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Mortality and hyperchloremia in the intensive care unit

Hipercloremia y mortalidad en la unidad de cuidados intensivos

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Abstract

Introduction: Administrating intravenous fluids is one of the most frequent practices in the care of critically ill patients, since most of them present shock or hypotension from any cause. The rapid and aggressive administration of these fluids may lead to adverse results, including acute renal failure and hydroelectrolytic disorders which are highly associated with fatal outcomes.

Objectives: To establish the association between hyperchloremia and mortality in patients admitted to the intensive care unit (ICU) of Hospital Universitario de San José between August 2013 and January 2017, in addition to their demographic characteristics, the incidence of chloride abnormalities, and its association to renal failure.

Methods: Analytic retrospective cohort study in the adult ICU at the Hospital Universitario de San José from August 1, 2013 to January 31, 2017.

Results: A total of 839 patients were evaluated, 210 exposed and 629 not exposed. The relative risk of death for those who developed hyperchloremia was 3.12 (95% confidence interval [CI] 2.16–4.49) ($P < 0.001$). The multivariate analysis generated an hazard ratio of 2.31 (95% CI 1.47–3.63) adjusted for age, sex, APACHE II at admission, sepsis, neurocritical state, and development of renal failure.

Conclusion: Hyperchloremia is a frequent event in patients in the ICU; it may act as an independent variable for mortality in critical patients.

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Resumen

Introducción: La administración de líquidos endovenosos es de los actos que con mayor frecuencia se realizan en el cuidado de los pacientes críticamente enfermos, dado que gran parte de los mismos cursan con choque o hipotensión de cualquier causa, ésta se realiza de forma agresiva y rápida, dicha administración puede conllevar a eventos desfavorables como la falla renal aguda y alteraciones hidroelectrolíticas que están altamente relacionadas con desenlaces fatales.

Objetivos: Establecer la asociación entre hipercloremia y mortalidad en los pacientes hospitalizados en cuidados intensivos del hospital Universitario de San José entre agosto de 2013 y enero de 2017, así como sus características demográficas, incidencia de anormalidades del cloro y su asociación con falla renal.

Métodos: Estudio analítico de cohortes retrospectiva, en la Unidad de Cuidados intensivos (UCI) adultos del Hospital Universitario de San José, en el período comprendido entre el 1 de agosto de 2013 y el 31 de enero de 2017.

Resultados: Fueron evaluados 839 pacientes, 210 expuestos y 629 no expuestos. El riesgo relativo para muerte en los que desarrollaron hipercloremia fue 3.12 (IC95% 2.16–4.49) ($p < 0.001$). En el análisis multivariado se obtuvo un HR de 2.31 (IC95% 1.47–3.63) ajustado por las variables de edad, sexo, APACHE II al ingreso, sepsis, estado neurocrítico y desarrollo de falla renal.

Conclusiones: La hipercloremia es un evento frecuente durante la atención de los pacientes en la unidad de cuidados intensivos; puede actuar como una variable independiente de mortalidad en los pacientes críticos.

Introduction

At the beginning of the last century the administration of blood products was the most popular option for volume replacement in hypovolemic states of critical patients since no other options were available. Later, with the advent of Ringer's lactate and the subsequent development of other crystalloid solutions, blood products were replaced for the treatment of hypovolemia and these solutions became essential tools for resuscitation and maintenance of perfusion in multiple patients, particularly in the operating theaters, the intensive care units (ICUs), emergency departments, and prehospital care.

As the years went by, further experience was accumulated with the use of these drugs, identifying their benefits but also a few side effects associated with their volume, chemical composition, and osmolarity characteristics. Some of the most frequently described effects are cardiac volume overload (pulmonary edema, peripheral edema), protein dilution phenomena (coagulation factors, albumin), hydroelectrolytic disorders, and acid–base balance (hypernatremia, hyperchloremia).[1,2] National secondary studies attribute the reduction in pH and the increase in the chloride levels to the normal saline solution; this new knowledge led to changes in the fluid,[3] resulting in a number of new options, including different osmolar characteristics, ionic compositions, colloid mixtures, each addressing specific pathological conditions with variable outcomes[4,5] and also intended to attenuate potential adverse effects.

