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Changes in chloremia, secondary to hydric reanimation during the first 24 hours, increases hospital stay and complications in patients with acute pancreatitis.

Rafael Silva Olvera[1], Mauricio Pierdant Pérez[2], Gustavo Ibarra Cabañas[1], Iván Ledezma Bautista[2], Raúl Alejandro Hernández Rocha[2] and Antonio Augusto Gordillo Moscoso[2]

[1] Instituto Mexicano del Seguro Social. Hospital General Zona No. 50, San Luis Potosí, SLP, México

[2] Facultad de Medicina, Universidad Autónoma de San Luis Potosí, Departamento de Salud Pública y Ciencias Médicas, San Luis Potosí, SLP, México.

Key words: Pancreatitis; chlorides; isotonic solutions; length of stay.

Abstract. Acute pancreatitis (AP) requires first-line treatment with intensive fluid resuscitation. Hydroelectrolyte changes secondary to this management could be related to an increase in hospital stay, complications, and mortality. The objective of this study was to correlate the increase in serum chlorine (> 8mEq / L) during the first 24 hours (ISC) with a longer hospital stay, complications and mortality in patients with AP. A total of 110 patients with AP admitted to the emergency room were included. Fluid management and serum chlorine were recorded on admission and after 24 hours; duration of hospital stay, complications and mortality, were also registered. 37 patients had ISC (age 56.4 ± 18.4 years; 51% women), there were no differences in age, sex or type of fluid management with patients without ISC. In bivariate analysis, ISC was associated with severe AP (30% vs 12%, p = 0.02), higher APACHE II score at admission (8 [6-15] vs 6 [4-9] points, p = 0.006), and longer hospital stay (9 [7-12] vs 7 [5-10] days, p = 0.03). The overall mortality and complications rate were 16% and 25%, respectively, with no differences between the groups (24% vs. 12%, p = 0.1 and 35% vs. 19%, p = 0.06). After multivariate adjustment, independent predictors of hospital stay were ISC> 8 mEq / L (p = 0.01) and APACHE II scores at 24 hours (p = 0.02). We conclude that ISC is associated with a longer hospital stay in patients with AP from a second-level hospital care population.

Corresponding Author. Mauricio Pierdant Pérez, Av. Venustiano Carranza 2405, Colonia Los Filtros, Código Postal 78394, San Luis Potosí, SLP, México. E-mail: mpierdant@hotmail.com

Cambios en la cloremia secundaria a la reanimación hídrica, en las primeras 24 horas, incrementa la estancia hospitalaria y las complicaciones en los pacientes con pancreatitis aguda.

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Palabras clave: pancreatitis; cloruros; soluciones isotónicas; tiempo de internación.

Resumen. La pancreatitis aguda (PA) requiere tratamiento de primera línea con reanimación hídrica intensiva. Los cambios hidroelectrolíticos secundarios a este manejo podrían relacionarse a un incremento en la estancia hospitalaria, complicaciones y mortalidad. El objetivo de este estudio fue correlacionar el incremento de cloro sérico (>8mEq/L) en las primeras 24hrs (ICS), con una mayor estancia hospitalaria, complicaciones y mortalidad en pacientes con PA. Se incluyeron 110 pacientes con PA ingresados a urgencias, se registró el manejo hídrico y cloro sérico al ingreso y 24 horas después, la estancia hospitalaria, complicaciones y mortalidad. 37 pacientes tuvieron ICS (edad 56,4 ± 18,4 años; 51% mujeres) no hubo diferencias en edad, sexo o tipo de manejo hídrico en pacientes sin ISC. En el análisis bivariado, el ICS se asoció a PA grave (30% vs 12%, p = 0,02), mayor puntuación APACHE II al ingreso (8 [6-15] vs 6 [4-9] puntos, p = 0,006) y estancia hospitalaria más prolongada (9 [7-12] frente a 7 [5-10] días, p = 0,03). La tasa global de mortalidad y complicaciones fueron del 16% y el 25%, respectivamente, sin diferencias entre grupos (24% vs 12%, p = 0,1 y 35% vs 19%, p = 0,06). Después del ajuste multivariado, los predictores independientes de la estancia hospitalaria fueron ICS> 8 mEq/L (p = 0,01) y las puntuaciones APACHE II a las 24 horas (p = 0,02). Concluimos que el ICS se asocia a mayor estancia hospitalaria en pacientes con PA de una población de segundo nivel de atención hospitalaria.

