Bolus Injection Versus Infusion of Furosemide in Kidney Transplantation: A Randomized Clinical Trial

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Purpose: Furosemide is commonly administered to increase the urinary output in patients with transplanted kidneys. This study compared the two administration routes of furosemide (bolus versus infusion) in kidney transplanted patients.

Materials and Methods: Fifty patients who had undergone kidney transplantation in 2015 in a hospital in Tabriz, Iran, were included in this clinical trial. They were divided into two groups: bolus (120 mg stat) and infusion (4 mg/minute) groups. The primary outcome was urine onset time. Secondary outcomes were urine output volume, vital signs (blood pressure, heart rate), and electrolyte level (creatinine, blood urea nitrogen, sodium and potassium). After arterial and venous anastomoses, arterial clamp removal time and diuresis onset were recorded. Finally, the urinary output volumes of both groups were measured with regular urine bags for an hour after anastomosis. Then it was repeated each three hours for 24 hours, and eventually two and three days thereafter. Finally, all data were statistically analyzed.

Results: Around 72% of the patients were men (mean age of 37.15 ± 14.67 years). Urine output was higher in bolus group but it was not statistically significant. Diuresis duration was measured after arterial declamping and its averages were 5.41 ± 3.7 minutes and 9.36 ± 7.65 minutes in bolus and infusion groups, respectively (P = .040). Furosemide bolus injection and infusion had no significant effect on creatinine, blood urea nitrogen, sodium and potassium.

Conclusion: Furosemide bolus injection can reduce diuresis onset time compared to furosemide infusion.

Keywords: clinical trial; furosemide; infusion; kidney transplantation; loop diuretic.

INTRODUCTION

Kidney transplantation is the last stage of kidney failure treatment with a more favorable lifestyle results and a reduction in mortality rate. The main drawback of kidney transplantation is its rejection. Here, the acute transplantation rejection is the most important predictor. The transplanted kidney will have a good long-term prognosis if it has a proper function from the beginning.[1-3]

An important and fundamental issue regarding this procedure is the diuresis initiation. Currently, high dosages of diuretics are being used for speeding up the diuresis initiation. The longer it takes to initiate diuresis, further complications, such as fluid retention, pulmonary edema, and even acute kidney failure might occur.[3]

Administration of mannitol is a commonly used method to precipitate diuresis initiation. Mannitol is a major protective osmotic agent in kidney preservation.[4] Sufficient hydration during kidney transplantation is very important and the kidney requires sufficient perfusion for its maximum function. There is a relationship between kidney transplantation and acute tubular necrosis occurrence.[3] Thus, the strategy for preventing acute tubular necrosis includes limiting the extent and duration of kidney ischemia and establishing and preserving the abundant intravascular volume to reduce the incidence of acute tubular necrosis.[5]

Overhydration and diuretics, such as furosemide, have positive effects on reducing kidney transplant rejection. Diuresis initiation time is important for transplanted kidney's survival. A transplanted kidney with a good function from the beginning has a good long-term prognosis. Thus, this study has compared the effect of bolus injection versus infusion of furosemide on diuresis initiation time of patients who had received kidney transplantation.

MATERIALS AND METHODS

Written informed consent was obtained from them before their participation in the study. The inclusion criteria were: 1) having an end-stage kidney disease and being a kidney transplant candidate; 2) having blood pressure more than 100/60 mmHg at the start of surgery; and 3) not having a systematic disease (except for end-stage kidney disease). The exclusion criteria were: 1) being older than 65 years; 2) having metastatic tu-

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Table 1. Patients' demographic information.

Variables			Bolus group		Infusion group		*P* value
			Frequency	%	Frequency	%	
Age (years old)	< 20		8	32	1	4	.076
	21-30		3	12	3	12	
	31-40		7	28	11	44	
	> 40		7	28	10	40	
Sex	Male		21	84	15	60	.052
	Female		4	16	10	40	
Past Medical History	HTN	Yes	13	52	15	60	.0569
		No	12	48	10	40	
	DM	Yes	6	24	4	16	.149
		No	19	76	21	84	
	Seizure	Yes	0	0	2	8	
		No	25	100	23	92	
Surgery Duration (hours)	3-3.9		6	24	10	40	.322
	4-4.9		13	52	8	32	
	5-5.9		6	24	7	7	

Abbreviations: HTN, hypertension; DM, diabetes mellitus

mors; 3) having sever homeostatic alterations during transplantation (blood pressure less than 80/50 mmHg for more than half an hour); 4) presence of chronic hepatic disease; 5) urinary tract infections; 6) urinary tract anomalies; and 7) aortoiliac diseases.