Although in the past decades, chloride-ion disorders—particularly hyperchloremia—were considered an innocent witness amidst and endless number of entropic situations in critically ill patients, recent studies in animal models have suggested that hyperchloremia is associated with alterations in the local rheology, immune paralysis, coagulation disorders, and pulmonary dysfunction.[6] Some publications in the last decade, such as Méndez and Cetina[7,8] suggest that probably hyperchloremia per se may impact the final outcome of these patients, resulting in renal failure, longer hospital stay, or mortality. The latter has been underestimated until now, considering that the most frequently used scores to determine severity and prognosis fail to take this ion into account. The scales used to evaluate severity and prognosis fail to consider chloride (APACHE, SOFA, rapid SOFA), which accounts for the neglect of this electrolyte in the approach to the critical patient. However, some studies such as Cetina,[7] report an increased relative risk (RR) of 1.88 (95% confidence interval [CI] 1.41–2.51) as a measure to associate hyperchloremia and death, versus the nonhyperchloremic group.

Based on the above situation, this research was designed with a view to establishing the incidence of mortality and renal failure associated with elevated chloride levels in an ICU at a third-level university hospital in Bogotá-Colombia.

Materials and methods

An analytic retrospective cohort study was conducted in the adult ICU of the Hospital Universitario de San José from August 1, to January 31, 2017.

The patients were recruited using a convenience sequential sampling methodology, including the adult patients admitted to the ICU with a chloride value below 107 mEq/L. Patients with any of the following criteria were excluded: transferred from another ICU, receiving dialysis, having required plasmapheresis, creatinine level at admission above 1.3 mg/dL, incomplete medical records for the outcome variables of interest, and a hospital stay of less than 48 hours.

Using the TAMAMU® software (Pontificia Universidad Javeriana, Bogota, Colombia), the sample size was estimated with the arcsine formula that identifies the difference of 2 proportions in cohort studies. In view of the broad variability found in the literature with regard to the risk of death and renal failure, the decision was made to conduct a pilot test and develop assumptions. For death as an outcome, an incidence of 21% of exposed individuals was used and a nonexposed incidence of 10%, with a

resulting sample size of 330. In terms of the renal failure outcome, a 10% incidence of exposed individuals was used, and 5% incidence for nonexposed, with a sample size of 848 patients. An alpha value of 5% and an 80% power was established in both cases. Since the sample size of the latter outcome includes the former, the number of participants was established at 848, and this number was adjusted for 10% losses, for a final sample size of 932 subjects.

Hyperchloremia was considered the factor that determined the exposure status, in accordance with the following procedure: patients admitted to the study met the criterion of a chloride value below 107 mEq/L. If during hospitalization the chloride value was reported at ≥107 mEq/L, the patient was admitted to the exposed cohort, while the rest of the subjects followed were considered part of the nonexposed cohort. The major outcome was time until death from any cause and the secondary outcome was the incidence of renal failure.

During the ICU stay, a clinical follow-up is conducted daily, in addition to laboratory tests. The information is recorded in the *Vesalius*® App (Bogota, Colombia, Vesaliua 3, 2012, Cardiosafe), and then this information was used to develop the database. To check the quality of the information, a 10% sample was used to compare against the medical record and there were no documented errors in the database, ensuring the integrity, and the validity of the data.

The confounding variables considered for inclusion in the multivariate model were the presence of sepsis, dysnatremia, neurocritical state, APACHE II score, and the development of renal failure. Sepsis was defined as those patients admitted with a diagnosis of septic shock and severe sepsis; neurocritical referred to any patient with a principal diagnosis of neurological pathology at the time of admission; dysnatremia corresponds to sodium levels under 132 or above 145 mEq/L; APACHE II was defined as an APACHE II score at the time of admission; and renal failure was defined as a creatinine elevation during follow-up in the ICU above 1.3 mg/dL.

