Importância da Hipercloremia no Intraoperatório*

The Importance of Intraoperative Hyperchloremia

João Manoel Silva Junior, TSA[1], Eliete F Neves[2], Thassio C Santana[2], Ulisses P Ferreira[2], Yara N Marti[2], Jose Maria Correa Silva, TSA[3]

RESUMO

Silva Junior JM, Neves EF, Santana TC, Ferreira UP, Marti YN, Silva JMC - Importância da Hipercloremia no Intraoperatório.

***JUSTIFICATIVA E OBJETIVOS**: A hipercloremia associada à acidose proporciona pior evolução dos pacientes se não identificada e tratada corretamente. O objetivo deste estudo foi verificar a importância da hipercloremia no intraoperatório.*

***MÉTODO**: Estudo de coorte prospectivo, durante cinco meses. Incluiu-se no estudo pacientes com idade igual ou maior que 18 anos submetidos a intervenções cirúrgicas com pós-operatório em unidade de terapia intensiva. Moribundos, diabéticos e com insuficiência renal foram excluídos. Os pacientes foram divididos em dois grupos: CH (hipercloremia) e SH (sem hipercloremia). A determinação de hipercloremia foi através de análise de curva ROC (Receiver Operating Characteristic), ou seja, o ponto com maior sensibilidade e especificidade para óbito foi escolhido como limite para diferenciar entre hipercloremia ou não.*

***RESULTADOS**: O estudo envolveu 393 pacientes. As concentrações séricas de cloro foram 111,9 ± 6,7 mEq.L^{-1}, pH 7,31 ± 0,09 e diferença de bases de -5,6 ± 4,6 mmol.L^{-1}. A área sob a curva ROC dos valores de cloro foi de 0,76 com ponto de corte de 114 mEq.L^{-1}, sensibilidade = 85,7% e especificidade = 70,1%. Pacientes com cloro maior que 114 mEq.L^{-1} totalizaram 31,7% e foram determinados como grupo CH. O grupo CH apresentou maior mortalidade do que o grupo SH, 19,3% versus 7,4%, p = 0,001, acidose metabólica pH 7,27 (0,08) versus 7,32 (0,09) p = 0,001, diferença de bases -7,9 (3,8) mmol.L^{-1} versus -4,2 (4,6) mmol.L^{-1} p < 0,001, tempo cirúrgico 4,5 (1,8)h versus 3,6 (1,9)h p = 0,001 e quantidade de cristalóides no intra-operatório 4250 (2500-6000) mL versus 3000 (2000-5000) mL, p = 0,002. Não houve outras diferenças entre os grupos.*

***CONCLUSÕES**: Hipercloremia tem alta incidência no final do intraoperatório e esta associada à acidose metabólica, maior tempo cirúrgico, maiores quantidades de fluidos cristaloides e maior mortalidade no pós-operatório.*

Unitermos: EQUILÍBRIO ÁCIDO BASE: acidose; EQUILÍBRIO HIDRO-ELETROLÍTICO: hipercloremia; PROGNÓSTICO.

SUMMARY

Silva Junior JM, Neves EF, Santana TC, Ferreira UP, Marti YN, Silva JMC – The Importance of Intraoperative Hyperchloremia.

***BACKGROUND AND OBJECTIVES:** Hyperchloremia associated with acidosis is associated with worse patient evolution if it is not properly diagnosed and treated. The objective of this study was to determine the intraoperative importance of hyperchloremia.*

***METHODS:** This is a 5-month prospective study. Patients 18 years or older undergoing surgical procedures and admitted to the intensive care unit postoperatively. Terminal patients, diabetics, and with chronic renal failure were excluded. Patients were divided in two groups: CH (hyperchloremia) and SH (without hyperchloremia). Hyperchloremia was determined by analysis of the ROC (Receiver Operating Characteristic) curve, i.e., the point of greater sensitivity and specificity for death was chosen as the limit to differentiate hyperchloremia from normochloremia.*

