Effect of Low Dose Dopamine on Early Graft Function in Living Unrelated Kidney Donors

Hamzeh Hosseinzadeh, Samad Golzari, Mohammad Abravesh, Ata Mahmoodpoor, Davood Aghamohammadi, Afshar Zomorrodi, Parisa Hosseinzadeh

Department of Anesthesiology, Imam Khomeini Hospital, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

Corresponding Author: Ata Mahmoodpoor, MD; FCCM
General ICU, Shohada Hospital, El-Goli St., Tabriz, Iran

Tel: +98 914 116 0888
E-mail: amahmoodpoor@yahoo.com

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Purpose: To evaluate the effect of low-dose dopamine administration on the early function of the kidney in unrelated kidney donors after transplantation.

Materials and Methods: In this double-blinded clinical trial, 60 adult kidney donors and 60 recipients, younger than 50 years old, were studied. Donors and recipients were randomly divided into two groups; group 1 received dopamine 3 µg/kg/min and group 2 received similar regimen of placebo. During the first 3 days postoperatively, serum levels of urea and creatinine as well as urine output and early kidney function were compared between two groups.

Results: Serum levels of creatinine and urea and urine output during the first three days after the operation did not differ statistically significantly between two groups ($P = .549$, $P = .306$ and $P = .375$, respectively). Early kidney function was better significantly in group 1 (5.3 ± 3.2 versus 8.6 ± 8.0 hours; $P = .048$).

Conclusion: Premedication of the kidney transplant donors with low-dose dopamine accelerates early kidney function after transplantation, but has no effect on the hemodynamic status and serum levels of creatinine and urea in the donors.

Keywords: kidney transplantation, kidney function tests, dopamine, tissue donors

INTRODUCTION

Kidney transplantation is the treatment of choice for patients with end-stage renal disease. Delay in achieving transplanted kidney function after transplantation is a serious problem.[1] Although immunosuppressive medications have been able to prevent acute transplant rejection, chronic nephropathy still exists and disturbs the function of transplanted kidneys. There are numerous non-immunologic factors which can affect transplanted kidney function, including hemodynamic instability, manipulations during donor nephrectomy, renal vessels spasm in the donor and recipient, duration of cold ischemia, and ischemia and reperfusion-induced injuries. These conditions can lead to pro-inflammatory state and increase immunogenicity of graft, which in turn results in graft dysfunction and rejection.[2-4] Therefore, decreasing organ injury with medical pretreatment of donors may lead to better outcome of the kidney transplantation.

Instant urine production has been reported in 90% of the living donor transplantations and 40% to 70% of the cadaveric transplantations.[5] Some studies demonstrated that catecholamine administration could have protective effects on the transplanted kidney, reducing acute transplant rejection and increasing long-term survival after transplantation.[6-9] Among catecholamines, dopamine has the best effect on survival of transplanted kidneys. Dopamine induces heat shock protein heme oxygenase enzyme-1,[10] which plays an important role in preventing vascular damage in the transplanted kidney in animal models.[11] Dopamine can protect endothelial cells from oxidative stress with its dihydroxy-phenolic structure.[12] Although catecholamines protect against the increase of inflammatory molecules, such as intracellular adhesion molecule-1, and cold storage-induced endothelial cell damage,[13,14] there is controversy over protective effects of dopamine in kidney recipients by reviewing current strategies for renal transplantation.[15]

The majority of transplantations which are performed in Imam Khomeini Hospital in Tabriz are from the unrelated living donors, and delay in achieving kidney function reduces graft survival. This study was aimed to evaluate the effect of low-dose dopamine administration in the living donors on early function of the transplanted kidney.

MATERIALS AND METHODS

From May 2008 to October 2009, 120 subjects were studied. Sixty kidney donors were randomized into two groups, group 1 (n = 30) received 3 μg/kg/min dopamine and group 2 (n = 30) received similar regimen of placebo. Sixty recipients were allocated in respected groups. Randomization was done by random block. There were 60 sealed envelopes for each group with the name of dopamine [30] or control [30] inside them. Patients and anesthesiologist were blind to the study. This study was reviewed and approved by the Medical Ethics Committee of Tabriz University of Medical Sciences. Written informed consent was obtained from each participant.

Power calculations indicated that a sample of 60 patients and 60 controls would detect a proportion difference of at least 15% between two groups, with a significance ($\alpha = 0.05$) and a power of 80%. The kidney donors' conditions and short-term survival after kidney transplantation were compared between the two groups.

Blood pressure, central venous pressure, body temperature, end-tidal CO_2, and urine output were measured. Furthermore, pulse oximetry and electrocardiography were performed.

