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Normal Saline vs Plasma-Lyte A Use Intra- and Post-Operatively in Adult Kidney Transplant Recipients

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Abstract

Fluid management intra- and post-operatively for kidney transplant recipients (KTR) is essential to maintain adequate perfusion to the kidney. 0.9% normal saline (NS) is commonly used, but it can cause hyperchloremic metabolic acidosis, which may result in hyperkalemia and lead to delayed graft function (DGF). Plasma-Lyte A (PA) is an alternative option that has a lower amount of chloride and a neutral pH, which may offset the risk of hyperkalemia. The

aim of this study is to determine the incidence of DGF in KTRs comparing NS vs PA use intra- and initially post-operatively. This single-center, retrospective cohort study in adult KTRs from January 1, 2016 to February 1, 2021 consisted of two cohorts, those receiving NS vs PA. Multi-organ transplant recipients were excluded. The primary outcome was the incidence of DGF. A total of 244 KTRs in the NS group and 263 KTRs in the PA group were included. There was no significant difference in incidence of DGF between the groups, (NS 23.4% vs PA 25.9%, p = 0.537). The logistic regression for only deceased donors were not significantly different (OR 1.369 (0.819-2.288). There was no difference in the incidence of DGF when comparing NS vs PA.

Keywords
Kidney transplant; fluid management; delayed graft function

1. Introduction

Delayed graft function (DGF) in kidney transplant recipients (KTRs) is an expression of acute kidney injury following transplantation. This injury can be the result of an inflammatory response in the donor and recipient or during the perioperative phase due to multiple factors, including, but not limited to, the type of donor, donor and recipient comorbidities, recipient's time on dialysis, and cold and warm ischemia time. By definition, DGF is a requirement for dialysis within the first week after renal transplantation [1, 2]. The rate of DGF is around 30.8% in deceased donors, but increases at 45-55.1% in donors with higher kidney donor profile index (KDPI) and donation after cardiac death (DCD) [3, 4]. In addition, DGF has been shown to result in a decline in overall graft function and has been recognized as one of the clearest risk factors for chronic allograft nephropathy [5].

During the perioperative period of kidney transplantation, it is critical to maintain adequate intravascular volume to ensure appropriate perfusion to the renal allograft while avoiding vasopressors or other vasoconstrictors [6-8]. Due to the concerns of hyperkalemia, normal saline (NS) has historically been used as the standard fluid replacement in KTRs to prevent dehydration and improve renal perfusion. NS contains 154 mmol/L of sodium, 154 mmol/L of chloride, no potassium, an osmolality of 308 mOsmol/L, and a pH of 6.8. Because of these characteristics, it has the potential to cause hyperchloremic metabolic acidosis, which in turn can result in hyperkalemia. As a result, use of NS can exacerbate kidney injury. In contrast, Plasma-Lyte A (PA) contains 140 mmol/L of sodium, a lower amount of chloride at 98 mmol/L, 5 mmol/L of potassium, an osmolality of 294 mOsmol/L, and a neutral pH of 7.4, which may more closely resemble human plasma and provide more favorable outcomes after renal transplantation [9].

We aimed to determine the incidence of delayed graft function post-transplant when using PA compared to NS for fluid management in adult KTRs.

2. Methods

This single-center, retrospective cohort study analyzed adult KTRs who received a kidney transplant from January 1, 2016 to February 1, 2021. KTRs were categorized into one of two cohorts depending on initial use of NS or PA intra- and post-operatively. Recipients in the historical cohort

during the timeframe of January 1, 2016 to July 31, 2018 received NS for fluid replacement, whereas recipients between August 1, 2018 to February 1, 2021 received PA. Patients were included if they were 18 years of age or older and had received a kidney transplant during study's timeframe. Recipients who received multi-organ transplants were excluded. Waiver of the Health Insurance Portability and Accountability Act authorization was obtained through the institutional review board.

The primary endpoint was incidence of DGF, which was defined as the need for dialysis treatment at least once within the first week after transplantation. Secondary endpoints included length of stay, incidence of hyperkalemia within 72 hours post-transplant, reason for dialysis during inpatient stay and within 30 days post-transplant, fluid cost, and creatinine clearance (calculated using the Cockcroft-Gault method) at one week and one-month post-transplant. Other secondary endpoints included incidence of biopsy proven acute rejection (BPAR) within 3 months.