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INTRODUCTION

Acute Pancreatitis (AP) is an inflammatory disease that frequently involves peripancreatic tissue and can englobe distant organs and systems [1,2]. The incidence varies between 4.9 and 73.4 cases per 100,000 people in the world [3]. Its etiology is mainly attributed to biliary lithiasis and alcoholism, and between 10 and 30% is classified as idiopathic [1]. There are prognostic factors of mortality, like the Ranson, Glasgow-Imrie, POP, BISAP criteria, and Hong Kong scale that is based in glycemia-urea and gives a prognosis with adequate accuracy [4].

Initial management of AP is based in hydric reanimation with intravenous liquids, mainly isotonic solutions, such as saline solution 0.9% (SS0.9%) and Ringer lactate (RL), and pain control [1,2,5].

The recommendation is to administer balanced solutions in a range of 200 to 500 milliliters per hour or 5 to 10 mL per kg of weight per hour, with a range of 2,500 and 4,000 mL in 24 hours. There are few studies to support the decision of what type of solution to administer [1]. A meta-analysis showed no statistically significant differences in the incidence of necrotizing PA comparing the use of SS0.9% or RL [6].

Retrospective studies suggest that aggressive administration of fluids in the initial 12-24 hours reduces morbi-mortality [1]. Being that the SS0.9% is used globally as the first line of therapy despite having an osmolarity of 308, and a pH 5.5, and supra physiologic concentrations of sodium and chloride, and that could increase patient morbi-mortality [7].

Chloride (Cl^-) is the main anion of human body, with functions maintaining oncotic pressure, acid-base equilibrium, muscular activity, osmosis, and immunomodulation.

The SS0.9% could induce pathologic hyperchloremia (Table 1) and hyperchloremic metabolic acidosis [8]. In intensive care units, hyperchloremia was associated as an independent factor of mortality in major trauma [9], acute kidney injury [10] and systemic inflammatory response syndrome [8,11].

Metabolic hyperchloremic acidosis in experimental studies with septic animals has demonstrated that it increases the production of interleukin 6, tumor necrosis factor, and nitric oxide; thus hyperchloremia is a pro-inflammatory modulator in sepsis [4,11].

In accordance to Kumpers *et al*, an infusion of two liters of SS0.9% reduces 12% of the blood supply in the renal cortex of healthy patients, as demonstrated with angiography [12]. The hyperchloremia, according to Marttinen *et al.*, associates with the risk of acute kidney injury, secondary to vasoconstriction of the afferent renal artery [10], decreasing the glomerular filtration rate, which leads to that exposed patients to non-guided chloride management, require more replacement therapy [13].

Associated mortality with hyperchloremia is between 30-40%, with concentrations

Table 1
Causes of hyperchloremia.

Pseudohiperchloremia	Loss of water and electrolytes
- High concentrations of solids in serum (fatty acids or proteins), dilutional - Bromide or iodide intoxication	- Certain forms of diarrhea - Osmotic diuresis - Certain cases of post-obstructive diuresis
Administration of fluids with high chloride containing	**Associated with metabolic acidosis**
- Saline Solution 0.9% - Albumin - Ammonium Chloride - Parenteral nutrition	- Certain forms of diarrhea - Tubular renal acidosis - Inhibitors of carbonic anhydrase - Ureteral deviation (for example, ileal bladder). - Administration of ammonium chloride. - Administration of arginine chlorhidrate, hydrochloric acid, or lysine. -Certain cases of chronic kidney disease. Organic acidosis with fast excretion of acid anion (for example: toluene overdose).
Net loss of water	**Respiratory alkalosis**
- Exercise - Severe dehydration - Fever - Hypermetabolic status - Insipidus diabetes	

of chloremia higher of 130mEq/L, having basal chloride levels of 80 and 120mEq/L in patients with systemic inflammatory response syndrome, demonstrating that the greater input of intravenous solutions, the greater hospital mortality [8].