Intravenous anesthesia was performed using remifentanil, propofol, cisatracurium, and a gas mixture of N_2O + O_2 6 L/min. The administered gas was reduced by 50% every 10 minutes until reaching the flow of 2 L/min. Central venous pressure of the patients was maintained between 10 and 12 mmHg.

Subjects in group 1 received dopamine drip with 3 μg/kg throughout the operation with infusion pump and those in control group received normal saline with the same volume/hour as drip through infusion pump.

All donors received manitol 1 g/kg before nephrectomy. All kidney recipients received manitol 1 g/kg plus furosemide 1.5 mg/kg before removing arterial clamp. During reperfusing, bicarbonate 1 meq/kg was administered intravenously. Time to diuresis after removing vascular clamp was recorded. Diuresis below 60 minutes was considered early. All the subjects were followed up for 6 hours after diuresis. The follow-up period was 3 days after the operation. Subjects in each group received the same immunosuppressive regimen.

Demographic parameters and cold and warm ischemia duration were recorded. Serum levels of blood urea nitrogen and creatinine as well as urine volume were recorded before the operation and 12, 24, 36, 40, 60, and 72 hours postoperatively. Data were presented as mean ± standard deviation, frequency, and percentage.

Data were analyzed with SPSS software (the Statistical Package for the Social Sciences, Version 15.0, SPSS Inc, Chicago, Illinois, USA). Quantitative variables were compared using independent samples *t* test, and categorical variables were compared using contingency tables and Chi-Square or Fisher's Exact test. To compare the changes in the quantitative parameters between two groups, repeated measures analysis was used. *P* values less than .05 were considered statistically significant.

RESULTS

Kidney Donors

Demographic characteristics of kidney donors are shown in Table 1. No statistically significant difference was observed between two groups. As shown in Table 2, there were no significant differences regarding systolic blood pressure ($P = .100$), mean arterial pressure ($P = .547$), heart rate ($P = .618$), SPO_2 ($P = .413$), and body temperature ($P = .866$) between two groups.

Kidney Recipients

General quantitative variables in both groups are summarized in Table 1. No statistically significant difference was observed between two groups. Again, there was no significant difference regarding systolic blood pressure ($P = .299$), mean arte-

Table 1. Comparing demographic characteristics in kidney donors and recipients

Variables	Donors			Recipients		
	Intervention group	Control group	*P*	Intervention group	Control group	*P*
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Age, y	28.9 ± 5.0	26.9 ± 4.2	.093	37.6 ± 11.7	35.6 ± 9.7	.480
Weight, kg	70 ± 12.3	68.4 ± 11.6	.602	62.4 ± 10.1	62.3 ± 14.4	.983
Duration of anesthesia, h	3.7 ± 0.6	3.6 ± 0.4	.316	5.0 ± 0.8	4.9 ± 0.7	.427
Duration of surgery, h	2.9 ± 0.5	2.9 ± 0.5	.682	4.2 ± 0.7	4.2 ± 0.6	.780
Liquid volume, L	4.6 ± 0.9	4.3 ± 0.7	.056	4.7 ± 1.0	4.9 ± 0.9	.486
Urine , L	0.8 ± 0.4	0.9 ± 0.4	.772	0.3 ± 0.2	0.3 ± 0.2	.480
Bleeding, L	0.3 ± 0.1	0.3 ± 0.1	.184	0.6 ± 0.2	0.6 ± 0.1	.084
Hematocrit, %	43.3 ± 4.4	4 5 ± 4.3	.094	32.4 ± 2.3	33.3 ± 3.8	.118
Body mass index				22.7 ± 2.4	22.2 ± 2.4	.389
Duration of dialysis, month				17 ± 11.2	19.9 ± 0.6	.560
Warm ischemia duration, min				1.3 ± 0.5	1.2 ± 0.5	.552
Cold ischemia duration, min				94 ± 21.6	88.2 ± 17.9	.262

SD indicates standard deviation.

Table 2. Comparing quantities of general variables between two recipient groups

Variables	Time	Intervention group	Control group	*P*
		Mean ± SD	Mean ± SD	
Systolic blood pressure	Before surgery	89.8 ± 9.5	88.9 ± 13.8	.761
	After induction	84.7 ± 13.1	90.9 ± 12.2	.062
	After intubation	96.3 ± 18.7	94.6 ± 15.2	.821
	During surgery	92.6 ± 9.0	91.9 ± 11.2	.771
Heart rate	Before surgery	80.6 ± 13.5	82.4 ± 10.3	.564
	After induction	80.5 ± 12.5	85.1 ± 9.7	.116
	After intubation	87.4 ± 16.0	89.7 ± 18.6	.615
	During surgery	83.3 ± 9.6	79.4 ± 11.4	.157
SPO_2	Before surgery	95.3 ± 1.3	97.9 ± 1.1	.382
	After induction	98.6 ± 1.2	98. 8 ± 0.7	.508
	After intubation	98.9 ± 1.2	99.1 ±1.0	.561
	During surgery	99.4 ± 0.7	99.0 ± 1.2	.115
Body temperature	Before surgery	35.9 ± 0.7	35.7 ± 0.6	.239
	During surgery	34.6 ± 5.5	35.5 ± 0.5	.350
End-tidal CO_2		31.7 ± 4.3	30.1 ± 2.7	.096

SD indicates standard deviation.