Absolute and relative frequencies in the description of qualitative variables were used for the analysis; in the case of numerical variables, central tendency, and scatter descriptive statistics were used. The accumulated incidence of hyperchloremia for the total cohort was estimated, as well as the accumulated incidence of renal failure, and the incidence of mortality among the exposed and the nonexposed subjects. Based on these results, the RR was estimated with its corresponding 95% CIs. The incidence rate of the exposed and the nonexposed subjects was estimated for mortality and then the incidence rate ratio (IRR) was estimated with its respective 95% CI. To assess association or independence, the Chi-square test or Fisher's exact test were used as appropriate. The survival function was estimated for the time-to-death outcome using the Kaplan–Meier methodology; the curves were compared using the logarithmic range test. In the multivariate analysis, the Cox proportional hazards model was used for time-to-death as an outcome. The model included the clinically relevant variables that met the proportionality assumptions. To contrast the hypotheses, an alpha value of 0.05 was established. All the analyses were conducted using the STATA 14 software (StataCorp LP Lakeway Drive, College Station, Texas). The study was approved by the institutional ethics committee and was classified as a risk-free research under Resolution 008430.

Results

A total of 2273 patients were evaluated, of which 839 were eligible. From this group, 210 were classified as exposed,

Table 1. Baseline characteristics of the population

	Hyperchloremia (n = 210)	No hyperchloremia (n = 629)	Total population (n = 839)
Mean age (IQR)	61 (47–70)	58 (40–70)	58 (40–70)
Gender			
Males n (%)	104 (49.5)	323 (51.3)	427 (50.89)
Females n (%)	106 (50.5)	306 (48.7)	412 (50.89)
Mean hospital stay (IQR)	8 (5–14)	6 (4–9)	6 (4–10)
APACHE II at admission mean (IQR)	6 (3–11)	6 (3–10)	6 (3–10)
Sepsis n (%)	69 (32.9)	142 (22.6)	211 (25.15)
Neurocritical n (%)	46 (21.9)	124 (19.7)	170 (20.26)
Dysnatremia n (%)	91 (43.3)	141 (22.4)	232 (27.65)

IQR = interquartile range.
Source: Authors.

and 629 as nonexposed. All of the eligible patients completed the follow-up for the analysis. None of the patients were lost to follow-up; the general characteristics of the population are shown in Table 1. Significant differences between the groups were only found for sepsis and dysnatremia, with a *P* value of 0.003 and <0.001 respectively.

The accumulated incidence of hyperchloremia and renal failure in the total study population was 25.03% and 28.4%, respectively; the accumulated incidence of death in the exposed cohort was 23.8% versus 7.6% in the nonexposed cohort, with a RR of 3.12 (95% CI 2.16–4.49) and a statistically significant difference ($P < 0.001$). The accumulated incidence of renal failure was 41.9% in the exposed cohort and 23.8% in the nonexposed cohort, with a RR of 1.76 and a 95% CI of 1.42 to 2.17 ($P < 0.001$).

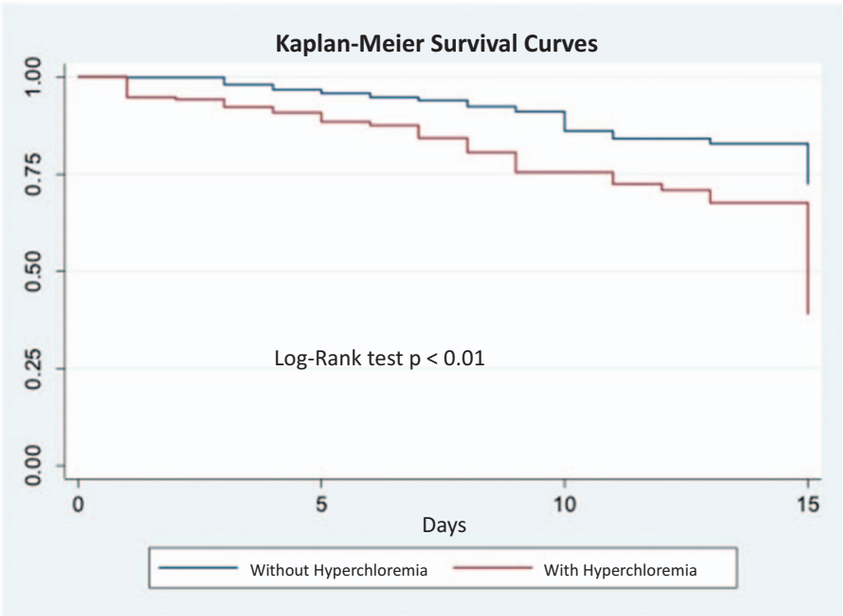
The incidence of death in the hyperchloremia group was 3.76×100 versus 1.2×100 days-patient, with an IRR of 3.18 and a 95% CI of 2.1 to 4.83, $P < 0.001$. Figure 1 illustrates the Kaplan–Meier survival curves, indicating a statistically significant difference (Table 2).

