Quantitative Approach for the Treatment of Hypovolemic Hyponatremia in the Emergency Department

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Abstract

Hyponatremia is the most frequent electrolyte derangement in clinical practice and is often associated with dehydration. This happens when the water deficit is combined with a larger solute deficit. This study, carried out in the Emergency Department, was aimed to explore efficacy and safety of two different therapeutic strategies, based on a quantitative approach (Adrogué-Madias formula) for treating hyponatremia associated with mild and moderate dehydration. The grade of dehydration was clinically established. Patients moderately dehydrated were treated by setting the desired correction rate at 12 mEq/L/24h to obtain with the formula a larger amount of isotonic saline in order to properly replace a larger volume deficit (Group A, 10 patients); for mildly dehydrated patients the target was set at 6 mEq/L/24h in order to focus treatment on [Na+] correction (Group B, 12 patients). We analyzed data at baseline and after the first 24 hours of treatment. The median baseline [Na+] was 126 mEq/L in Group A and 127 mEq/L in Group B (P-value = 0.665); after 24 hours the [Na+] was significantly higher in both groups, but no statistically significant differences were found between them (132 vs. 134 mEq/L, P-value = 0.355). 59.1% of patients had correction rates within the optimal range (4-8 mEq/L/24h); no statistically significant differences were observed between groups in the correction kinetics outcome. Therefore, hypovolemic hyponatremic patients may be treated, if required by their volume deficit, with amounts of isotonic saline larger than those predicted by formulas set on international efficacy and safety cut-offs with a negligible risk of overcorrection.

ABBREVIATIONS

ED: Emergency Department; [Na+]: Plasma Sodium Concentration; CSWS: Cerebral Salt Wasting Syndrome; AVP: Arginine-Vasopressin; RAA: Renin-Angiotensin-Aldosterone; SABP: Systolic Arterial Blood Pressure; HR: Heart Rate; Fena+: Na+ Fractional Excretion; BUN: Blood Urea Nitrogen; [Copeptin]: Plasma Copeptin Concentration; SIADH: Syndrome of Inappropriate Anti Diuretic Hormone Secretion; TBW: Total Body Water; Egrf: Estimated Glomerular Filtration Rate; IQR: Interquartile Range; BMI: Body Mass Index

INTRODUCTION

Hyponatremia is defined as a plasma sodium concentration ([Na+]) below 136 mEq/L; according to the [Na+] it can be mild (130-135 mEq/L), moderate (125-129 mEq/L) or severe (< 125 mEq/L) [1]. Hyponatremia is the most common electrolyte imbalance encountered in clinical practice as its prevalence in hospitalized patients reaches 15-30% [2]; the risk increases with age and is related to comorbidities and multi-drug treatments [3,4]. The prevalence of hyponatremia has been estimated at about 15-20% among patients admitted to the Emergency Department (ED) [5].

Hyponatremia is associated with adverse events (attention deficit, gait instability and falls) [6], and is considered an independent negative prognostic factor and predictor of mortality, even though it is still to be defined whether hyponatremia reflects the severity of the underlying disorder or plays an active role in increasing mortality [7], costs of hospitalization and readmission rates [8].

Despite its clinical relevance, hyponatremia is still underestimated and undertreated [9].

The correct approach to hyponatremia needs to be...
preceded by an accurate assessment of body fluids volume. In fact, hyponatremia is classified as hypovolemic, euvoletic or hypervolemic [11,10], and it is well known that a correct categorization and diagnosis significantly improves the clinical outcome [11,12], since different forms require different therapeutic strategies.

In this paper, we will focus attention on the proper therapeutic approach to patients with hypovolemic hyponatremia.

Hypovolemic hyponatremia develops when solute depletion (both Na⁺ and K⁺) is larger than volume depletion [13,14]. It can be due to renal or extrarenal losses of Na⁺, K⁺ or both: renal Na⁺ losses are attributable to diuretics use or misuse [15,16], to primary or secondary mineralocorticoid deficiency, to salt-losing nephropathies and to the Cerebral Salt Wasting Syndrome (CSWS) [17]; extrarenal Na⁺ losses are associated with protracted diarrhea or vomiting and excessive sweating. K⁺ depletion (usually due to diuretics use, vomiting or dietary deficiency) indirectly causes hyponatremia since intracellular (K⁺) and extracellular (Na⁺) are deeply related and influence each other [18,19].

All the conditions associated with volume depletion are characterized by renin-angiotensin-aldosterone (RAA) axis activation and arginine-vasopressin (AVP) release: many clinical features observed in these patients are due to the effects of these mechanisms [20,21].

