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Urinary strong ion difference is a major determinant of plasma chloride concentration changes in postoperative patients

Diferença de íons fortes na urina como determinante importante das alterações na concentração plasmática de cloreto em pacientes no pós-operatório

ABSTRACT

Objective: To show that alterations in the plasma chloride concentration ($[Cl^-]_{plasma}$) during the postoperative period are largely dependent on the urinary strong ion difference ($[SID]_{urine}=[Na^+]_{urine}+[K^+]_{urine}-[Cl^-]_{urine}$) and not on differences in fluid therapy.

Methods: Measurements were performed at intensive care unit admission and 24 hours later in a total of 148 postoperative patients. Patients were assigned into one of three groups according to the change in $[Cl^-]_{plasma}$ at the 24 hours time point: increased $[Cl^-]_{plasma}$ (n=39), decreased $[Cl^-]_{plasma}$ (n=56) or unchanged $[Cl^-]_{plasma}$ (n=53).

Results: On admission, the increased $[Cl^-]_{plasma}$ group had a lower $[Cl^-]_{plasma}$ (105 ± 5 versus 109 ± 4 and 106 ± 3mmol/L, p<0.05), a higher plasma anion gap concentration ($[AG]_{plasma}$) and a higher strong ion gap concentration ($[SIG]$). After

24 hours, the increased $[Cl^-]_{plasma}$ group showed a higher $[Cl^-]_{plasma}$ (111 ± 4 versus 104 ± 4 and 107 ± 3mmol/L, p<0.05) and lower $[AG]_{plasma}$ and $[SIG]$. The volume and $[SID]$ of administered fluids were similar between groups except that the $[SID]_{urine}$ was higher (38 ± 37 versus 18 ± 22 and 23 ± 18mmol/L, p<0.05) in the increased $[Cl^-]_{plasma}$ group at the 24 hours time point. A multiple linear regression analysis showed that the $[Cl^-]_{plasma}$ on admission and $[SID]$ urine were independent predictors of the variation in $[Cl^-]_{plasma}$ 24 hours later.

Conclusions: Changes in $[Cl^-]_{plasma}$ during the first postoperative day were largely related to $[SID]_{urine}$ and $[Cl^-]_{plasma}$ on admission and not to the characteristics of the infused fluids. Therefore, decreasing $[SID]_{urine}$ could be a major mechanism for preventing the development of saline-induced hyperchloremia.

Keywords: Postoperative care; Isotonic solutions/adverse effects; Urine/analysis; Chlorides/metabolism

INTRODUCTION

Chloride is the primary anion in the extracellular fluid. The chloride concentration differs in different compartments and cell types, and the concentrations in the plasma ($[Cl^-]_{plasma}$) and interstitial fluid are approximately 105 and 117mmol/L, respectively. The intracellular chloride ion concentration is low because of the presence of other anions, such as DNA, RNA, proteins, and phosphate. Three major mechanisms that determine the homeostasis of chloride include input through digestive or parenteral routes, output primarily through the urine and secondarily by the feces, and the ion shift among body compartments.[1]

The evaluation of $[Cl^-]_{plasma}$ is a key step in the analysis of the acid-base status of critically ill patients. Chloride is a strong anion; therefore, its changes modify the strong ion difference in the plasma ($[SID]_{plasma}$). According to the Stewart approach, the $[SID]_{plasma}$ is an independent variable that induces changes in the dissociation of water and, as a consequence, changes in pH.[2] Examples of these alterations are hyperchloremic metabolic acidosis and hypochloremic metabolic alkalosis.

Hyperchloremic metabolic acidosis is a common condition in postoperative patients. Despite the lack of definitive evidence, experimental and clinical studies suggest that this disorder produces deleterious effects.[3-7] The pathogenesis of hyperchloremic metabolic acidosis is often attributed to the infusion of large amounts of saline solutions that have supraphysiological concentrations of chloride.[8,9] Another major mechanism that could theoretically contribute to the development of this condition is the elimination of chloride in the urine. An inadequate renal response in the face of a chloride load could facilitate the development or perpetuate the occurrence of hyperchloremia over time. Although critically ill patients with metabolic acidosis frequently exhibit an abnormal renal response,[10] this mechanism has not yet been assessed as a determinant of postoperative hyperchloremia.

Our goal was to evaluate the determinants of $[Cl^-]_{plasma}$ during the first postoperative day, especially with respect to the relationship between strong ion input through intravenous fluids and strong ion output by the kidneys. Our hypothesis was that the modifications in $[Cl^-]_{plasma}$ are largely dependent on the behavior of the urinary strong ion difference ($[SID]_{urine}=[Na^+]_{plasma}+[K^+]_{plasma}-[Cl^-]_{urine}$) and not on differences in the fluids administered.

