

Saline *versus* Lactated Ringer's Solution: The SOLAR fluid trial

An Anesthesia Institute Quality Improvement Project

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Background

About 51 million inpatient surgeries were performed in United States in 2010, based on National Hospital Discharge Survey.¹ Nearly all operations require intravenous (IV) fluids for drug administration and vascular volume repletion. Mismanagement of fluid administration — in volume, type, or timing — may cause postoperative complications and worsen survival.² Complications are in fact common, with as many as half of high-risk surgical patients experiencing substantive morbidity.^{3,4}

Many IV fluid preparations are currently used and how best to manage perioperative fluids remain controversial.⁵⁻⁷ For example, when to use crystalloid fluids and when to use colloids remains unclear. And even within the crystalloid category, there are two general types of fluids: non-buffered (saline) and buffered solutions (lactated Ringer's and similar mixtures, Table 1). Both buffered and unbuffered solutions remain in common use worldwide. In United States, saline is the most commonly used fluid, more than 200 million liters/yr. Also, intraoperative use of saline is 30 times more common than balanced solutions.⁸

Table 1: Typical properties of commonly used intravenous solutions (NICE)⁹

Type of Fluid*	Sodium mmol/L	Potassium mmol/L	Chloride mmol/L	Osmolarity mosm/L	Weight average Mol Wt kD	Plasma volume expansion duration hrs+
Plasma	136-145	3.5-5.0	98-105	280-300	-	-
5% Dextrose	0	0	0	278	-	-
Dextrose 4% saline 0.18%	30	0	30	283	-	-
0.9% "normal" saline	154	0	154	308	-	0.2
0.45% "half normal" saline	77	0	77	154	-	-
Ringer's Lactate	130	4	109	273	-	0.2
Hartmann's	131	5	111	275	-	0.2
Gelatine 4%	145	0	145	290	30,000	1-2
5% albumin	150	0	150	300	68,000	2-4
20% albumin	-	-	-	-	68,000	2-4
HES 6% 130/0.4	154	0	154	308	130,000	4-8
HES 10% 200/0.5	154	0	154	308	200,000	6-12
HES 6% 450/0.6	154	0	154	308	450,000	24-36

While enormous (supra-clinical) volumes of saline provoke substantial hyperchloremic metabolic acidosis,¹⁰⁻¹³ typical perioperative volumes have little effect and have never been convincingly linked to important morbidity.^{14,15} As might thus be expected, a recent Cochrane review reported that major morbidity and mortality were comparable with each type of fluid although saline-based fluids provoked mild and transient hyperchloremia and metabolic acidosis.¹⁶

Animal studies

In a hemorrhagic swine model, resuscitation with 256 ± 145 mL/kg of normal saline compared to 126 ± 67 mL/kg lactated Ringer's resulted in significantly lower fibrinogen concentrations: 99 ± 21 mg/dL versus 123 ± 20 mg/dL, $p = 0.02$. (Both are huge volumes.) Serum lactate was 4.7 ± 2.2 mg/dl in the lactated Ringer's group versus 1.7 ± 1.7 mg/dl in swine given normal saline at the end of the study ($p < 0.01$). The authors concluded that resuscitation of uncontrolled hemorrhagic shock with normal saline requires significantly greater volume and is associated with greater urine output, hyperchloremic acidosis, and dilutional coagulopathy than with lactated Ringer's solution.¹⁷

In another pig hemorrhagic model for trauma resuscitation (N=20), the authors concluded normal saline may be inferior to lactated Ringer's solution due to vasodilatory effects, metabolic acidosis and hyperkalemia.¹⁸ Both these studies showed that normal saline is inferior to lactated Ringer's for resuscitation in hemorrhagic animal models. But in both, the swine were given many times more fluid than would be used during normal surgery.