Per institutional protocols, tacrolimus immediate-release was started on the evening of post-operative day (POD) 0 or morning of POD 1 at starting dose of 0.05 mg/kg orally twice daily and mycophenolate mofetil at 750 mg orally twice a day unless receiving induction with basiliximab, in which case recipients were started at 1000 mg orally twice daily. The majority of patients received a rapid steroid withdrawal with the last dose given on POD 3. During the SARS-CoV-2 pandemic, our institution preferred anti-thymocyte globulin over alemtuzumab. The goal tacrolimus trough concentration for the first 3 months was 8-10 ng/mL. The initial NS dose was 50 mL per hour with urine output 1 mL to1 mL replacement of alternating NS and ½ NS plus 25 mL per hour. The initial PA dose was 50 mL per hour plus replacement of urine output 1 mL to 1 mL of PA.

Comparisons were calculated using *t*-tests and χ^2/Fisher's exact tests. We used logistic regression, and we performed two analyses on combined living and deceased donor data and on deceased donor only data. Covariates were treatment with PA, patient age, gender, race, calculated panel reactive antibody (cPRA), age of donor, donor type, cold ischemia time, warm ischemia time, body mass index, years on dialysis prior to transplant, and induction medication. Since kidney donor profile index (KDPI) is only applicable for deceased donor transplants, it was not included in the combined data analysis. The logistic regression of DGF for deceased donors included the coefficients above with the exception of donor type and age as well as included the KDPI. Wilcoxon rank sum test and log-rank test were performed to non-parametrically test whether the length of stay was significantly different between the two cohorts. Kaplan-Meier estimator of survival curves were plotted for the two groups. Also, a cox proportional hazard regression model on the length of stay was fitted, to observe if there was any association between the outcome and treatment group while adjusting for other covariates.

3. Results

A total of 244 KTRs in the NS group and 263 KTRs in the PA group were included in the analysis. Demographics were similar between the two groups, except for significantly more hypertension in the PA group, and higher mean warm ischemia time and mean cPRA in the NS group, and differences in induction agents. There was more alemtuzumab induction in NS group and more thymoglobulin induction in the PA group (Table 1). When comparing recipients with DGF vs non-DGF, there were variables that were statistically significant. KTRs who developed DGF were older (54 yo vs 49.6 yo, $p = 0.001$), were more likely to be African American (65.6% vs 43.2%, $p < 0.001$), had a higher mean KDPI (45.5% vs 37.8%, $p = 0.001$), more often had a DCD donor (40% vs 14.1%, <0.001), had longer

mean cold ischemia time (837 min vs 588 min, p < 0.001), had more years on dialysis (7.05 years vs 4.43 years, p < 0.001), and had a higher mean body mass index (30.2 kg/m^2 vs 28 kg/m^2, p < 0.001).

Table 1 Demographics.

	NS (n = 244)	**PA (n = 263)**	**p-value**
Recipient			
Age at time of transplant, years; mean (SD)	50.5 (13.2)	50.9 (13.8)	0.748
Gender, male, n (%)	147 (60.2)	136 (51.7)	0.06
Race, n (%)			
African American	117 (48)	130 (49.4)	0.748
Caucasian	95 (38.9)	92 (35)	
Asian	8 (3.3)	9 (3.4)	
Other	24 (9.8)	32 (12.2)	
Comorbidities			
HTN	190 (77.9)	224 (85.2)	**0.04**
DM	72 (29.5)	78 (29.7)	1
CAD	24 (9.8)	21 (8)	0.533
CVD	20 (8.2)	32 (12.2)	0.146
Etiology of kidney disease			
HTN nephrosclerosis	52 (21.3)	67 (25.5)	0.295
DM	57 (23.4)	47 (17.9)	0.152
FSGS	28 (11.5)	20 (7.6)	0.434
IgA nephropathy	17 (7)	14 (5.3)	0.172
Other	90 (36.9)	115 (43.7)	0.124
cPRA, mean (SD); median [min, max]	4.75 (18.6); 0 [0, 100]	1.81 (10.8); 0 [0, 100]	**0.032**
0	186 (76.2)	189 (71.9)	0.267
0-20	13 (5.3)	12 (4.6)	0.838
21-80	26 (10.6)	37 (14)	0.281
>80	19 (7.8)	25 (9.5)	0.53
DSA prior to transplant, n (%)	30 (12.3)	26 (9.9)	0.4
class I	13 (43.3)	7 (26.9)	0.267
class II	15 (50)	17 (65.4)	0.288
class I and II	2 (6.7)	2 (7.7)	1
Body mass index (kg/m^2), mean (SD)	28.5 (5.3)	28.6 (5.4)	0.951
Dialysis prior, n (%)	210 (86.1)	235 (89.4)	0.28
HD	137 (56.1)	164 (62.4)	0.114
PD	46 (18.9)	46 (17.5)	
history of both HD and PD	27 (11.1)	20 (7.6)	
unknown	0	5 (1.9)	
Years on dialysis prior, mean (SD); median [min, max]	4.93 (4.26); 4.75 [0, 21.3]	5.22 (3.99); 5.36 [0, 17.5]	0.439
Prior kidney transplant, n (%)	37 (15.2)	35 (13.3)	0.611

