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Comparison of the effects of 7.2% hypertonic saline and 20% mannitol on electrolyte and acid-base variables in dogs with suspected intracranial hypertension

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Abstract

Background: Hyperosmolar agents frequently are used to decrease intracranial pressure but their effects on electrolyte and acid-base variables have not been prospectively investigated.

Objectives: Compare duration and magnitude of changes in electrolyte and acid-base variables after hyperosmolar treatment.

Animals: Twenty-eight client-owned dogs with intracranial hypertension caused by various pathologies.

Methods: Prospective, randomized, nonblinded, experimental cohort study. Fifteen dogs received a single dose (4 mL/kg) of 7.2% hypertonic saline (HTS), 13 dogs received 20% mannitol (MAN) 1 g/kg IV. Electrolyte and acid-base variables were measured before (T_0), and 5 (T_5), 60 (T_{60}), and 120 (T_{120}) minutes after administration. Variables were compared between treatments and among time points within treatment groups.

Results: Mean plasma sodium and chloride concentrations were higher after HTS than MAN at T_5 (158 vs 141 mEq/L; 126 vs 109 mEq/L) and significant differences were maintained at all time points. After HTS, plasma sodium and chloride concentrations remained increased from T_0 at all time points. After MAN, plasma sodium and chloride concentrations decreased at T_5, but these changes were not maintained at T_{60} and T_{120}. Plasma potassium concentration was lower at T_5 after HTS compared with T_0 (3.6 vs 3.9 mEq/L) and compared to MAN (3.6 vs 4.1 mEq/L). At T_{60} and T_{120}, plasma ionized calcium concentration was lower after HTS than MAN (1.2 vs 1.3 mmol/L). No significant differences were found in acid-base variables between treatments.

Conclusions and Clinical Importance: At the administered dose, dogs receiving HTS showed sustained increases in plasma sodium and chloride concentrations, whereas dogs receiving MAN showed transient decreases. Future studies should assess the

Abbreviations: AG, anion gap; AG_{corr}, anion gap corrected for albumin concentration; BE, base excess; CT, computed tomography; HTS, hypertonic saline; ICH, intracranial hypertension; LH, lithium heparin; MAN, mannitol; MRI, magnetic resonance imaging; $PvCO_2$, venous partial pressure of carbon dioxide; RI, reference interval; SID, strong ion difference; SIG, strong ion gap; TBI, traumatic brain injury.

effects of multiple doses of hyperosmolar agents on electrolyte and acid-base variables.

KEYWORDS
canine, hyperosmolar treatment, metabolic, traumatic brain injury

1 | INTRODUCTION

Intracranial hypertension (ICH) is a potentially life-threatening neurological emergency that can develop secondary to a variety of acute and chronic intracranial disease processes, such as traumatic brain injury (TBI), intracranial neoplasia, meningoencephalitis, hemorrhage, and status epilepticus.[1-4] Treatment for acute ICH is multimodal and influenced by the underlying cause, but a mainstay of medical treatment in both humans and small animals is the early administration of hyperosmolar agents.[4-8] The goal of IV hyperosmolar agents is osmotic mobilization of intracellular and interstitial water from non-traumatized brain tissue into the intravascular space. An intact blood-brain barrier is a prerequisite for the efficacy of hyperosmolar treatment. If this condition is met, osmotic shifts decrease intracranial volume and intracranial pressure, and cerebral perfusion pressure improves.[4,9]

Mannitol (MAN) and hypertonic saline (HTS) are the most extensively studied hyperosmolar agents for the treatment of ICH, and MAN remains the gold standard for the treatment of ICH in TBI patients.[5,6,10] More recently, HTS solutions of variable concentrations have been advocated as an alternative to MAN. It has been suggested that HTS might be superior in the treatment of ICH and in improving cerebral perfusion in humans and dogs.[11-15] Furthermore, HTS does not cause the pronounced and sustained diuresis that can be seen after MAN administration and therefore is less likely to put patients at risk of dehydration and hypovolemia.[16-18]

Both HTS and MAN administration have been implicated in the pathogenesis of clinically relevant alterations in electrolyte and acid-base balance in people and dogs. Plasma sodium concentrations are expected to increase after HTS administration, whereas MAN administration can cause dilutional hyponatremia because of water shifts into the intravascular space.[19] In people, potentially life-threatening hyperkalemia can occur after hyperosmolar IV volume expansion.[20-23] The most noticeable change in acid-base balance after administration of HTS is hyperchloremic metabolic acidosis, as a result of a more marked increase in plasma chloride concentration as compared with sodium concentration.[24-26] In contrast, by the induction of diuresis, MAN is more likely to favor development and maintenance of metabolic alkalosis.[18,27,28] Extensive literature on HTS and MAN treatment exists, but prospective, randomized comparisons of the electrolyte and acid-base effects of these 2 agents in dogs suffering from naturally occurring ICH caused by various underlying pathologies are lacking.

Our objective was to compare the duration and magnitude of effects on commonly measured electrolyte concentrations and acid-base variables of IV administered 7.2% HTS and 20% MAN in client-owned dogs with evidence of ICH, measured at 5 (T_5), 60 (T_{60}), and 120 (T_{120}) minutes after administration.

2 | MATERIALS AND METHODS

Data collection for our study occurred simultaneously with data collection for a study investigating the effects of 7.2% HTS and 20% MAN in dogs with ICH on osmolarity, whole blood coagulation, and platelet function previously conducted at our institution.[29]

The study was designed as a prospective, randomized, nonblinded experimental trial. Client-owned dogs presented to the Veterinary Medical Teaching Hospital at the University of Bern, Switzerland with evidence of ICH were prospectively screened for study enrollment between March 2013 and March 2016.

