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Original article

A normal sodium diet preserves serum sodium levels during treatment of acute decompensated heart failure: A prospective, blind and randomized trial

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SUMMARY

Background: We tested the hypothesis that a normal sodium diet could be associated with preservation of serum sodium during treatment of acute decompensated heart failure (ADHF).

Methods and results: Forty-four patients hospitalized for ADHF were blindly randomized by using block method to a low sodium diet (LS: 3 g/day of dietary sodium chloride; n = 22, 59.5 ± 11.9 y.o., 50% males. LVEF = 30.0 ± 13.6%); and a normal sodium diet (NS: 7 g/day; n = 22, 56.4 ± 10.3 y.o., 68% males; LVEF = 27.8 ± 11.7%), and both groups were submitted to fluid restriction of 1.000 mL/day. At the 7th day of intervention 16 patients of LS group and 15 patients of NS group were assessed for difference in serum sodium. Both groups had equivalent decongestion, reflected by similar percent reduction of body weight (LS: −5.0 ± 4.7% vs NS: −4.5 ± 5.2%. p = 0.41). Reduction of the N terminal fragment of type B natriuretic peptide (NT-proBNP) was significant only in the NS (−1497.0 [−18843.0 − 1191.0]. p = 0.04). The LS group showed lower levels of serum sodium (135.4 ± 3.5 mmol/L) compared to the NS group (137.5 ± 1.9 mmol/L; p = 0.04). Four cases of hyponatremia were observed only in the LS group (22%). The NS group exhibited higher mean blood pressure values (79.4 ± 2.4 mmHg vs 75.5 ± 3.0 mmHg. p = 0.03), and lower heart rate (73.2 ± 1.6 bpm vs 75.5 ± 2.1 bpm. p = 0.02).

Conclusions: These results suggest that a normal sodium diet, when compared to a low sodium diet, is associated with similar degrees of decongestion, but with higher levels of natremia, blood pressure and lower neurohormonal activation during ADHF treatment.

Trial Registration: clinicaltrials.gov Identifier no. NCT03722069.

Introduction

Heart failure (HF) is an important public health problem affecting approximately 6.5 million Americans older than 20 years [1–3], with about 1.9–3.8/1000 persons-year acquiring the disease [4–6]. It is a highly lethal syndrome, the estimate being that one in two subjects with HF will die within 5 years after the diagnosis [4–8].

The natural history of chronic HF is frequently marked by episodes of rapid progression of signs and symptoms such as dyspnea and fatigue characterizing acutely decompensated heart failure (ADHF) that requires hospitalization [9,10]. In the US, more than 1 million persons per year are hospitalized with ADHF as a primary diagnosis [3].

Despite the uncontested severity of this syndrome, several aspects of its treatment are not based on solid scientific evidence or on randomized clinical studies specially designed for this purpose, as is the case for the dietary management of sodium intake. Treatment guidelines recommend restriction of dietary sodium chloride [10,11] without considering the potential risks of the use of a low sodium diet, especially the development of hyponatremia and the impact on blood pressure levels.

Previously reported data suggest that there is no benefit in the adoption of a low sodium diet for patients with chronic HF and that

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a normal sodium diet in addition to fluid restriction may be more beneficial, involving lower levels of neurohormonal activation, a lower number of hospital readmissions due to ADHF, and lower mortality [12–15]. However, those results were obtained with the use of an unusually high dose of loop diuretics and a very restrictive fluid restriction, factors that may confound the real contribution of diet sodium content for the outcomes.

Although few studies of patients with ADHF are available, a recent report has shown that there was no difference in weight loss or in the improvement of clinical parameters between patients receiving a low sodium diet with severe fluid restriction and patients receiving a diet with free sodium and fluid intake [16]. Thus, these results suggest that the use of a low sodium diet is not beneficial for the resolution of congestive manifestations.

Therefore, the study hypothesis is that the use of a low sodium diet during the treatment of ADHF may be associated with a reduction of serum sodium and blood pressure levels.

Indeed, previous studies have shown that hyponatremia is a common occurrence among patients hospitalized for the treatment of ADHF, affecting about 20% of them [17]. It should be pointed out that in ADHF hyponatremia may be caused both by excessive water retention secondary to neurohormonal activation and by a negative sodium balance associated with low dietary intake and high doses of loop diuretics [18]. In view of the fact that a low serum sodium level is recognized as an independent marker of a worse prognosis and is associated with high rates of morbidity-mortality on a short- and long-term basis [14–16], we consider the investigation of the influence of dietary sodium intake on serum sodium levels during the treatment of ADHF to be of clinical importance.

