Excessive Positive Fluid Balance Has A Negative Effect On Short-Term Renal Outcomes After Kidney Transplantation

Jun Gyo Gwon

Korea University College of Medicine

Cheol Woong Jung

Korea University College of Medicine

Chang Hun Lee

Hyundai General Hospital

Myung-Gyu Kim (✉ gyu219@hanmail.net)

Korea University College of Medicine

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Abstract

Background: Optimized postoperative fluid management is important for maintaining early allograft function after kidney transplantation (KT). However, there is still no clear guidance regarding fluid treatment after KT. In this study, we investigated the effect of perioperative fluid balance on postoperative allograft function.

Methods: Recipients who underwent KT between March 2012 and August 2018 were included, and their medical records were reviewed retrospectively. We calculated fluid balance, which is the difference between total input and output during the 3 days after KT, and analyzed the change in estimated glomerular filtration rate (eGFR) according to fluid balance.

Results: A total of 178 patients were included after excluding those with delayed graft function or urine output <2000 ml on the first day after KT. Among them, 116 received kidneys from living donors and 62 received kidneys from deceased donors. The total fluid balance up to day 3 was $4,236.9 \pm 2830.4$ ml. Old age, high body mass index (BMI), excessive positive fluid balance of the recipient, and high final creatinine of the donor were significantly associated with low eGFR at 1 week. In addition, old age, BMI, and fluid balance of the recipient predicted the 1-month eGFR. In multivariate analysis, an excessive positive fluid balance was an independent predictor of low 1-week eGFR ($p=0.031$).

Conclusions: This study demonstrated that excessive positive fluid balance can negatively affect early graft function after KT. Proper fluid management strategies based on volume conditions may provide important therapeutic opportunities to improve early renal outcomes after KT.

Background

Proper fluid management is necessary to optimize tissue perfusion in critically ill patients, as supported by international guidelines [1]. However, fluid overload in critically ill adults and children has been associated with increased mortality and other complications, including organ dysfunction and requirement for ventilator support [2-4]. Regarding the kidney, some studies have reported that fluid overload increases the risk of kidney dysfunction [5-8]. The importance of fluid management is the same in renal transplant patients. Optimized perioperative fluid management is effective in preventing early allograft dysfunction [9-11]. Early graft dysfunction is associated with decreased graft and patient survival, impaired long-term graft function, and increased acute rejection [12]. Therefore, proper fluid management is essential to avoid early and late graft dysfunction. However, there are no guidelines for immediate postoperative fluid management. Until now, maximal volume infusion to the point of no further fluid responsiveness has long been considered the best fluid management in the perioperative period [13, 14]. Many centers follow the postoperative fluid management protocol described in textbooks [15]. In practice, however, fluid management following this protocol can result in a positive fluid balance. Currently, there are no studies on the effect of perioperative fluid balance on transplanted kidney function. The aim of this study was to determine the effect of early fluid balance after kidney transplant (KT) on early allograft function.

Methods

Patients and study design

This study evaluated the outcomes of 206 consecutive patients who underwent KT and postoperative management under a single surgeon in a single center between March 2012 and August 2018. Of the 206 patients, we excluded three patients who underwent dual KT, four patients who underwent multi-organ transplantation, five patients who died within 1 month after surgery due to any cause, and 16 patients with urine output <2000 ml on postoperative day (POD) 1. Among the deceased donors, there were no donors after cardiac death, and all donations were from brain-dead donors. Fluid balance was defined as the difference between oral intake and/or intravenous fluid administration and urine output. Other potential causes of fluid loss, including vomiting and diarrhea, were not recorded. The fluid balance was calculated based on the total input and output on POD 0, 1, 2, and 3. We evaluated the estimated glomerular filtration rate (eGFR) at 1 week and 1 month postoperatively according to the total fluid balance. The study was approved by the Institutional Review Board of the Korea University College of Medicine (IRB No. 2021-0811-001) and was conducted in accordance with the Declaration of Helsinki guidelines. The IRB waived the requirement for informed consent due to the retrospective design of the study, and all data were anonymized before analysis.

