

Ionized hypocalcemia as a prognostic indicator in dogs following trauma

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Abstract

Objective – To determine the incidence of ionized hypocalcemia (iHCa) in dogs with blunt and penetrating traumatic injuries upon presentation to a hospital, and to determine the association of iHCa with mortality, duration of hospitalization, and requirement for intensive care therapies.

Design – Retrospective study (January 2007–December 2008).

Setting – University veterinary teaching hospital.

Animals – Eighty-eight dogs admitted to the ICU within 24 hours of a traumatic event and with assessment of a venous blood gas sample, including ionized calcium, at hospital admission.

Interventions – None.

Measurements and Main Results – Most dogs (72%) sustained injuries as a result of a motor vehicle accident. iHCa (<1.25 mmol/L [<2.50 mEq/L]) was present in 14 of 88 dogs (16%). Dogs with abdominal trauma were significantly more likely to have iHCa ($P = 0.020$) than dogs with other injuries. Dogs with iHCa spent significantly longer time in the hospital ($P = 0.036$) and ICU ($P = 0.005$), and were more likely to require oxygen supplementation ($P = 0.048$), synthetic colloids ($P = 0.020$), vasopressors ($P = 0.0043$), and blood transfusions ($P < 0.0001$). Six of 14 dogs (43%) with iHCa demonstrated clinical signs consistent with hypocalcemia during the course of hospitalization, and calcium gluconate was administered intravenously to one dog. Overall mortality was 16% (14/88) and dogs with iHCa were significantly less likely to survive ($P < 0.001$).

Conclusions – The incidence of iHCa upon hospital admission in this group of dogs with blunt and penetrating trauma is similar to the incidence of iHCa in critically ill dogs. Findings further suggest that dogs with iHCa are more severely injured and subsequently require increased intensive care therapies and have a lower likelihood of survival compared to dogs with normocalcemia. Ionized calcium concentration may therefore be a useful prognostic indicator in dogs with blunt and penetrating traumatic injuries.

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Introduction

Trauma is a common cause for animals to present to veterinary hospitals on an emergency basis. Injuries vary depending on the nature of the trauma, and the severity of the injuries and organ systems affected often determine the likelihood of survival. Several scoring systems have been developed in people to predict outcome following trauma based on the anatomical location and degree of the injuries.¹ The Animal Trauma Triage (ATT) score² was designed for this purpose in veterinary

medicine, but to date, it has not been validated prospectively in a large veterinary trauma population. Recent large retrospective studies in dogs with blunt trauma show that thoracic, extremity, and abdominal injuries are the most common; polytrauma or head injuries predict a higher mortality; and dogs with higher ATT scores are less likely to survive and have a higher cost of care.^{3,4}

Accurate prediction of the likelihood of survival and hospital discharge following traumatic injuries remains a challenge. Predictors of euthanasia or death in previous veterinary studies include cardiac arrhythmias, body wall hernias, severe soft tissue injuries, vertebral fractures, or recumbency at admission.^{3,4} In people, age, severity of injury, degree of physiologic derangement, and comorbidities are determinants of outcome following trauma.^{5–7} Additionally, studies in people have determined that lactate and base deficit measured on hospital admission are sensitive indicators of the severity of hemorrhagic shock and can be used to predict outcome.^{8–12}

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Recently, human studies have focused on the use of ionized calcium (iCa) to predict outcome following trauma.^{13–15} The incidence of ionized hypocalcemia (iHCa) in human trauma patients varies depending on the institution and iCa cut-off used, and ranges from 23% to 97%.^{13–15} iCa concentration measured at admission in people following trauma is a sensitive predictor of mortality; human patients with iHCa suffer from more severe injuries and are less likely to survive.^{14,15} Additionally, iHCa is associated with an increased risk of prehospital hypotension¹⁴ and cardiac arrest.¹³ When comparing iCa to other variables used to predict mortality in people, its sensitivity exceeds that of base deficit.^{14,15} In spite of this, a large retrospective study found no statistical difference in base deficit, lactate, or iCa between surviving and nonsurviving dogs following severe blunt trauma.³

Consequences of iHCa are numerous due to the multitude of physiologic roles of iCa including regulating vascular tone and myocardial contraction, and acting as a second messenger during cell signal transduction and a cofactor during hemostasis.¹⁶ iCa is also required for enzymatic reactions, nerve conduction, neuromuscular transmission, muscle contraction, hormone secretion, bone formation and resorption, and cell growth and division.¹⁶ The effect of iHCa on coagulation and vascular smooth muscle tone is of particular concern in trauma patients suffering from hemorrhagic shock. Recent recommendations suggest measuring iCa in trauma patients with hemorrhage, especially those requiring massive transfusions.^{17,18} While the evidence regarding treatment of iHCa in trauma patients is somewhat lacking, consensus guidelines recommend that in trauma patients requiring massive transfusions, if the iCa is low or electrocardiography (ECG) is suggestive of iHCa, that calcium supplementation be administered.¹⁸