METHODS

This was a prospective cohort study conducted in a teaching intensive care unit. We included consecutive patients admitted during the immediate postoperative period over ten months. Patients with renal failure (serum creatinine levels >1.7mg/dL) or bladder irrigation, patients without urinary catheterization, and patients with incomplete data were excluded.

Our study was approved by the Institutional Review Board (#17,032,010). Standard procedures were applied in the diagnosis; thus, only permission to use these data was requested from patients or relatives.

Measurements

At intensive care unit (ICU) admission, demographic data (age, gender), the Acute Physiology and Chronic Health Evaluation II (APACHE II) score,[11] the predicted risk of mortality, and the Sequential Organ Failure Assessment (SOFA) score[12] were calculated. Arterial blood samples were analyzed for gases (AVL OMNI 9, Roche Diagnostics, Graz, Austria); strong ion concentrations, including $[Na^+]$, $[K^+]$ and $[Cl^-]$ (selective electrode ion, AEROSET, Abbott Laboratories, Abbott Park, Illinois, U.S.A.); $[Ca^{++}]$ (selective electrode ion, AVL OMNI 9), $[Mg^{++}]$ (Arsenazo dye/Mg complex); [albumin] (Bromcresol-sulfonphthaleinyl); $[Pi^-]$ (molybdate-vanadate); and [lactate] (selective electrode ion, AVL OMNI 9). $[Na^+]$, $[K^+]$ and $[Cl^-]$ were also measured in the urine. These measurements were repeated 24 hours later. The volume and characteristics of the fluids administered during the surgery and the first postoperative day were also recorded.

We calculated the $[HCO_3^-]$ and extracellular base excess ([BE]) using the Henderson-Hasselbalch[13,14] and Van Slyke equations.[15,16] The plasma anion gap ([AG]) was calculated as $[AG]=([Na^+]+[K^+])-([Cl^-]+[HCO_3^-])$[17] and was corrected for the effects of an abnormal albumin concentration:[18] $[AG]_{corrected}$ (mmol/L)=$[AG]_{observed}$+0.25 * ([normal albumin] - [observed albumin]) (in g/L). The $[SID]_{urine}$ was calculated as $[SID]_{urine}=([Na^+]_{urine}+[K^+]_{urine})-[Cl^-]_{urine}$,[10] and the [SID] effective was calculated as $[SID]_{effective}=[HCO_3^-]+[albumin^-]+[Pi^-]$.[19] Normal values of $[SID]_{effective}$ are 40±2mmol/L.[20] The apparent [SID] was calculated as $[SID]_{apparent}=[Na^+]+[K^+]+[Ca^{++}]+[Mg^{++}]-[Cl^-]$.[20] The $[albumin^-]$ (g/L) and $[Pi^-]$ (mmol/L) were calculated based on measured values and pH using the following equations: $[albumin^-]$=[albumin] * (0.123 * pH−0.631) and $[Pi^-]$=[Pi] * (0.309 * pH−0.469), respectively.[19] The strong ion gap ([SIG]) consists of strong anions other than $[Cl^-]$, including lactate, ketoacids and other organic anions, and sulfate, and was calculated as $[SIG]=[SID]_{apparent}-[SID]_{effective}$.[19] We adjusted the $[Cl^-]$ and [SIG] for water excess/deficit by multiplying the observed value by a correcting factor ($[Na^+]_{normal}/[Na^+]_{observed}$).[19] Normal values of [SIG] are 2±2mmol/L.[20]

Data analysis

Patients were assigned to one of three groups according to their variation in $[Cl^-]_{plasma}$ over the 24 hours period: increased $[Cl^-]_{plasma}$ (increase ≥2mmol/L), decreased $[Cl^-]_{plasma}$ (decrease ≥2mmol/L), and unchanged $[Cl^-]_{plasma}$ (change <2mmol/L).

A normal distribution was confirmed using the Kolmogorov-Smirnov test. One-way or two-way repeated measures ANOVA followed by post-hoc tests was used to identify specific differences between and within groups. A multiple linear regression analysis was performed to identify independent predictors of the 24 hours $[Cl^-]_{plasma}$ variation. A p value <0.05 was considered significant.

RESULTS

A total of 220 patients were screened. Out of these patients, 148 of them were included, and 72 were excluded because of serum creatinine levels >1.7mg/dL (n=11), bladder irrigation (n=20), a lack urinary catheterization (n=23), incomplete data registration (n=15), or death during the study period (n=3).

The $[Cl^-]_{plasma}$ increased in 39 patients, decreased in 56, and remained unchanged in 53. Table 1 summarizes the epidemiologic and clinical conditions of the patients. There were no differences in the plasma creatinine levels among the three groups. The 24 hours changes in creatinine plasma concentration were 0.0±0.2, 0.0±0.3, and –0.1±0.4 in the increased $[Cl^-]_{plasma}$, decreased $[Cl^-]_{plasma}$, and unchanged $[Cl^-]_{plasma}$ groups, respectively (p=NS). The percentages of patients who met the criterion for stage 1 of the AKIN classification (increase in the plasma creatinine concentration ≥0.3mg%) were 10, 14, and 15%, respectively (p=NS).

