ANESTHESIOLOGY

Perioperative Normal Saline Administration and Delayed Graft Function in Patients Undergoing Kidney Transplantation: A Retrospective Cohort Study

Kerstin Kolodzie, M.D., Ph.D., M.A.S., Ozlem S. Cakmakkaya, M.D., Ph.D., Eshandeep S. Boparai, M.D., Mehdi Tavakol, M.D., John R. Feiner, M.D., Mi-Ok Kim, Ph.D., Thomas B. Newman, M.D., M.P.H., Claus U. Niemann, M.D.

ANESTHESIOLOGY 2021; 135:621–32

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Randomized controlled trials of balanced crystalloids *versus* normal saline have not demonstrated superiority of either strategy in the generalized surgical population
- Patients undergoing kidney transplantation and receiving normal saline experience the metabolic complications of hyperchloremia
- The association of normal saline administration with delayed graft function, defined as renal replacement therapy within 1 week of transplant, is unclear

What This Article Tells Us That Is New

- In a single-center analysis of 2,515 patients undergoing kidney transplantation between 2004 and 2015, delayed graft function occurred in 21% of patients receiving greater than or equal to 80% normal saline, in 17.5% of patients receiving between 30 and 80% normal saline, and in 15.8% of patients receiving less than or equal to 30% normal saline
- For patients receiving greater than or equal to 80% normal saline compared with patients receiving less than or equal to 30% normal saline, the adjusted odds ratios for delayed graft function were 1.52 (95% CI, 1.05 to 2.21; $P = 0.028$) for deceased donor transplants (n = 1,472) and 1.66 (95% CI, 0.65 to 4.25; $P = 0.287$) for living donor transplants (n = 1,043)

ABSTRACT

Background: Perioperative normal saline administration remains common practice during kidney transplantation. The authors hypothesized that the proportion of balanced crystalloids *versus* normal saline administered during the perioperative period would be associated with the likelihood of delayed graft function.

Methods: The authors linked outcome data from a national transplant registry with institutional anesthesia records from 2005 to 2015. The cohort included adult living and deceased donor transplants, and recipients with or without need for dialysis before transplant. The primary exposure was the percent normal saline of the total amount of crystalloids administered perioperatively, categorized into a low (less than or equal to 30%), intermediate (greater than 30% but less than 80%), and high normal saline group (greater than or equal to 80%). The primary outcome was the incidence of delayed graft function, defined as the need for dialysis within 1 week of transplant. The authors adjusted for the following potential confounders and covariates: transplant year, total crystalloid volume, surgical duration, vasopressor infusions, and erythrocyte transfusions; recipient sex, age, body mass index, race, number of human leukocyte antigen mismatches, and dialysis vintage; and donor type, age, and sex.

Results: The authors analyzed 2,515 records. The incidence of delayed graft function in the low, intermediate, and high normal saline group was 15.8% (61/385), 17.5% (113/646), and 21% (311/1,484), respectively. The adjusted odds ratio (95% CI) for delayed graft function was 1.24 (0.85 to 1.81) for the intermediate and 1.55 (1.09 to 2.19) for the high normal saline group compared with the low normal saline group. For deceased donor transplants, delayed graft function in the low, intermediate, and high normal saline group was 24% (54/225 [reference]), 28.6% (99/346; adjusted odds ratio, 1.28 [0.85 to 1.93]), and 30.8% (277/901; adjusted odds ratio, 1.52 [1.05 to 2.21]); and for living donor transplants, 4.4% (7/160 [reference]), 4.7% (14/300; adjusted odds ratio, 1.15 [0.42 to 3.10]), and 5.8% (34/583; adjusted odds ratio, 1.66 [0.65 to 4.25]), respectively.

Conclusions: High percent normal saline administration is associated with delayed graft function in kidney transplant recipients.

(ANESTHESIOLOGY 2021; 135:621–32)

During kidney transplantation, crystalloid solutions are the first-line therapy for perioperative fluid management. The purpose is to maintain intravascular volume and to ensure adequate allograft perfusion without the use of synthetic colloids and vasoconstrictors, which are thought to cause renal vasoconstriction and possible additional acute kidney injury.[1] Normal saline was the first-choice

This article is featured in "This Month in Anesthesiology," page A1. This article is accompanied by an editorial on p. 564. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). This article has an audio podcast. This article has a visual abstract available in the online version. Parts of these results were presented as posters at the Association of University Anesthesiologists 2019 Annual Meeting in Montreal, Canada, May 16, 2019; the International Anesthesia Research Society 2019 Annual Meeting in Montreal, Canada, May 20, 2019; and the American Transplant Conference 2019 in Boston, Massachusetts, June 1, 2019.

Submitted for publication July 22, 2020. Accepted for publication June 7, 2021. Published online first on July 15, 2021. Corrected on November 9, 2021. From the Department of Anesthesia and Perioperative Care (K.K., J.R.F., C.U.N.), Department of Epidemiology and Biostatistics (K.K., M.-O.K., T.B.N.), Department of Surgery, Division of Transplantation (M.T., C.U.N.), and Department of Pediatrics (T.B.N.), University of California, San Francisco, San Francisco, California; the Department of Medical Education, Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul, Turkey (O.S.C.); and George Washington University School of Medicine and Health Sciences, Washington, D.C. (E.S.B.).

 Anesthesiology 2021; 135:621–32. DOI: 10.1097/ALN.0000000000003887

<zdoi;. DOI: 10.1097/ALN.0000000000003887>

crystalloid for kidney transplantation over decades based on hyperkalemia concerns with balanced potassium-containing crystalloids.[1,2] Normal saline is potassium-free but contains 154 mM sodium and 154 mM chloride with an osmolality of 285 mOsmol/kg. In contrast, balanced crystalloids such as lactated Ringer's solution or different formulations of PlasmaLyte (Baxter International Inc., USA) more closely resemble human plasma in their content of electrolytes and osmolality. Depending on formulation, their potassium content ranges between 4 and 5 mEq/l.

Numerous randomized controlled trials and one systematic review have described adverse physiologic and metabolic effects of fluid resuscitation with normal saline compared with balanced crystalloids in kidney transplant recipients. The high chloride content causes hyperchloremia, decreases the strong ion difference, and consequently can result in metabolic acidosis.[3–11] In turn, metabolic acidosis induces a potassium shift from intra- to extracellular, clinically often resulting in hyperkalemia. In consequence, mean serum potassium levels were actually higher in kidney transplant recipients who received normal saline as compared with balanced crystalloids in several studies.[5–7,9,10] Based on these results, some institutions and providers worldwide have already shifted away from normal saline in kidney transplantation.[12]

In contrast, the effects of normal saline administration on clinical outcomes, especially on kidney graft function, remain unclear. In fact, none of the cited randomized trials was powered to detect a meaningful difference in function of the grafted kidney. Research in large medical and surgical hospitalized patient cohorts demonstrated that normal saline is associated with a clinically relevant decrease in kidney function.[13–15] However, one recent cluster randomized clinical trial could not confirm these findings.[16] A small retrospective study in a combined cohort of deceased and living donor kidney transplant recipients found higher odds of renal replacement therapy within 48 h after transplantation for patients who received normal saline compared with balanced crystalloids.[17] We sought to build on this work with a larger cohort and a larger set of adjustment variables, using delayed graft function as the outcome.

