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Volume of packed red blood cells and fresh frozen plasma is associated with intraoperative hypocalcaemia during large volume intraoperative transfusion

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Abstract

Background: Severe hypocalcaemia is associated with increased transfusion in the trauma population. Furthermore, trauma patients developing severe hypocalcaemia 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 fresh frozen plasma transfused intraoperatively is associated with lower nadir ionised calcium in the surgical population receiving massive resuscitation.

Methods: We performed a retrospective observational study at an academic quaternary care centre to characterise hypocalcaemia 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 ionised calcium. We then used multivariable logistic regressions to assess the association between ionised calcium and transfusion with: (i) mortality, (ii) acute kidney injury, and (iii) postoperative coagulopathy.

Results: Hypocalcaemia 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 hypocalcaemia on multivariable linear regression. Hypocalcaemia, intraoperative transfusion of packed red blood cells, and intraoperative transfusion of fresh frozen plasma were not shown to be associated with clinical outcomes.

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

KEYWORDS
calcium repletion, hypocalcaemia, intraoperative transfusion, massive transfusion, perioperative medicine

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 minimise coagulation during storage, massive transfusion can lead to systemic citrate toxicity with associated electrolyte abnormalities—hypocalcaemia and hypomagnesaemia. Calcium in the ionised form is required for coagulation of blood and muscular contraction. Citrate-associated hypocalcaemia 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 hypocalcaemia 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 hypocalcaemia following massive transfusion were recently evaluated in trauma patients.[6] In this population, severe hypocalcaemia was associated with increased transfusion of packed red blood cells and fresh frozen plasma. Additionally, patients developing severe hypocalcaemia had higher mortality and higher activated partial thromboplastin time (PTT) than those who did not experience hypocalcaemia. 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 hypocalcaemia, without postoperative haemodynamic instability or metabolic acidosis.[7] Differences in clinical significance between the trauma and perioperative populations are hypothesised 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 characterise the incidence and risk factors for abnormalities, like hypocalcaemia, 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 characterisation of hypocalcaemia 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 ionised calcium in the surgical population receiving large volume (4 or more units of packed red blood cells) resuscitation. Secondarily, we tested whether nadir ionised calcium is associated with postoperative mortality, acute kidney injury (AKI), or coagulopathy.

2 | MATERIAL AND METHODS

2.1 | Study design

For this retrospective observational study performed at our academic quaternary care centre, 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 21 March 2018 prior to data access.[14]

2.2 | Data collection

Study data were collected via combined queries of the electronic perioperative anaesthesia 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 utilised in previous studies. Quality assurance was maintained through a standardised 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 1 January 2008 and 1 August 2018. We excluded cardiac surgeries, liver transplantations, other cases requiring preoperative or intraoperative cardiovascular support (cardiopulmonary bypass, extracorporeal membrane oxygenation, ventricular assist devices, or intraaortic 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) ionised 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 post-operative all-cause mortality, (ii) post-operative AKI, and (iii) post-operative coagulopathy. AKI was defined according to the *Kidney Disease—Improving Global Outcomes* (KDIGO) definition[18] (specifically an increase in serum creatinine by ≥0.3 mg/dl within 48 h of anaesthesia end time, or a ≥50% increase within seven post-operative calendar days. Coagulopathy was defined by an abnormal PT/INR or PTT within 24 h of anaesthesia 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 anaesthesia 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 anaesthetic and surgical record and included: (i) procedural details (case duration, general anaesthetic), (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 ionised calcium*. For example, *case duration* does not reflect overall case duration, but is the duration of time from anaesthesia start until time corresponding with nadir ionised calcium, nor does volume transfused reflect the whole case but only the amount transfused before nadir ionised calcium. The full list of preoperative and intraoperative variables collected can be seen in Table S1.

2.8 | Statistical analyses

Perioperative characteristics were summarised using means and SDs 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 ionised calcium. To analyse 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 hypocalcaemia group, a mean of 6.35 units of PRBC in the group without severe hypocalcaemia, and a common SD 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 were 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 two-sided *t*-test at 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 as follows: 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 ± 17 years, and mean BMI of 28.3 ± 7.3 kg/m^2. Fifty-nine percent ($n = 959$) were male and the mean ASA Physical Status Classification system was 3 ± 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 ionised calcium

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		χ^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/m^2)		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/gynaecology/ urology	150	9.3						146	10.4						4	1.9							
	Oral/maxillofacial/ dentistry/ otolaryngology	123	7.6						122	8.7						1	0.5							
	Orthopaedics	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	
	Anaemia (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	

TABLE 1 (Continued)

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		χ^2	t-test
	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
	Haematocrit (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
	Ionised 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

(Continues)

TABLE 1 (Continued)

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		χ^2	*t*-test
	Haematocrit (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		
	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	Ionised 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; cm, centimetre; kg, kilograms; L, litre; m, metre; mcg, micrograms; mEq, milliequivalents; min, minutes; mmol, millimoles.

