- SUPPLEMENTAL CONTENT -

The Effects of Perioperative Intravenous Fluid Administration Strategy on Renal Outcomes in Patients undergoing Cardiovascular Surgery: An Observational Study

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Expanded Methods that describes our cardiovascular surgery and perioperative management strategies

Anesthesia was maintained in all patients by a continuous infusion of propofol, remifentanil, and rocuronium. To maintain the cardiac preload, intravenous crystalloid and HES solutions were administered. The patient's intravascular volume was assessed by conventional hemodynamic parameters, including heart rate, mean arterial pressure, central venous pressure, pulmonary capillary wedge pressure, and cardiac output. Patients with low mean arterial pressure and cardiac output despite optimization of circulating blood volume were administered inotropic or vasopressor agents to avoid excessive fluid administration, and those with hemoglobin concentration < 8 g/dl were administered packed red blood cells. A cell salvage device (AUTOLOGTM, Medtronic Inc., Minneapolis, MN) was used in all patients, and salvaged blood was reinfused before the end of surgery. Intravenous heparin was administered at a dose of 150 IU/kg for 250–350 seconds of target activated clotting time during off-pump surgery, and at a dose of 300 IU/kg for more than 500 seconds of target activated clotting time during on-pump surgery. Activated clotting time was checked every 30 minutes, and heparin was added to maintain adequate activated clotting time. The cardiopulmonary bypass circuit was primed with 20% mannitol, 20% albumin, and crystalloid solution. The hematocrit value was maintained between 23% and 27%, and the mean arterial pressure was maintained between 60 and 70 mmHg during the cardiopulmonary bypass period. If necessary, packed red blood cells, phenylephrine, or nicardipine hydrochloride was administered. The arterial carbon dioxide tension was maintained throughout the bypass at 35 to 40 mmHg (not corrected for temperature), with the arterial oxygen tension maintained at 250 to 300 mmHg. Patients were cooled to a nasopharyngeal temperature of 34℃ to 28℃ during the bypass and rewarmed to a nasopharyngeal or rectal temperature of 37℃ prior to separation from the bypass. Nonpulsatile perfusion was maintained at a flow rate corresponding to a cardiac index of 2 to 2.4 L/min/m^2. All surgical procedures were performed by five experienced surgeons. After completion of the surgery, all patients were transferred to the intensive care unit. The endotracheal tube was removed when the hemodynamics were stable, after which respiration recovered spontaneously and adequate blood gases

were achieved. Fluid management consisted of an infusion of 5% dextrose with additional 0.9% saline or HES solution to maintain normovolemia. Blood products, such as packed red blood cells, fresh-frozen plasma, platelet concentrate, or cryoprecipitate, were transfused to maintain a hemoglobin > 9 g/dl and to correct blood coagulation. Patients were discharged from the intensive care unit to the general ward when their clinical status became stabilized and intensive care unit monitoring and care were no longer necessary.

Expanded Methods that describes our outcome variables and definitions

Postoperative AKI was defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria (an increase in serum creatinine by ≥ 0.3 mg/dl within 48 h of surgery; or an increase in serum creatinine to ≥ 1.5 times baseline within 7 days of surgery). Patients who met the KDIGO criteria were classified as "AKI"; whereas, those who did not were classified as "no AKI". Patients with AKI were staged according to the maximum KDIGO criteria. Stage 1 was defined as an increase in sCr of ≥ 0.3 mg/dl or ≥ 1.5 times baseline; stage 2 as an increase in sCr 2.0 to 2.9 times baseline; and stage 3 as an increase in sCr ≥ 3.0 times baseline, of ≥ 4.0 mg/dl, or the initiation of RRT. Chronic dialysis was defined as ongoing dialysis support beyond 90 days after initiation within 12 months of cardiovascular surgery, with the start date defined as the date of the first of these treatments. The sCr levels were measured preoperatively, on arrival at the ICU, within 7 days of the operation, at discharge, and additionally as needed according to the clinical situation. After discharge, sCr was measured at variable follow-up times for monitoring the patients' renal function. The concentration that was measured closest to the time of surgery (but within 30 days of surgery) was considered to be the baseline creatinine level. The highest concentration that was measured in the first seven days after surgery was used for the AKI evaluation. We did not use data on urine output for diagnosis of AKI due to incomplete recording and the effects of administered diuretics.