Volume status can be assessed through clinical, laboratory or instrumental criteria [22]. In patients' history, the most important indicators of dehydration or hypovolemia are protracted diarrhea or vomiting, diuretic treatment, fever in the last few days and thirst [23]; on the other hand, the main physical findings consistent with dehydration/hypovolemia are hypotension (a systolic blood pressure, SABP, ≤ 100 mmHg), orthostatic hypotension, tachycardia, dry mucosae, dry axillary sweat, cold extremities, shallow pulse, thirst [24]. Among laboratory data, a Na⁺ fractional excretion (FENa⁺) < 1.0% is suggestive of volume depletion as well as a high BUN-to-creatinine ratio [22]. Additionally, urine sodium concentration ([Na⁺]) can help identify the site of solute losses (extrarenal losses if [Na⁺] < 20 mEq/L and renal losses if [Na⁺] ≥ 20 mEq/L) [22,24].

Copeptin, a 39 amino acids long glycoprotein containing the C-terminal region of pre-pro-vasopressin, is released in equimolar amounts together with AVP [25,26]; thanks to its stability, it can be used as a surrogate marker of AVP secretion in clinical practice [27]. The plasma copeptin concentration ([copeptin]) vary with plasma osmolality and in the presence of multiple diseases (acute coronary syndrome, stroke, shock, trauma). It has been demonstrated that copeptin concentration is lower in hypovolemic hyponatremia and progressively higher in euvoletic and hypervolemic hyponatremia [28]. Other studies highlighted an undesirable variability in copeptin levels, but described the [copeptin]-to-[Na⁺] ratio as a valuable tool in distinguishing hyponatremia primarily due to AVP secretion (syndrome of inappropriate anti Diuretic hormone, SIADH) from that associated with secondary AVP secretion (following either real or virtual volume depletion), the best cut-off value being 0.30 pmol/mEq, with lower values in SIADH and higher in hypovolemic and hypervolemic patients [29].

To date, despite the large number of indexes reported as useful in the evaluation of volume status, a gold standard test is lacking, and clinical criteria are the most readily available, the least expensive and still the most useful and used, particularly in an ED context.

Different formulas can be used to calculate the proper amount of fluids to be infused in order to reach an effective correction. The Adrogué-Madias formula [1], and its variants are the most commonly used in clinical practice (Formula 1):

\[
\text{Change in } [Na^+] \times 10^3 = \left( \frac{\text{infsateNa}^+ \times \text{infisateK}^+}{\text{totalbodywater}} \right) - \text{baseline } [Na^+] \\
\]

or (Formula 2)

\[
Na^+ \text{ requirement} = \text{totalbodywater} \times \left( \frac{\text{desired } [Na^+]}{\text{baseline } [Na^+]} \right)
\]

Total body water (TBW) is usually estimated by multiplying body weight by 0.60 (a reliable approximation of the proportion of body composition attributable to water).

Desired [Na⁺] has to be decided before starting treatment. In this regard, because of gradual brain adaptation to plasma hypotonicity [30], the correction of chronic hyponatremia (developed in more than 48 hours) implicates serious risks regardless of the underlying cause. In order to balance risks and benefits of treatment, the latest review of the Literature set the optimal range of correction at 4-8 mEq/L over 24 hours and the safe upper limit at 12 mEq/L/24h [31]; in fact, previous studies showed that a correction of about 4-6 mEq/L over 24 hours can usually remove all symptoms [32], and a correction rate ≤ 12 mEq/L/24h is associated with a negligible risk of osmotic demyelination syndrome (ODS). Before these recommendations were introduced in clinical practice, the suggested correction rate over 24 hours was less restrictive (10-12 mEq/L/24h) [33,34].

The present study is aimed to verify efficacy and safety of this quantitative treatment in the ED.

MATERIALS AND METHODS

In this pilot study we enrolled patients with moderate-to-severe hypovolemic hyponatremia ([Na⁺] ≤ 130 mEq/L) admitted to the ED of the University Hospital of Novara from April 2012 to June 2015. Patients’ volume status was assessed by the dinician using anamnestic, physical and laboratory criteria. Dehydration/hypovolemia was defined by the presence of at least two criteria among: vomiting, diarrhea, fever, hypotension, orthostatic hypotension, tachycardia, dry mucosae, dry axillary skin, positive pinch test, cold extremities, shallow pulse, thirst and a Na⁺ fractional excretion ([FENa⁺] < 1.0%). We excluded hyponatremic patients who did not meet these criteria as well as those who showed at the same time signs of hypervolemia (peripheral edema, distended neck veins, hepato-jugular reflux, wet lung sounds and serious effusions). Other exclusion criteria were age < 18 years, presence of severe symptoms (seizures,
deep drowsiness or a Glasgow Coma Score < 9), presence of severe hypovolemia and shock, acute coronary syndrome, respiratory distress, major trauma, stroke, shock, hyperglycemia (blood glucose > 250 mg/dL), chronic kidney disease (eGFR < 30 mL/min), lack of informed consent.