Table 1 - Epidemiological and clinical data

	Increased $[Cl^-]_{plasma}$	Decreased $[Cl^-]_{plasma}$	Unchanged $[Cl{-}]_{plasma}$
N	39	56	53
Gender, male	16 (41)	23 (39)	23 (43)
Age (years)	68±18*	61±16	61±16
APACHE II score	11±5*	9±5	8±4
SOFA score	3±3#	2±2	1±2
ICU mortality	8	2	4
Actual hospital mortality	10	2	4
ICU length of stay (days)	5±7	6±8	3±3*
Hospital length of stay (days)	12±10	13±9	9±6*
Mechanical ventilation[a]	8 (21)	6 (11)	5 (9)
Type of surgery			
Gastrointestinal	20 (51)	28 (50)	28 (53)
Orthopedic	5 (13)	8 (14)	14 (26)
Neurosurgery	2 (5)	5 (9)	3 (6)
Obstetric/gynecologic	5 (13)	2 (4)	3 (6)

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Thoracic	2 (5)	10 (18)	4 (8)
Urologic	5 (13)	3 (5)	1 (2)
Oncologic	12 (31)	22 (39)	14 (26)
Emergency	11 (28)	30 (54)	23 (43)
Shock[b]	8 (21)	10 (18)	6 (11)
Blood urea (mg/dL)	42±22	34±17	36±13
Plasma creatinine (mg/dL)	1.1±0.7	0.9±0.3	1.0±0.4
Furosemide use	5 (13)	7 (13)	3 (6)
Fluids administered during surgery (L)	1.783±1.070	2.552±1.616*	2.052±1.056
Strong-ion difference of fluids administered during surgery (mmol/L)	1±2*	6±11	6±8

APACHE II - Acute Physiology and Chronic Health Evaluation II; SOFA - Sequential Organ Failure Assessment; ICU - intensive care unit. [a] Mechanical ventilation at any moment during the first postoperative day; [b] shock during surgery or on ICU admission. * p<0.05 versus the other groups; # p<0.05 versus the unchanged $[Cl^-]_{plasma}$ group. The results are expressed as the mean and standard deviation or number and percentage.

On admission, the increased $[Cl^-]_{plasma}$, decreased $[Cl^-]_{plasma}$, and unchanged $[Cl^-]_{plasma}$ groups showed similar plasma values for pH (7.34±0.07, 7.33±0.06, and 7.33±0.05, respectively), PCO_2 (37±7, 39±7, and 39±6mmHg, respectively), $[HCO_3^-]$ (19±3, 20±3, and 20±2mmol/L, respectively), [BE] (–6±4, –5±3, and –5±2mmol/L, respectively), and $[SID]_{plasma}$ (30±4, 31±4, and 31±3mmol/L, respectively). The increased $[Cl^-]_{plasma}$ group had a lower $[Cl^-]_{plasma}$ (Figure 1) and a higher [AG] (22±5, 18±4, and 20±4mmol/L, p<0.05) and [SIG] (11±5, 6±5, and 8±4mmol/L, p<0.05) when compared with the other groups.
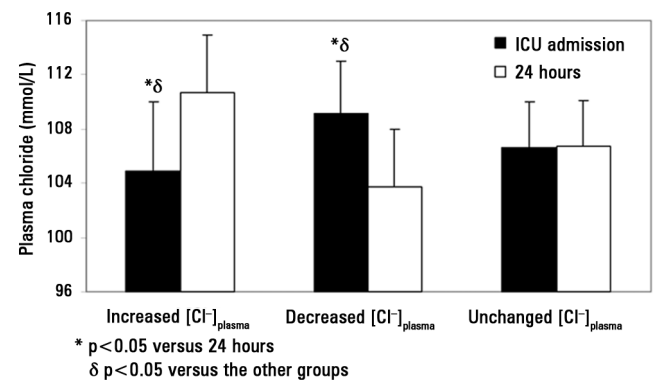
Figure 1 - Variation in the plasma chloride concentration in the increased $[Cl^-]_{plasma}$, decreased $[Cl^-]_{plasma}$, and unchanged $[Cl^-]_{plasma}$ groups. ICU - intensive care unit.

