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Association between hyponatremia, mortality and hospitalization in patients with acute decompensated Heart Failure

Asociación entre hiponatremia, mortalidad y estancia hospitalaria en pacientes con falla cardíaca descompensada

Associação entre hiponatremia, mortalidade e internação hospitalar em pacientes com insuficiência cardíaca descompensada

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ABSTRACT

Introduction. Hyponatremia is the most common electrolyte disorder in patients with chronic heart failure affecting up to 28% of patients at admission. It has been shown to be an independent predictor of mortality, extended length of hospital stay and rehospitalization. The objective is to evaluate the presence of hyponatremia in patients with decompensated heart failure and describe its relationship with length of hospital stay and mortality.

Methodology. A prospective cohort study in patients hospitalized at internal medicine service at a high level of complexity hospital in Bogotá, Colombia diagnosed with decompensated heart failure between April 2011 and March 2012. Sodium was measured on admission, 72 hours and at the seventh day of hospitalization. We evaluated the association between hyponatremia at hospital admission, mortality at 30 days and length of hospital stay.

Results. 162 patients were included with an average age of 72 years, 52.5% male. Forty-one (25.3%) had hyponatremia at admission. Among the patients with normal sodium at admission, 6 had hyponatremia at 72 hours and 2 at the seventh day. In-hospital mortality in the total population was 9.2%, in the hyponatremia group 12.2%, and 8.2% in those who did not have it ($p = 0.45$). The average length of hospital stay was higher in patients with hyponatremia, 6.6 vs 8.4 days ($p = 0.12$).

Discusión. The incidence of hyponatremia at admission in this group of patients was similar to that reported in the literature.

Conclusions. The results showed a trend towards higher mortality and hospital stay in patients with hyponatremia, even though it was not statistically significant.

Key words:

Heart failure; Hyponatremia; Prognosis; Mortality; Hospitalization

RESUMEN

Introducción. La hiponatremia es la alteración electrolítica más frecuente en pacientes con falla cardíaca crónica, que afecta hasta el 28% de pacientes en el ingreso hospitalario. Se ha demostrado que es un predictor independiente de mortalidad, estancia prolongada y rehospitalización. El objetivo es describir la frecuencia de hiponatremia en pacientes con falla cardíaca descompensada y su relación con la estancia hospitalaria y mortalidad.

Metodología. Cohorte prospectiva en pacientes hospitalizados por el servicio de Medicina Interna en un hospital de cuarto nivel de Bogotá, Colombia, con diagnóstico de falla cardíaca descompensada entre abril de 2011 y marzo de 2012. Se midió el sodio al ingreso, a las 72 horas y al día séptimo de hospitalización. Se evaluó la relación de la hiponatremia al ingreso con la estancia hospitalaria y la mortalidad intrahospitalaria a 30 días.

Resultados. Se incluyeron 162 pacientes, con promedio de edad de 72 años, 52.5% hombres. Cuarenta y uno (25.3%) presentaron hiponatremia al ingreso. Entre los pacientes que presentaron sodio normal al ingreso, 6 presentaron hiponatremia a las 72 horas y 2 a los 7 días. La mortalidad intrahospitalaria en la población total fue 9.2%, en el grupo de hiponatremia 12.2%, y 8.2% en los que no la tuvieron ($p = 0.45$). El promedio de estancia hospitalaria fue superior en los pacientes con hiponatremia,

6.6 vs. 8.4 días ($p = 0.12$).

Discusión. La incidencia de hiponatremia al ingreso en este grupo de pacientes fue semejante a la reportada en la literatura.

Conclusiones. Existe una tendencia hacia una mayor mortalidad y estancia hospitalaria en pacientes con hiponatremia, aun cuando no fue estadísticamente significativa.

Palabras clave:

Insuficiencia cardíaca; Hiponatremia; Pronóstico; Mortalidad; Hospitalización.

RESUMO

Introdução. A hiponatremia é o desequilíbrio hidroeletrólítico mais frequente em pacientes com insuficiência cardíaca crônica, que afeta até 28% dos pacientes internados. Demonstrou ser um preditor independente de mortalidade, permanência prolongada e re-internação. O objetivo é descrever a frequência de hiponatremia em pacientes com insuficiência cardíaca descompensada e sua relação com internação hospitalar e mortalidade.