Fluid management

Fluid management can be divided into “maintenance fluid” and “replacement fluid.” Maintenance fluid comprised 5% dextrose administered at 40–80 ml/h until POD 1, according to the patient’s body weight. Replacement fluid was administered as half saline when the sodium level was above 135 mEq and normal saline when the sodium level was below 135 mEq. From the immediate postoperative period to POD 3, replacement fluid was administered to patients strictly according to the standardized replacement fluid protocol (Table 1). Regarding dietary management, fasting was maintained on the day of surgery, sips of water were permitted from POD 1, and a soft diet was started from POD 2.

Statistical analysis

Descriptive statistics are presented as mean $\pm$ standard deviation (mean $\pm$ SD) for continuous variables or numbers (percentages) for categorical variables. The association between subjects’ characteristics and eGFR values was investigated using Pearson’s correlation analysis, Student’s t-test, or analysis of variance (ANOVA), as appropriate. The relationships between fluid balance and eGFR are also presented as scatter plots with regression lines and 95% confidence bands of the regression lines. Multiple linear regression analysis was performed to explain the relationship between eGFR as a dependent variable and fluid balance while adjusting for other covariates. The adjusting covariates were variables with $p < 0.1$ in the univariate analysis of correlation between variables and eGFR at 1 week or 1 month postoperatively. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC, USA), and a two-sided P-value < 0.05 was considered statistically significant.

Result

A total of 178 KT performed over a period of 6 years was included in the study. Among these patients, 116 underwent living donor KT. All deceased donors were diagnosed with brain death. Baseline clinical and laboratory data of the 178 patients included in this study are described in Table 1. The total fluid balance up to POD 3 was $4,236.98 \pm 2830.46$ ml. The total urine output up to POD 3 was $27,140.04 \pm 10,091.13$ ml. The correlation between the initial fluid balance and total output was not statistically significant ($p = 0.149$). Initial fluid balance up to POD3 was found to affect eGFR at 1 week ($p < 0.001$) and 1 month ($p = 0.002$) after KT (Fig 1). Post-transplant eGFR 1 week after KT was significantly lower in recipients with old age, high body mass index (BMI), long cold ischemia time, multiple human leukocyte antigen (HLA) mismatches, initial positive postoperative fluid balance, and high donor creatinine. Initial positive fluid balance, old age, high BMI, and cadaver donors were also associated with lower eGFR up to 1 month after KT (Table 2). In multivariate analysis, initial positive fluid balance significantly correlated with low eGFR at 1 week after KT ($p = 0.031$), but not with eGFR at 1 month ($p = 0.093$) (Table 3). The patients were divided into living and deceased donor KT groups for subgroup analysis. In the living donor group, low eGFR at 1 week after KT significantly correlated with initial fluid balance ($p = 0.001$), but the correlation between 1-month eGFR and initial fluid balance was non-significant ($p = 0.053$) (Fig 2). In the deceased donor group, there was no significant correlation between eGFR and initial fluid balance in recipients at 1 week and 1 month after KT ($p = 0.448$ and 0.083 , respectively, Fig 3). The clinical data of living donor KT patients and deceased donor KT patients are shown in Table 4.

Discussion

This study retrospectively investigated the effects of initial postoperative fluid balance on early outcomes in KT recipients at a single center using a conventional fluid management protocol. All patients with urine output <2000 ml on POD 1 were excluded from the study to exclude patients whose renal function was initially impaired due to other risk factors. Since there was no correlation between urine output and total fluid balance, it was found that total fluid balance was not significantly affected by urine volume. Importantly, early eGFR was found to be low with increasing initial fluid balance up to 3 days after KT, suggesting that postoperative management with excessive amounts of fluid may adversely affect renal function recovery after KT. Studies have shown that fluid overload is a risk factor for acute kidney injury (AKI) [5, 6, 8, 16]. Encapsulated kidney structures limit compliance with higher hydrostatic pressures. High renal venous pressure due to fluid overload reduces the pressure gradient for renal perfusion, while increased tubular pressure may decrease the glomerular filtration pressure gradient. Increased pre-glomerular resistance further decreases renal blood flow and glomerular capillary hydrostatic pressure. The development of intra-abdominal hypertension according to edema of the abdominal organ restricts renal venous outflow. All these factors can adversely affect AKI recovery [17]. Procured kidneys from donors are under various hostile conditions. First, the kidney is hemodynamically placed in an ischemic state, followed by reperfusion injury after vascular anastomosis [18]. Renal inflammation during KT can also worsen kidney function by activating various innate and adaptive immune cells [19]. In addition, the transplanted kidney is denervated and lacks neurogenic regulation of renal blood flow [20]. Therefore,

excessive positive fluid balance early after KT may lead to poor renal perfusion, slow the recovery of damaged transplanted kidneys, and eventually affect renal outcomes.