Thus, the objective of the present study is to test the hypothesis that a normal sodium diet combined with fluid restriction may have a positive impact on preservation of natremia and blood pressure during the treatment of ADHF.

Methods

General study design

The present study was a single-blind randomized clinical trial conducted on patients hospitalized with a primary diagnosis of ADHF. The intervention was conducted on two parallel investigative groups at the 1:1 proportion, with different levels of daily sodium intake and restriction of 1000 mL fluid per day. The patients were monitored up to the 7th day of intervention (Fig. 1).

After being allocated to one of the two study groups, the selected patients were submitted to baseline evaluation consisting of the following procedures: measurement of body weight, collection of a blood sample for the determination of serum sodium and potassium (by an enzymatic method), haemoglobin (by the cyanomethaemoglobin method), serum urea (by an enzymatic-colorimetric method), serum creatinine (by the method of Jaffé, modified) and natriuretic peptide (N-terminal fragment of type B natriuretic peptide, NT-proBNP, by Enzyme-Linked Fluorescent Assay, ELFA), evaluation of dyspnea (with 0 corresponding to marked shortness of breath and 10 to no shortness of breath) and of general well-being (with 0 representing the greatest possible malaise and 10 the maximum sensation of well-being) using a visual analogue scale [19,20], measurement of blood pressure (systolic arterial pressure – SAP, diastolic arterial pressure – DAP, mean arterial pressure – MAP) and heart rate (HR) determined daily in the morning before breakfast, with classification of the clinical-hemodynamic profile (CHP) at hospital admission. The MAP was calculated following the formula: [PAS+(2x PAD)]/3, and mean daily was considerate like mean of the 7 days of intervention. Information was also obtained daily about diuresis and 24 h water balance, as well as the degree of acceptance of the main meals of the hospital diet by means of 24-h recall. The 24-h dietary recall was performed every day by an experienced dietitian, who was blinded to the patient allocation group. The diet consumption was monitored and adequate acceptance was defined as diet intake of at least 80% of the entire meal. The patient was oriented to use the entire sodium chloride sachet content. The adherence to the intervention was assessed by estimating the consumption of salt through the 24-h dietary recall using a nutritional software.

The final evaluation was performed on the 7th day of intervention.

The doses of the medications used for the treatment of ADHF were also computed throughout the period of hospitalization, and left ventricle ejection fraction (LVEF) and left ventricle end diastolic diameter (LVEDD) were recorded from the results of the last routine echocardiogram present in the medical records of the patient.

Study population

Patients admitted to the hospital with a primary diagnosis of ADHF according to the Framingham criteria [15,21] were investigated prospectively as long as they could be included in the study within a maximum period of 24 h after admission to the hospital. Exclusion criteria were: patients with estimated creatinine clearance <30 mL/min/1.73 m^2, acute coronary syndrome, cerebrovascular accident, dementia, severe cognitive alteration, cancer, decompensated diabetes mellitus, severe liver disease, septic shock, and evidence of acute or chronic primary disease of the renal parenchyma [12–15]. Also excluded were patients with nutritional disorders or unable to ingest food by mouth, with vomiting, dysphagia or gastroenteritis. The study was approved by the local Ethics Committee (Protocol n° 5719/2014) and all patients who accepted to participate in the study gave written informed consent.

Randomization, implementation and blinding

The selected patients were randomly allocated to the 2 intervention groups by the permuted block method, with 11 blocks containing 4 subjects each. An external investigator who had no access to the patients or to the patient clinical data performed this procedure. Another investigator was in charge to deliver the assigned sachets of sodium chloride to the respective patients, but this investigator had no access to allocation information or clinical data, and had no responsibilities regarding patient care or outcome assessment. The investigator who was in charge of patient care and outcome assessment had no contact with sodium chloride sachets and was unaware of patient group allocation.