We hypothesized that the choice of the perioperative crystalloid solution in kidney transplant recipients affects the risk of delayed graft function. We therefore investigated the association between higher percentages of perioperative normal saline on the total volume of crystalloids and delayed graft function in patients undergoing kidney transplantation.

Materials and Methods

Design, Study Population, and Record Linkage

This is a retrospective cohort study to investigate the association of perioperative normal saline *versus* balanced crystalloid administration on delayed graft function in patients undergoing kidney transplantation between 2005 and 2015 at a single academic medical center. Patients undergoing combined transplant surgeries were not eligible for inclusion. After Institutional Review Board approval and a waiver of informed consent was received (University of California San Fransisco, San Francisco, California), we submitted a finder file to the Scientific Registry of Transplant Recipients. The Scientific Registry of Transplant Recipients is a national database under custody of the U.S. Department of Health and Human Services (Washington, D.C.). All U.S. transplant centers are required to report their data. The Scientific Registry of Transplant Recipients manages these data, and supplies data, summary reports, and analyses to the transplant community to support ongoing evaluation of the national organ transplant system and to facilitate research. The Scientific Registry of Transplant Recipients data system includes data on all donors, wait-list candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources and Services Administration, U.S. Department of Health and Human Services, provides oversight to the activities of the Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients contractors.

The finder file submitted to the Scientific Registry of Transplant Recipients contained name, date of surgery, and transplant number to identify institutional cases within the national database. The file was a broad and untested extraction from our institutional transplant database that was readily available but not linked to the anesthesia databases. It contained 3,955 identifiers of kidney transplant recipients from 2004 to 2015. Of those, 3,891 records could be linked to Scientific Registry of Transplant Recipients data.

Simultaneously, we extracted kidney transplant records from two consecutive institutional electronic anesthesia record databases (Picis Clinical Solutions, Inc., USA, from 2005 to 2012; and Epic, USA, from 2012 to 2015) and merged both datasets to create the file of available institutional anesthesia records from 2005 to 2015. The merged file of anesthesia records contained 3,183 records.

Subsequently, we linked our final anesthesia record dataset (n = 3,183) with the identified Scientific Registry of Transplant Recipients data and obtained 2,951 records. After exclusion of combined transplants (n = 46) and pediatric patients (n = 166), our eligible cohort consisted of 2,739 records. Of those, 2,515 had any crystalloids charted perioperatively and were included in the data analysis (fig. 1, flowchart).

Our original protocol included pediatric patients (age less than 18 yr). However, we later realized that body mass index, number of transfusions, and crystalloid volume would all need to be normalized to age or weight for pediatric patients to have a physiologic interpretation similar

to adults. Therefore, for simplicity, we restricted our main analyses to adults and report these results in this manuscript.

Institutional Fluid Management Recommendations

At our institution, the choice of crystalloid is solely at the discretion of the anesthesia provider. The recommendations for intraoperative fluid administration during kidney transplantation are accessible on the departmental intranet since 2009 and suggest 40 ml/kg of crystalloids but do not recommend a specific type. The routinely used hemodynamic endpoint is the noninvasive mean arterial blood pressure to be within 20% of the baseline value. Synthetic colloids are discouraged. Albumin 5% can be used if indicated. The preferred vasopressor, if indicated, is dopamine. Since 2009, routine placement of central venous lines or arterial lines is not recommended. Adjustment of these general recommendations based on patients' comorbidities is at the discretion of the anesthesia provider (Supplemental Digital Content 1, http://links.lww.com/ALN/C654).

Independent Variables

The primary exposure of interest was the perioperative administration of normal saline. The perioperative time period was defined as the time from anesthesia start to discharge from the postanesthesia care unit. Volume and type of crystalloids were extracted from the anesthesia records. In both anesthesia databases, crystalloids are usually charted in increments from 100 to 1,000 ml throughout the perioperative period. The sum of each type of crystalloid administered during the perioperative period was extracted from the anesthesia databases based on an algorithm, and 101 charts were then manually reviewed to validate the extraction process.

Because we expected that a significant proportion of patients received a combination of different crystalloid solutions, we defined the percent normal saline of the total amount of crystalloids as our primary exposure of interest. This was an *a priori* definition based on the rationale that the percent normal saline administered perioperatively is solely the choice of the anesthesia provider. In contrast, the total volume of crystalloids administered is often dictated by perioperative conditions and patients' characteristics such as body weight.

After accessing the data, we could not confirm a linear association between the percent normal saline and the log odds of delayed graft function. Therefore, we categorized the variable into a low normal saline group (30% or less), an intermediate normal saline group (greater than 30% but less than 80%), and a high normal saline group (80% or more). We chose these cutoffs based on a bimodal distribution of the percent normal saline variable and clinical considerations: The less than 30% category roughly represents all patients receiving less than 1 l of normal saline.

