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TITLE PAGE

Title:

Volume of Packed Red Blood Cells and Fresh Frozen Plasma is Associated with Intraoperative Hypocalcemia during Large Volume Intraoperative Transfusion

Running Title: Hypocalcemia following Massive Intraoperative Transfusion

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ABSTRACT (250 out of 250 words)

Background: Severe hypocalcemia is associated with increased transfusion in the trauma population. Furthermore, trauma patients developing severe hypocalcemia have higher mortality and coagulopathy. Electrolyte abnormalities associated with massive transfusion have been less studied in the surgical population. Here, we tested the primary hypothesis that volume of packed red blood cells and volume fresh frozen plasma transfused intraoperatively is associated with lower nadir ionized calcium in the surgical population receiving massive resuscitation.

Methods: We performed a retrospective observational study at an academic quaternary care center to characterize hypocalcemia following large volume (4 or more units packed red blood cells) intraoperative transfusion. We used multivariable linear regression to assess if volume of transfusion with packed red blood cells and fresh frozen plasma were independently associated with a lower ionized calcium. We then used multivariable logistic regressions to assess the association between ionized calcium and transfusion with: (i) mortality, (ii) acute kidney injury, and (iii) postoperative coagulopathy.

Results: Hypocalcemia following large volume resuscitation in the operating room is a very frequent occurrence (70% of cases). After controlling for demographic variables and intraoperative variables, the volume transfused intraoperative was independently associated with hypocalcemia on multivariable linear regression. Hypocalcemia, intraoperative transfusion of packed red blood cells, and intraoperative transfusion of fresh frozen plasma, were not shown to be associated with clinical outcomes.

Conclusions: Hypocalcemia was associated with increased transfusion volume in this single center study. Unlike the trauma population, hypocalcemia was not associated with increased mortality during surgical care. Our findings suggest that despite improved practice patterns of calcium supplementation, intraoperative hypocalcemia occurs with relatively high frequency following large volume intraoperative transfusion.

Key Words: massive transfusion, perioperative medicine, hypocalcemia, calcium repletion, intraoperative transfusion.

1. Introduction:

Massive transfusion is essential in the treatment of hypovolemic shock, but is associated with multiple infectious, immunologic, and physiologic complications.[1] Because blood products contain citrate, a calcium binder, to minimize coagulation during storage, massive transfusion can lead to systemic citrate toxicity with associated electrolyte abnormalities - hypocalcemia and hypomagnesemia. Calcium in the ionized form is required for coagulation of blood and muscular contraction. Citrate-associated hypocalcemia can cause reduced vascular tone and myocardial contractility leading to hypotension and arrhythmias including prolongation of the QT interval and ventricular fibrillation.[1–3] Furthermore, severe hypocalcemia has been linked with increased mortality in critically ill patients and an increased incidence of adverse cardiac events.[4,5]

The incidence and associated risk factors for hypocalcemia following massive transfusion were recently evaluated in trauma patients.[6] In this population, severe hypocalcemia was associated with increased transfusion of packed red blood cells and fresh frozen plasma. Additionally, patients developing severe hypocalcemia had higher mortality and higher activated partial thromboplastin time (PTT) than those who did not experience hypocalcemia. Electrolyte and metabolic abnormalities associated with massive transfusion have been less extensively studied in the surgical population, as compared to the trauma population. An earlier study of massive transfusion in elective surgical patients demonstrated that despite no calcium supplementation, patients developed only transient hypocalcemia, without postoperative hemodynamic instability or metabolic acidosis.[7] Differences in clinical significance between the trauma and perioperative populations are hypothesized to result from alterations in citrate clearance

secondary to hypotension, acidosis, and hypothermia in the trauma cohort.[6] Recent studies on intraoperative and perioperative massive resuscitation have been limited to specific surgeries, such as abdominal aortic aneurysm,[8] placenta accreta,[9] or liver transplantation,[10] which may not be widely generalizable. The largest study in non-cardiac surgery patients found that transfusion with 5 or more units of red blood cells was associated with increased 30-day mortality and greater rate of postoperative complications, however, this study did not specifically characterize the incidence and risk factors for abnormalities, like hypocalcemia, in the massive transfusion population.[11]

Studies in the perioperative population are limited to non-generalizable surgical sub-populations[8–10] or are not reflective of current clinical practice.[7] Furthermore, trauma may precipitate altered citrate metabolism, which limits generalizability between trauma and surgical populations.[6,12] Therefore, a comprehensive characterization of hypocalcemia following massive transfusion in the perioperative period and the associated clinical consequences is needed. We thus tested the primary hypothesis that volume of packed red blood cells and volume of fresh frozen plasma transfused are associated with nadir ionized calcium in the surgical population receiving large volume (4 or more units of packed red blood cells) resuscitation. Secondarily, we tested whether nadir ionized calcium is associated with postoperative mortality, acute kidney injury, or coagulopathy.

2. Material and Methods

2.1 Study Design

For this retrospective observational study performed at our academic quaternary care center, we obtained Institutional Review Board (HUM00052066) approval. This article was prepared in accordance with the standards set forth by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[13] Study methods including data collection, outcomes, and statistical analyses were established prospectively and presented at an institutional peer-review committee on March 21, 2018 prior to data access.[14]

2.2 Data Collection

Study data were collected via combined queries of the electronic perioperative anesthesia database (Centricity; General Electric Healthcare, Waukesha, WI) and the hospital electronic health record (Epic, Verona, WI).[15,16] Methods for data input, validation, storage, and extraction within the MPOG consortium have been described elsewhere[17] and utilized in previous studies. Quality assurance was maintained through a standardized set of data diagnostics with limited manual review by clinicians to assess and attest to the accuracy of data extraction and source data.

2.3 Study Population

Inclusion criteria for the study were adult patients (≥18 years) who underwent a surgical procedure involving intraoperative transfusion with at least 4 units of packed

red blood cells. We studied cases between January 1, 2008 and August 1, 2018. We excluded cardiac surgeries, liver transplantations, other cases requiring preoperative or intraoperative cardiovascular support (cardiopulmonary bypass, extracorporeal membrane oxygenation, ventricular assist devices, or intra-aortic balloon pump), and *American Society of Anesthesiologists* (ASA) physical classification 6.

2.4 Primary Outcome

The primary outcome of this analysis was nadir (lowest value during the operation) ionized calcium (mmol/L) occurring *after* transfusion of the *first* unit of packed red blood cells and prior to completion of the procedure.

2.5 Secondary Outcomes

Secondary outcomes included: (i) 30-day postoperative all cause mortality, (ii) postoperative acute kidney injury (AKI), and (iii) postoperative coagulopathy. AKI was defined according to the *Kidney Disease - Improving Global Outcomes* (KDIGO) definition[18] (specifically an increase in serum creatinine by $\geq$ 0.3 mg/dL within 48 hours of anesthesia end time, or a $\geq$ 50% increase within seven postoperative calendar days. Coagulopathy was defined by an abnormal PT/INR or PTT within 24 hours of anesthesia completion.

2.6 Exposure Variables

The exposure variables tested were volume of packed red blood cells and volume of fresh frozen plasma transfused. At our institution, packed red blood cells and fresh frozen plasma are typically documented in unit increments, which typically are 350 mL for packed red blood cells and 250 mL for fresh frozen plasma. In cases where the clinical provider documented transfusion in mL, instead of units, the transfusion was converted to units.