In contrast to the results summarized above, Watters et al evaluated inflammatory markers and tissue mRNA concentrations of interleukin-6 (IL-6), granulocyte colony-stimulating factor (G-CSF), and tumor necrosis factor-alpha (TNF-alpha) in swine model of hemorrhagic shock. They found no substantive differences in any marker in animals resuscitated with lactated Ringer's or normal saline.¹⁹ Zhou et al compared balanced electrolyte solution (Plasma-Lyte) with 0.9% saline, for resuscitation in rat sepsis model and reported significantly greater blood chloride concentrations, decreased pH, and exaggerated base excess. But in healthy animals, there was no difference between the fluids and no increase in acute kidney injury.²⁰

Human studies

In a prospective open-label, sequential-period pilot study, chloride-rich intravenous fluids (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution) when

compared to chloride-poor (lactated Ringer's, Plasma-Lyte 148, and chloride-poor 20% albumin) solutions was associated with a significant decrease in the incidence of Acute Kidney Injury (AKI) and use of Renal Replacement Therapy (RRT) in critically ill patients.²¹ In another retrospective study of the Premier Perspective Database, use of calcium-free balanced crystalloid for replacement of fluid losses on the day of major surgery was associated with less postoperative morbidity and fivefold less risk of use of dialysis than normal saline.⁸

In contrast, a retrospective cohort study comparing buffered fluids with saline, (N = 6,730) showed that buffered fluids were associated with lower in-hospital mortality (19.6% vs 22.8%; relative risk, 0.86; 95% CI: 0.78, 0.94). But the authors did not find significant differences in the prevalence of acute kidney injury, with or without renal replacement therapy, or in-hospital or ICU lengths of stay.²²

In an another retrospective study of ICU patients (N = 172) recovering from major abdominal surgery, post-operative acidosis was associated with longer intensive care unit (ICU) and hospital length of stay (LOS). Large volumes of normal saline were associated with hyperchloremic acidosis whereas large volumes of lactated Ringer's solution were associated with lactic acidosis.²³ Even in critical care settings, it remains unclear whether buffered solutions are preferable by normal saline.

There is even less evidence directly comparing perioperative use of normal saline and lactated Ringer's solution. For example, O'Malley et al compared used of normal saline with lactated Ringer's in renal transplant surgery and reported no significant difference in renal function, although lactated Ringer's solution caused less hypokalemia and acidosis.²⁴ In abdominal aortic aneurysm repairs, use of normal saline had little impact on outcome as assessed by duration of mechanical ventilation, intensive care unit stay, hospital stay, and postoperative complications. However, perioperative blood loss was greater with saline than lactated Ringer's solution.²⁵

In healthy adults, differences consequent to fluid choice are almost nonexistent and clinically irrelevant. Williams et al found no significant differences in serum sodium, potassium, urea, or osmolality in healthy adults given a 2-liter bolus of either normal saline or balanced Hartman's solution.²⁶ Similarly, large volumes of lactated Ringer's solution given to healthy humans provokes a small and transient reduction in serum osmolality, whereas osmolality was preserved when large volumes of sodium chloride were given.²⁷

Some clinicians are concerned about mixing lactated Ringer's with blood because calcium in the solution might activate the coagulation system. However, breakdown products of thrombin generation are below physiologic value when blood is mixed with either normal saline or lactated Ringer's solution.²⁸ Specifically, the threshold value for ionized calcium that potentially activates clotting (0.23 mM/L) is not reached if the RBC-to- lactated Ringer's volume ratio exceeds 2:1.²⁹ Furthermore, there is no significant difference between infusion time, filtered particulates, or clot formation when either lactated Ringer's solution or normal saline were given rapidly.³⁰

Lactated Ringer's has been studied in renal transplant surgery and authors found hyperkalemia and acidosis was more frequent in normal saline group whereas thrombotic complication were more in lactated Ringer's group.³¹ O'Malley et al compared used of normal saline with lactated Ringer's in renal transplant surgery and reported no significant difference in renal function, although lactated Ringer's solution caused less hyperkalemia and acidosis.²⁴