Metodologia. Coorte prospectiva em pacientes internados pelo serviço de Medicina Interna em um hospital de quarto nível em Bogotá, Colômbia, com diagnóstico de insuficiência cardíaca descompensada, entre abril de 2011 e março de 2012. Foi medido o sódio na admissão, às 72 horas e no sétimo dia de internação. Foi avaliada a relação de hiponatremia na admissão com internação e a mortalidade hospitalar aos 30 dias.

Resultados. Foram incluídos 162 pacientes, com idade média de 72 anos, 52,5% homens. Quarenta e um (25,3%) apresentaram hiponatremia na admissão. Entre os pacientes que apresentaram sódio normal na admissão, seis apresentaram hiponatremia às 72 horas, e dois aos sete dias. A mortalidade hospitalar na população total foi de 9,2%, no grupo de hiponatremia 12,2% e 8,2% naqueles que não apresentaram ($p = 0,45$). O tempo médio de internação foi maior nos pacientes com hiponatremia, 6,6 vs. 8,4 dias ($p = 0,12$).

Discussão. A incidência de hiponatremia na admissão nesse grupo de pacientes foi semelhante à relatada na literatura.

Conclusões. Existe uma tendência de maior mortalidade e permanência hospitalar em pacientes com hiponatremia, mesmo que não tenha sido estatisticamente significativa.

Palavras-chave:

Insuficiência cardíaca; Hiponatremia; Previsão; Mortalidade; Hospitalização.

Introduction

Hyponatremia is the most common electrolyte disorder in hospitalized patients with heart failure in developed countries, because it affects between 14% and 28% of patients admitted to hospital (1-4). Additionally, between 15% and 25% of patients with normal sodium levels upon admission to hospital develop hyponatremia during diuretic treatment (5,6), especially patients with lower left ventricular ejection fraction, which is associated with an increase in mortality among patients who did not develop hyponatremia during their hospital stay (5, 6).

Neurohormonal activation is predominant in the pathophysiology of heart failure, which generates a complex interaction between the renin-angiotensin-

aldosterone system, the sympathetic nervous system through the activation of baroreceptors, and the nonosmotic release of arginine vasopressin. Out of these events, nonosmotic release of vasopressin and the flow reduction in distal tubule segments of the nephron are the key pathophysiological mechanisms in the development of hyponatremia.

This activation, initially produced to preserve hemodynamic integrity after a heart lesion, subsequently leads to progressive cardiac dysfunction with the consequent water and salt retention that predisposes to hyponatremia (7-12). Additionally, as part of the treatment for heart failure, medications such as diuretics are administered, which improve the congestive symptoms of heart failure but can generate electrolyte disorders, such as hypokalemia and hyponatremia, which

are associated with neurohormonal activation and renal dysfunction in some cases, and further compromise the patient (13, 14). Yamazoe et al. documented that the risk of hyponatremia contracted in hospital was significantly higher when using thiazide diuretics compared to the use of non-thiazide diuretics, and in a propensity analysis of this study, the cardiovascular mortality rate was 30% in the group that received thiazide diuretics compared to 14% in the group that did not receive them (15).

The prognostic importance of hyponatremia in patients with severe, chronic heart failure was described for the first time in 1986 by Lee and Parker, who found that hyponatremia was the prognostic predictor with the highest degree of association with mortality and rehospitalization due to heart failure (16). Similarly, different studies have demonstrated that hyponatremia is a predictor of morbimortality regardless of the state of health and ventricular function (17-19).

In Colombia, there was a study that assessed hyponatremia in the context of patients with heart failure, and an analysis by Chaves et al. that involved sodium upon admission as part of an analysis of in-hospital mortality and at 30 days for patients hospitalized for acute heart failure, without conducting measurements in series (20, 21). Studies on this topic are limited in Colombia and the importance of generating local and regional information has been discussed and highlighted, taking into account the biological and social reality of our population and the need to keep consolidating a scientific tradition in this area, which collectively justifies carrying out this kind of research. The aim of this study was to assess the frequency of hyponatremia in hospitalized patients for decompensated heart failure and assess its relationship with in-hospital mortality, mortality at 30 days and the hospital stay.