2.7 Covariables

Covariables were divided into preoperative and intraoperative categories. Preoperative variables were those defined prior to induction of anesthesia and remained unchanged throughout the course of the procedure. Categories of preoperative variables included: (i) demographic (age, sex, race, height, weight, admission type, ASA classification, and emergency surgery),[19] (ii) social history, (iii) comorbidities,[16] (iv) preoperative medications, and (v) baseline laboratory results. Dynamic intraoperative variables were also defined based upon the anesthetic and surgical record and included: (i) procedural details (case duration, general anesthetic), (ii) fluid resuscitation and transfusion, (iii) vasopressor/inotrope requirement, and (iv) calcium repletion. To ensure the predictive utility of our model, all variables were censored at the time point corresponding to our primary outcome: *nadir ionized calcium*. For example, *case duration* does not reflect overall case duration, but is the duration of time from Anesthesia start until time corresponding with nadir ionized calcium, nor does volume transfused reflect the whole case but only the amount transfused before nadir ionized

calcium. The full list of preoperative and intraoperative variables collected can be seen in Supplementary Table 1.

2.8 Statistical Analyses

Perioperative characteristics were summarized using means and standard deviations for normally distributed continuous covariates, medians and interquartile range for non-normally distributed continuous variables, and counts and percentages for categorical covariates. Statistical analysis was performed in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).[20] We used multivariable regression models to determine associations between our exposure variables (transfusion of packed red blood cells and transfusion of fresh frozen plasma) and our primary outcome, nadir ionized calcium. To analyze this outcome, we performed a multivariable linear regression with variable selection by least absolute shrinkage and selection operator (LASSO) to identify which preoperative and intraoperative factors were independently associated. As previously described, we used least absolute shrinkage and selection operator using the glmnet package (Palo Alto, CA; http://www.jstatsoft.org/v33/i01/) in R to select variables for inclusion in our final models.[16,21] Next we assessed independent association between our exposure variables (transfusion of packed red blood cells and transfusion of fresh frozen plasma) and each of our secondary, clinical outcomes using multivariable logistic regressions with variable selection by LASSO. Our primary outcome was also included as a covariable in each of these logistic regressions.

2.9 Power Analysis

Preliminary power analysis was calculated based upon a mean of 10.07 units of PRBC in the severe hypocalcemia group, a mean of 6.35 units of PRBC in the group without severe hypocalcemia, and a common standard deviation of 5.96. These numbers selected were based upon descriptive statistics obtained as part of an unpublished departmental quality improvement initiative. While the inclusion criteria for the study was transfusion with at least 4 units of packed red blood cells, we expected that most patients included would actually receive more than 4-units. In order to have 90% power to detect a difference between the two groups using a 2-sided t-test at an 0.05 significance level, 55 patients were needed per group. The power analysis was conducted using PASS version 20.0.2.

3 Results

A total of 1614 procedures met our inclusion criteria. The most common surgeries were: abdominal (n=272, 16.9%), vascular/plastics (n=229, 14.2%), neurosurgery (n=227, 14.1%), and hepatobiliary/transplant (kidney, pancreas) (n=198, 12.3%). Patients had a mean age of 56 $\pm$ 17 years, and mean BMI of 28.3 $\pm$ 7.3 kg/m^2. Fifty-nine percent (n=959) were male and the mean ASA Physical Status Classification system was 3 $\pm$ 1. Other notable *preoperative covariates* include: (i) 32.2% (N=519) of patients had a history of coagulopathy, (ii) 35.2% (n=568) cardiac arrhythmia, and (iii) 16.6% (n=268) unintended weight loss. At the time nadir ionized calcium occurred, a median 4 (interquartile range = 2- 5) units of packed red blood cells and median 1 (0 - 3) fresh frozen plasma units had been transfused. *Intraoperatively*, nadir calcium occured 4.5 $\pm$ 3.1 hours into the case. At the time of nadir calcium, patients had been replete with 12.9 mEq (5.5, 23.5) of calcium. Twenty-three percent of patients received epinephrine, 20% received vasopressin, and 14% received norepinephrine. Patients spent 12 $\pm$ 21 minutes with a mean arterial pressure (MAP) less than 55 mmHg. A full description of our cohort can be found in Table 1.

3.1 Primary Outcome: Nadir Ionized Calcium

The mean nadir ionized calcium was 0.92 +/- 0.18 mmol/L. Most patients (n=1099, 70%) developed intraoperative hypocalcemia (ionized calcium $\leq$ 1.0 mmol/L). Twenty-two percent (n=378) demonstrated severe hypocalcemia (ionized calcium $\leq$ 0.80 mmol/L). The distribution of severity of hypocalcemia can be visualized in

Supplementary Figure 1. Using multivariable linear regression to adjust for other factors that may be associated with calcium levels (eg, patient age, baseline laboratory values, medical comorbidities, and intraoperative details), we found that transfusion of each additional unit of packed red blood cells was independently associated with only a slight decrease (-0.013 mmol/L, 95% CI, -0.0218 to -0.0048; *P* = 0.002) in nadir calcium and each additional unit of fresh frozen plasma was similarly associated with a lower ionized calcium (-0.012 mmol/L; 95% CI, -0.0202 to -0.0029; *P* = 0.009). History of coagulopathy and unintended weight loss were also associated with higher ionized calcium. Cases involving larger resuscitation with crystalloid, more calcium repletion, and larger vasopressin receipt were associated with higher ionized calcium. Full details of the multivariable linear regression can be found in Table 2.

3.2 Secondary Outcome: 30-Day Mortality

Patients receiving at least 4-units of packed red blood cells intraoperatively had a 30-day mortality of 13% (n=206). The mean ionized calcium in the group with no in-hospital mortality was 0.93 $\pm$ 0.17 and was 0.90 $\pm$ 0.25 in the mortality group (*P* = 0.205). Nadir ionized calcium was not associated with 30-day mortality (adjusted odds ratio (aOR) = 0.787; 95% CI, 0.258 to 2.398; *P* = 0.674). Emergent surgery (aOR = 1.946; 95% CI, 1.196 to 3.166; *P* = 0.007), history of peripheral vascular disorders (aOR = 2.137; 95% CI, 1.360 to 3.357; *P* = 0.001), history of coagulopathy (aOR = 1.652; 95% CI, 1.050 to 2.599; *P* = 0.030), and transfusion of platelets (aOR = 1.189; 95% CI, 1.063 to 1.330; *P* = 0.002) were all associated with *higher* 30-day mortality on logistic

regression, while amount of RBC or FFP units transfused had no association with mortality. Full details of the multivariable logistic regression can be found in Table 3.

3.3 Secondary Outcome: Postoperative Acute Kidney Injury (AKI)

AKI occurred following 24% (n=382) procedures involving large volume resuscitation. The mean ionized calcium in the group that did not develop postoperative AKI was 0.92 +/- 0.17 compared to 0.93 +/- 0.19 in the group that did develop an AKI. Nadir ionized calcium was not associated with postoperative AKI (aOR = 0.733; 95% CI, 0.286 to 1.877; *P* = 0.518), so could not serve as an intermediate variable for mediation analysis. Furthermore, none of our transfusion exposure variables were associated with postoperative AKI. Age (aOR = 1.012; 95% CI, 1.001 to 1.023; *P* = 0.028), weight (aOR = 1.011; 95% CI, 1.004 to 1.018; *P* = 0.003), history of fluid/electrolyte disorders (aOR = 1.836; 95% CI, 1.324 to 2.545; *P* < 0.001) were associated with higher incidence of postoperative AKI. Administration of norepinephrine (aOR = 1.004; 95% CI, 1.000 to 1.007; *P* = 0.027) and phenylephrine (aOR = 1.009; 95% CI, 1.011 to 1.017 to 1.018; *P* = 0.018) were also associated with higher rates of postoperative AKI. Full details of the multivariable logistic regression can be found in Table 3.

