ANESTHESIOLOGY

Saline *versus* Lactated Ringer's Solution

The Saline or Lactated Ringer's (SOLAR) Trial

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ABSTRACT

Background: Both saline and lactated Ringer's solutions are commonly given to surgical patients. However, hyperchloremic acidosis consequent to saline administration may provoke complications. The authors therefore tested the primary hypothesis that a composite of in-hospital mortality and major postoperative complications is less common in patients given lactated Ringer's solution than normal saline.

Methods: The authors conducted an alternating cohort controlled trial in which adults having colorectal and orthopedic surgery were given either lactated Ringer's solution or normal saline in 2-week blocks between September 2015 and August 2018. The primary outcome was a composite of in-hospital mortality and major postoperative renal, respiratory, infectious, and hemorrhagic complications. The secondary outcome was postoperative acute kidney injury.

Results: Among 8,616 qualifying patients, 4,187 (49%) were assigned to lactated Ringer's solution, and 4,429 (51%) were assigned to saline. Each group received a median 1.9 l of fluid. The primary composite of major complications was observed in 5.8% of lactated Ringer's *versus* 6.1% of normal saline patients, with estimated average relative risk across the components of the composite of 1.16 (95% CI, 0.89 to 1.52; $P = 0.261$). The secondary outcome, postoperative acute kidney injury, Acute Kidney Injury Network stage I–III *versus* 0, occurred in 6.6% of lactated Ringer's patients *versus* 6.2% of normal saline patients, with an estimated relative risk of 1.18 (99.3% CI, 0.99 to 1.41; $P = 0.009$, significance criterion of 0.007). Absolute differences between the treatment groups for each outcome were less than 0.5%, an amount that is not clinically meaningful.

Conclusions: In elective orthopedic and colorectal surgery patients, there was no clinically meaningful difference in postoperative complications with lactated Ringer's or saline volume replacement. Clinicians can reasonably use either solution intraoperatively.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Infusion of large volumes of saline causes hyperchloremic metabolic acidosis
- A recent Cochrane review based on 18 small trials reported that major morbidity and mortality were comparable with perioperative saline or lactated Ringer's use

What This Article Tells Us That Is New

- In a large single-center alternating cohort trial of patients having elective colorectal or orthopedic surgery, there was no clinically meaningful difference in the risk of a composite of in-hospital mortality and major postoperative complications including renal, respiratory, infectious, and hemorrhagic complications

About 51 million inpatient surgeries were performed in the United States in 2010, based on National Hospital Discharge Survey.[1] Nearly all surgeries require intravenous crystalloid fluids for drug administration and vascular volume repletion. Saline (0.9% sodium chloride; "normal saline") is a commonly used crystalloid, but it has a much higher chloride concentration than human plasma, and is thus unbalanced.[2] In contrast, another commonly used crystalloid, lactated Ringer's solution, is a mixture of sodium chloride, sodium lactate, potassium chloride, and calcium chloride. The chloride concentration in lactated Ringer's is similar to that in plasma, and the solution is therefore considered to be balanced.

This article is featured in "This Month in Anesthesiology," page 1A. This article is accompanied by an editorial on p. 609. This article has a related Infographic on p. 19A. 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. This work was presented at the American Society of Anesthesiologists Annual Meeting in Orlando, Florida, October 22, 2019.

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Infusion of large volumes of saline causes hyperchloremic metabolic acidosis.[2–5] However, typical volumes used during noncardiac surgery have never been convincingly associated with worse clinical outcomes such as renal dysfunction, coagulopathy, increased transfusion requirement, or overall morbidity and mortality.[3,6] A recent Cochrane review reported that major morbidity and mortality were comparable with perioperative saline or lactated Ringer's use.[7,8] Although intravenous fluids are widely used, an ideal fluid is yet to be developed.[9] Despite ready availability of balanced fluids, saline remains in common use for vascular volume replacement.

We conducted the Saline or Lactated Ringer's (SOLAR) controlled trial to determine the relative safety of lactated Ringer's and saline solutions in patients having elective noncardiac surgery. We tested the primary hypothesis that a composite of major in-hospital postoperative complications is lower in patients given lactated Ringer's solution than saline. Our secondary hypothesis was that postoperative acute kidney injury is less common in patients given lactated Ringer's solution than saline.

Materials and Methods

We conducted this single-center, alternating cohort controlled trial from September 2015 through August 2018 at Cleveland Clinic Main Campus (Cleveland, Ohio). The trial was conducted in accordance with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and relevant regulatory requirements. The Cleveland Clinic Institutional Review Board approved the trial and waived written individual informed consent. Consent waiver was based on the cohort design, and because the comparative effectiveness trial evaluated two commonly used treatments, both of which were deemed low-risk. The trial was registered in ClinicalTrials.gov; NCT02565420; Principal Investigator Kamal Maheshwari; October 1, 2015. The Department of Outcomes Research supported development of the protocol (Supplemental Digital Content, http://links.lww.com/ALN/C171), managed conduct of the trial, collected and managed the data, monitored trial staff, and conducted the statistical analysis.

We included adults who had colorectal or orthopedic surgery at Cleveland Clinic Main Campus in 12 specific operating rooms that alternated between using either normal saline or lactated Ringer's solution as the intraoperative intravenous crystalloid of choice at 2-week intervals. We used lactated Ringer's as the balanced crystalloid, which has a near-physiologic strong ion difference[10] because it contains less chloride than saline, thereby reducing the risk of hyperchloremic metabolic acidosis.[11] Analysis was restricted to the first surgery for each patient. We excluded surgeries lasting less than 2 h, urgent/emergency procedures, and patients with American Society of Anesthesiologists (Schaumburg, Illinois) physical status score 5 or greater, chronic renal failure requiring preoperative dialysis, or missing preoperative creatinine values.

Outcomes

Our primary outcome was a composite of in-hospital mortality and major postoperative complications including renal, respiratory, infectious, and hemorrhagic complications. Renal complications were defined as a twofold increase in creatinine from baseline per definition of the Acute Kidney Injury Network (stage II injury and above). We identified respiratory, infectious, and hemorrhagic complications using International Classification of Diseases, Ninth Revision and Tenth Revision, hospital discharge codes with present-on-admission indicator and International Classification of Diseases, Ninth Revision and Tenth Revision, codes from a problem list with exact diagnosis date (Supplemental Digital Content table S1, http://links.lww.com/ALN/C166).