The cause of iHCa in critically injured patients is unknown but several mechanisms have been investigated and are likely involved. These include increased calciuresis,¹⁹ dilution during fluid resuscitation,¹³ and cellular uptake of calcium following musculoskeletal injuries.²⁰ Other suggestions are chelation with citrate in patients administered blood products or lactate in patients with lactic acidosis.^{13,14} Other proposed mechanisms for iHCa in critical patients include aberrations in the hormones and electrolytes that regulate iCa such as parathyroid hormone (PTH), calcitonin, vitamin D, and magnesium.^{21–24} Koch et al¹⁹ investigated regulators of calcium homeostasis in a small group of human trauma patients and found that calcitonin was increased in people with iHCa, whereas PTH and vitamin D were normal.¹⁹ To date, veterinary studies investigating the incidence and etiology of iHCa in dogs with traumatic injuries and its impact on morbidity and mortality have not been reported. A prospective study investigating iCa in

critically ill dogs demonstrated a 16% incidence of iHCa; 13 dogs admitted for traumatic injuries were included but those dogs did not have an increased incidence of iHCa compared to other dogs in the study.²⁵

The objective of this study was to determine the incidence of iHCa upon presentation to the hospital in dogs with blunt and penetrating traumatic injuries, and to determine the association of iHCa with mortality, duration of hospitalization, and requirement for intensive care therapies. The authors hypothesized that, similar to other critically ill dogs,²⁵ dogs would have an incidence of iHCa of approximately 20% following trauma, and that dogs with iHCa would have increased mortality, a longer duration of hospitalization, and increased requirements for intensive care therapies.

Materials and Methods

Cases were selected by searching the Ontario Veterinary College Teaching Hospital database for dogs with trauma (ie, blunt or penetrating) admitted for emergency stabilization between January 1, 2007 and December 31, 2008. Cases were excluded if a venous blood gas (VBG) was not analyzed upon hospital admission, hospitalization in the ICU was not required, euthanasia was elected for financial reasons, dogs presented >24 hours following the traumatic episode, synthetic colloids or blood products were administered prior to admission, or information was missing from the medical record.

Medical records were reviewed and data were transcribed into a spreadsheet. Admission parameters recorded were as follows: signalment, body weight, body condition score, temperature, heart rate (HR), respiratory rate, blood pressure (BP), physical examination findings, and presence of arrhythmias (review of ECG recordings or medical record documentation). Data relating to the trauma were recorded as: cause of trauma, penetrating or blunt trauma, and location of the injuries (skin, appendage, thorax, head, abdomen, spine). Dogs were given a systems score of 1–6 depending on how many of these sites were affected. A modified Glasgow Coma Scale score²⁶ and ATT score² were calculated for each patient.

At the author's institution, all animals presenting as emergencies to the hospital are taken to the ICU where initial assessments are made, vital signs are recorded, and an IV catheter is placed. Thus, an emergency laboratory database consisting of packed cell volume, total plasma proteins, and VBG including electrolyte, glucose, and lactate concentrations, was obtained from dogs on admission to the hospital via direct venipuncture or evacuation from an IV catheter at the time of placement. The blood sample was obtained using a 3-mL commercial blood gas syringe^a containing lyophilized

heparin, filled with 1 mL of blood, and analyzed within 5 minutes of collection. Activated clotting time was also determined in most patients and was performed using standardized blood tubes^b and an activated clotting time test system.^c Other diagnostic test results (eg, complete blood count^d or biochemistry profile^e) were recorded if samples were obtained within 24 hours of admission. Additional data recorded included whether or not the dog received treatment at a referring veterinary clinic or experienced cardiopulmonary arrest prior to admission. Requirement for oxygen supplementation, synthetic colloids, vasopressors, blood transfusions, or mechanical ventilation was also recorded as an indication of the degree of intensive care provided for each patient.

Dogs were classified as having iHCa if the iCa was <1.25 mmol/L (<2.50 mEq/L), which is the low end of the analyzer^f reference interval established in clinically healthy dogs. Need for IV calcium supplementation and signs of iHCa (muscle tremors or fasciculations, stiff gait, restlessness, hypersensitivity to stimuli, facial pruritus, or seizures) were recorded. Outcome was classified as survivor (alive to discharge from the hospital) or non-survivor (euthanized due to a perceived grave prognosis or died despite ongoing medical care). Hospitalization was recorded as total days in hospital and days in ICU.

Statistical Methods

Continuous variables were analyzed for normality with a Shapiro Wilk test. Depending on normality, a Pooled Student or Wilcoxon Mann-Whitney test was used to assess differences in the mean or median for clinical and laboratory parameters between dogs with and without iHCa. Univariate exact conditional logistic regression was used to assess iHCa as a risk factor for provision of intensive care therapies during hospitalization or if iHCa was a risk factor for identification of arrhythmias. Exact conditional logistic regression was used to determine if continuous or categorical variables such as vital signs, VBG parameters, ATT scores, Glasgow Coma Scale scores, or other laboratory parameters were associated with an increased risk of iHCa. Univariate exact conditional logistic regression was used to assess iHCa as a risk factor for nonsurvival. Receiver operating characteristic (ROC) curves were generated to establish cutoff values for iCa for predicting mortality and the need for intensive care therapies. Probability curves were generated from ROC curves. A Spearman's correlation analysis was used to estimate the correlation between iCa and total calcium. Total hypocalcemia (tHCa) was defined as serum total calcium below the reference interval (<2.50 mmol/L [<5.0 mEq/L]). Exact conditional logistic regression was also used to assess tHCa as a risk factor for iHCa. Sensitivity, specificity, positive predictive value

(PPV), and negative predictive value (NPV) of tHCa as a predictor for iHCa were also estimated. Data analysis was performed by use of computer software.^g A value of $P < 0.05$ was considered significant for all comparisons.