In major trauma it was associated with 30-days mortality, analyzing chloremia at admission and 48 hours later, showing and elevation of serum levels in non-surviving patients, compared with survivors, with a chloride delta (ΔCl, that is the difference between chloremia at admission minus 48 hours chloremia) higher in the non-survivors (ΔCl 10.3±11.1mmol/L *vs* 1.7±5.2mmol/L, $p<0.001$). The administration of less than 1,500ml SS0.9% was not associated with mortality [9] and it has a limit of maximum 1 Liter in 24 hours [14].

The aim of this study was to correlate a significant increment of chloremia during the first 24 hours in patients with acute pancreatitis, with hospital stay and mortality of any cause, and to describe the presence of complications.

PATIENTS AND METHODS

Study design and patients

The present study was reviewed and approved by IMSS scientific and ethics committees with the number R-2017-2402-39 and was made with a database of IMSS Zone 50 Hospital registry, San Luis Potosi, Mexico. This database processed the registry of all consecutive admitted adults in the emergency room between January 2015 and December 2016, with diagnosis of acute pancreatitis. It includes demographic data and clinical information, medical procedures, etiology of pancreatitis, and subsequent laboratory findings. The data are periodically integrated, reviewed, and checked for accuracy.

For this retrospective, observational and analytic study, data from all patients admitted in the mentioned period was examined. We included patients who met the following criteria: (i) diagnosis of acute pancreatitis based in clinical characteristics, radiologic findings and pancreatic inflammation markers, following the 2012 Atlanta criteria revision, (ii) had serum basal electrolytes at admission and 24 hours later, (iii) underwent hospitalization without volunteer discharge. We excluded patients: (i) referred from other medical units with diagnosis of acute pancreatitis that received previous initial management, (ii) patients that had treatment with drugs that could affect chloremia, such as thiazides, diuretics, potassium-sparring diuretics, etc., and (iii) patients that had a disease that affected their renal function.

Outcome

The primary outcome of this study was hospital stay (measured in days); mortality for any cause, besides the presence of regional complications, such as peri-pancreatic collection, pancreatic and peri-pancreatic necrosis, gastric juice secretion, splenic infarct, colonic necrosis, pseudoaneurisms, splenic and portal vein thrombosis, and pancreatic ascites. Besides systemic complications defined as preexisting comorbidity exacerbation; coronary disease, pulmonary chronic disease, were registered and analyzed in the same complications category.

Laboratory procedures

The chloremia measures at admission and after 24 hours, was performed with indirect potentiometry (cobas c 501 analyzer, Roche Diagnostics, Indianapolis, IN, USA) and the results were expressed in milliequivalents per liter (mEq/L). We define ISC as the increment of >8 mEq/L through the first 24 hours, according to our observation in clinical practice and results of the data base.

Statistical analysis

Data distribution was assessed using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation for normal distribution, and as median [inter-

quartile range] for non-normal distribution, while categorical variables were described as percentages and proportions. To evaluate differences, we used Student's t test/U-Mann Whitney test, and Chi-square/Fisher exact test, as appropriated. The primary outcome was the hospital stay in days, defined as the period between their emergency room admission and medical discharge; due to improvement or death (we excluded transferred patients and voluntary discharges). The chloremia delta was defined as chloremia after 24 hours minus chloremia at admission, expressed in mEq/L. Multivariate analysis was performed with multiple regression to determine the role of different variables with hospital stay in days. To estimate the power, we used post-study power-test with the pwr function, setting the significance in 0.05. All analyses were two-tailed and a P value of <0.05 was set for significance. R Studio version 3.4.1 statistical software was used for data analysis.

RESULTS

One hundred and ten patients were selected for the analysis, its baseline and clinic characteristics are shown in Table 2.

