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Original Research / Özgün Araştırma

Norepinephrine infusion in brain dead organ donor: A retrospective study on its effects on graft function after renal transplant

Beyin ölümü organ donörlerinde norepinefrin infüzyonunun greft fonksiyonu üzerine etkileri: Retrospektif bir çalışma

Hamide Ayben Korkmaz[1], İlkay Ceylan[1], Yılmaz Apaydın[1]

[1] University of Health Sciences, Bursa Training and Research Hospital, Department of Anesthesia and Reanimation, Bursa, Turkey

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Yazışma / Correspondence
Hamide Ayben Korkmaz, MD
Bursa Training and ResearchHospital, Department of Neurosurgery, Bursa, Turkey
E-mail: aybenkorkmaz73@gmail.com

ORCID

H.A.K.	0000-0002-2845-0586
Y.A.	0000-0003-0583-8198
İ.C.	0000-0003-3306-3107

Özet

Amaç: Beyin ölümü gerçekleşen organ donörlerinde vazoaktif ilaç kullanımının renal alıcı greft fonksiyonu üzerindeki etkisini araştırmak.

Gereç ve Yöntemler: Merkezimizde Temmuz 2017 ile Kasım 2021 arasında, beyin ölümü gerçekleşen 30 organ bağışçısından ve 30 alıcıdan alınan klinik veriler geriye dönük olarak analiz edilmiştir.

Bulgular: 30 kadavra donörünün hepsinde norepinefrin infüzyonu kullanılmıştı. 11 donörün inotrop ilaç kombinasyonuna sahip olduğu görüldü. Norepinefrin infüzyonlarının ortalama dozu 0.2 mcg/kg/dk idi. Donörlerde norepinefrin süresi ve dozları ile böbrek alıcılarında greft reddi, greft kaybı ve diyaliz gereksinimi arasında ilişki yoktu.

Sonuç: Beyin ölümü organ bağışçısında sıvı resüstasyonunun yeterli olduğu durumlarda .0.2 mcg/kg/dk'nın altındaki intravenöz norepinefrin infüzyonunun, renal greft fonksiyonu üzerine etkisi olmadığı görüldü.

Anahtar Kelimeler: Beyin ölümü, donör, vazoaktif ilaçlar, greft sağkalımı

Abstract

Objective: To investigate the effect of vasoactive drugs use in brain-dead organ donors in renal recipient graft function.

Material and Methods: Clinical data from 30 brain-dead organ donors, and 30 recipients in our center were analyzed retrospectively between July 2017 and November 2021.

Results: Norepinephrine infusion was used in all 30 cadaveric donors, where 11 donors had inotropic combinations. Norepinephrine was infused at a median dose of 0.2mcg/kg/min. There was no relationship between duration and doses of norepinephrine in donors and graft rejection, graft loss, and dialysis requirement in renal recipients.

Conclusion: Intravenous norepinephrine infusion below 0.2mcg/kg/min had no effect on graft function in the renal recipient, where fluid resuscitation was sufficient in the cadaveric donor.

Keywords: Brain dead, organ donors, vasoactive drugs, graft survival.

The study was approved by Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital (Approval Date15.12.2021 and Protocole Number: 2011-KAEK-25 2021/12-09). All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

INTRODUCTION

The mortality rate of the patients on the waiting list for organ transplants remains high (1). It was reported in 2021 that 17 individuals, who waited for a transplant, died each day in the United States (2). There are 23,955 patients on the transplant waiting list according to 2020 data in Turkey (3). Whereas, one individual dies every three hours and eight individuals every day while waiting for an organ transplant (4). Efforts were aimed at early brain death diagnosis and increase the number of donations in place to find a solution to waiting queues. Nevertheless, the fact that organs harvested from potential donors diagnosed with brain death are often rejected due to insufficient quality has an adverse impact on the situation. Further efforts should be in place to optimize the quality of organs from donors (5).