Results

Of the records reviewed, 88 met inclusion criteria. Of these cases, 45 dogs were male (67% castrated) and 43 were female (74% spayed). Penetrating trauma (bite wounds) occurred in 16 dogs (18%) and the other 72 dogs (82%) sustained blunt trauma including motor vehicle accidents (63/72, 88%) and falls from height (9/72, 12%). Overall, 72% of dogs sustained injuries as a result of a motor vehicle accident. Fifty-five dogs sustained injuries to the skin (eg, abrasions, wounds, lacerations, degloving injuries, punctures), 47 dogs had injured appendages (eg, fractures, tendon ruptures, luxations), 37 dogs had evidence of thoracic trauma (eg, pneumothorax, hemothorax, rib fractures, pulmonary contusions, diaphragmatic hernia, tracheal tear), 20 dogs sustained head injuries (eg, traumatic brain injury [TBI], skull or jaw fractures, ocular injuries), 19 dogs sustained injuries to the abdomen (eg, hemoabdomen, intestinal rupture, abdominal hernia, bladder rupture, urethral tear), and 9 dogs had an injured spine (eg, fracture, luxation) (Figure 1).

iHCa (iCa <1.25 mmol/L [<2.50 mEq/L]) was documented in 14 of 88 dogs (16%). None of the dogs had ionized hypercalcemia. Admission characteristics and laboratory parameters in normocalcemic and hypocalcemic dogs are depicted in Tables 1 and 2, respectively. Dogs with iHCa had a significantly higher HR ($P = 0.021$), lower systolic BP ($P = 0.020$), higher ATT score ($P = 0.0071$), and higher systems score ($P = 0.0072$) than dogs with normal iCa (Table 1). Additionally, dogs with iHCa had significantly lower bicarbonate ($P = 0.010$) and base excess ($P = 0.019$) and significantly higher lactate ($P = 0.001$) and creatinine ($P = 0.049$) than normocalcemic dogs (Table 2).

The cause of trauma ($P = 0.88$) and classification of blunt versus penetrating trauma ($P = 1.0$) were not associated with the presence of iHCa on admission. Dogs with abdominal trauma were significantly more likely to have iHCa on admission ($P = 0.020$, OR = 2.3, CI = 1.1–4.6); however, none of the other affected body systems were associated with iHCa. Ventricular arrhythmias were documented on admission in 15 dogs (17%) but the presence of iHCa on admission was not associated with documentation of ventricular arrhythmias ($P = 0.69$). Sixty-two dogs (70%) received crystalloid fluid resuscitation at a referring veterinary clinic and 2 dogs suffered cardiopulmonary arrest prior to

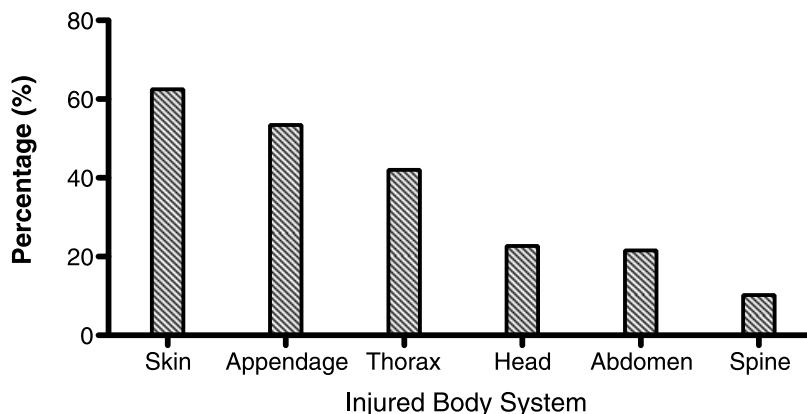


Figure 1: Percentage of injured body systems in 88 dogs following blunt and penetrating trauma.

admission; however, these dogs were not more likely to have iHCa ($P > 0.2$).

Dogs with iHCa upon admission to the hospital spent significantly more time in the hospital ($P = 0.036$, OR = 1.2, CI = 1.0–1.5) and ICU ($P = 0.005$, OR = 1.4, CI = 1.1–1.8) compared to normocalcemic dogs (Table 3). Dogs with iHCa upon admission were more likely to require intensive care therapies including oxygen supplementation ($P = 0.048$, OR = 90.9, CI = 1.0–1,000), synthetic colloids ($P = 0.020$, OR = 2.2, CI = 1.1–4.6), vasopressors ($P = 0.0043$, OR = 3.5, CI = 1.4–9.7), and blood transfusions ($P < 0.0001$, OR = 5.4, CI = 2.4–17.4) during hospitalization (Figure 2). The probability of requiring these interventions significantly increased as iCa decreased (Figure 3). Documentation of iHCa on admission was not associated with mechanical ventilation ($P = 1.00$) (Figure 2).