***RESULTS:** Three hundred and ninety-three patients participated in the study. Serum levels of chloride were 111.9 ± 6.7 mEq.L^{-1}, pH 7.31 ± 0.09, and base excess –5.6 ± 4.6 mmol.L^{-1}. The area under the ROC curve of chloride levels was 0.76 with a cutting point of 114 mEq.L^{-1}, sensitivity = 85.7%, and specificity = 70.1%. The CH group, with chloride levels of 114 mEq.L^{-1} or more was formed by 31.7% of the patients. Mortality was higher in the CH group than in SH, 19.3% versus 7.4%, p = 0.001, as well as the incidence f metabolic acidosis, pH 7.27 (0.08) versus 7.32 (0.09), p = 0.001, base excess –7.9 (3.8) mmol.L^{-1} versus –4.2 (4.6) mmol.L^{-1}, p < 0.001, length of surgery 4.5 (1.8) h versus 3.6 (1.9) h, p = 0.001, and volume of intraoperative crystalloid administration, 4,250 (2,500 – 6,000) mL versus 3,000 (2,000 – 5,000) mL, p = 0.002. Other differences between both groups were not observed.*

***CONCLUSIONS:** The incidence of hyperchloremia at the end of surgery is elevated, and it is associated with metabolic acidosis, longer surgeries, greater volumes of crystalloids, and higher postoperative mortality.*

Keywords: ACID-BASE BALANCE: acidosis; HYDROELECTROLYTIC BALANCE: hyperchloremia; PROGNOSIS.

** Recebido do (**Received from**) CET/SBA do Hospital Servidor Publico Estadual de São Paulo (HSPE), São Paulo, SP*

1. Corresponsável pelo CET/SBA HSPE; Coordenador da Unidade Critica de Pacientes Cirúrgicos do HSPE
2. Residente do HSPE/SP
3. Corresponsável da Residência de Anestesiologia do HSPE/SP

*Apresentado (**Submitted**) em 29 de dezembro de 2008*
*Aceito (**Accepted**) para publicação em 11 de fevereiro de 2009*

*Endereço para correspondência (**Correspondence to**):*
Dr. João Manoel Silva Junior
Rua Pedro de Toledo, 1800/6º andar
Vila Clementino.
04039-901 São Paulo, SP
E-mail: joao.s@globo.com

The Importance of Intraoperative Hyperchloremia

João Manoel Silva Junior, TSA, M.D.; Eliete F Neves, M.D.; Thassio C Santana, M.D.; Ulisses P Ferreira, M.D.; Yara N Marti, M.D.; Jose Maria Correa Silva, TSA, M.D.

INTRODUCTION

Chlorides are the most abundant anions in the extracellular fluid, playing a fundamental role in water distribution in the body, and they enter the cells to maintain the anion-cation balance.

Plasma bicarbonate and chloride are frequently associated with acidosis and alkalosis [1]. Thus, this inverse relationship received special attention when investigators demonstrated that intraoperative acidosis is associated with excessive intravenous administration of sodium chloride [2,3], being called hyperchloremic metabolic acidosis [4]. On the other hand, reduced plasma concentrations of chloride, resulting in alkalosis, are associated with the administration of diuretics and loss o gastric fluids [5,6].

In fact, fast infusion of normal saline results in hyperchloremic acidosis [7], which is a consequence of the increase in anion gap caused by the excessive increase in plasma chloride and subsequent renal excretion of bicarbonate.

Metabolic acidosis does not have specific clinical signs or symptoms; however, it can cause pulmonary, cardiovascular, neurologic, and skeletal musculature changes. Besides, lactic acidosis has been clearly associated with an increase in mortality [8].

Although those changes can be caused by hyperchloremia, acidosis, or both, the literature is unsure regarding the clinical relevance of those results.

Therefore, very few prospective clinical studies in surgical patients evaluating the real impact of intraoperative hyperchloremia can be found in the literature. In this context, evaluating the importance of measuring intraoperative chloride levels is relevant, besides considering possible complications associated with this problem.

The objective of this study was to evaluate the consequences of intraoperative hyperchloremia and verify related factor.

METHODS

The study was conducted in the operating room of a tertiary hospital after approval by the Ethics Commission of the hospital, and the author did not receive any grants.