Study design

The participants were divided into two groups, i.e. bolus and infusion groups, using the simple randomization, according to the codes assigned to each group by Minitab software. Then, the codes were categorized and the patients were divided accordingly. In the bolus group, 120 mg of bolus furosemide was administered within one minute immediately before arterial declamping. In the infusion group, the infusion dosage began with 4 mg/min thirty minutes before declamping and continued afterwards.

All participants received dialysis 24 hours before surgery. Biochemical tests for sodium, potassium, urea, and creatinine were performed. Personal characteristics, including age, sex, and body weight, were recorded. All open nephrectomy procedures were done on living donors by the same expert surgeon and all transplant recipients were operated by the same surgery team. In all cases, kidney veins were anastomosed to external iliac veins and arteries were anastomosed to the internal iliac arteries.

Throughout the procedure, systolic blood pressure was preserved in the range of 120-140 mmHg. Central venous pressures were maintained within 10-12 and 14-16 cmH2O before and after arterial clamping, respectively. Blood transfusion was done as needed based on hemoglobin and hematocrit levels. Following arterial and venous anastomoses, the arterial clamp removal time and diuresis onset were recorded. Finally, urinary output volumes were measured for an hour after anastomosis. Then it was repeated each three hours for 24 hours, and eventually two and three days thereafter. In addition, the levels of sodium, potassium, blood urea nitrogen, and creatinine were recorded preoperatively and then daily for four days after the surgery.

Outcome assessment

The primary outcome was urine onset time. Therefore, when the arterial blood declamping was established, the patient's urine was measured in minutes. Secondary outcomes included volume of urine output, vital signs (blood pressure, heart rate), and electrolyte level (creatinine, blood urea nitrogen, sodium and potassium).

Statistical analysis

Statistical differences were presented as mean ± standard deviation. Data analysis was done using statistical package for the social sciences (SPSS) software version 16.0 (Chicago, IL, USA). Numerical variables were compared by independent samples t-test. Categorical variables were compared by chi square or Fisher's exact tests as appropriate.

RESULTS

A number of 50 patients who received kidney transplantation participated in this clinical trial (25 participants in each group, **Figure 1**). Their mean ages were 32.96 ± 1.48 and 40.2 ± 10.68 years old in bolus and infusion groups, respectively (P = .084). The surgery duration was 4.16 hours in bolus group and 4.19 hours

Table 2. Heart rate, systolic and diastolic blood pressure of patients before induction and during surgery

		Heart Rate			Systolic Blood Pressure			Diastolic Blood Pressure		
Time (minutes)	**Study Groups**	**Mean**	**SD**	***P* Value**	**Mean**	**SD**	**P Value**	**Mean**	**SD**	***P* Value**
Before induction	Bolus	84.25	15.81	.125	151	17.4	.117	91.7	13	0.76
	Infusion	80.69	23.34		140.6	26.5		85.47	18.3	
0-15	Bolus	83.08	17.75	.419	136.8	22.4	.59	85.7	15.8	.120
	Infusion	79.54	11.68		125	16.4		79.6	14.8	
16-30	Bolus	78.08	15.02	.497	138.2	19.2	.052	89.5	14	.102
	Infusion	80.83	12.7		128.7	13		84.8	12.2	
31-45	Bolus	79	16.77	.678	127.1	13.9	.875	75.8	13.1	.685
	Infusion	80.08	14.19		126.4	16.7		77.2	10.7	
46-60	Bolus	86.5	19.21	.395	130.3	14.9	.134	75.3	9.5	.770
	Infusion	82.16	15.54		123.4	16.4		77.2	11.9	
61-75	Bolus	90.39	17.55	.580	131.3	14.7	.300	75.3	9.8	.451
	Infusion	87.6	16.27		126.7	14.7		74.4	10.7	
76-90	Bolus	91.78	17.69	.727	131.9	10.1	.212	74.6	11.2	.959
	Infusion	93.7	16.15		127	14.2		74.8	8.6	
91-105	Bolus	88.5	17.38	.218	135	12.2	.818	76.8	11.2	.230
	Infusion	95.29	15.96		136.1	17.8		81.2	11.1	
106-120	Bolus	89.47	19.87	14.03	133.1	11.9	.433	75.8	13.7	.206
	Infusion	95	14.03		139	24.8		82.2	13.6	