3.4 Secondary Outcome: Postoperative Coagulopathy

Postoperative coagulopathy occurred following 32% (n=519) procedures involving large volume resuscitation. The mean ionized calcium in the group that did not develop postoperative coagulopathy was 0.93 +/- 0.18 and 0.91 +/- 0.18 in the

group that did develop coagulopathy. Nadir ionized calcium was not associated with postoperative coagulopathy (aOR = 0.507; 95% CI, 0.218 to 0.180; *P* = 0.115), so could not serve as an intermediate variable for mediation analysis. Furthermore, none of our transfusion exposure variables were associated with postoperative coagulopathy. Increasing weight (aOR = 0.986; 95% CI, 0.979 to 0.992; *P* < 0.001), increasing preoperative serum albumin (aOR = 0.672; 95% CI, 0.560 to 0.809; *P* < 0.001), neurosurgical (aOR = 0.401; 95% CI, 0.257 to 0.623; *P* < 0.001) and orthopedic (aOR = 0.620; 95% CI, 0.387 to 0.992; *P* = 0.046) procedures were associated with lower rates of coagulopathy. Transplant surgeries (aOR = 2.305; 95% CI, 1.342 to 3.959; *P* = 0.003), history of renal failure (aOR = 1.542; 95% CI, 1.082 to 2.199; *P* = 0.017), history of liver disease (aOR = 1.692; 95% CI, 1.145 to 2.500; *P* = 0.008), and phenylephrine administration before nadir (250 mcg doses) (aOR = 1.009; 95% CI, 1.002 to 1.016; *P* = 0.011) were associated with *higher* rates of postoperative coagulopathy. Colloid resuscitation (Liters) (aOR = 1.856; 95% CI, 1.471 to 2.340; *P* < 0.001) and minutes with mean arterial pressure (MAP) < 55 mmHg (aOR = 1.008; 95% CI, 1.002 to 1.014; *P* = 0.007) were also associated with increased rates of coagulopathy. Full details of the multivariable logistic regression can be found in Table 3.

3.5 Calcium Repletion

We also determined the amount of elemental calcium (in mEq) per unit of packed red blood cells or fresh frozen plasma transfused in the cohort never developing hypocalcemia compared with the cohort developing severe hypocalcemia (defined as nadir ionized calcium $\leq$ 0.80 mmol/L). We found 4.01 $\pm$ 2.76 mEq of calcium were administered per unit of citrate containing blood products in the group not developing

hypocalcemia compared to 2.90 ± 2.32 mEq per unit of citrate containing blood products in the group developing severe hypocalcemia. We then assessed repletion strategy. The majority of providers repleted entirely with calcium gluconate (n=945, 59%). Fourteen percent (n=222) repleted exclusively with calcium chloride, 23% (n=378) adopted a mixed repletion, and 4% (n=69) had no intraoperative calcium repletion. Patients repleted with calcium chloride had higher nadir ionized calcium than those replete entirely with calcium gluconate (0.94 ± 0.22 compared to 0.92 + 0.16, $P <$ 0.001), on univariate analysis; however, repletion strategy was not selected in the LASSO multivariate models. Ionized calcium had normalized (defined as ≥ 1.0 mmol/L) at case completion in 73 percent of cases and the mean calcium at case completion was 0.95 ± 0.18 mmol/L.

4 Discussion

We found the volume of packed red cells and fresh frozen plasma are independently associated with intraoperative hypocalcemia during large volume transfusion. We did not detect an association between intraoperative hypocalcemia or intraoperative transfusion and postoperative clinical outcomes of 30-day mortality, acute kidney injury, or coagulopathy.

4.1 Concordance with previous studies

Our primary findings that volume of blood products are associated with hypocalcemia agree with a smaller, retrospective study of massive resuscitation in the trauma population.[6] Unlike the trauma population, we could not demonstrate any association between hypocalcemia and mortality or coagulopathy. This difference could be caused by multiple mechanisms, including differences in baseline health between populations, a more controlled environment in the operating room, and improved calcium repletion processes. While differing from the trauma population, the lack of association between hypocalcemia and clinical outcomes agrees with previous reports from the perioperative, non-trauma population.[7] Additionally, a patient's hepatic and renal function may decrease the metabolism of citrate, putting these patients at higher risk of hypocalcemia following massive transfusion. Pre-existing liver disease and renal failure based upon prior *International Classification of Diseases* (ICD) diagnoses,[22] as well as, preoperative serum creatinine were included in our model (Supplementary Table 1), but were ultimately not selected for inclusion within the final regression based upon the LASSO selection.

Our research suggests that despite improvements in the administration of blood products, specifically when compared to a prior study of intraoperative transfusion where calcium repletion was not performed as standard practice;[7] hypocalcemia still occurs with high frequency following large volume transfusion in the operating room. Specifically, we noted severe hypocalcemia (defined as nadir ionized calcium $\leq$ 0.80 mmol/L) occurred in 22% of cases and mild hypocalcemia (defined as nadir ionized calcium $\leq$ 1.00 mmol/L) occurred in 70% of cases. Our inability to demonstrate an association between intraoperative hypocalcemia and meaningful postoperative outcomes is hypothesis generating. Potential reasons may be (i) more frequent monitoring and aggressive resuscitation in the operating room, compared to the emergency department or the intensive care unit (ii) differences in etiology of bleeding between surgery versus trauma, and (iii) more rapid, transient control of surgical bleeding. In fact, ionized calcium had normalized by case completion in 73 percent of cases and the mean calcium at case completion was 0.95 + 0.18.

Recommendations on the rate of calcium repletion in massive transfusion vary greatly and range from 2.28 - 4.56 mEq of calcium gluconate or 1.36 - 3.4 mEq of calcium chloride per unit of packed red blood cells.[23,24] Our results showed 4.01 $\pm$ 2.76 mEq of calcium were administered per unit of citrate containing blood products in the group not developing hypocalcemia compared to 2.90 $\pm$ 2.32 mEq per unit of citrate containing blood products in the group developing hypocalcemia. This suggests that perhaps clinicians should replete towards the upper limit of recommended, as the patients in the severe hypocalcemia group received a mean dose of calcium that was still within the recommended range. As calcium chloride contains more elemental

calcium and has greater bioavailability than calcium gluconate (13.6 mEq per 1000 mg of chloride compared to 4.56 mEq of gluconate), calcium chloride provides more rapid correction of hypocalcemia, however, the greater toxicity to blood vessels makes it less desirable for prolonged administration.[5,25] Patients repleted with calcium chloride had higher nadir ionized calcium than those replete entirely with calcium gluconate (0.94 $\pm$ 0.22 compared to 0.92 + 0.16, $P < 0.001$) on univariate analysis, however, since this was not demonstrated on multivariable modeling, additional research is necessary on optimal repletion strategy in different surgical populations.

4.2 Cohort Definition

The classic definition for *massive transfusion*, $\geq$10 units packed red blood cells in a 24-hour period, approximates total blood for an average adult patient.[26,27] Because of the potential for drastic changes in blood volume over a much shorter duration, this classic definition is not always generalizable to the surgical and trauma populations.[27] Newer metrics that account for both rate and timing have, therefore, been proposed.[26] Our inclusion criteria: transfusion with $\geq$ 4 units of packed red blood cells intraoperatively was selected to capture the largest cohort for analysis. Because this is notably different from the definition used in the trauma population: $\geq$ 3 units of packed red blood cells over a single hour,[12] we distinguish our population as a *large volume* intraoperative transfusion (instead of *massive* transfusion).

4.3 Strengths and Limitations of Study Methodology

Our study has multiple limitations. As a single-center effort, our results may not be generalizable to other institutions or populations. Because the study was done

retrospectively, significant covariates may be associated, but we cannot speculate a causal relationship with our outcomes - limiting the influence on clinical practice. A notable strength of our study is that we account for the confounding effect of calcium administration through the intraoperative period (showing that every 10 mEq of calcium repletion increases nadir ionized calcium by 0.015 mmol/L (95% CI, 0.001 to 0.028; P = 0.037). Future studies will attempt to further understand changes in supplementation strategy and characterize successful versus inadequate repletion strategies.