Consecutive patients undergoing surgeries who required postoperative care in the intensive care unit, from March 2008 to June 2008, participated in this study.

All patients older than 18 years were included. Patients excluded from the study included those with renal failure and diabetes because they could have acid-base imbalance secondary to other causes, patients with a low probability of surviving due to their baseline condition, end-stage cancer, and patients who refused to participate in the study.

To standardize data collection, the worse levels of physiologic and laboratorial parameters 24 hours before the surgery were used to calculate the SAPS III score (Simplified Acute Physiology Score) [9], used to determine the severity of patients' conditions, as well the ASA (American Society of Anesthesiologists) classification [10].

The SAPS III score has three parts: a physiologic score with 10 parameters, representing the severity of the disease, evaluation of patients' health before hospital admission, which indicated the pre-morbid condition, and patient location before admission to the intensive care unit.

Arterial blood gases and measurements of plasma levels of chloride were obtained at the end of the surgery to classify both groups. The investigators did not influence patient treatment in any way.

Patients were followed until the final hospital outcome, and determined whether patients developed any organic failure.

Data were inserted in an electronic data base (Excel – Microsoft®) for posterior analysis by a statistical program (SPSS 13.0).

Initially, the demographic, clinical, and physiological characteristics of the patients were described. Frequencies and percentages were calculated to describe categorical parameters. Measures of central tendency and dispersion were used to describe quantitative parameters.

Patients were divided in two groups. Group CH: patients who developed hyperchloremia at the end of the surgery; and Group SH: patients with normochloremia. Hyperchloremia was determined by analyzing the ROC curve (Receiver Operating Characteristic), i.e., the point of greater sensitivity and specificity for death was chosen as the limit to differentiate hyperchloremia from normochloremia.

The ROC curve verifies the predictive ability of a parameter related with a specific response. It is plotted by calculating sensitivity and specificity for all points of a specific parameter in relation to the desired response to determine the optimal cutting point. In this case, the level of chloride that expressed better which patients would evolve to death was verified. This optimal cutting point corresponds to that level that maximizes the sum of specificity and sensitivity. The area under the ROC curve is the parameter that determines the discriminatory power of the prediction.

Patients with hyperchloremia (CH group) were compared to patients without hyperchloremia (SH group) to find the factors related with the increase in plasma chloride levels and worse prognosis. The Chi-square test was used for categorical parameters, the Student *t* test was used for parametric continuous parameters, and non-parametric continuous parameters by the Mann-Whitney test. All statistical tests were bicaudal and a level of significance of 0.05 was used.

The Spearman test was used to identify the correlation between metabolic acidosis and chloride.

RESULTS

During the evaluation period, 393 patients, 156 males and 237 females, mean age 66.6 years, were included in the study. Elective surgeries were more common (91.5%); and orthopedic surgical procedures were prevalent, representing 33.6% of the cases; general anesthesia was more frequent (55.5%), followed by neuroaxis block (31.8%) (Table I).

Table I - Patients' Characteristics

Parameters	Characteristics
Age (years)	66.6 ± 15.9
Female (%)	62.8
White (%)	82.4
Mortality (%)	10.4
SAPS III	35.9 ± 15.9
Physical status (%)	
ASA I	11.7
ASA II	72.8
ASA III	15.5
Need of blood products (%)	13.3
Length of surgery (hours)	4.0 ± 1.8
Chloride ($mEq.L^{-1}$)	112.0 ± 6.7
pH	7.31 ± 0.1
Base difference ($mmol.L^{-1}$)	-5.6 (-8.3 - -2.2)
Total intraoperative NS administration (mL)	3,000 (2,000 – 5,000)
Total intraoperative volume of colloids (3rd generation) administered (mL)	500 (500 – 1,000)
Length of stay in the ICU (days)	1.0 (1.0-2.0)
Length of hospital stay (days)	10.0 (6.0 – 18.0)

Characteristics in parenthesis represent medians and 25th and 75th percentiles

SAPS III - *Simplified Acute Physiology Score;* ICU – intensive care unit

Mean chloride levels, pH, and base excess were similar in all patients, namely 112.0 ± 6.7 mEg.L^{-1}, 7.31 ± 0.09, and –5.6 ± 4.6 mmol.L^{-1}, respectively.