None of the normocalcemic dogs exhibited signs consistent with hypocalcemia, whereas 6 of 14 dogs (43%)

with iHCa demonstrated clinical signs consistent with hypocalcemia. Calcium was supplemented in one dog that was hit by a car and had a ruptured bladder, hemoabdomen, pulmonary contusions, and a fractured left talus with luxation of the talocalcaneal joint. The admission iCa was 1.07 mmol/L (2.14 mEq/L); however, following an abdominal exploratory approximately 24 hours after hospital admission, 2 transfusions of packed red blood cells (totaling 53 mL/kg), and a transfusion of fresh frozen plasma (28 mL/kg), the iCa decreased to 0.84 mmol/L (1.68 mEq/L) and the dog exhibited persistent hypotension (Doppler blood pressure of 70 mm Hg) requiring vasopressor support in the form of an IV constant rate infusion of norepinephrine (0.1–0.2 mcg/kg/min). Three hours after becoming hypotensive, calcium gluconate 0.5 mL/kg was administered IV over 20 minutes and raised the iCa to 1.01 mmol/L (2.02 mEq/L). Vasopressor therapy was discontinued 10 hours later and calcium supplementation was not

Table 1: Admission characteristics of normocalcemic and ionized hypocalcemic (iHCa) dogs following trauma

Parameter	Normocalcemic dogs					Hypocalcemic dogs					P-value
	N	Median	Min–max	Mean	SD	N	Median	Min–max	Mean	SD	
Age (years)	74	3.0	0.17–15	4.6	4.0	14	4.0	0.5–8.0	4.0	2.8	0.57
BW (kg)	73	17.2	1.2–47.8	20.0	13.8	13	7.0	4.1–51.5	14.4	14.7	0.18
BCS (0–5)	53	3	1–5	2.8	0.7	7	3	2.5–4.5	3.4	0.7	0.10
Temperature (°C)	72	38.0	34.9–39.5	38.0	0.9	13	37.3	35–41.3	37.6	1.9	0.29
HR (bpm)	74	120	40–196	117.0	35.8	14	142	0–250	145.1	63.1	0.021
RR (breaths/min)	52*	36	12–128	44.8	27.8	9	40	25–72	44.1	15.9	1.0
Systolic BP (mm Hg)	68	142	97–189	145.5	22.0	13	123	70–180	128.0	34.8	0.020
Mean BP (mm Hg)	66	111	61–172	107.8	18.4	10	107	74–151	107.7	22.8	0.98
Diastolic BP (mm Hg)	68	85	38–164	83.0	24.1	12	79	33–134	80.9	29.6	0.79
GCS score (0–18)	62	17	13–18	17.2	1.0	10	17	15–18	16.7	1.3	0.27
ATT score (0–15)	74	4	0–10	3.9	2.1	14	6	1–12	6.4	3.4	0.0071
Systems score (1–6)	74	2	1–5	2.1	1.1	14	3	1–6	3.1	1.6	0.0072

*RR was obtained in all dogs; however, values were excluded if recorded as “panting.” Bolded rows represent variables that were significantly different ($P < 0.05$) between normocalcemic and ionized hypocalcemic dogs. BW, body weight; BCS, body condition score; HR, heart rate; BP, blood pressure; GCS, Glasgow Coma Scale; ATT, Animal Trauma Triage.

Table 2: Laboratory parameters from normocalcemic and ionized hypocalcemic dogs following trauma

Parameter	Normocalcemic dogs					Ionized hypocalcemic dogs					P-value
	N	Median	Min-max	Mean	SD	N	Median	Min-max	Mean	SD	
pH	74	7.35	6.79–7.6	7.34	0.081	14	7.32	6.80–7.38	7.28	0.15	0.052
PvO ₂ (mmHg)	74	50.8	26.7–82.5	51.0	13.2	14	51.6	28.8–88.0	50.3	18.9	0.87
PvCO ₂ (mmHg)	74	41.8	27.6–76.5	42.7	7.4	14	41.2	28.8–60.4	41.7	9.6	0.68
SvO ₂ (%)	74	50.8	26.7–82.5	51.0	13.2	14	51.6	28.8–88.0	50.3	18.9	0.88
HCO ₃ (mmol/L)	74	22	10.5–28.8	22.0	3.1	14	20.3	8.1–25.2	19.2	4.6	0.010
BE (mmol/L)	73	-2.6	-25.7–3.2	-3.0	3.7	14	-6.2	-24.1–0.2	-6.4	5.8	0.019
Sodium (mmol/L)	74	147	141–156	147.8	3.4	14	146	140–166	147.6	7.0	0.98
Potassium (mmol/L)	74	3.7	2.7–6.7	3.8	0.6	14	3.7	2.9–5.8	3.9	0.8	0.41
iCa (mmol/L)	74	1.32	1.25–1.50	1.32	0.05	14	1.21	0.82–1.24	1.14	0.14	<0.001
iCa (mEq/L)	74	2.64	2.50–3.00	2.64	0.10	14	2.42	1.64–2.48	2.28	0.28	<0.001
Glucose (mmol/L)	74	7.3	4.4–49.0	8.4	5.7	14	8.5	3.9–27.0	9.8	5.5	0.40
Glucose (mg/dL)	74	132	79–883	151.4	102.7	14	153	70–486	176.6	99.1	0.40
Lactate (mmol/L)	74	1.7	0.5–15.0	2.3	1.9	14	4.3	1.6–17.0	5.9	4.3	0.001
PCV (%)	71	43	16–60	42.4	9.2	13	35	20–60	38.5	12.9	0.20
Total plasma protein (g/L)	71	62	40–96	62.4	11	13	58	38–86	56	13	0.066
Total plasma protein (g/dL)	71	6.2	4.0–9.6	6.24	1.1	13	5.8	3.8–8.6	5.6	1.3	0.066
ACT (seconds)	48	111	60–140	110.3	13.1	8	111	96–158	114.8	19.7	0.41
Platelet count (×10 ⁹ /L, ×10 ³ /μL)	44	216	78–495	227.3	95.3	11	165	13–427	192.1	124.6	0.31
Creatinine (μmol/L)	44	55.5	10.0–166.0	61.8	30.7	11	77.0	32.0–219.0	89.7	57.3	0.049
Creatinine (mg/dL)	44	0.63	0.11–1.88	0.70	0.35	11	0.87	0.36–2.48	1.01	0.65	0.049
Albumin (g/L)	45	33	19–41	32	5.2	11	31	17–47	30.5	9.6	0.39
Albumin (g/dL)	45	3.3	1.9–4.1	3.2	0.5	11	3.1	1.7–4.7	3.1	1.0	0.39
Total Ca (mmol/L)	48	2.49	1.69–2.99	2.45	0.25	12	2.24	1.31–2.71	2.19	0.41	0.027
Total Ca (mg/dL)	48	9.96	6.76–11.96	9.80	1.0	12	8.96	5.24–10.84	8.76	1.64	0.027
Phosphorus (mmol/L)	47	1.28	0.56–2.80	1.38	0.49	11	1.49	0.60–3.16	1.55	0.75	0.34
Phosphorus (mg/dL)	47	3.96	1.73–8.67	4.27	1.52	11	4.61	1.86–9.78	4.80	2.32	0.34