A diagnosis of ICH was made based on patient history, compatible clinical signs on neurologic examination, and supportive findings on magnetic resonance (MRI) or computed tomographic (CT) imaging studies, if available. Patient histories that included head trauma or polytrauma, preexisting intracranial neurologic signs raising a suspicion for or previously diagnosed intracranial neoplasia, inflammatory or infectious encephalopathies, ingestion of toxic substances with the potential for central nervous system manifestations, or prolonged status epilepticus in conjunction with compatible clinical signs were considered supportive of ICH. Neurologic examination by a board-certified neurologist was performed on every patient. Patients admitted by the Neurology Service had a neurologic examination conducted immediately, whereas consultation by a board-certified neurologist was performed within the first hour of patient admission for patients of the Emergency and Critical Care Service. Clinical criteria to substantiate the suspicion of ICH included a neuroanatomical localization to the forebrain or multifocal disease, severely altered mentation and miotic pupils, presence of a documented Cushing reflex (bradycardia and concurrent systemic hypertension), lack of improvement after cardiovascular stabilization, or deterioration of a patient's modified Glasgow Coma Scale score.[30] Evidence of intracranial mass effects, perilesional edema, transtentorial brain herniation, or other shifts of brain parenchyma on CT or MRI studies were considered indicative of ICH.[31]

The decision to administer hyperosmolar treatment to any patient with the aforementioned criteria was at the primary clinician's discretion. Patients were included in the study if they had evidence of ICH warranting hyperosmolar treatment. Exclusion criteria from study participation included azotemia (plasma creatinine concentration >1.58 mg/dL), body weight <7 kg, age <6 months or >12 years,

presence of diseases known to affect whole blood coagulation or platelet function, anemia, thrombocytopenia, and previous administration of hyperosmolar agents, synthetic colloids, or blood products within 2 weeks of study enrollment. Patients that were euthanized during the study period because of the severity of disease were not excluded from the study.

If hyperosmolar treatment was deemed indicated, dogs were randomized to receive either 7.2% HTS (Dr G. Bichsel AG, Interlaken, Switzerland) or 20% MAN (Dr G. Bichsel AG, Interlaken, Switzerland) by drawing a sealed study envelope containing a numbered card. A single bolus of the assigned study drug was administered as 7.2% HTS 4 mL/kg IV over 5 minutes or 20% MAN 1 g/kg (5 mL/kg) IV over 15 minutes using a syringe pump. Animals were excluded from the study if additional hyperosmolar treatments were administered during the study period. Additional isotonic crystalloid fluid therapy during the study period was allowed and administered at the primary clinician's discretion.

The Animal Experiment Committee of the Swiss Federal Veterinary Office approved the trial (registration number BE 90/13) and written informed owner consent was obtained for enrolled dogs. Clinical data collected on study participants included signalment (breed, age, and sex), body weight, the diagnosed or suspected underlying disease causing ICH, and the type and amount of additional isotonic crystalloid fluids administered throughout the study period.

Blood samples for assessment of electrolyte and acid-base variables were obtained before (T_0) administration of the hyperosmolar treatment and 5 (T_5), 60 (T_{60}), and 120 (T_{120}) minutes thereafter by direct venipuncture of the lateral saphenous vein. All blood samples were obtained using a 21G butterfly needle and vacutainer system and were collected by the same investigator (author I.D. Yozova). Blood samples for this study and the study evaluating the effects of hyperosmolar treatments on whole blood coagulation and platelet function[29] were collected in the following order: discard tube, 2 3.2% buffered sodium citrate tubes (BD vacutainer 1.8 mL coagulation tube, buffered trisodium citrate 3.2%, BD, Plymouth, United Kingdom) for coagulation assessments, 1 heparin tube (Li-Heparin LH 1.3, 1.3 mL tubes, Sarsteds AG, Sevelen, Switzerland) for assessment of plasma electrolyte concentrations and acid-base variables, and 1 K_2-EDTA tube (K_2EDTA 2 mL tubes, Sarstedt AG) for hematological analyses. Full plasma biochemical profiles were not performed as part of this study and their request was at the discretion of the primary clinician.

Electrolyte and acid-base analyses were performed within 5 minutes of sample collection using a commercial blood gas analyzer (RAPIDPoint 500; Siemens Healthcare AG). Analytes measured by the analyzer included pH, venous partial pressure of carbon dioxide ($PvCO_2$), and plasma concentrations of sodium, chloride, potassium, and ionized calcium. Corrected chloride concentration was calculated based on the following formula: $[Chloride_{corrected}] = [Chloride_{measured}] \times ([Sodium_{normal}]/[Sodium_{measured}])$[32] and 147 mEq/L was used as the mid-range normal plasma sodium concentration based on previously established institutional reference intervals (RI).[33] Actual bicarbonate and standardized bicarbonate concentrations, anion gap (AG), and extracellular and blood base excess (BE) were calculated by the analyzer. The AG corrected for albumin concentration (AG_{corr}) was calculated based on the following formula: $AG_{corr} = AG + 4.2 \times (3.77 - \text{plasma albumin concentration in g/dL})$.[34]

Strong ion difference (SID) was calculated based on the following formula: SID = ([sodium] + [potassium] + [ionized calcium]) − [chloride] in mmol/L.[35] Institutional RI for the RAPIDPoint 500 blood gas analyzer had been established previously using healthy dogs.[33]

2.1 | Statistical Analysis

A sample size calculation was performed to allow the detection of meaningful differences in acid-base status and the primary endpoint was pH. It rendered at least 9 vs 7 patients required in each treatment group to detect differences in pH from 7.35 to 7.45 and standard deviation (SD) of 0.07 for significance levels of 0.05 and 0.01, respectively, and 80% power (Software PASS, https://www.ncss.com/software/pass/). Secondary endpoints included plasma electrolyte concentrations and respiratory and metabolic acid-base variables.