5 Conclusion

In patients requiring intraoperative transfusion with at least 4 units of packed red blood cells, we retrospectively observed that volume of packed red blood cells and volume of fresh frozen plasma are both associated with lower nadir of intraoperative ionized calcium. We failed to demonstrate that intraoperative hypocalcemia or transfusion is associated with meaningful postoperative clinical outcomes including mortality, acute kidney injury, or coagulopathy. Our findings suggest that despite improved practice patterns of calcium supplementation[7,28] intraoperative hypocalcemia occurs with relatively high frequency following large volume transfusion. Our regression models also provide insight into populations with higher or lower risk for hypocalcemia and optimal repletion strategies.

Figures and Tables

Table 1. Characteristics of Patients Requiring Intraoperative Transfusion with at least 4 units of Packed Red Blood Cells with Comparison by 30-Day Mortality.

Abbreviations: ASA = American Society of Anesthesiologists; BMI = Body Mass Index; kg = kilograms; m = meter; cm = centimeter; mmol = millimoles; L = Liter; mcg = micrograms; mEq = milliequivalents; min = minutes.

Table 2. Multivariable Linear Regression for Primary Outcome: Nadir Ionized Calcium.

Abbreviations: kg = kilograms; mmol = millimoles; L = Liter; mEq = milliequivalents; mcg = micrograms.

Table 3. Multivariable Logistic Regressions for Secondary Outcomes

A. 30-Day Mortality

B. Acute Kidney Injury

C. Postoperative Coagulopathy

Abbreviations: dL = deciliter; ENT = Ear, Nose, and Throat (Otolaryngology); FFP = fresh frozen plasma; L = Liter; MAP = mean arterial pressure; m = meter; mmol = millimoles; mcg = micrograms; mEq = milliequivalents; pRBC = packed red blood cells.

Disclosure and Competing Interests Statements:

Nicholas Douville, M.D., Ph.D. reports grant from Foundation for Anesthesia Education and Research (FAER) during the conduct of the study.

Ryan Davis, M.D., declares no conflicts of interest.

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Nicholas J. Douville, M.D., Ph.D. was responsible for the conception and design of the work; the interpretation of data for the work; developing first and final drafts of the work; and the assimilation of intellectual content from all co-authors.

Ryan Davis, M.D., was responsible for the acquisition and analysis of data for the work; interpretation of data for the work, and critically revising the work for important intellectual content

Elizabeth Jewell, M.S., was responsible for the acquisition and analysis of data for the work; interpretation of data for the work, and critically revising the work for important intellectual content

Douglas A. Colquhoun, M.B.Ch.B., M.Sc., M.P.H., was responsible for the interpretation of data for the work, and critically revising the work for important intellectual content.

Satya Krishna Ramachandran, M.D., FRCA., was responsible for the interpretation of data for the work, and critically revising the work for important intellectual content.

Satya Krishna Ramachandran, M.D., FRCA. was responsible for the conception and design of the work; interpretation of data for the work, and critically revising the work for important intellectual content.

Milo C. Engoren, M.D., was responsible for the conception and design of the work; the interpretation of data for the work; developing first and final drafts of the work; and the assimilation of intellectual content from all co-authors.

Paul Picton, M.B.Ch.B., was responsible for the conception and design of the work; interpretation of data for the work, and critically revising the work for important intellectual content.

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Table 1. Characteristics of Patients Requiring Intraoperative Transfusion with at least 4 units of Packed Red Blood Cells with Comparison by 30-Day Mortality.

Characteristics of Patients Requiring => 4 Units Packed Red Blood Cells																						
		All data (n=1614)							No In Hospital Mortality (n=1408)							In Hospital Mortality (n=206)							*P*-value	
Variable	Level	N	%	Mean	SD	Median	IQR		N	%	Mean	SD	Median	IQR		N	%	Mean	SD	Median	IQR		$\chi 2$	t-test
Age (years)		1614	100.0	56	17	59	45	68	1408	100.0	55.7	16.7	58.0	45.0	68.0	206	100.0	58.2	17.1	61.0	48.3	71.0		0.046
Emergent		569	35.3						422	30.0						147	71.4						<0.001	
ASA Status	I	25	1.5						24	1.7						1	0.5						<0.001	
	II	267	16.5						260	18.5						7	3.4							
	III	721	44.7						681	48.4						40	19.4							
	IV	503	31.2						400	28.4						103	50.0							
	V	98	6.1						43	3.1						55	26.7							
BMI (kg/m2)		1598	99.0	28.3	7.3	26.9	23.5	32.1	1401	99.5	28.2	7.2	26.8	23.4	31.9	197	95.6	29.2	8.1	27.7	23.7	34.9		0.097
Height (cm)		1599	99.1	170.7	10.8	171.5	162.6	177.8	1401	99.5	170.7	10.8	170.4	162.6	177.8	198	96.1	170.5	11.4	172.7	163.1	177.8		0.820
Weight (kg)		1613	99.9	83.8	23.4	80.7	67.4	96.3	1407	99.9	83.6	23.4	80.3	67.3	95.8	206	100.0	85.3	23.6	81.6	68.8	98.4		0.334
Gender	Female	655	40.6						580	41.2						75	36.4							0.219
	Male	959	59.4						828	58.8						131	63.6							
Race	White/Caucasian	1181	73.2						1050	74.6						131	63.6						<0.001	
	Other	163	10.1						155	11.0						8	3.9							
	Unknown	270	16.7						203	14.4						67	32.5							
Procedure	Abdominal	272	16.9						220	15.6						52	25.2						<0.001	
	Neurosurgery	227	14.1						211	15.0						16	7.8							
	Obstetrics/Gynecology/Urology	150	9.3						146	10.4						4	1.9							
	Oral/Maxillofacial/Dentistry/Otolaryngology	123	7.6						122	8.7						1	0.5							
	Orthopedics	159	9.9						155	11.0						4	1.9							
	Thoracic	39	2.4						32	2.3						7	3.4							
	Transplant/Hepatobiliary	198	12.3						179	12.7						19	9.2							
	Trauma	68	4.2						41	2.9						27	13.1							
	Vascular/Plastics	229	14.2						190	13.5						39	18.9							
	Other/Unknown/Radiology	149	9.2						112	8.0						37	18.0							
Elixhauser Comorbidities	Alcohol or Drug Abuse	185	11.5						152	10.8						33	16.0						0.007	

