Major Complications, Mortality, and Resource Utilization After Open Abdominal Surgery

0.9% Saline Compared to Plasma-Lyte

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Objective: To assess the association of 0.9% saline use versus a calcium-free physiologically balanced crystalloid solution with major morbidity and clinical resource use after abdominal surgery.

Background: 0.9% saline, which results in a hyperchloremic acidosis after infusion, is frequently used to replace volume losses after major surgery.

Methods: An observational study using the Premier Perspective Comparative Database was performed to evaluate adult patients undergoing major open abdominal surgery who received either 0.9% saline (30,994 patients) or a balanced crystalloid solution (926 patients) on the day of surgery. The primary outcome was major morbidity and secondary outcomes included minor complications and acidosis-related interventions. Outcomes were evaluated using multivariable logistic regression and propensity scoring models.

Results: For the entire cohort, the in-hospital mortality was 5.6% in the saline group and 2.9% in the balanced group ($P < 0.001$). One or more major complications occurred in 33.7% of the saline group and 23% of the balanced group ($P < 0.001$). In the 3:1 propensity-matched sample, treatment with balanced fluid was associated with fewer complications (odds ratio 0.79; 95% confidence interval 0.66–0.97). Postoperative infection ($P = 0.006$), renal failure requiring dialysis ($P < 0.001$), blood transfusion ($P < 0.001$), electrolyte disturbance ($P = 0.046$), acidosis investigation ($P < 0.001$), and intervention ($P = 0.02$) were all more frequent in patients receiving 0.9% saline.

Conclusions: Among hospitals in the Premier Perspective Database, the use of a calcium-free balanced crystalloid for replacement of fluid losses on the day of major surgery was associated with less postoperative morbidity than 0.9% saline.

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The prescription of crystalloid therapy in medical and surgical care is so common that it is often viewed as routine and delegated to the most junior member of a clinical team.[1] Despite the recognition nearly a century ago[2] that infusion of 0.9% saline (often referred to as "normal saline") may cause hyperchloremic metabolic acidosis, it remains the most commonly used intravenous solution in the world, with more than 200 million liters sold in the United States last year.[3–4] Controversy has arisen recently regarding the potential dangers of prescribing hypotonic solutions to postoperative children,[5–8] but there is a paucity of adult data to inform the decision of which crystalloid solution to use for replacement of intravascular volume losses in perioperative care.

Both preclinical and clinical studies have shown that when 0.9% saline is given as the primary resuscitative fluid in surgery, the result is a predictable hyperchloremic metabolic acidosis.[9–13] Moreover, the acidosis associated with 0.9% saline infusion may also give rise to adverse effects including immune dysfunction,[14] gastrointestinal dysfunction,[15] and decreased renal blood flow.[16–19]

Although solutions containing physiologic levels of chloride and buffer—often called "balanced solutions" (eg, Ringer's acetate, Ringer's lactate, and other multiple electrolyte solutions)—are widely available, they are used less frequently than 0.9% saline.[20,21] Banked blood in the United States is preserved in a citrate-based anticoagulant and is incompatible with calcium containing solutions[22]; however, most balanced solution alternatives to 0.9% saline, such as Ringer's lactate, contain calcium, which should not be infused in the same intravenous line as citrate-preserved blood.[22] Alternative solutions to 0.9% saline that are both physiologically balanced and safe to administer with blood products have not been broadly investigated.

We developed the hypothesis that in comparison to a balanced crystalloid solution, 0.9% saline use in major abdominal surgery would have a detrimental effect on clinical outcomes. To test this hypothesis, we examined the association between crystalloid fluid use in major open abdominal surgery and clinical outcomes (major morbidity and mortality), and physician prescribing behaviors relating to evaluation and treatment of acidosis. Because clinicians commonly use 0.9% saline for reasons related to stored-blood compatibility, we chose to compare 0.9% saline with a stored-blood compatible isotonic balanced crystalloid fluid that does not contain calcium (Plasma-Lyte, Baxter, IL).

METHODS

Study Design

We conducted a retrospective cohort study using data from a large, US automated hospital claims database, the Premier perspective comparative database. The study protocol was approved by the Duke University institutional review board before commencement, and a waiver of the requirement for written informed consent was obtained. The data analysis plan was lodged with the institutional review board before data extraction and included details of the primary (major complications) and secondary (minor complications) endpoints, the stratification plan (emergency and elective surgery), and the propensity score method of risk adjustment. Because we recognized in advance that patients receiving balanced fluids may differ substantially from patients receiving 0.9% saline, to reduce bias and

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confounding we planned a priori to evaluate the outcomes using propensity score adjustment and matching. The costs of the study (ie, access to the data files held by Premier and payment for data analysis services performed by a Premier statistician [M.D.]) were paid by Baxter Healthcare Inc, Deerfield, Illinois.

Data Source

The Premier perspective comparative database is currently the largest available US clinical and health-economic database, covering approximately 600 US acute care hospitals and health care facilities. The database acts as a repository of hospital administrative data that includes approximately one-sixth of all hospitalizations in the United States. Annually, more than 5 million hospital discharges are processed and recorded in the database. Upon receiving data from participating hospitals, Premier undertakes an extensive data validation and correction process that includes more than 95 quality assurance checks. Premier compiles any missing or invalid required data elements and transmits errors to each facility through secure Health Insurance Portability Accountability Act (HIPAA) channels for error corrections, which are uploaded before a final data validation. Data are stored in standard hospital discharge files arranged as a date-stamped log of billed items including procedures, medications, laboratory orders, diagnostic, and therapeutic services at the individual patient level. The analyses were performed using fully de-identified data, in compliance with the 1996 HIPAA regulation.