The area under the ROC curve of chloride levels for hospital mortality was 0.76 with a cutting point of 114 mEq.L^{-1}, sensitivity = 85.7%, specificity = 70.1%, p = 0.02 (area = 0.5) (95%CI 0.69 - 0.81). Thus, patients with plasma chloride levels greater than 114 mEq.L^{-1} were considered hyperchloremics (Figure 1).

Patients with hyperchloremia represented 31.7% of the cases (Figure 2).

Parameters with statistically significant differences between patients with and without hyperchloremia according to the multivariate analysis included: pH, BE, duration of surgery, and crystalloids (NS) administered intraoperatively, which were more elevated in patients with higher serum levels of chloride (Table II).

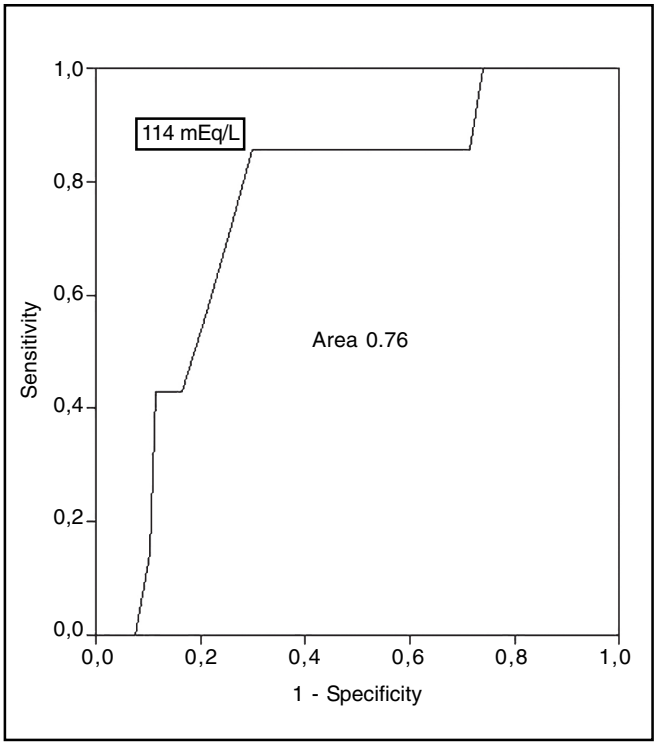

Figure 1 - ROC Curve for Chloride Relative to Hospital Death. The most sensitive and specific level of chloride was 114 mEq.L^{-1}, sensitivity = 85.7%, specificity = 70.1%. Area under the curve = 0.76; p = 0.02.

In the dispersion curve, chloride showed an inverse correlation with base excess, $r^2 = 0.67$ p < 0.001, suggesting some type of interaction between those two parameters (Figure 3).

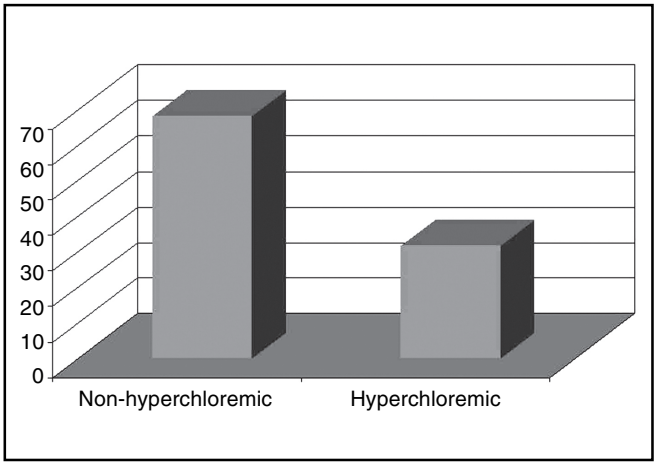

Figure 2 - Percentage of Patients with Hyperchloremia. Columns represent the percentage of patients with or without hyperchloremia.