Intervention

The two intervention groups consisted of: 1. Patients receiving low sodium diet (LS), containing 3 g dietary sodium chloride (1200 mg sodium) per day by means of the addition of 1 g sodium chloride to each main meal (lunch and dinner), and assuming that the hospital diet contains approximately 1 g sodium chloride intrinsically present in the food. The estimate content of 1 g of sodium chloride for the hospital diet, without any addition of sodium, was assessed by an expert team of dietitian using a commercially available software for diet composition calculation, inputted with Brazilian food composition data [22,23]. 2. Patients receiving normal sodium diet (NS), containing 7 g dietary sodium chloride (2.800 mg sodium) per day by means of the addition of 3 g sodium chloride to each main meal. Besides, both groups were submitted to the same fluid intake restriction per day (1000 mL), since we considered that an uncontrolled fluid intake might

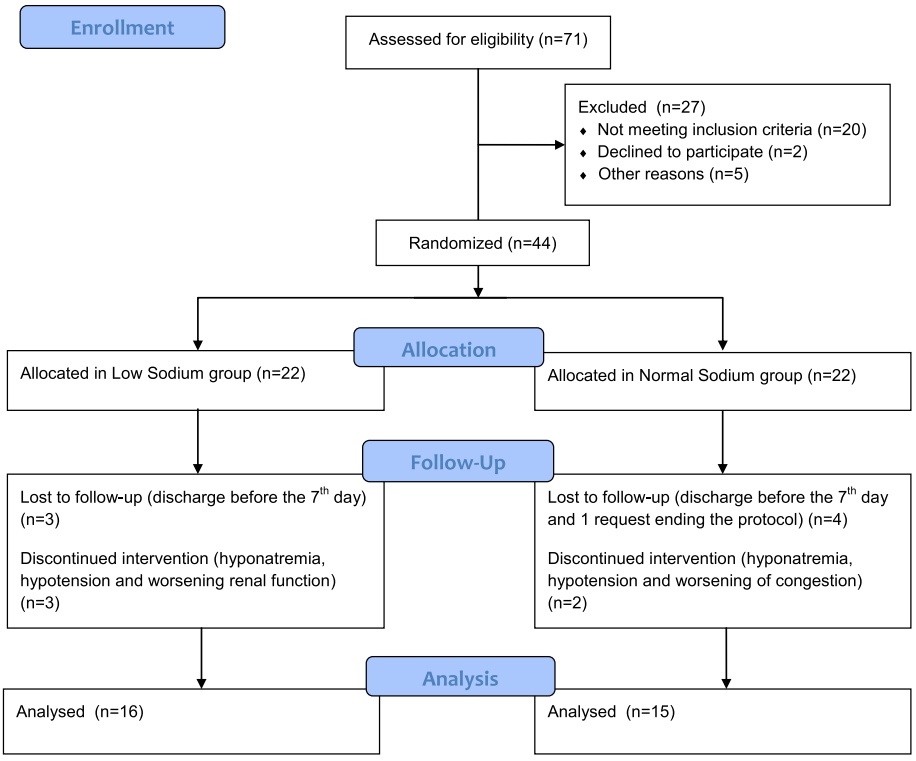

Fig. 1. Flow diagram of patient participation in the research protocol.

influence the serum sodium levels, as shown in previous studies [14,15].

The intervention was performed as follows: 1. Initially all patients received a diet with no salt added and two sachets of sodium chloride were given to them to be added to the main meals; 2. the quantity of sodium contained in each sachet was 1 g for patients of the LS group and 3 g for patients of the NS group. The fluid component (water intake, juice, milk, soup and water rich's fruits) was delivered by the nursing team and controlled by the investigator who delivered the sachets.

The sachets were produced by the industrial pharmacy of our institution and the investigator who accessed the database and performed the analyses was blind to the group of patient allocation and to the sodium content of the sachets.

The remaining therapeutic measures followed the clinical management routine of the Cardiology Division of the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto – Universidade de São Paulo (HCFMRP-USP) for patients with ADHF. Specially, the dose and route of diuretics were adjusted according to the evaluation performed by the clinical staff responsible for the patient care, without being aware of the study treatment.

In case of clinical indication defined by the medical team responsible for the treatment of the patient based on the occurrence of hypotension, hyponatremia, or worsening of renal function, the intervention could be stopped before the 7th day of hospitalization.

Study outcomes

The difference in serum sodium value between groups on the 7th day of intervention was considered to be the primary outcome.

Secondary and safety outcomes were: incidence of hyponatremia, variation in body weight, blood pressure and heart rate, serum creatinine levels, variation in the perception of the degree of dyspnea and general well-being determined with the use of visual analogue scales, cumulative loop diuretic dose during the period of intervention, and variation in serum NT-proBNP levels.