PvO₂, partial pressure of venous oxygen; PvCO₂, partial pressure of venous carbon dioxide; HCO₃, bicarbonate; BE, base excess; PCV, packed cell volume; Ca, calcium. Bolded rows represent variables that were significantly different ($P < 0.05$) between normocalcemic and ionized hypocalcemic dogs.

continued or repeated. Five days later the dog was discharged with an iCa of 1.20 mmol/L (2.40 mEq/L).

Overall mortality in this study was 16% (14/88) including 2 dogs that died and 12 dogs that were euthanized due to a perceived grave prognosis (Table 4). Dogs with iHCa on admission were significantly less likely to survive ($P < 0.001$, OR = 3.6, CI = 1.6–8.4). Five of 6 dogs (83%) with an iCa <1.20 mmol/L (2.40 mEq/L) on admission did not survive. ROC curve analysis (AUC =

0.774) revealed that an iCa value <1.20 mmol/L (2.40 mEq/L) on admission had a 35% sensitivity and 99% specificity for predicting mortality, whereas an iCa value <1.25 mmol/L (2.50 mEq/L) on admission had a 79% sensitivity and 60% specificity for predicting mortality in dogs following trauma.

Serum total calcium was moderately correlated with iCa (Figure 4). However, when the lower number for the reference interval (2.50 mmol/L [7.73 mg/dL]) was used as a cutoff for tHCa, the presence of tHCa was not predictive of iHCa ($P = 0.22$). Using an iCa of <1.25 mmol/L (2.50 mEq/L) as the gold standard for detecting hypocalcemia following trauma, tHCa (total calcium < 2.50 mmol/L [5.0 mEq/L]) had an 86% sensitivity and 32% specificity for detecting iHCa. The PPV of tHCa for iHCa was 19% and the NPV of tHCa for iHCa was 92%.

Discussion

The incidence of iHCa upon hospital admission following blunt and penetrating trauma in this group of dogs was 16%, similar to the incidence of iHCa found at ICU

Table 3: Length of hospitalization of normocalcemic and ionized hypocalcemic dogs following trauma

Calcium status	Days in Hospital*		Days in ICU**	
	Median (min-max)	Mean (±SD)	Median (min-max)	Mean (±SD)
Normocalcemic	3 (1–10)	3.7 (2.4)	3 (1–8)	3.1 (1.9)
Ionized hypocalcemic	5 (1–14)	5.5 (3.9)	5 (1–14)	5.3 (3.8)

*Dogs with iHCa spent significantly more days in hospital ($P = 0.036$) compared to dogs with normal iCa.

**Dogs with iHCa spent significantly more days in ICU ($P = 0.005$) compared to dogs with normal iCa.

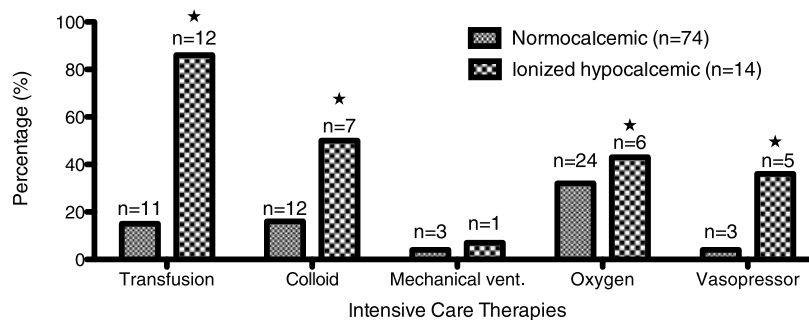


Figure 2: Percentage of normocalcemic and ionized hypocalcemic dogs (iHCa) requiring intensive care therapies following trauma. A star denotes a significant difference ($P < 0.05$) between dogs with normal ionized calcium (iCa) and iHCa.

admission in critically ill dogs previously.²⁵ More than 80% of dogs in this study suffered from blunt trauma, mostly due to motor vehicle accidents. The survival rate of these dogs was 84%, which is similar to that found in previous studies evaluating dogs with blunt trauma in which survival rates were between 86% and 88%.^{3,4,27} However, unlike a previous study that found no difference in iCa between survivors and non-survivors of blunt trauma in dogs,³ our study showed that dogs with an iCa < 1.25 mmol/L (2.50 mEq/L) were more likely to die, compared to dogs with a normal iCa concentration. Dogs with iHCa had a survival rate of 57% compared to normocalcemic dogs that had a survival rate of 89%.