The secondary outcomes were new-onset postoperative kidney injury based on Acute Kidney Injury Network criteria, and an economic analysis. Exploratory outcomes were postoperative nausea and vomiting, myocardial injury after noncardiac surgery, cardiac complications, postoperative medication use (calcium, magnesium, potassium, bicarbonate), and in-hospital blood transfusion. Cardiac complications were defined by International Classification of Diseases, Ninth Revision and Tenth Revision, hospital discharge diagnosis and procedure codes (Supplemental Digital Content table S1, http://links.lww.com/ALN/C166). Myocardial injury was defined by peak fourth-generation troponin T concentration 0.03 ng/ml or greater within 3 postoperative days.[12] Since troponin is not consistently evaluated in colorectal and orthopedic patients in Cleveland Clinic, only 2,501 (29%) of the 8,616 included patients had postoperative troponin values. We assumed that troponin was within the normal range in patients without troponin measurements.

Three unplanned *post hoc* analyses were added after initial data analysis. The first was on the number of erythrocyte transfusions. The second was serum electrolyte concentrations, on an as-available basis. The third was a subgroup analysis based on age, crystalloid volume, preoperative creatinine, surgical duration, type of surgery, and diabetes.

The General Equivalence Mappings tool was used to convert data from International Classification of Diseases, Ninth Revision–Clinical Modification to International Classification of Diseases, Tenth Revision–Clinical Modification; the General Equivalence Mappings tool was developed by the Centers for Medicare and Medicaid Services (Baltimore, Maryland; https://www.cms.gov/).

Statistical Analysis

The analysis was intent-to-treat, and thus patients were analyzed according to assigned study group. To control for potential confounding, we used the inverse probability of treatment weighting method for all analyses. Specifically, we fit a logistic regression model with fluid assignment as the

outcome variable and all observed confounding variables, continuously scaled, as the independent variables. We then estimated propensity scores (*i.e.,* the probability of receiving lactated Ringer's solution) for each patient. Patients in the lactated Ringer's group were assigned a weight equal to the reciprocal of the propensity score, while patients in the saline group were assigned a weight equal to the reciprocal of 1 minus the propensity score. Success of the control for confounding was assessed by comparing the two groups on all potential confounding variables using absolute standardized difference, after weighting each observation by the propensity score weights. Confounding variables with an absolute standardized difference greater than $1.96 \times \sqrt{\frac{1}{n_1}+\frac{1}{n_2}} = 0.042$ would be adjusted for in all analyses. SAS 9.4 (SAS Institute, Cary, North Carolina) was used for all analyses.

Primary Analysis. The average relative effect of lactated Ringer's *versus* saline was assessed across the five categories of major complications using a generalized estimating equation "distinct effects" log-link model with a compound symmetry working correlation matrix (*i.e.,* the within-subject correlation on outcomes between the components) adjusting for any imbalanced variables after weighting.[13,14] This model first estimates the treatment effect for each component (here, the log relative risk) and then averages them and tests for an overall treatment effect using the robust generalized estimating equation covariance matrix in a Wald test. The average relative effect method has been shown to be superior to the traditional "collapsed composite" analysis of "any *versus* one" and also the "common effect generalized estimating equation" method in that it (1) uses more information because each component is analyzed, (2) accounts for the within-subject correlation among the components, and (3) gives equal weight to each component when estimating the treatment effect, as opposed to the traditional approaches for which the treatment effect is highly driven by the component with the highest frequency. The heterogeneity of the fluid effect across components was assessed by testing the treatment-by-component interaction, with a significance criterion of 0.1. The effect on each component was also reported individually, regardless of the finding of a significant interaction, using separate logistic regression models.

Given that we missed postoperative 48-h creatinine measurements in about 12% of patients, missing creatinine values were imputed by multivariable imputation with five imputation datasets. The imputation model included all the baseline variables listed in table 1 together with preoperative creatinine level, intraoperative variables listed in Supplemental Digital Content table S2 (http://links.lww.com/ALN/C167), and all the primary, secondary, and tertiary outcomes, except renal and acute kidney injury outcomes. This imputation was similar to the approach used by Semler *et al.*[15] We conducted two sensitivity analyses using alternative approaches to address the issue of missing data on postoperative creatinine level, as explained in (1) and (2) below.

A total of four sensitivity analyses were conducted: (1) a "complete cases" analysis excluding patients missing 48-h postoperative creatinine values; (2) assumption of normal postoperative renal status for the patients with missing 48-h postoperative creatinine values; (3) without adjustment for slight imbalance in patients' characteristics; and (4) the primary analysis where hemorrhagic outcome was defined by the volume of blood transfusion, rather than by International Classification of Diseases, Ninth Revision, codes (Supplemental Digital Content table S3, http://links.lww.com/ALN/C170). This last sensitivity analysis was proposed *post hoc* after manual review of 51 patients' records who had International Classification of Diseases, Ninth Revision, codes indicating hemorrhagic complications: more than half did not experience major blood loss. Generally, patients with major hemorrhage will receive substantial blood transfusion. We therefore assessed the major hemorrhagic component of the primary composite using the substantial transfusion definition: 750 ml of packed erythrocytes during the hospital stay.

In our group sequential design, the overall significance level for the primary outcome across the three interim analyses and a final analysis was 0.05. This resulted in a significance level of 0.044 for testing the average treatment effect on the primary outcome at the final analysis, with a significance criterion of $P < 0.009$ (*i.e.,* 0.044/5) for each component of the composite.

Secondary and Tertiary Analyses. We assessed the effect of fluids on renal injury stage using a multivariable proportional odds model including propensity score weights and adjusting for unbalanced baseline covariables as appropriate; we further assessed the effect of fluids on the binary acute kidney injury outcome of stages I, II, and III *versus* stage 0 using a generalized estimating equation model with log link (to estimate relative risk) and similarly adjusting for confounding. We also assessed the effect of fluids on the number of plasma electrolytes measurements using a multivariable negative binomial regression model. The effect of fluids on postoperative nausea and vomiting, myocardial injury, cardiac complications, postoperative electrolyte administration (calcium, magnesium, potassium, bicarbonate), and in-hospital blood transfusion (erythrocytes, platelets, plasma) was assessed through separate multivariable logistic regression models. We use an overall alpha of 0.05 for the secondary/tertiary analyses, using a significance criterion of 0.007 for each secondary/tertiary analysis (*i.e.,* 0.05/7; Bonferroni correction); no adjustment for interim analyses was made here since the group sequential monitoring only included the primary outcome.