The study took place in the ED Observation Unit, where patients were kept for a 24-hour period.

The treatment was based on a quantitative estimate of water and solute deficit. Patients were treated by the infusion of normal saline (0.9% NaCl), if necessary enriched with minimal amounts of a solution containing 2 mEq/mL NaCl. The protocol, designed before the publication of the latest guidelines and their more restrictive cut-offs [5,31], was meant to obtain the desired fluid replacement as well as an adequate increase in the P(Na+). For this purpose, patients were evaluated by two expert emergency physicians in order to establish their grade of dehydration: patients with a moderate dehydration/hypovolemia were included in Group A, while patients with mild dehydration/hypovolemia were included in Group B. Patients from both groups were then treated according to the Adrogué-Madias formula [1]. In Group A the desired correction rate was set at 12 mEq/L/24h in order to infuse a larger volume of water with respect to patients in Group B

(Formula 3):

$$\frac{Na^+}{24h} = (\text{bodyweight} \times 0.60) \times 12 \frac{mEq}{L} / 24h$$

In Group B the desired correction rate was set at 6 mEq/L/24h, a correction rate exactly consistent with the latest international recommendations

(Formula 4):

$$\frac{Na^+}{24h} = (\text{bodyweight} \times 0.60) \times 6 \frac{mEq}{L} / 24h$$

After these first 24 hours, patients were either discharged or admitted to the hospital ward depending on whether or not their P(Na+) had been corrected and the other clinical problems solved. A telephonic follow-up was performed after 1 month.

The information needed to compute water and Na+ balance (such as urine output, body weight, fluid intake, plasma and urine electrolytes concentration) were collected both at admission and after 24 hours. Drugs potentially responsible for hyponatremia (above all, diuretics) were withdrawn.

Patients had free access to water and were encouraged to drink according to their thirst.

If the P(Na+) did not improve and the clinical conditions of the patients tended to deteriorate, an infusion of 2 mL/kg of hypertonic saline solution (3% NaCl) was performed as a rescue treatment.

Clinical and laboratory parameters were used to assess the efficacy of fluid replacement after 24 hours of treatment.

The increase in the P(Na+) (ΔP(Na+)) obtained over 24 hours was then used to analyze both efficacy and safety of our quantitative correction. On the basis of the most recent recommendations [31], we created four different groups based on the correction kinetics:

- low degree of correction: < 4 mEq/L/24h;
- optimal correction: 4-8 mEq/L/24h;
- mild (or low risk) overcorrection: 9-12 mEq/L/24h;
- severe (or high risk) overcorrection: > 12 mEq/L/24h.

If potentially harmful overcorrection occurred, the infusion was stopped and an oral load of 500 mL of water over 3 hours was given to the patient.

Blood samples were collected from each patient at ED admission and later centrifuged at 3500 rpm for 15 minutes: the plasma was then stored at -80°C and used at the end of the study to measure copeptin with a commercial immunoenzymatic assay provided by Thermo Fisher Scientific® (Thermo Fisher Scientific Snc – Waltham, MA, USA).

The primary endpoint was to evaluate the efficacy of this therapeutic strategy in reaching a statistically significant increase in the P(Na+) compared to baseline values. The correction kinetics was used to evaluate the percentage of patients who experienced correction rates within the optimal range [29] or, on the opposite side, above the safety limits. The relationship between copeptin and P(Na+) values at arrival was investigated as well as the potential clinical impact of this marker.

Clinical variables suggestive of hypovolemia were combined into a dehydration score: each variable scored 1 point, and the final score, given by the sum of the individual points, was considered remarkable if > 3.

Moreover, we divided patients into two different groups depending on the formula used to set the treatment. Baseline characteristics and treatment outcomes were then compared.

Eventually each patient was asked to check his P(Na+) 30 days later and was then contacted by telephone for a structured interview.

Statistical analysis were performed using the MedCalc® software v12.5.0 (MedCalc software bvba – Ostend, Belgium). Normal distribution was preliminarily assessed using the Kolmogorov-Smirnov test. Continuous data were analyzed through the Mann-Whitney U test, while the two-tailed Fisher’s exact test was used to analyze categorical data. The relationships between different variables were investigated through regression tests. Statistical significance was set at $P < 0.05$.