Induction Medication			
Alemtuzumab	208 (85.2)	200 (76)	**<0.001**
Basiliximab	16 (6.6)	12 (4.6)	
Anti-thymocyte globulin	20 (8.2)	51 (19.4)	
Basiliximab (1 dose) and alemtuzumab	0 (0)	1 (0.4)	
Donor			
Age; mean (SD)	36.8 (14.5)	38.9 (13)	0.076
KDPI, mean (SD)	38.8 (20.7)	41.9 (21.5)	0.168
Donor type, n (%)			
DBD	127 (52)	127 (48.3)	0.399
DCD	44 (18)	60 (22.8)	
Living	73 (29.9)	74 (28.1)	
Unknown DBD or DCD	0 (0)	2 (0.8)	
Cold ischemia time (min), mean (SD); median [min, max]	657 (455); 712 [15, 1730]	643 (438); 642 [2, 2960]	0.734
Warm ischemia time (min), mean (SD); median [min, max]	50.4 (14); 48 [21, 168]	43.5 (15.5); 40 [18, 169]	**<0.001**

CAD = coronary artery disease; cPRA = calculated panel reactive antibodies; CVD = cardiovascular disease; DBD = death after brain death; DCD = death after cardiac death; DM = diabetes mellitus; DSA = donor specific antibodies; FSGS = focal segmental glomerulosclerosis; HD = hemodialysis; HTN = hypertension; KDPI = kidney donor profile index; PD = peritoneal dialysis.

There was not significantly difference in our primary outcome of DGF in terms of treatment, (NS: n = 57, 23.4% vs PA: n = 68, 25.9%, p = 0.537). The logistic regression of DGF for combined living and deceased donors and for deceased donors only were not significantly different (OR 1.098 (0.662-1.822), p = 0.718 and OR 1.369 (0.819-2.288), p = 0.23, respectively) (Table 2). The logistic regression of DGF for deceased donors only data shows that the odds of getting DGF for patients in PA group is 1.37 times the odds of getting DGF for patients in NS group. The incidence of dialysis post-transplant secondary to hyperkalemia was not significantly different between NS and PA, respectively (63.2% vs 57.4%, p = 0.584).

Table 2 Logistic Regression.

All Kidney Transplant Recipients		
Variable	**Odds Ratio (95% CI)**	**p-value**
Treatment Arm (reference NS), PA	1.098 (0.662-1.822)	0.718
Patient Age at Time of Transplant	1.013 (0.992-1.034)	0.237
Gender, female	0.544 (0.330-0.897)	**0.017**
Race, African American	1.204 (0.643-2.254)	0.561
cPRA	0.991 (0.973-1)	0.316
Age of Donor	1.011 (0.99-1.032)	0.306
DCD	26.192 (6.9-99.323)	0
CIT	1 (0.999-1)	0.484
WIT	1 (0.991-1.022)	0.426

BMI	1.091 (1.042-1.143)	1.091
Dialysis Prior to Transplant	1.4×10^7 (0-infinity)	0.983
Years on Dialysis Prior to Transplant	1.029 (0.958-1.107)	1.029
Induction medication, Anti-thymocyte globulin	0.862 (0.439-1.692)	0.862
Deceased Donor, Kidney Transplant Recipients		
Variable	**Odds Ratio (95% CI)**	**p-value**
Treatment Arm (reference NS), PA	1.369 (0.819-2.288)	0.23
Patient Age at Time of Transplant	1.007 (0.985-1.029)	0.544
Gender, female	0.455 (0.272-0.762)	**0.003**
Race, African American	1.068 (0.558-2.044)	0.842
cPRA	0.990 (0.972-1.007)	0.249
KDPI	1.013 (1-1.027)	0.052
CIT	1 (0.999-1.001)	0.61
WIT	1.008 (0.992-1.025)	0.317
BMI	1.088 (1.038-1.140)	0
Dialysis Prior to Transplant	5.4×10^6 (0-infinity)	0.979
Years on Dialysis Prior to Transplant	1.021 (0.95-1.097)	0.57
Induction medication, Anti-thymocyte globulin	0.797 (0.401-1.586)	0.518

cPRA = calculated panel reactive antibodies; BMI = body mass index; CIT = cold ischemia time; DCD = death after cardiac death; KDPI = kidney donor profile index; NS = normal saline; PA = Plasma-Lyte A; WIT = warm ischemia time.