Sensitivity Analyses for Potential Unmeasured Confounding. Although important confounding was not expected due the controlled nature of our trial, in a *post hoc* analysis, we used the E-value[16] to assess the magnitude of an unmeasured confounding variable (or set of variables) that would be needed to (1) reduce an observed relative risk to 1.0 and (2) reduce the upper or lower confidence limit to 1.0. For example, an E-value of 2.0 for reducing an

Table 1. Baseline Patient Characteristics (N = 8,616)

Variables	Nmiss	LR (N = 4,187)	Nmiss	Saline (N = 4,429)	ASD* before IPTW	ASD* after IPTW
Age, yr		58 ± 17		59 ± 16	0.079	< 0.001
Sex, female		2,257 (54%)		2,383 (54%)	0.002	< 0.001
BMI, kg/m^2	198	29 ± 7	176	29 ± 8	0.020	0.011
Race					0.044	< 0.001
Caucasian		3,421 (82%)		3,671 (83%)		
African American		517 (12%)		548 (12%)		
Other		249 (6%)		210 (5%)		
ASA score					0.036	< 0.001
I		58 (1%)		70 (2%)		
II		1,000 (24%)		1,027 (23%)		
III		2,835 (68%)		2,942 (66%)		
IV		294 (7%)		390 (9%)		
AKI risk class	1				0.056	< 0.001
I		2,576 (62%)		2,635 (62%)		
II		966 (23%)		1,019 (23%)		
III		459 (11%)		547 (12%)		
IV		158 (4%)		195 (4%)		
V		27 (1%)		33 (1%)		
Medical history						
COPD		780 (19%)		808 (18%)	0.010	< 0.001
Diabetes		805 (19%)		922 (21%)	0.039	< 0.001
Ascites		171 (4%)		186 (4%)	0.006	< 0.001
CHF		73 (2%)		88 (2%)	0.018	< 0.001
Medication use						
Diuretics		997 (24%)		1,109 (25%)	0.029	< 0.001
ACEI		1,249 (30%)		1,417 (32%)	0.047	< 0.001
ARB		659 (16%)		752 (17%)	0.034	< 0.001
Surgery type					0.002	< 0.001
Colorectal		1,594 (38%)		1,681 (38%)		
Orthopedic		2,593 (62%)		2,748 (62%)		
Initial serum electrolytes						
Blood urea nitrogen, mg/dl	231	16 ± 7.6	247	16 ± 7.9	0.047	0.006
Chloride, mmol/l	232	101 ± 3.1	247	101 ± 3.3	0.027	0.019
Creatinine, mg/dl	225	0.94 ± 0.31	243	0.96 ± 0.36	0.052	0.002
Potassium, mmol/l	234	4.2 ± 0.42	252	4.2 ± 0.44	0.015	< 0.001
Sodium, mmol/l	232	140 ± 2.7	247	140 ± 2.9	0.044	0.031
Bicarbonate, mmol/l	4,316	26 ± 4.7	4,316	25 ± 5.5	0.087	0.053

Summary statistics presented as N (%) of patients or mean ± SD for factors or symmetric continuous variables, respectively.

*Any variable with an ASD greater than 0.04 was considered unbalanced.

ACEI, angiotensin-converting enzyme inhibitors; AKI, acute kidney injury; ARB, angiotensin receptor blockers; ASA, American Society of Anesthesiologists physical status score; ASD, absolute standardized difference; BMI, body mass index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; IPTW, inverse probability of treatment weighting; LR, lactated Ringer's; Nmiss, missing information.

observed relative risk to 1.0 means that there would need to be an unmeasured confounding variable that was associated with the exposure with a relative risk of 2.0 and also associated with the outcome with relative risk of 2.0, both after adjusting for other confounding variables already included in the analyses.

Because there were no clinically meaningful differences in the primary or secondary outcomes, we deferred the planned economic analysis.

Sample Size Considerations. This study was designed to have 90% power at the 0.05 significance level to detect a 20% relative decrease in major complications (for each component of the composite) in the lactated Ringer's group *versus* the saline group. We estimated the incidence of complications in the control group based on a preliminary query of a similar population. The expected incidence of complications was 0.5% in-hospital mortality, 1.8% renal, 2.3% respiratory, 24% infections, and 2.6% hemorrhagic complications. Sample size was calculated assuming a conservative correlation of 0.3 between outcomes, and using the MULTBINPOW SAS macro, which estimates power for average relative effect generalized estimating equation models given varying correlations and sample sizes, based on the seminal paper for this statistical method.[17] After accounting for three interim analyses and one final analysis, we concluded that we would need to enroll a maximum of 8,548 patients for this study.

For accuracy in reporting the study power, after enrollment we recalculated the power of the average relative effect test using the actual study estimates of two "nuisance" parameters—the incidence of each outcome component in the normal saline (control) group and, roughly, the observed

correlations between components (ranging from 0.20 to 0.10). We did not use the observed treatment effect, but rather assessed power to detect the planned 20% relative decrease in each major complication at the overall 0.05 significance level. Using the same MULTBINPOW SAS macro, actual power was 65 to 70% with the given sample size (total of ~8,600 patients).

Results

Patients having 13,475 surgeries were given alternating fluid treatment during the 35-month trial period. There was a total of 76 cycles, each 2 weeks long, with lactated Ringer's and saline each being given for 38 cycles. A total of 8,616 patients met inclusion and exclusion criteria (see study flow chart in fig. 1). A total of 4,187 (49%) qualifying patients were assigned to lactated Ringer's, and 4,429 (51%) were assigned to normal saline. A total of 332 (4%) patients did not receive the assigned treatment. Among lactated Ringer's patients, 4,084 (98%) received assigned lactated Ringer's, and 103 (2%) received saline; among saline patients, 4,200 (95%) received assigned saline, and 229 (5%) received lactated Ringer's. Each group received a median [quartiles] of 1.9 [1.3, 2.6] l of the assigned intraoperative fluid (Supplemental Digital Content table S2, http://links.lww.com/ALN/C167).

Demographic characteristics, medical history, medications, and surgical details are summarized in table 1 and Supplemental Digital Content table S2 (http://links.lww.com/ALN/C167). The two groups were initially well balanced and were even better balanced after inverse probability of treatment weighting, with very low absolute standardized differences (table 1; Supplemental Digital Content fig. S1, http://links.lww.com/ALN/C168).