Table 3. Comparing hemodynamic parameters and vital signs in recipients

Variables	Time	Intervention group	Control group	*P*
		Mean ± SD	Mean ± SD	
Mean arterial pressure	Before surgery	102.3 ± 18.1	102.3 ± 12.5	.993
	After induction	96.8 ± 17.5	95.1 ± 13.9	.684
	After intubation	95.9 ± 20.0	101.4 ± 23.9	.327
	During surgery	88.4 ± 12.4	92.5 ± 12.9	.218
Heart rate	Before surgery	88.9 ± 17.0	85.8 ± 14.1	.450
	After induction	88.5 ± 15.4	86.0 ± 18.1	.561
	After intubation	90.2 ± 18.5	86.5 ± 17.3	.418
	During surgery	75.8 ± 15.0	73.4 ± 12.3	.502
SPO_2	Before surgery	96.7 ± 1.7	96.4 ± 1.5	.373
	After induction	97.9 ± 1.0	98.4 ± 1.3	.150
	After intubation	98.2 ± 1.1	98.7 ± 0.8	.048
	During surgery	98.2 ± 1.3	98.9 ± 0.9	.035
Body temperature	Before surgery	36.4 ± 0.5	36.2 ± 0.9	.206
	After induction	35.4 ± 5.4	36.2 ± 0.7	.469
	During surgery	35.8 ± 1.8	35.9 ± 0.8	.975
Central venous pressure	Before surgery	12.6 ± 3.8	11.8 ± 2.9	.387
	After induction	13.2 ± 3.2	12.7 ± 3.5	.587
	After intubation	13.6 ± 3.3	13.7 ± 3.8	.914
	During surgery	13.7 ± 3.1	13.6 ±2 .3	.816
End-tidal CO_2		31.9 ± 3.4	31.7 ± 3.0	.810

SD indicates standard deviation.

rial pressure ($P = .538$), heart rate ($P = .429$), SPO_2 ($P = .179$), body temperature ($P = .973$), and central venous pressure ($P = .667$) (Table 3).

Changes in serum levels of creatinine and urea and urine volume during the study in both groups are presented in Table 4. Mean serum level of urea and mean urine volume after 24 hours were significantly higher in group 1 ($P = .367$ and $P = .480$, respectively). There was no statistically significant difference regarding other variables. Studying the variables mentioned above revealed no statistically significant difference between two groups regarding serum creatinine ($P = .549$), serum urea ($P = .306$), and urine volume ($P = .375$).

The mean time for initiation of diuresis after clamp removal was 5.3 ± 3.2 hours (range, 1 to 13 hours) in group 1 and 8.6 ± 8.0 hours (range, 1 to 29 hours) in group 2 ($P = .048$). Instant delay function was observed in 1 subject (3.3%) in the intervention group and in 2 subjects (6.7%) in the control group. There was no statistically significant difference between two groups in this regard ($P = .500$).

DISCUSSION

There are few studies about the effect of low-dose dopamine on transplanted kidney function. Schnuelle and colleagues reported that low-dose dopamine administration in intensive-care unit significantly reduced the probability of acute transplant rejection and increased transplanted organ survival.[16] In another study, they also concluded that low-dose dopamine administration in the kidney donors reduced the need for hemodialysis after transplantation.[17] In a randomized controlled trial, Grundmann and associates showed a higher urine output in the immediate post transplant period with the use of low dosage of dopamine, without any effect on creatinine clearance.[18] In another study, the effect of low-dose dopamine (5 μ/kg/min) on the kidney donors' status before transplantation was evaluated. In a 3-year follow-up period, transplant rejection rate was significantly lower in the intervention group. Although dopamine administration significantly increased systolic blood pressure in the donors, it was not clinically significant or influential.[19]

Low-dose dopamine administration in donors has a positive effect on the recipient status and transplanted organ survival in all the above-mentioned conditions. However, the method of results evaluation and follow-up duration after transplantation are different in our study compared to others. The core objective of the above-mentioned studies was the evaluation of hemodialysis need after transplantation. While in our study, we focused on the changes of serum levels of urea and creatinine after transplantation for 3 days, which can directly reflect status of the kidney recipients as core parameters.