Statistical analysis

The continuous variables are reported as mean ± standard deviation or median (25th-75th percentiles) if not Gaussian. The Kolmogorov-Smirnov test was used to determine Gaussian distribution of the variables. The differences between groups in the quantitative variables were compared by the t-test (for normal distribution) with Welch correction when necessary, or by the Mann–Whitney and Wilcoxon tests (for non-normal distribution). A paired 2-tailed t-test was used for within-group analysis. The percentages were compared by the Fisher Exact Test. The level of significance was set at $p < 0.05$ in all analyses. The calculations were made with the aid of the GraphPad Instat® statistical software.

Calculation of sample size

Sample size was calculated using the OpenEpi software, version 3.01, available at www.openepi.com. The primary outcome for the calculation of sample size was considered to be a difference in serum sodium ≥3 mmol/L, with an estimated standard deviation of ±3.5 [24], a 95% confidence interval and 80% test power. On this basis, the sample size was defined as 22 patients per study group.

Results

Clinical, demographic and basal characteristics of the patients

The baseline characteristics of the subjects did not differed significantly between study groups and are listed in Table 1.

Table 1
Demographic, clinical and laboratory characteristics of the patients at baseline evaluation.

Characteristics	All patients (n = 44)	LS (n = 22)	NS (n = 22)
Demographic data			
Age (years)	57.9 ± 12.0	59.5 ± 11.9	56.4 ± 12.3
% Male gender	59.1	50.0	68.2
Clinical data			
% Hemodynamic B profile	79.5	77.3	81.8
LVEF (%)	28.9 ± 12.6	30.0 ± 13.6	27.8 ± 11.6
LVEDD (mm)	63.2 ± 12.2	62.8 ± 12.8	63.6 ± 11.8
Etiology			
CCC %	43.2	50.0	36.4
Hypertensive %	31.8	31.8	31.8
Ischemic %	18.2	13.6	22.7
Others %	6.8	5.0	9.1
Serum sodium (mmol/L)	135.3 ± 4.9	136.4 ± 3.7	136.4 ± 3.8
Initial weight (kg)	77.1 ± 23.7	81.7 ± 29.0	72.4 ± 16.1
SAP (mmHg)	109.2 ± 23.1	106.0 ± 15.4	112.5 ± 29.4
DAP (mmHg)	70.8 ± 18.2	67.7 ± 10.5	74.1 ± 23.8
MAP (mmHg)	83.7 ± 19.5	80.5 ± 11.7	86.9 ± 25.2
HR (bpm)	73.6 ± 12.2	74.6 ± 11.9	73.1 ± 12.6
Medication of home use			
Furosemide n (%)	39 (95)	18 (90)	21 (100)
ACEI n (%)	19 (46)	7 (35)	12 (57)
ARB n (%)	9 (22)	5 (25)	4 (19)
Beta blocker n (%)	35 (85)	18 (90)	17 (81)
Hydralazine n (%)	13 (32)	8 (40)	5 (24)
Nitrate n (%)	13 (32)	6 (30)	7 (33)

Data are reported as mean ± SD, or as number (percent). LS, Low sodium diet; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NS, normal sodium diet; hf, left ventricle ejection fraction; LVEDD, left ventricle end-diastolic diameter; CCC, Chronic Chagas Cardiomyopathy; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure.

The wet/warm CHP was the most prevalent in the sample (80%). LVEF was reduced (<50%) in most subjects (n = 40), with a mean value of 28.9 ± 12.6%. The Chronic Chagas Cardiomyopathy (CCC) (43%) was the most prevalent within the sample, followed by hypertensive (32%) and ischemic (18%) myocardiopathy. Baseline serum sodium levels did not differ between groups (p = 0.71). At baseline, SAP, DAP and MAP did not differ significantly between groups. Body weight and basal NT-proBNP (Table 2) were also similar.

Patient monitoring

All patients were collected between August 2014 and January 2016, when we achieved the enrolment of 44 patients. Interruptions of the research protocol before the 7th day of intervention occurred during hospitalization (Fig. 1). Three patients per group were discharged before the seventh day of intervention because of resolution of their congestive signs and symptoms. Two patients per group had to interrupt the protocol due to hyponatremia or hypotension. Three patients interrupted the protocol due to other causes, i.e., worsening of renal function (LS. n = 1), worsening of congestion (NS. n = 1) and request by the patient himself (NS. n = 1) (Fig. 1). Thus, 16 LS patients and 15 NS patients completed the 7 days of intervention.