In this study, the effect of initial positive fluid balance was found in living donor KT but not in deceased donor KT. Many confounding factors during deceased donor KT may have influenced these results. In fact, the deceased donors were more likely to be diabetic and were older than the living donors and had worse renal function just before KT. In addition, the cold ischemia time was longer, and the recipients were older. These donor and recipient factors can contribute to early functional deterioration and delayed recovery after KT [21, 22], and the effects of postoperative initial fluid balance may not be sufficient to regulate AKI recovery. It is very important to assess volume and manage fluid administration appropriately after surgery. In particular, KT surgery requires a large amount of fluid to be administered initially to prevent negative fluid balance caused by a large amount of diuresis. However, it is difficult to properly monitor volume, and fluid overload can cause a variety of problems. Central venous pressure (CVP) monitoring is the most commonly used method for measuring volume conditions. However, some limitations have been reported in transplant patients. Ferris et al. reported that decreased CVP was observed in the postoperative period in KT recipients, independent of the patient's volume status [23]. This phenomenon may be related to increased vascular permeability or release of vasodilator during periods of ischemia. Marik et al. also reported that only 57% of critically ill patients who appeared to be hypovolemic based on the CVP were fluid responders, whereas the others were unnecessarily loaded with fluids [24]. Several methods such as pulmonary capillary wedge pressure, echocardiography, stroke volume, and pulse pressure variation are used as part of volume assessment, but effective volume assessment in dynamic situations where massive uremic diuresis occurs early after KT has not been studied yet. The kidney is a critical organ that is affected by volumetric status; therefore, appropriate assessment of volume after KT can be an important step to improve renal outcomes, and the development of protocol-based fluid management is required. This study had some limitations. First, due to the retrospective design, the possibility that graft function negatively affects fluid balance cannot be excluded, although patients with insufficient urine output were not analyzed in the study. Second, because the volume status of the patients was not accurately measured, the balance of excessive amounts of fluid may not reflect volumetric overload. Nevertheless, the independent association of fluid balance and early graft function in live donor KT recipients with relatively good graft function suggests that preoperative fluid balance has a significant effect on the recovery from graft injuries.

Conclusions

In this study, we found that excessive positive fluid balance during the first 3 days negatively correlated with eGFR during the first month after KT. Therefore, it is important to establish treatment strategies, considering that excessive administration of fluids early after surgery can not only lead to volume overload, but may also delay recovery of renal function.

List Of Abbreviations

KT: kidney transplantation; POD: postoperative day; eGFR: estimated glomerular filtration rate; BMI: body mass index; HLA: human leukocyte antigen; AKI: acute kidney injury; CVP: central venous pressure

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of the Korea University College of Medicine (IRB No. 2021-0811-001) and was conducted in accordance with the Declaration of Helsinki guidelines. The IRB waived the requirement for informed consent due to the retrospective design of the study, and all data were anonymized before analysis.

Consent for Publication

Not applicable.

Availability of data and material

The datasets generated and/or analysed during the current study are not publicly available due to the principle of patient medical record reveal prevention in medical institution but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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No funding was obtained for this study.

Authors' contributions

MGK is the guarantor of this manuscript and its content. CHL had full access to the data and performed the analyses. JGG, CWJ contributed to the study design. All authors meaningfully interpreted the results. MGK and JGG. contributed to writing the manuscript. All authors approved the manuscript.