in infusion group (P = .879, **Table 1**). There was no significant difference between the two groups regarding heart rate and systolic and diastolic blood pressures before and 120 minutes after anesthesia induction (**Table 2**). Diuresis duration was measured after arterial declamping. Its averages were 5.41 ± 3.7 minutes and 9.36 ± 7.65 minutes in bolus and infusion groups (P = .040). There was no significant difference between the two groups in terms of urinary output since the arterial anastomosis until four days after it, postoperatively

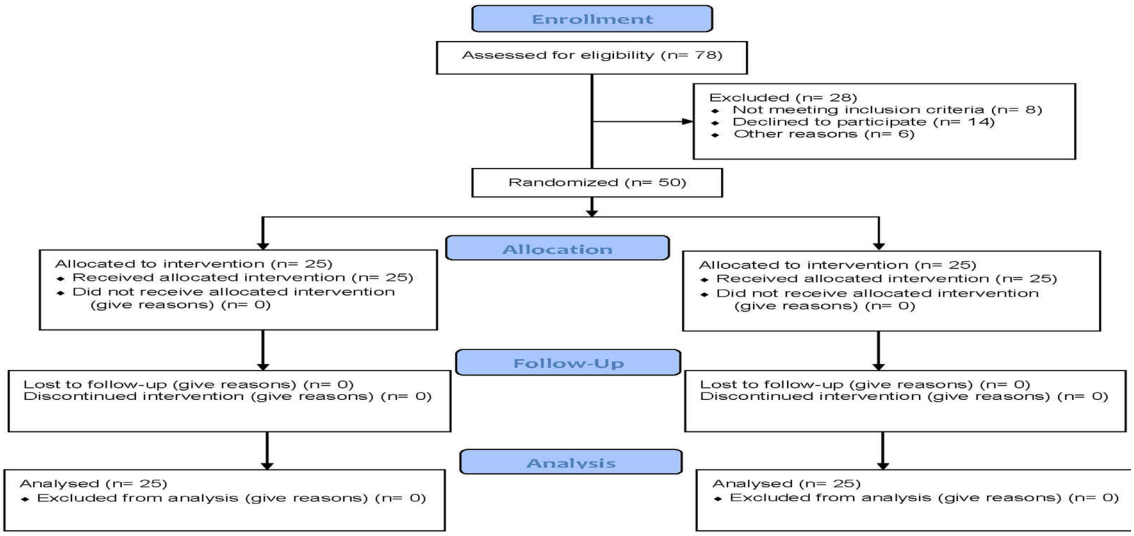

Figure 1. Patients' flow diagram

Table 3: Urine output of the patients since arterial anastomosis up to four days after the surgery

Time	Study Groups	Mean	SD	*P* Value
Anastomosis or one hour after surgery	Bolus	568	322.06	.811
	Infusion	542.8	412.31	
2-3 hours after surgery	Bolus	1924	1131.1	.118
	Infusion	1472	818.13	
4-6 hours after surgery	Bolus	3086	1127	.151
	Infusion	2682.25	776.1	
7-9 hours after surgery	Bolus	3186	466.2	.100
	Infusion	2597.91	588.3	
10-12 hours after surgery	Bolus	2558	831.6	.154
	Infusion	2264.58	553.9	
2nd day after surgery	Bolus	11883.6	6522.7	.871
	Infusion	1211875	2794	
3rd day after surgery	Bolus	7594	2986	.776
	Infusion	7816	2429.7	
4th day after surgery	Bolus	5224	1821.4	.798
	Infusion	5335.83	1119	

(**Table 3**). Furthermore, there was no significant difference in electrolyte levels before and four days after the surgery between both groups (**Table 4**).