The multivariate analysis resulted in a hazard ratio of 2.28 (95% CI 1.45–3.56) for the time-to-death outcome, adjusted for age, sex, APACHE II at admission, sepsis, neurocritical state, dysnatremia, and development of renal failure The APACHE II and age variables entered the model independently as continuous and discrete variables. The receiver operating characteristic (ROC) curve was used to dichotomize the variables with mortality as the outcome, and the cut point giving the best sensitivity/specificity ratio was used for a value of 9 and 55 years for APACHE II and age, respectively. The final model used APACHE II and age in a dichotomous manner, since these 2 variables provided the best fit with the model. The assumption of proportionality was checked for each one of the variables included (Table 3).

Discussion

The development of hypochloremia while the patient is in the ICU is a frequent event and it is associated with a 2-fold mortality versus patients that do not develop hypochloremia. This association is maintained when adjusted for severity of the condition at admission to the ICU, age, development of renal failure, dysnatremia, the presence of sepsis, or a neurocritical condition.

Screening for patients with normal chloride levels at admission is intended to control the impact of volume



Day	With Hyperchloremia		Without Hyperchloremia	
	Survival function	95% CI	Survival function	95% CI
1	0.9476	0.9074 – 0.9706	0.9984	0.9888 – 0.9998
5	0.8837	0.8233 – 0.9244	0.9576	0.9365 – 0.9718
10	0.7532	0.6580 – 0.8254	0.8602	0.8009 – 0.9030
15	0.6748	0.5648 – 0.7628	0.7224	0.6143 – 0.8050

Figure 1. Kaplan–Meier survival curves for time-to-death as an outcome.
Source: Authors.

Table 2. Relative risk and incidence rate ratio for death as an outcome

Incidence in the total population	11.7%
Incidence in exposed subjects	23.8%
Incidence in nonexposed subjects	7.6%
Relative risk	3.12 (95% CI 2.17–4.49)
Rate of incidence in exposed subjects	3.76 × 100 days-patient
Rate of incidence in nonexposed subjects	1.18 × 100 days-patient
Incidence rate ratio	3.18 (95% CI 2.09–4.83)

CI = confidence interval.
Source: Authors.

resuscitation that may influence the absolute amount of the electrolyte plasma concentration (difficult to reconstruct retrospectively), and becomes a confounding factor since more severe patients could have received larger volumes of crystalloids, since they are subject to more aggressive resuscitation.

In this cohort evaluated, the frequency of chloride disorders was around 25%, with a value close to that described by Neyra[9] and Lee[10], but with a number far below that reported by the papers by Aguilar[7], Boniatti[11], and Van Regenmortel[12]. In addition to this finding, some similarities were found with regard to Lee's paper, in which normal chloride levels is also the starting point in multiple trauma patients, with a follow-up of 30 days; hyperchloremia was defined as chloride levels above 110 mEq/L. Lee found in its multivariate logistical regression an odds ratio (OR) of 1.075 (95% CI 1.027–1.169) per every 1 mmol/dL rise in the chloride level from the time of admission, describing a base deficit, the use of vasopressors, and renal failure as independent risk factors for mortality at 30 days. In contrast to this study cohort that includes all the pathologies present in a polyvalent ICU, with 15-day follow-up, both share the idea that developing hyperchloremia in the ICU is an independent risk factor for mortality.