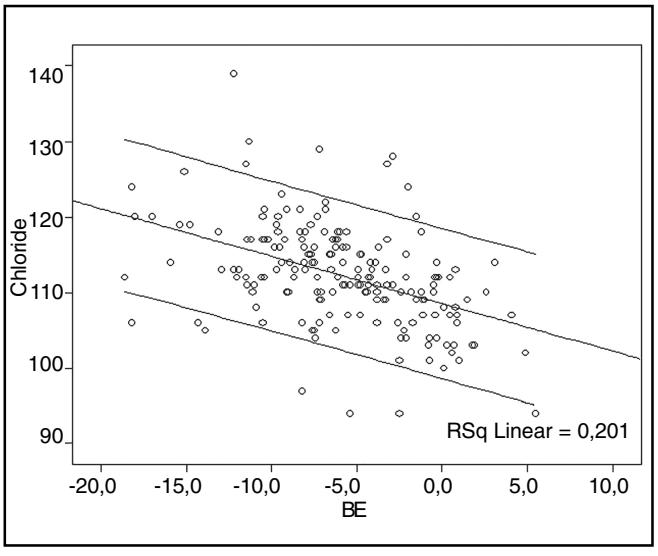

Figure 3 - Correlation between Chloride and Base Difference. $r^2 = -0.67$ p < 0.001 (Spearman test). Plotting is derived from the chloride levels and base difference found. The central line represents the tendency for plotting conversion. The other lines represent the 95% confidence interval.

Table II - Univariate Analysis Between Patients with Hyperchloremia and Normal Individuals

Parameters	CH (n = 124)	SH (n = 269)	p
Age (years)	66.3 ± 16.9	67.4 ± 15,5	0.64
Female (%)	63.2	64.8	0.83
White (%)	76.0	82.2	0.19
SAPS III	34.0 (23.5 – 42.7)	34.0 (26.2 – 45.5)	0.99
Physical status (%)			0.37
ASA I	14.3	9.6	
ASA II	73.2	70.2	
ASA III	12.5	19.2	
General anesthesia (%)	60.7	58.3	0.45
Length of surgery (hours)	4.6 ± 1.8	3.8 ± 1.9	0.0001
Chloride ($mEq.L^{-1}$)	119.7 ± 4.7	108.6 ± 4.3	0.000
pH	7.27 ± 0.1	7.32 ± 0.1	0.001
Base difference ($mmol.L^{-1}$)	-7.9 (-10.4 - -6.1)	-4.2 (-7.5 - -0.7)	0.000
Packed red blood cells (UI)	2.0 ± 1.0	2.1 ± 0.9	0.830
Plasma (UI)	2.0 ± 0,6	2.3 ± 0.5	0.340
Total intraoperative administration of NS (mL)	4,250 (2,500 – 6,000)	3,000 (2,000 – 5,000)	0.002
Total intraoperative administration of colloids (mL)	500 (500 – 1,000)	500 (500 – 1,000)	1.00
Length of stay in the ICU	2.0 (1.0 – 3.0)	2.0 (1.0 – 3.0)	0.89
Length of hospital stay	13.0 (8.0 – 19.5)	10.0 (6.0 – 18.0)	0.74
Mortality (%)	19.3	7.4	0.001

Characteristics in parenthesis represent medians and 25th and 75th percentiles
SAPS III - *Simplified Acute Physiology Score;* ICU – intensive care unit

DISCUSSION

This study showed that intraoperative hyperchloremia is frequently associated with the administration of large volumes of NS.

A study with patients undergoing large major surgeries, patients who received NS, 6% hetastarch, and glucose solutions concluded that two thirds of the patients who received NS developed hyperchloremic metabolic acidosis [11]. Other randomized, double-blind study comparing NS and Ringer's lactate in patients undergoing surgeries of the aorta confirmed those results, and the patients with acidosis required interventions, such as infusion of bicarbonate, and hyperchloremic acidosis was associated with greater administration of blood products [12].

A study by Kellum et al. [13] suggested another reason for hyperchloremia by demonstrating in animals that part of the hyperchloremia could be considered endogenous, i.e., it was not related with the exogenous infusion or reduction in renal excretion. Those authors suggested the possibility of rerouting of chloride among water compartments. Those detours could have been more pronounced in those that did not survive due to the probable more exacerbated inflammatory state of those patients.