Study Patients

The study population included all adult (age $\geq$18 years) hospitalized patients who received intravenous crystalloid replacement therapy during an elective or emergency open (not laparoscopic) general surgical operation between January 1, 2005, and December 31, 2009 (full details of the operation types and the *International Classification of Diseases, Ninth Revision* [*ICD-9*] codes describing them are provided in the supplementary material Appendix A available at http://links.lww.com/SLA/A242). To evaluate the impact of the crystalloid type on patients with similar surgical and complication risks, only patients with a potential need for blood transfusion—that is, those undergoing major surgery—were selected for study. However, patients undergoing major abdominal operations for traumatic injuries, as defined by their *ICD-9* admission codes, were excluded.

To clearly define exposure groups, patients were included only if they received *exclusively* 0.9% saline or a calcium-free isotonic balanced crystalloid solution (Plasma-Lyte A or Plasma-Lyte 148) on the day of surgery. The electrolyte content of Plasma-Lyte A and Plasma-Lyte 148 is identical: sodium 140 mEq/L, potassium 5 mEq/L, magnesium 3 mEq/L, choride 98 mEq/L, acetate 27 mEq/L, and gluconate 23 mEq/L. The solutions only differ in pH, where Plasma-Lyte A has a pH of 7.4 and Plasma-Lyte 148 has a pH of 5.5. Because we were interested in studying patients at risk for receiving high volumes of crystalloid and blood transfusion, patients who received calcium-containing crystalloids such as Ringer's lactate were not included. In addition, patients receiving dextrose-based crystalloids or combinations of crystalloid solutions were excluded. Patients were stratified a priori according to the urgency of their surgery (elective or emergency, defined as admission via the emergency department).

Classification of Exposure and Outcome

Patients were assigned to the balanced crystalloid therapy group if they received exclusively balanced crystalloid solution. Patients were assigned to the 0.9% saline group if they received exclusively 0.9% saline on the day of surgery. For both fluids, only doses of 500 mL and 1000 mL were included to differentiate volume replacement from fluid being used as a drug diluent.

The primary outcome was major morbidity defined as a composite of one or more major complications. Secondary outcomes included electrolyte disturbances, physician orders related to acidosis evaluation and management, and rehospitalization within 30 days. Major complications included (1) respiratory failure for more than 24 hours postoperatively, (2) cardiac complications requiring intervention (ie, cardioversion or cardiac catheterization), (3) major gastrointestinal dysfunction (ie, bleeding or perforated ulcer), (4) infectious complications (eg, septicemia, bloodstream infection, deep wound infection, or pneumonia (urinary tract infections were not considered major infectious complications), and (5) acute renal failure. Specific *ICD-9* codes used to define the complications are described in supplementary material Appendix B available at http://links.lww.com/SLA/A242. Minor complications of gastrointestinal dysfunction (nausea, vomiting, and ileus) and electrolyte disturbances such as sodium, potassium, magnesium, and phosphorus disorders were evaluated but because they were considered minor complications were not included in the composite. We also investigated whether receiving 0.9% saline would be associated with changes in physician orders for tests to evaluate, or medications to treat, acidosis or complications arising from acidosis. These included the ordering of additional tests such as arterial blood gases or lactic acid levels, the ordering of buffers, and the provision of more fluids and stored red blood cells.

Statistical Analysis

Baseline Descriptors

Input (predictor/risk/independent) variables included patient demographic data (including age, race, gender, admission type), hospital demographic data (including size, teaching status, urban/rural), and comorbidity data. Univariate comparisons of input data fields were conducted after examination of their distributions. For continuous variables, mean (SD [standard deviation]) values were compared using t tests; for categorical variables, proportions were compared using χ^2 tests. Data were analyzed using SAS/STAT, SAS/Base, SAS/SQL software, Version 9.1 (Cary, NC) of the SAS System for Windows XP Professional and Linux Platform. Modeling procedures used were Proc Reg, Proc Logistic, and Proc Princomp. In all cases, a 2-sided P value of less than 0.05 indicated statistical significance.

Outcome Models

Three outcome models were constructed: ordinary logistic regression, ordinary logistic regression including propensity score (observed probability of receiving each type of fluid) as a model predictor, and ordinary logistic regression on a sample of patients matched by propensity score 3:1, 0.9% saline to balanced crystalloid. Matching was performed using the Mahalanobis metric method with the width of the caliper set at 25% of the SD of the logit of the propensity score. Multivariate analyses were conducted using those demographic and hospital variables exhibiting a univariate difference at a threshold P value of less than 0.1. These were included in the model along with type of crystalloid therapy and a comorbidity score (derived using Elixhauser's algorithm—see later) to predict outcome. In each case, backward inclusion of the relevant predictors was conducted, and the overall performance of each model was determined using Hosmer-Lemeshow statistics and receiver operating characteristic curve methods. Outcome models are reported as percentages, odds ratios (ORs), and C statistic to assess model fit. For the composite outcome of major complications, defined as the presence of one or more major complications, the reported OR represents the ratio of the odds of the occurrence of at least one major complication over the odds of no occurrence of a major complication.