	Anemia (Iron Deficiency)	190	11.8						176	12.5						14	6.8						0.066	
	Cardiac Arrhythmias	568	35.2						483	34.3						85	41.3						0.003	
	Valvular Diseases of the Heart	108	6.7						88	6.3						20	9.7						0.031	
	COPD	316	19.6						270	19.2						46	22.3						0.087	
	Coagulopathy	519	32.2						414	29.4						105	51.0						<0.001	
	Diabetes	347	21.5						305	21.7						42	20.4						0.745	
	Fluid and Electrolyte Disorders	725	44.9						597	42.4						128	62.1						<0.001	
	Hypertension	854	52.9						761	54.0						93	45.1						0.348	
	Hypothyroidism	197	12.2						179	12.7						18	8.7						0.292	
	Liver Disease	338	20.9						263	18.7						75	36.4						<0.001	
	Metastatic Cancer	295	18.3						277	19.7						18	8.7						0.001	
	Neurologic Disorders	21	1.3						19	1.3						2	1.0						1.000	
	Peripheral Vascular Disorders	308	19.1						242	17.2						66	32.0						<0.001	
	Pulmonary Circulation Disorders	142	8.8						117	8.3						25	12.1						0.029	
	Renal Failure	304	18.8						255	18.1						49	23.8						0.064	
	Unexpected or Unanticipated Weight Loss	268	16.6						238	16.9						30	14.6						0.884	
Other Comorbidities	Cerebrovascular Disease	63	3.9						50	3.6						13	6.3						0.086	
Baseline Labs	Serum Creatinine (Cr)	1614	100.0	1.2	1.2	0.9	0.6	1.3	1408	100.0	1.2	1.2	0.9	0.6	1.3	206	100.0	1.4	1.2	1.1	0.8	1.7		0.002
	Blood Urea Nitrogen (BUN)	1614	100.0	21.0	17.5	17.0	11.0	26.0	1408	100.0	20.0	16.2	16.0	11.0	25.0	206	100.0	27.8	23.5	21.0	14.3	33.0		<0.001
	Hematocrit (Hct)	1579	97.8	30.9	7.4	30.6	24.9	36.4	1380	98.0	31.3	7.3	31.1	25.5	36.7	199	96.6	27.8	7.6	27.4	22.0	33.3		<0.001
	Total Calcium	1425	88.3	8.6	1.6	8.7	7.9	9.4	1237	87.9	8.6	1.4	8.8	7.9	9.4	188	91.3	8.8	2.2	8.4	7.6	9.4		0.358
	Ionized Calcium (iCal)	547	33.9	1.2	0.2	1.2	1.1	1.2	420	29.8	1.2	0.1	1.2	1.1	1.2	127	61.7	1.1	0.2	1.2	1.1	1.2		0.326
	Albumin	1264	78.3	3.5	0.9	3.6	2.7	4.2	1094	77.7	3.5	0.8	3.7	2.8	4.2	170	82.5	3.0	0.9	2.9	2.3	3.8		<0.001
	Partial Thromboplastin Time (PTT)	1419	87.9	1.7	3.4	1.1	1.0	1.5	1227	87.1	1.6	3.6	1.1	1.0	1.4	192	93.2	2.0	1.3	1.5	1.1	2.2		0.016
Intraoperative Data (at nadir)	Estimated Blood Loss (L)	1614	100.0	1.5	1.9	1.0	0.0	2.3	1408	100.0	1.5	1.8	1.0	0.0	2.3	206	100.0	1.1	2.2	0.0	0.0	1.2		0.011

Fluid Resuscitation	Urine Output (mL)	1614	100.0	8.8	11.8	5.6	2.1	11.9	1408	100.0	9.3	11.7	6.2	2.7	12.7	206	100.0	5.5	12.2	1.0	0.0	5.6		<0.001
	Lactated Ringer (LR) (L)	1614	100.0	1.7	1.7	1.3	0.4	2.6	1408	100.0	1.9	1.7	1.5	0.6	2.7	206	100.0	0.9	1.3	0.4	0.0	1.3		<0.001
	Crystalloid (L)	1614	100.0	2.8	2.0	2.4	1.4	3.8	1408	100.0	2.9	2.0	2.5	1.5	3.9	206	100.0	2.0	1.9	1.6	0.6	3.0		<0.001
	Colloid (L)	1614	100.0	0.5	0.7	0.3	0.0	1.0	1408	100.0	0.5	0.7	0.5	0.0	1.0	206	100.0	0.4	0.9	0.0	0.0	0.5		0.169
	Calcium Repletion (mEq)	1614	100.0	52.8	1054.3	12.9	5.5	23.5	1408	100.0	42.1	977.4	12.5	5.7	22.6	206	100.0	126.1	1477.8	16.3	4.6	28.2		0.430
Case Details	Duration (hour)	1614	100.0	4.5	3.1	3.9	2.1	6.2	1408	100.0	4.7	3.1	4.2	2.3	6.4	206	100.0	2.9	2.5	2.1	1.1	4.0		<0.001
	Hematocrit (Hct)	1609	99.7	22.1	4.2	22.0	19.0	25.0	1403	99.6	22.2	4.1	22.0	19.6	25.0	206	100.0	21.9	5.2	21.0	18.0	24.0		0.435
	Mean Arterial Pressure < 55 mmHg (min)	1614	100.0	11.9	21.0	4.0	1.0	13.0	1408	100.0	11.6	21.1	4.0	1.0	13.0	206	100.0	13.8	20.5	6.0	1.0	18.0		0.157
Medications	Norepinephrine administered (1 mcg)	226	14.0						1408	100.0	79.1	481.6	0.0	0.0	0.0	206	100.0	216.4	645.9	0.0	0.0	149.6		0.004
	Vasopressin administered (1 unit)	314	19.5						1408	100.0	1.0	3.4	0.0	0.0	0.0	206	100.0	3.3	6.3	0.0	0.0	4.0		<0.001
	Epinephrine administered	376	23.3						1408	100.0	0.1	0.7	0.0	0.0	0.0	206	100.0	0.9	2.5	0.0	0.0	0.2		<0.001
Transfusion	Packed Red Blood Cells (pRBC) (units)	1614	100.0	4.2	3.4	4.0	2.0	5.0	1408	100.0	4.0	2.9	4.0	2.0	5.0	206	100.0	5.5	5.5	4.0	2.0	6.0		<0.001
	Fresh Frozen Plasma (FFP) (units)	1614	100.0	2.0	3.0	1.0	0.0	3.0	1408	100.0	1.8	2.7	1.0	0.0	3.0	206	100.0	3.2	4.3	2.0	0.9	4.0		<0.001
	Platelets (5-packs)	1614	100.0	0.1	0.5	0.0	0.0	0.0	1408	100.0	0.1	0.5	0.0	0.0	0.0	206	100.0	0.3	0.7	0.0	0.0	0.0		0.004
	Cryoprecipitate (5-packs)	1614	100.0	0.1	0.3	0.0	0.0	0.0	1408	100.0	0.0	0.2	0.0	0.0	0.0	206	100.0	0.2	0.6	0.0	0.0	0.0		0.007
	Cell Salvage (mL)	1614	100.0	133.8	629.6	0.0	0.0	0.0	1408	100.0	121.5	466.8	0.0	0.0	0.0	206	100.0	217.9	1270.9	0.0	0.0	0.0		0.283
Primary Outcome	Ionized Calcium (iCal)	1614	100.0	0.92	0.18	0.93	0.82	1.03	1408	100.0	0.92	0.17	0.93	0.83	1.03	206	100.0	0.90	0.25	0.93	0.77	1.04		0.205

Abbreviations: ASA = American Society of Anesthesiologists; BMI = Body Mass Index; kg = kilograms; m = meter; cm = centimeter; mmol = millimoles; L = Liter; mcg = micrograms; mEq = milliequivalents; min = minutes.

Table 2. Multivariable Linear Regression for Primary Outcome: Nadir Ionized Calcium

Nadir ionized Calcium				
Exposure Variables		*Estimate*	*95% CI*	*P-Value*
	Transfusion packed red blood cells (units)	-0.013	-0.022 to -0.005	0.002
	Transfusion fresh frozen plasma (units)	-0.012	-0.020 to -0.003	0.009
Preoperative Variables				
	Weight (10 kg)	0.005	0.002 to 0.0116	0.170
	Male Gender	-0.019	-0.015 to 0.053	0.266
	Preoperative ionized calcium (mmol/L)	0.1531	0.044 to 0.263	0.006
	History of Cardiac Arrhythmia	0.020	-0.011 to 0.050	0.212
	History of Coagulopathy	0.037	0.005 to 0.070	0.026
	History of Weight Loss	0.058	0.022 to 0.095	0.002
	Vascular/Plastic Surgery Procedure	0.052	0.009 to 0.095	0.019
Intraoperative Variables				
	Estimated blood loss (1L)	0.015	0.003 to 0.027	0.015
	Calcium repletion (10 mEq)	0.015	0.001 to 0.028	0.037
	Crystalloid Resuscitation (1L)	-0.020	-0.029 to -0.010	<0.001
	Case Duration (hours)	0.007	-0.001 to 0.0143	0.091
	Epinephrine administered (100 mcg)	-1.291	-2.601 to 0.019	0.054
	Vasopressin administered (4 units)	0.024	0.007 to 0.041	0.005
	Norepinephrine administered (80 mcg)	0.001	-0.001 to 0.004	0.290

Abbreviations: kg = kilograms; mmol = millimoles; L = Liter; mEq = milliequivalents; mcg = micrograms.