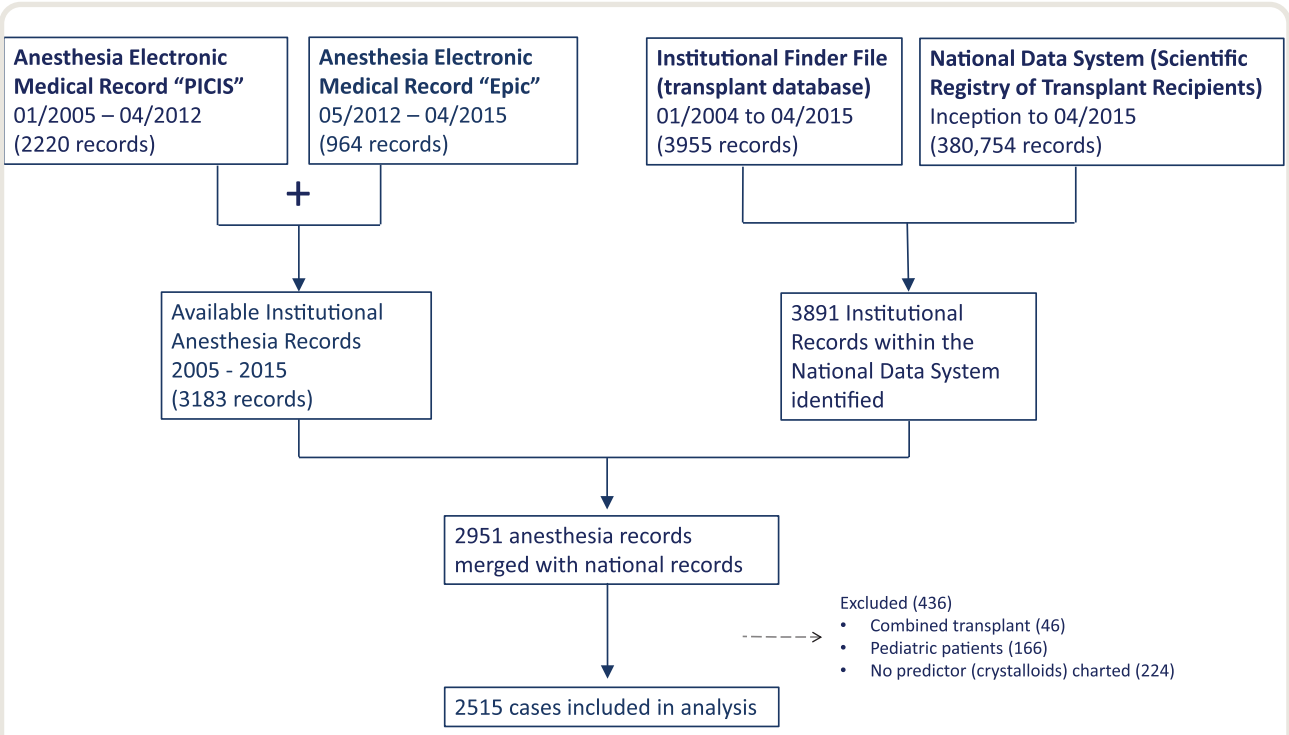

Fig. 1. Flowchart of database linkage.

Patients' demographic data such as age, sex, and body mass index, and perioperative data such as surgery duration, medications, type and volume of crystalloids, and all other fluids administered were extracted from the electronic anesthesia records. Transplant and donor data were derived from the Scientific Registry of Transplant Recipients Standard Analysis File for kidney transplant recipients.

Outcome Variable

The *a priori* defined primary outcome was the occurrence of delayed graft function, defined as the need for dialysis within 1 week after transplant surgery. Delayed graft function is a well-established endpoint for allograft dysfunction in kidney transplantation and often used as a primary endpoint in research studies.[18,19] All outcome data were derived from the Scientific Registry of Transplant Recipients Standard Analysis File for kidney transplant recipients.

Subgroup Analysis (*A Priori*)

To explore possible heterogeneity of our mixed cohort of deceased and living donor transplants, we re-ran our primary logistic regression model for both subgroups separately and tested for interactions between the primary exposure and the type of donor.

Statistical Analysis

All analyses were performed based on an *a priori* study protocol unless indicated as *post hoc* analysis. A data analysis and statistical plan was written after the data were accessed.

Bivariate associations were assessed with the chi-square test, Fisher exact test, Mann–Whitney U test, or independent samples *t* test. Data were mostly complete except that cold ischemia time was missing in a relevant number of records. Assuming missingness at random, where the propensity for a data point to be missing is related to some of the observed data, we used multiple imputation with ordinal logit regression and imputed missing cold ischemia time categories (less than or equal to 2 h, greater than 2 to 10 h, greater than 10 to 20 h, greater than 20 h).[20] The imputation model included all independent variables plus the outcome variable of the analysis models. Twenty imputed datasets were generated.

To compare delayed graft function among the low, intermediate, and high normal saline groups, we determined the unadjusted risks by study group and for relevant subgroups. To adjust for potential confounding from nonrandom treatment assignment, we then fit a multivariable logistic regression model. Model development was based on four consecutive steps to investigate for potential confounders and covariates for inclusion into the model in a forward selection process.

1. Creation of a directed acyclic graph and identification of the minimal sufficient adjustment set before starting data analysis.
2. Consideration of variables that showed unadjusted statistical differences ($P \leq 0.2$) between the normal saline groups (primary exposure) as well as between the outcome categories (delayed graft function or not).
3. Identification and inclusion of variables extremely strongly associated with the outcome to reduce variability of the model.
4. Consideration of variables of general interest that commonly are included into models of delayed graft function in the literature.

If nonlinearity of the association between continuous covariates and the log odds of the outcome delayed graft function was suspected, we categorized the covariates, either based on clinically established cutoff values or based on sample quartiles. We verified that no significant interactions were present. We assessed the overall model fit with the Hosmer–Lemeshow test using deciles of fitted risks, and we report the C-statistic as a marker of the discriminative ability of our model. We also assessed the contribution of the normal saline variable to the overall model fit with the likelihood ratio test.

No statistical power calculation was conducted before the study. The sample size was solely based on the available data. A minimum clinically meaningful effect size was not defined *a priori*.

Post Hoc Analyses

To further investigate the robustness to misspecification of our primary parsimonious logistic regression model, we developed an alternative regression model with adjustment for treatment propensity scores. Using a logistic regression model, we calculated the propensity of treatment with 50% or more *versus* less than 50% normal saline. We used all covariates of the primary model to fit the treatment model. We created restricted cubic splines of the propensity score with five knots. We then regressed delayed graft function on the two normal saline groups adjusting for cubic splines of the propensity score.

To address concerns that our primary exposure variable, percent normal saline, does not reflect the amount of normal saline administration, we created three strata of total normal saline administration: no normal saline, 2 l or less, and more than 2 l. We then used this alternative exposure variable with our primary logistic regression model.

To address concerns that our decision to split the percent normal saline variable at 30% and 80% cutoffs might introduce bias, we have created an alternative variable of percent normal saline groups with cutoffs at 20%, 40%, 60%, and 80% normal saline. We then used this alternative exposure variable with our primary logistic regression model.

To explore a possible effect of kidney transplant recipients who have not been on dialysis at the time of transplant, we reran our primary model excluding this subgroup.

Data are presented as mean ± SD. All *P* values are drawn for two-sided hypothesis testing, and statistical significance was evaluated at the significance level of 0.05. We used Stata 14.2 (Stata Corp., USA) for all statistical analyses.

Results

The dataset included 2,515 kidney transplant cases. Twenty-two patients underwent two kidney transplant procedures between 2005 and 2015. Mean ± SD age of the cohort was 52 ± 14 yr, 58.1% (1,461) were male, and 58.5% (1,472) received a deceased donor graft. Sixteen (0.6%) donor kidneys were machine-perfused before transplant. Three hundred eighty-five cases (15%) received 30% normal saline or less (low normal saline group), 646 cases (26%) received greater than 30% but less than 80% normal saline (intermediate normal saline group), and 1,484 cases (59%) received 80% or more normal saline (high normal saline group). Of the 2,515 cases, 216 (9%) did not receive any normal saline, and 1,402 (56%) received normal saline exclusively. Over the years, the proportion of patients receiving 80% or more normal saline decreased from 75% (348/465) in the period from 2005 to 2007, to 27% (106/397) from 2014 to 2015.

Baseline characteristics in the low, intermediate, and high normal saline groups are displayed in table 1. The mean ± SD volume of normal saline administration was 264 ± 384 ml in the low percent normal saline group and 2,861 ± 1,344 ml in the high normal saline group. The mean normal saline volume, mean balanced crystalloid volume, and mean volume of crystalloids per percent normal saline group are displayed in table 2. We also assessed the bivariate association of individual covariates with the outcome delayed graft function. As expected, several patient- and donor-related characteristics were associated with delayed graft function. Of the anesthesia- and surgery-related characteristics, surgery duration and the normal saline group were associated with delayed graft function (Supplemental Digital Content 2, http://links.lww.com/ALN/C655).