The primary composite of major complications was observed in 5.8% of lactated Ringer's *versus* 6.1% of normal

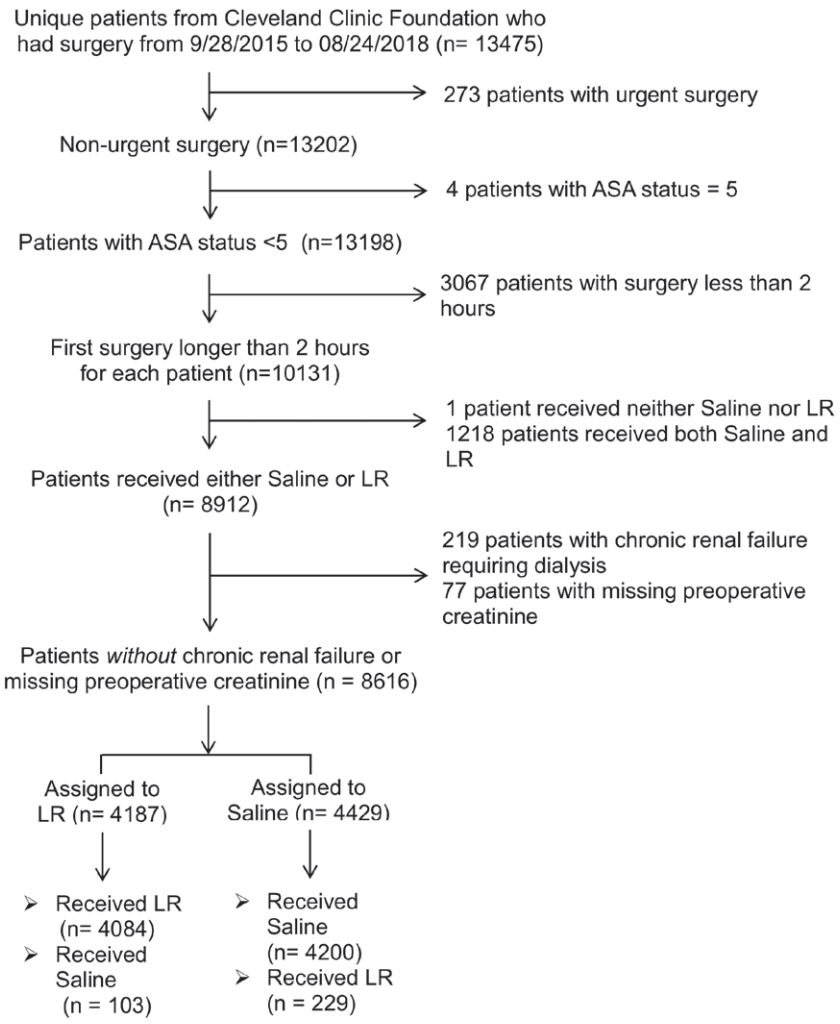

Fig. 1. Study flow chart. ASA, American Society of Anesthesiologists; LR, lactated Ringer's.

Table 2. Effects of Lactated Ringer's (LR) *versus* Saline on the Primary, Secondary, and Tertiary Outcomes (N = 8,616)

	LR (N = 4,187)		Saline (N = 4,429)		Treatment Effect (CI)	
Outcomes	**Missing**	**N (%)**	**Missing**	**N (%)**	**(LR *vs.* Saline)**	***P* Value**
Primary outcome*					RR (95% CI)†	
Overall		241 (5.8%)		272 (6.1%)		
Average relative effect					1.16 (0.89–1.52)	0.261
Treatment–component interaction§					—	0.012§
Individual effects					RR (99% CI)‖	
Mortality		12 (0.29%)		10 (0.23%)	1.54 (0.69–3.43)	0.157
Renal‡	513	25 (0.68%)	541	40 (1.0%)	0.68 (0.43–1.09)	0.032
Infectious		135 (3.2%)		178 (4.0%)	0.84 (0.68–1.03)	0.025
Respiratory		88 (2.1%)		86 (1.9%)	1.2 (0.91–1.59)	0.082
Hemorrhagic		33 (0.79%)		18 (0.41%)	1.99 (1.16–3.43)	< 0.001
Secondary outcome#					OR (99.3% CI)	
AKI status‡	513		541		1.19 (0.99–1.44)**	0.011
No AKI		3,414 (93%)		3,647 (94%)		
Stage 1		235 (6%)		201 (5%)		
Stage 2		20 (0.54%)		26 (0.67%)		
Stage 3		5 (0.14%)		14 (0.36%)	RR (99.3% CI)	
Any AKI		260 (6.6%)		241 (6.2%)	1.18 (0.99–1.41)	0.009
Tertiary outcomes#					RR (99.3% CI)	
MINS††		33 (0.79%)		50 (1.1%)	0.82 (0.54–1.25)	0.208
Cardiac complications		64 (1.5%)		89 (2.0%)	0.86 (0.63–1.17)	0.181
PONV	305	133 (3.4%)	293	140 (3.4%)	1.00 (0.79–1.25)	0.968
Postoperative medication						
Calcium		682 (16%)		774 (18%)	0.95 (0.87–1.04)	0.120
Magnesium		3,428 (82%)		3,599 (81%)	1.01 (0.99–1.03)	0.144
Potassium		2,029 (49%)		2,277 (51%)	0.94 (0.91–0.98)	< 0.001
Bicarbonate		26 (0.62%)		70 (1.6%)	0.45 (0.29–0.68)	< 0.001
Blood transfusion during hospitalization‡‡						
RBC		410 (9.8%)		541 (12%)	0.84 (0.75–0.94)	< 0.001
RBC, median [Q1, Q3], cc,§§ if any		658 [350, 934]		637 [359, 1,014]		
Platelets		17 (0.4%)		24 (0.5%)	0.84 (0.46–1.51)	0.415
Platelets, median [Q1, Q3], cc,§§ if any		451 [252, 740]		290 [250, 477]		
FFP		23 (0.55%)		33 (0.75%)	0.81 (0.49–1.35)	0.263
FFP, median [Q1, Q3], cc,§§ if any		460 [278, 532]		521 [305, 799]		
					Ratio of Mean Counts (99.3% CI)	
Number of tests for plasma electrolyte concentrations,‖‖ median [Q1, Q3]	218	2 [1, 5]	232	2 [1, 5]	0.93 (0.87–1.004)	0.011

For additional control for observed confounding variables, the inverse probability of treatment weighting method was used in all the primary, secondary and tertiary analyses.