DISCUSSION

In human kidney transplantation, attaining good immediate homograft function is an important factor for its ultimate success. When this is achieved, there will be massive postoperative diuresis along with improvement in the patient's general condition.[6] One way to trigger diuresis is using diuretics such as furosemide.

Most of the participants of our study were men in their fourth decades of lives. In similar studies the majority of patients have been men with the age range of 30-40 years old.[7,8] This is the range in which the person is actively present in the society and kidney transplantation can significantly impact his/her life quality.

In this study, it was observed that the bolus injection of furosemide increased the urinary output in kidney transplanted patients, but it was not statistically significant. However, the diuresis initiation time reduced

Table 4. Patients' electrolyte level before and four days after the surgery

		Creatinine		Urea Nitrogen		Sodium		Potassium	
Time	Study Groups	Mean	*P* value	Mean	*P* value	Mean	*P* value	Mean	*P* value
Preoperative	Bolus	6.93	.207	94.69	.210	137.18	.132	4.91	.154
	Infusion	7.86		115		139.72		4.43	
Surgery day	Bolus	4.95	.944	75.5	.577	136.6	.122	4.58	.217
	Infusion	4.99		82.7		139.37		4.2	
1st day after surgery	Bolus	3.3	.337	65.88	.334	138.76	.769	4.13	.641
	Infusion	3.22		77.65		139.16		4	
2nd day after surgery	Bolus	1.47	.146	62.64	.953	138.72	.721	3.96	.841
	Infusion	1.79		61.91		138.12		3.92	
3rd day after surgery	Bolus	1.31	.061	62.6	.597	138.5	.971	4.14	.209
	Infusion	1.75		56.87		138.54		3.77	
4th day after surgery	Bolus	1.55	.920	64.56	.396	139.52	.244	4.57	.244
	Infusion	1.6		55.04		132.65		3.99	

significantly. In a study by Lachance and colleagues the urinary output was 2.2 liters per day in patients who had received furosemide and 1 liter per day in their control group (who had not received furosemide) ($P < 0.05$). So, furosemide had increased the urinary output.[9] Razzaghi and colleagues reported that urine outputs were significantly higher in one, four, and 24 hours after transplantation in Lidocaine receiving group than furosemide receiving group ($P < .001$). In a meta-analysis, Alqahtani and colleagues found that in eight examined cases, there was no significant difference in urinary output of patients who had received furosemide by bolus or infusion. But in eight other cases, the urinary output was significantly higher in patients who had received continuous furosemide than in those who had received furosemide frequently.[11] We did not find any other similar studies in the literature. So, most studies support the furosemide bolus administration. This method, in comparison with infusion method, was able to further precipitate the diuresis onset.

In our study, no significant difference was observed in the levels of sodium, potassium, blood urea nitrogen, and creatinine between the two studied groups. Lachance and colleagues reported that furosemide significantly reduced creatinine level in kidney transplanted patients compared to their control group (who had not received furosemide).[9] In Razzaghi and colleagues' study, which compared the continuous injection versus bolus administration of furosemide in patients with heart failure, it was observed that furosemide injection increased creatinine level in the bolus group by 0.8 mg/dl and decreased it in the infusion group by 0.8 mg/dl ($P < .001$). In addition, the level of glomerular filtration rate decreased by 9 mL/min/1.73 m^2 in their bolus group and was increased by 6 ml/min/1.73 m2 in their infusion group ($P < .05$).[10]

In Palazzuoli and colleagues' study, it was observed that patients who had received continuous dosages of furosemide had higher serum creatinine level and lower glomerular filtration rate compared to those who received bolus dosages. Furosemide can contribute considerably to electrolyte excretion and serum creatinine level reduction by increasing glomerular filtration rate.[12] In our study, furosemide administration method did not change electrolyte level.

A limitation of our study was lack of a control group to measure the amount of urine output without receiving furosemide.

CONCLUSIONS

Bolus injection of furosemide can reduce diuresis onset time compared to furosemide infusion.

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CONFLICT OF INTEREST

None declared.

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