After 24 hours, no differences were found in the pH (7.36±0.08, 7.38±0.05, and 7.39±0.04), $[HCO_3^-]$ (21±4, 22±3, and 23±2mmol/l), [BE] (–4±5, –3±3, and –2±2mmol/L), and $[SID]_{plasma}$ (31±5, 32±3, and 33±3mmol/L) among the increased $[Cl^-]_{plasma}$, decreased $[Cl^-]$

$_{plasma}$, and unchanged [Cl$^-$]$_{plasma}$ groups. The increased [Cl$^-$]$_{plasma}$ group exhibited a higher [Cl$^-$]$_{plasma}$ and a lower [AG] (15±5, 21±5, and 17±4mmol/L, p<0.05) and [SIG] (4±5, 10±5, and 6±4mmol/L, p<0.05) when compared with the other groups (Table 2 and Figure 1). After 24 hours, the arterial pH and [BE] improved in the decreased and unchanged [Cl$^-$]$_{plasma}$ groups but not in the increased [Cl$^-$]$_{plasma}$ group (Table 2). Accordingly, the 24 hours change in pH (0.03±0.07 versus 0.06±0.07 and 0.05±0.06, p<0.05) and [BE] (0.8±4 versus 3±3 and 3±2mmol/L, p<0.05) was lower in the increased [Cl$^-$]$_{plasma}$ group than in the other two groups.

Table 2 - Acid-base variables at admission and after 24 hours in the increased, decreased, and unchanged [Cl$^-$]$_{plasma}$ groups

	Group	On admission	24 hours
pH	Increased [Cl$^-$]$_{plasma}$	7.34±0.07	7.36±0.08
	Decreased [Cl$^-$]$_{plasma}$	7.33±0.06	7.38±0.05*
	Unchanged [Cl$^-$]$_{plasma}$	7.33±0.05	7.39±0.04*
PCO$_2$ (mmHg)	Increased [Cl$^-$]$_{plasma}$	37±7	37±7
	Decreased [Cl$^-$]$_{plasma}$	39±7	37±5*
	Unchanged [Cl$^-$]$_{plasma}$	39±6	38±5*
HCO$_3^-$ (mmol/L)	Increased [Cl$^-$]$_{plasma}$	19±3	21±4*
	Decreased [Cl$^-$]$_{plasma}$	20±3	22±3*
	Unchanged [Cl$^-$]$_{plasma}$	20±2	23±2*
Base excess (mmol/L)	Increased [Cl$^-$]$_{plasma}$	−6±4	−4±5*
	Decreased [Cl$^-$]$_{plasma}$	−5±3	−3±3*
	Unchanged [Cl$^-$]$_{plasma}$	−5±2	−2±2*
Anion gap$_{corrected}$ (mmol/L)	Increased [Cl$^-$]$_{plasma}$	22±5§	15±5*
	Decreased [Cl$^-$]$_{plasma}$	18±4§	21±5*§
	Unchanged [Cl$^-$]$_{plasma}$	20±4§	17±4*
Strong-ion difference$_{effective}$ (mmol/L)	Increased [Cl$^-$]$_{plasma}$	30±4	31±5*
	Decreased [Cl$^-$]$_{plasma}$	31±4	32±3*
	Unchanged [Cl$^-$]$_{plasma}$	31±3	33±3*
Strong-ion gap$_{corrected}$ (mmol/L)	Increased [Cl$^-$]$_{plasma}$	11±5§	4±5*
	Decreased [Cl$^-$]$_{plasma}$	6±5§	10±5*§
	Unchanged [Cl$^-$]$_{plasma}$	8±4§	6±4*
Non-volatile weak anions (mmol/L)	Increased [Cl$^-$]$_{plasma}$	11±2	10±2
	Decreased [Cl$^-$]$_{plasma}$	11±2	10±2
	Unchanged [Cl$^-$]$_{plasma}$	11±2	11±2
Albumin (g%)	Increased [Cl$^-$]$_{plasma}$	3.2±0.6	3.0±0.6
	Decreased [Cl$^-$]$_{plasma}$	3.4±0.6	3.2±0.5
	Unchanged [Cl$^-$]$_{plasma}$	3.2±0.7	3.1±0.6
Phosphate (mg%)	Increased [Cl$^-$]$_{plasma}$	3.6±1.2	3.0±1.1*
	Decreased [Cl$^-$]$_{plasma}$	3.6±0.8	2.8±0.7*
	Unchanged [Cl$^-$]$_{plasma}$	3.3±1.1	2.9±0.9*
Lactate (mmol/L)	Increased [Cl$^-$]$_{plasma}$	2.3±1.4	1.8±0.9*
	Decreased [Cl$^-$]$_{plasma}$	1.9±0.9	1.6±0.9*
	Unchanged [Cl$^-$]$_{plasma}$	2.1±1.3	1.5±0.8*

* p<0.05 on admission versus 24 hours; § p<0.05 versus the other groups. The results expressed as the mean and standard deviation.