Methodology

A prospective cohort study was conducted, which included patients admitted to hospital by the general medicine service of a level-four hospital in Bogotá, Colombia, with an admission diagnosis of decompensated heart failure in the period between April 1, 2011, and March 31, 2012.

The following inclusion criteria were identified: patients older than 18 years who were admitted through the emergency department, whose main diagnosis was decompensated heart failure, who met the Framingham diagnostic criteria (24) and who were admitted to hospital for more than 24 hours. Patients with the

following conditions were excluded: hyperglycemic crises of diabetes mellitus (ketoacidosis or hyperosmolar state), dialytic emergency or patients undergoing kidney replacement therapy, cirrhosis in Child-Pugh class C/D or acute liver insufficiency, nephrotic syndrome, hypovolemic shock, septic shock, terminal neoplastic disease documented in the medical record, and absence of sodium measurement upon admission.

The sodium levels were measured upon admission, at 72 hours and on the seventh day of the hospital stay. Hyponatremia was defined as a blood sodium level of less than 135 meq/L (25). The data of left ventricular ejection were obtained from the reports of the echocardiogram carried out in the institution or an echocardiogram report taken in the three months prior to hospitalization.

Information was collected in a structured format for this aim, in which the data on comorbidity and prescription of medication prior to admission were recorded. The information of all patients involved was verified by two co-researchers. In the case of inconsistencies, the primary source of information was consulted to clarify them. The patients were monitored until their discharge from hospital, and to report the mortality at 30 days, the mortality established in the Single Patient Registration System (RUAF, for the Spanish original) of the National Civil Status Registry was verified.

The database was created in Excel 2007 and the statistical analysis was conducted in STATA 10. The quantitative variables were summarized with central tendency and dispersion measures: average, standard deviation, minimum, maximum value or median and interquartile range (IQR). The qualitative variables are presented with absolute and relative frequencies. Fisher's exact test was used to assess the association between the incidence of hyponatremia and in-hospital mortality, mortality at 30 days and an extended hospital stay (defined as a hospital stay of more than five days). The differences in the incidence of hyponatremia during the average hospital stay were also measured using the student's t-test. This study was approved by the Research Committee of the Medicine Faculty of Fundación Universitaria de Ciencias de la Salud, Minutes no. 222 of November 22, 2010.

Results

Between April 1, 2011, and March 31, 2012, 173 patients with decompensated heart failure were hospitalized, of which 11 were excluded from the study. Therefore, 162

patients were analyzed in total (**Figure 1**). The average age was 72 years (± 13.8), 124 (76.6%) were older than 65 years, 85 were men (52.5%) and 77 were women (47.5%). The number of patients with hyponatremia upon admission was 41 (25.3%), while 121 (74.7%) had sodium ≥ 135 meq/L. The population's characteristics are described in **Table 1**. No statistically significant differences were found in the reported characteristics,

although a tendency of a lower incidence of chronic kidney failure was observed in the hyponatremia group.

During the hospital stay, out of the 121 patients without hyponatremia upon admission, 93 (76%) completed 72 hours of hospitalization, of which sodium measurements were taken from 76 (the rest of the patients did not have a sodium test order) and hyponatremia was found in six of them. Out of the 70 patients with hyponatremia