The potential conversion of lactate to glucose via the Cori cycle has been the proposed mechanism of hyperglycemia.³² However, a recent study demonstrated that perioperative glycemic control is comparable after administration of lactated Ringer's solution or normal saline.³³

In a recent observational study comparing saline with calcium free balanced solutions, the use of saline was associated with significantly greater morbidity and mortality.³⁴ Cardiac complications were significantly higher in the saline group whereas no difference in kidney injury was noted. Cardiac complications and specifically myocardial injury after noncardiac surgery (MINS) are associated with significant postoperative mortality.^{35 36}

In summary, no compelling studies identify substantive harm from use of normal saline rather than lactated Ringer's solution in routine clinical practice or in the perioperative setting. Consequently, Guidet et al concluded that there is no convincing evidence that the mild hyperchloremic acidosis that occurs with infusion of normal saline is associated with detrimental effects on renal function, coagulation status, need for blood transfusion, and overall morbidity and mortality in perioperative setting.¹⁴ Animal studies and mostly retrospective data suggest that normal saline provokes a mild and transient hyperchloremic metabolic acidosis, which in turn can increase incidence of kidney injury and postoperative morbidity. However, there is no evidence that the mild acidosis that results from

normal saline administration results in kidney injury, especially with volumes used in typical clinical situations.

Objectives and Hypotheses

Perioperative volumes of saline cause a mild acidosis compared with buffered fluids. On the other hand, saline administration maintains plasma osmolality and better repletes vascular volume which is an important goal of perioperative fluid administration. Currently, there is no convincing evidence that either saline or buffered solutions are preferable. Consequently, both types of fluid remain in common use at the Clinic and worldwide.

There has never been a large trial of perioperative saline and balanced salt solutions comparing the incidence of major complications including acute kidney injury. Our primary objective is thus to determine the relative safety of perioperative saline and lactated Ringer's solution. Specifically, we propose to test the:

1. Primary hypothesis that a composite of major in-hospital postoperative complications is lower in patients given lactated Ringer's solution compared to normal saline.
2. Secondary hypothesis that acute kidney injury, measured by AKIN criteria, is lower in patients given lactated Ringer's solution compared to normal saline.

The acquisition cost of saline and lactated Ringer's solutions is similar in the United States. (Curiously, buffered solutions are far more expensive than saline in Great Britain.) But to the extent that one fluid or the other provokes more complications, cost of care may be increased with that fluid selection. Cost may also be increased by the need for additional electrolyte monitoring and electrolyte replacement.

We will therefore secondarily conduct an economic evaluation to determine the relative incremental hospital cost of each fluid. To the extent that one fluid or the other reduces cost (assuming similar complication rates), the Clinic will be able to reduce cost by specifying the appropriate fluid without impairing quality.

Evidence that one fluid or the other causes few complications would be a strong quality indicator that the Clinic should standardize perioperative fluid selection.

Outcomes

1. **Primary:** Post-operative morbidity, as assessed by a composite outcome consisting of the following major complication components: renal, respiratory, infectious and hemorrhagic.
2. **Secondary:**
 - a. Acute kidney injury (AKIN criteria);
 - b. Economic evaluation.
3. **Tertiary:**
 - a) Blood transfusion;
 - b) Number of plasma electrolytes determinations;
 - c) Electrolyte replacement (i.e., administration of calcium, magnesium, potassium, or bicarbonate);
 - d) Post-operative nausea vomiting.
 - e) Myocardial Injury after Noncardiac Surgery
 - f) Cardiac complication

Methods

We propose an alternating intervention quality study comparing intraoperative fluid management with normal saline and lactated Ringer's solutions. This general approach to quality questions has been used at the Clinic and shown to produce more reliably clinical guidance than propensity-matched retrospective analyses.³⁷

This project will focus on colorectal and orthopedic surgery because these operations are conducted in physically distinct units that are normally staffed by small groups of anesthesiologists. Furthermore, most of the cases are substantial and require postoperative hospitalization. Both the anesthesia and surgical teams have agreed to the proposed project and representatives are co-investigators.