Statistical analyses were performed using commercially available software (Prism 8.0, Graph Pad Software, La Jolla, California). Normality testing was performed on continuous variables using the Shapiro-Wilk test and by visually examining histogram plots. Data are presented as mean ± SD for normally distributed data and median (range) or median (interquartile range) for nonnormally distributed data. Population characteristics between the 2 patient groups receiving HTS and MAN were evaluated using Student's *t* test or Mann-Whitney *U* test for normally and non-normally distributed continuous data, respectively. Fisher's exact test was used for categorical data.

Comparison of electrolyte and acid-base variables among patients receiving HTS and those receiving MAN at each sampling time point was performed using Student's *t* test or Mann-Whitney *U* test. Within each treatment group, changes in electrolyte and acid-base variables with respect to a previous time point were assessed using repeated measures analysis of variance, Friedman test, or residual maximum likelihood ratio mixed effects models, for complete normally distributed, complete nonnormally distributed, and incomplete sets of paired data, respectively. Post hoc analyses were performed using Tukey's or Dunn's multiple comparisons tests. Bonferroni corrections were applied to adjust for multiple comparisons where appropriate. To avoid discarding weak but relevant effects, and because of the presence of missing values for some variables, use of a strict level of significance was avoided and *P* values interpreted as the gradient from 0 to 1.

3 | RESULTS

3.1 | Study population

Twenty-eight dogs with suspected ICH were prospectively included in the study, 15 in the HTS group and 13 in the MAN group. Available measurements from the 28 dogs at the individual sampling time points are

presented in Tables 1 and 2. Represented breeds included French bulldog (n = 4), Golden Retriever (n = 4), mixed-breed (n = 4), Labrador Retriever (n = 2), Border Collie (n = 2), and 1 each of Flat Coated Retriever, Cocker Spaniel, Boxer, Fox Terrier, German Shepherd Dog, Great Dane, Jack Russell-Terrier, Keeshond, Malinois, Saint Bernard, Tervuren, and Mudi. Sixteen dogs were male (9 intact, 7 neutered) and 12 were female (4 intact, 8 spayed). Dogs had a median age of 6 years and 3 months (range, 1 year and 1 month to 12 years and 6 months) and median body weight of 24.3 kg (range, 7.2-52.8 kg). No significant differences in signalment or body weight were found between the 2 treatment groups (age, $P = .87$; sex, $P = .45$; body weight, $P = .40$). Diagnostic imaging was available for 22 dogs and consisted of an MRI study in 21 and CT study in 2 dogs. One dog had both an MRI and CT of the head performed. Underlying diseases suspected to cause ICH included intracranial neoplasia (HTS group, n = 8; MAN group, n = 7), intoxication (HTS group, n = 1; MAN group, n = 2), head trauma (HTS group, n = 1; MAN group, n = 2), meningoencephalitis (MAN group, n = 2), hydrocephalus (HTS group, n = 1), presumptive hypertensive encephalopathy (HTS group, n = 1), and undetermined in 3 dogs in the HTS group.

In some patient samples, not all planned measurements could be carried out because of technical difficulties (blood clotting or machine electrode errors). In addition, blood samples from 5 dogs at T_{60} and another 3 dogs at T_{120} could not be obtained because of euthanasia before the measurement time points.

3.2 | Additional IV isotonic crystalloid fluid therapy

Twenty-three dogs (HTS group, n = 12, MAN group, n = 11) received balanced isotonic crystalloid fluids IV during the study period. Three dogs in the HTS and 2 in the MAN group received lactated Ringer's solution (Fresenius Kabi [Schweiz] AG, Kriens, Switzerland) solution and the remaining dogs (HTS n = 9, MAN n = 9) received Plasma-Lyte A (Baxter AG, Opfikon, Switzerland). The mean administered isotonic crystalloid fluid amount in ml/kg over the study period was not significantly

TABLE 1 Electrolyte concentrations measured before (T_0) and 5 (T_5), 60 (T_{60}), and 120 minutes (T_{120}) after IV administration of 7.2% HTS or 20% MAN to dogs with suspected intracranial hypertension