The overall incidence of delayed graft function was 19.3% (485/2,515). In the subgroups of deceased donor transplants, the incidence of delayed graft function was 29.2% (430/1,472), and in living donor transplants 5.3% (55/1,043). For the full cohort, the unadjusted incidence of delayed graft function in the low, intermediate, and high normal saline group was 15.8% (61/385), 17.5% (113/646), and 21% (311/1,484), respectively. Stratified by donor type, delayed graft function in the low, intermediate, and high normal saline group for deceased donor transplants was 24% (54/225), 28.6% (99/346), and 30.8% (277/901), respectively; and for living donor transplants, 4.4% (7/160), 4.7% (14/300), and 5.8% (34/583), respectively. The incidence of delayed graft function over time is displayed in Supplemental Digital Content 3 (http://links.lww.com/ALN/C656).

The primary logistic model regressed delayed graft function on the three normal saline groups. Based on the directed acyclic graph, we included year of transplant surgery, total crystalloid volume, duration of surgery, the perioperative use of a vasopressor infusion, and erythrocyte transfusions as covariates. In addition, we included recipient sex, age, body mass index, race, number of human leukocyte antigen mismatches, and dialysis vintage; and donor type, age in quartiles, and sex. Age thresholds for quartiles of donor age are shown in Supplemental Digital Content 4 (http://links.lww.com/ALN/C657). The adjusted odds ratio of delayed graft function was 1.24 (95% CI, 0.85 to 1.81; $P = 0.258$) for the intermediate normal saline group and 1.55 (95% CI, 1.09 to 2.19; $P = 0.014$) for the high normal saline group compared with the low normal saline group (table 3).

The model fit was satisfactory (Hosmer–Lemeshow $P = 0.576$). The discriminative ability of our model was 0.791 (C-statistic). The likelihood ratio test revealed a significantly better fit of the model that included the normal saline variable as compared to the same model without the normal saline variable ($P = 0.049$).

Other covariates significantly associated with delayed graft function in our model were male recipients, higher recipients' body mass index, black race compared with white, dialysis vintage, deceased donor compared with living donor, donor age, and male donor (table 3). We did not find significant interactions between the primary exposure variable and any covariate in the model. Specifically, there was no evidence for interaction between the normal saline groups and donor type, and between normal saline groups and total crystalloid volume.

In bivariate analysis, cold ischemia time was significantly associated with the primary exposure normal saline group and with the outcome delayed graft function and therefore a potential confounder (table 1 and Supplemental Digital Content 2, http://links.lww.com/ALN/C655). However, values for cold ischemia time were missing in 423 cases (16.8%). All missing values were from living donor transplantations between 2005 and 2012. After multiple imputation of cold ischemia time as described above, we fit a second logistic regression model that included imputed data for cold ischemia time. In the imputed model, the odds ratio of delayed graft function was higher with longer cold ischemia times, but this association was not statistically significant (Supplemental Digital Content 5, http://links.lww.com/ALN/C658). We compared the two logistic regression models with and without imputed cold ischemia time. This comparison revealed no relevant difference in point estimates and variances for the primary exposure and most covariates (Supplemental Digital Content 5, http://links.lww.com/ALN/C658). For simplicity, we therefore used the primary best-fit model without imputed cold ischemia time for all further analyses.

Table 1. Baseline Demographic, Perioperative, and Donor Characteristics per Normal Saline Group

	Total N	Low Normal Saline Group (30% or Less)	Intermediate Normal Saline Group (> 30% to < 80%)	High Normal Saline Group (80% or More)	*P* Value
Characteristics	2,515	385	646	1,484	
Recipient characteristics					
Sex					0.199
Male	1,461	208 (54)	384 (59.4)	869 (58.6)	
Age (yr), mean ± SD		52 ± 14	51 ± 14	51 ± 14	0.504
Height (cm), mean ± SD		167.8 ± 10.9	168.3 ± 10.5	168 ± 10.5	0.723
Weight (kg), mean ± SD		76.4 ± 17.9	76.7 ± 17.6	75.8 ± 18	0.547
Body mass index (kg/m^2), mean ± SD		27.0 ± 5.2	27.0 ± 5.1	26.7 ± 5.2	0.482
Lean body mass (kg), mean ± SD		53.7 ± 11.2	54.2 ± 10.8	53.8 ± 10.9	0.591
Race, n (%)					0.782
White	1,553	243 (63.1)	401 (62.1)	909 (61.3)	
Asian	582	86 (22.3)	146 (22.6)	350 (23.6)	
Black	324	47 (12.2)	80 (12.4)	197 (13.3)	
Other	56	9 (2.3)	19 (2.9)	28 (1.9)	
Ethnicity, n (%)					
Latino	666	112 (29.1)	165 (25.5)	389 (26.2)	0.429
Years on dialysis, n (%)					0.451
Not on dialysis	400	64 (16.6)	114 (17.7)	222 (15)	
≤ 2 yr	709	112 (29.1)	185 (28.6)	412 (27.8)	
> 2 yr	1,406	209 (54.3)	347 (53.7)	850 (57.3)	
Human leukocyte antigen mismatches, n (%)	*				0.453
0	293	38 (9.9)	68 (10.5)	187 (12.6)	
1/2	222	33 (8.6)	56 (8.7)	133 (9)	
3/4	895	136 (35.4)	248 (38.5)	511 (34.4)	
5/6	1,103	177 (46.1)	273 (42.3)	653 (44)	
Perioperative variables					
Year of transplant, n (%)					< 0.001
2005–2007	465	39 (10.1)	78 (12.1)	348 (23.5)	
2008/2009	515	30 (7.8)	81 (12.5)	404 (27.2)	
2010/2011	556	60 (15.6)	151 (23.4)	345 (23.3)	
2012/2013	582	113 (29.4)	188 (29.1)	281 (19)	
2014/2015	397	143 (37.1)	148 (22.9)	106 (7.1)	
Hydromorphone, n (%)					0.254
Yes	2,076	317 (82.3)	520 (80.5)	1,239 (83.5)	
Vasopressor infusion					0.279
Yes	807	128 (33.3)	191 (29.6)	488 (32.9)	
Surgery duration, n (%)		183 (66)	186 (64)	174 (51)	< 0.001
≤ 150 min	841	120 (31.2)	200 (31)	521 (35.1)	
150–300 min	1,593	251 (65.2)	409 (63.3)	933 (62.9)	
> 300 min	81	14 (3.6)	37 (5.7)	30 (2)	
Cold ischemia time, n (%)	†				< 0.001
≤ 2 h	528	103 (29.8)	172 (31.1)	253 (21.2)	
> 2–10 h	626	97 (28)	157 (28.3)	372 (31.2)	
> 10–20 h	736	122 (35.3)	183 (33)	431 (36.2)	
> 20 h	202	24 (6.9)	42 (7.6)	136 (11.4)	
Crystalloid volume, n (%)					< 0.001
≤ 2 l	551	84 (21.8)	82 (12.7)	385 (25.9)	
> 2–4 l	1,616	247 (64.2)	461 (71.4)	908 (61.2)	
> 4 l	348	54 (14)	103 (15.9)	191 (12.9)	
Albumin, n (%)					0.299
Yes	104	13 (3.4)	22 (3.4)	69 (4.7)	
Synthetic colloid, n (%)					0.528
Yes	49	7 (1.8)	16 (2.5)	26 (1.8)	
Erythrocyte transfusion, n (%)					0.418
None	2,378	358 (93)	613 (94.9)	1,407 (94.8)	
≤ 500 ml	99	22 (5.7)	23 (3.6)	54 (3.6)	
> 500 ml	38	5 (1.3)	10 (1.6)	23 (1.6)	