As in this study, studies in adult human trauma patients show that admission iCa is predictive of mortality with mortality rates substantially increased in those patients with iHCa.^{14,15}

Similar to recent studies evaluating iCa in traumatized people, this study included dogs sustaining either blunt or penetrating injuries. No difference was found in the presence of iHCa in dogs with blunt versus penetrating injuries; however, dogs with abdominal injuries were more likely to have iHCa. Interestingly, 6 of the 19 dogs with abdominal injuries had a documented hemoabdomen but whether the iHCa contributed to the hemorrhage is unknown. Posttraumatic pancreatitis has been

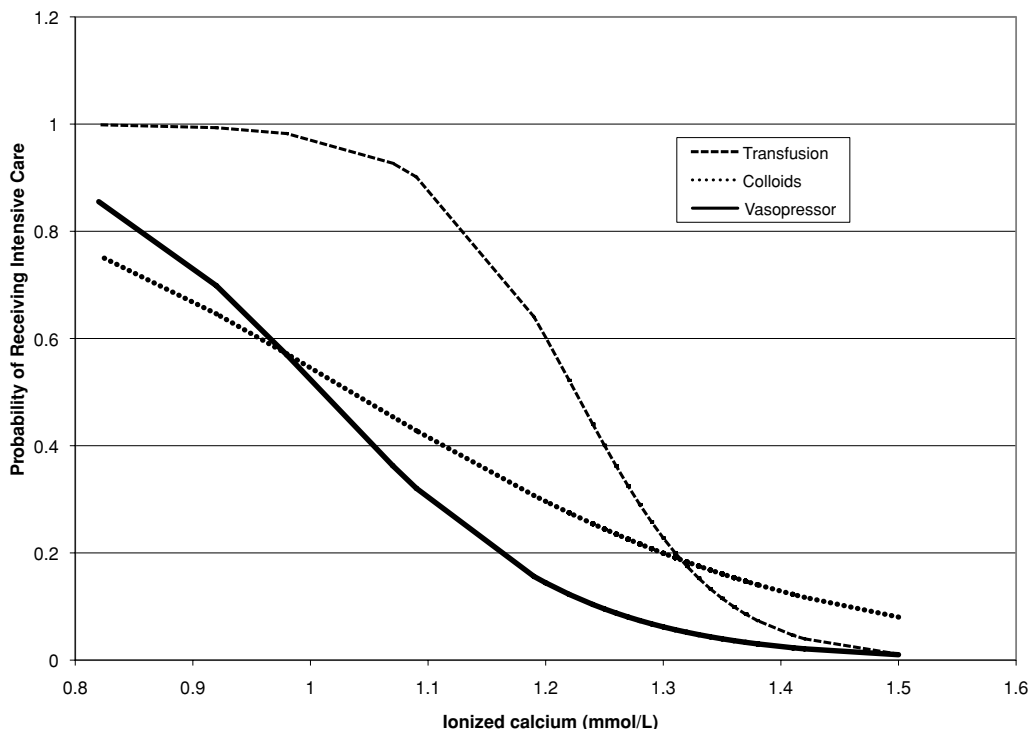


Figure 3: Probability curves for colloid, vasopressor, and blood transfusion administration in dogs following trauma with varying iCa concentrations.

Table 4: Mortality rate of normocalcemic and ionized hypocalcemic dogs following trauma

Calcium status	Survivors (n = 74)	Nonsurvivors (n = 14)	Mortality (%)
Normocalcemic	66	8	10.8
Ionized hypocalcemic	8	6	42.9

documented in adults and children following blunt abdominal injuries,²⁸⁻³⁰ and may have also been present in these dogs and contributed to the iHCa. Acute pancreatitis is a suggested cause of iHCa in dogs, presumably due to peri-pancreatic calcium accumulation.³¹ Posttraumatic pancreatitis has not been documented in dogs to the knowledge of the authors.

In contrast to our study, the incidence of electrolyte abnormalities including iHCa is significantly higher in human trauma patients with head trauma.^{13,32} In our study, of the 20 dogs with evidence of head trauma, 9 dogs had clinical signs consistent with TBI, 2 of those dogs received hypertonic saline, and 1 dog received mannitol. The small number of dogs included with severe TBI-requiring therapy may have precluded finding an increased incidence of iHCa in dogs with head injuries.

Upon admission, dogs with iHCa exhibited a significantly higher HR and lower systolic BP compared to normocalcemic dogs. Calcium is required for normal cardiac conduction, and hypocalcemia has been linked to tachycardia, prolonged QT syndromes, and tachyarrhythmias including torsades de pointes.^{33,34} While dogs with iHCa did not have a higher incidence of ventricular tachycardia, other arrhythmias may have been missed since not all dogs had a recorded ECG available for evaluation. Thus, the increased HR may be directly related to the iHCa, the severity of injuries and subsequent pain in the iHCa dogs, or an appropriate response to the lower systolic BP. In a group of human trauma patients, an iCa <1 mmol/L was associated with a systolic BP <90 mm Hg during transport to the hospital.¹⁴ Calcium is required to maintain vasomotor tone; therefore, it is logical that dogs with iHCa would be more likely to exhibit hypotension. Vivien et al¹³ showed that a low iCa was predictive of both prehospital hypotension and cardiopulmonary arrest in human patients with severe trauma. We did not find that pre-hospital cardiopulmonary arrest was increased in dogs with iHCa in this study; however, only 2 dogs with pre-hospital cardiopulmonary arrest were included.