TABLE 2 Multivariable linear regression for primary outcome: Nadir ionised calcium

Nadir ionised calcium			
	Estimate	**95% CI**	***p* Value**
Exposure variables			
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 ionised 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 (1 L)	0.015	0.003 to 0.027	0.015
Calcium repletion (10 mEq)	0.015	0.001 to 0.028	0.037
Crystalloid resuscitation (1 L)	−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; L, litre; mcg, micrograms; mEq, milliequivalents; mmol, millimoles.

occurred, a median of 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 occurred 4.5 ± 3.1 h 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 ± 21 min 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 ionised calcium

The mean nadir ionised calcium was 0.92 ± 0.18 mmol/L. Most patients (n = 1099, 70%) developed intraoperative hypocalcaemia (ionised calcium ≤1.0 mmol/L). Twenty-two percent (n = 378) demonstrated severe hypocalcaemia (ionised calcium ≤0.80 mmol/L). The distribution of severity of hypocalcaemia can be visualised in Figure S1. Using multivariable linear regression to adjust for other factors that may be associated with calcium levels (e.g., 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 ionised 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 ionised calcium. Cases involving larger resuscitation with crystalloid, more calcium repletion, and larger vasopressin receipt were associated with higher ionised 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 ionised calcium in the group with no in-hospital mortality was 0.93 ± 0.17 and was 0.90 ± 0.25 in the mortality group (p = 0.205). Nadir ionised calcium was not associated with 30-day mortality (adjusted odds ratio [aOR] = 0.787; 95% CI, 0.258–2.398; p = 0.674). Emergent surgery (aOR = 1.946; 95% CI, 1.196–3.166; p = 0.007), history of peripheral vascular disorders (aOR = 2.137; 95% CI, 1.360–3.357; p = 0.001), history of coagulopathy (aOR = 1.652; 95% CI, 1.050–2.599; p = 0.030), and transfusion of platelets (aOR = 1.189; 95% CI, 1.063–1.330; 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: Post-operative AKI

AKI occurred following 24% (n = 382) procedures involving large volume resuscitation. The mean ionised calcium in the group that did not

TABLE 3 Multivariable logistic regressions for secondary outcomes

A. 30-day mortality (c-statistic = 0.845)				
Variable		**aOR**	**95% CI**	***p* Value**
Nadir ionised 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. Postoperative acute kidney injury (c-statistic = 0.806)				
Variable		**aOR**	**95% CI**	***p* Value**
Nadir ionised 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/gynaecology/urology	1.722	1.0195–2.908	0.042
	Oral surgery/ENT/dentistry	0.509	0.234–1.108	0.089
	Orthopaedic 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 (c-statistic = 0.784)				
Variable		**aOR**	**95% CI**	***p* Value**
Nadir ionised 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

TABLE 3 (Continued)

C. Postoperative coagulopathy (c-statistic = 0.784)				
Variable		**aOR**	**95% CI**	***p* Value**
Procedural category				
	Neurosurgery	0.401	0.257–0.623	<0.001
	Obstetrics/gynaecology/urology	0.620	0.374–1.026	0.063
	Orthopaedic 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 haematocrit (%)		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, decilitre; ENT, ear, nose, and throat (otolaryngology); FFP, fresh frozen plasma; L, litre; m, metre; MAP, mean arterial pressure; mcg, micrograms; mEq, milliequivalents; mmol, millimoles; pRBC, packed red blood cells.