(*Continued*)

Table 1. (Continued)

	Total N	Low Normal Saline Group (30% or Less)	Intermediate Normal Saline Group (> 30% to < 80%)	High Normal Saline Group (80% or More)	*P* Value
Donor characteristics					
Donor—age (yr), mean ± SD		41 ± 15	40 ± 15	39 ± 15	0.012
Donor—sex, n (%)					0.130
Male	1,276	211 (54.8)	312 (48.3)	753 (50.7)	
Donor—history of diabetes, n (%)	‡				0.457
Yes	109	13 (3.4)	26 (4)	70 (4.7)	
Donor type, n (%)					0.142
Deceased	1,472				
Donation after brain death	1,377				
Standard criteria	1,228	186 (48.3)	288 (44.6)	754 (0.8)	
Extended criteria	149	23 (6)	37 (5.7)	89 (6.0)	
Donation after cardiac death	95				
Standard criteria	86	16 (4.2)	19 (2.9)	51 (3.4)	
Extended criteria	9	0	2 (0.3)	7 (0.5)	
Living, n (%)	1,043	160 (41.6)	300 (46.4)	583 (39.3)	
Donor deceased	1,472				
Creatinine > 1.5, n (%)	242	45 (20)	51 (14.7)	146 (16.2)	0.242
History of hypertension, n (%)	363	48 (21.3)	89 (25.8)	226 (25.3)	0.418
Cause of death, n (%)					0.793
Anoxia	412	60 (26.7)	89 (25.7)	263 (29.2)	
Cerebrovascular/stroke	489	82 (36.4)	114 (33)	293 (32.5)	
Head trauma	528	75 (33.3)	131 (37.9)	322 (35.7)	
CNS tumor	7	1 (0.4)	2 (0.6)	4 (0.4)	
Other	36	7 (3.1)	10 (2.9)	19 (2.1)	
Hepatitis C antibodies	30	6 (2.7)	4 (1.2)	20 (2.2)	0.379
Donor living	1,043				
Preoperative creatinine (mg/dl), mean ± SD	978	0.84 ± 0.41	0.79 ± 0.2	0.8 ± 0.26	0.191

N indicates total number of observations; n, number of observations in subgroups; %, percent observations.

*Total N for human leukocyte antigen mismatch is 2,513. †Total N for cold ischemia time is 2,092. ‡Total N for donor—history of diabetes is 2,508.

CNS, central nervous system.

As defined in our analysis plan, we repeated our primary logistic regression model for the subgroups of deceased (n = 1,472) and living (n = 1,043) donor transplants separately. The odds ratio of delayed graft function was 1.52 (95% CI, 1.05 to 2.21; $P = 0.028$) for the high normal saline group compared with the low normal saline group for deceased donor transplants; and 1.66 (95% CI, 0.65 to 4.25; $P = 0.287$) for living donor transplants (Supplemental Digital Content 6, http://links.lww.com/ALN/C659). Within the full model, the interaction terms of the normal saline groups with donor type were nonsignificant ($P = 0.733$ and $P = 0.808$).

Post Hoc Analyses

Propensity Score Regression. Adjusting for cubic splines of the propensity of treatment with high *versus* low normal saline, the odds ratio of delayed graft function was 1.33 (95% CI, 1.02 to 1.74; $P = 0.036$) for the group receiving 50% or more normal saline as compared with less than 50% normal saline.

Total Volume of Normal Saline Administration. This alternative logistic regression model regressed delayed graft function on the total amount of normal saline (no normal saline, 2 l or less normal saline, or more than 2 l normal saline). The odds ratio of delayed graft function was 1.48 (95% CI, 0.95 to 2.29; $P = 0.080$) for the administration of more than 2 l of normal saline as compared to the no normal saline group (Supplemental Digital Content 7, http://links.lww.com/ALN/C660).

Percent Normal Saline Groups with Cutoffs in 20% Intervals. Splitting the percent normal saline variable into five groups in intervals of 20%, 12.2% (307) transplant cases received less than 20% normal saline, 7.6% (190) received between 20% and less than 40%, 8.2% (206) received between 40% and less than 60%, 12.3% (310) received between 60% and less than 80%, and 59.7% (1,502) received 80% or more normal saline. The odds ratio of delayed graft function was 1.13 (95% CI, 0.65 to 1.97; $P = 0.671$) for the 20% to less than 40% normal saline group, 1.06 (95% CI, 0.63 to 1.80; $P = 0.828$) for the 40% to less than 60% group, 1.54 (95% CI, 0.96 to 2.46; $P = 0.71$) for the 60% to less than 80% group, and 1.61 (95% CI, 1.10 to 2.35; $P = 0.014$) for the group that received 80% or more normal saline as compared with the group that received less than 20%. Estimated point estimates of all other covariates were comparable to the primary model. The full model is shown in table 4.

Table 2. Mean Normal Saline Volume, Mean Balanced Crystalloid Volume, and Mean Total Volume of Crystalloids per Percent Normal Saline Group

Percent Normal Saline	N	Normal Saline (ml), Mean ± SD	Balanced Crystalloids (ml), Mean ± SD	Total Crystalloids (ml), Mean ± SD
≤ 30%	385	264 ± 384	2,813 ± 1,152	3,077 ± 1,265
> 30 to < 80%	646	1,877 ± 817	1,376 ± 645	3,253 ± 1,049
≥ 80%	1,484	2,861 ± 1,344	26 ± 122	2,887 ± 1,361
Total	2,515	2,211 ± 1,455	799 ± 1,174	3,010 ± 1,282

Preemptive Kidney Transplants. In our cohort, 400 patients received a preemptive kidney transplant, *i.e.*, did not require dialysis before transplant. Of those, 13 (3.3%) developed delayed graft function (four living donor recipients and nine deceased donor recipients). Using our primary logistic regression model excluding patients who were not on dialysis at the time of transplant (n = 2,113), the odds of delayed graft function were 56% (95% CI, 1.1 to 2.22; $P = 0.014$) higher for the high as compared with the low normal saline group. All covariates in the model showed point estimates and variances comparable to our primary model (Supplemental Digital Content 8, http://links.lww.com/ALN/C661).

Discussion

In patients undergoing kidney transplantation, a high percentage of 80% or more normal saline administered perioperatively demonstrated a higher crude risk and a higher adjusted odds of delayed graft function. In our dataset, the low, intermediate, and high percent normal saline groups overlapped with the mean total volume of normal saline administered while the total volume of crystalloids was comparable between groups (table 2).