Table 3. Cox regression model for time-to-death outcome

	Hazard ratio	95% CI	P
Hyperchloremia	2.28	1.45–3.56	0.000
Age	1.72	1.05–2.82	0.033
Sex	0.99	0.66–1.48	0.95
Renal failure	2.03	1.3–3.16	0.002
Neurocritical state	1.42	0.89–2.28	0.144
Sepsis	0.76	0.48–1.19	0.229
APACHE II	1.53	1.02–2.3	0.04
Dysnatremia	0.88	0.57–1.36	0.571

P for the model was <0.001. CI = confidence interval.
Source: Authors.

Boniatti develops a retrospective cohort in a polyvalent Brazilian ICU trying to show the relationship between mortality and acid–base balance disorders. He therefore suggests a prognostic/diagnostic model expressed in a ROC curve. Contrary to this study, the patients included were admitted to the cohort with dyschloremia and a logistic regression model was generated that could be predictive of mortality in these patients. Although showing that the strong ions difference does not represent a risk factor, hyperchloremia in the bivariate analysis does show an OR of 1.065 (95% CI 1.015–1.118), although the lower limit of the CI is close to 1.

Van Regenmortel developed a large retrospective cohort recruiting 6480 patients (surgical and medical), using the same cut points to define hyperchloremia as this study (107 mEq/L); furthermore, he classified moderate hyperchloremia between 107 and 110 mEq/L and more than 110 mEq/L as severe. Van Regenmortel's logistic regression produced an OR of 1.46 (95% CI 1.14–1.96) for mortality among patients that developed severe hyperchloremia, as compared against the normal chloride patients.

Neyra conducted a similar study in septic patients, allowing the inclusion of patients with hyperchloremia in the cohort, considering as a risk factor for mortality a chloride increase at 72 hours. He found an OR of 1.37 (95% CI 1.11–1.69), per each 5 mEq/L increase versus the level at admission.

The results seem to indicate that hyperchloremia is associated with the severity of the disease, particularly cases of sepsis, renal failure, and dysnatremia. The clinical significance of increasing chloride levels has been controversial in previous papers.

The previously described aspects regarding the time at which abnormality is identified and the difficulty to standardize the conditions that may act as independent factors for the development of mortality, particularly those relating to the initial resuscitation stages, are a common denominator for the various above-mentioned retrospective studies as well as for this study.

The study has several limitations. Because of its retrospective nature, it is not possible to assess the impact of the initial fluid resuscitation of the patient, or the type of solutions used; this may influence, both the development of hyperchloremia, and the mortality outcome. However, the fact that patients with hyperchloremia were excluded at admission, as well as those with less than 48 hours in the ICU, could have helped to reduce the impact on the results.

Notwithstanding the fact that the proposed sample size was not achieved—which initially could be considered a limitation—since there were no follow-up losses and there was a 10% margin, the power of the study was not compromised.

The study was carried out in only 1 institution and this fact may limit the external validity of the findings; however, the fact that it was conducted in a polyvalent ICU, in addition to the large number of patients, favors the generalization of the conclusions.

Conclusion

After evaluating the results of this study, and the comparisons against other studies, one may conclude that the concern about understanding the impact of chloride disorders on negative outcomes is rising; there seems to be a link between chloride disorders and negative outcomes, particularly death, in the ICU setting; one could theorize the need to rationalize the use of solutions with electrolyte components separate from the physiological solutions; and consider the presence or the development of hyperchloremia as a prognostic factor, without taking into consideration the severity of the critical patient.

Elevated chloride levels may act as an independent variable for mortality in critical patients; the strength of the association shall be confirmed with a prospective follow-up, analyzing the control of resuscitation time, infection from resistant germs, and morbidity as independent variables.

Ethical responsibilities

Protection of persons and animals. The authors declare that no experiments in humans or in animals were conducted for this research.

Confidentiality of the data. The authors declare that they have followed the protocol of their workplace on the publication of patient data.

Right to privacy and informed consent. The authors declare that this article does not disclose any patient information.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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