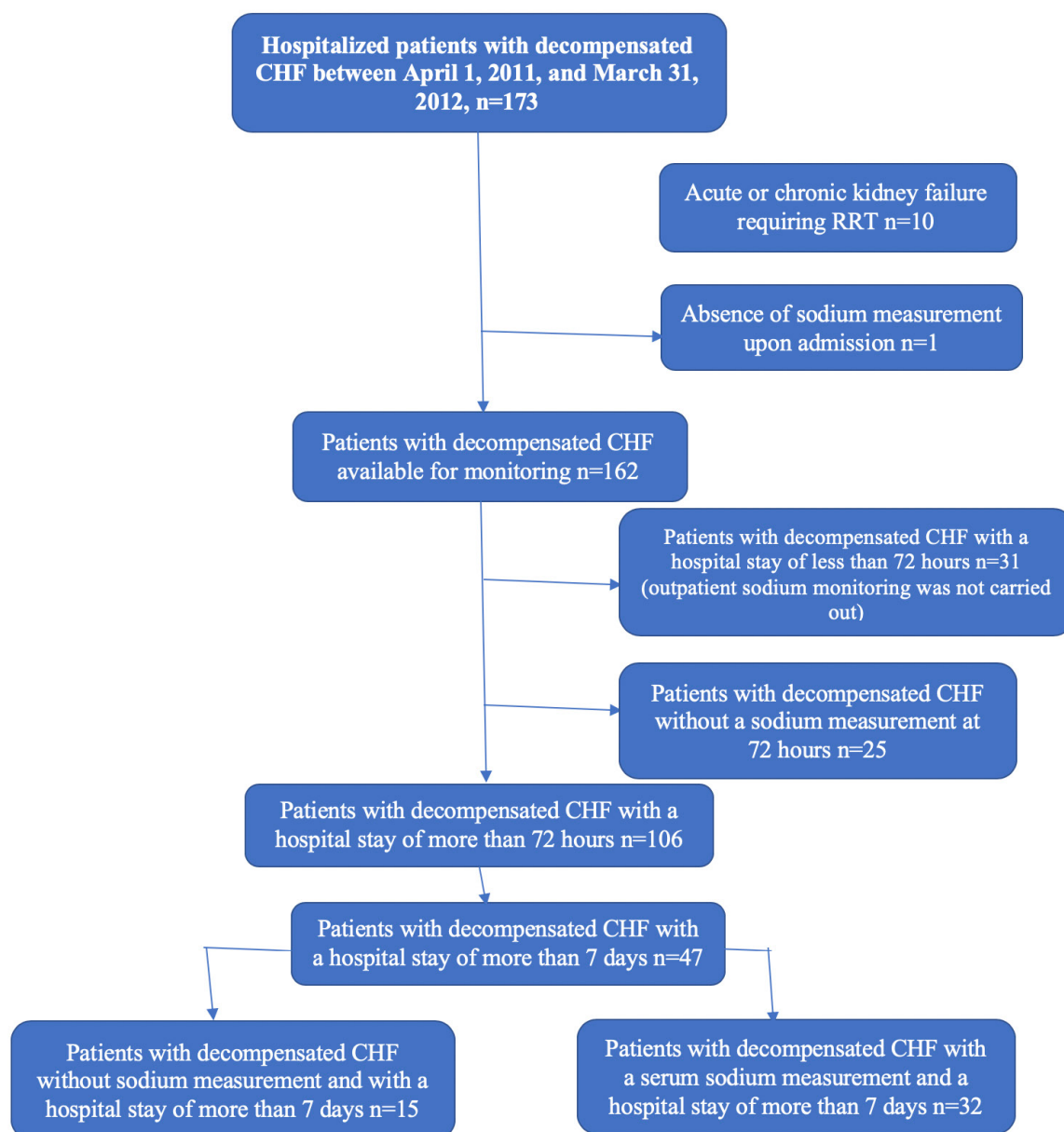


Figure 1. Distribution and Monitoring of Hospitalized Patients with a Diagnosis of Decompensated Heart Failure

Source: Prepared by the authors.