To ensure that complication codes referred to postoperative events rather than preoperative comorbidities, suspected

complications were linked to procedures (such as cardioversion of arrhythmias) or orders (such as antibiotics for infections) *after* the index operation. Complications were included if they occurred on postoperative day 1 or later. For example, an infection was included if it had the proper *ICD-9* code (supplement Appendix B) and an antibiotic order on postoperative day 1 or later during the hospitalization. Because laboratory measures of renal function were not available, we could only reliably determine acute renal failure (defined here as the proper *ICD-9* code) as opposed to acute kidney injury. Acute renal failure was not included as a complication if the patient had a diagnosis code of chronic kidney disease or chronic renal failure (585.x, 404.x). In addition, the occurrence of continuous or intermittent dialysis for at least 1 day during the incident hospitalization was evaluated. Length of stay was calculated only for survivors.

Controlling for Confounding

Observational studies may be limited in estimating treatment effects due to differences in observed or unobserved covariates. To reduce bias from observable covariates, we developed a propensity score that described the probability a patient would receive balanced crystalloid therapy, and included it in 2 of the multivariate outcome models, one as a variable in the regression model and the other as a method to match subjects according to their propensity to receive balanced fluids.[23] Other potential confounding risk factors for morbidity and mortality considered in the analyses included age, gender, geographic region, hospital characteristics, and patient comorbidities. All models included the Elixhauser algorithm[24] to control for differences in observed baseline comorbidity across the 2 treatment groups, as this technique has been validated in other studies using administrative data to generate risk prediction models. The Elixhauser code is available in the public domain and has been widely used for this purpose. The propensity score was calculated on the basis of patient demographics, patient and hospital characteristics, and Elixhauser comorbidities (see Tables 1 and 2 for included characteristics).

RESULTS

The overall study flow with cohort assembly characteristics is shown in Figure 1. Of the nearly half million patients in the database who had a major open abdominal operation, 110,325 received fluids deemed incompatible with citrate preserved blood, leaving 356,806 who received at least one dose of the balanced or unbalanced fluid during hospitalization, of which only 271,189 (58%) received the fluids on the day of surgery. Among the 271,189 patients, receiving either fluid on the day of surgery, 30,994 received only 0.9% saline and 926 patients received only the balanced fluid. Table 1 represents the baseline characteristics of the sample in the unmatched and matched cohorts and Table 2 represents the Elixhauser comorbidities in the unmatched and matched cohorts. For the entire cohort, the patients receiving 0.9% saline were more likely to be minorities, admitted via the emergency department, and have Medicare as the primary payor (despite not being any older), and less likely to have commercial insurance. The balanced fluid group was more likely to be cared for in larger, teaching hospitals and to have commercial insurance. From the Elixhauser comorbidity listing, the patients in the balanced fluid group were only more likely to have metastatic cancer whereas nearly all other comorbidities such as heart failure, diabetes, and renal failure were greater in the 0.9% saline group. In summary, patients receiving 0.9% saline differed from those receiving balanced fluids illustrating the need for propensity scoring to decrease residual bias that may not be accounted for in ordinary logistic regression modeling.

After propensity score matching on a 3:1 basis, the groups were well matched on all comorbidity parameters. Matching on the baseline characteristics was also excellent except for race and primary payor with the proportions of minority race in the match being greater in the balanced fluid group and slightly fewer Medicare but more Medicaid recipients in the balanced fluid group.

Outcomes are presented in Table 3. For all models of the major complication index, the direction of the association (a negative parameter estimate) was in favor of balanced fluid use (see Fig. 2). In addition, in all 3 models, the odds of developing a major infection were significantly lower in the balanced fluid group. The most common major infections were pneumonia and sepsis for both groups. For all 3 mortality models, the direction of the parameter estimate appeared to favor balanced fluid use but only the unadjusted mortality rates differed significantly between patients receiving balanced and unbalanced fluids (2.9% [95% confidence interval (CI) 2.0–4.2] vs 5.6% [95% CI 5.3–5.8]; $P < 0.001$). In addition, multivariate analysis of the emergency general surgery stratum showed the adjusted odds of death in the balanced cohort nearly 50% lower than in the 0.9% saline cohort (OR 0.51; 95% CI 0.28–0.95).

All multivariate models of acute renal failure by *ICD-9* coding demonstrated parameter estimates in the direction supporting balanced fluid use though none were statistically significant. However, the use of dialysis was nearly fivefold greater in the 3:1 matched saline cohort (1.0% [95% CI 0.05–1.8] vs 4.8% [95% CI 4.1–5.7], $P < 0.001$; Table 4). Similarly, for major hemorrhage and respiratory failure, although the multivariate models show parameter estimates consistently in the direction favoring balanced fluid use, there were no statistically significant associations. However, consistent with the renal failure data, although the major hemorrhage and respiratory failure multivariate models were not statistically significant, the resource utilization data (Table 4) show that the group receiving 0.9% saline was more likely to receive a blood transfusion and spend more days on the ventilator. There appears to be no impact of fluid type on either major gastrointestinal or cardiac complications. For the minor complications, the main and propensity-scored multivariate models showed the odds of developing an electrolyte disturbance such as hypo- or hyperkalemia, hypo- or hypernatremia, and disorders of magnesium metabolism as approximately 30% lower in the balanced fluid group (Table 3). However, although the antinausea medication use did not differ between groups and trended toward favoring the balanced fluid, the odds of developing a minor indicate gastrointestinal complication (nausea, vomiting, and ileus) favored the saline group.