Protocol

We propose that all orthopedic and colorectal surgery operating rooms will alternate between using either normal saline or lactated Ringer's solution for 2-week periods. For example, the first period will use normal saline; the second will use lactated Ringer's, and so on for a maximum total of approximately 36 cycles. Thus, fluid choice will not be randomized on a per-patient or even per-period basis. Patients will not be informed of their group assignments, but will be told what fluids they received in the event they ask.

There will be no other restriction on anesthetic management and practitioners will be free to use intravenous anesthetics and neuraxial analgesia per their preference. Intraoperative clinicians will not be blinded to type of crystalloid and will be free to use whichever fluid they deem preferable if clinically indicated. Normal saline will always be available for blood dilution. Crystalloid volume and timing will be determined by the anesthesia care team as usual. Other fluid, blood products, electrolyte replacement will be used at the discretion of anesthesia care team.

Measurements

All study outcomes will be obtained from electronic medical records including demographic and morphometric characteristics. Types of surgery will be characterized from ICD-9 codes using AHRQ Clinical Classifications Software. All routine anesthetic variables, including inspired oxygen fraction and expired carbon dioxide partial pressure, will be recorded per routine by our electronic anesthetic record-keeping system. Preoperative laboratory test, including but not limited to hemoglobin, hematocrit, BUN, creatinine, glucose, electrolytes and blood gas measurements, will be recorded. Transfusions will be recorded. Core temperature will be recorded, and patients will be kept normothermic per routine.

In colorectal surgery database, baseline risk of infection will be gathered evaluated using the Center for Disease Control (CDC) SENIC score, where one point each was assigned for ≥ 3 diagnoses, surgical duration ≥ 2 h, abdominal site of surgery, and the presence of a contaminated or dirty-infected wound.³⁸ The score will be slightly modified from its original form by our use of admission — rather than discharge — diagnoses.

Infection risk will be further quantified using the National Nosocomial Infection Surveillance System (NNISS), in which risk is predicted based on type of surgery, American Society of Anesthesiologists Physical Status score, and the duration of surgery.³⁹ Surgical wounds will be considered infected when they met the 1992 revision⁴⁰ of the CDC criteria for surgical wounds originally proposed in 1987.⁴¹ These data will be obtained from the Department of Colorectal Surgery registry and from orthopedic surgery departments, where they are recorded per routine.

Primary outcome

1. **One or more major complications**, including in-hospital mortality, renal (AKIN criteria 2+), respiratory, infectious, and hematological complications.

Our composite of major complications is a modification of a previously published composite used by Bennett⁴²; similar composites have been used in previous fluid management studies.^{8,43-45} Specifically, we selected major complications that were identified as significant (or near-significant) in one of the largest retrospective analyses comparing normal saline to balanced solution that was based on the Premier database.⁸ Major complications and their associated ICD-9 codes are described in the Appendix.

Secondary outcomes

1. Acute kidney injury (AKIN criteria) :

Risk Injury Failure Loss End stage (RIFLE)⁴⁶ and Acute Kidney Injury Network (AKIN)⁴⁷ criteria are useful tools to assess kidney injury after surgery.⁴⁸ Both criteria are sensitive to kidney injury, but in cardiac surgery⁴⁹, burn⁵⁰ patient's AKIN classification correlated better with mortality than did the RIFLE criteria. We will thus quantify kidney injury with AKIN criteria.

2. Economic evaluation:

The cost of care analysis will incorporate only costs directly relevant to the intervention. The costs for each group will be broken into two components: uncomplicated care (standard care), and care of associated complications.

Costs to be included for uncomplicated care will include LOS, electrolyte management, electrolyte replacement, plasma electrolyte determination, and post-operative nausea and vomiting. Costs to be included for associated complications will include the cost to treat any major complications (Table 3), and blood transfusions.

Costs for each outcome will be sourced from Medicare allowable rates for reimbursement, CC billing data and Elsevier Rx Price Verify Database.