*Incidence for an individual effect is presented as No. (%) of patients who had the corresponding complication. Incidence for the collapsed composite is presented as the No. (%) of patients who had at least one complication. †The relative risk on average relative effect was estimated using a generalized estimating equation distinct effects model. The treatment-by-outcome interaction *P* value = 0.012, meaning that there is a significant heterogeneity of the effect across the individual components. *P* value of 0.044 or less (adjusted for three interim analyses) was considered significant for the average relative effect on the composite outcome and *P* value of 0.009 or less (*i.e.,* 0.044/5 Bonferroni correction for multiple comparisons) for each component of the composite. ‡Renal complications for the primary outcome defined as Acute Kidney Injury Network stage 2 or higher. A total of 1,054 patients (12%) were missing 48-h postoperative creatinine. While the raw incidence of renal complications and AKI was reported based on the subset with "complete" postoperative creatinine, both analyses were based on all 8,616 patients after imputing the missing 48-h creatinine values using multiple imputation. §Test of whether the treatment effect differs across the five components. ‖The relative risks on individual effects were estimated from separate logistic regression models. CIs were adjusted for multiple testing by Bonferroni correction and the three interim analyses. Correspondingly, *P* values of 0.009 (*i.e.*, 0.044/5) or less were considered significant for individual components. #An overall alpha of 0.05 was used for secondary/tertiary analyses, using a significance criterion of 0.0071 for each secondary/tertiary outcome of group of outcomes (*i.e.,* 0.05/7; Bonferroni correction for AKI [yes/no] and ordinal categories, MINS, cardiac, PONV, postop medication outcomes, blood transfusion outcomes, number of tests for plasma electrolyte concentrations). We only adjusted the alpha for the interim monitoring for the primary outcome. **Proportional odds logistic regression considering the ordered categories of the outcome. ††MINS was defined as peak fourth generation troponin T level 0.03 ng/ml or greater during the initial three postoperative days. Troponin was obtained based on retrospective patients' medical records review; troponin is not routinely measured in all colorectal and orthopedic patients in the Cleveland Clinic. Only 2,501 (29%) of 8,616 patients had postoperative troponin measured; we assumed troponin within the normal range and no postoperative MINS for the patients with unmeasured troponin. ‡‡Transfusion reported intraoperatively and any time after surgery during hospitalization. §§Intraoperative blood transfusion volume is summarized only for patients who received corresponding transfusion. ‖‖The number of tests for plasma electrolyte concentrations from the start of surgery until hospital discharge, including basic metabolic panel, comprehensive metabolic panel, arterial blood gas analysis, and venous blood gas analysis.

AKI, acute kidney injury; FFP, fresh frozen plasma; MINS, myocardial injury after noncardiac surgery; OR, odds ratio; PONV, postoperative nausea and vomiting; RBC, erythrocyte (red blood cells); [Q1, Q3], [first quartile, third quartile]; RR, relative risk.

saline patients (absolute difference of –0.3%; 95% CI, –1.3% to 0.7%; table 2). Using an intent-to-treat approach, the estimated average relative risk of lactated Ringer's *versus* saline across the individual components was 1.16 (95% CI, 0.89 to 1.52; $P = 0.261$; table 2; Supplemental Digital Content figure S2, http://links.lww.com/ALN/C169). The relationship was inconsistent across the individual components of the composite, as indicated by a significant

treatment-by-outcome component interaction ($P = 0.012$). However, none of the component incidences differed by more than 0.8%, and most by much less. There was thus no clinically meaningful difference in any component or the overall composite of serious complications. Results of all sensitivity analyses on the composite outcome were similar to those of the primary analysis (Supplemental Digital Content table S3, http://links.lww.com/ALN/C170).

Secondary and tertiary results are reported in table 2. Postoperative acute kidney injury, Acute Kidney Injury Network stage I–III, occurred in 6.6% of lactated Ringer's patients *versus* 6.2% of normal saline patients, with relative risk of 1.18 (99.3% CI, 0.99 to 1.41; $P = 0.009$, significance criterion of 0.007). There were no significant differences in Acute Kidney Injury Network acute kidney injury stages, and the magnitude of the changes was not clinically meaningful. However, intraoperative use of lactated Ringer's solution reduced erythrocyte transfusion, with relative risk of 0.84 (0.75, 0.94), $P < 0.001$. *Post hoc* subgroup analyses for both the primary composite outcome and acute kidney injury are presented in figure 2. Patients assigned to lactated Ringer's had lower postoperative chloride and sodium concentrations and higher bicarbonate concentrations than those assigned to normal saline (fig. 3).

E-value estimates for the primary outcome indicate that reducing the average relative risk ratio of 1.16 to 1.0 would require an unmeasured confounder with relative risk of 1.6 (the E-value) or stronger. Reducing the observed relative risk of 0.68 for the primary outcome renal complication variable to 1.0 would require an unmeasured confounder with relative risk of 2.3 (the E-value) or stronger. Reducing the observed relative risk of 1.99 for bleeding complications to 1.0 would require an E-value of 3.4 or stronger, and 1.6 to make the result nonsignificant. Reducing the observed relative risk of 1.19 for the secondary outcome acute kidney injury (yes/no) to 1.0 had an E-value of 1.7. Reducing the relative risk for erythrocyte transfusions from 0.84 to 1.0 requires an E-value of 1.7, and 1.3 to make it nonsignificant.

Discussion

Participating patients were given a median of nearly 2 l of lactated Ringer's or saline in less than 4 h. Our primary composite comprising mortality, moderate or severe acute kidney injury, infections, respiratory complications, and hemorrhage reflects major perioperative morbidity. We therefore evaluated a range of plausible consequences of administration of unbalanced salt solutions. There was no significant difference in the primary composite outcome between groups, and the absolute incidence difference for having any event in the composite was only 0.3% (95% CI, −1.3% to 0.7%). While there was heterogeneity within the composite components, none differed by clinically meaningful amounts—thus supporting our conclusion that the incidence of serious complications is similar in patients given saline and lactated Ringer's solution.

Our results are consistent with the findings of a recent Cochrane review of 18 small randomized trials with a total of 1,096 surgical patients (about an eighth the number in our trial) concluding that fluid types did not differentially affect mortality or organ function.[18] Our results are at odds with a large registry analysis of patients who had noncardiac surgery concluding that postoperative morbidity is worse with saline than with a balanced solution.[19] Presumably the randomized trial conclusions that indicate comparable results with each fluid constitute the more reliable evidence.

Our secondary outcomes were acute kidney injury as defined by Acute Kidney Injury Network stage and a binary acute kidney injury outcome of stage I–III *versus* stage 0. As with the composite of serious complications, there were no clinically meaningful differences in renal injury assessed either way. Lack of harm from saline administration intraoperatively contrasts with harm reported in other contexts by Shaw *et al.*,[19] the Isotonic Solutions and Major Adverse Renal Events Trial in the Medical Intensive Care Unit (SMART-MED) trial,[15] and the Saline Against Lactated Ringer's or Plasmalyte in the Emergency Department (SALT-ED) trial.[20] For example, the SMART-MED trial in critically ill patients reported fewer major adverse kidney events in patients assigned to balanced crystalloid than to saline.[15] The SALT-ED trial compared saline with balanced crystalloids in noncritically ill emergency department patients. While there was no significant difference in the primary outcome of hospital-free days, fewer patients given balanced crystalloid experienced acute kidney injury.[20] Presumably, the key distinction is that surgical patients are relatively healthy and the amount of intraoperative fluid given is relatively small. Available evidence thus suggests that modest volumes of intraoperative saline do not cause more renal injury than lactated Ringer's solution, but that prolonged administration of large volumes in critically ill patients does.