Table 3. Multivariable Logistic Regressions for Secondary Outcomes

A. 30-Day Mortality

30-Day Mortality (c-statistic = 0.845)				
Variable		*aOR*	*95% CI*	*P-Value*
Nadir ionized Calcium		0.787	0.258-2.398	0.674
Emergent Surgery		1.946	1.196-3.166	0.007
Race	Unknown	3.480	2.126-5.696	<0.001
Procedural Category	Trauma	4.272	1.861-9.805	0.001
	Other/Radiologic	2.168	1.158-4.060	0.016
History of Peripheral Vascular Disorders		2.137	1.360-3.357	0.001
History of Liver Disease		1.400	0.865-2.266	0.171
History of Coagulopathy		1.652	1.050-2.599	0.030
History of Fluid or Electrolyte Disorder		1.560	0.949-2.511	0.067
Case Duration (min)		0.998	0.997-0.999	0.005
Vasopressin administered (4U)		1.101	0.912-1.329	0.317
Norepinephrine administered (8mcg)		1.002	1.000-1.004	0.033
Platelet Transfusion (5-packs)		1.189	1.063-1.330	0.002

B. Acute Kidney Injury

Postoperative Acute Kidney Injury (c-statistic = 0.806)				
Variable		*aOR*	*95% CI*	*P-Value*
Nadir ionized Calcium		0.733	0.286-1.877	0.518
Age (years)		1.012	1.001-1.023	0.028
Weight (kg)		1.011	1.004-1.018	0.003
Procedural Category				
	Neurosurgery	0.201	0.097-0.415	<0.001
	Obstetrics/Gynecology/Urology	1.722	1.0195-2.908	0.042
	Oral Surgery/ENT/Dentistry	0.509	0.234-1.108	0.089
	Orthopedic Surgery	0.207	0.097-0.442	<0.001
	Transplant	2.171	1.349-3.454	0.001
	Vascular Surgery/Plastics	1.685	1.077-2.634	0.022
History of Coagulopathy		1.149	0.820-1.610	0.420
History of Fluid or Electrolyte Disorder		1.836	1.324-2.545	<0.001
Preoperative Creatinine (mg/dL)		0.569	0.440-0.735	<0.001
EBL at nadir (L)		1.105	0.905-1.221	0.389
Transfusion FFP at nadir (units)		1.029	0.941-1.125	0.532
Urine Output at Nadir (500 mL)		0.000	0.000-0.399	0.033
Norepinephrine administered (8 mcg)		1.004	1.000-1.007	0.027
Phenylephrine administered (250 mcg)		1.009	1.011-1.017	0.018
EBL at Case Completion (L)		1.000	0.905-1.105	0.776
Transfusion FFP at Case Completion (units)		0.995	0.926-1.070	0.898
Transfusion pRBC at Case Completion (units)		1.018	0.958-1.081	0.565
Platelet Transfusion at Case Completion (5-packs)		1.082	0.961-1.212	0.191
Cryoprecipitate Transfusion at Case Completion (5-packs)		1.014	0.789-1.302	0.917

C. Postoperative Coagulopathy

Postoperative Coagulopathy (c-statistic = 0.784)				
Variable		*aOR*	*95% CI*	*P-Value*
Nadir ionized Calcium		0.507	0.218-1.180	0.115
Weight (kg)		0.986	0.979-0.992	<0.001
Emergent Surgery		1.317	0.941-1.844	0.108
Race	Unknown	1.625	1.125-2.347	0.010
Procedural Category				
	Neurosurgery	0.401	0.257-0.623	<0.001
	Obstetrics/Gynecology/Urology	0.620	0.374-1.026	0.063
	Orthopedic Surgery	0.620	0.387-0.992	0.046
	Transplant	2.305	1.342-3.959	0.003
	Vascular Surgery/Plastics	1.132	0.757-1.691	0.547
History of Coagulopathy		1.568	1.153-2.133	0.004
History of Fluid or Electrolyte Disorder		1.093	0.819-1.457	0.546
History of Renal Failure		1.542	1.082-2.199	0.017
History of Liver Disease		1.692	1.145-2.500	0.008
History of Chronic Pulmonary Disease		1.416	1.023-1.961	0.036
Preoperative Serum Albumin (g/dL)		0.672	0.560-0.809	<0.001
Colloid Resuscitation at Nadir (L)		1.856	1.471-2.340	<0.001
Phenylephrine administered at nadir (250 mcg)		1.009	1.002-1.016	0.011
Transfusion pRBC at Case Completion (units)		1.016	0.983-1.050	0.338
Final Hematocrit (%)		0.989	0.952-1.026	0.551
Norepinephrine administered (8 mcg)		1.001	0.994-1.003	0.178
Time with MAP < 55 mmHg (minutes)		1.008	1.002-1.014	0.007

Abbreviations: dL = deciliter; ENT = Ear, Nose, and Throat (Otolaryngology); FFP = fresh frozen plasma; L = Liter; MAP = mean arterial pressure; m = meter; mmol = millimoles; mcg = micrograms; mEq = milliequivalents; pRBC = packed red blood cells.

Table 1. Characteristics of Patients Requiring Intraoperative Transfusion with at least 4 units of Packed Red Blood Cells with Comparison by 30-Day Mortality.

Characteristics of Patients Requiring => 4 Units Packed Red Blood Cells																						
		All data (n=1614)							No In Hospital Mortality (n=1408)							In Hospital Mortality (n=206)							*P*-value	
Variable	Level	N	%	Mean	SD	Median	IQR		N	%	Mean	SD	Median	IQR		N	%	Mean	SD	Median	IQR		$\chi 2$	t-test
Age (years)		1614	100.0	56	17	59	45	68	1408	100.0	55.7	16.7	58.0	45.0	68.0	206	100.0	58.2	17.1	61.0	48.3	71.0		0.046
Emergent		569	35.3						422	30.0						147	71.4						<0.001	
ASA Status	I	25	1.5						24	1.7						1	0.5						<0.001	
	II	267	16.5						260	18.5						7	3.4							
	III	721	44.7						681	48.4						40	19.4							
	IV	503	31.2						400	28.4						103	50.0							
	V	98	6.1						43	3.1						55	26.7							
BMI (kg/m2)		1598	99.0	28.3	7.3	26.9	23.5	32.1	1401	99.5	28.2	7.2	26.8	23.4	31.9	197	95.6	29.2	8.1	27.7	23.7	34.9		0.097
Height (cm)		1599	99.1	170.7	10.8	171.5	162.6	177.8	1401	99.5	170.7	10.8	170.4	162.6	177.8	198	96.1	170.5	11.4	172.7	163.1	177.8		0.820
Weight (kg)		1613	99.9	83.8	23.4	80.7	67.4	96.3	1407	99.9	83.6	23.4	80.3	67.3	95.8	206	100.0	85.3	23.6	81.6	68.8	98.4		0.334
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Procedure	Abdominal	272	16.9						220	15.6						52	25.2						<0.001	
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	Obstetrics/Gynecology/Urology	150	9.3						146	10.4						4	1.9							
	Oral/Maxillofacial/Dentistry/Otolaryngology	123	7.6						122	8.7						1	0.5							
	Orthopedics	159	9.9						155	11.0						4	1.9							
	Thoracic	39	2.4						32	2.3						7	3.4							
	Transplant/Hepatobiliary	198	12.3						179	12.7						19	9.2							
	Trauma	68	4.2						41	2.9						27	13.1							
	Vascular/Plastics	229	14.2						190	13.5						39	18.9							
	Other/Unknown/Radiology	149	9.2						112	8.0						37	18.0							
Elixhauser Comorbidities	Alcohol or Drug Abuse	185	11.5						152	10.8						33	16.0						0.007	
	Anemia (Iron Deficiency)	190	11.8						176	12.5						14	6.8						0.066	