Tertiary outcomes

1. **Blood transfusion:** Number of units transfused during hospitalization of red cells, platelets, and fresh-frozen plasma (each considered separately, Table 5);

2. **Plasma electrolytes determinations:** a count of the number of times blood is drawn for electrolyte determination, for example basic metabolic panel, arterial blood gas analysis, venous blood gas analysis, potassium, magnesium, and calcium determination;
3. **Administration of calcium, magnesium, potassium, or bicarbonate;**
4. **Postoperative nausea vomiting** during PACU (post anesthesia care unit) stay: Postoperative Nursing Progress Record (NPR) - Records nausea vomiting severity as: 0=none, 1= mild, 2=moderate, 3= severe; analysis will compare nausea vomiting (1, 2, 3) to no nausea vomiting (0).
5. **Myocardial Injury after Noncardiac Surgery³⁵** – MINS is defined as at least one postoperative value of fourth-generation troponin T ≥ 0.03 ng/ml apparently of ischemic origin, in the 3 days after operation. Eligible patients without postoperative cardiac enzyme determinations will be assumed not to have acute myocardial injury.
6. **Cardiac complication³⁴** – See ICD codes appendix E.

We will exclude following patients from analysis as they have medical conditions that can influence outcomes:

1. Urgent or emergent surgery;
2. ASA physical status 5. That is, patients who are not expected to survive with or without surgery;
3. Chronic renal failure requiring preoperative dialysis;
4. Pulmonary and cardiac surgery – different pathophysiology, and thoracic surgery typically have strict fluid restriction on type and volume of fluid used;
5. Liver resection surgery- strict fluid limits or type and volume of fluids;
6. Surgeries lasting less than 2 hours which typically require small amount of fluids, thus making the type of fluid relatively unimportant.

Data Analysis

Because this trial will not be randomized, we will control for observed potential confounding variables using the inverse propensity score weighting method. We will first fit a multivariate logistic regression model with fluid assignment as the outcome variable and all observed confounding variables as the independent variables. From this model we will estimate propensity scores (i.e., probability of receiving lactated Ringer's solution) for each patient. After weighting observations by their respective inverse propensity score, the success of confounding control will be assessed by comparing groups on potentially confounding baseline characteristics (appendix) using absolute standardized difference (ASD), defined

as the absolute difference in means or proportions divided by the pooled standard deviation. Observations in all primary and tertiary analyses below will be weighted by the inverse of the relevant propensity score. In addition, any confounding variable with an ASD greater than the smaller of 0.2 or $1.96 \times \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$ will be adjusted for in all analyses.

Primary analysis

Because the incidence and severity of the individual major complications vary considerably, we will analyze morbidities in a multivariate (one record per outcome per patient) analysis instead of a collapsed composite approach. A multivariate approach allows us to capture information regarding individual morbidities and the correlation between morbidities.

The average relative effect of lactated Ringer's solution versus saline will be assessed across the five categories of major complications using generalized estimating equations (GEE) 'distinct effects' model with an unstructured working correlation matrix.⁵¹ To assess heterogeneity of the fluid effect across components of the primary outcome, we will assess the treatment-by-component interaction in a distinct effects GEE model. We will assess whether the average component-specific treatment effect was equal to zero using an average relative effect test. However, if the baseline incidences are either quite different from each other or if some are very small (say < 1%), will instead use the common effect GEE test. All analyses will adjust for unbalanced potentially confounding baseline characteristics.

Secondary analysis

The economic evaluation will be conducted from the hospital/payer perspective to determine the optimal strategy for economic outcomes between the two interventions. The evaluation will determine the incremental costs between the two interventions; uncomplicated care and care of complications, as well as a combined incremental cost. An example analysis is listed below showing the incremental difference between the interventions for various outcomes for standard care and complications. A cost is assigned to each outcome and a total cost per patient calculated.