The single clinically meaningful difference we observed was in the number of blood transfusions. Patients assigned to lactated Ringer's were less likely to require blood transfusion than those given saline solution (9.8% *vs.* 12%, relative risk, 0.84 [99.3% CI, 0.75 to 0.94], $P < 0.001$). Nonetheless, we caution that whether or not a patient received a transfusion was a tertiary outcome and should be considered exploratory. Furthermore, there was no clinically meaningful difference in major hemorrhage, as defined in our primary composite.

A further consideration is that there is no obvious mechanism by which saline administration would increase the need for erythrocyte transfusions. The well-documented acidosis consequent to saline administration may cause coagulopathy,[21,22] but the degree of acidosis caused by saline administration is relatively small and unlikely to provoke enough bleeding to require major transfusion. Most major postoperative bleeding is due to surgical complications, which are presumably not influenced by fluids selection.[23] Furthermore, perioperative coagulopathy is mostly

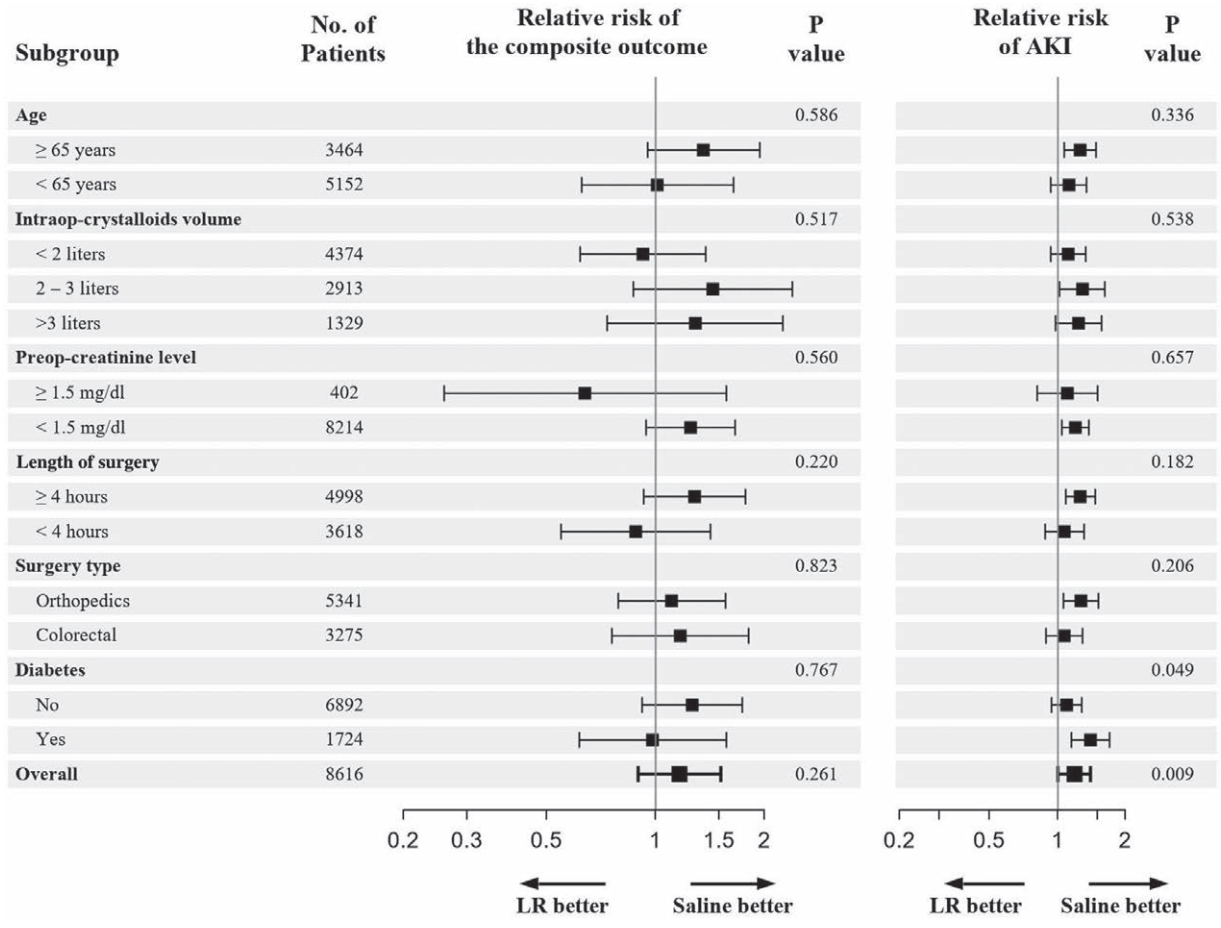

Fig. 2. *Post hoc* subgroup analyses for the primary composite and secondary acute kidney injury (AKI) outcomes. The results are shown as relative risk of increased primary composite or more severe postoperative AKI comparing lactated Ringer's (LR) *versus* saline. Displayed *P* value is an interaction *P* value for each of six subgroup analyses; overall *P* values are corresponding to the relative risk of the primary composite outcome and the relative risk of more severe AKI for LR *versus* saline. The *box* represents the estimate of the relative risk, and the *line* represents the confidence intervals. Intraop, intraoperative; Preop, preoperative.

dilutional, irrespective of the fluid given.[24] Finally, patients with major blood loss are almost always given colloids, which themselves cause coagulopathy.[25,26] In summary, patients given saline received more packed erythrocytes, but there is no compelling mechanism, and it remains possible that the apparent difference in this comparison is spurious.

Despite long-standing concerns, saline is still commonly used. Clinicians tend to use saline in diabetic patients and patients with renal dysfunction to avoid hyperkalemia—although patients given saline actually have more hyperkalemia, hyperchloremia, and acidosis.[27] Saline is presumed to be safe when mixed with packed erythrocytes. However, lactated Ringer's solution can also be safely mixed with packed erythrocytes without provoking clot formation.[28] Saline is often believed to be less expensive than balanced salt solutions, but their costs are actually nearly identical (and low), both in the United States and in most other countries.[29]

Alternating intervention trials are efficient, fast, and inexpensive compared to conventional individual-patient randomized trials. Alternating intervention trials are, in effect, cluster trials with the clusters distributed in time rather than in space. However, a limitation is that allocation is not concealed, and investigators are necessarily unblinded. Since it is unlikely that patients were scheduled to receive particular fluids, allocation was effectively random. Consistent with this assertion, baseline balance was excellent. Importantly, 97% of qualifying patients were given the assigned fluid.