RRT was defined as any use of intermittent dialysis or continuous venovenous hemodiafiltration. The choice and initiation of RRT modality was made by the attending physicians after considering the clinical characteristics of the patients. Renal outcome at the time of discharge was determined by comparing the creatinine level at discharge to the baseline creatinine level. Persistent AKI was defined as a sCr at discharge > 1.5 times baseline or the requirement for dialysis at discharge. Chronic renal function was assessed using sCr values measured until 1 year after cardiovascular surgery (at least two sCr measurements). CKD was defined as a persistent decline in renal function (eGFR < 60 ml/min/1.73 m^2) lasting > 90 days that never again increased above 60 ml/min/1.73 m^2 of eGFR within 1 year after surgery or the need for chronic dialysis after surgery. The start date for the development of CKD was defined as the first day when eGFR initially went down to < 60

ml/min/1.73 m^2. The sCr was measured using the kinetic Jaffe method (Cobas® 8000 modular analyzer series; Roche Diagnostics GmbH, Vienna, Austria). The eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (eGFR = 141 × min [sCr/κ, 1]$^{\alpha}$ × max [sCr/κ, 1]$^{-1.209}$ × 0.993^{age} × 1.018 [if female] × 1.159 [if Black], where κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of sCr/K or 1, and max indicates the maximum of sCr/K or 1). Serum chloride levels were measured preoperatively and on arrival at the ICU. The maximal cardiovascular component of the sequential organ failure assessment (SOFAc) score observed within the first 24 hours after surgery was used for evaluating the postoperative cardiovascular function.

Expanded Methods that demonstrates detailed descriptions of the propensity score matching, inverse probability of treatment weighting and sensitivity analyses

The propensity scores were estimated without regard to the outcome variables, using a non-parsimonious multivariable logistic regression analysis in which the choice of the perioperative fluid administration strategy was the dependent variable and all baseline characteristics shown in Table 1 were included as covariates. To develop the propensity score-matched pairs without replacement (a 1:1 match), calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score was used. After propensity score matching was performed, we identified two comparable groups of 792 patients each. In the matched cohort, between-group differences in preoperative and intraoperative characteristics and postoperative outcomes were compared using the paired t-test or Wilcoxon signed rank test for continuous variables and the McNemar's test for categorical variables. Matching balance was also assessed with standardized differences for each covariate.

To reduce the impact of a treatment selection bias and potential confounding in an observational study, we also performed rigorous adjustment for significant differences in patient characteristics with the inverse probability of treatment weighting using the propensity score. Weights for patients in the RPF group were the inverse of 1–propensity score, and weights for patients in the control group were the inverse of the propensity score. The propensity scores were estimated by multivariable logistic regression analysis. To create the propensity score, all prespecified covariates listed in Table 1 were included in the full non-parsimonious models. The characteristics of the patients in the inverse probability weighted groups are presented in Supplemental Table S1. The discrimination and calibration abilities of the propensity score model were assessed by the C statistic and the Hosmer–Lemeshow statistic. Finally, the inverse probability of treatment weights were incorporated into the weighted logistic regression and weighted Cox proportional hazards regression analyses to compare the renal outcomes after cardiovascular surgery.

Sensitivity analyses were conducted as a logistic regression identical to the final model above, except: (1) using transfusions and reoperation for bleeding as confounders rather than mediators; (2) excluding all patients who received a transfusion and/or underwent reoperation for bleeding; (3)

excluding all patients with an immediate postoperative serum chloride level > 110 mmol/L; (4) excluding all patients receiving cumulative amounts > 20 ml/kg body weight of HES solution during the perioperative period; and (5) with the primary outcome AKI redefined using the AKI Network criteria.

Table S1. Baseline data in the inverse probability of treatment weighting populations