Dogs with iHCa were also significantly more likely to have evidence of a metabolic acidosis including a decreased pH and bicarbonate, more negative base excess (increased base deficit), and a higher lactate on admission, which is consistent with human trauma

patients.^{14,15} Interestingly, alkalosis is an understood cause of iHCa in dogs, due to the subsequent increase in protein binding to calcium,³⁵ whereas acidosis has been associated with increases in iCa in dogs.³⁶ The association between lactic acidosis and iHCa in dogs following trauma may be of etiologic importance, as the lactate may chelate calcium leading to a reduction in iCa.^{13,14} However, other factors such as the severity of injury and shock could produce both the iHCa and lactic acidosis.

Dogs with iHCa had significantly higher ATT scores, suggesting that the severity of injury was greater in dogs with iHCa. Previous studies performed on large cohorts of human trauma patients have developed scoring systems to predict outcome based on injury severity.^{5,6} Therefore, it is logical that if iHCa is predictive of mortality, that it would also be found in conjunction with other mortality predictors such as injury severity. Dogs in this study with iHCa also had significantly higher systems scores, which indicated the number of body systems injured during the trauma. A previous study evaluated 42 human trauma patients with musculoskeletal injuries and found that as iCa decreased, the Acute Physiology and Chronic Health Evaluation (APACHE) II score significantly increased, suggesting an association between iHCa and severity of illness.²⁰ Another finding suggesting that dogs with iHCa in this study were more severely injured was their longer hospital and ICU stays. This was likely due to the prolonged recovery of these dogs due to their more severe injuries.

Increased morbidity in the dogs with iHCa was also exhibited by their increased need for intensive care therapies. As admission iCa decreased in traumatized dogs, the requirement for oxygen, synthetic colloids, vasopressors, and blood transfusions increased in an almost linear fashion. The increased requirement for colloids and vasopressors in trauma patients with iHCa is documented in people as well, and is likely due to the fact that hypotension is more frequently seen in people and dogs with iHCa. Hypotension is a common finding in traumatized people with iHCa,^{13,14} and has also been recognized in other critically ill hypocalcemic people.^{37,38} Studies in people with iHCa document an increase in arterial BP following IV calcium administration.^{39,40} While massive transfusions are a well-known cause of iHCa in human trauma patients, there is no documentation in the human literature as to whether admission iHCa predicts the need for transfusions in people following trauma, although, lower iCa concentrations are associated with lower hemoglobin concentrations in adult trauma patients.¹³ Given calcium's important role as a cofactor in coagulation, it is possible that the iHCa may have decreased clot formation and contributed to hemorrhage and the subsequent increased need for blood transfusions in these dogs.

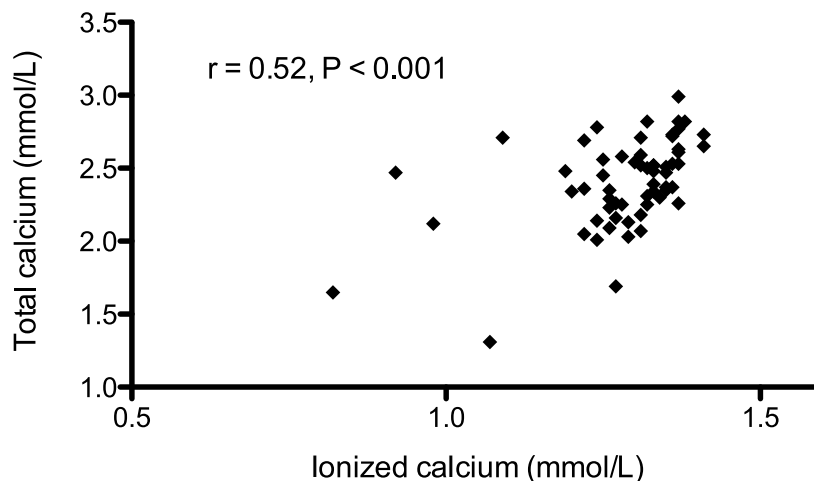


Figure 4: Spearman correlation between iCa and total calcium concentrations in dogs following trauma.

Treatment of iHCa in trauma patients is controversial as there is no clear evidence that parenteral calcium supplementation impacts the outcome of critically ill patients, mostly due to a lack of published studies evaluating the effects of calcium administration on morbidity and mortality.⁴¹ Dickerson et al published 2 studies evaluating the response to empiric calcium gluconate therapy in adult patients in a trauma ICU.^{42,43} Patients with documented iHCa (iCa < 1.13 mmol/L) were administered 1–4 g of IV calcium gluconate based on the severity of their iHCa. These studies confirmed that calcium gluconate, dosed based on the severity of iHCa, was effective in correcting iHCa. However, the studies were small and there were no data presented regarding the effect of calcium administration on BP, transfusion requirement, or outcome. Only one dog in this study was treated with IV calcium gluconate. Ideally, a prospective randomized study is warranted to evaluate the effect of calcium supplementation on outcome in trauma patients with iHCa.