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Tables

Table 1. Replacement fluid protocol

Urine output			Replacement fluid
< 100cc			: Urine output + 50cc
101cc	-	200cc	: Urine output + 25cc
201cc	-	300cc	: Urine output
301cc	-	400cc	: Urine output - 50cc
401cc	-	600cc	: Urine output - 100cc
601cc	-	800cc	: Urine output - 200cc
>801cc			: 90% of Urine output

Table 2. Baseline characteristics and association between characteristics and estimated glomerular

filtration rate

	Baseline character	1 week eGFR			1 month eGFR		
	Mean $\pm$ SD or n(%)	Mean $\pm$ SD	Correlation coefficient	<i>p</i>	Mean $\pm$ SD	Correlation coefficient	<i>p</i>
Recipient							
Age	45.0 $\pm$ 12.3		-0.298	<.001		-0.260	0.001
Sex				0.781			0.631
Male	122 (68.5)	70.0 $\pm$ 21.6			67.0 $\pm$ 17.0		
Female	56 (31.5)	67.0 $\pm$ 27.2			62.5 $\pm$ 18.0		
BMI	23.4 $\pm$ 3.6		-0.225	0.003		-0.314	<.001
HTN				0.691			0.353
No	19 (10.7)	60.0 $\pm$ 39.0			58.8 $\pm$ 24.9		
Yes	159 (89.3)	56.3 $\pm$ 22.3			53.2 $\pm$ 17.3		
DM				0.130			0.506
No	82 (46.1)	59.7 $\pm$ 25.8			54.8 $\pm$ 20.9		
Yes	96 (53.9)	54.1 $\pm$ 23.0			52.9 $\pm$ 15.8		
Cold ischemic time	122.9 $\pm$ 116.6		-0.253	0.001		-0.128	0.089
Donor type				<.001			0.001
Cadaver	62 (34.8)	44.0 $\pm$ 21.5			47.8 $\pm$ 15.9		
Living	116 (65.2)	63.5 $\pm$ 23.3			57.0 $\pm$ 18.7		
Induction				0.619			0.716
Simulect	120 (67.4)	56.1 $\pm$ 23.0			53.4 $\pm$ 18.8		
ATG	58 (32.6)	58.0 $\pm$ 27.4			54.5 $\pm$ 17.2		

	Baseline character	1 week eGFR			1 month eGFR		
	Mean ± SD or n(%)	Mean ± SD	Correlation coefficient	<i>p</i>	Mean ± SD	Correlation coefficient	<i>p</i>
Maintenance				0.267			0.975
Tacrolimus	171 (96.1)	56.7 ± 24.6			53.8 ± 18.5		
Sirolimus	4 (2.25)	44.5 ± 13.7			54.5 ± 16.8		
Cyclosporin	3 (1.69)	74.8 ± 20.9			51.6 ± 11.9		
HLA mismatch				0.023			0.278
0-2	54 (30.3)	63.8 ± 26.9			55.6 ± 18.2		
3-4	79 (44.4)	55.1 ± 21.5			54.7 ± 19.4		
5-6	45 (25.3)	50.9 ± 24.8			50.0 ± 16.1		
Total fluid balance	4237.0 ± 2830.6		-0.283	<.001		-0.226	0.002
Donor							
Age	47.6 ± 12.5		-0.144	0.056		-0.292	<.001
Sex				0.509			0.274
Male	98 (55.1)	76.79 ± 23.5			76.1 ± 18.4		
Female	80 (44.9)	58.0 ± 25.7			52.1 ± 18.1		
BMI	24.9 ± 3.7		-0.148	0.059		-0.358	0.619
HTN				0.660			0.024
No	142 (79.8)	57.1 ± 25.0			55.3 ± 18.6		
Yes	36 (20.2)	55.1 ± 22.5			47.6 ± 15.7		
DM				0.062			0.116

	Baseline character	1 week eGFR			1 month eGFR		
	Mean $\pm$ SD or n(%)	Mean $\pm$ SD	Correlation coefficient	<i>p</i>	Mean $\pm$ SD	Correlation coefficient	<i>p</i>
No	159 (89.3)	57.9 $\pm$ 24.2			54.5 $\pm$ 18.4		
Yes	19 (10.7)	46.8 $\pm$ 24.7			47.5 $\pm$ 16.3		
Last eGFR	85.49 $\pm$ 31.82		-0.297	<.001		-0.129	0.085

eGFR, estimated glomerular filtration rate; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus

Table 3. Multivariate analysis to identify variables affecting eGFR

Variables	1 week eGFR				1 month eGFR			
	Coeff.	SE	Stand. Coeff.	p-value	Coeff.	SE	Stand. Coeff.	p-value
Recipient								
Age	-0.249	0.142	-0.125	0.081	-0.130	0.106	-0.087	0.221
BMI	-1.557	0.464	-0.229	0.001	-1.674	0.347	-0.330	<.001
Cold ischemic time	0.001	0.020	0.006	0.947	0.007	0.015	0.042	0.657
Donor type								
Cadaver	Ref.							
Living	11.910	5.326	0.233	0.027	4.052	3.982	0.106	0.311
HLA_mismatch								
0-2	Ref.							
3-4	-4.937	3.679	-0.101	0.182	1.584	2.751	0.043	0.565
5-6	-3.628	4.347	-0.065	0.405	0.341	3.250	0.008	0.917
Total fluid balance (per 100)	-0.120	0.055	-0.139	0.031	-0.070	0.04	-0.108	0.093
Donor								
Age	-0.152	0.134	-0.078	0.256	-0.379	0.100	-0.258	<.001
BMI	0.194	0.469	0.029	0.681	0.471	0.351	0.094	0.181
HTN								
No	Ref.							
Yes	1.416	4.073	0.023	0.729	-4.409	3.045	-0.097	0.150
DM								
No	Ref.							
Yes	-1.725	5.414	-0.022	0.750	0.864	4.048	0.015	0.831
Last eGFR	-7.335	2.484	-0.216	0.004	-3.452	1.857	-0.136	0.065

eGFR, estimated glomerular filtration rate; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus

Table 4. Baseline characteristics of patients classified according to donor type

Variables	Cadaver (N=62)	Living (N=116)	p
Recipient			
Age	49.3 ± 10.2	42.7 ± 12.7	< 0.001
Sex			0.736
Male	41 (66.1%)	81 (69.8%)	
Female	21 (33.9%)	35 (30.2%)	
BMI	22.6 ± 2.9	23.8 ± 3.9	0.017
HTN			0.952
No	6 (9.7%)	13 (11.2%)	
Yes	56 (90.3%)	103 (88.8%)	
DM			0.334
No	25 (40.3%)	57 (49.1%)	
Yes	37 (59.7%)	59 (50.9%)	
Cold ischemic time	239.6 ± 130.0	60.5 ± 26.5	< 0.001
Induction			0.001
Simulect	31 (50.0%)	89 (76.7%)	
ATG	31 (50.0%)	27 (23.3%)	
Maintenance			0.054
Tacrolimu	58 (93.5%)	113 (97.4%)	
Sirolimus	1 (1.6%)	3 (2.6%)	
Cyclosporin	3 (4.8%)	0 (0.0%)	
HLA mismatch	3.3 ± 1.9	3.2 ± 1.6	0.555
Total fluid output	22919.1 ± 7268.3	29396.0 ± 10675.7	< 0.001
Total fluid balance	4913.4 ± 2616.8	3875.5 ± 2884.6	0.019
Donor			
Age	52.7 ± 12.3	44.9 ± 11.7	< 0.001
Sex			0.044
Male	41 (66.1%)	57 (49.1%)	
Female	21 (33.9%)	59 (50.9%)	

Variables	Cadaver (N=62)	Living (N=116)	p
Recipient			
BMI	23.2 ± 3.2	25.9 ± 3.6	< 0.001
HTN			0.121
No	45 (72.6%)	97 (83.6%)	
Yes	17 (27.4%)	19 (16.4%)	
DM			0.013
No	50 (80.6%)	109 (94.0%)	
Yes	12 (19.4%)	7 (6.0%)	
Donor last eGFR	70.49 ± 38.12	93.50 ± 25.46	< 0.001

eGFR, estimated glomerular filtration rate; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; ATG, anti-thymocyte globulin

Figures

Figure 1

Correlation between fluid balance and estimated glomerular filtration rate in all patients

Figure 2

Correlation between fluid balance and estimated glomerular filtration rate in living donor patients

Figure 3

Correlation between fluid balance and estimated glomerular filtration rate in cadaver donor patients