At 24 hours, 37 (33%) patients were classified with an ISC ($\Delta Cl>8mEq/L$). There were no differences in baseline characteristics (age, sex and pancreatitis etiology) between the two groups ($\Delta Cl>8mEq/L$, $\Delta Cl<8mEq/L$). (Table 3).

Table 2
Descriptive statistical. Baseline and clinical characteristics of the population.

	N=110 (%)	Median [Q1-Q3]	Mean ± SD
Age (years)		56 [42.2-69.7]	55.9±17.7
Sex (women)	63 (57)		
Etiology			
- Biliary	75 (68)		
- Alcoholic	9 (8)		
- Triglycerides	15 (14)		
- Drugs	1 (1)		
- Idiopathic	7 (6)		
- Others	3 (3)		
Severity			
- Mild	78 (71)		
- Moderate	12 (11)		
- Severe	20 (18)		
Chloremia at admission (mEq/L)		96.1 [93.5-99]	55.9±5.6
Admission APACHE II score		6 [4-7.7]	7.8±5.8
Used solution			
- SS0.9%	58 (53)		
- Hartmann	13 (12)		
- SS0.9%>Hartmann	24 (22)		
- Hartmann>SS0.9%	14 (13)		
- Others	1 (1)		
Quantity used (L)		4 [3.5-4.5]	4.06 ± 0.99

%: Percentage, Q1-Q3: Quartile 1 (P25) – Quartile 3 (P75), SD: Standard Deviation, h: hours, mEq/L: milliequivalents per liter, APACHE II: score of Acute Physiology and Chronic Health Evaluation II, SS0.9%: Saline Solution 0.9%, L: Liters.

Table 3
Bivariate analysis between increase in serum chlorine in 24 hours
ΔCl ≤8mEq/L vs ΔCl>8mEq/L.

	N=110 (%)	ΔCl ≤8mEq/L N=73 (%)	ΔCl >8mEq/L N=37 (%)	p
Age (years)				
Median [Q1-Q3]	56 [42.2-69.7]	56 [43-69]	56 [42-71]	0.81U
Mean ± SD	55.9 ± 17.7	55.6 ± 4.7	56.4 ± 18.4	
Sex (women)	63 (57)	44 (60)	19 (51)	0.37X
Etiology				
- Biliary	75 (68)	47 (64)	28 (75)	0.6F
- Alcoholic	9 (8)	5 (15)	4 (11)	
- Triglycerides	15 (14)	11 (15)	4 (11)	
- Drugs	1 (1)	1 (1)	0	
- Idiopathic	7 (6)	6 (8)	1 (3)	
- Others	3 (3)	3 (4)	0	
Severity				
- Mild	78 (71)	58 (79)	20 (54)	0.02X
- Moderate	12 (11)	6 (8)	6 (16)	
- Severe	20 (18)	9 (12)	11 (30)	
Chloremia at admission (mEq/L)				
Median [Q1-Q3]	96.1 [93.5-99]	97 [94.5-100]	96 [92-97.5]	0.03U
Mean ± SD	55.9 ± 5.6	97.1 ± 4.7	94.1 ± 6.6	
Chloremia after 24 h (mEq/L)				
Median [Q1-Q3]	103 [99.2-106]	102 [99-104.2]	105 [103.8-108]	0.0002U
Mean ± SD	102.9 ± 5.4	101.9 ± 5.1	105.1 ± 5.6	
Admission APACHE II (points)				
Median [Q1-Q3]	6 [4-7.7]	6 [4-9]	8 [6-15]	0.006U
Mean ± SD	7.8 ± 5.8	6.5 ± 4.5	10.2 ± 7.2	
24 hours APACHE II (points)				
Median [Q1-Q3]	5 [3-7.3]	5 [3-7]	6 [4-13]	0.13U
Mean ± SD	7.3 ± 7.4	6.3 ± 6.4	9.4 ± 8.8	
Hospital Stay (days)				
Median [Q1-Q3]	8 [6-9.5]	7 [5-10]	9 [7-12]	0.03U
Mean ± SD	9.5 ± 6.9	8.1 ± 4.2	12.3 ± 9.9	
Surgery				
- Elective	18 (16)	11 (15)	7 (19)	0.22F
- Urgency	1 (1)	0	1 (3)	
- Not surgery performed	60 (55)	38 (52)	22 (59)	
- Not needed	31 (28)	24 (32)	7 (19)	
Complications	27 (25)	14 (19)	13 (35)	0.06X
Mortality	18 (16)	9 (12)	9 (24)	0.10X