The hemodynamic responses upon brain death were identified. Hemodynamic instabilities during that period constitute the main difficulty in the management of brain-dead organ donors (BDDs) (6). Approximately 20% of the organs of brain-dead donors are lost due to hemodynamic instabilities. Therefore, hemodynamic management of donors plays a key role in the donation process (7).

Elevation in arterial blood pressure is the primary destructive response upon brain death and is induced by the activation of the sympathetic nervous system. This is followed by vasoplegia; the hypotensive phase requiring fluid and/or vasoactive therapy. Available information regarding the vasoactive agent that could be selected during that phase is unclear/insufficient (8). Furthermore, catecholamine preparations (Dopamine, Dobutamine, Adrenaline, Noradrenaline), which are used to maintain the target average arterial pressure at 60-100 mmHg may also have undesirable effects especially on the renal graft functions in the recipient (9-11).

The present study aims to investigate the effects of vasoactive agents and doses used in management of donor candidates who donated organs upon brain death, on graft rejection, graft loss, and dialysis requirement in renal recipients and to determine the appropriate agent and dose.

MATERIAL AND METHODS

The present study was commenced upon the approval of the Ethics Committee, Bursa Yüksek İhtisas Training and Research Hospital, Health Sciences University (2011-KAEK-25-25 2021/12-21). Patient records were retrieved from the hospital archival system. The first kidney transplant in our hospital was performed on July 20, 2017.

The study therefore included donors aged above 18 years, diagnosed with brain death, whose kidneys were transplanted in our hospital between July 2017 and November 2021. Brain-dead individuals aged below 18 years or did not donate organs were not included in the study.

The information of the donors in the study on age, gender, co-morbidities, hemogram values before organ removal, kidney function tests, sodium level, blood gas analysis values, intravenous fluid therapy for the last 24 hours, urine output (per hour), length of stay in the intensive care unit, the cause of brain death and tests used for the diagnosis of brain death, vasoactive drugs used, and blood products consumption were recorded. The international guidelines for hemodynamic management of donor care were taken as a basis in our clinic and doses of 0.5μg/kg/min and below were accepted as low doses as regards the norepinephrine dose (8,12).

Recipient information in the study on age, gender, co-morbidities, cause of renal failure, duration of transplantation operation, serum creatinine (CRE), blood urea nitrogen (BUN), glomerular filtration rate (GFR), and other laboratory values at Day 1, Month 1, and Month 3, duration of cold ischemia, delayed graft function (DGF), graft rejection, and graft loss and renal replacement therapy (requirement for dialysis), were recorded.

The acute rejection episode in the recipient was diagnosed by renal cortex biopsy in our hospital and each patient was treated with immunosuppressive treatment pursuant to hospital protocols (13). The primary endpoint was taken as the relationship of vasoactive drugs used in donor management with the requirement for dialysis in the first three months following transplant, where the relationship with graft

rejection and graft loss were taken as the secondary endpoint.

Statistical Method

The IBM Statistical Package for the Social Sciences (SPSS 23.0-IBM, NY, USA) for Windows 23.0 software was used to analyze the patient data collected within the scope of the study. Descriptive values for categorical data were presented in frequency and percentage and in median, minimum, and maximum for continuous values. The Friedman test was used to review the difference between laboratory parameters measured over time.

Spearman's Correlation Analysis was used to test the relationship between treatment duration and treatment doses and laboratory parameters of donors. The logistic regression analysis was used to test whether the treatment used in donor patients posed a risk for graft rejection and graft loss in the recipients. The results were considered statistically significant when the p value was less than 0.05.

RESULTS

There were 149 cases of brain death in our hospital within the study interval. A total of 68 of those cases had organ donation approvals from families, where the organs of 10 cadavers in the foregoing group were not medically suitable for transplantation, and the cadaveric kidneys harvested from 28 cases were transferred to other centers. Therefore, 30 brain-dead donors and 30 recipients of renal transplant in our center were included in the present study.