		Osmotherapeutic solution and sample size				
Variable	Time point	N	HTS	N	MAN	*P* value
Sodium (mEq/L [mmol/L]) (RI: 143-151 mEq/L)	T_0	15	148.0 ± 5.15	13	149.3 ± 5.38	.52
	T_5	15	157.8 ± 5.28*	13	141.0 ± 6.16*	<.001
	T_{60}	13	154.6 ± 5.65*,**	9	147.3 ± 6.55**	.01
	T_{120}	12	152.9 ± 4.78*,**	7	148.0 ± 3.99**	.03
Chloride (mEq/L [mmol/L]) (RI: 109-117 mEq/L)	T_0	15	112.5 ± 5.01	13	113.2 ± 5.54	.75
	T_5	15	125.8 ± 6.33*	13	109.1 ± 6.30*	<.001
	T_{60}	13	121.6 ± 5.17*,**	10	111.9 ± 6.17**	<.001
	T_{120}	12	120.7 ± 5.38*,**	8	111.6 ± 4.30**	<.001
$Chloride_{corrected}$ (mEq/L [mmol/L])	T_0	15	111.8 ± 4.11	13	111.4 ± 3.46	.79
	T_5	15	117.2 ± 4.01*	13	113.7 ± 3.94*	.03
	T_{60}	13	115.7 ± 3.48*	9	112.1 ± 3.52	.02
	T_{120}	12	116.0 ± 3.69*	7	111.4 ± 3.51**	.01
Potassium (mEq/L [mmol/L]) (RI: 3.6-4.8 mEq/L)	T_0	15	3.92 ± 0.43	13	3.98 ± 0.36	.70
	T_5	15	3.56 ± 0.37*	13	4.07 ± 0.44	.002
	T_{60}	13	4.01 ± 0.48**	10	4.03 ± 0.51	.89
	T_{120}	12	3.91 ± 0.38	8	3.81 ± 0.45	.58
Ionized Calcium (mg/dL [mmol/L]) (RI: 4.92-5.60 mg/dL [1.23-1.40 mmol/L])	T_0	15	4.96 (4.72-5.12) (1.24 [1.18-1.28])	13	5.0 (4.96-5.36) (1.25 [1.24-1.34])	.09
	T_5	15	4.68 ± 0.2 (1.17 ± 0.05)	13	4.88 ± 0.36 (1.22 ± 0.09)*	.07
	T_{60}	13	4.88 ± 0.36 (1.22 ± 0.09)	10	5.2 ± 0.32 (1.30 ± 0.08)**	.03
	T_{120}	12	4.48 ± 0.28 (1.21 ± 0.07)	8	5.12 ± 0.28 (1.28 ± 0.07)**	.03

Note: Data are presented as mean ± SD for normally distributed data or median (interquartile range) for nonnormally distributed data.
Abbreviations: HTS, hypertonic saline; MAN, mannitol; N, sample size; RI, institutional reference interval.[33]
Note: P-values refer to differences between HTS and MAN treatment at a given time point. *Different with respect to T_0 within a treatment group (adjusted $P < .05$). **Different with respect to T_5 within a treatment group (adjusted $P < .05$). ***Different with respect to T_{60} within a treatment group (adjusted $P < .05$).

TABLE 2 Acid-base variables measured before (T_0) and 5 (T_5), 60 (T_{60}), and 120 minutes (T_{120}) after IV administration of 7.2% HTS or 20% MAN to dogs with suspected intracranial hypertension

		Osmotherapeutic solution and sample size				
Variable	Time point	N	HTS	N	MAN	*P* value
pH (RI: 7.35-7.45)	T_0	15	7.36 ± 0.07	13	7.33 ± 0.10	.31
	T_5	15	7.35 ± 0.06	13	7.35 ± 0.07	.90
	T_{60}	13	7.37 (7.34-7.43)	10	7.37 (7.30-7.39)	.43
	T_{120}	12	7.39 (7.32-7.43)	8	7.37 (7.30-7.41)	.50
$PvCO_2$ (mm Hg) (RI: 28.6-44.7 mm Hg)	T_0	15	39.59 ± 8.98	13	43.35 ± 13.39	.38
	T_5	15	38.54 ± 9.57	13	38.55 ± 6.95	.99
	T_{60}	13	35.88 ± 6.20	10	40.74 ± 6.07	.07
	T_{120}	12	36.25 (28.98-40.85)	8	40.70 (36.35-50.48)	.13
Bicarbonate (act) (mEq/L [mmol/L]) (RI: 18.1-26.3 mEq/L)	T_0	15	21.93 ± 4.13	13	21.75 ± 3.12	.89
	T_5	15	20.52 ± 3.85*	13	20.75 ± 3.07	.86
	T_{60}	13	20.42 ± 3.13	10	21.86 ± 3.20	.29
	T_{120}	12	20.50 ± 3.23	8	23.31 ± 2.36**	.04
Bicarbonate (std) (mEq/L [mmol/L]) (RI: 19.7-24.8 mEq/L)	T_0	15	21.87 ± 2.88	13	21.11 ± 2.39	.45
	T_5	15	20.72 ± 2.69*	13	20.82 ± 2.65	.92
	T_{60}	13	21.30 (14.9-23.4)	10	22.2 (14.8-25.0)	.81
	T_{120}	12	21.05 ± 2.39	8	21.95 ± 1.88	.38
BE (ecf) (mEq/L [mmol/L]) (RI: −6.7 to 1.5 mEq/L)	T_0	15	−3.44 ± 4.36	13	−4.16 ± 3.22	.62
	T_5	15	−5.10 ± 3.98*	13	−4.83 ± 3.65	.85
	T_{60}	13	−4.80 (−5.95-[−1.95])	10	−2.8 (−4.8-[−1.5])	.45
	T_{120}	12	−4.71 ± 3.43	8	−2.56 ± 1.90**	.12
BE (B) (mEq/L [mmol/L]) (RI: −5.3 to 1.3 mEq/L)	T_0	15	−3.00 ± 3.72	13	−4.16 ± 3.22	.38
	T_5	15	−4.55 ± 3.43*	13	−4.42 ± 3.31	.91
	T_{60}	13	−3.70 (−13.0-[−1.1])	10	−2.40 (−12.2-0.50)	.65
	T_{120}	12	−4.03 ± 3.17	8	−2.70 ± 2.17	.31
AG (mEq/L [mmol/L]) (RI: 11.6-21.2 mEq/L)	T_0	15	17.43 ± 5.23	13	18.35 ± 4.14	.61
	T_5	15	15.04 ± 4.52*	13	15.23 ± 4.76*	.91
	T_{60}	13	16.58 ± 4.89	9	17.21 ± 3.26	.73
	T_{120}	12	15.64 ± 4.58	7	16.80 ± 4.50	.59
Albumin (g/dL) (RI: 3.0-4.1 g/dL)	T_0	14	3.90 ± 0.45	11	3.56 ± 0.64	.12
AG_{corr} (mEq/L [mmol/L])	T_0	14	17.43 ± 4.15	11	20.21 ± 4.01	.10
SID (mEq/L [mmol/L]) (RI: 34-40 mEq/L)	T_0	15	40.56 ± 4.85	13	41.37 ± 3.70	.62
	T_5	15	36.75 ± 4.60*	13	37.21 ± 3.93*	.77
	T_{60}	13	38.21 ± 4.36*	9	40.27 ± 3.61**	.25
	T_{120}	12	37.35 ± 4.16*	7	40.90 ± 3.85**	.08