The study by Schnuelle and colleagues, which has been still the most comprehensive study on the living kidney donors,[19] had several limitations. The most important drawback in their study is that the researchers and evaluating staff were not blind to the study and the results were obtained according to the patients' grouping (epinephrine or placebo). In comparison, our study has been carried out as a double-blind study, which can be considered a major advantage. On the other hand, the study by Schnuelle and associates was carried out on brain death donors whereas the present study was carried out on healthy donors in the age range of 20 to 30 years. Considering the intervention and controlled status of brain death cases, generalizing the obtained results to the non-brain death living donors might be inaccurate. Furthermore, the status of dopamine administration during kidney transplantation surgery in the recipients and status of receiving other common medications related to kidney transplantation by donors, such as thyroxin, corticosteroid, vasopressin, insulin, iron chelator, etc, have not been studied.[20-22]

Gottmann and coworkers evaluated the effect of low-dose dopamine (5μ//kg/min) in the kidney

donors in rat models. They demonstrated that dopamine administration in kidney donors improved both short-term and long-term prognoses.[23] As it was mentioned, early kidney function was significantly better in the intervention group in our study, but no significant effect was observed regarding serum levels of creatinine and urea within three days after transplantation. Novitzky and colleagues and Wood and associates concluded that dopamine administration in the kidney donors only increased systolic blood pressure whereas it had no significant effect on transplant rejection rates within 30 days and on allograft and patient survival until 36 months after transplantation.[24,25]

De Los Angeles and colleagues reported that low-dose dopamine administration (3µg/kg/min) in combination with furosemide in kidney donors had no significant effect on urine output or creatinine clearance in the recipients after transplantation compared to the placebo.[26] Spicer and associates using Doppler ultrasonography in their study showed that dopamine administration in the kidney donors had no significant effect on speed and degree of blood stream in the transplanted tissue.[27] As it can be seen, the results obtained in this field differ greatly. One of the reasons can be the effect of confounding factors on final results, such as the age of donors, the weight of recipients, and cold ischemia duration.[24] In our study, all the above-mentioned factors were matched between two groups. To the best of our knowledge, this study is the first study carried out on non-brain death donors. Limitations of our study were the short duration of study, monitoring of kidney function based

Table 4. Serum levels of creatinine and urea, and urine volume after transplantation in recipients

Variables	Time	Intervention group	Control group	*P*
		Mean ± SD	Mean ± SD	
Serum creatinine	Basic	7.2 ± 3.6	13.8 ± 36.3	.322
	After 12 hours	6.5 ± 3.5	5.4 ± 2.0	.139
	After 24 hours	4.7 ± 3.2	4.5 ± 2.5	.701
	After 36 hours	4.1 ± 2.9	3.5 ± 2.1	.338
	After 48 hours	3.3 ± 2.7	2.9 ± 1.9	.605
	After 60 hours	2.8 ± 2.4	2.6 ± 1.8	.666
	After 72 hours	2.0 ± 2.0	2.6 ± 1.9	.272
Serum urea	Basic	84.0 ± 32.6	66.4 ± 26.8	.026
	After 12 hours	81.0 ± 27.9	75.8 ± 27.2	.468
	After 24 hours	78.0 ± 4.7	70.0 ± 26.2	.367
	After 36 hours	80.8 ± 49.3	70.3 ± 27.4	.309
	After 48 hours	78.9 ± 52.8	68.4 ± 30.7	.349
	After 60 hours	77.3 ± 57.1	68.1 ± 34.4	.450
	After 72 hours	68.2 ± 50.3	72.4 ± 35.4	.706
Urine volume, L	Basic	0.9 ± 0.9	0.7 ± 0.9	.470
	After 12 hours	2.4 ± 2.2	2.9 ±1.9	.359
	After 24 hours	2.2 ± 1.8	3.9 ± 2.4	.004
	After 36 hours	1.8 ± 1.6	2.2 ± 1.0	.274
	After 48 hours	1.8 ± 1.7	2.3 ± 1.6	.306
	After 60 hours	3.0 ± 7.6	1.7 ± 1.1	.355
	After 72 hours	1.4 ± 0.9	1.9 ± 1.1	.072

SD indicates standard deviation.

on early diuresis and urea/creatinine, and short-term patients' follow-up.

CONCLUSION

We concluded that low-dose dopamine in the unrelated kidney donors, compared to the placebo, significantly increases the speed of diuresis initiation in the recipients after transplantation. Furthermore, it has no statistically significant effect on reducing serum level of creatinine and/or urea in the kidney recipients after transplantation.

CONFLICT OF INTEREST

None declared.

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