For the primary outcome assessment, we used International Classification of Diseases codes reported in electronic health records, as did Shaw *et al.*[19,30] Even the best electronic records suffer from measurement and reporting error. Also, increasing granularity of diagnosis codes does not necessarily improve electronic record data quality and may lead to diagnosis error.[31] However, such random error

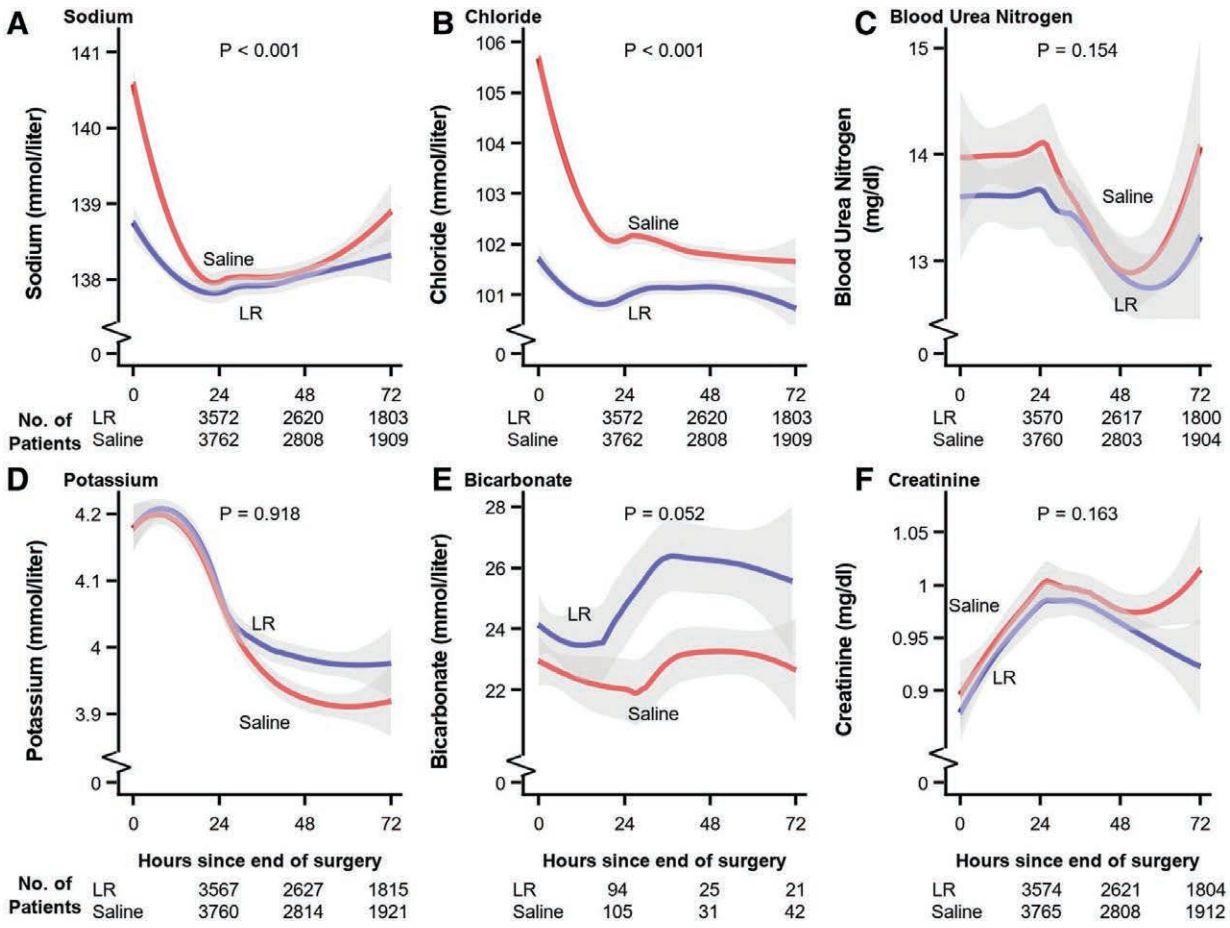

Fig. 3. *Post hoc* analysis of serum electrolyte concentrations during the initial 72 postoperative hours: (*A*) sodium, (*B*) chloride, (*C*) blood urea nitrogen, (*D*) potassium, (*E*) bicarbonate, (*F*) creatinine. *Lines* and *bands* represent means and 95% confidence intervals, respectively. Plots were generated with the use of locally weighted scatterplot smoothing. The *P* values in the figure represent the overall difference between the two study groups, calculated with the use of linear mixed models (for modeling purposes, we assumed linearity despite of curvilinear smoothing in the plots), which allowed adjusting for the correlation present among repeated measurements obtained from a given patient (using unstructured correlation). Over time, the separation between groups changed for sodium ($P < 0.001$ for interaction) and chloride ($P < 0.001$ for interaction); interaction terms for the other variables were not significant (significance criterion for interaction was $P > 0.10$). All serum electrolyte concentration measurements before surgery were similar for the two study groups (table 1). LR, lactated Ringer's.

would have influenced both groups and is unlikely to have influenced our conclusions. We only included patients having colorectal or orthopedic surgery, which well represent the noncardiac surgical population, but our results should be extrapolated with caution to neurologic and cardiac surgery. Finally, although confounding would not be expected in our controlled trial, we conservatively use the E-value[16] method to assess the magnitude of unmeasured confounding that would be required to move observed relative risks to 1.0, and significant results to nonsignificant. For example, moderate unmeasured confounding relative risks of 1.6 would be required to make our results for bleeding complications nonsignificant, and 1.3 for erythrocyte transfusions. Given our trial design, that level of unobserved confounding seems unlikely.

Our study was designed for 90% power to detect a 20% relative reduction in the primary composite outcome, but a poststudy reanalysis of the power given the lower-than-expected incidences for components of the composite resulted in an effective 65 to 70% power. Our nonsignificant results thus might be explained by type II error, *i.e.,* we had a 30 to 35% chance of failing to detect an underlying 20% reduction. Power was also reduced by the observed treatment effect heterogeneity across components of the composite. Nonetheless, the absolute differences between groups were small for our primary and secondary outcomes, and not clinically meaningful. Furthermore, confidence intervals around our estimates of treatment effect were quite precise given our large sample size.

We did not control the postoperative care of patients, and one might argue that the intraoperative intervention could be diluted by postoperative administration of various types of intravenous fluid. However, it seems that our intervention of clinical interest, even if limited to the intraoperative period, was substantial, with a median volume of nearly 2 l in nearly 4 h.

In conclusion, our primary composite outcome of death and serious complications and our secondary outcome of kidney injury outcome did not differ meaningfully in patients assigned to intraoperative infusion of normal saline or lactated Ringer's solution. Clinicians can reasonably use either fluid for routine vascular volume replacement in patients having noncardiac surgery.