Note: Data are presented as mean ± SD for normally distributed data or median (interquartile range) for nonnormally distributed data.
Abbreviations: AG, anion gap; AG_{corr}, anion gap corrected for albumin concentration; BE (ecf, extracellular base excess; BE (B), blood base excess; Bicarbonate (act), actual bicarbonate concentration; Bicarbonate (std), standard bicarbonate concentration; HTS, hypertonic saline; MAN, mannitol; N, sample size; $PvCO_2$, venous partial pressure of carbon dioxide; RI, institutional reference interval[33] except for SID, which was derived from[35]; SID, strong ion difference.
Note: P-values refer to differences between HTS and MAN treatment at a given time point. *Different with respect to T_0 within a treatment group (adjusted $P < .05$). **Different with respect to T_5 within a treatment group (adjusted $P < .05$). ***Different with respect to T_{60} within a treatment group (adjusted $P < .05$).

different between HTS and MAN groups (7.5 ± 7.4 and 6.7 ± 5.3 mL/kg; $P = .74$). Further details on dose and type of additionally administered IV crystalloid fluids can be found in Supplemental Table 1. Dogs in the HTS group received a median of 3.7 mL/kg/h (range, 0-17 mL/kg/h) and dogs in the MAN group received a median of 5 mL/kg/h (range, 0-10 mL/kg/h) of additional isotonic crystalloid fluids ($P = .71$).

3.3 | Plasma electrolyte concentrations

Plasma electrolyte concentrations in the 2 treatment groups at the 4 sampling time points are summarized in Table 1. No significant differences in plasma electrolyte concentrations were found at T_0 between the HTS and MAN group. Plasma sodium and chloride concentrations were significantly higher in the HTS group than in the MAN group at T_5, T_{60}, and T_{120}. Plasma potassium concentrations were significantly higher in the MAN group at T_5, as were ionized plasma calcium concentrations at T_{60} and T_{120}.

Plasma sodium and chloride concentrations were significantly increased from T_0 at T_5, T_{60}, and T_{120} after administration of HTS. At T_{60} and T_{120}, plasma sodium and chloride concentrations had returned to being significantly lower than at T_5. After MAN administration, plasma sodium and chloride concentrations were significantly decreased from T_0 at T_5, but this difference was not maintained at T_{60} and T_{120}. Plasma potassium concentrations after HTS administration were transiently significantly lower at T_5 compared with T_0. After MAN administration, plasma ionized calcium concentrations were transiently significantly lower at T_5 compared with T_0.

3.4 | Acid-base variables

Acid-base variables for both treatment groups at the 4 sampling time points are summarized in Table 2. Actual bicarbonate concentration at T_{120} was significantly higher in the MAN group. No statistically significant differences were found in any other acid-base variables between the 2 treatment groups at any time points.

The pH and $PvCO_2$ did not differ significantly over time within treatment groups. In the HTS group, actual bicarbonate concentration, extracellular BE, and AG were significantly lower at T_5 than at T_0, whereas in the MAN group actual bicarbonate and extracellular BE were significantly higher at T_{120} than at T_5 and AG was lower at T_5 than at T_0. Strong ion difference in the HTS group was significantly lower than at T_0 at all subsequent time points. In the MAN group, SID at T_5 was significantly lower than at T_0 and at T_{60} and T_{120} was significantly higher than at T_5.

3.5 | Plasma albumin concentration

Full plasma biochemical results including albumin concentrations were available for 25 dogs at T_0 and are included in Table 2. No repeat plasma albumin concentrations were available at any study time points. Seven measured plasma albumin concentrations fell outside of the institutional RI for dogs. In the HTS group, they included hypoalbuminemia of 2.97 g/dL in 1 dog and hyperalbuminemia ranging from 4.45 to 4.61 g/dL in 3 dogs. In the MAN group, they included hypoalbuminemia ranging from 2.30 to 2.95 g/dL in 3 dogs.