Resource utilization data are presented in Table 4. Even after propensity score matching, patients receiving 0.9% saline received more fluid (1976 [SD 1560] mL vs 1658 [SD 1288] mL, $P < 0.001$), more orders for buffer (6.3% [95% CI 5.5–7.3] vs 4.2% [95% CI 3.1–5.7], $P = 0.02$), were more likely to be transfused (11.5% [95% CI 10.3–12.7] vs 1.8% [95% CI 1.2–2.9], $P < 0.001$), and among those patients who were transfused, 0.9% saline patients received more blood ($P = 0.005$). Patients receiving 0.9% saline were also more likely to undergo tests to evaluate acidosis (arterial blood gases 22.3% [95% CI 21.3–24.5] vs 13.7% [95% CI 11.7–16.1] and lactic acid levels 8.0% [95% CI 7.0–9.1] vs 3.3% [95% CI 2.4–4.7], $P < 0.001$). Figure 3 depicts acidosis management in general. The 0.9% saline group was no more likely to be mechanically ventilated but had more days on the ventilator ($P < 0.001$). As discussed earlier, patients in the 0.9% saline group were 4.8 times more likely to receive dialysis ($P < 0.001$). Among patients who survived, the balanced group had a longer length of stay in the hospital (6.4 [SD 4.8] days balanced vs 5.9 [SD 4.4] saline, $P < 0.001$). Both groups had similar 30-day readmission rates.

DISCUSSION

The principal findings of this study of major open abdominal surgery patients are that, compared to physiologically balanced crystalloid solutions, administration of saline was associated with a significantly greater risk of complications and greater utilization of

TABLE 1. Baseline Characteristics of Unmatched and Matched Samples Undergoing Major Abdominal Surgery

	Original Cohort			Matched Cohort		
	Balanced (N = 926)	0.9% Saline (N = 30,994)	*P*	Balanced (N = 926)	0.9% Saline 3:1 Match (N = 2778)	*P*
Age group			0.12			0.99
0–17	1.6%	2.0%		1.6%	1.5%	
18–35	7.0%	9.1%		7.0%	7.1%	
36–50	16.3%	16.3%		16.3%	16.6%	
51–64	28.6%	26.2%		28.6%	28.2%	
65–80	33.4%	31.8%		33.4%	33.0%	
81+	13.1%	14.5%		13.1%	13.6%	
Gender			0.98			0.54
Male	47.2%	47.3%		47.2%	48.3%	
Female	52.8%	52.7%		52.8%	51.7%	
Unknown		0.0%				
Race			<0.001			<0.001
White	69.1%	66.7%		69.1%	71.2%	
Black	6.4%	14.3%		6.4%	5.9%	
Asian/Pacific	6.4%	1.8%		6.4%	4.9%	
Hispanic	12.1%	4.6%		12.1%	8.5%	
Other	6.0%	12.6%		6.0%	9.5%	
Admission source			<0.001			0.16
Non–health care facility	65.9%	40.7%		65.9%	62.9%	
Transferred from another care setting	2.3%	4.9%		2.3%	1.8%	
Emergency department	25.6%	49.3%		25.6%	29.3%	
Other/Unknown	6.3%	5.1%		6.3%	5.9%	
Admission type			<0.001			0.23
Emergency	26.0%	49.6%		26.0%	29.4%	
Urgent	5.9%	15.1%		5.9%	5.8%	
Elective	67.6%	34.7%		67.6%	64.5%	
Other/Unknown	.4%	.7%		.4%	.3%	
Discharge status			<0.001			0.75
Death	2.9%	5.6%		2.9%	3.3%	
Transferred to another care setting	10.8%	16.3%		10.8%	10.5%	
Discharged to home	85.9%	77.8%		85.9%	85.9%	
Other/Unknown	0.4%	0.4%		0.4%	0.3%	
Primary payor			<0.001			0.04
Medicare	42.2%	52.2%		42.2%	47.0%	
Medicaid	9.7%	8.3%		9.7%	7.1%	
Commercial	41.4%	31.2%		41.4%	39.7%	
Self-pay/Indigent	4.1%	5.0%		4.1%	3.6%	
Any other payor	2.6%	3.4%		2.6%	2.5%	
Hospital characteristics	N = 23	N = 433		N = 23	N = 187	
Teaching hospital	52.2%	30.3%	0.03	52.2%	30.4%	0.17
Urban location	87.0%	79.7%	0.39	87.0%	85.6%	0.86
Bed number						
0–99	13.0%	13.6%		13.0%	12.3%	
100–199	8.7%	17.6%		8.7%	19.8%	
200–249	13.0%	21.0%		13.0%	4.8%	
300–499	47.8%	31.6%		47.8%	38.5%	
500+	17.4%	16.2%		17.4%	24.6%	

*$P < 0.05$

resources. Specifically, patients receiving saline had more postoperative infections, renal failure requiring dialysis, blood transfusions, and electrolyte disturbances. Furthermore, physicians caring for these patients ordered more tests (arterial blood gases and lactate levels) and more treatments (buffers, blood products, and dialysis) presumably to investigate and manage observed acid–base abnormalities and their consequences in these patients.