Male cadaveric donors accounted for 56.7% (17 individuals) and 43.3% (13 individuals) were female. The most prevalent cause of death was primary cerebrovascular lesions (96.7%), where the most prevalent concomitant disease was hypertension (33.3%). Computed tomography (CT) angiography was used in the diagnosis of brain death in 76.6% (23 individuals), mean duration of cold ischemia was 819 (515-1047) minutes, mean daily intravenous fluid treatment for donors during the last 24 hours was 4525 (2050-9360) cc/day, and mean urine output was 152.9 cc/h (0-400). Clinical and demographic characteristics of cadaveric donors are presented in Table 1. All the donors received at least one vasopressor during their intensive care unit stay.

Table 1. A Distribution of Clinical and Demographic Characteristics of Organ Donor Patients

Variables (n=30)*	n (%) or Mean±SD
Gender	
Male	17 (56.7)
Female	13 (43.3)
Age (years)	51±14.1
Hospitalization reason	
Primary cerebrovascular disease	29 (96.7)
Meningitis	1 (3.3)
Smoking	4 (13.3)
Comorbidities	12 (40.0)
Hypertension	10 (33.3)
Diabetes Mellitus	4 (13.3)
Coronary artery disease	1 (3.3)
Others	3 (9.9)
Brain death diagnosis	
CT angiography	23 (76.7)
Apnea	7 (23.3)
Length of stay intensive care unit (days)	3.5±1.9
pH	7.4±0.08
pCO_2 (mmHg)	39.5±6.3
pO_2 (mmHg)	134.2±50.1
HCO3 (mg/dl)	24.7±3.1
Osmolarity	318.1±24.0
Total fluid intake (ml/day)	5144.1±1773.6
Last 24 hours balance (ml)	1517.8±1773.9
Urine output (ml/h)	158.7±90.8
Na (mmol/L)	155.7±11.5
Urea (mg/dl)	19±18.8
Creatinine (mg/dl)	1.0±0.45
Hgb (g/dl)	11.6±2.8
GFR	92.3±33.1
Duration of cold ischemia (minute)	828.6±125.8

***SD:** Standard deviation; **HCO3:** Bicarbonate, **GFR:** Glomerular filtration rate; **Hgb:** Hemoglobulin, **pO2:** Partial oxygen pressure, **pCO2:** Partial carbon dioxide pressure

Norepinephrine was used in the treatment of all the donors (100%), 11 (36.6%) had combination therapy. The median treatment dose of norepinephrine, epinephrine, dopamine and dobutamine used in the patients was 0.2mcg/kg/min (min: 0.02, max: 0.55 mcg/kg/min), 0.28mcg/kg/min (min: 0.11, max: 0.44 mcg/kg/min), 11.3 mcg/kg/min (min:8, max: 22 mcg/kg/min), and 20 mcg/kg/min (min: 20, max: 20 mcg/kg/min), respectively. Treatments specific to clinical symptoms of brain death and the durations thereof in cadaveric donor treatment are presented in Table 2. A distribution of the clinical and demographic characteristics of the patients, who received renal transplant within the scope of the study, is provided in Table 3. The mean age of the organ transplant patients was 46 (Min: 26, Max: 68), and hypertension was the most prevalent reason for transplantation. The median postoperative dialysis requirement was 2(Min: 1-Max: 6). There were five (16.6 %) renal recipients with graft rejection and three (10%) with graft loss. Reasons for rejection were immunological in two patients, vascular thrombosis in two patients and hematoma at the surgical site in one patient. Also the causes of graft loss were immunological in one patient and thrombosis in two patients.

Spearman correlation analysis was performed separately to investigate the relationship between the dose and duration of norepinephrine treatment in donor patients, and the renal function parameters of the renal transplant recipients (Table 4). There was no statistically significant relationship between the dose and duration of norepinephrine treatment and the renal function parameters measured at all times ($p>0.05$). A review of the relationship between the duration and dose of norepinephrine treatment in BDDs and the number of dialysis requirement of renal transplant recipients indicated that there was no statistically significant relationship ($p>0.05$) (Table 5). There was no significant relation between the duration and dose of norepinephrine treatment in BDDs and graft rejection and graft loss in the renal transplant recipients ($p>0.05$) upon risk analysis (Table 6).