4 | DISCUSSION

In our study, the duration and magnitude of electrolyte and acid-base effects of IV administered 7.2% HTS and 20% MAN to a cohort of dogs with suspected ICH were evaluated. Plasma electrolyte concentrations differed significantly between the 2 treatment groups for at least 1 of the assessed time points. In dogs receiving HTS, plasma sodium and chloride concentrations were significantly higher than in dogs receiving MAN throughout the study period. Plasma sodium and chloride concentrations in the HTS group increased significantly by T_5 compared to baseline, and these increases were maintained at all time points. In contrast, after MAN administration, they decreased significantly by T_5 compared to baseline, and these changes were not maintained at T_{60} and T_{120}. A transient decrease in plasma potassium concentration was seen in the HTS group at T_5, followed by mild increases above baseline at T_{60} in the HTS and MAN groups. The plasma ionized calcium concentration transiently decreased at T_5 in the MAN group, followed by increases above baseline at T_{60} and T_{120}. No changes in pH or respiratory acid-base variables were observed between groups or over time within either treatment group. Actual bicarbonate concentration in the MAN group was higher than in HTS at T_{120} and, in the HTS group, actual bicarbonate concentration, extracellular BE, and AG were significantly lower at T_5 than at baseline. The changes in acid-base variables were minor and considered unlikely to be of clinical relevance in dogs with normal acid-base balance before administration of hyperosmolar agents.

4.1 | Plasma electrolyte concentrations

In addition to osmotherapy, HTS solutions can be used in patients with symptomatic hyponatremia to accomplish controlled increases in serum sodium concentration.[4,9,36,37] As such, a significant and parallel increase in plasma sodium and chloride concentrations after the administration of HTS but not MAN in the current study was expected. The prescribed dose of 4 mL/kg of 7.2% HTS equates to 4.9 mEq/kg of sodium, which, based on sodium deficit calculations, should increase a patient's plasma sodium concentration by approximately 7 mEq/L and the magnitude of the mean plasma sodium concentration increase observed in our study was consistent with these calculations.[36] As previously published, the maximum plasma osmolarity in this cohort of dogs occurred at T_5 after both HTS and MAN administration.[29] It therefore appears most likely that the decrease in plasma sodium and chloride concentrations in the MAN group at the same time point is secondary to the significant osmolarity increase. With the addition of MAN to the intravascular space, water moves from the intracellular and interstitial spaces to the intravascular space, thereby decreasing plasma electrolyte concentrations by dilution.[19] The return of plasma sodium and chloride concentrations to values similar to baseline could be explained by 2 factors: either a rapid decrease in osmolarity and dilutional effect, or the onset of MAN induced diuresis. Because osmolarity at T_{60} and T_{120} in this group of dogs remained significantly increased from baseline, it seems more

likely that urinary losses and intravascular fluid volume contractions contributed to normalization of plasma sodium and chloride concentrations.[18,29] Hypertonic saline and MAN both increase plasma osmolarity[29] and cause significant changes in plasma sodium and chloride concentrations over time that are more pronounced after HTS administration. Hypertonic saline therefore should be used cautiously in patients with unknown baseline plasma electrolyte concentrations, especially in patients in which dysnatremia or dyschloremia could be present. Alternatively, in patients with confirmed underlying electrolyte abnormalities, MAN could be considered. Because of MAN's potential to alter intravascular fluid volume and (to a lesser extent than HTS) plasma electrolyte concentrations, close monitoring of cardiovascular status and serial measurements of plasma electrolyte concentrations still should be performed. Mannitol furthermore should only be administered to euvolemic and euhydrated patients to minimize the risk of hypovolemia and more pronounced electrolyte changes.

In the HTS group, plasma potassium concentration showed a significant transient decrease below baseline at T_5, which most likely was caused by a dilutional effect at the time of peak osmolarity.[29] After T_5, the plasma potassium concentrations in both treatment groups followed a pattern of increase by T_{60} and then decrease to slightly below baseline by T_{120}. In people, transient hyperkalemia is described after intravascular volume expansion with both HTS and MAN.[20,22,38] The most commonly cited mechanism for hyperkalemia development is cellular dehydration leading to increased intracellular potassium concentrations with a subsequent increase in passive potassium outflow from the intracellular space down its concentration gradient, and it is likely that it was also the primary mechanism at play in the dogs in our study.[22,38] In contrast to our study, people receiving MAN during intracranial tumor resection show prolonged increases in serum potassium concentrations up to 180 minutes postinfusion. However, the administered MAN doses were higher at 1.5 g/kg IV,[38] and our shorter follow-up time and patients lost because of euthanasia limit the comparison. Patients with renal impairment also have been shown to experience transient, clinically relevant hyperkalemia after infusion of 5% HTS, with peak plasma potassium concentrations occurring at 150 to 180 minutes.[20] In our patient population of dogs suffering from ICH, changes in plasma potassium concentration were milder, more transient, and unlikely to be clinically relevant. Enrolled patients did not show evidence of renal failure, but the risk of prolonged or more pronounced hyperkalemia should be kept in mind if administering hypertonic agents to patients with concurrent renal dysfunction or at higher doses, and plasma potassium concentrations should be monitored closely in patients at risk for developing hyperkalemia.

In the HTS group, plasma ionized calcium concentration did not differ significantly from baseline at any sampling time point, but decreased below RI after HTS administration. In the MAN group, plasma ionized calcium concentration decreased significantly but transiently by T_5 and then increased to concentrations higher than baseline, but this difference was not significant. Alkalemia is a well-established cause of ionized hypocalcemia, and experimental metabolic and respiratory alkalosis decrease the concentration of and response to parathyroid hormone, thus enabling hypocalcemia.[39,40] Based on normal mean pH and actual bicarbonate concentrations at T_5, alkalemia or metabolic alkalosis do not appear to be responsible for the transient hypocalcemia, and a dilutional effect at the time of peak osmolarity seems more likely.[29] The increase in plasma ionized calcium concentration and the significant difference in the HTS group at T_{60} and T_{120} after MAN administration could be secondary to decreased calciuresis during extracellular volume depletion. Extracellular volume contraction may impair renal clearance of ionized calcium.[41,42] Mannitol has been shown to induce a significant and sustained diuresis after IV administration and it remains possible that extracellular volume contraction contributes to the increases in plasma ionized calcium concentration.[18] However, the beginning decrease in plasma ionized calcium concentration by T_{120}, when MAN diuresis and volume contraction should still be ongoing, makes it less likely that it is the main mechanism at play. More likely, the fading of a dilutional effect that was present 5 minutes after MAN administration could explain the apparent increase in plasma ionized calcium concentration.