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

3.4 | Secondary outcome: Post-operative coagulopathy

Post-operative coagulopathy occurred following 32% ($n = 519$) procedures involving large volume resuscitation. The mean ionised calcium in the group that did not develop post-operative coagulopathy was 0.93 ± 0.18 and 0.91 ± 0.18 in the group that did develop coagulopathy. Nadir ionised calcium was not associated with post-operative coagulopathy (aOR = 0.507; 95% CI, 0.218–0.180; $p = 0.115$), so could not serve as an intermediate variable for mediation analysis. Furthermore, none of our transfusion exposure variables were associated with post-operative coagulopathy. Increasing weight (aOR = 0.986; 95% CI, 0.979–0.992; $p < 0.001$), increasing preoperative serum albumin (aOR = 0.672; 95% CI, 0.560–0.809; $p < 0.001$), neurosurgical (aOR = 0.401; 95% CI, 0.257–0.623; $p < 0.001$) and orthopaedic (aOR = 0.620; 95% CI, 0.387–0.992; $p = 0.046$) procedures were associated with lower rates of coagulopathy. Transplant surgeries (aOR = 2.305; 95% CI, 1.342–3.959; $p = 0.003$), history of renal failure (aOR = 1.542; 95% CI, 1.082–2.199; $p = 0.017$), history of liver disease (aOR = 1.692; 95% CI, 1.145–2.500; $p = 0.008$), and phenylephrine administration before nadir (250 mcg doses) (aOR = 1.009; 95% CI, 1.002–1.016; $p = 0.011$) were associated with *higher* rates of post-operative coagulopathy. Colloid resuscitation (Litres) (aOR = 1.856; 95% CI, 1.471–2.340; $p < 0.001$) and minutes with mean arterial pressure (MAP) < 55 mmHg (aOR = 1.008; 95% CI, 1.002–1.014; $p = 0.007$) 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 hypocalcaemia compared with the cohort

developing severe hypocalcaemia (defined as nadir ionised calcium ≤0.80 mmol/L). We found 4.01 ± 2.76 mEq of calcium were administered per unit of citrate containing blood products in the group not developing hypocalcaemia compared with 2.90 ± 2.32 mEq per unit of citrate containing blood products in the group developing severe hypocalcaemia. 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 ionised calcium than those replete entirely with calcium gluconate (0.94 ± 0.22 compared with 0.92 + 0.16, $p < 0.001$), on univariate analysis; however, repletion strategy was not selected in the LASSO multivariate models. Ionised calcium had normalised (defined as ≥1.0 mmol/L) at case completion in 73% 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 volume of fresh frozen plasma are independently associated with intraoperative hypocalcaemia during large volume transfusion. We did not detect an association between intraoperative hypocalcaemia or intraoperative transfusion and post-operative clinical outcomes of 30-day mortality, AKI, or coagulopathy.

4.1 | Concordance with previous studies

Our primary findings that volume of blood products are associated with hypocalcaemia 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 hypocalcaemia 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 hypocalcaemia 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 hypocalcaemia 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 (Table S1), 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 with a prior study of intraoperative transfusion where calcium repletion was not performed as standard practice,[7] hypocalcaemia still occurs with high frequency following large volume transfusion in the operating room. Specifically, we noted severe hypocalcaemia (defined as nadir ionised calcium ≤0.80 mmol/L) occurred in 22% of cases and mild hypocalcaemia (defined as nadir ionised calcium ≤1.00 mmol/L) occurred in 70% of cases. Our inability to demonstrate an association between intraoperative hypocalcaemia 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 aetiology of bleeding between surgery versus trauma, and (iii) more rapid, transient control of surgical bleeding. In fact, ionised calcium had normalised by case completion in 73% 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 to 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 ± 2.76 mEq of calcium were administered per unit of citrate containing blood products in the group not developing hypocalcaemia compared with 2.90 ± 2.32 mEq per unit of citrate containing blood products in the group developing hypocalcaemia. This suggests that perhaps clinicians should replete towards the upper limit of recommended, as the patients in the severe hypocalcaemia 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 hypocalcaemia; however, the greater toxicity to blood vessels makes it less desirable for prolonged administration.[5,25] Patients repleted with calcium chloride had higher nadir ionised calcium than those replete entirely with calcium gluconate (0.94 ± 0.22 compared with 0.92 + 0.16, $p < 0.001$) on univariate analysis; however, since this was not demonstrated on multivariable modelling, additional research is necessary on optimal repletion strategy in different surgical populations.

4.2 | Cohort definition

The classic definition for *massive transfusion*, ≥10 units packed red blood cells in a 24-h 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 ≥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: ≥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-centre 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 ionised calcium by 0.015 mmol/L (95% CI, 0.001–0.028; $p = 0.037$). Future studies will attempt to further understand changes in supplementation strategy and characterise 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 ionised calcium. We failed to demonstrate that intraoperative hypocalcaemia or transfusion is associated with meaningful post-operative clinical outcomes including mortality, AKI, or coagulopathy. Our findings suggest that despite improved practice patterns of calcium supplementation,[7,28] intraoperative hypocalcaemia occurs with relatively high frequency following large volume transfusion. Our regression models also provide insight into populations with higher or lower risk for hypocalcaemia and optimal repletion strategies.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Nicholas J. Douville: 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:** 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:** 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:** Responsible for the interpretation of data for the work, and critically revising the work for important intellectual content. **Satya Krishna Ramachandran:** 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:** 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:** 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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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