Table 1. Population Characteristics

Serum sodium	≥135 meq/L	<135 meq/L	Total
	N=121 (74.7%)	N=41 (25.3%)	N=162 (100%)
Variables			
Age, years, average (SD)	71.1 (12.9)	74.7 (15.8)	72 (13.8)
≥ 65 years n(%)	91 (75.2)	33 (80.5)	124 (76.6)
Male gender, n(%)	64 (52.9)	21 (51.2)	85 (52.5)
Comorbidity, n(%)			
High blood pressure n(%)	102 (84.3)	34 (82.9)	136 (84)
Diabetes mellitus n(%)	28 (23.1)	11 (26.8)	39 (24)
Hypothyroidism n(%)	29 (23.7)	7 (17)	36 (22.2)
Chronic kidney disease* n(%)	12 (9.8)	2 (4.8)	14 (8.6)
COPD n(%)	52 (43)	16 (39)	68 (42)
Type of Diuretic Used			
Furosemide n(%)	50 (41.3)	19 (46.3)	69 (42.6)
Hydrochlorothiazide	13 (10.7)	8 (19.5)	21 (12.8)
Spironolactone n(%)	25 (20.6)	7 (17)	32 (19.8)
Other pharmaceuticals n(%)			
Tricyclic antidepressants n(%)	2 (1.6)	0 (0)	2 (1.2)
Serotonin reuptake inhibitors n(%)	0 (0)	1 (2.4)	1 (0.61)
Opiates	0 (0)	1 (2.4)	1 (0.61)
Carbamazepine n(%)	2 (1.6)	1 (2.4)	3 (1.8)
Creatinine, mg/dL, median (IQR)	1 (0.8-1.2)	1 (0.7-1.3)	1 (0.8-1.2)
Urea nitrogen, mg/dL, median	22 (18-30)	27 (20-38)	24 (18-33)
LVEF‡ <40%, n(%)	39 (36.4)	13 (33.3)	52 (35.6)
Systolic blood pressure, mmHg, median (IQR)	133 (122-146)	126 (115-140)	131 (120-145)
Heart rate, beats/min, median (IQR)	82 (72-93)	80 (70-96)	80 (70-93)

* Patients who do not require renal replacement therapy.

‡ The LVEF is only available for 146 patients (107 in the group with sodium ≥135 meq/l, and 39 in the group with sodium <135 meq/l).

SD: Standard deviation.

Source: Prepared by the authors.

at 72 hours, 26 completed a hospital stay of more than seven days. The sodium level was tested for 17 of these patients (the rest of the patients did not have a sodium test order) and it was found that two had developed hyponatremia.

Fifteen patients died during hospitalization (9.2% of the total population studied). Five of these patients were in the group that had hyponatremia upon admission (12.2%) and the other ten patients were in the group that did not (8.2%) ($p=0.45$) (**Table 2**). Out of the patients who developed hyponatremia within 72 hours from admission, three died in the hospital, compared to eight patients who did not develop hyponatremia in that time. With respect to mortality at 30 days, no patient in the hyponatremia group died during this monitoring, while five died in the group without hyponatremia (4.1%) ($p=0.18$) (**Table 2**).

The average hospital stay was seven days (± 6.4) for the total sample population, 8.4 days (± 6.1) for patients with hyponatremia and 6.6 (± 6.4) for the group without hyponatremia upon admission ($p=0.12$). When the hospital stay of more than

five days was assessed, significant statistical differences were found between the groups, 61% and 43% respectively ($p=0.04$) (**Table 3**). It is worth mentioning that out of the patients with hyponatremia upon admission, three (7.3%) had a hospital stay of less than 72 hours, compared to 28 (22.9%) who did not have hyponatremia.

Discussion

This study assessed hyponatremia in a population of patients hospitalized for decompensated heart failure. Upon admission, the incidence of hyponatremia was 25.1%, which is similar to that of other reports, such as the report by Rossi et al. (18), who reported an incidence of 20%; Gheorghiadu et al., who reported incidences between 23.8% (17) and 19.7% (26); and Patel et al., who documented a prevalence of 21% in patients with conserved ejection fraction (27). The study also documented that some patients who were admitted without hyponatremia subsequently showed hyponatremia in one of the two subsequent assessments. However, a definitive prevalence of in-

Table 2. Mortality according to Sodium Levels upon Admission

Serum sodium levels	≥ 135 meq/L	< 135 meq/L	Total Patients	p value
	N=121	N=41	N=162	
In-hospital mortality, n (%)	10 (8.2)	5 (12.2)	15 (9.2)	0.45
Cumulative mortality at 30 days* n (%)	15 (12.3)	5 (12.2)	20 (12.2)	0.97

* Death in the first 30 days of release from hospital.