Delayed graft function occurs in about 20 to 40% of deceased donor kidney transplants and in about 5% of living donor kidney transplants in the United States.[18,21,22] It is highly relevant as an outcome in kidney transplant because it is associated with a higher risk of acute rejection, poorer long-term graft survival, and higher healthcare costs.[18,19,23]

The robustness of our results is supported by an *a priori* subgroup analysis and *post hoc* analyses. We did not find evidence for a heterogenous effect of the percent normal saline group on delayed graft function caused by the inclusion of deceased as well as living donor transplants or caused by the inclusion of patients not on dialysis before transplant. Additionally, the *post hoc* analyses based on propensity score regression and on alternative primary exposure variables showed comparable odds of delayed graft function with high percent or high absolute volume of normal saline as we have demonstrated with our primary model. Our *post hoc* regression model with an alternative primary exposure variable of percent normal saline categories with cutoffs at regular 20% intervals specifically addressed concerns of bias in our primary model because the choice of cutoffs for the percent normal saline categories at 30% and 80% was made after accessing the data (table 4). The very comparable results do not indicate bias based on the choice of the exposure categories. Overall, the similar results of our subgroup and *post hoc* analyses support the meaningfulness of our choice of primary exposure variable and statistical analysis.

Our findings are in line with the growing evidence of an unfavorable effect of normal saline on kidney function in specific populations. We confirmed the results of one previous study in kidney transplant recipients comparing normal saline with balanced crystalloids on graft function.[15] Previous animal research and one volunteer study have shown that administration of chloride rich fluids such as normal saline reduces kidney perfusion and glomerular filtration rate, and prolongs time to micturition.[24,25] A large propensity-matched cohort study in patients undergoing major abdominal surgery found an almost fivefold higher need for postoperative dialysis in patients receiving normal saline compared with balanced crystalloids on the day of surgery.[13] In 2018, the results from the Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial, a large pragmatic crossover trial, were reported.[15] The authors investigated the effects of normal saline as compared with balanced crystalloids in noncritically ill adult surgical and medical patients admitted to the hospital *via* the emergency department. They found a statistically significant 0.9% higher absolute risk of their composite endpoint of major adverse kidney events in their normal saline group.

We report a markedly larger unadjusted absolute effect size of more than 7% for deceased donor transplants, which we attribute to the higher vulnerability of the transplanted kidney as compared with the native organs studied in the SALT-ED trial. In addition, the median crystalloid volume administered in the SALT-ED trial (1.1 l; interquartile range, 1 to 2) was roughly one third of what we found in our cohort (3 l; interquartile range, 2.2 to 3.6). Even though the percentages of normal saline administered during the study period are comparable between our high normal saline group (80% or more) and the normal saline group in the SALT-ED trial (93% adherence), the higher total crystalloid volume in our cohort translates into a higher absolute normal saline volume. That might also contribute to the larger effect size found in our study.

Table 3. Adjusted Multivariable Logistic Regression of Delayed Graft Function on Normal Saline Group (Including All Adjustment Variables)

Variable	Odds Ratio (95% CI)	*P* Value
Primary exposure variable		
Normal saline group		
Low (≤ 30%)	Reference (1.0)	
Intermediate (> 30% to < 80%)	1.24 (0.85–1.81)	0.258
High (≥ 80%)	1.55 (1.09–2.19)	0.014
Recipient characteristics		
Sex		
female (*vs.* male)	0.59 (0.47–0.75)	< 0.001
Age (yr)	1.00 (0.99–1.01)	0.867
Body mass index (kg/m^2)	1.07 (1.05–1.10)	< 0.001
Race		
White	Reference (1.0)	
Asian	1.01 (0.77–1.33)	0.942
Black	1.68 (1.24–2.27)	0.001
Other	1.13 (0.53–2.40)	0.752
Years on dialysis		
Not on dialysis	Reference (1.0)	
≤ 2 yr	2.68 (1.44–5.01)	0.002
> 2 yr	5.25 (2.89–9.52)	< 0.001
Human leukocyte antigen mismatches		
0	Reference (1.0)	
1/2	1.18 (0.63–2.21)	0.605
3/4	1.09 (0.74–1.60)	0.679
5/6	1.11 (0.76–1.62)	0.591
Perioperative variables		
Year of transplant		
2005–2007	Reference (1.0)	
2008/09	1.64 (1.14–2.36)	0.008
2010/11	1.27 (0.88–1.83)	0.211
2012/13	1.40 (0.97–2.03)	0.072
2014/15	1.40 (0.93–2.12)	0.111
Crystalloid volume		
> 2–4 l	Reference (1.0)	
≤ 2 l	1.03 (0.79–1.35)	0.830
> 4 l	1.34 (0.95–1.90)	0.099
Surgery duration		
> 150–300 min	Reference (1.0)	
≤ 150 min	0.99 (0.78–1.26)	0.937
> 300 min	1.44 (0.63–3.26)	0.387
Vasopressor infusion		
Yes (*vs.* none)	0.95 (0.75–1.20)	0.662
Erythrocyte transfusion		
None	Reference (1.0)	
≤ 500 ml	1.49 (0.88–2.53)	0.143
> 500 ml	1.96 (0.83–4.65)	0.127
Donor characteristics		
Donor type		
Deceased (*vs.* living)	4.72 (3.29–6.76)	< 0.001
Donor—age		
1st quartile	Reference (1.0)	
2nd quartile	1.25 (0.91–1.73)	0.173
3rd quartile	1.76 (1.29–2.40)	< 0.001
4th quartile	1.66 (1.19–2.32)	0.003
Donor—sex		
Female (*vs.* male)	0.71 (0.57–0.90)	0.004

Table 4. Adjusted Multivariable Logistic Regression of Delayed Graft Function on Categories of Percent Normal Saline with Cutoffs at 20% Intervals