	Cardiac Arrhythmias	568	35.2						483	34.3						85	41.3						0.003	
	Valvular Diseases of the Heart	108	6.7						88	6.3						20	9.7						0.031	
	COPD	316	19.6						270	19.2						46	22.3						0.087	
	Coagulopathy	519	32.2						414	29.4						105	51.0						<0.001	
	Diabetes	347	21.5						305	21.7						42	20.4						0.745	
	Fluid and Electrolyte Disorders	725	44.9						597	42.4						128	62.1						<0.001	
	Hypertension	854	52.9						761	54.0						93	45.1						0.348	
	Hypothyroidism	197	12.2						179	12.7						18	8.7						0.292	
	Liver Disease	338	20.9						263	18.7						75	36.4						<0.001	
	Metastatic Cancer	295	18.3						277	19.7						18	8.7						0.001	
	Neurologic Disorders	21	1.3						19	1.3						2	1.0						1.000	
	Peripheral Vascular Disorders	308	19.1						242	17.2						66	32.0						<0.001	
	Pulmonary Circulation Disorders	142	8.8						117	8.3						25	12.1						0.029	
	Renal Failure	304	18.8						255	18.1						49	23.8						0.064	
	Unexpected or Unanticipated Weight Loss	268	16.6						238	16.9						30	14.6						0.884	
Other Comorbidities	Cerebrovascular Disease	63	3.9						50	3.6						13	6.3						0.086	
Baseline Labs	Serum Creatinine (Cr)	1614	100.0	1.2	1.2	0.9	0.6	1.3	1408	100.0	1.2	1.2	0.9	0.6	1.3	206	100.0	1.4	1.2	1.1	0.8	1.7		0.002
	Blood Urea Nitrogen (BUN)	1614	100.0	21.0	17.5	17.0	11.0	26.0	1408	100.0	20.0	16.2	16.0	11.0	25.0	206	100.0	27.8	23.5	21.0	14.3	33.0		<0.001
	Hematocrit (Hct)	1579	97.8	30.9	7.4	30.6	24.9	36.4	1380	98.0	31.3	7.3	31.1	25.5	36.7	199	96.6	27.8	7.6	27.4	22.0	33.3		<0.001
	Total Calcium	1425	88.3	8.6	1.6	8.7	7.9	9.4	1237	87.9	8.6	1.4	8.8	7.9	9.4	188	91.3	8.8	2.2	8.4	7.6	9.4		0.358
	Ionized Calcium (iCal)	547	33.9	1.2	0.2	1.2	1.1	1.2	420	29.8	1.2	0.1	1.2	1.1	1.2	127	61.7	1.1	0.2	1.2	1.1	1.2		0.326
	Albumin	1264	78.3	3.5	0.9	3.6	2.7	4.2	1094	77.7	3.5	0.8	3.7	2.8	4.2	170	82.5	3.0	0.9	2.9	2.3	3.8		<0.001
	Partial Thromboplastin Time (PTT)	1419	87.9	1.7	3.4	1.1	1.0	1.5	1227	87.1	1.6	3.6	1.1	1.0	1.4	192	93.2	2.0	1.3	1.5	1.1	2.2		0.016
Intraoperative Data (at nadir)	Estimated Blood Loss (L)	1614	100.0	1.5	1.9	1.0	0.0	2.3	1408	100.0	1.5	1.8	1.0	0.0	2.3	206	100.0	1.1	2.2	0.0	0.0	1.2		0.011
Fluid Resuscitation	Urine Output (mL)	1614	100.0	8.8	11.8	5.6	2.1	11.9	1408	100.0	9.3	11.7	6.2	2.7	12.7	206	100.0	5.5	12.2	1.0	0.0	5.6		<0.001
	Lactated Ringer (LR) (L)	1614	100.0	1.7	1.7	1.3	0.4	2.6	1408	100.0	1.9	1.7	1.5	0.6	2.7	206	100.0	0.9	1.3	0.4	0.0	1.3		<0.001

	Crystalloid (L)	1614	100.0	2.8	2.0	2.4	1.4	3.8	1408	100.0	2.9	2.0	2.5	1.5	3.9	206	100.0	2.0	1.9	1.6	0.6	3.0		<0.001
	Colloid (L)	1614	100.0	0.5	0.7	0.3	0.0	1.0	1408	100.0	0.5	0.7	0.5	0.0	1.0	206	100.0	0.4	0.9	0.0	0.0	0.5		0.169
	Calcium Repletion (mEq)	1614	100.0	52.8	1054.3	12.9	5.5	23.5	1408	100.0	42.1	977.4	12.5	5.7	22.6	206	100.0	126.1	1477.8	16.3	4.6	28.2		0.430
Case Details	Duration (hour)	1614	100.0	4.5	3.1	3.9	2.1	6.2	1408	100.0	4.7	3.1	4.2	2.3	6.4	206	100.0	2.9	2.5	2.1	1.1	4.0		<0.001
	Hematocrit (Hct)	1609	99.7	22.1	4.2	22.0	19.0	25.0	1403	99.6	22.2	4.1	22.0	19.6	25.0	206	100.0	21.9	5.2	21.0	18.0	24.0		0.435
	Mean Arterial Pressure < 55 mmHg (min)	1614	100.0	11.9	21.0	4.0	1.0	13.0	1408	100.0	11.6	21.1	4.0	1.0	13.0	206	100.0	13.8	20.5	6.0	1.0	18.0		0.157
Medications	Norepinephrine administered (1 mcg)	226	14.0						1408	100.0	79.1	481.6	0.0	0.0	0.0	206	100.0	216.4	645.9	0.0	0.0	149.6		0.004
	Vasopressin administered (1 unit)	314	19.5						1408	100.0	1.0	3.4	0.0	0.0	0.0	206	100.0	3.3	6.3	0.0	0.0	4.0		<0.001
	Epinephrine administered	376	23.3						1408	100.0	0.1	0.7	0.0	0.0	0.0	206	100.0	0.9	2.5	0.0	0.0	0.2		<0.001
Transfusion	Packed Red Blood Cells (pRBC) (units)	1614	100.0	4.2	3.4	4.0	2.0	5.0	1408	100.0	4.0	2.9	4.0	2.0	5.0	206	100.0	5.5	5.5	4.0	2.0	6.0		<0.001
	Fresh Frozen Plasma (FFP) (units)	1614	100.0	2.0	3.0	1.0	0.0	3.0	1408	100.0	1.8	2.7	1.0	0.0	3.0	206	100.0	3.2	4.3	2.0	0.9	4.0		<0.001
	Platelets (5-packs)	1614	100.0	0.1	0.5	0.0	0.0	0.0	1408	100.0	0.1	0.5	0.0	0.0	0.0	206	100.0	0.3	0.7	0.0	0.0	0.0		0.004
	Cryoprecipitate (5-packs)	1614	100.0	0.1	0.3	0.0	0.0	0.0	1408	100.0	0.0	0.2	0.0	0.0	0.0	206	100.0	0.2	0.6	0.0	0.0	0.0		0.007
	Cell Salvage (mL)	1614	100.0	133.8	629.6	0.0	0.0	0.0	1408	100.0	121.5	466.8	0.0	0.0	0.0	206	100.0	217.9	1270.9	0.0	0.0	0.0		0.283
Primary Outcome	Ionized Calcium (iCal)	1614	100.0	0.92	0.18	0.93	0.82	1.03	1408	100.0	0.92	0.17	0.93	0.83	1.03	206	100.0	0.90	0.25	0.93	0.77	1.04		0.205

Abbreviations: ASA = American Society of Anesthesiologists; BMI = Body Mass Index; kg = kilograms; m = meter; cm = centimeter; mmol = millimoles; L = Liter; mcg = micrograms; mEq = milliequivalents; min = minutes.