Source: Prepared by the authors.

Table 3. Mortality according to Sodium Levels upon Admission

Serum sodium levels	≥ 135 meq/L	< 135 meq/L	Total Patients	p value
	N=121	N=41	N=162	
Average hospital stay in days (SD)	6.6 (6.4)	8.4 (6.1)	7 (6.4)	0.12
Extended hospital stay (more than five days) n (%)	52 (43)	25 (61)	77 (47.5)	0.04

SD: Standard deviation.

Source: Prepared by the authors.

hospital hyponatremia could not be established, because there was not information on all the patients and a total of three assessments were carried out during the hospital stay, without testing the sodium in all patients on the day of hospital discharge, which is important taking into account the dynamics of the blood sodium concentrations during the treatment of these patients.

A greater incidence of hyponatremia was observed in patients using a combination of thiazide and furosemide diuretics, although the result was not statistically significant. This finding is in accordance with that found in the cohort study of Yamazoe et al., who documented a greater risk of in-hospital hyponatremia when patients received the combination of thiazide and loop diuretics (OR=2.67, CI 95% 1.13–6.34 when low doses of loop diuretics were used, and OR=2.31, CI 95% 1.50–5.13 when high doses of loop diuretics were received) (15).

The association between in-hospital mortality and long-term mortality in patients with heart failure and hyponatremia is well established (7, 27-30). In the ATTEND record, all-cause mortality and cardiovascular death in patients with hyponatremia were 15% and 11.4%, respectively, significantly higher than in patients with normonatremia, which had a mortality of 5.3% and 3.6%, respectively (28). In the ESCAPE trial, the HR (Hazard Ratio) for mortality at six months was 1.23 (CI 95% 1.05-1.43) for every 3 meq/l decrease in sodium. The association was greater if the hyponatremia was persistent during hospitalization (HR = 1.82 CI 95% 1.03-3.22, $p=0.04$) (17). In the OPTIMIZE-HF study, the in-hospital mortality rate was 6% in the hyponatremia group, compared to 3.2% in the general heart failure population ($p<0.0001$) (26). In turn, in the OPTIME-CHF study, the in-hospital mortality was 5.9% in patients located in the lower quartile for the sodium levels, compared to 2.3% for patients in the upper quartile (Q4) ($p=0.015$) (30).

In our results, no statistically significant difference was found in mortality between the group with hyponatremia upon admission compared to the group without hyponatremia, even when the difference between the two groups was 3%; a similar percentage to the OPTIME and OPTIMIZE-HF studies, in which a statistical significance was found in these results. It is possible that the lower number of patients included in this study limits the possibility of finding statistical significance in this result. Furthermore, a high in-hospital mortality was observed in the general group, which could be connected to the incidence of related pathologies.

An increase in the hospital stay was also found. The average hospital stay was longer in the hyponatremia group; likewise, more patients in this group had a hospital stay of more than five days. However, only this last result achieved statistical significance. The findings are consistent with the results of other studies, such as OPTIMIZE-HF, where patients with hyponatremia had an average stay of 6.4 days, compared to the stay of 5.5 days for patients without hyponatremia (26).

A limitation of this study was the lack of a statistical analysis that would have permitted the control of confounding variables that could alter the result for the association with the extended hospital stay. Also, the sodium test was not carried out on all patients with a stay of more than seven days, so it was not possible to conduct an analysis taking into account the development of hyponatremia during hospitalization or its persistence; an important topic for this analysis. Additionally, given that the official sample size was not calculated, it is not possible to establish whether the number of patients studied was sufficient to find statistically significant differences for the tests conducted. Finally, the study was carried out at a single hospital center, which limits the interpretation of the results in terms of external validity.

Conclusion

The incidence of hyponatremia in hospitalized patients with decompensated heart failure upon admission to this institution is similar to the rate reported in international literature. A higher percentage of in-hospital mortality and the average days of hospitalization of patients with hyponatremia was found, even when the differences were not statistically significant.

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Conflicts of Interest

The authors of this study do not have any conflict of interest.

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