	Control	**RPF**	***P* value**	**SD mean,%**
N	1610 (61.6)	1003 (38.4)		
Preoperative				
Age (yr)	59.9 ± 12.3	59.7 ± 12.9	.73	1.38
Male	988 (61.4)	610 (60.8)	.78	1.13
Body mass index (kg/m^2)	23.9 ± 3.4	23.8 ± 3.3	.80	1.02
EuroSCORE (logistic)	6.0 ± 7.8	6.2 ± 8.2	.61	2.03
Hematocrit (%)	38.6 ± 4.9	38.6 ± 5.2	.89	0.53
Creatinine (mg/dl)	0.8 ± 0.2	0.8 ± 0.2	.64	1.89
Bilirubin, total (mg/dl)	0.8 ± 0.4	0.9 ± 0.7	.18	5.08
Albumin (g/dl)	3.8 ± 0.5	3.8 ± 0.5	.44	3.11
Uric acid (mg/dl)	5.5 ± 1.7	5.5 ± 1.8	.92	0.40
LVEF (%)	57.1 ± 10.5	57.1 ± 10.8	.99	0.07
Chloride level (mmol/L)	104.0 ± 3.5	103.8 ± 3.4	.19	5.19
Diabetes mellitus	359 (22.3)	216 (21.5)	.65	1.84
Hypertension	771 (47.9)	473 (47.2)	.72	1.46
Congestive heart failure	121 (7.5)	80 (8.0)	.64	1.72
Cerebrovascular disease	178 (11.1)	109 (10.9)	.85	0.60
Peripheral vascular disease	188 (11.7)	119 (11.9)	.91	0.58
COPD	49 (3.0)	29 (2.9)	.87	0.90
ACEI or ARB	679 (42.2)	419 (41.8)	.84	0.81
β-blocker	708 (44.0)	433 (43.2)	.69	1.62
Calcium channel blocker	760 (47.2)	458 (45.7)	.44	3.09
Diuretics	606 (37.6)	380 (37.9)	.88	0.51
Insulin	167 (10.4)	102 (10.2)	.89	0.67

OHA	276 (17.1)	167 (16.7)	.73	1.32
Aspirin	634 (39.4)	387 (38.6)	.71	1.63
Clopidogrel	368 (22.9)	223 (22.2)	.72	1.49
Statins	756 (47.0)	463 (46.2)	.72	1.59
Intraoperative data				
Elective operation	1516 (94.2)	940 (93.7)	.68	1.86
Type of surgery			.96	
CABG	503 (31.2)	304 (30.3)		2.02
Valve	724 (45.0)	460 (45.9)		1.79
Aorta	125 (7.8)	78 (7.8)		0.05
Combined	258 (16.0)	161 (16.1)		0.07
On-pump surgery	1169 (72.6)	758 (75.6)	.09	6.77
CPB time (min)	149.5 ± 79.2	146.4 ± 69.5	.38	4.08
Operation time (min)	296.6 ± 108.6	296.8 ± 103.6	.96	0.19

Data are expressed as the number of patients (%) or the mean ± standard deviation.

RPF = renal-protective intravenous fluid administration strategy group, SD mean = standardized difference of the mean, EuroSCORE = European System for Cardiac Operative Risk Evaluation, LVEF = left ventricle ejection fraction, COPD = chronic obstructive pulmonary disease, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, OHA = oral hypoglycemic agent, CABG = coronary artery bypass grafting, CPB = cardiopulmonary bypass.

Table S2. Perioperative fluid administration and postoperative outcome data in the inverse probability of treatment weighting populations

	Control	**RPF**	***P* value**
N	1610 (61.6)	1003 (38.4)	
Intraoperative data			
Crystalloid (L)	1.6 ± 1.1	2.0 ± 1.1	< .001
Colloid (L)	0.9 ± 0.6	0.6 ± 0.4	< .001
Colloid per weight (ml/kg)	14.9 ± 8.9	10.4 ± 6.6	< .001
Colloid-to-crystalloid volume ratio	0.7 ± 0.6	0.4 ± 0.3	< .001
Cell saver blood (ml)[a]	182.3 ± 547.4	116.4 ± 291.2	< .001
Urine output (L)	0.9 ± 0.6	0.7 ± 0.6	< .001
Postoperative data			
Weight gain (%)	2.5 ± 3.4	2.9 ± 3.3	< .001
Chloride level (mmol/L)	111.5 ± 4.2	108.1 ± 4.4	< .001
Hyperchloremia (> 110 mmol/L)	984 (61.1)	287 (28.6)	< .001
Cumulative crystalloid (L)[b]	2.9 ± 1.2	3.4 ± 1.6	< .001
Cumulative crystalloid per weight (ml/kg)[b]	47.0 ± 20.3	56.1 ± 28.5	< .001
Cumulative colloid (L)[b]	2.0 ± 1.0	0.8 ± 0.5	< .001
Cumulative colloid per weight (ml/kg)[b]	33.0 ± 17.0	12.6 ± 8.6	< .001
Cumulative colloid-to-crystalloid volume ratio (L)[b]	0.8 ± 0.4	0.3 ± 0.2	< .001
Packed red blood cell (unit)[b]	3.8 ± 5.8	3.3 ± 5.2	< .001
Use of fresh frozen plasma[b]	1138 (70.7)	632 (63.0)	< .001
Use of platelet concentrate[b]	1021 (63.4)	520 (51.9)	< .001
Use of cryoprecipitate[b]	259 (16.1)	181 (18.0)	.19
Postoperative outcomes			
Re-exploration for bleeding	107 (6.7)	30 (3.0)	< .001