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Competing Interests

Dr. Maheshwari reports an ongoing financial relationship with Edwards Lifesciences (Irvine, California). Dr. Higuera-Rueda reports ongoing Zimmer Biomet (Warsaw, Indiana), KCI, and Pfizer (New York, New York) consulting fees, PSI stock options, and ongoing financial relationships with Stryker (Kalamazoo, Michigan), Zimmer Biomet, KCI (San Antonio, Texas), 3M (Maplewood, Minnesota), the National Institutes of Health (Bethesda, Maryland), CyMedica (Scottsdale, Arizona), and CD Diagnostics (Claymont, Deleware). The other authors declare no competing interests.

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References

1. CDC: National Hospital Discharge Survey. 2010. Available at: http://www.CDC.gov. Accessed July 5, 2015.
2. Prough DS, Bidani A: Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology 1999; 90:1247–9
3. Handy JM, Soni N: Physiological effects of hyperchloraemia and acidosis. Br J Anaesth 2008; 101:141–50
4. Kellum JA: Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: Improved short-term survival and acid-base balance with Hextend compared with saline. Crit Care Med 2002; 30:300–5
5. Scheingraber S, Rehm M, Sehmisch C, Finsterer U: Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999; 90:1265–70
6. Liu B, Finfer S: Intravenous fluids in adults undergoing surgery. BMJ 2009; 338:b2418
7. Burdett E, Dushianthan A, Bennett-Guerrero E, Cro S, Gan TJ, Grocott MP, James MF, Mythen MG, O'Malley CM, Roche AM, Rowan K: Perioperative buffered *versus* non-buffered fluid administration for surgery in adults. Cochrane Database Syst Rev 2012; 12:CD004089
8. Guidet B, Soni N, Della Rocca G, Kozek S, Vallet B, Annane D, James M: A balanced view of balanced solutions. Crit Care 2010; 14:325
9. Myburgh JA, Mythen MG: Resuscitation fluids. N Engl J Med 2013; 369:1243–51
10. Carlesso E, Maiocchi G, Tallarini F, Polli F, Valenza F, Cadringher P, Gattinoni L: The rule regulating pH changes during crystalloid infusion. Intensive Care Med 2011; 37:461–8
11. Raghunathan K, Nailer P, Konoske R: What is the ideal crystalloid? Curr Opin Crit Care 2015; 21:309–14
12. Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, Srinathan SK, Walsh M, Abraham V, Pearse R, Wang CY, Sessler DI, Kurz A, Szczeklik W, Berwanger O, Villar JC, Malaga G, Garg AX, Chow CK, Ackland G, Patel A, Borges FK, Belley-Cote EP, Duceppe E, Spence J, Tandon V, Williams C, Sapsford RJ, Polanczyk CA, Tiboni M, Alonso-Coello P, Faruqui A, Heels-Ansdell D, Lamy A, Whitlock R, LeManach Y, Roshanov PS, McGillion M, Kavsak P, McQueen MJ, Thabane L, Rodseth RN, Buse GAL, Bhandari M, Garutti I, Jacka MJ, Schünemann HJ, Cortes OL, Coriat P, Dvirnik N, Botto F, Pettit S, Jaffe AS, Guyatt GH; Writing Committee for the VISION Study Investigators: Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. JAMA 2017; 317:1642–51
13. Mascha EJ, Imrey PB: Factors affecting power of tests for multiple binary outcomes. Stat Med 2010; 29:2890–904
14. Mascha EJ, Sessler DI: Statistical grand rounds: Design and analysis of studies with binary-event composite endpoints: Guidelines for anesthesia research. Anesth Analg 2011; 112:1461–71
15. 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
16. VanderWeele TJ, Ding P: Sensitivity analysis in observational research: Introducing the E-value. Ann Intern Med 2017; 167:268–74
17. Mascha EJ: Power Calculations for Tests on a Vector of Binary Outcomes (MULTBINPOW), 2010. Cleveland Clinic Statistical Software Series. Available at: http://www.lerner.ccf.org/qhs/software/multbinpow.php. Accessed January 8, 2020.
18. Bampoe S, Odor PM, Dushianthan A, Bennett-Guerrero E, Cro S, Gan TJ, Grocott MP, James MF, Mythen MG, O'Malley CM, Roche AM, Rowan K, Burdett E: Perioperative administration of buffered *versus* non-buffered crystalloid intravenous fluid to improve outcomes following adult surgical procedures. Cochrane Database Syst Rev 2017; 9:CD004089
19. 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
20. 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
21. Martini WZ: Coagulopathy by hypothermia and acidosis: Mechanisms of thrombin generation and fibrinogen availability. J Trauma 2009; 67:202–8; discussion 208–9
22. Martini WZ, Cortez DS, Dubick MA: Comparisons of normal saline and lactated Ringer's resuscitation on hemodynamics, metabolic responses, and coagulation in pigs after severe hemorrhagic shock. Scand J Trauma Resusc Emerg Med 2013; 21:86
23. Tasu JP, Vesselle G, Herpe G, Ferrie JC, Chan P, Boucebci S, Velasco S: Postoperative abdominal bleeding. Diagn Interv Imaging 2015; 96:823–31
24. Coats TJ, Brazil E, Heron M: The effects of commonly used resuscitation fluids on whole blood coagulation. Emerg Med J 2006; 23:546–9
25. Brazil EV, Coats TJ: Sonoclot coagulation analysis of in-vitro haemodilution with resuscitation solutions. J R Soc Med 2000; 93:507–10
26. Egli GA, Zollinger A, Seifert B, Popovic D, Pasch T, Spahn DR: Effect of progressive haemodilution with hydroxyethyl starch, gelatin and albumin on blood coagulation. Br J Anaesth 1997; 78:684–9
27. 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
28. Lorenzo M, Davis JW, Negin S, Kaups K, Parks S, Brubaker D, Tyroch A: Can Ringer's lactate be used safely with blood transfusions? Am J Surg 1998; 175:308–10
29. Laplante S, Makhija DU, Munson SH, Khangulov VS, Peyerl FW, Paluszkiewicz SM, Ravindranath AJ, Schermer CR: Impact of fluid choice in systemic inflammatory response syndrome patients on hospital cost savings. Pharmacoecon Open 2018; 2:325–35
30. Shaw AD, Schermer CR, Lobo DN, Munson SH, Khangulov V, Hayashida DK, Kellum JA: Impact of intravenous fluid composition on outcomes in patients with systemic inflammatory response syndrome. Crit Care 2015; 19:334
31. Navar AM: Electronic health record data quality issues are not remedied by increasing granularity of diagnosis codes. JAMA Cardiol 2019; 4:465