Variable	Odds Ratio (95% CI)	*P* Value
Primary exposure variable		
Normal saline group		
< 20%	Reference (1.0)	
20% to < 40%	1.13 (0.65–1.97)	0.671
40% to < 60%	1.06 (0.63–1.80)	0.828
60% to < 80%	1.54 (0.96–2.46)	0.071
≥ 80%	1.61 (1.10–2.35)	0.014
Recipient characteristics		
Sex		
Female (*vs.* male)	0.60 (0.47–0.75)	< 0.001
Age (yr)	1.00 (0.99–1.01)	0.844
Body mass index (kg/m^2)	1.07 (1.05–1.10)	< 0.001
Race		
White	Reference (1.0)	
Asian	1.02 (0.77–1.34)	0.911
Black	1.68 (1.24–2.27)	0.001
Other	1.14 (0.54–2.42)	0.732
Years on dialysis		
Not on dialysis	Reference (1.0)	
≤ 2 yr	2.63 (1.41–4.92)	0.002
> 2 yr	5.18 (2.86–9.41)	< 0.001
Human leukocyte antigen mismatches		
0	Reference (1.0)	
1/2	1.20 (0.64–2.24)	0.575
3/4	1.07 (0.73–1.59)	0.721
5/6	1.10 (0.75–1.60)	0.638
Perioperative variables		
Year of transplant		
2005–2007	Reference (1.0)	
2008/09	1.63 (1.13–2.35)	0.009
2010/11	1.27 (0.88–1.84)	0.208
2012/13	1.41 (0.98–2.05)	0.066
2014/15	1.42 (0.94–2.15)	0.097
Crystalloid volume		
> 2–4 l	Reference (1.0)	
≤ 2 l	1.06 (0.81–1.39)	0.683
> 4 l	1.36 (0.96–1.93)	0.084
Surgery duration		
> 150–300 min	Reference (1.0)	
≤ 150 min	1.00 (0.79–1.27)	0.978
> 300 min	1.39 (0.61–3.16)	0.437
Vasopressor infusion		
Yes (*vs.* none)	0.95 (0.75–1.20)	0.664
Erythrocyte transfusion		
None	Reference (1.0)	
≤ 500 ml	1.47 (0.86–2.49)	0.160
> 500 ml	1.93 (0.81–4.58)	0.138
Donor characteristics		
Donor type		
Deceased (*vs.* living)	4.75 (3.31–6.82)	< 0.001
Donor—age		
1st quartile	Reference (1.0)	
2nd quartile	1.26 (0.91–1.75)	0.158
3rd quartile	1.76 (1.29–2.39)	< 0.001
4th quartile	1.67 (1.19–2.33)	0.003
Donor—sex		
Female (*vs.* male)	0.71 (0.57–0.90)	0.004

The recently published Saline or Lactated Ringer's (SOLAR) trial assigned alternating cohorts of patients undergoing elective orthopedic or colorectal surgery to receive either lactated Ringer's solution or normal saline.[16] This trial did not find a meaningful difference in postoperative acute kidney injury between study groups. Even though these results seem to contradict an effect of normal saline on kidney function,

the authors note that key differences of their trial compared to previous publications are the relatively healthy elective surgery patient population and the low amount of intraoperative fluid administration (median, 1.9 l, interquartile range, 1.3 to 2.6; compared with median, 3 l, interquartile range, 2.2 to 3.6 in our study). Considering these distinctly different cohorts, the SOLAR trial does not contradict our study results.

Our study also demonstrates that fluid management practice during kidney transplantation already changed over the years at our institution. In the time period from 2014 to 2015, only 27% of all kidney transplant patients received 80% or more normal saline, down from 75% from 2005 to 2007. This is in accordance with a national trend.[12]

The marked increase in delayed graft function between 2005 and 2013 (Supplemental Digital Content 3, http://links.lww.com/ALN/C656) has previously been reported.[26] This is attributed to the increasing utilization of expanded criteria donors in an effort to meet the high demand of kidney donations.

In our primary model, several covariates show a significant association with the outcome delayed graft function. These findings are consistent with the transplant literature.[27,28] However, we cannot rule out additional confounding or interactions between these covariates and delayed graft function. Interpretation of these findings should therefore be cautious.

This observational study has limitations. It relies on three different databases. The purpose of the Scientific Registry of Transplant Recipients dataset is primarily research and quality assurance and includes mandatory data validation. On the other hand, both anesthesia databases used routinely collected clinical data extracted from the electronic anesthesia record. Data entry is human operator–dependent, and especially fluid administration data might be imprecise. There is no objective data check, validation, or control mechanism in place to validate the original data entries. However, errors in the underlying perioperative intravenous fluid documentation are likely to be similar across exposure groups and therefore unlikely to lead to a false association between normal saline load and delayed graft function.

The outcome variable delayed graft function, defined as the need for dialysis within 1 week after transplant, has limitations. Criteria and thresholds for initiation of dialysis can vary between centers and also between providers. Based on our clinical routine, we believe that the criteria for initiation of dialysis are relatively consistent within our center, and our outcome measurement is valid. However, varying clinical practice and criteria used to ascertain the outcome could impact the results. Our dataset did not include complete data on alternative outcome measures such as a decline in creatinine after transplant.

In addition, given the nearly sixfold variation in the incidence of delayed graft function across living *versus* deceased donor renal transplantation, the observations should be interpreted with caution in the living donor population. Although similar adjusted effect sizes were observed, the subgroup analysis of living donors did not demonstrate statistical significance.

The retrospective nature of this study limits the availability of data that might yet be of relevance. In our dataset, the variables "recipient diabetes," "donor hypertension," and "donor terminal creatinine" were highly missing but are described in the literature as strong predictors of the outcome.[27] As such, these variables would have qualified for inclusion in our regression model, even though we did not classify them as confounders. Inclusion of these variables might have modified the effect size but are unlikely to reverse the effect. Another potential predictor of the outcome is type and volume of fluid administration after discharge from the recovery room. However, our datasets only included fluid data for the perioperative period, defined from anesthesia start to discharge from the recovery unit.

In addition, these are single center data that might not reflect practices at other centers, reducing the generalizability of our observations. The type and volume of crystalloids administered perioperatively at our center might differ from fluid management practice elsewhere. Our results are not applicable to centers that use no normal saline or less total crystalloids during kidney transplantation. On the other hand, our dataset decreases variability in surgical technique since a consistent group of only eight kidney transplant surgeons performed all procedures from 2005 to 2015 with an equal distribution within every year. Variability in surgical technique, often a point of criticism in research investigating delayed graft function as the primary outcome, is therefore unlikely to affect the results.

In conclusion, our study demonstrated an association of high percentages of normal saline with delayed graft function in patients undergoing kidney transplantation.

Acknowledgments

The data reported here have been supplied by the Hennepin Healthcare Research Institute (Minneapolis, Minnesota) as the contractor for the Scientific Registry of Transplant Recipients (U.S. Department of Health and Human Services, Washington, D.C.). The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the Scientific Registry of Transplant Recipients or the U.S. Government.

Research Support

This study was supported by an internal grant from the Department of Anesthesia and Perioperative Care, University of California, San Francisco (San Francisco, California).

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Kolodzie: Department of Anesthesia and Perioperative Care, Box 1605, 1600 Divisadero Street, Room B-640, University of California, San Francisco, San Francisco, California 94143. kerstin.kolodzie@ucsf.edu.