Table 2. A Distribution of Treatment of Organ Donor Patients

Variables (n=30) *	**n (%) or Mean±SD**
Steroid Use	14 (46.7)
Blood product	5 (16.7)
Norepinephrine (number of donors)	30 (100)
Norepinephrine duration (hours)	33.2±18.0
Norepinephrine dose, (mcg/kg/min)	0.23± 0.14
Epinephrine (number of donors)	6 (20)
Epinephrine duration, (hours)	30.2±25.8
Epinephrine dose (mcg/kg/min)	0.28 ± 0,13
Dopamine (number of donors)	11 (36.6)
Dopamine duration (hours)	38.6±21.6
Dopamine dose (mcg/kg/min)	11.3 ± 4,69
Dobutamine (number of donors)	1 (3.3)
Dobutamine duration (hours)	4±0
Dobutamine dose (mcg/kg/min)	20

*mcg/kg/min: microgram/kilogram/minuet; SD: Standart deviation

Table 3. A Distribution of Clinical and Demographic Characteristics of Renal Transplant Recipients

Variables (n=30)	**n (%) or Mean±SD**
Age (years)	46±13
Reason for transplantation	
Unknown	4 (13.3)
Diabetes Mellitus	1 (3.3)
Hypertension	13 (43.3)
Hypertension-PCB	5 (16.7)
Hypertension+ Diabetes Mellitus	4 (13.3)
Hypertension+ Diabetes Mellitus -PCB	1 (3.3)
PCB	2 (6.7)
Operation time (hours)	5.2±0.9
Recipient's postoperative dialysis requirement	15 (50)
Number of dialysis requirement of patients	1±2
Delayed Graft Function	1 (3.3)
Graft rejection	5 (16.6)
Graft loss	3 (10)

Table 4. An Assessment of the Relationship between Dose and Duration of Norepinephrine Treatment in Donor and Renal Function Parameters in Recipient

Norepinephrine dose (n=30) *	**Day 1** **r*/ p-value**	**Month 1** **r*/ p-value**	**Month 3** **r*/ p-value**
BUN	-0.069 / 0.721	0.138 / 0.477	0.039 / 0.842
Creatinine	0.028 / 0.886	-0.050 / 0.797	0.295 / 0.121
GFR	-0.099 / 0.610	-0.063 / 0.745	0.256 / 0.181
Norepinephrine duration (N=30)			
BUN	0.022 / 0.910	0.081 / 0.676	0.157 / 0.417
Creatinine	0.075 / 0.699	-0.067 / 0.731	-0.185 / 0.338
GFR	0.076 / 0.695	0.001 / 0.997	0.173 / 0.369

***BUN:** Blood urea nitrogen, **GFR:** Glomerular filtration Rate * **r:** Correlation coefficient

Table 5. As Assessment of Recipients' Requirement for Dialysis by Duration and Dose of Treatment in Donor

	Number of dialysis requirement	
	Correlation coefficient	**p-value**
Norepinephrine duration	0.146	0.451
Norepinephrine dose	-0.182	0.345

Table 6. An Assessment of Graft Rejection and Graft Loss Risk in Recipients by Treatment in Donor

	Graft rejection		Graft loss	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Norepinephrine duration	0.997 (0.947-1.049)	0.908	0.989 (0.923-1.060)	0.764
Norepinephrine dose	1.000 (0.998-1.002)	0.932	1.000 (0.996-1.002)	0.470

DISCUSSION

There was hypotension in all the donors and norepinephrine was used as the first choice in hemodynamic management in the present study. There was no relationship between the dose and duration of norepinephrine used in the BDDs and the graft function.