Maximal SOFAc score	2.3 ± 1.3	2.2 ± 1.4	.48
Extubation time (hr)	24.2 ± 59.2	22.5 ± 59.7	< .001
Intensive care unit stay (d)	3.8 ± 9.3	3.7 ± 9.1	.05
Hospital stay (d)	15.7 ± 24.0	14.1 ± 17.5	.02
30-day death	34 (2.1)	25 (2.5)	.56
1-yr death	82 (5.1)	43 (4.3)	.36

Data are expressed as the number of patients (%) or the mean ± standard deviation.

RPF = renal-protective intravenous fluid administration strategy group, SOFAc = cardiovascular sequential organ failure assessment in the first 24 hours

[a]Cell saver blood, given blood volume of blood return from the blood salvage device.

[b]used intraoperatively and for 48 hours after surgery.

Table S3. Renal outcomes after adjusting with the inverse probability of treatment weighting

	No. (%)		IPTW Adjusted	
	Control	RPF	Odds Ratio (95% CI)	*P* value
AKI by KDIGO	704 (43.7)	228 (22.7)	0.37 (0.30–0.46)	< .001
AKI by AKIN	637 (39.6)	197 (19.7)	0.38 (0.31–0.47)	< .001
≥ KDIGO stage2	270 (16.8)	56 (5.6)	0.27 (0.17–0.43)	< .001
≥ AKIN stage2	199 (12.4)	37 (3.7)	0.29 (0.20–0.42)	< .001
In-hospital RRT	83 (5.1)	32 (3.2)	0.61 (0.35–1.05)	.07
Persistent AKI at discharge	201 (12.5)	48 (4.8)	0.35 (0.24–0.51)	< .001
			Hazard Ratio (95% CI)	*P* value
1-yr CKD[a]	134 (8.4)	31 (3.1)	0.35 (0.24–0.53)	< .001
1-yr chronic dialysis	42 (2.6)	4 (0.4)	0.15 (0.06–0.39)	< .001

IPTW = inverse probability of treatment weighting, CI = confidence interval, KDIGO = Kidney Disease Improving Global Outcomes classification, AKIN = Acute Kidney Injury Network classification, RRT = renal replacement therapy, CKD = chronic kidney disease.

[a]CKD was available only in 1444 (89.7%) patients of the control group and 944 (94.1%) patients of the RPF group.

Table S4. Multivariable predictors for acute kidney injury after cardiovascular surgery

Predictor	**Odds Ratio**	**95% CI**	***P* value**
RPF group	0.289	0.234–0.356	< .001
Age (year)	1.025	1.016–1.033	< .001
Diabetes mellitus	1.742	1.304–2.328	< .001
Hypertension	1.450	1.197–1.757	< .001
Preoperative hematocrit level (%)	0.940	0.921–0.960	< .001
Preoperative serum albumin level (g/dl)	0.707	0.573–0.873	.001
Preoperative serum uric acid level (mg/dl)	1.116	1.055–1.180	< .001
Preoperative serum chloride level (mmol/L)	1.035	1.008–1.062	.01
Cardiopulmonary bypass time (min)	1.004	1.003–1.006	< .001
Operation time (min)	1.004	1.002–1.005	< .001

CI = confidence interval, RPF = renal-protective intravenous fluid administration strategy group

Hosmer-Lemeshow test; $P = .53$, C statistic = 0.76.

Table S5. Comparison of results for the primary analysis of acute kidney injury compared with the sensitivity analyses

	RPF strategy	
	Adjusted Odds Ratio (95% CI)	*P* value
Primary model[a]	0.289 (0.234–0.356)	< .001
Adjusted for transfusions and reoperation for bleeding	0.296 (0.238–0.368)	< .001
subgroup without transfusion and/or reoperation for bleeding	0.333 (0.137–0.810)	.015
subgroup with postoperative serum chloride level ≤ 110 mmol/L	0.301 (0.230–0.393)	< .001
subgroup with perioperative cumulative amounts of HES ≤ 20 ml/kg	0.301 (0.218–0.415)	< .001

RPF = renal-protective intravenous fluid administration strategy group, CI = confidence interval, HES = hydroxyethyl starch.

[a]adjusted age, diabetes mellitus, hypertension, preoperative hematocrit, preoperative serum albumin, preoperative serum uric acid, preoperative serum chloride level, cardiopulmonary bypass time, and operation time.