Congestion variables

Table 2 presents the progression of the variables used to assess congestion. None of the congestion variables showed a significant difference between groups when compared at baseline and at the end of intervention.

Weight loss was considered to be significant with both diets employed (p < 0.01), with percent weight loss normalized according to basal body weight being −5.0 ± 4.7% for LS and −4.5 ± 5.2% for NS. p = 0.42. The water balance accompanied the weight loss, with the LS group losing on average −4.3 ± 3.0 L

Table 2
−Results of the laboratory parameters and body weight obtained at the basal and final conditions of the investigated subjects.

Characteristic	Low sodium diet (n = 16)		Normal sodium diet (n = 15)	
	Basal	Final	Basal	Final
NT-proBNP (pg/mL)	4733 (503–25,000)	3954 (273–10,816)	4069 (1486–25,000)	3151 (282–6157)#
Weight (kg)	80.9 ± 32.7	76.2 ± 31.8*	68.5 ± 13	64.8 ± 14.0*
Serum creatinine (mg/dL)	1.5 ± 0.5	1.7 ± 0.5	1.5 ± 0.5	1.7 ± 0.5
Serum urea (mg/dL)	68.4 ± 40.2	76.9 ± 36.6	66.6 ± 30.2	72.9 ± 27.2
Serum potassium (mmol/L)	4.0 ± 0.4	4.1 ± 0.5	4.2 ± 0.6	4.5 ± 0.6
Serum sodium (mmol/L)	136.3 ± 3.2	135.3 ± 3.7	136.5 ± 2.2	137.7 ± 1.9†
Serum hemoglobin (g/dL)	11.8 ± 2.2	12.4 ± 2.4	11.7 ± 1.8	12.4 ± 2.0*
Visual analogue scales				
General well-being	5.0 ± 2.3	8.1 ± 1.9*	5.7 ± 2.2	8.2 ± 2.0*
Dyspnea	4.8 ± 1.6	8.5 ± 1.4*	6.3 ± 1.8	9.2 ± 1.0*

Data are reported as mean ± S, except for NT-proBNP, which is expressed as median and 25th-75th percentiles.
#p < 0.05 for the comparison of basal and final results in the same group by using Wilcoxon test.
*p < 0.05 for the comparison of basal and final results in the same group by using the paired Student t-test.
†p < 0.05 for the comparison at final condition between groups by using the unpaired Student t-test.

and the NS group losing −2.9 ± 2.1 L. It should be pointed out that, even though fluid loss was greater in the LS group, there was no significant difference between groups at the end of intervention (p = 0.17).

Subjective perception of improvement by the patient throughout treatment, assessed with the use of visual analogue scales of general well-being and dyspnea, showed a significant improvement when the basal and final scores of both groups were compared. In addition, there was no difference in the variation of these indices between the two groups (general well-being: p = 0.59; dyspnea: p = 0.30).

Serum NT-proBNP levels, which is a peptide secreted by the cardiomyocytes in response to the distention of cardiac fibers itself and reflect neurohormonal activation, were reduced in both groups, although this reduction was statistically significant only in the NS group compared to the initial values (p = 0.04).

Variation in serum sodium levels

Baseline serum sodium levels were similar in the two groups, whereas at the final evaluation the LS group showed lower sodium levels than the NS group (Table 2). Figure 2 illustrates the evolution of the serum sodium in the patients that completed the study protocol and shows the progressive reduction of the values in the LS group. In addition, the mean daily values of NS patients were higher (137.8 ± 0.7 mmol/L) than those of LS patients (136.2 ± 0.6 mmol/L). p < 0.01. Furthermore, on the last day of intervention there were 4 cases of hyponatremia, all of them among LS patients (22%).

Assessment of blood pressure and heart rate

Table 3 summarizes blood pressure and heart rate results. Baseline blood pressure did not differ between groups and a non-significant fall in its levels occurred during the intervention in both groups. However, mean daily SAP, DAP and MAP were higher in the NS group than in the LS group.

HR did not differ between groups at baseline but its mean daily values were lower in the NS group than in the LS group.

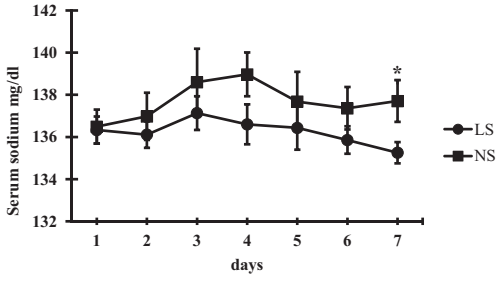

Fig. 2. Plot showing the evolution of the serum sodium values (mmol/L), mean ± standard error, throughout the intervention in the patients that completed the study protocol. LS = low sodium diet (n = 16); NS = normal sodium diet (n = 15). *p < 0.05.