Dysfunction of the sympathetic and parasympathetic nerves upon brain death led to vascular tone instability, and a decrease in blood pressure, causing hot ischemia of the organ. Hemodynamic instability upon brain death in donors can lead to donation failure in 25% of potential donors, and more than 80% of potential donors need vasoactive drugs to restore hemodynamic stability on the grounds that prolonged hypotension would increases the risk of primary dysfunction (14,15). Improved donor care and vasoactive drug use are therefore important factors for improved graft function and long-term graft survival. The role of vasoactive drugs in organ preservation is still controversial despite the said critical need (16-18).

Norepinephrine is the vasoactive drug of choice in a number of countries, including Europe, with increased use in recent years (19). Birtan et al. (11) reported in their study of 270 kidney recipients that norepinephrine use might have a beneficial effect in donor management due to reduced rates of graft rejection and loss upon norepinephrine treatment. Schnuelle et al. (16) showed that dopamine pretreatment reduced the risk of hemodialysis upon renal transplantation, despite the fact that there was no significant difference by long-term survival rate of the grafts between the dopamine and dopamine-free groups ($p>0.05$). A study of 152 renal transplant recipients suggested that dopamine use in donors reduced graft rejection and increased the long-term survival of transplanted kidneys (16).

There are also contrary opinions, which suggested that vasoactive drugs inflicted harm to graft function. O'Brien et al. (20) found that vasoactive drugs increased the incidence of acute tubular necrosis upon renal transplantation. Shao et al. (21) investigated the risk factors for graft dysfunction in 2012 upon renal transplantation and reported that 72.2% of the donors in the delayed graft function (DGF) group used norepinephrine, while only 10% of the donors in the fast-healing graft function group used norepinephrine.

Vasoactive drugs, especially norepinephrine, were used in all the donors in the present study. The present study focused on the effect of the said agent on the recipient's kidney since norepinephrine was the most frequently used vasoactive agent in patients. The dose of norepinephrine used for the purposes of donor management was lower (mean 0.2 mcg/kg/min) in our study population (22). Half of the recipients required dialysis following transplantation and three patients had graft loss. This loss was not directly attributed to the recipients use of vasopressors. There was no statistically significant relationship between the dose and duration of norepinephrine treatment, and the recipients BUN, creatinine, and GFR parameters in our analysis ($p>0.05$). The rate of delayed graft function in recipients of renal transplant from brain-dead donors ranged from 5% to 70% (23,24). It may develop due to a number of factors related to donor, recipient, and transplantation procedures. In the present study, there was one (3.3%) renal transplant recipient with delayed graft function despite vasoactive

agents were used in all the brain-dead donors. The fact that hemodynamic stability was achieved by low-dose norepinephrine treatment in BDDs might have been effective in protecting renal function regarding the lower rates in the present study. Birtan et al.(11) reported norepinephrine used in the management of brain death that 46.3% of the renal transplant recipients required hemodialysis after transplantation, where 53.7% did not need any support, and that vasoactive agents reduced the number of recipients, who required dialysis. The vasoactive drug use rate in their study population was 85.8%. Birtan et al. (11) did not record the number of dialysis sessions following transplantation. All the patients were on vasoactive medications in our donor population, and therefore we were not able to determine the need for dialysis in treatment-naive recipients. Nevertheless, there was no relationship between the norepinephrine doses and the number of patients, who needed dialysis after transplantation, and the number of dialysis sessions. In our study, vasoconstrictors were used to achieve a mean arterial pressure of 60 mmHg in all brain-dead donors, according to general recommendations (8). This suggested that maintaining hemodynamic stability in BDDs had a more dominant effect on renal function in the recipients rather than norepinephrine support.

