Association between perioperative normal saline and delayed graft function in deceased-donor kidney transplantation: a retrospective observational study

Association entre l'administration périopératoire de soluté salé isotonique et le retard de reprise de fonction du greffon après transplantation rénale à partir de donneurs cadavériques : une étude observationnelle rétrospective

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Abstract

Purpose Isotonic 0.9% sodium chloride (normal saline; NS) solution use is common, but its high chloride content has been shown to contribute to acid-base disturbances and acute kidney injury (AKI). As kidney transplant recipients are at high risk of postoperative AKI and renal replacement therapy, we aimed to evaluate the impact of perioperative NS administration on graft function after kidney transplantation.

Methods All adult patients undergoing deceased-donor kidney transplantation between January 2010 and December 2014 at the Rennes University Hospital were included. Logistic regression models were constructed to evaluate the association of hyperchloremia and hyperchloremic acidosis on delayed graft function (DGF), defined as the need for renal replacement therapy within the first week after transplantation.

Results Three hundred and fifty-nine patients were included, 20% developed DGF. The mean (standard deviation) volume of NS infused in the operating room and in the standard postoperative intensive care unit stay was 4,832 (2,242) mL. In the first 24 postoperative hours, 11% of patients developed hyperchloremia and 11% developed hyperchloremic acidosis. These outcomes were not associated with significantly higher total volumes of NS administration or with DGF. In contrast, multivariable analysis showed that cold ischemia time, donor terminal

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creatinine, and perioperative NS volume were all independent predictors of DGF.

Conclusion Perioperative NS infusion volume was associated with DGF in deceased-donor kidney transplant recipients. Conversely, postoperative hyperchloremia and hyperchloremic acidosis were not associated with an increased risk of DGF, suggesting other mechanisms than a chloride effect.

Résumé

Objectif Le soluté salé isotonique (NaCl) 0,9 % est communément utilisé comme solution de remplissage. Sa teneur élevée en chlore contribuerait à la genèse de perturbations acido-basiques avec un risque d'insuffisance rénale aiguë (IRA). Les patients transplantés rénaux constituent une population à risque accru d'IRA et d'épuration extra-rénale (EER) postopératoires. Notre objectif était d'évaluer l'impact de l'administration périopératoire de NaCl 0,9 % sur la reprise de fonction du greffon.

Méthodes Tous les patients adultes ayant bénéficié d'une transplantation rénale issue de donneurs cadavériques au Centre hospitalier universitaire de Rennes, France entre 2010 et 2014 étaient inclus. Des modèles de régression logistique ont permis d'évaluer l'impact de l'acidose hyperchlorémique et de l'hyperchlorémie sur le retard de reprise de fonction du greffon (RRFG) défini par le recours à l'EER dans la semaine qui suivait la transplantation.

Résultats Sur les trois cent cinquante-neuf patients inclus, 20 % ont présenté un RRFG. Le volume moyen (écart type) de NaCl 0,9 % périopératoire administré était de 4832 ± 2242 mL. Dans les 24 h postopératoires, 11 % des patients ont présenté une acidose hyperchlorémique et 11 % une hyperchlorémie, sans qu'ils aient reçu significativement plus de NaCl 0,9 %. Le temps d'ischémie froide, la créatinine plasmatique terminale du donneur et le volume de NaCl 0,9 % périopératoire sont apparus comme facteurs de risque indépendants de RRFG dans une analyse

multivariée. À l'inverse, l'acidose hyperchlorémique et l'hyperchlorémie postopératoires n'étaient pas associées à un RRFG.

Conclusion Au contraire du volume de NaCl 0,9 % périopératoire administré, l'acidose hyperchlorémique et l'hyperchlorémie postopératoires n'étaient pas associées à un risque accru de RRFG après transplantation rénale issue de donneurs cadavériques, suggérant un mécanisme autre que la toxicité du chlore.