The crystalloid solutions administered during surgery and the first 24 hours in the ICU were normal saline (77% of the total volume use) and Ringer lactate (23%). Colloid solutions were not used. During surgery, the increased [Cl$^-$]$_{plasma}$ group received a smaller volume of fluids with a lower [SID] than the decreased [Cl$^-$]$_{plasma}$ group (Table 1). In the ICU, the volume and [SID] of the fluids administered were similar among the three groups, but the 24 hours [SID]$_{urine}$ was higher in the increased-[Cl$^-$]$_{plasma}$ group (Figure 2). The fluid balance was similar in all three groups (2,405±2,475, 2,235±2,099, 1,872±1,405mL/24 hours, p=NS). The volume (6,160±2,382, 6,887±3,155, 5,912±1,706mL, p=NS) and [SID] (6±5, 6±6, 6±4mmol/L, p=NS) of the fluids administered during the perioperative period (surgery and the first 24 hours in the ICU) were similar.

A multiple linear regression analysis showed that the [Cl$^-$]$_{plasma}$ at admission and [SID]$_{urine}$ were independent predictors of the 24 hours variation in [Cl$^-$]$_{plasma}$ (Table 3).

DISCUSSION

That the changes in [Cl$^-$]$_{plasma}$ during the first postoperative day are related to the behavior of [SID]$_{urine}$ and not to the differences in either the volume or the [SID] of the fluids administered constitutes the main finding of this study. This result suggests that the renal ability to decrease the [SID]$_{urine}$ is a major mechanism for avoiding postoperative hyperchloremia. Nevertheless, other processes may also be involved in the regulation of [Cl$^-$]$_{plasma}$ because the [Cl$^-$]$_{plasma}$ on admission was also an independent determinant of the 24 hours variation in [Cl$^-$]$_{plasma}$.

Hyperchloremic metabolic acidosis is commonly found in surgical patients after volume expansion with saline solution. Moreover, a recent study showed that a restriction in the administration of chloride-rich fluids in critically ill patients decreased the incidence of both metabolic acidosis and hyperchloremia.[21] The patients included in our study received hyperchloremic solutions with a low [SID] during the surgical procedure and thereafter in the ICU. Consequently, 28% of them were admitted to the ICU with hyperchloremia (defined as [Cl$^-$]$_{plasma}$ ≥110mmol/L), while a further 16% developed hyperchloremia within the next 24 hours (data not shown).

Although the Stewart approach has the same prognostic and diagnostic capabilities as the conventional analysis of acid-base metabolism,[20] this alternative method can provide a better understanding of the underlying mechanisms of saline-induced metabolic acidosis.[2,22] According to the Stewart approach, the
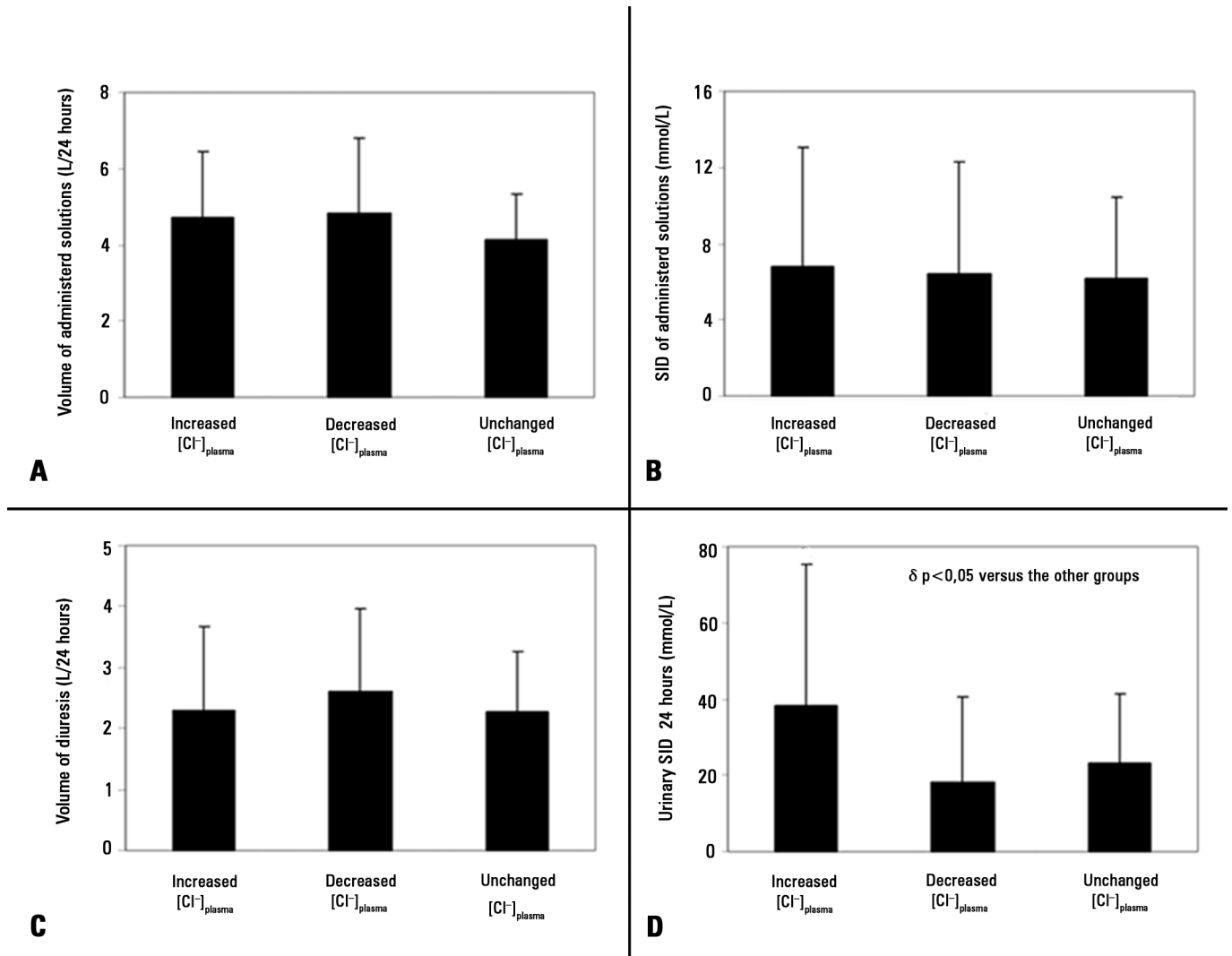
Figure 2 - Volumes and strong ion differences of the administered solutions and urine in the increased $[Cl^-]_{plasma}$, decreased $[Cl^-]_{plasma}$, and unchanged $[Cl^-]_{plasma}$ groups. Panel A: Volume of the administered solutions. Panel B: Strong ion difference of the administered solutions. Panel C: Volume of diuresis. Panel D: 24 hours urine strong ion difference. SID - strong ion difference.