In the present study, there was graft rejection in 16.6% recipients, while 10% recipients had graft loss and dose and duration of norepinephrine treatment were not significantly related to graft rejection and loss. Thereported rates of graft rejection (17.4%) and graft loss (10.3%) were higher than the results of the present study, despite the fact that 14.15% of donors had no vasoactive drug infusion although the sample size of Birtan et al. (11) study was larger compared to the present study. There was a graft rejection rate of 29.8% in recipients of renal transplants from donors, who used low-dose norepinephrine in a study by Zhang et al. (12). In the said study, the procedure of removing organs after cardiac death might have been effective in higher rates of graft dysfunction and rejection by noradrenaline use. Upon a comparison with the groups that received higher doses of norepinephrine and no norepinephrine, they did not find a relationship between graft rejection and norepinephrine administration although the above rate was higher than that the rejection rate of the present study.

The donor management guidelines emphasize the importance of prevention or immediate correction of hypovolemia to maintain perfusion in potentially transplantable organs. It is adopted to start vasopressor treatment in case of non-response to bolus fluid therapy in our clinic. It is still the primary therapeutic goal although euvolemic volume status is a concept that has not yet been completely defined (25). Euvolemic volume status was targeted during intravenous fluid treatment in the donor care period at the intensive care unit, and the mean urine output was 152.9 (0-400) cc/h.

Zhang et al. (12) investigated in their retrospective evaluation of cardiac post-mortem kidney transplants, the relationship between high-dose norepinephrine (≥1.3 μg/kg/min) infusions in donors, and the postoperative renal function and complications in recipients. Creatinine was significantly higher in the high-dose group compared to the low-dose and drug-free group ($p<0.05$) on postoperative Day 1 and 7. They reported that blood urea nitrogen values were also significantly higher in the high-dose group compared to the lowdose and drug-free group ($p<0.05$). Whereas in our study population, there was no significant relationship between the dose and duration of norepinephrine used in donor management at day one, first and third month after transplantation ($p>0.05$). In addition, we were not able to comment due to the fact that there was no vasopressor-free group in the present study. Furthermore, direct comparison was not available since the donors were brain-dead patients.

Limitations

The retrospective nature of our research, and the relatively smaller sample size are the limitations of the present study. In addition, the likelihood of differences by practitioners cannot be excluded although donor

care was based on guidelines. Moreover, the lack of vasopressor-free patients among the study groups prevented the investigation of the direct effect of vasopressors. Nevertheless, due to the impossibilities in conducting a study in which the direct effect is investigated, we still consider that our study will contribute to the literature.

Furthermore, there is no certainty regarding determination of high and low doses of vasopressors used in transplant patients. The cutoff value for the doses was calculated on the basis of Bassi et al. (26) study and further studies should definitely investigate the use of different cutoff values. The first agent to consider in case of hypotension is not norepinephrine in the legacy organ transplantation guidelines, where it has recently become the agent of choice. Therefore, dopamine and epinephrine was started in addition to norepinephrine in some of our patients, especially who were included in the early period of the study. In our study, dopamine was used together with norepinephrine in %36.6 of the patients. We determined the average dopamine doses in our donors were over 10 mcg/kg/min. Although we think that this effect can be determined in the presence of a larger sample, clinically, we determined that it had no effect on the number of dialysis needs and graft survival in recipients. Thus, there is a need for further studies, which would investigate and differentiate the effects of only a single agent.

CONCLUSIONS

The use of vasoactive drugs in BDDs may positively contribute to the improvement of renal function in renal transplant recipients. We believe that the low-dose norepinephrine used in the management of donors in intensive care unit has minimal or no effect on graft rejection, graft loss, and dialysis need in the renal recipient. We suggest, on the contrary, that hemodynamic stability may prevent delayed graft function in recipients if achieved at low vasopressor norepinephrine doses.

Conflict of Interest

The authors declare to have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

The study was approved by Ethics Committee of Bursa Yüksek İhtisas Training and Research Hospital (Approval Date15.12.2021 and Protocole Number: 2011-KAEK-25 2021/12-09). The study protocol conformed to the ethical guidelines of the Helsinki Declaration.

Author Contributions

All authors contributed equally to this work.

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