References

1. Mittel AM, Wagener G: Anesthesia for kidney and pancreas transplantation. Anesthesiol Clin 2017; 35:439–52
2. O'Malley CM, Frumento RJ, Bennett-Guerrero E: Intravenous fluid therapy in renal transplant recipients: Results of a US survey. Transplant Proc 2002; 34:3142–5
3. Weinberg L, Harris L, Bellomo R, Ierino FL, Story D, Eastwood G, Collins M, Churilov L, Mount PF: Effects of intraoperative and early postoperative normal saline or Plasma-Lyte 148® on hyperkalaemia in deceased donor renal transplantation: A double-blind randomized trial. Br J Anaesth 2017; 119:606–15
4. Wan S, Roberts MA, Mount P: Normal saline versus lower-chloride solutions for kidney transplantation. Cochrane Database Syst Rev 2016; 8:CD010741
5. Potura E, Lindner G, Biesenbach P, Funk GC, Reiterer C, Kabon B, Schwarz C, Druml W, Fleischmann E: An acetate-buffered balanced crystalloid *versus* 0.9% saline in patients with end-stage renal disease undergoing cadaveric renal transplantation: A prospective randomized controlled trial. Anesth Analg 2015; 120:123–9
6. O'Malley CM, Frumento RJ, Hardy MA, Benvenisty AI, Brentjens TE, Mercer JS, Bennett-Guerrero E: A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. Anesth Analg 2005; 100:1518–24, table of contents
7. Modi MP, Vora KS, Parikh GP, Shah VR: A comparative study of impact of infusion of Ringer's lactate solution *versus* normal saline on acid-base balance and serum electrolytes during live related renal transplantation. Saudi J Kidney Dis Transpl 2012; 23:135–7
8. Kim SY, Huh KH, Lee JR, Kim SH, Jeong SH, Choi YS: Comparison of the effects of normal saline *versus* Plasmalyte on acid-base balance during living donor kidney transplantation using the Stewart and base excess methods. Transplant Proc 2013; 45:2191–6
9. Khajavi MR, Etezadi F, Moharari RS, Imani F, Meysamie AP, Khashayar P, Najafi A: Effects of normal saline vs. lactated Ringer's during renal transplantation. Ren Fail 2008; 30:535–9
10. Hadimioglu N, Saadawy I, Saglam T, Ertug Z, Dinckan A: The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation. Anesth Analg 2008; 107:264–9
11. Arslantas R, Dogu Z, Cevik BE: Normal saline *versus* balanced crystalloid solutions for kidney transplantation. Transplant Proc 2019; 51:2262–4
12. Efune GE, Zerillo J, Zhou G, Mazzeffi MA, Demaria S, Wang C; Society for the Advancement of Transplant Anesthesia Research Committee Writing Group: Intravenous fluid management practices in kidney transplant patients: A multicenter observational cohort pilot study. Semin Cardiothorac Vasc Anesth 2020; 24:256–64
13. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, Kellum JA: Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg 2012; 255:821–9
14. Semler MW, Self WH, Wanderer JP, Ehrenfeld JM, Wang L, Byrne DW, Stollings JL, Kumar AB, Hughes CG, Hernandez A, Guillamondegui OD, May AK, Weavind L, Casey JD, Siew ED, Shaw AD, Bernard GR, Rice TW; SMART Investigators and the Pragmatic Critical Care Research Group: Balanced crystalloids *versus* saline in critically ill adults. N Engl J Med 2018; 378:829–39
15. Self WH, Semler MW, Wanderer JP, Wang L, Byrne DW, Collins SP, Slovis CM, Lindsell CJ, Ehrenfeld JM, Siew ED, Shaw AD, Bernard GR, Rice TW; SALT-ED Investigators: Balanced crystalloids *versus* saline in noncritically ill adults. N Engl J Med 2018; 378:819–28
16. Maheshwari K, Turan A, Makarova N, Ma C, Esa WAS, Ruetzler K, Barsoum S, Kuhel AG, Ritchey MR, Higuera-Rueda C, Kopyeva T, Stocchi L, Essber H, Cohen B, Suleiman I, Bajracharya GR, Chelnick D, Mascha EJ, Kurz A, Sessler DI: Saline *versus* lactated Ringer's solution: The Saline or Lactated Ringer's (SOLAR) Trial. Anesthesiology 2020; 132:614–24
17. Adwaney A, Randall DW, Blunden MJ, Prowle JR, Kirwan CJ: Perioperative Plasma-Lyte use reduces the incidence of renal replacement therapy and hyperkalaemia following renal transplantation when compared with 0.9% saline: A retrospective cohort study. Clin Kidney J 2017; 10:838–44
18. Yarlagadda SG, Coca SG, Formica RN Jr, Poggio ED, Parikh CR: Association between delayed graft function and allograft and patient survival: A systematic review and meta-analysis. Nephrol Dial Transplant 2009; 24:1039–47
19. Siedlecki A, Irish W, Brennan DC: Delayed graft function in the kidney transplant. Am J Transplant 2011; 11:2279–96
20. Rubin DB: Multiple Imputation for Nonresponse in Surveys. New York, Wiley, 1987
21. Redfield RR, Scalea JR, Zens TJ, Muth B, Kaufman DB, Djamali A, Astor BC, Mohamed M: Predictors and

outcomes of delayed graft function after living-donor kidney transplantation. Transpl Int 2016; 29:81–7
22. Niemann CU, Feiner J, Swain S, Bunting S, Friedman M, Crutchfield M, Broglio K, Hirose R, Roberts JP, Malinoski D: Therapeutic hypothermia in deceased organ donors and kidney-graft function. N Engl J Med 2015; 373:405–14
23. Incerti D, Summers N, Ton TGN, Boscoe A, Chandraker A, Stevens W: The lifetime health burden of delayed graft function in kidney transplant recipients in the United States. MDM Policy Pract 2018; 3:2381468318781811
24. Wilcox CS: Regulation of renal blood flow by plasma chloride. J Clin Invest 1983; 71:726–35
25. Chowdhury AH, Cox EF, Francis ST, Lobo DN: A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and Plasma-Lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg 2012; 256:18–24
26. Bahl D, Haddad Z, Datoo A, Qazi YA: Delayed graft function in kidney transplantation. Curr Opin Organ Transplant 2019; 24:82–6
27. Irish WD, Ilsley JN, Schnitzler MA, Feng S, Brennan DC: A risk prediction model for delayed graft function in the current era of deceased donor renal transplantation. Am J Transplant 2010; 10:2279–86
28. Kawakita S, Beaumont JL, Jucaud V, Everly MJ: Personalized prediction of delayed graft function for recipients of deceased donor kidney transplants with machine learning. Sci Rep 2020; 10:18409

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Sharing the Limelight of History: Paul Wood at Morton's Ether Demonstration?

This photographic reenactment of William T. G. Morton's 1846 ether administration (*above*) was a centerpiece of the nine historical vignettes featured in the anesthesia exhibit at the 1939 New York World's Fair. Paul M. Wood, M.D. (1894 to 1963, *third from right*), and his physician colleagues were seeking recognition for anesthesiology as an independent medical specialty almost a century after Morton had publicly used ether as a surgical anesthetic. Featuring a live mock anesthetic within a modern operating room, Wood's anesthesia section enthralled millions of visitors with its eye-catching and educational displays. At the same time, the exhibit also highlighted anesthesia's prominent role in the history of medicine. As we celebrate the 175th anniversary (demisemiseptcentennial!) of Morton's ether demonstration this October, let us also recognize Dr. Paul Wood for his advocacy and his founding of the Wood Library-Museum of Anesthesiology, which continues to "advance our specialty by preserving and sharing its heritage and knowledge." (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

Melissa L. Coleman, M.D., Penn State College of Medicine, Hershey, Pennsylvania, and Jane S. Moon, M.D., University of California, Los Angeles, California.