Table 3 - Multiple linear regression analysis of 24 hours changes with $[Cl^-]_{plasma}$ as the dependent variable

Independent variable	Coefficient	SE	t	p value	[95% CI]
$[Cl^-]_{plasma}$ at ICU admission	0.523	0.085	6.14	<0.0001	0.354-0.691
24 hours $[SID]_{urine}$	-0.0365	0.014	-2.64	0.009	0.064-0.009

SE - standard error; 95% CI - 95% confidence intervals; ICU - intensive care unit. Coefficient, partial regression coefficient. The square of the coefficient of multiple correlation (R^2) in this model=0.26.

proton concentration is independently determined by the volatile and nonvolatile weak acids and by the [SID]. The [SID] is the difference between the sums of all the strong (i.e., fully dissociated, chemically nonreactive) cations and anions, such as $[Na^+]$, $[K^+]$, $[Ca^{++}]$, $[Mg^{++}]$, and $[Cl^-]$. Changes in $[Cl^-]_{plasma}$ induced by the administration of fluids with chloride levels in excess of the sodium content will decrease the [SID] and increase the dissociation of water, producing acidosis.

In critically ill patients, hyperchloremia can also result from a physiological compensation for hypoalbuminemia. Capillary leakage and partial alteration of the Donan equilibrium with the diffusion of albumin from the intravascular space can result in a shift in chloride from the interstitial space to balance the loss of negative charge.[23] In addition, Wilkes showed that the loss of weak acids secondary to hypoproteinemia is counteracted by a renal-mediated increase in $[Cl^-]_{plasma}$ to decrease the [SID].[24] However,

albumin and nonvolatile weak anions were similar among our three patient groups over the 24 hours evaluation period.

Another mechanism that could explain the development of hyperchloremia is the renal handling of chloride. The kidney plays a central role in the regulation of $[SID]_{plasma}$ by modulating the urinary excretion and reabsorption of strong ions, such as sodium, potassium, and chloride. However, few studies have investigated the interactions between $[SID]_{urine}$ and $[SID]_{plasma}$. In patients with metabolic alkalosis, changes in $[SID]_{urine}$ induced by the administration of acetazolamide account for the alterations in $[SID]_{plasma}$.[25] In a series of 98 critically ill patients with simple metabolic acidosis, a shift in the $[SID]_{urine}$ to negative values was associated with a higher $[SID]_{plasma}$ and a less severe acidemia when compared with patients that had a more positive $[SID]_{urine}$.[10] As a result, patients with a positive $[SID]_{urine}$ showed higher $[Cl^-]_{plasma}$. These observations indicate that an inappropriate renal response may facilitate the development of hyperchloremia.

In the present study, all groups of patients received equivalent amounts of fluids and electrolytes. Nevertheless, the changes in $[Cl^-]_{plasma}$ varied significantly. We found that the main determinant of $[Cl^-]_{plasma}$ was the $[SID]_{urine}$. The variation in the $[SID]_{urine}$ may have been triggered by the characteristics of the metabolic acidosis that the patients presented with at admission to the ICU. Despite similar pH values, the acidosis was largely due to unmeasured anions in the increased $[Cl^-]_{plasma}$ group and by hyperchloremia in the decreased $[Cl^-]_{plasma}$ group. The different types of metabolic acidosis observed cannot be explained by the administration of fluids during the surgery. In fact, the increased $[Cl^-]_{plasma}$ group (i.e., those patients with the lower $[Cl^-]_{plasma}$, and the higher [AG] and [SIG] levels on admission) received fluids with a lower [SID]. The incidence of shock was also similar among the three groups.