Table 3. CONTINUACIÓN

	N=110 (%)	ΔCl ≤8mEq/L N=73 (%)	ΔCl >8mEq/L N=37 (%)	p
Utilized solution				
- SS0.9%	58 (53)	34 (47)	24 (65)	
- Hartmann	13 (12)	12 (16)	1 (3)	
- SS0.9%>Hartmann	24 (22)	15 (21)	9 (24)	0.08χ
- Hartmann>SS0.9%	14 (13)	11 (15)	3 (8)	
- Others	1 (1)	1 (1)	0	
Quantity utilized (L)				
Median [Q1-Q3]	4 [3.5-4.5]	3.9 [3.5-4.3]	4.25 [3.6-5]	0.04ᵁ
Mean ± SD	4.06 ± 0.99	3.94 ± 0.86	4.31 ± 1.18	

%: Percentage, Q1-Q3: Quartile 1 (P25) – Quartile 3 (P75), SD: Standard Deviation, mEq/L: milliequivalents per liter, APACHE II: score of Acute Physiology and Chronic Health Evaluation II scale, SS0.9%: Saline Solution 0.9%, L: Liters. χ: Chi-Square test, ǂ: Exact Fisher Test, ᵁ: U-Mann-Whitney test, ᵀ: T-Student test.

Pancreatitis severity was stablished using the Atlanta criteria, and found as severe in the 30% of all patients with ΔCl>8mEq/L, compared with 12% of the patients with chloremia delta ≤8mEq/L (p=0.02). There were no differences in surgery indication in both groups.

Considering the clinical results, admission APACHE II score was higher in the group with ΔCl>8mEq/L (8 [6-15] *vs* 6 [4-9] points, p=0.006), but had no differences in APACHE II score 24 hours after (5 [3-7] *vs* 6 [4-13] points, p=0.13).

Hospital stay was longer in the group with ΔCl>8mEq/L (9 [7-12] *vs* 7 [5-10] days, p=0.03). The power (β) of this asseveration is 0.99 with a significance level (α) of 0.05.

There were not statistically significant differences in complications (35% vs 19%, p=0.06) and mortality (24% *vs* 12%, p=0.1).

Regarding the quantity of utilized solution in the first 24 hours from admission, we found that in the ΔCl>8mEq/L the median volume used was 4.25 [3.6-5] *vs* 3.9 [3.5-4.3] liters in the ΔCl≤8mEq/L group (p=0.04).

The Table 3 summarize the bivariated analysis of baseline and clinical outcomes of the patients, divided following their chloremia change.

In multivariate analysis modeling hospitalization days, final model was obtained with step-wise regression using backward variable elimination, showed that a ΔCl>8mEq/L (p=0.01) and 24 hours APACHE II score (p=0.02) stayed as the main predictors for longer hospital stay in patients with acute pancreatitis.

DISCUSSION

In this retrospective study of 110 patients with acute pancreatitis, we found that the significant chloremia increment in 24 hours (ΔCl>8mEq/L) could be an independent associated factor to prolong the hospital stay in the adult population. Chloremia concentration reflects patient's electrolyte and water balance; its change is attributed fundamentally to the management with crystalloid solutions. Thus, chloremia changes are intimately related with the kind and quantity of utilized solutions. Hyperchloremia at the same time is related with the acid-base equilibrium. In fact, the chloremia concentration increment is one of three causes of metabolic acidosis, which in animal studies increases the production of interleukin 6 and tumoral necrosis factor, as well as nitric oxide, therefore, chlo-

ride is a pro-inflammatory modulator [11]. It has been found that this ion is important in neutrophil functions, which requires constant influx through the chloride channels to produce hypochlorous acid from myeloperoxidase. For this reason, low extracellular chloride concentration is associated with neutrophil disfunction. This could provide a plausible pathophysiological link between the increment of chloremia and pro-inflammatory state and longer hospital stay in patients with acute pancreatitis. Recent studies in cells and animals indicate that hyperchloremic acidosis, through the increment of hydrochloric acid, significantly increases cytokines expression, besides the gene induction through κB nuclear factor and DNA junction. This seems to be especially relevant in states with important inflammatory response such as acute pancreatitis [11].