Blood for measurement of electrolyte and acid-base variables in our study was collected into nonbalanced lithium heparin (LH) tubes instead of blood gas syringes containing dry calcium-balanced LH typically recommended for the measurement of ionized calcium concentrations. Nonbalanced LH can complex and decrease the amount of measurable ionized calcium, leading to significant concentration differences measured from LH tubes and blood gas syringes in dogs.[33,43,44] The blood sampling method used in our study therefore could have contributed to low measured plasma ionized calcium concentrations. However, given that the same sampling method was employed at every sampling time point, changes of plasma ionized calcium concentration over time should still be evaluable. Overall, at the doses described herein, changes in plasma ionized calcium concentration were small in both groups and unlikely to be clinically relevant if patients have normal plasma ionized calcium concentration at the time of treatment.

4.2 | Acid-base variables

Neither HTS nor MAN was found to cause clinically relevant alterations in acid-base balance in this cohort of dogs with suspected ICH. No abnormalities in $PvCO_2$ as the marker of the respiratory system were observed between groups or within groups over time. Venous blood samples were used for acid-base analysis in our study and the site of blood sample collection might have influenced acid-base variables. Statistically significant differences in pH, PCO_2, and bicarbonate concentrations exist when comparing arterial with venous blood samples in healthy research dogs.[45] These differences are relatively small and in critically ill people with adequate peripheral perfusion, venous blood samples are considered an adequate substitute for arterial blood samples for the purpose of acid-base analysis.[46,47] Although arterial PCO_2 would have been ideal to assess the respiratory system, $PvCO_2$ is considered an acceptable replacement in this cohort of

cardiovascularly stable dogs, and the added anesthesia time required for placement of, and increased potential morbidity risk associated with, arterial catheter placement could not be justified.

In our study, the recorded pH remained within institutional RI in both groups at most time points, indicating that the few statistically significant differences in metabolic variables were also unlikely to be clinically relevant.

The actual bicarbonate concentration in the HTS group decreased significantly by T_5 and remained decreased throughout the study period. In the MAN group, the actual bicarbonate concentration at T_{120} was significantly higher than at T_5 and at that time point was significantly higher than in the HTS group. Metabolic acidosis is a known consequence of the administration of both isotonic saline and HTS solutions.[26,48] The most abundant strong ions that are completely or nearly completely dissociated in plasma are sodium and chloride and their difference (the SID) makes blood plasma alkaline.[25] When equal amounts of sodium and chloride ions, such as in HTS, are added to plasma with a lower baseline chloride than sodium concentration, SID decreases and the blood plasma becomes more acidic.[24,25] Hypertonic saline induced hyperchloremia was documented in our patient population and is therefore the most likely explanation for this observed relative metabolic acidosis compared to baseline. Despite statistically significant changes over time, actual bicarbonate concentrations remained within institutional RI at all time points and changes are considered unlikely to be of clinical importance. The dogs in the HTS group however had a low normal mean plasma chloride concentration and minimally increased mean SID before administration of HTS. This likely contributed to their ability to tolerate the administered chloride load without a potentially clinically relevant decrease in bicarbonate concentration and pH below RI. These findings therefore cannot be extrapolated to patients with preexisting hyperchloremia or metabolic acidosis. Additional studies are needed to investigate the extent of HTS-induced metabolic acidosis in such patient populations and, until more information is available, HTS should only be used cautiously in ICH patients with concurrent hyperchloremia or metabolic acidosis.

In contrast, patients treated with MAN in our study experienced a statistically significant increase of actual bicarbonate concentration by T_{120}, and different pathophysiological processes could have contributed to the development of this relative metabolic alkalosis. The administration of 2 g/kg of MAN to dogs with concurrent ICH and hypotension induces significant and prolonged diuresis, starting at 90 minutes after administration, and is maintained beyond 210 minutes.[18] Although the aforementioned study showed no impairment of macroperfusion parameters despite pronounced diuresis, metabolic alkalosis secondary to a decrease in effective circulating volume also has been described.[27,28] In our study, neither urine output nor cardiovascular parameters were recorded at the blood sampling intervals, and an assessment of effective circulating volume status at the time of bicarbonate increase was not possible. Based on previous studies, it is unlikely for substantial diuresis and hypovolemia to be present 1 hour after MAN administration, but they could have developed and contributed to the increase in bicarbonate concentration by T_{120}. Alternatively, osmotic diuretics previously have been shown to induce increased renal bicarbonate production.[49] Given the relatively rapid increase in bicarbonate concentration in this group of dogs, however, this seems to be a less likely explanation than a decrease in effective circulating volume. Mean actual bicarbonate concentrations before MAN administration was in the lower half of the institutional RI in this cohort of dogs. The exacerbation or development of clinically relevant metabolic alkalosis after MAN administration remains possible and, especially in patients with preexisting metabolic alkalosis or suspicion for hypovolemia, MAN should be used with caution.