Isotonic 0.9% sodium chloride or normal saline (NS) solution is a common resuscitation fluid used in the intensive care unit (ICU).^{1,2} Nevertheless, the high chloride content has been shown to contribute to acid-base disturbances and acute kidney injury (AKI).^{3,4} Early experimental data suggest that hyperchloremia may lead to renal vasoconstriction and a decreased glomerular filtration rate.^{5,6} In a double-blind randomized study of healthy volunteers, intravenous infusion of NS, but not a buffered crystalloid infusion, resulted in decreased renal cortical perfusion.⁷ The clinical impact of high-chloride fluids on kidney function or other outcomes in critically ill or perioperative patients, however, remains a topic of debate.^{8–10} Three large clinical trials comparing buffered crystalloid solution with NS infusion in the ICU have produced contradictory results with regard to the influence of fluid selection on renal function.^{11–13}

Kidney transplant recipients are at particularly high risk of postoperative AKI and renal replacement therapy (RRT). Delayed graft function (DGF), defined as the need for RRT within the first week after transplantation, occurs in about 25–30% of deceased-donor transplants and is associated with higher costs, prolonged hospitalizations, and an increased risk of long-term graft loss.^{14,15} Transplant recipients often receive aggressive fluid resuscitation in an effort to reduce the incidence of DGF.^{16–18} Normal saline is usually the first choice of fluid in these patients, to avoid the potassium in buffered crystalloids such as Ringer's lactate, and the renal toxicity of synthetic colloids.^{19,20} The currently available data on the impact of perioperative NS resuscitation on renal graft function remain inconclusive.²¹ Most of the available studies focused on the intraoperative period, enrolled mainly living donors, or chose as the main endpoint either postoperative metabolic profile or non-standard definitions of DGF.^{22–28} Therefore, the aim of our study was to evaluate the impact of intraoperative and postoperative NS administration on graft function after kidney transplantation.

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Methods

We performed a retrospective study based on data prospectively collected in the CRISTAL database. The CRISTAL database was approved by the French Data Protection Authority (Authorization no. 363505). In accordance with French law, research studies based on the national registry CRISTAL are part of the transplant assessment activity and therefore do not require institutional review board approval or written informed consent.

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.²⁹ The primary outcome was defined and the statistical analysis plan was made before accessing the data.

Fluid management

Our institutional protocol recommended NS as the primary appropriate intravenous fluid for the perioperative resuscitation of kidney transplant patients. Artificial colloid and potassium-containing balanced crystalloids were discouraged. All patients at our institution are admitted to our level-3 ICU following kidney transplantation, and the majority are discharged to the hospital floor 24 hr postoperatively. According to our protocol, fluid infusion was considered if clinically indicated (systolic arterial pressure < 90 mmHg, tachycardia, cutaneous vasoconstriction, or relative oliguria) and the central venous pressure was < 5 mmHg.

Data collection

CRISTAL is a national database administered by the French transplant authority “Agence de la biomédecine” (ABM). Data of all organ transplant candidates, donors, and transplant outcomes are prospectively collected. The data collection is mandatory. Completeness and accuracy are double-checked by the ABM research technicians. Additional data were extracted retrospectively by chart review. All adult patients undergoing deceased-donor kidney transplantation between January 1 2010 and December 3 2014 at the Rennes University Hospital (Brittany, France) were included.

Donor-specific data

The following kidney donor parameters were assessed: age and body mass index (BMI), cause of brain death, treatment with catecholamines in the perioperative period, and terminal serum creatinine.

Recipient-specific data

The following recipient parameters were assessed: recipient age, sex and BMI, graft cold ischemic time, and multiple organ transplantation. We recorded the volume of NS administered intraoperatively, and within the postoperative ICU period. We noted the use of any non-saline fluid for resuscitation, and recorded the serum levels of sodium, potassium, chloride, and bicarbonate on postoperative day 0 and day 1. Finally, we recorded the need for any RRT within the first postoperative week, and mortality at one year.