However, the influence of hyperchloremia on the outcome of patients is unknown, but the present study demonstrated higher mortality in this population, even when paired to similar patients without hyperchloremia.

A randomized, controlled study showed a reduction in the perfusion of the gastric mucosa determined by gastric tonometry [11] in patients with hyperchloremic acidosis. Besides, hyperchloremia itself has deep effects on the synthesis of eicosanoids released in renal tissue causing vasoconstriction and reducing glomerular filtration rate [14], which could also explain the reduced gastric perfusion mentioned above and the worst prognosis.

Besides, animal studies demonstrated that chloride works as a modulator of oxygen transport in the blood, i.e., chloride reduced the affinity of oxygen by hemoglobin [15]. Gustin et al. [16], studying bovines determined that, in normal conditions (pH 7.4, PCO_2 40 Torr, temperature 37° C), chloride modulated oxygen binding by erythrocytes, shifting the oxygen dissociation curve to the right.

In sepsis models in rats, hyperchloremia can also worsen hypotension, which is partially mediated by nitric oxide [17], and in experimental models of sepsis, a reduction in survival was observed when crystalloid solution were used when compared with synthetic colloid solutions [18].

This study demonstrated a strong inverse relationship between metabolic acidosis and hyperchloremia, i.e., lower BE are associated with higher plasma levels of chloride, which is caused by the reduction in strong anion gap, i.e., the excessive increase of chloride in the plasma, as well as excessive renal excretion of bicarbonate.

However, hyperchloremic acidosis is the main adverse effect when large volumes of NS are administered, and the actions taken to control this abnormality are often more harmful because acidosis is frequently considered a reflex of poor perfusion or poor myocardial function, and the negative base difference may indicate the need to administer more NS, exacerbating the acidosis, use of blood products, inotropic support, and mechanical ventilation [19,20].

Historically, hyperchloremic metabolic acidosis has been considered a "necessary evil" due to the importance of volume resuscitation in critical patients; however, especially in patients with comorbidities, such as renal disease, that are commonly associated with acidosis, solutions like Ringer's lactate are sometimes preferable instead of NS, and protocols of balanced fluid resuscitation are safer and recommended instead of fast infusions of NS.

Hyperchloremic acidosis is frequently iatrogenic, and it is associated with a worse prognosis and, therefore, should be avoided whenever possible by using other fluids for volume replacement.

REFERENCES

01. Haldane JBS - Experimental and therapeutic alterations of human tissue alkalinity. Lancet 1924;537-538.
02. Scheingraber S, Rehm M, Sehmisch C et al. - Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999;90:1265-1270.
03. Reid F, Lobo DN, Williams RN et al. - (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study. Clin Sci (Lond) 2003;104:17-24.
04. Constable PD - Hyperchloremic acidosis: the classic example of strong ion acidosis. Anesth Analg 2003;96:919-922.
05. Greenberg A - Diuretic complications. Am J Med Sci 2000;319: 10-24.
06. Worthley LIG - Acid-base Balance and Disorders. In: Bersten AD, Soni N - Oh's Intensive Care Manual. Sydney, Butterworth-Heinemann 2003;873-883.
07. Prough DS, Bidani A - Hyperchloremic metabolic acidosis is a predictable consequence of intraoperative infusion of 0.9% saline. Anesthesiology 1999;90:1247-1249.
08. Silva Jr JM, Rezende E, Campos EV et al. - It Is Not Possible To Predict Elevated Arterial Lactate Level Using Measurement of Base Excess in Severe Sepsis Patients at Early Resuscitation Phase. Rev Bras Terap Intens 2005;17:119-123.
09. Moreno RP, Metnitz PG, Metnitz B et al. - Modeling in-hospital patient survival during the first 28 days after intensive care unit admission: a prognostic model for clinical trials in general critically ill patients. J Crit Care 2008;23:339-348.
10. Anonymous - New classification of physical status. Anesthesiology 1963;24:111.
11. Wilkes NJ, Woolf R, Mutch M et al. - The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid-base and electrolyte status and gastric mucosal perfusion in elderly surgical patients. Anesth Analg 2001;93:811-816.
12. Waters JH, Gottlieb A, Schoenwald P et al. - Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. Anesth Analg 2001,93:817-822.
13. Bullivant EM, Wilcox CS, Welch WJ - Intrarenal vasoconstriction during hyperchloremia: role of thromboxane. Am J Physiol 1989; 256:F152-157.
14. Gustin P, Detry B, Cao ML et al. - Chloride and inorganic phosphate modulate binding of oxygen to bovine red blood cells. J Appl Physiol 1994;77:202-208.
15. Gustin P, Detry B, Robert A et al. - Influence of age and breed on the binding of oxygen to bovine red blood cells in calves. J Appl Physiol 1997;82:784-790.
16. Kellum JA, Bellomo R, Kramer DJ et al. - Etiology of metabolic acidosis during saline resuscitation in endotoxemia. Shock 1998; 9:364-368.
17. Kellum JA, Song M, Venkataraman R - Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. Chest 2004;125:243-248.
18. 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;30:300-305.
19. Skellett S, Mayer A, Durward A et al. - Chasing the base deficit: hyperchloremic acidosis following 0.9% saline fluid resuscitation. Arch Dis Child 2000;83:514-516.
20. Brill SA, Stewart TR, Brundage SI et al. - Base deficit does not predict mortality when secondary to hyperchloremic acidosis. Shock 2002;17:459-462.