Renal function and post-operative potassium were not significantly different at studied time points; however, chloride levels were significantly lower in the PA group (Table 3). BPAR within three months post-transplant did not differ between the two groups (4.5% NS vs 4.6% PA, p = 0.913) and did not differ by type of rejection. The mean time from transplant to BPAR was 46.1 days in the NS group vs 24.8 days in the PA group (p = 0.082 for Wilcoxon rank sum test; p = 0.084 for Log-rank test). Kaplan-Meier estimator of length of stay probability over time for each group is shown in Figure 1.

Table 3 Renal function and electrolyte outcomes.

	NS (n = 244)	**PA (n = 263)**	**p-value**
Serum creatinine, mg/dL, mean (SD)			
1 week	3.51 (3.25)	3.26 (2.91)	0.349
1 month	2.28 (6.73)	1.78 (1.16)	0.249
eCrCl, ml/min/1.73 m^2, mean (SD)			
1 week	41.5 (24.7)	41.9 (26.7)	0.881
1 month	53.3 (20.6)	53.5 (22)	0.912
Potassium levels (mmol/L, highest from corresponding day), mean (SD)			
Baseline	4.3 (0.63)	4.4 (0.61)	0.06
POD 1	4.8 (0.95)	4.9 (1.02)	0.247
POD 2	4.6 (0.7)	4.6 (0.7)	0.874

POD 3	4.5 (0.63)	4.5 (0.59)	0.896
Chloride levels (mmol/L, highist from corresponding day), mean (SD)			
POD 1	105 (5.1)	102 (5.1)	<0.001
POD 2	105 (6.2)	102 (5.10	<0.001
POD 3	106 (5.94)	103 (5.65)	<0.001

NS = normal saline; PA = Plasma-Lyte A; POD = post-operative day.

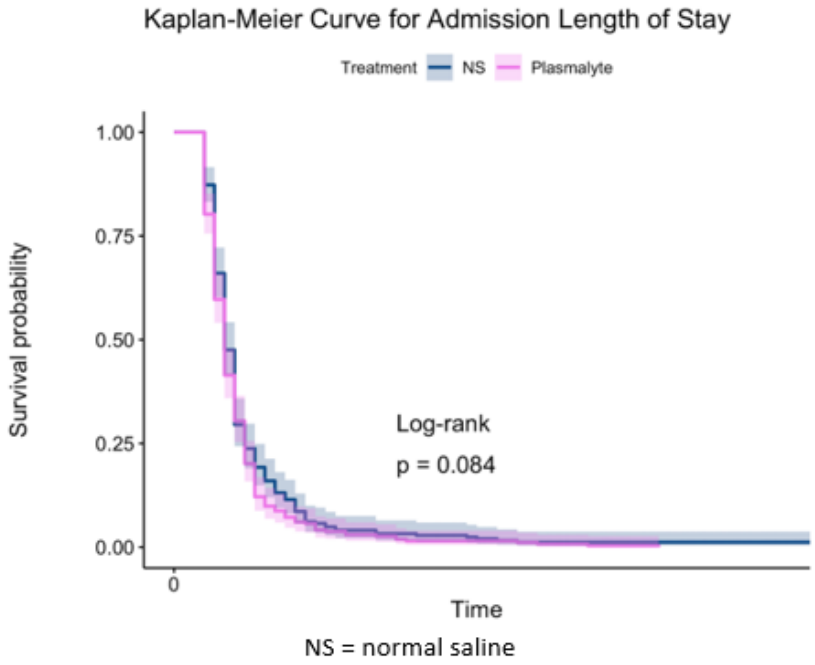

Figure 1 Length of Stay.