Even though the cause remains unclear, the different types of metabolic acidosis on admission could have determined the subsequent renal handling of chloride. In fact, $[Cl^-]_{plasma}$ on admission was an independent predictor of the changes in $[Cl^-]_{plasma}$. As shown by the higher $[SID]_{urine}$, the unmeasured anion acidosis in the increased $[Cl^-]_{plasma}$ group was associated with a decreased ability to eliminate chloride. We speculate that the renal excretion of nonabsorbable anions and sodium reduced the magnitude of the decrease in $[SID]_{urine}$. In contrast, the decreased $[Cl^-]_{plasma}$ group, exhibited hyperchloremic metabolic acidosis and displayed an improved ability to

eliminate chloride and decrease the $[SID]_{urine}$. These effects may be due to the excretion of chloride with ammonium (a weak cation) and not sodium.

A potentially confounding condition was the use of furosemide. This drug decreases the $[SID]_{urine}$ and induces metabolic alkalosis. Nevertheless, the furosemide in the study was used similarly in only few patients across the different groups.

The relevance of hyperchloremic metabolic acidosis as an independent predictor of outcome in critically ill patients has been the subject of intense discussion.[6,7,26,27] Our study demonstrated the presence of a more severe underlying disease, as shown by a higher APACHE-II score, in patients with increased $[Cl^-]_{plasma}$. Therefore, the lack of an adequate response in the face of a chloride load could constitute another manifestation of a more severe condition. We have previously shown that the failure to decrease $[SID]_{urine}$ is a common feature in critically ill patients with metabolic acidosis and could be the expression of a form of renal dysfunction.[10] In our former study, patients with an abnormal response of $[SID]_{urine}$ had higher APACHE-II and SOFA scores and a more severe degree of metabolic acidosis.

Our present study has certain limitations. We decided to group patients according to the $[Cl^-]_{plasma}$ trend observed during the first 24 hours in the ICU because these first measurements were heterogeneous. However, this pattern may have been influenced by unevaluated factors. In addition, we only studied patients during the postoperative period. The basal data prior to surgery and a comprehensive evaluation of the fluid balance and output during the surgery were unavailable because the $[SID]_{urine}$ was not measured during that period. Last, this observational study did not address the underlying mechanisms responsible for the different response patterns of the $[SID]_{urine}$.

CONCLUSIONS

Although the volume and the composition of fluids administered during the first postoperative day were similar between patients with opposite behaviors of $[Cl^-]_{plasma}$, the $[SID]_{urine}$ was higher in patients who developed hyperchloremia. Our results suggest that the ability to decrease $[SID]_{urine}$ is a major mechanism for avoiding saline-induced hyperchloremia. In addition, other mechanisms, such as the type of metabolic acidosis, may also act as relevant determinants of $[Cl^-]_{plasma}$.

Authors' contributions

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RESUMO

Objetivo: Demonstrar que alterações na concentração plasmática de cloreto ($[Cl^-]_{plasma}$) durante o período pós-operatório são amplamente dependentes da diferença de íons fortes urinária ($[SID]_{urina}=[Na^+]_{urina}+[K^+]_{urina}-[Cl^-]_{urina}$) e não de diferenças na terapia hídrica.

Métodos: Foram realizadas mensurações na admissão à unidade de terapia intensiva e 24 horas mais tarde em um total de 148 pacientes pós-operatórios. Os pacientes foram designados para um de três grupos segundo a alteração na concentração plasmática de cloreto após 24 horas: $[Cl^-]_{plasma}$ aumentada (n=39), $[Cl^-]_{plasma}$ diminuída (n=56) ou $[Cl^-]_{plasma}$ inalterada (n=53).

Resultados: Quando da admissão, o grupo com $[Cl^-]$ plasma aumentada tinha $[Cl^-]_{plasma}$ mais baixa (105 ± 5 *versus* 109 ± 4 e 106 ± 3mmol/L; p<0,05), um ânion *gap* plasmático ($[AG]_{plasma}$) mais alto e um íon *gap* forte mais alto. Após 24 horas, o grupo com $[Cl^-]_{plasma}$ aumentada mostrou $[Cl^-]_{plasma}$ mais alta (111 ± 4 *versus* 104 ± 4 e 107 ± 3mmol/L;

p<0,05) e nível plasmático mais baixo de $[AG]_{plasma}$ e íon *gap* forte. O volume e íon *gap* forte dos fluidos administrados foram similares entre os grupos, exceto que os $[SID]_{urina}$ eram mais altos (38 ± 37 *versus* 18 ± 22 e 23 ± 18mmol/L; p<0,05) no grupo com $[Cl^-]_{plasma}$ aumentada na avaliação após 24 horas. Uma análise de regressão linear múltipla demonstrou que a $[Cl^-]_{plasma}$ na admissão e $[SID]_{urina}$ eram preditores independentes de variação na $[Cl^-]_{plasma}$ 24 horas mais tarde.