Standard Care - Example

	Intervention A	Intervention B	Incremental Dif.	Estimated Cost	Total Cost
LOS	1	0.8	0.2	100	20
Electrolyte Measures	10	8	2	10	20
Electrolyte Replacement	2	1	1	20	20
				Total Cost/pt	60

Complications - Example

	Intervention A incidence	Intervention B incidence	Incremental Dif.	Estimated Cost	Total Cost
MI	0.1	0.05	0.05	10,000	500
DVT	0.2	0.1	0.1	1000	100
Pneumonia	0.3	0.2	0.1	2000	200
				Total Cost/pt	800

Using the example results above, results would indicate that using intervention B can save 0.2 days, 2 electrolyte measures and an electrolyte replacement equating to \$60 in savings considering only standard care. Incorporating the potential cost savings from avoiding complications, intervention can reduce the incidence of MI, DVT, and pneumonia equating to a potential cost savings of \$800 per patient. For a hospital performing 1,000 procedures a year, using intervention B would potentially save the hospital \$60,000 in standard care costs and \$800,000 costs from avoiding complications.

Using the methods outlined in the example analysis, the analysis will be performed using the relevant outcomes from the clinical trial. The robustness of the results to changes in variable values will be tested using sensitivity analysis. Sensitivity analysis will include one-way and two-way analyses around the baseline values using the confidence intervals derived from the study. Any values where a confidence interval is unknown including cost variables, a 25% range will be used. Any change in values to which the choice strategy is highly sensitive, further sensitivity analysis will be conducted including threshold analysis.

Tertiary outcomes analysis

We will assess the association between fluids and AKIN classification using a multivariable proportional odds model including propensity score weights and adjusting for unbalanced baseline co-variables as appropriate. If AKIN categories have low incidence, we will combine them and perform a multivariable logistic regression analysis instead.

The association of fluids on blood transfusion will be assessed using separate multivariable Poisson or negative binomial regression models for each transfusion type, as appropriate. We will also assess the association of fluids on plasma electrolytes determination using a multivariable Poisson or negative binomial regression model. The association of fluids with the administration of electrolyte replacement and postoperative nausea and vomiting will be assessed through separate multivariable logistic regression models. All above tertiary analyses will adjust for confounding variables that are unbalanced after propensity score weighting.

We will use an overall alpha of 0.05 for both the primary and secondary/tertiary analyses, using a significance criterion of 0.05 for the primary analysis and 0.006 for each secondary/tertiary analysis (i.e., 0.05/8; Bonferroni correction). SAS Version 9.3 (SAS Institute, Cary, NC, USA) and R statistical software version 2.15.3 (R Project for Statistical Computing, Vienna, Austria) will be used for the analyses.

Pilot patients

We will enroll at least 5 pilot patients to test the feasibility of protocol adherence and data collection.

Interim analyses

At each quarter of the maximum enrollment (8,548), we will conduct an interim analysis to assess for efficacy and futility of using lactated Ringer's solution versus saline on our composite of major complications. The interim analysis will use the gamma spending function with parameters -4 for alpha (efficacy) and -1 for beta (futility). Boundaries for efficacy (futility on parentheses) at each stage are $P \leq 0.00160$ ($P > 0.92646$), $P \leq 0.00482$ ($P > 0.62368$), $P \leq 0.01472$ ($P > 0.2011$), and $P \leq 0.04404$ ($P > 0.04404$), respectively.

Sample size

Based on a preliminary query of the PHDS database, we found the incidence of complications among all patients who would have met the inclusion/exclusion criteria for this study:

Outcome	No. Missing	Overall Incidence (%)	Estimated Saline
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		(N = 12,182)	Incidence (%)
In-hospital mortality	0	65 (0.53)	0.59
Renal (AKI classification > 1)	0	213 (1.75)	1.94
Respiratory	90	285 (2.34)	2.60
Infectious	83	2895 (23.76)	26.40
Hematologic	83	311 (2.55)	2.83