No differences in extracellular BE and AG were seen between treatment groups at any time point. The significant differences from baseline and T_5 at T_5 and T_{120} respectively can be explained by changes in the bicarbonate concentration at the same time points. Four dogs in the current study were hypoalbuminemic before study drug administration, which can lead to decreases in AG and mask the presence of unmeasured anions.[34,35] Anion gap at baseline, where plasma albumin concentration was known, therefore was corrected and was not significantly different between treatment groups. Although changes in plasma albumin concentration over time were not monitored in our study, the changes in uncorrected AG after HTS and MAN administration suggest a lack of accumulation of unmeasured anions.

The changes in SID over time in the MAN group can be explained by the previously discussed shifts in total body water distribution and associated changes in plasma sodium and chloride concentrations. As water shifts from the intracellular to the intravascular space, the excess in free water and dilutional decrease in plasma sodium concentration lead to a decrease in SID that is only maintained until MAN-induced diuresis sets in. In the HTS group, decreases in SID compared with baseline can be explained by an imbalance of strong ions because of a more pronounced increase in plasma chloride concentration compared with sodium concentration.[24,50]

4.3 | Limitations

Despite its prospective nature, our study had several limitations. First, a small number of dogs receiving a single dose of a hyperosmolar agent were enrolled in the study. This number was decreased further by technical difficulties or euthanasia that precluded the measurements of every electrolyte and acid-base variable at every sample time point for all initially enrolled patients. Although the exclusion of dogs requiring additional doses of hyperosmolar treatment might have introduced a selection bias toward less severely affected dogs, the fact that some of the dogs initially entered into the study were euthanized speaks against it.

Second, nonbalanced LH tubes were used for electrolyte and acid-base sample collection via vacutainer system. This system was chosen to allow for the most consistent sampling method for evaluation of coagulation parameters in our accompanying study.[29] For most consistent and reliable measurements of acid-base variables, samples ideally should be anaerobically collected into purpose-made blood gas

syringes and analyzed immediately.[51] In comparison with anaerobic blood samples, samples collected into LH tubes show a significantly lower $PvCO_2$, a decrease in bicarbonate concentration, and an increase in pH.[51] Similar findings have been reported when comparing the 2 sampling methods using the RAPIDpoint 500 system in dogs.[33] Panels derived from LH tubes showed significant differences in pH, $PvCO_2$, actual bicarbonate, extracellular BE, ionized calcium, and AG.[33] Blood BE, standardized bicarbonate, and the remaining electrolyte concentrations were not significantly different.[33] Because of these reports, standard bicarbonate and blood BE were included in our data analysis and found to show very similar changes between and within groups as actual bicarbonate and extracellular BE.

Third, full plasma biochemistry results were inconsistently available at baseline and were not repeated at subsequent sampling time points. Albumin is an anion that contributes substantially to the normal AG. If hypoalbuminemia is present, the AG is decreased and may fail to identify the presence of unmeasured anions.[34,35] Strong ion gap (SIG) would have been an alternative measure to evaluate for the presence of unmeasured anions that is not influenced by plasma albumin concentrations. The calculation of SIG most commonly includes phosphorus, which was not measured in our study, and therefore SIG could not be evaluated.[52] The decision to only assess RAPIDpoint 500 panels after study drug administration was made to minimize patient blood loss, and because of our concurrent study, blood samples for complete coagulation and hematological analyses were prioritized.[29] A substantial accumulation of unmeasured anions that would have justified the reevaluation of biochemical panels furthermore was not expected secondary to HTS or MAN administration.

Most dogs in our study received isotonic crystalloid fluid therapy in addition to the hypertonic treatment assigned. Treatment with isotonic crystalloid fluids was at the discretion of the primary clinician if deemed indicated for additional patient stabilization, and could not be withheld for the purpose of our study for ethical reasons. The variable amount of isotonic crystalloid fluids administered in our study is a confounding variable and it is possible that this intervention blunted or contributed to changes in the variables evaluated. However, the administered amounts were similar in both the HTS and MAN groups.

Lastly, our study evaluated changes in plasma electrolyte concentrations and acid-base variables in dogs with suspected ICH that, in the majority of patients, was secondary to intracranial neoplasia or TBI. No comorbidities leading to clinically relevant metabolic derangements were evident in the study population, and therefore the results cannot be extrapolated to dogs with concurrent preexisting metabolic abnormalities. The lack of blinding and the exclusion of dogs that required additional doses of hyperosmolar therapy from the study constitute sources of bias. It is likely that more pronounced changes in electrolyte and acid-base variables can be observed in patients with more severe ICH requiring multiple doses of hyperosmolar agents and further prospective studies are necessary to investigate the extent and importance of such changes.

In conclusion, dogs suffering from ICH treated with HTS or MAN showed significant changes in plasma electrolyte concentrations. Hypertonic saline administration led to an increase in plasma sodium and chloride concentrations sustained until 2 hours after administration, whereas transient decreases 5 minutes after MAN administration were observed. Changes in acid-base variables were mild and unlikely to be clinically relevant in this cohort of dogs with normal baseline acid-base status. Care should be taken when using hyperosmolar agents in dogs with preexisting electrolyte or acid-base abnormalities and volume status and electrolyte and acid-base variables should be monitored carefully.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by University of Bern and the Animal Experiment Committee of the Swiss Federal Veterinary Office (No. BE 90/13). Informed owner consent was obtained before study enrollment.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

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