Table 2. Multivariable Linear Regression for Primary Outcome: Nadir Ionized Calcium

Nadir ionized Calcium				
Exposure Variables		*Estimate*	*95% CI*	*P-Value*
	Transfusion packed red blood cells (units)	-0.013	-0.022 to -0.005	0.002
	Transfusion fresh frozen plasma (units)	-0.012	-0.020 to -0.003	0.009
Preoperative Variables				
	Weight (10 kg)	0.005	0.002 to 0.0116	0.170
	Male Gender	-0.019	-0.015 to 0.053	0.266
	Preoperative ionized calcium (mmol/L)	0.1531	0.044 to 0.263	0.006
	History of Cardiac Arrhythmia	0.020	-0.011 to 0.050	0.212
	History of Coagulopathy	0.037	0.005 to 0.070	0.026
	History of Weight Loss	0.058	0.022 to 0.095	0.002
	Vascular/Plastic Surgery Procedure	0.052	0.009 to 0.095	0.019
Intraoperative Variables				
	Estimated blood loss (1L)	0.015	0.003 to 0.027	0.015
	Calcium repletion (10 mEq)	0.015	0.001 to 0.028	0.037
	Crystalloid Resuscitation (1L)	-0.020	-0.029 to -0.010	<0.001
	Case Duration (hours)	0.007	-0.001 to 0.0143	0.091
	Epinephrine administered (100 mcg)	-1.291	-2.601 to 0.019	0.054
	Vasopressin administered (4 units)	0.024	0.007 to 0.041	0.005
	Norepinephrine administered (80 mcg)	0.001	-0.001 to 0.004	0.290

Abbreviations: kg = kilograms; mmol = millimoles; L = Liter; mEq = milliequivalents; mcg = micrograms.

Table 3. Multivariable Logistic Regressions for Secondary Outcomes

A. 30-Day Mortality

30-Day Mortality (c-statistic = 0.845)				
Variable		*aOR*	*95% CI*	*P-Value*
Nadir ionized Calcium		0.787	0.258-2.398	0.674
Emergent Surgery		1.946	1.196-3.166	0.007
Race	Unknown	3.480	2.126-5.696	<0.001
Procedural Category	Trauma	4.272	1.861-9.805	0.001
	Other/Radiologic	2.168	1.158-4.060	0.016
History of Peripheral Vascular Disorders		2.137	1.360-3.357	0.001
History of Liver Disease		1.400	0.865-2.266	0.171
History of Coagulopathy		1.652	1.050-2.599	0.030
History of Fluid or Electrolyte Disorder		1.560	0.949-2.511	0.067
Case Duration (min)		0.998	0.997-0.999	0.005
Vasopressin administered (4U)		1.101	0.912-1.329	0.317
Norepinephrine administered (8mcg)		1.002	1.000-1.004	0.033
Platelet Transfusion (5-packs)		1.189	1.063-1.330	0.002

B. Acute Kidney Injury

Postoperative Acute Kidney Injury (c-statistic = 0.806)				
Variable		*aOR*	*95% CI*	*P-Value*
Nadir ionized Calcium		0.733	0.286-1.877	0.518
Age (years)		1.012	1.001-1.023	0.028
Weight (kg)		1.011	1.004-1.018	0.003
Procedural Category				
	Neurosurgery	0.201	0.097-0.415	<0.001
	Obstetrics/Gynecology/Urology	1.722	1.0195-2.908	0.042
	Oral Surgery/ENT/Dentistry	0.509	0.234-1.108	0.089
	Orthopedic Surgery	0.207	0.097-0.442	<0.001
	Transplant	2.171	1.349-3.454	0.001
	Vascular Surgery/Plastics	1.685	1.077-2.634	0.022
History of Coagulopathy		1.149	0.820-1.610	0.420
History of Fluid or Electrolyte Disorder		1.836	1.324-2.545	<0.001
Preoperative Creatinine (mg/dL)		0.569	0.440-0.735	<0.001
EBL at nadir (L)		1.105	0.905-1.221	0.389
Transfusion FFP at nadir (units)		1.029	0.941-1.125	0.532
Urine Output at Nadir (500 mL)		0.000	0.000-0.399	0.033
Norepinephrine administered (8 mcg)		1.004	1.000-1.007	0.027
Phenylephrine administered (250 mcg)		1.009	1.011-1.017	0.018
EBL at Case Completion (L)		1.000	0.905-1.105	0.776
Transfusion FFP at Case Completion (units)		0.995	0.926-1.070	0.898
Transfusion pRBC at Case Completion (units)		1.018	0.958-1.081	0.565
Platelet Transfusion at Case Completion (5-packs)		1.082	0.961-1.212	0.191
Cryoprecipitate Transfusion at Case Completion (5-packs)		1.014	0.789-1.302	0.917

C. Postoperative Coagulopathy

Postoperative Coagulopathy (c-statistic = 0.784)				
Variable		*aOR*	*95% CI*	*P-Value*
Nadir ionized Calcium		0.507	0.218-1.180	0.115
Weight (kg)		0.986	0.979-0.992	<0.001
Emergent Surgery		1.317	0.941-1.844	0.108
Race	Unknown	1.625	1.125-2.347	0.010
Procedural Category				
	Neurosurgery	0.401	0.257-0.623	<0.001
	Obstetrics/Gynecology/Urology	0.620	0.374-1.026	0.063
	Orthopedic Surgery	0.620	0.387-0.992	0.046
	Transplant	2.305	1.342-3.959	0.003
	Vascular Surgery/Plastics	1.132	0.757-1.691	0.547
History of Coagulopathy		1.568	1.153-2.133	0.004
History of Fluid or Electrolyte Disorder		1.093	0.819-1.457	0.546
History of Renal Failure		1.542	1.082-2.199	0.017
History of Liver Disease		1.692	1.145-2.500	0.008
History of Chronic Pulmonary Disease		1.416	1.023-1.961	0.036
Preoperative Serum Albumin (g/dL)		0.672	0.560-0.809	<0.001
Colloid Resuscitation at Nadir (L)		1.856	1.471-2.340	<0.001
Phenylephrine administered at nadir (250 mcg)		1.009	1.002-1.016	0.011
Transfusion pRBC at Case Completion (units)		1.016	0.983-1.050	0.338
Final Hematocrit (%)		0.989	0.952-1.026	0.551
Norepinephrine administered (8 mcg)		1.001	0.994-1.003	0.178
Time with MAP < 55 mmHg (minutes)		1.008	1.002-1.014	0.007

Abbreviations: dL = deciliter; ENT = Ear, Nose, and Throat (Otolaryngology); FFP = fresh frozen plasma; L = Liter; MAP = mean arterial pressure; m = meter; mmol = millimoles; mcg = micrograms; mEq = milliequivalents; pRBC = packed red blood cells.

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