2 (9.1%)	3 (13.6%)	0.999****
Presence of complications	3 (13.6%)	4 (18.2%)	0.999****
Types of complications			
Dialysis	2 (9.1%)	2 (9.1%)	0.999****
Rejection	1 (4.5%)	1 (4.5%)	0.999****
Hematoma	0 (0.0%)	2 (9.1%)	0.511****

Data were expressed as mean \pm SD, median (range), or frequency (%).

*Independent Sample T test was used to compare the mean difference between groups.

**Mann Whitney U test was used to compare the median difference between groups.

***Chi square test was used to compare the proportion difference between groups.

****Fisher Exact test was used to compare the proportion difference between groups.

group N, *P*-value< 0.001 and between both groups, *P*-value=0.013). There were no significant differences between both groups regarding postoperative urea and RSI, other laboratory data, between both groups were not clinically significant as shown in Figure 2 and Table 2.

Regarding the hemodynamic data (MBP, HR, CVP, and UOP), after perfusion of the new renal graft, there was significant difference over time between both groups regarding MBP, HR, and UOP, *P*-value< 0.001, and only over time in group D for CVP, *P*-value = 0.031. Regarding HR at 30 min where the norepinephrine group had lower HR than dopamine group (*P*-value = 0.031), CVP at 20 and 30 min where the norepinephrine group had higher CVP than dopamine group (*P*-value = 0.015 and 0.022 respectively), and UOP at immediate time of perfusion (0 time) and 20 min post perfusion, where the dopamine group had higher UOP than norepinephrine group (*P*-value = 0.012 and 0.001 respectively) as shown in Table 3. Regarding the postoperative hemodynamic data, there was significant difference over time between both groups regarding HR (group N, *P*-value< 0.031 and group D, *P*-value < 0.017), and only over time for MBP in group N, *P*-value = 0.036 as shown in Table 4.

The complications were compared between both groups; dialysis (two in each group), rejection (one in each group), and perirenal hematoma (two patients in dopamine group) as shown in Table 1.

4. Discussion

Since kidney transplantation extends a patient's life and enhances their quality of life, it has emerged as the best alternative therapy for those with end-stage renal illness. This study looked at how postoperative serum creatinine and RRI in recipients of renal transplants were affected by

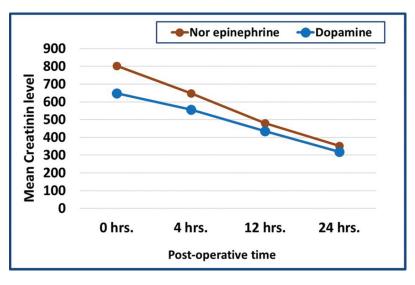


Figure 2. Postoperative follow up of creatinine among studied groups.

Table 2. Comparison of postoperative lab between the two studied groups.

		Dopamine		
Parameters	Norepinephrine (n=22)	(<i>n</i> =22)	P-value	
Creatinine				
 Creatinine 0 h 	802.32 ± 220.56	649.41 ± 137.55	0.009*	
 Creatinine 4 h 	648.05 ± 205.59	556.23 ± 173.49	0.117*	
 Creatinine 12 h 	481.18 ± 195.19	436.41 ± 160.46	0.411*	
 Creatinine 24 h 	352.95 ± 215.70	318.64 ± 146.87	0.541*	
P-Value	<0.001**	<0.001**	0.013***	
Urea				
 Urea 0 h 	19.55 ± 7.14	16.06 ± 6.45	0.097*	
 Urea 4 h 	16.10 ± 6.37	15.62 ± 6.50	0.803*	
 Urea 12 h 	13.14 ± 4.38	12.83 ± 5.51	0.836*	
 Urea 24 h 	11.26 ± 3.88	12.05 ± 4.42	0.537*	
P-Value	<0.001**	0.005**	0.043***	
RRI				
 RRI pacu 	0.66 ± 0.07	0.64 ± 0.10	0.562*	
• RRI 4 h	0.65 ± 0.06	0.62 ± 0.07	0.259*	
• RRI 12 h	0.65 ± 0.07	0.62 ± 0.05	0.176*	
• RRI 24 h	0.64 ± 0.07	0.61 ± 0.05	0.145*	
P-Value	0.513**	0.222**	0.829***	
HB 24 h	9.81 ± 0.84	9.81 ± 1.22	0.984*	
HCT 24 h	24 h 28.49 ± 2.56		0.648*	
PLTs 24 h	198.79 ± 43.90	191.01 ± 51.91	0.594*	
WBCs 24 h	11.746 ± 1.83	11.550 ± 2.33	0.758*	
Albumin 24 h	2.941 ± 0.35	2.942 ± 0.36	0.993*	

Data were expressed as mean \pm SD/median (range).