In the present study, a serum total calcium measurement was obtained in 60 dogs during the first 24 hours of hospitalization. Total calcium was significantly decreased in dogs with iHCa and was moderately correlated with iCa in these dogs following trauma. Total calcium had a high NPV suggesting that, following trauma, dogs with normal total calcium concentrations are very unlikely to have iHCa. However, the specificity and PPV of total calcium for iHCa were poor, indicating that low total calcium is not always associated with iHCa. Likewise, when dogs were defined as hypocalcemic based on their total calcium concentrations, there was no statistical association with iHCa. These findings are similar to the recent human and veterinary literature suggesting that total calcium should not be used to estimate iCa in critically ill patients.^{44–47} Schenck and Chew evaluated

over 1,600 serum samples in dogs and found that serum total calcium concentrations, even when adjusted for albumin, were inaccurate at predicting iCa in 37% of the dogs and tended to underestimate hypocalcemia.⁴⁷ The relationship between total calcium, adjusted total calcium, and iCa was also evaluated in 100 human trauma patients in whom total calcium or correction formulas to predict iHCa resulted in an average of 75% false negatives.⁴⁸ Although total calcium correlated modestly with iCa in that study, the authors recommended that the direct measurement of iCa be used in human trauma patients.⁴⁸ Interestingly, Ward et al⁴⁹ evaluated total calcium in a population of human trauma patients and found it to be a good predictor of outcome; however, the minimum total calcium, measured during fluid resuscitation, was a less accurate predictor of outcome, compared to the final calcium concentration measured before discharge or death.⁴⁹ This suggests that timing of the calcium measurement may affect its utility as a prognostic indicator.

The most significant limitation of this study is its retrospective design. Because of this, we were unable to control for exactly how and when the VBG and other clinical and laboratory data were collected following admission. It is protocol at this institution to obtain a blood sample immediately upon admission via direct venipuncture or withdrawal through an IV catheter at the time of placement, so it is very likely that all blood samples, including those for the VBG, complete blood count, and biochemistry profile, were obtained immediately following hospital admission. However, serum total calcium concentrations taken from biochemistry profiles not obtained upon admission to the hospital may have been affected by IV fluid administration or other treatments performed; therefore, comparing those values to iCa obtained on hospital admission would not be

accurate. Lyophilized heparin syringes are always used to obtain the sample and a standard volume is collected. Therefore, the likelihood of heparin dilution causing the iHCa is low.⁵⁰ However, other causes of iHCa such as concurrent disease were not ruled out in dogs in this study since diagnostic evaluation for underlying causes of iHCa was not performed in most cases.

We limited data entry to 2 researchers; however, there is likely some degree of subjectivity in the interpretation of the medical record findings with regards to clinical signs of iHCa and reasons for euthanasia. While the authors attempted to exclude dogs that were euthanized due to perceived financial constraints and include dogs that were euthanized due to a perceived poor prognosis, this may be difficult to differentiate retrospectively due to incomplete documentation of communications or subjective interpretation of records. There may also be institutional bias given the data were collected from a single veterinary teaching hospital, although we sought to include patients who would most likely reflect those at other institutions by excluding those patients referred to our hospital >24 hours after injury. Nevertheless, we recognize that variables collected on admission may have been confounded by treatments performed by the referring veterinarian or upon admission to the hospital prior to blood collection. However, we did not include dogs that had received colloids or blood products prior to admission, as these may have affected the iCa concentrations. We did not elect to exclude dogs receiving prior crystalloid therapy because, as a tertiary referral hospital, prior treatment by a veterinarian is extremely likely. Ultimately, the administration of crystalloids by the referring veterinarian was not statistically significantly associated with iHCa at hospital admission; however, it is possible that these dogs had alterations in serum iCa that subsequently changed in the face of crystalloid fluid therapy.

Conclusions

The incidence of iHCa in this group of dogs with blunt and penetrating trauma was 16%, which is similar to the incidence of iHCa in critically ill dogs. Overall survival was 84%, with the mortality of dogs with iHCa significantly increased compared to normocalcemic dogs. Dogs with abdominal trauma, increased ATT scores, and more injured body systems were significantly more likely to have iHCa. Additionally, dogs with iHCa had a higher likelihood of tachycardia, hypotension, and lactic acidosis. Dogs with iHCa were also significantly more likely to require intensive care interventions including oxygen supplementation, colloid therapy, vasopressors, and blood transfusions. Due to the retrospective nature of this study, a cause and effect relationship between these

variables cannot be determined. However, these findings suggest that dogs with iHCa are more severely injured and subsequently require increased intensive care therapies and have a lower likelihood of survival compared to dogs with normocalcemia. A prospective study including a large number of severely injured dogs is required to investigate iCa and other prognostic indicators such as base deficit and lactate and to lend support to the findings in this study.

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Footnotes

- ^a Marquest Gaslyte, Vital Signs Colorado, Englewood, CO.
- ^b Actalyke MAX-ACT, Helena Laboratories, Beaumont, TX.
- ^c Actalyke Mini Activated Clotting Time Test System, Helena Laboratories.
- ^d Cobas 501, Roche Canada, Mississauga, ON, Canada.
- ^e Advia 120, Siemens, Burlington, ON, Canada.
- ^f ABL800 FLEX, Radiometer Canada, London, ON, Canada.
- ^g SAS OnlineDoc 9.1.3, SAS Institute, Cary, NC.

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