Study outcomes

The primary outcome was DGF, defined as the need for any RRT within one week after transplantation. An additional outcome was the fall in ratio of postoperative creatinine of at least 30%, an alternative creatinine-based definition of DGF.^{30,31} The creatinine reduction ratio (CRR) was calculated as follows: $CRR = (\text{day 0 creatinine} - \text{day 1 creatinine} / \text{day 0 creatinine}) \times 100$.

Study definitions

Hyperchloremia was defined as serum chloride > 110 mmol·L⁻¹ within the first 24 hr postoperatively, hyperchloremic acidosis was defined as serum chloride > 110 mmol·L⁻¹ and serum bicarbonate < 24 mmol·L⁻¹ within the first 24 hr postoperatively.

According to the Stewart’s physical-chemical approach, strong ion difference (SID) may better reflect the acidifying effects of large volumes of saline compared with direct measurement of serum chloride or bicarbonate.³² Therefore, abbreviated SID was also calculated as $SID = Na^+ - Cl^-$. SID Acidosis was defined by a SID < 40 within the first 24 hr postoperatively.

Statistical analysis

Continuous data were expressed as the mean (standard deviation [SD]) and compared by a Student’s *t* test or a Wilcoxon rank sum test. Categorical data were expressed as numbers and percentages and compared by a χ^2 test or a Fisher’s exact test. A Wilcoxon test was used to compare total saline infusion according to the pre-specified groups.

The relationship between DGF (dependent variable), hyperchloremic acidosis, hyperchloremia, and the SID were studied using three separate logistic regression models adjusted on potential confounders. Variables included as potential confounders were chosen *a priori*, and informed by the works of Schnuelle *et al.*³³ and Irish *et al.*¹⁴ based on factors known to influence the risk of

DGF. The first model included donor age, donor resuscitation with norepinephrine, donor terminal creatinine, cold ischemic time, recipient sex, recipient BMI, and hyperchloremic acidosis. The second model included the prior variables, with hyperchloremia in the place of hyperchloremic acidosis. The third model included the prior variables, with SID in the place of hyperchloremic acidosis. As a sensitivity analysis, the three models were then performed using an alternative definition of DGF (CRR < 30%). Finally, as the association between hyperchloremic acidosis or hyperchloremia and DGF might reflect a fluid resuscitation effect with higher NS volumes rather than an effect of high chloride itself, we built multivariable models adjusted for total perioperative NS volume infused in addition to prior variables, as an additional sensitivity analysis.

As the rate of missing values was low (< 2%), with the exception of total NS volume (10%), we used a single imputation method for the main analysis (mode for categorical variables and median for continuous variables) and multiple imputation methods for sensitivity analysis adjusted for total NS assuming a missing at random assumption.

A *P* value of < 0.05 for a two-sided test was considered statistically significant. Outputs of the logistic regression models were presented as the adjusted odds ratio (OR) and its 95% confidence interval (CI). Statistical analysis was performed using SAS statistical software (SAS 9.3, SAS Institute, Cary, NC, USA).

Results

Three hundred and fifty-nine patients were included, of whom 70 (20%) developed DGF. The mean (SD) volume of saline infused in the OR, and in the standard postoperative ICU stay was 4,832 (2,242) mL. Postoperatively, 11% of patients developed hyperchloremia, 11% developed hyperchloremic acidosis, and 91% developed a SID < 40 within the first 24 hr. Recipient and donor characteristics are displayed in Tables 1 and 2 respectively.