RESUMEN

Silva Junior JM, Neves EF, Santana TC, Ferreira UP, Marti YN, Silva JMC - Importancia de la Hipercloremia en el Intraoperatorio.

JUSTIFICATIVA Y OBJETIVOS*: La hipercloremia asociada a la acidosis, proporciona una evolución peor en los pacientes si no se identifica a tiempo y si no se trata correctamente. El objetivo de este estudio, fue verificar la importancia de la hipercloremia en el intraoperatorio.*

MÉTODO*: Estudio de cohorte prospectivo, durante cinco meses. En el estudio se incluyeron pacientes con edad igual o mayor a 18 años, sometidos a intervenciones quirúrgicas con postoperatorio en unidad de cuidados intensivos. Fueron excluidos los moribundos, diabéticos y con insuficiencia renal. Los pacientes se dividieron en dos grupos: CH (hipercloremia) y SH (sin hipercloremia). La determinación de hipercloremia, fue a través de análisis de curva ROC (Receiver Operating Characteristic), o sea, el punto con mayor sensibilidad y especificidad para óbito fue escogido como límite para diferenciar entre la hipercloremia o no.*

***RESULTADOS**: El estudio contó con 393 pacientes. Las concentraciones séricas de cloro fueron 111,9 ± 6,7 mEq.L-1, pH 7,31 ± 0,09 y diferencia de bases de -5,6 ± 4,6 mmol.L-1. El área bajo la curva ROC de los valores de cloro fue de 0,76 con punto de corte de 114 mEq.L-1, sensibilidad = 85,7% y especificidad = 70,1%. Los pacientes con cloro mayor que 114 mEq.L-1 totalizaron un 31,7% y fueron determinados como grupo CH. El grupo CH presentó una mayor mortalidad que el grupo SH, un 19,3% versus 7,4%, p = 0,001, acidosis metabólica pH 7,27 (0,08) versus 7,32 (0,09) p = 0,001, diferencia de bases -7,9(3,8) mmol.L-1 versus -4,2(4,6) mmol.L-1 p < 0,001, tiempo quirúrgico 4,5 (1,8) h versus 3,6 (1,9) h p = 0,001 y cantidad de cristaloides en el intraoperatorio 4250 (2500-6000) mL versus 3000 (2000-5000) mL, p = 0,002. No hubo otras diferencias entre los grupos.*

***CONCLUSIONES**: La hipercloremia tiene una alta incidencia al término del Intraoperatorio, y está asociada a la acidosis metabólica, mayor tiempo quirúrgico, mayores cantidades de fluidos cristaloides y a una mayor mortalidad en el postoperatorio.*