The risk of postoperative infection was significantly greater when saline was used; indeed in the propensity-matched cohort, the OR between balanced fluids and saline was 0.6 (95% CI 0.43–0.85). Although the reason for this effect is unclear, we note that both in vitro and animal data have previously shown that hyperchloremic metabolic acidosis can result in changes in the immune response.[14,25–27] We therefore speculate that significant fluid replacement with 0.9% saline may induce sufficient changes in acid–base balance to affect a patient's immune response. Although our data are unable to explain the reasons why such associations occur, we note that the clinical effects we observe are broadly consistent with prior experimental findings that hyperchloremic acidosis alters cytokine expression in both cultured cells and in intact animals.[26]

An alternative mechanism whereby saline could be associated with increased infection is through a potential effect on renal function. Acute kidney injury (AKI) severe enough to require dialysis occurred at a rate more than 8 times greater in patients treated with

saline compared to those receiving balanced crystalloids. Even in the matched cohort, this degree of AKI was seen in nearly fivefold greater frequency with 0.9% saline. Decreased renal function of this degree is associated with neutrophil dysfunction and decreased bacterial clearance.[28]

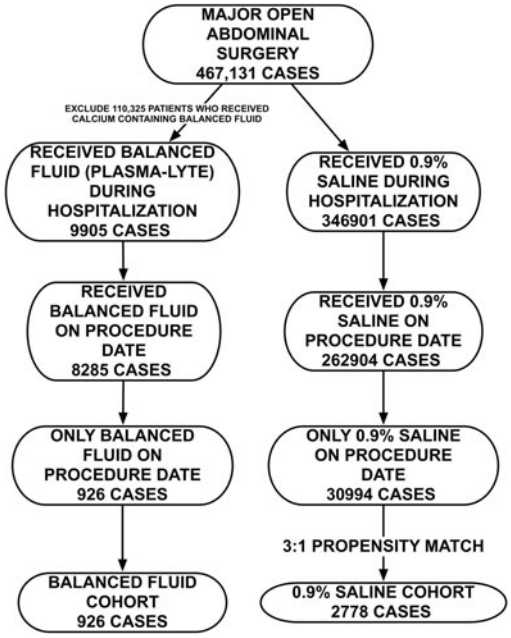

FIGURE 1. Flow of patients through the study.

The reason for the increased use of dialysis is presumed to be secondary to worsening renal function in patients receiving saline. Data from denervated dog kidneys[16] suggest that renal blood flow reduces as the chloride concentration in the perfusate increases. Similar effects in humans receiving saline have not been shown, but studies in healthy volunteers have shown delayed urination with saline when compared to lactated Ringers solution.[15,29] An alternative explanation for the increased use of dialysis seen in this study could be that a similar degree of AKI occurred in patients receiving saline versus balanced fluids, but more severe acid-base and electrolyte abnormalities occurred in patients treated with saline. This explanation is supported in part by the lack of statistical difference in acute renal failure diagnosis (by *ICD-9* code) between the groups, but an increase in electrolyte disorders in the saline group. Thus our results should be seen as suggestive of worsening renal function in the patients treated with saline, but perhaps not as definitive evidence.

The increased occurrence of electrolyte abnormalities seen in the patients treated with 0.9% saline may have been due to primary effects of administering a nonphysiologic electrolyte solution. Alternatively, the acidosis induced by saline may have resulted in electrolyte imbalances because of shifts in ions from the vascular space into cells. Similar results have been reported in other studies wherein hyperkalemia was more common among patients receiving saline than in those receiving a balanced fluid.[30,31]

Whatever the cause of these various complications, they clearly resulted in increased resource utilization. Clinicians were sufficiently concerned that they investigated and/or treated these conditions. Although costs were not considered in our analysis, it seems reasonable

TABLE 2. Elixhauser Comorbidities in unmatched and Matched Samples Undergoing Major Abdominal Surgery

Comorbidity	Balanced (N = 926)	0.9% Saline (N = 30,994)	*P*	Balanced (N = 926)	0.9% Saline 3:1 Match (N = 2778)	*P*
Congestive heart failure	6.4%	11.2%	<0.001	6.4%	5.6%	0.37
Valvular disease	6.4%	5.0%	0.07	6.4%	5.1%	0.16
Pulmonary circulation disease	1.6%	2.0%	0.36	1.6%	1.5%	0.75
Peripheral vascular disease	4.0%	7.4%	<0.001	4.0%	3.8%	0.77
Hypertension	49.1%	51.9%	0.10	49.1%	46.7%	0.19
Paralysis	2.1%	2.0%	0.83	2.1%	2.0%	0.95
Other neurological disorders	4.6%	5.5%	0.25	4.6%	4.0%	0.37
Chronic pulmonary disease	14.3%	17.8%	0.005	14.3%	12.9%	0.27
Diabetes (no chronic complications)	16.5%	21.5%	<0.001	16.5%	14.0%	0.06
Diabetes (chronic complications)	2.5%	5.1%	<0.001	2.5%	2.4%	0.95
Hypothyroidism	9.7%	9.7%	0.94	9.7%	7.8%	0.07
Renal failure	6.9%	16.1%	<0.001	6.9%	5.9%	0.29
Liver disease	5.1%	4.9%	0.83	5.1%	4.1%	0.19
Peptic ulcer disease × bleeding	0.3%	0.1%	0.17	0.3%	0.1%	0.28
AIDS	0.2%	0.2%	0.75	0.2%	0.2%	1.0
Lymphoma	0.4%	0.6%	0.57	0.4%	0.4%	0.88
Metastatic cancer	9.0%	6.2%	<0.001	9.0%	7.4%	0.13
Solid tumor w/o metastasis	3.7%	2.9%	0.19	3.7%	3.0%	0.30
Rheumatoid arthritis/collagen vas	1.0%	2.4%	0.004	1.0%	1.0%	1.0
Coagulopathy	3.9%	6.1%	0.005	3.9%	3.1%	0.22
Obesity	6.9%	8.8%	0.004	6.9%	5.9%	0.27
Weight loss	5.2%	10.1%	<0.001	5.2%	4.8%	0.66
Chronic blood loss anemia	2.5%	3.3%	0.15	2.5%	2.4%	0.85
Deficiency anemias	17.2%	23.1%	<0.001	17.2%	14.5%	0.05
Alcohol abuse	1.9%	3.3%	0.02	1.9%	1.9%	0.89
Drug abuse	0.9%	1.5%	0.12	0.9%	0.9%	1.0
Psychoses	3.1%	2.6%	0.36	3.1%	2.5%	0.29
Depression	8.3%	8.4%	0.91	8.3%	6.2%	0.03