Conclusões: Alterações na $[Cl^-]_{plasma}$ durante o primeiro dia pós-operatório foram amplamente relacionadas com $[SID]_{urina}$ e $[Cl^-]_{plasma}$ na admissão, e não às características dos fluidos infundidos. Portanto, a diminuição da $[SID]_{urina}$ deve ser um mecanismo importante para prevenção do desenvolvimento de hipercloremia induzida por solução salina.

Descritores: Cuidados pós-operatórios; Soluções isotônicas/efeitos adversos; Urina/análise; Cloretos/metabolismo

REFERENCES

1. Koch SM, Taylor RW. Chloride ion in intensive care medicine. Crit Care Med. 1992;20(2):227-40.
2. Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol. 1983;61(12):1444-61.
3. Bullivant EM, Wilcox CS, Welch WJ. Intrarenal vasoconstriction during hyperchloremia: role of thromboxane. Am J Physiol. 1989;256(1 Pt 2):F152-7.
4. Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. Chest. 2004;125(1):243-8.
5. Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid-base balance with Hextend compared with saline. Crit Care Med. 2002;30(2):300-5.
6. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA. 2012;308(15):1566-72.
7. Shaw AD, Bagshaw SM, Goldstein SL, Scherer LA, Duan M, Schermer CR, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg. 2012;255(5):821-9.

8. Prough DS, Bidani A. Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology. 1999;90(5):1247-9.
9. Scheingraber S, Rehm M, Sehmisch C, Finsterer U. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology. 1999;90(5):1265-70.
10. Masevicius FD, Tuhay G, Pein MC, Ventrice E, Dubin A. Alterations in urinary strong ion difference in critically ill patients with metabolic acidosis: a prospective observational study. Crit Care Resusc. 2010;12(4):248-54.
11. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.
12. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707-10.
13. Henderson LJ. The theory of neutrality regulation in the animal organism. Am J Physiol. 1908;21(4):427-48.
14. Hasselbalch KA. Die Berechnung der Wasserstoffzahl des blutes aus der freien und gebundenen Kohlensäure desselben, und die Sauerstoffbindung des Blutes als Funktion der Wasserstoffzahl. Biochem Z. 1916;78:112-44.
15. Astrup P, Jorgensen K, Andersen OS, Engel K. The acid-base metabolism. A new approach. Lancet. 1960;1(7133):1035-9.

16. Siggaard-Andersen O. The van Slyke equation. Scand J Clin Lab Invest Suppl. 1977;146:15-20.

17. Emmett M, Narins RG. Clinical use of anion gap. Medicine (Baltimore). 1977;56(1):38-54.

18. Figge J, Jabor A, Kazda A, Fencl V. Anion gap and hypoalbuminemia. Crit Care Med. 1998;26(11):1807-10.

19. Fencl V, Jabor A, Kazda A, Figge J. Diagnosis of metabolic acid-base disturbances in critically ill patients. Am J Respir Crit Care Med. 2000;162(6):2246-51.

20. Dubin A, Menises MM, Masevicius FD, Moseinco MC, Kutscherauer DO, Ventrice E, et al. Comparison of three different methods of evaluation of metabolic acid-base disorders. Crit Care Med. 2007;35(5):1264-70.

21. Yunos NM, Kim IB, Bellomo R, Bailey M, Ho L, Story D, et al. The biochemical effects of restricting chloride-rich fluids in intensive care. Crit Care Med. 2011;39(11):2419-24.

22. Kellum JA. Determinants of blood pH in health and disease. Crit Care. 2000;4(1):6-14.

23. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Etiology of metabolic acidosis during saline resuscitation in endotoxemia. Shock. 1998;9(5):364-8.

24. Wilkes P. Hypoproteinemia, strong-ion difference, and acid-base status in critically ill patients. J Appl Physiol. 1998;84(5):1740-8.

25. Moviat M, Pickkers P, van der Voort PH, van der Hoeven JG. Acetazolamide-mediated decrease in strong ion difference accounts for the correction of metabolic alkalosis in critically ill patients. Crit Care. 2006;10(1):R14.

26. Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. Crit Care. 2006;10(1):R22.

27. Boniatti MM, Cardoso PR, Castilho RK, Vieira SR. Is hyperchloremia associated with mortality in critically ill patients? A prospective cohort study. J Crit Care. 2011;26(2):175-9.