Patients who developed DGF received significantly higher NS volumes in the study period than those who did not [*n* = 64 vs 261; mean (SD) total volume, 5,240 (2,126) mL vs 4,731 (2,263) mL, respectively; difference in means, 509; 95% CI, 8 to 765; *P* = 0.03]. Conversely, patients who developed hyperchloremic acidosis or hyperchloremia did not receive significantly higher volumes of NS than those who did not [*n* = 37 vs 288; mean (SD) total volume, 5,543 (2,234) mL vs 4,740 (2,230) mL; difference in means, 802 mL; 95% CI, -1 to 1606; *P* = 0.06; and *n* = 38 vs 287; total volume, 5,543 (2,234) vs

4,744 (2,234) mL; difference in means, 798 mL; 95% CI, -5 to 1602; *P* = 0.09, respectively]. There was also no difference in NS volume infused between patients who developed hyperkalemia (> 6 mmol·L⁻¹) and those who did not (*n* = 26 vs 296; mean (SD) total volume, 4,776 (2,248) vs 5,398 (2,211) mL, difference in means, 621 mL; 95% CI, -279 to 1522; *P* = 0.18).

Upon multivariable analysis, recipient cold ischemic time (per ten-minute increase) and donor terminal creatinine level (per 10-μmol·L⁻¹ increase) were independent risk factors for DGF (Tables 3, 4, and 5). There was no significant relationship between hyperchloremic acidosis, hyperchloremia, or a SID < 40 and DGF.

One-hundred and fifty-three (43%) patients developed a CRR < 30%. In the multivariable analysis (eTables 1, 2, and 3, available as Electronic Supplementary Material [ESM]), BMI (per 1 kg·m⁻² increase), donor age (per-one-year increase), and donor terminal creatinine level were independent risk factors for CRR < 30%. Again, there was no significant relationship between hyperchloremic acidosis, hyperchloremia, or a SID < 40 and CRR < 30%.

Adjusting the model for the total volume of NS infused did not significantly alter the relationship between hyperchloremic acidosis or hyperchloremia and DGF, but did show that total NS volume infused was significantly associated with DGF (Tables 6 and 7, and eTables 1, 2, and 3, available as ESM).

Discussion

In this cohort of patients undergoing deceased-donor kidney transplantation and resuscitated with NS, patients received large volumes of NS in the perioperative period. Only 11% of the patients developed hyperchloremia or hyperchloremic acidosis, but the majority of patients developed a SID < 40. Nevertheless, neither the development of hyperchloremia or hyperchloremic acidosis, nor a SID < 40 were associated with an increased risk of DGF.

Perioperative intravenous infusion of chloride-rich fluids has been associated with hyperchloremia and hyperchloremic acidosis in numerous studies.³⁴ The supraphysiologic chloride content leads to an increase in the dominant strong anion in plasma, which in turn promotes an increase in hydrogen, and thus acidosis. Animal and human experimental data seems to support a potential chloride-related renal toxicity. Chloride influx in the afferent artery may cause vasoconstriction, decreasing the renal blood flow and glomerular filtration rate.^{5,7}

In our study, patients who developed hyperchloremic acidosis or hyperchloremia had not received higher

Table 1 Characteristics of the organ recipients

	All patients <i>n</i> =359	Delayed graft function		<i>P</i> value
		Yes <i>n</i> =70	No <i>n</i> =289	
Age (yr)	52 (14)	54 (13)	52 (15)	0.37
Sex (male)	208 (58%)	42 (60%)	166 (57%)	0.69
BMI (kg·m ⁻²)	25 (5)	26 (6)	25 (4)	0.27
Saline infused in the OR (mL) <i>n</i> =341	2,058 (1,007)	2,397 (1,236)	2,058 (932)	0.19
Total saline infused, OR and ICU (mL) <i>n</i> =325	4,832 (2,242)	5,240 (2,126)	4,732 (2,263)	0.03
Other fluids infused <i>n</i> =341				
Albumin	10 (3%)	3 (4%)	7 (2%)	0.42
Gelatin	36 (10%)	12 (17%)	24 (8%)	0.04
HES	38 (11%)	8 (11%)	30 (10%)	0.83
Buffered crystalloids	31 (9%)	11 (16%)	20 (7%)	0.03
Cold ischemic time (min) <i>n</i> =358	1,031 (362)	1,125 (368)	1,007 (358)	0.001
Serum chloride (mmol·L ⁻¹)				
Day 0 <i>n</i> =357	103 (5)	103 (4)	104 (5)	0.18
Day 1 <i>n</i> =357	104 (5)	102 (5)	104 (5)	0.003
Hyperchloremic acidosis (within the first 24 hr) <i>n</i> =358	38 (11%)	4 (6%)	34 (12%)	0.14
Hyperchloremia (>110 mmol/L within the first 24 hr) <i>n</i> =357	38 (11%)	4 (6%)	34 (12%)	0.14
SID				
Day 0	34 (4)	34 (4)	36 (4)	0.01
Day 1	33 (4)	33 (4)	35 (5)	0.001
SID <40 (within the first 24 hr)	328 (91%)	60 (86%)	268 (93%)	0.06
Hyperkalemia >6 mmol·L ⁻¹	29 (8%)	20 (29%)	9 (3%)	0.001
Multiple organ transplants				
Kidney/liver	11 (3%)	4 (6%)	7 (2%)	0.24
Heart/liver	2 (3%)	1 (1%)	1 (0.4%)	0.35
One-year mortality	14 (4%)	3 (4%)	11 (4%)	0.74