All other biochemical variables

Serum creatinine, urea and potassium and hemoglobin levels did not differ significantly between groups at baseline or at the final evaluation (Table 2). Only serum hemoglobin differed significantly between baseline and final assessment, with an increase in both groups. Worsening of renal function, represented by an increase in serum creatinine ≥0.3 mg/dL, occurred similarly in both groups (7 cases in each group).

Drug therapy

Table 4 shows the drug therapy used for ADHF during hospitalization. It can be seen that no statistically significant difference was observed between groups for most of the medications used either regarding the dose or the percentage of patients taking them, except for angiotensin converting enzyme inhibitor, which showed a significant higher cumulative dose in the NS group (p = 0.04). The cumulative dose of loop diuretics was higher in the LS group, but the difference was not statistically significant.

Hospital evolution and monitoring

Mean hospitalization duration was shorter for NS patients (11.4 ± 3.5 days) than for LS patients (18.1 ± 9.6 days) (p = 0.02). Acceptance of the hospital diet was discretely better in the NS group (88.1 ± 12.3%) than in the LS group (79.6 ± 14.3%), although the difference was not statistically significant (p = 0.08). The mean consumption of dietary sodium in NS group was 6.17 ± 1.08 g of sodium chloride (2467,11 ± 431,93 mg of sodium) and in LS group 2.50 ± 0.44 g of sodium chloride (998,43 ± 174,11 mg of sodium). During the 30 days of follow-up after hospital discharge, 31% of LS patients and 33% of NS patients were readmitted (p = 1.0). No deaths occurred during hospitalization and 2 deaths occurred in each group after discharge from the hospital (p = 1.0).

Discussion

The main results of our study show that the two levels of sodium intake were associated with similar levels of decongestion and that the NS diet was associated with better preservation of natremia in ADHF.

In present study, we chose 7 g of sodium chloride for the NS diet since epidemiological studies have shown that this is the mean sodium consumption in a diet associated with a low risk of cardiovascular diseases [25,26]. Conversely, the LS diet containing 3 g of sodium chloride was based on recommendations of a Brazilian

Table 3
Blood pressure and heart rate values obtained for the two groups during the basal, final and mean evaluations.

	LS			NS		
	Basal	Final	Mean daily value	Basal	Final	Mean daily value
SAP (mmHg)	106.0 ± 15.4	101.5 ± 12.1	104.0 ± 2.2	112.5 ± 29.4	105.9 ± 19.6	107.5 ± 4.2†
DAP (mmHg)	67.7 ± 10.5	62.7 ± 10.4	64.4 ± 3.4	74.1 ± 23.8	68.9 ± 17.0	69.2 ± 3.3†
MAP (mmHg)	80.5 ± 11.7	76.0 ± 9.3	76.4 ± 4.1	86.9 ± 25.2	81.4 ± 17.4	82.0 ± 3.5†
HR (b.p.m.)	75.9 ± 13.8	73.9 ± 14.5	77.6 ± 2.7	75.0 ± 13.7	71.9 ± 11.8	73.9 ± 1.6†

Data are reported as mean ± SD. LS, low sodium diet; NS, normal sodium diet; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; HR, heart rate; bpm., beats per minute.
†p < 0.05 for the comparison of daily mean values, unpaired Student t-test.

Table 4
Frequency of the use and doses of medication administered during hospitalization and in the final condition, and cumulative dose during hospitalization.

	LS			NS		
	Final dose (mg)	n (%)	Cumulative dose (mg)	Final dose (mg)	n (%)	Cumulative dose (mg)
Furosemide	81.3 ± 36.6	15 (94)	517.5 ± 209.6	67.1 ± 21.6	14 (93)	414.0 ± 113.8
ACEI	47.5 ± 25.6	5 (31)	263.8 ± 175.8	91.7 ± 51.2	12 (55)	613.6 ± 297.2†
ARB	100.0 ± 0	1 (6)	475.0 ± 318.2	50.0 ± 0.0	2 (13)	300.0 ± 86.6
Beta blocker	39.7 ± 27.0	14 (88)	247.8 ± 155.2	33.5 ± 20.5	14 (93)	223.0 ± 141.9
Hydralazine	184.6 ± 98.7	13 (81)	1172.3 ± 584.0	158.3 ± 88.4	8 (53)	881.9 ± 527.4
Nitrate	70.9 ± 33.6	11 (69)	468.5 ± 248.2	82.7 ± 40.0	11 (73)	471.0 ± 279.2