Previous studies had stablished the association between hyperchloremia and increased mortality in critically ill patients [8,9,11]. Isolated hyperchloremia has been recognized as an independent factor associated with acute kidney injury [10]. In our study, although it did not reach statistical significance, maybe because of the sample size, we can see a trend in the increment of mortality with significant changes in chloremia, as well as in the incidence of complications. Nevertheless, there is still controversy that chloremia changes are a consequence of aggressive fluid therapy in patients with deplored hydration level, or if they truly are the cause of mortality trough the inflammatory mechanisms mentioned before. Controlled prospective studies are needed to answer this question.

Regarding the use of solutions, Forsmark *et al* recommend administration of a range of 2.5 to 4 L in 24 hours; however, in our population the average was 4.07 ± 0.99 L, even reaching 7.2 L in the first 24 hours. Although recommendation is the use of crystalloids, either saline solution 0.9% or Hartmann solution, there is still no consensus as to which solution to use, although it has been seen that Ringer lactate may be associated with an anti-inflammatory effect [1].

In this population, a higher prevalence of biliary lithiasis as etiology (68%) of acute pancreatitis was noted. In the last 12 years, overweight and obesity, directly related to formation of biliary stones, have reached 71.3% in the adult population, an increase of almost 10% compared to the year 2000 [15].

In our study, the presence of ΔCl> 8mEq/L was an important predictor for hospital stay, even better than the APACHE II scale at admission and at 24 hours, only comparable with severity due to Atlanta classification in acute pancreatitis, even when it was adjusted in multivariate analysis.

We are aware that our study has limitations, mainly the lack of measurement of other electrolytes, acid-base and inflammatory balance parameters, such as sodium, potassium, calcium, magnesium, serum pH, bicarbonate (HCO_3) and C-reactive protein (CRP), even though several of these elements are routinely measured in this pathology.

Finally, the type of solution (Hartmann vs saline solution 0.9%), as well as the volume of liters used, should be evaluated in prospective controlled studies given its potential therapeutic effect and prognosis on days of hospital stay.

We conclude that changes greater than 8mEq/L of chloremia at 24 hours after admission identifies a subset of patients with acute pancreatitis with an increased risk of lengthening their hospital stay and probably mortality and complications, independently of other prognostic factors, such as APACHE II. Hyperchloremia remains a factor of poor prognosis, highly controllable with adequate fluid management, as well as being an easily measurable laboratory parameter that can better predict an increased probability of longer hospital stay in adult patients with acute pancreatitis.

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Author's ORCID numbers

• Rafael Silva Olvera (RSO): 0000-0002-3895-1149
• Mauricio Pierdant Pérez (MPP): 0000-0002-4606-0071
• Gustavo Ibarra Cabañas (GIC): 0000-0002-5319-4879
• Iván Ledezma Bautista (ILB): 0000-0003-4747-1777
• Raúl Alejandro Hernández Rocha (RAHR): 0000-0002-2395-1736
• Antonio Augusto Gordillo Moscoso (AAGM): 0000-0002-7351-4614

Authors participation

• RSO: participation in the design of the study, data acquisition final approval of the manuscript.

• MPP: participation in the design of the study, data analysis, writing of the manuscript, critical intellectual review, final approval of the manuscript.

• GIC: data acquisition, data analysis.

• ILB: data analysis, critical intellectual review, final approval of the manuscript.

• RAHR: writing of the manuscript, critical intellectual review, final approval of the manuscript.

• AAGM: data analysis, critical intellectual review final approval of the manuscript.

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