Results are presented as *n* (%) or mean (SD). *n* apart from the header row indicates the number of patients without missing data for the variable. BMI = body mass index; HES = hydroxyethyl starch; ICU = intensive care unit; OR = operating room; SID = strong ion difference.

volumes of NS than those who did not suggesting that NS administration might not be the only cause of hyperchloremic acidosis or hyperchloremia. Interestingly, after adjustment, increased total volume of NS received was associated with increased odds of DGF, whereas hyperchloremic acidosis or hyperchloremia were not. This observation might reflect a more aggressive fluid resuscitation in patients with early oliguria who subsequently will develop DGF. Conversely, fluid overload might result in increased venous pressure and kidney congestion, which lead to renal subcapsular pressure increase and reduced renal blood flow and glomerular filtration rate.³⁵ Although, the recent Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery (RELIEF) trial found a significantly higher risk of kidney injury in the restrictive group, others observed a U-shaped distribution of risk associated with intravenous fluid dosing during non-cardiac surgery.^{36,37} Indeed, in the latter work, the risk for postoperative AKI

was lowest in a moderately liberal group but was increased with both restrictive and liberal fluid practices.³⁷ Similarly, a single-centre retrospective case series involving 1,966 kidney transplants on a 29-year period found that volume administration $\geq 2,500$ mL was an independent risk factor of graft failure.³⁸

The question of whether saline-induced hyperchloremia or hyperchloremic acidosis result in clinically significant renal toxicity remains controversial. NS and other chloride-rich fluids have been associated with impaired renal function after liver transplantation or open abdominal surgery but not after cardiac surgery or emergent laparotomy with temporal abdominal closure.^{3,39–41} Non-cardiac, non-transplant surgical patients with postoperative hyperchloremia are more likely to have postoperative renal dysfunction.⁴² Nevertheless, a 2017 Cochrane review concluded that there was insufficient evidence to show a difference between perioperative administration of buffered versus non-buffered crystalloid fluids on renal

Table 2 Characteristics of the organ donors

	All patients <i>n</i> =359	Delayed graft function		<i>P</i> value
		Yes <i>n</i> =70	No <i>n</i> =289	
Age (yr)	52 (16)	55 (13)	51 (16)	0.04
BMI (kg·m ⁻²)	26 (5)	27 (6)	25 (5)	0.06
Cause of brain death				-
Vascular	194 (54%)	35 (50%)	159 (55%)	
Trauma	109 (30%)	21 (30%)	88 (30%)	
Anoxia	51 (14%)	14 (20%)	37 (13%)	
Other	5 (1%)	0	5 (2%)	
Amines infusion <i>n</i> =357				
Norepinephrine	318 (90%)	64 (93%)	254 (89%)	0.53
Epinephrine	8 (3%)	40 (4%)	4 (2%)	0.05
Dobutamine	10 (4%)	5 (7%)	5 (2%)	0.03
Terminal creatinine (μmol·L ⁻¹)	138 (92)	201 (177)	123 (38)	0.001

Results are presented as *n* (%) or mean (SD). BMI = body mass index.