This study is designed to have about 90% power at the 0.05 significance level to detect a 20% relative decrease in major complications LR versus saline. We estimated the incidence of complications in the control group (saline) assuming that the two groups average out to the overall incidence. Sample size was calculated assuming a conservative correlation of 0.3 between outcomes. We estimated sample size using the MULTBINPOW SAS macro, which can estimate power for average relative effect GEE models given varying correlations and sample sizes (Mascha EJ Power Calculations for Tests on a Vector of Binary Outcomes (MULTBINPOW)).⁵¹ Cleveland Clinic Statistical Software Series 10 edn Cleveland; 2011: SAS program uses simulations to compute and display comparative power of several parallel-group multivariate tests for treatment effect on a vector of binary events.⁵² After accounting for 3 interim analyses and 1 final analysis, we will need to enroll a maximum of 8,548 patients for this study. If the Average Relative Effect analysis proves insufficient, we expect to nonetheless have > 99% power to detect a 20% relative increase in major complications in saline versus LR using either the collapsed composite or common effect GEE methods.

However, it is likely that the study would stop early. The table below provides boundary crossing probabilities for possible true underlying treatment effects: Null (no effect), Alternative (20% relative increase), half-way between the null and alternative, and 1.5 times the alternative effect. If the alternative hypothesis were true, the probability of crossing either the efficacy or futility boundary would be a cumulative 40% and 78% at interim analyses 2 and 3 (see “Alternative” row). Thus, there would be a 40% chance of stopping the study after N = 3,420 patients and 78% chance when N = 6,668 patients were enrolled if the alternative hypothesis is true. With an estimated 6,240 eligible patients available every year, we can expect this study to take a maximum of 1.37 years.

Expected Cumulative Boundary Crossing Probabilities (i.e., boundary crossing probabilities for either efficacy or futility)					
Effect*	Expected Crossing Stage	Boundary Crossing Probabilities			
		Interim 1	Interim 2	Interim 3	Final
Null	2.7	0.08	0.42	0.84	1.0
Alternative	2.7	0.09	0.40	0.78	1.0
½ Null, Alternative	3.0	0.06	0.28	0.63	1.0
Alt x 1.5	1.9	0.29	0.81	0.98	1.0

* True treatment effect in the population

Internal pilot study

Before the first interim analysis (at approximately 1,000 patients), an internal pilot study for sample size extension may be proposed if the observed incidence of any complication differs considerably from the estimated incidence (i.e., original sample size estimates above fall outside the 95% CI for the estimated internal pilot study incidence). A second stage with new stopping boundaries would be designed with sample size and planned interim analyses to detect a 20% increase in complications based on the revised control group incidence.

Human subjects

The proposed study is primarily for the purpose of quality improvement and cost reduction, although the results may be sufficiently interesting to publish. We will use a non-randomized alternating treatment design in which each fluid regimen will be used for successive 2-week periods in designated physically distinct surgical units.

Evidence and current clinical practice support that crystalloids, both lactated Ringer's and normal saline, are clearly safe; furthermore, both are widely used in perioperative patients. However, each has potential advantages and disadvantages, and potentially different costs of care. We do not propose obtaining informed consent for the proposed quality project since both fluids are widely used in clinical practice and there is currently no compelling reason to believe one is superior to the other.

The project will coincide with another ongoing project “Supplemental Oxygen in Colorectal Surgery: A Quality Improvement Project” in colorectal surgery department in which intraoperative usage of oxygen is prospectively standardized between 2 alternating groups (30% vs. 80%). Surgical site infection is the primary outcome. Some patients in the proposed SOLAR study will also be enrolled in the ongoing study of Supplemental Oxygen.

Although an interaction between fluid choice and oxygen therapy is possible, one seems highly unlikely because the putative mechanisms of each differ. Furthermore, we will stagger group enrollment for this study versus the Oxygen study, starting enrollment in the middle of an Oxygen study 2-week period, so that fluid and oxygen interventions will be fully balanced for those patients whose enrollment overlaps with both studies, as in a factorial-design trial.

Significance

The study we propose will determine whether normal saline or buffered salt solutions are superior for intraoperative vascular volume repletion during major non-cardiac surgery.

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