*$P < 0.05$

TABLE 3. Effect of Balanced Fluid use on Complications by model

	Standard Logistic Regression (B = 926, S = 30,994)	Standard Logistic Regression Elective Surgery (B = 626, S = 10,742)	Standard Logistic Regression Emergency Surgery (B = 300, S = 20,252)	Standard Logistic Regression Propensity Score in Model (B = 926, S = 30,994)	Standard Logistic Regression 3:1 Matched Sample (B = 926, S = 2778)
Major complication					
Mortality	B = 27, S = 1726	B = 16, S = 245	B = 11, S = 289*	B = 27, S = 1726	B = 27, S = 93
Parameter estimate	−0.26	0.23	−0.67	−0.29	−0.26
OR (CI)	0.767 (0.515, 1.144)	1.259 (0.737, 2.152)	0.513 (0.277, 0.949)	0.745 (0.501, 1.119)	0.769 (0.484, 1.220)
C statistic	0.77	0.74	0.79	0.77	0.77
Major complication index	B = 213, S = 10,453	B = 105, S = 2255	B = 108, S = 8198	B = 213, S = 10453	B = 213, S = 714*
Parameter estimate	−0.15	−0.08	−0.16	−0.15	−0.23
OR (CI)	0.864 (0.728, 1.026)	0.925 (0.732, 1.168)	0.850 (0.657, 1.099)	0.863 (0.726, 1.026)	0.798 (0.656, 0.970)
C statistic	0.77	0.76	0.74	0.77	0.77
Major infection	B = 51, S = 4149	B = 7, S = 492	B = 44, S = 3657	B = 51, S = 4149	B = 51, S = 229
Parameter estimate	−0.38*	−1.04	−0.12	−0.38*	−0.50*
OR (CI)	0.681 (0.505, 0.981)	0.353 (1.64, 0.760)	0.885 (0.633, 1.236)	0.683 (0.505, 0.922)	0.608 (0.434, 0.851)
C statistic	0.78	0.80	0.72	0.78	0.82
Acute renal failure	B = 5, S = 382	B = 3, S = 100	B = 2, S = 282	B = 5, S = 382	B = 5, S = 23
Parameter estimate	−0.48	−0.22	−0.45	−0.52	−0.80
OR (CI)	0.618 (0.252, 1.516)	0.800 (0.247, 1.461)	0.636 (0.155, 2.602)	0.593 (0.241, 1.461)	0.451 (0.160, 1.273)
C statistic	0.83	0.86	0.80	0.83	0.86
Major hemorrhage	B = 18, S = 719	B = 16, S = 289	B = 2, S = 430	B = 18, S = 719	B = 18, S = 76
Parameter estimate	−0.26	−0.04	−1.11	−0.29	−0.41
OR (CI)	0.770 (0.477, 1.242)	0.956 (0.571, 1.601)	0.329 (0.081, 1.331)	0.749 (0.462, 1.214)	0.662 (0.391, 1.121)
C statistic	0.66	0.67	0.65	0.66	0.68
Respiratory failure	B = 40, S = 1990	B = 23, S = 521	B = 17, S = 1469	B = 40, S = 1990	B = 40, S = 134
Parameter estimate	−0.17	−0.14	−0.18	−0.23	−0.32
OR (CI)	0.841 (0.605, 1.17)	0.867 (0.556, 1.350)	0.831 (0.502, 1.377)	0.798 (0.572, 1.113)	0.732 (0.490, 1.067)
C statistic	0.75	0.78	0.73	0.75	0.76
Major gastrointestinal	B = 51, S = 2744	B = 22, S = 409	B = 29, S = 2355	B = 51, S = 2744	B = 52, S = 176
Parameter estimate	−0.12	0.09	−0.21	−0.13	−0.20
OR (CI)	0.884 (0.659, 1.187)	1.098 (0.698, 1.728)	0.809 (0.547, 1.197)	0.882 (0.656, 1.187)	0.822 (0.588, 1.149)
C statistic	0.72	0.73	0.66	0.72	0.74
Cardiac	B = 99, S = 4050	B = 51, S = 1018	B = 48, S = 3032	B = 99, S = 4050	B = 99, S = 286
Parameter estimate	0.02	−0.07	0.07	0.01	0.00
OR (CI)	1.017 (0.806, 1.284)	0.928 (0.676, 1.274)	1.074 (0.760, 1.519)	1.007 (0.796, 1.274)	1.00 (0.769, 1.305)
C statistic	0.81	0.81	0.80	0.81	0.81
Minor complication					
Electrolyte disturbances	B = 82, S = 4749	B = 40, S = 1010	B = 42, S = 3739	B = 82, S = 4749	B = 82, S = 297
Parameter estimate	−0.28*	−0.30	−0.25	−0.34*	−0.28*
OR (CI)	0.755 (0.595, 0.958)	0.779 (0.555, 1.094)	0.742 (0.529, 1.041)	0.712 (0.560, 0.906)	0.753 (0.571, 0.994)
C statistic	0.73	0.75	0.70	0.73	0.76
Minor gastrointestinal	B = 140, S = 3564	B = 101, S = 1358	B = 39, S = 2206	B = 140, S = 3564	B = 140, S = 309
Parameter estimate	0.32	0.35	0.21	0.30	0.37
OR (CI)	1.38 (1.142, 1.661)*	1.42 (1.131, 1.776)*	1.24 (0.879, 1.747)	1.35 (1.115, 1.632)*	1.45 (1.165, 1.79)*
C statistic	0.62	0.63	0.61	0.62	0.59
Readmission (30d)	B = 249, S = 9203	B = 161, S = 2950	B = 88, S = 6253	B = 249, S = 9203	B = 249, S = 708
Parameter estimate	−0.02	−0.09	−0.01	0.06	0.05
OR (CI)	0.975 (0.804, 1.133)	0.918 (0.761, 1.108)	0.988 (0.767, 1273)	1.057 (0.909, 1.23)	1.050 (0.885, 1.246)
C statistic	0.59	0.59	0.60	0.59	0.60