Table 3 Factors associated with delayed graft function according to the multivariable analysis (logistic regression model including hyperchloremic acidosis)

Variable	Adjusted odds ratio	95% CI	<i>P</i>
Recipient sex (male)	1.08	0.62 to 1.88	0.78
Recipient BMI (per 1 kg·m ⁻² increase)	1.03	0.97 to 1.09	0.32
Norepinephrine use in recipient resuscitation (yes)	1.44	0.53 to 3.92	0.48
Donor age (per 1-year increase)	1.02	0.99 to 1.03	0.12
Donor terminal creatinine level (per 10-μmol·L ⁻¹ increase)	1.07	1.01 to 1.13	0.02
Cold ischemic time (per 10-min increase)	1.01	1.00 to 1.02	0.02
Hyperchloremic acidosis	0.59	0.20 to 1.79	0.36

BMI = body mass index; CI = confidence interval.

Table 4 Factors associated with delayed graft function according to the multivariable analysis (logistic regression model including hyperchloremia)

Variable	Adjusted odds ratio	95% CI	<i>P</i>
Recipient sex (male)	1.07	0.61 to 1.86	0.81
Recipient BMI (per 1 kg·m ⁻² increase)	1.03	0.97 to 1.09	0.32
Norepinephrine use in recipient resuscitation (yes)	1.44	0.53 to 3.93	0.47
Donor age (per 1-year increase)	1.02	0.99 to 1.03	0.12
Donor terminal creatinine level (per 10-μmol·L ⁻¹ increase)	1.07	1.01 to 1.13	0.01
Cold ischemic time (per 10-min increase)	1.01	1.00 to 1.02	0.02
Hyperchloremia	0.59	0.19 to 1.78	0.35

BMI = body mass index; CI = confidence interval.

Table 5 Factors associated with delayed graft function according to the multivariable analysis (logistic regression model including SID < 40)

Variable	Adjusted odds ratio	95% CI	P
Recipient sex (male)	1.10	0.63 to 1.92	0.74
Recipient BMI (per 1 kg·m ⁻² increase)	1.03	0.97 to 1.09	0.34
Norepinephrine use in recipient resuscitation (yes)	1.45	0.53 to 3.95	0.47
Donor age (per 1-year increase)	1.02	1.00 to 1.04	0.09
Donor terminal creatinine level (per 10-μmol·L ⁻¹ increase)	1.07	1.01 to 1.13	0.02
Cold ischemic time (per 10-min increase)	1.01	1.00 to 1.02	0.02
SID < 40	0.52	0.22 to 1.2	0.12

BMI = body mass index; CI = confidence interval; SID = strong ion difference.

Table 6 Factors associated with delayed graft function according to the multivariable analysis (logistic regression model including hyperchloremic acidosis and total saline volume infused)

Variable	Adjusted odds ratio	95% CI	P
Recipient sex (male)	0.97	0.55 to 1.72	0.93
Recipient BMI (per 1 kg·m ⁻² increase)	1.04	0.98 to 1.10	0.19
Norepinephrine use in recipient resuscitation (yes)	1.49	0.54 to 4.08	0.44
Donor age (per 1-year increase)	1.02	1.00 to 1.04	0.08
Donor terminal creatinine level (per 10-μmol·L ⁻¹ increase)	1.07	1.01 to 1.13	0.02
Cold ischemic time (per 10-min increase)	1.01	1.00 to 1.02	0.03
Total saline volume infused (per 1-L increase)	1.14	1.00 to 1.29	0.04
Hyperchloremic acidosis	0.52	0.17 to 1.60	0.26

BMI = body mass index; CI = confidence interval.