*Independent Sample T test was used to compare the difference between groups.

**One-way repeated measure ANOVA compare difference within each group separately over time.

***Two-way repeated measure ANOVA compares difference between the two group over time.

norepinephrine versus dopamine. We observed that norepinephrine and dopamine had similar effects on renal transplant recipients in our trial.

Patients who experience persistent hypotension may need to be given inotropes, which improve cardiac contractility, or vasopressors, which cause vasoconstriction and raise MAP. Both effects are common in medications. Vasopressin (V1a receptor antidiuretic hormone), beta-1 adrenergic inotrope (dobutamine), α -1 adrenergic vasopressors (norepinephrine, epinephrine, phenylephrine, and dopamine), and phosphodiesterase enzyme 3 inhibitor inotrope (milrinone) are the main categories of vasopressors and inotropes used in the treatment of acute hypotensive states and shock. Regular usage of "renal dose" dopamine is not advised as it may have negative effects [9].

Renal failure has long been treated with dopamine. On the other hand, two sizable meta-analyses have demonstrated that dopamine negatively affects renal function in cases of acute renal failure [10]. The first option is norepinephrine, which is followed by either

 Table 3. Comparison of hemodynamic data of patients between the two studied groups during graft perfusion.

	Dopamine	
Norepinephrine (n=22)	(<i>n</i> =22)	P-value
91.18 ± 10.81	92.05 ± 8.65	0.771*
94.91 ± 9.97	94.91 ± 8.32	0.999*
98.36 ± 9.62	99.55 ± 12.48	0.727*
104.36 ± 6.76	105.05 ± 6.49	0.735*
<0.001**	<0.001**	0.958***
87.32 ± 7.94	86.32 ± 8.03	0.680*
96.95 ± 10.74	99.73 ± 10.34	0.388*
99.68 ± 10.76	102.36 ± 10.46	0.407*
99.82 ± 9.10	105.32 ± 7.07	0.031*
<0.001**	<0.001**	0.110***
12.14 ± 2.66	11.41 ± 2.84	0.386*
12.73 ± 1.90	11.73 ± 2.07	0.103*
12.27 ± 3.29	10.27 ± 1.69	0.015*
12.73 ± 2.64	11.18 ± 1.50	0.022*
0.472**	0.031**	0.270***
0.00 (0-90)	67.50 (0–210)	0.012*
77.50 (0–300)	150.00 (0-300)	0.064*
100.00 (0–150)	150.00 (0–250)	0.001*
200.00 (50-300)	205.00 (50-400)	0.247*
<0.001**	<0.001**	0.853***
	$\begin{array}{c} 91.18 \pm 10.81 \\ 94.91 \pm 9.97 \\ 98.36 \pm 9.62 \\ 104.36 \pm 6.76 \\ < 0.001^{**} \\ 87.32 \pm 7.94 \\ 99.68 \pm 10.76 \\ 99.82 \pm 9.10 \\ < 0.001^{**} \\ 12.14 \pm 2.66 \\ 12.73 \pm 1.90 \\ 12.27 \pm 3.29 \\ 12.73 \pm 2.64 \\ 0.472^{**} \\ 0.00 (0-90) \\ 77.50 (0-300) \\ 100.00 (50-300) \\ 200.00 (50-300) \end{array}$	Norepinephrine $(n=22)$ $(n=22)$ 91.18 ± 10.8192.05 ± 8.6594.91 ± 9.9794.91 ± 8.3298.36 ± 9.6299.55 ± 12.48104.36 ± 6.76105.05 ± 6.49<0.001**

Data were expressed as mean \pm SD/median (range).

*Independent Sample T test was used to compare the difference between groups.

**One-way repeated measure ANOVA compare difference within each group separately over time.

***Two-way repeated measure ANOVA compares difference between the two group over time.

Table 4. Comparison of	postoperative	hemodynamic	data	between	the two	studied
groups.						