Data are reported as mean ± SD and n (%) of patients receiving the medication. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; LS, low sodium diet; NS, normal sodium diet.
†$p < 0.05$ for the comparison of cumulative doses between groups, unpaired Student t-test.

guideline [11]. We also applied water restriction of 1000 mL per day for both groups since we considered that an uncontrolled fluid intake might influence the resolution of congestion and the levels of natremia [15].

The series predominantly consisted of patients with HF with a reduced LVEF in agreement with the epidemiology of ADHF in Brazil based on recent I Brazilian Registry of HF. Similarly, the warm/wet CHP at hospital admission was the most prevalent in our sample [27].

The present results suggest that the LS diet has no advantage in terms of the resolution of congestion compared to the NS diet, involving similar degrees of weight loss, relief of dyspnea and reduction of NT-proBNP in both study groups. In this respect, our results corroborate those reported in other studies. Aliti et al. [16] compared the effect of a diet with severe restriction of sodium (2 g sodium chloride) and fluid (800 mL/day) to that of a diet with no restriction (approximately 7.5–12.5 g sodium chloride and at least 2.500 mL/day fluids) in patients with ADHF. Similar to our findings, they also detected comparable weight loss, improvement of clinical congestion and reduction of BNP levels in both intervention groups after 3 days of intervention. Furthermore, the mean sodium intake of LS group was lower than 1.000 mg which could result in nutritional deficiencies in long term because this diet could be not palatable and could decrease the global intake [28].

It should be pointed out that the present results were obtained with the use of equivalent doses of loop diuretics in both groups, supporting the notion that the similar degrees of decongestion did not occur depending on the use of different loop diuretics doses. It can be seen that the cumulative water balance accompanied weight loss in both groups, thus clearly indicating that weight loss occurred as a function of water loss and reduction of congestion, producing the expected clinical result.

NT-proBNP which is a marker of congestion intensity presented high baseline values in both groups, confirming the presence of severe congestion. In addition, the reduction in NT-proBNP levels was significantly only in the group receiving the NS diet, suggesting that this diet was more effective in reducing the filling pressure of cardiac chambers.

Other studies on chronic HF have shown the benefit of the NS diet. In their studies on patients with ambulatory HF, Paterna et al. [14,15] observed that an NS diet (7 g sodium chloride) in combination with water restriction (1.000 mL) and high diuretic doses produced better results with a lower rate of hospital readmission due to decompensated HF, a lower degree of neurohormonal activation and preservation of renal function compared to an LS diet (4.5 g sodium chloride). In a prospective study assessing the acute effect of a LS diet on stable patients with chronic HF, Nakasato et al. [29] observed that the LS diet (2 g sodium chloride) increased the degree of neurohormonal activation compared to the NS diet (6.6 g sodium chloride) and that patients receiving a NS diet also showed a greater weight loss within 7 days.

Ours results also suggest that the NS diet provided the additional benefit of guaranteeing higher natremia levels during the treatment of ADHF when compared to the LS diet. It should be pointed out that, although the difference in the final values of natremia was of small magnitude, 22% of the patients in the LS group had hyponatremia at the end of the intervention, emphasizing the relevance of this result.

It is conceivable to suppose that the mechanism leading to hyponatremia or lower serum sodium levels in the LS group involves a negative sodium balance caused by the combined effect of the increased natriuresis, triggered by the loop diuretics, and the low levels of dietary sodium intake. The alternative mechanism of a dilutional change caused by the neurohormonal activation and excessive water retention to explain the hyponatremia presented by the LS group is not suitable, as both groups presented the same degree of decongestion during the ADHF treatment and the initial serum sodium levels were comparable between groups. Therefore, our data indicate that the mechanism of hyponatremia in the LS group is essentially depletional.