*$P < 0.05$

that this increase in resource utilization would have resulted in greater costs for the patients treated with saline. The only resource use that was greater in the balanced group was length of hospital stay, the clinical significance of which remains unclear.

A related finding was the increased rate of transfusions in patients treated with saline and the greater crystalloid volumes administered to these patients. In large quantities, saline is known to result in coagulation abnormalities,[31–33] which may have been avoided in patients receiving balanced fluids. However, the volume difference (300–400 mL) would suggest that this is not the cause. Isotonic crystalloids theoretically have identical distribution characteristics and there is no reason to suspect that balanced fluids would result in better resuscitation efficacy. Although we do not have physiologic data, lower blood pressure could have led to greater use of fluids. In animals, hyperchloremic acidosis results in lower blood pressure possibly due to the induction of nitric oxide.[25] In severe shock, it could be postulated that extremes in acidosis decreased cardiac output sufficiently to decrease blood pressure.

This phenomenon of less balanced fluid being required has also been seen in a rat model of hemorrhagic shock in which approximately one-third less balanced fluid was needed (compared with saline) to restore blood pressure after hemorrhage (Pr Can

Ince, Academic Medical Center, University of Amsterdam, personal communication). In many disease states, acidosis is associated with inadequate tissue perfusion and increased morbidity, and clinicians may feel obliged to address the acidosis. Hence another possible explanation for the increased 0.9% saline volume is that clinicians may have misinterpreted saline-induced acidosis as underperfusion and administered further fluid in an attempt to treat this condition.

It should be noted that the clinical implications of at least some of the adverse effects found to occur at greater frequency with saline in this study are uncertain. The only model demonstrating a mortality benefit was in the unmatched sample of emergency surgical patients. In that analysis balanced fluid administration conferred a nearly 50% reduction in mortality. However, overall mortality was not significantly different between groups within the matched cohort. This is not surprising. Overall mortality for this cohort was 3%. To detect even a very large effect such as a 20% relative risk reduction, we would have needed more than 22,000 patients. However, increased use of fluids, along with greater incidence of renal and acid–base abnormalities may have resulted in more time on mechanical ventilation. Patients treated with saline required 3.2 days on mechanical ventilation compared to 2.5 days for patients treated with balanced crystalloids ($P < 0.001$). However, this difference did not translate into shorter hospital stays. In fact, hospital duration was actually 0.5 days greater with balanced fluids, a finding we are unable to explain.

Our study has some important limitations that require careful interpretation. First, as shown in Figure 1, of the 467,131 patients undergoing major abdominal surgery, only 271,189 (58%) received blood compatible crystalloids on the day of surgery. Of these, a minority (12%) of patients received purely saline or purely balanced fluids; the rest received a mixture of fluids. To examine the "pure" effect of balanced versus unbalanced fluid use, we are examining only the extremes and thus our results likely represent a worse case scenario. However, this was the intent of our study. By maximizing differences between the groups, our analysis was extremely sensitive to differences in clinical outcomes. Nevertheless, this small cohort did

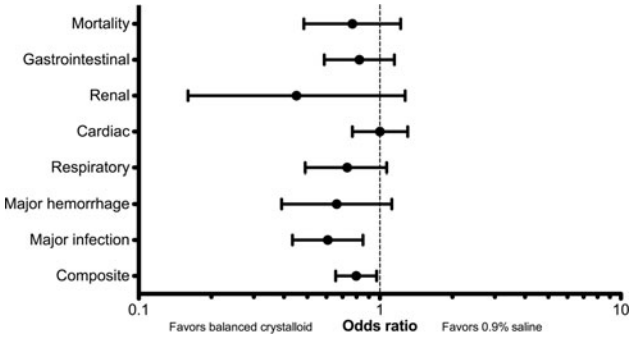

FIGURE 2. Odds ratios and 95% confidence intervals for prespecified clinical outcomes.