Parameters	Norepinephrine (n=22)	Dopamine (n=22)	P-value
MBP			
 MBP 0 h 	94.50 ± 11.68	95.18 ± 9.69	0.834*
• MBP 1.	97.27 ± 7.57	96.73 ± 9.52	0.835*
• MBP 2 h.	98.27 ± 4.47	97.91 ± 8.37	0.858*
 MBP 3 h 	99.64 ± 3.97	99.05 ± 5.41	0.682*
P-Value	0.036**	0.117**	0.938***
Heart rate			
• HR 0 h	98.32 ± 4.94	95.05 ± 7.16	0.085*
• HR 1 h	95.95 ± 6.29	93.05 ± 8.07	0.190*
• HR 2 h	95.27 ± 6.01	92.45 ± 6.60	0.146*
• HR 3 h	93.14 ± 6.93	90.77 ± 8.42	0.315*
P-Value	<0.001**	0.017**	0.953***
CVP			
 CVP 0 h 	12.86 ± 1.83	12.27 ± 1.85	0.294*
• CVP 1 h	12.09 ± 1.84	11.77 ± 2.30	0.616*
 CVP 2 h 	11.73 ± 2.58	12.27 ± 1.98	0.437*
 CVP 3 h 	11.77 ± 2.13	11.91 ± 2.04	0.830*
P-Value	0.197**	0.641**	0.566*
24 h UOP	14536.82 ± 4886.69	15062.73 ± 4967.25	0.725***

Data were expressed as mean \pm SD/median (range).

*Independent Sample T test was used to compare the difference between groups.

One-way repeated measure ANOVA compare difference within each group separately over time. *Two-way repeated measure ANOVA compares difference between the two group over time.

vasopressin or epinephrine. Dopamine and angiotensin II have limited uses. Future vasopressor selection may be guided by predictive biomarkers, and new vasopressors may be developed. Dopamine, on the other hand, is recommended only in bradycardic patients [11].

In agreement with our research, Jan et al. [12] showed that dopamine infusion could be given at a predetermined rate in a non-ICU setting, while vasopressin and norepinephrine infusions were limited to the ICU. Additionally, a cohort of five critically ill oliquric (<0.5 mL of urine per kilogram per hour) renal transplant patients showed increased urine production with dopamine when LDD was introduced by Flancbaum et al. [13]. A study performed by Maraghi et al. [14] showed that a rise in serum creatinine of one unit is associated with a four-fold greater chance of graft failure. Grundmann et al. [15] also showed that LDD helped patients produce more urine in the first posttransplant interval while having no effect on creatinine clearance in a randomly controlled experiment including 50 patients. Epinephrine is equally efficacious as norepinephrinedobutamine when considering global hemodynamic effects [16]. Nevertheless, epinephrine is associated with a transient lactic acidosis, higher heart rate and arrhythmia, and inadequate gastric mucosa perfusion. Thus, the combination norepinephrine-dobutamine appears to be a more reliable and safer strategy.

On the other hand, Friedrich et al. [17], stated that the recipient's regular use of renal dosage dopamine following transplantation is not supported by the evidence currently available from clinical investigations. Despite brief increases in renal medullary perfusion, these results are consistent with a large body of clinical evidence showing that low-dose dopamine does not preserve kidney function in critically sick patients with imminent or overt renal failure. Study was performed by Bajpai et al.'s [18], comparing the two vasopressors in kidney transplant recipients, discovered that while the difference in mortality was not statistically significant, dopamine was linked to more arrhythmias and a higher risk of death in patients experiencing cardiogenic shock. However, there is no consensus on the optimal choice of vasopressor or the specific goals for blood pressure and fluid management in these patients. Further research is needed to determine the most effective approach to hemodynamic support in renal transplant recipients.

The study was limited in that it recruited a small number of patients which may be due to the special type of patient and procedure and was single center study that may result in different findings than elsewhere. Our findings suggest that administration of Norepinephrine and dopamine infusion during and after the graft anastomosis, reduce the risk of graft rejection and improve the outcome.

In conclusion, our research shows that administration of Norepinephrine and dopamine have comparable effects on graft function in the renal recipient patients, regarding the hemodynamic data during the period of graft anastomosis and postoperatively, and perfusion renal index.

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Authorship

All authors were involved in the drafting of the work, approved the final manuscript, and stated that the manuscript represents an honest work.

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