In contrast to the present results, Aliti et al. [16] did not detect a difference in sodium levels after 7 days of intervention. However, the cited study did not use fluid restriction for the patient receiving the NS diet. It is important to point out that, the same way the LS diet can reduce serum sodium levels, a high fluid intake can reduce the serum sodium concentration by hemodilution and cancel the effect of the preservation of natremia. In our study, the NS diet was simultaneously submitted to water restriction. We may assume that the use of water restriction contributed to higher serum sodium levels in patients with preserved dietary sodium intake, and we can identify the euvolemic profile of our patients by observing comparable increase in serum haemoglobin level in both groups, discarding the contribution of different degrees of hemodilution in generating the results.

In the scenario of chronic HF, some studies have suggested that not only sodium intake, but also water restriction are important for the preservation of natremia. In the study by Paterna et al. [15], 2 groups received 7 g sodium chloride, high doses of diuretics and different levels of water restriction (1.000 mL × 2.000 mL). The group receiving a smaller amount of fluids per day exhibited higher serum sodium levels after 6 months of intervention, whereas the group with no water restriction showed a significant fall in natremia, suggesting the occurrence of dilution hyponatremia provoked by the increase in fluid intake.

The present results show that there was a reduction in BP in both groups, although BP levels were higher in the NS group throughout the intervention. As proposed by others [14,30], this is probably due to displacement of interstitial fluids towards the vessels secondary to increased intravascular osmolarity, resulting in an increase in plasma volume and in the preservation of effective arterial filling and maintenance of a more adequate euvolemic state.

During the treatment of ADHF, arterial hypotension is a frequent intercurrence [11,31], and is associated to an increased risk of hospital mortality [32,33]. These aspects support the relevance of our findings of a better preservation of BP achieved by a NS diet.

Our study revealed higher mean HR levels in the LS group. We may assume that these higher HR levels in the LS group reflected the adrenergic activation secondary to the lower BP levels in this group as compared to the NS group.

Previous studies [33] have also showed that increased HR is a predictor of intrahospital mortality, emphasizing the clinical importance of the lower HR values associated with the use of the NS diet in the present study.

In our study, patients receiving the NS diet for 7 days presented shorter hospitalization time, representing a considerable cost saving. Even more important, this shorter hospitalization time indicates that more preserved natremia status is associated with faster heart failure compensation. This result probably reflects that the maintenance of a normal sodium diet contributes to obtain a normal euvolemic state, associated to higher blood pressure values with its benefits in decreasing the neurohormonal activation, providing earlier resolution of congestive state and clinical compensation of HF. This is concordant with previous studies indicating that the maintenance of normal natremia has been associated with a better prognosis and with lower rates of neurohormonal activation and of hospital readmissions and with a longer survival [34–38].

Limitations

The main limitations of our study were the reduced sample size at the end of intervention due to unforeseen defections, although the assessment of serum sodium at the end of the study was sufficient to reveal a significant difference between groups.

Another limitation was the fact that we did not use any objective estimation of the real sodium intake, which could be obtained by collecting and analysing a weighted food record [39]. The assessment of natriuresis could also have been valuable, but has not been performed. However, the investigation was conducted in a controlled hospital environment in which the patients were maintained under similar dietary and medication conditions.

Despite the interest in obtaining longer follow-up data, the intervention ended at the 7th day of hospitalization, and was not continued after patients discharge, as we considered that maintaining a diet with high control of sodium intake would be very difficult in the out-patient setting.

Finally, another important limitation was that the sample and the duration of follow up were not dimensioned in order to obtain prognostic results after discharge from the hospital.

Conclusions

The use of NS diet for patients hospitalized with ADHF resulted in similar reduction of congestive manifestations and in similar improvement of symptoms when compared to the LS diet. In addition, the NS diet in combination with fluid restriction resulted in the additional benefit of a better preservation of serum sodium levels, higher blood pressure and lower heart rate values.

Our results suggest that a LS diet combined with fluid restriction should not be routinely used during the treatment of patients with ADHF. On the other hand, further studies on larger series are needed for the proper investigation of the impact of different levels of dietary sodium and fluid on relevant clinical outcomes such as number of hospital readmissions and mortality.

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Contribution of each author

CGF, CAFA and MVS conceived and designed the study; CGF, DMT and JRSG generated, collected, assembled and carried out sample analyses; CGF and MVS analysed and interpreted the data, and drafted and revised the manuscript. CGF, MVS, FM, PVS and AS did the analysis and interpretation of data and revision of the manuscript. All authors have read and approved the final manuscript.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Registration

Registered under ClinicalTrials.gov Identifier no. NCT03722069. The full trial protocol can be accessed: https://clinicaltrials.gov/ct2/show/NCT03722069.

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