The total charges of all fluids were not significantly different (NS $1990 (±2750) vs PA $1930 (±2840), p = 0.0809) along with the total charge per day ($352 (±393) vs $406 (±765), p = 0.316). Between the two groups the total number of bags of all fluids did not vary (10.1 (±4.61), median 9 [range 1-42] vs 9.38 (±3.72), median 9 [range 3-33], p = 0.074). The mean number of PA bags in the PA group was 5.64 (±3.15) with a median of 5, range of 1-32. The total number of NS bags and total charges of NS were significantly higher in the NS group (8.4 (±3.62) vs 3.63 (±2.48), p < 0.001 and $1650 (±1840) vs $626 (±773), p < 0.001, respectively). The number of ½ NS bags and total charges of ½ NS between the two groups were not significantly different (1.89 (±1.67) vs 1.91 (±1.43), p = 0.921; $388 (±1240) vs $350 (±544), p = 0.734). The cost per day of fluids for those with DGF compared to non-DGF recipients differed with fluids in the non-DGF group costing $453 (690) vs DGF $157 (117), p < 0.001.

4. Discussion

This study shows PA use intra- and immediately post-operatively did not reduce the incidence of DGF compared to NS. The lower chloride content in the PA group was expected given a lower chloride content than NS (98 mmol/L vs 154 mmol/L). The rationale for using PA was the lower chloride content would reduce hyperchloremic metabolic acidosis compared to NS. Prior studies

have corroborated higher rates of hyperchloremic metabolic acidosis as well as our findings of higher serum chloride in the post-operative period in patients that use NS over a balanced electrolyte solution [10-13]. The potassium values in our study were not different between the two groups nor was the incidence of dialysis due to hyperkalemia. This suggests either PA did not reduce metabolic acidosis, which can then cause hyperkalemia, or it did not make a difference overall compared to NS in changes to hyperkalemia despite reducing metabolic acidosis. We did not assess metabolic acidosis post-operatively to answer this question. While there are many factors contributing to DGF, several of which occur prior to transplant. Our multivariable analysis was able to account for these factors.

One consideration that might have altered our outcome is that PA was converted to NS usually by 24-48 hours post-transplant rather than KTRs continuing on PA if fluid management was still required. This was in contrast to other studies showing lower DGF in PA patients [14, 15]. The shorter duration with this method of conversion post-transplant may have minimized the benefit of PA. Kolodzie and colleagues reported that a higher percent of NS (≥80%) of total amount of crystalloids administered was associated with DGF in KTRs [15] Overall, the amount of PA administered in our study compared to majority of KTR's would have been >20% of their total fluids, which suggests PA group would have still had a potential benefit compared to the NS group.

The average cost of both NS and ½ NS was around $2 per 1000 mL bag. Depending on timing and context of purchase, PA per 1000 mL bag was between $3 and $13. Cost at time of use was accounted for in our analysis. There was overall no difference in total charges or administrations between the two groups, which may have been due to the shorter usage of PA and length of stay for recipients. Based on an institution's contracted purchasing costs of PA, there may be potential cost savings with NS over PA.

This study did not assess peri-operative events nor the need and type of vasopressor used in the peri- or immediate post-operative setting. These factors may have further affected the need for dialysis post-transplant. Due to increased volume of kidney transplants over the study timeframe and limited supply of alemtuzumab through the manufacturer distribution program, the PA group had more KTRs receiving anti-thymocyte globulin for induction. However, both alemtuzumab and anti-thymocyte globulin are depleting induction agents and were included in the logistic regression model (getting DGF with alemtuzumab was 0.86 times the odds of getting DGF with anti-thymocyte globulin). Other limitations include the overall sample size and potential individual variation in total amount of fluid during admission.

It will be interesting to compare our institution outcomes to the BEST-Fluids Study, which is double-blind, randomized, multi-center study [16]. Our logistic regression included additional variables, and a benefit of our study was that site specific care and practices were the same between the two groups.

5. Conclusion

Overall, this study found the use of PA intra- and post-operatively to have no significant difference in overall incidence of DGF.

Abbreviations

DCD	donation after cardiac death
DGF	delayed graft function
KDPI	kidney donor profile index
KTR	kidney transplant recipients
NS	0.9% normal saline
PA	Plasma-Lyte A
POD	post-operative day

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Author Contributions

Kristen R Szempruch: Concept/Design, data analysis/interpretation, drafting article, critical revision of article, data collection. Alec D Martschenko: Data collection, data analysis/interpretation, drafting article, revising article. Harendra Arora: Data interpretation, drafting article, critical revision of article. Robert S Isaak: Data interpretation, drafting article, critical revision of article. Ravindra Prasad: Data interpretation, drafting article, critical revision of article. John L Schmitz: Data collection, data interpretation, critical revision of article. Chuning Liu: Data analysis/interpretation, revising article. Fei Zou: Data analysis/interpretation, revising article. Pablo Serrano: Concept/Design, data interpretation, drafting article, critical revision of article.

Competing Interests

The authors have declared that no competing interests exist.

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