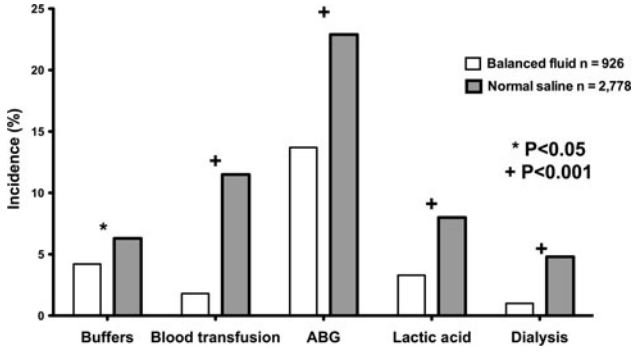

FIGURE 3. Interventions related to metaboloic acidosis diagnosis and management.

TABLE 4. Impact of Balanced Fluid Use on Resource Utilization

	Original Cohort			Matched Cohort		
	Balanced (N = 926)	0.9% Saline (N = 30994)	*P*	Balanced (N = 926)	0.9% Saline 3:1 Match (N = 2778)	*P*
Medication						
Albumin	10.0%	11.1%	0.30	10.0%	9.3%	0.52
Antinausea medication	0.5%	1.3%	0.03	0.5%	1.2%	0.10
Buffers	4.2%	9.0%	<0.001	4.2%*	6.3%*	0.02
Diuretics	25.7%	29.1%	0.03	25.7%	22.8%	0.07
Crystalloid used mean mL (SD)	1658 (1288)	2003 (1531)	<0.001	1658 (1288)*	1976 (1560)*	<0.001
Blood transfusions						
Yes	1.8%	13.3%	<0.001	1.8%*	11.5%*	<0.001
Median units if transfused	2.69	2.88	0.01	2.69*	2.92*	0.005
Extra tests						
Arterial blood gas	13.7%	21.3%	<0.001	13.7%*	22.9%*	<0.001
Lactic acid level	3.3%	9.8%	<0.001	3.3%*	8.0%*	<0.001
Blood culture	16.4%	21.3%	<0.001	16.4%	16.1%	0.80
CT scan abdomen	15.2%	21.1%	<0.001	15.2%	15.5%	0.85
CT scan chest	3.8%	5.4%	0.03	3.8%	3.6%	0.84
CT scan brain	2.7%	4.7%	0.005	2.7%	3.5%	0.26
LOS days, mean (SD)	6.4 (4.8)	6.9 (5.0)	<0.001	6.4 (4.8)*	5.9 (4.4)*	<0.001
Ventilator usage	10.9%	15.9%	<0.001	10.9%	10.9%	0.98
Ventilator days, mean (SD)	2.5 (2.5)	3.3 (3.5)	<0.001	2.5 (2.5)*	3.0 (3.2)*	<0.001
Readmission within 30 days	26.9%	29.7%	0.07	26.9%	25.5%	0.39
Additional procedures						
Dialysis	1.0%	8.3%	<0.001	1.0%*	4.8%*	<0.001

not look particularly different from the overall population of 467,131 whose age (30.7% aged 65–80 years), race 67.1% white), sex (46.5% male), payor (45.2% Medicare) distributions, and overall mortality (3.6%) were similar to the final study cohort.

Second, patients receiving only balanced or unbalanced fluids were clearly different from each other. As shown in Table 2, patients in the 0.9% saline group were more likely to have undergone emergency surgery, have been admitted through the emergency department, and have had Medicare insurance despite being slightly younger. We controlled for these differences using a variety of modeling techniques. Although our findings are consistent across models without changes in direction of the effect and only small changes in magnitude, the balanced sample was relatively small. Propensity scoring is not a perfect solution to control for group differences but is perhaps the most robust method available to reduce residual bias. However, propensity scoring is limited by calculating the probability of receiving the treatment based on observed and measured variables. Hence, although superior to traditional covariance analysis methods[23] used to decrease bias in observational data, it does not account for unobserved covariates that may be relevant but not present in the dataset but assumes that the probability is based solely on the covariate score.

Correcting for observed and unobserved bias in observational studies is often attempted using statistical techniques such as propensity scoring for the former and instrumental variable analysis for the latter. These are not perfect, but observational studies are not definitive and thus interpretation of their results requires an appreciation of the clinical context in which they are placed. Randomized clinical trials can rarely be generalized to mainstream clinical practice (which in emergency surgery often includes the elderly and infirm) and thus observational studies that include as many patients from mainstream practice are valuable as descriptors of what actually goes on in hospitals. The large sample sizes found in observational studies increase the confidence with which we may inform our clinical decision making, but with them come results that may be statistically significantly different but clinically unimportant. Thus our data should be interpreted in the context of the broader intravenous fluid literature.

In conclusion, our analysis of hospital administrative data for patients undergoing major open abdominal surgery, involving more than 30,000 saline recipients in comparison with nearly 1000 balanced crystalloid recipients supports the hypothesis that there is an increased risk of major morbidity and resource utilization among recipients of 0.9% saline. Whether the increased risk is due to hyperchloremic acidosis alone or to other effects of saline administration is unclear but it does not appear to be due to chance or to patient or hospital characteristics. Perhaps the most concerning findings were the dramatic differences in postoperative infection and renal dysfunction, both suggested previously by in vitro and animal studies. Further research is needed to determine if these risks are extended to patients receiving saline along with balanced fluids and to better understand the mechanisms underlying these risks.

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