Table 7 Factors associated with delayed graft function according to the multivariable analysis (logistic regression model including hyperchloremia and total saline volume infused)

Variable	Adjusted odds ratio	95% CI	P
Recipient sex (male)	0.97	0.55 to 1.70	0.91
Recipient BMI (per 1 kg·m ⁻² increase)	1.04	0.98 to 1.10	0.20
Norepinephrine use in recipient resuscitation (yes)	1.50	0.55 to 4.10	0.43
Donor age (per 1-year increase)	1.02	1.00 to 1.04	0.09
Donor terminal creatinine level (per 10-μmol·L ⁻¹ increase)	1.07	1.01 to 1.13	0.02
Cold ischemic time (per 10-min increase)	1.01	1.00 to 1.02	0.03
Total saline volume infused (per 1-L increase)	1.14	1.00 to 1.29	0.04
Hyperchloremia	0.52	0.17 to 1.59	0.25

BMI = body mass index; CI = confidence interval.

function.⁴³ Two clinical trials comparing NS and balanced crystalloids in critically ill medical and surgical patients came to opposite conclusions regarding the impact on renal function. One found that the risk of AKI was not reduced whether NS or balanced solutions was used, the other found a decrease in a composite outcome of death from any cause, new RRT, or persistent renal dysfunction with the use of a balanced solution rather than NS.^{12,13}

With respect to kidney transplantation, seven randomized trials comparing NS and balanced solutions

have attempted to address this question.^{22–28}

Nevertheless, five of the studies included more than 90% living donor kidney transplant recipients, who typically have a much lower risk of DGF. One study enrolled 150 patients, but sample sizes were often low with fewer than 90 patients. Only one study evaluated kidney graft function as the main endpoint represented by the plasma creatinine concentration on postoperative day 3 and no differences were found between groups.²² The other studies evaluated acid-base disturbances or

occurrence of hyperkalemia as the main endpoints. Four studies reported DGF as the need for RRT in the first week after transplantation, without showing significant differences between groups, but all were underpowered to draw conclusions regarding that endpoint.^{23–25,28} While lower pH or bicarbonate and higher chloride concentrations were consistently observed in saline groups, only two studies reported significantly more hyperkalemia in the NS group.^{22,24} Of note, the proportion of patients with hyperkalemia > 6 mmol·L⁻¹ in the Weinberg *et al.* study was far higher than in ours, including 25% in the patients treated with Plasma-Lyte® and 60% in the NS group. In contrast, O'Malley *et al.*, reported that only patients in the NS group developed hyperkalemia (19%). Importantly, O'Malley *et al.* evaluated patients only intraoperatively. Finally, a Cochrane systematic review which included six of the seven trials confirmed the association of NS use with hyperchloremic acidosis but was unable to reach a conclusion regarding the impact of NS on graft function compared with balanced solutions.²¹

Our study has several strengths. First, unlike most prior studies we chose DGF rather than acid-base status as the primary outcome. We also used the standard definition of DGF (need for RRT in the first postoperative week).³⁰ In our work, the rate of DGF was 20%, similar to the rates recently reported in the US.^{44,45} Second, the risk factors associated with DGF or CRR $< 30\%$ found in our study (donor BMI, donor terminal serum creatinine value, donor age, and cold ischemic time) were congruent with the risk factors previously identified associated with DGF underlying the consistency of our cohort.^{14,46} Third, results were confirmed in sensitivity analysis using a creatinine-based definition of DGF. Finally, the sample size is also notable given the lower sample size of the previous trials available on the topic. Our study also has several limitations that warrant discussion. The retrospective design limits our insight into why patients received the fluid volumes that they did. The single-centre nature of the study may also limit the generalizability of the results. Although potential confounders chosen were factors known to influence the risk of DGF according to the literature, all observational studies have some degree of residual confounding.

In conclusion, our data showed that perioperative NS infusion volume was associated with an increased risk of DGF in deceased-donor kidney transplant recipients. Conversely, hyperchloremia and hyperchloremic acidosis were not associated with an increased risk of DGF, suggesting other mechanisms than a chloride effect.

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