RESULTS

Twenty-two patients with a median age of 79 years (min 39, max 91; interquartile range, IQR, 67-85) were enrolled in this study. The medians and IQR of the most important continuous variables recorded at baseline are shown in Table (1). Thirteen patients (59.1%) presented at least 3 anamnestic findings which put them at risk of being dehydrated; and these findings as well as other clinical data that were helpful in volume status assessment are reported in detail in Table (2). 10 subjects (45.5%) presented with 4 or more elements consistent with
Castello et al. (2017)
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Table 1: Medians and interquartile range of the main continuous variables collected at baseline.ca

<table>
<thead>
<tr>
<th>Continuous variable</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>79 (67 – 85)</td>
</tr>
<tr>
<td>Systolic arterial blood pressure (mmHg)</td>
<td>135 (110 – 150)</td>
</tr>
<tr>
<td>Diastolic arterial blood pressure (mmHg)</td>
<td>80 (70 – 90)</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td>96.7 (85.0 – 106.7)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>77 (64 – 81)</td>
</tr>
<tr>
<td>External temperature (° C)</td>
<td>36.0 (36.0 – 36.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.0 (53.0 – 74.3)</td>
</tr>
<tr>
<td>Estimated TBW (L)</td>
<td>35.4 (31.8 – 44.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3 (19.6 – 26.8)</td>
</tr>
<tr>
<td>Glycemia (mg/dL)</td>
<td>133 (111 – 151)</td>
</tr>
<tr>
<td>(Cr) (mg/dL)</td>
<td>1.00 (0.60 – 1.42)</td>
</tr>
<tr>
<td>(Na⁺) (mEq/L)</td>
<td>126 (123 – 128)</td>
</tr>
<tr>
<td>(Cl⁻) (mEq/L)</td>
<td>92 (90.75 – 95.50)</td>
</tr>
<tr>
<td>(K⁺) (mEq/L)</td>
<td>4.1 (3.9 – 4.4)</td>
</tr>
<tr>
<td>(Cr) (mg/dL)</td>
<td>67.2 (49.7 – 89.4)</td>
</tr>
<tr>
<td>(Na⁺) (mEq/L)</td>
<td>44 (23 – 71)</td>
</tr>
<tr>
<td>(Cl⁻) (mEq/L)</td>
<td>62 (31 – 79)</td>
</tr>
<tr>
<td>(K⁺) (mEq/L)</td>
<td>3.62 (2.56 – 40.0)</td>
</tr>
<tr>
<td>FENa⁺ %</td>
<td>0.53 (0.34 – 0.82)</td>
</tr>
<tr>
<td>(copeptin) (pmol/L)</td>
<td>38.05 (9.71 – 100.95)</td>
</tr>
<tr>
<td>(copeptin)/(Na⁺) (pmol/mEq)</td>
<td>0.82 (0.32 – 3.55)</td>
</tr>
</tbody>
</table>

Abbreviations:
- TBW: Total Body Water
- BMI: Body Mass Index
- (Cr): Plasma Creatinine Concentration
- (Na⁺): Plasma Sodium Concentration
- (Cl⁻): Plasma Chloride Concentration
- (K⁺): Plasma Potassium Concentration
- (Cr): Urine Creatinine Concentration
- (Na⁺): Urine Sodium Concentration
- (Cl⁻): Urine Chloride Concentration
- (K⁺): Urine Potassium Concentration
- Fena+: Na⁺ Fractional Excretion
- (Copeptin): Plasma Copeptin Concentration

Table 2: Percentage frequencies of the main categorical variables recorded at the moment of volume assessment.

<table>
<thead>
<tr>
<th>Categorical variable</th>
<th>Yes (%)</th>
<th>No (%)</th>
<th>Missing data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient at risk of dehydration</td>
<td>59.1</td>
<td>40.9</td>
<td>0</td>
</tr>
<tr>
<td>Age ≥ 85 years*</td>
<td>31.8</td>
<td>70.6</td>
<td>0</td>
</tr>
<tr>
<td>Female sex*</td>
<td>68.2</td>
<td>31.8</td>
<td>0</td>
</tr>
<tr>
<td>≥ 3 chronic active diseases*</td>
<td>40.9</td>
<td>59.1</td>
<td>0</td>
</tr>
<tr>
<td>≥ 4 drugs daily*</td>
<td>72.7</td>
<td>27.3</td>
<td>0</td>
</tr>
<tr>
<td>Diuretics*</td>
<td>36.4</td>
<td>63.6</td>
<td>0</td>
</tr>
<tr>
<td>Laxatives*</td>
<td>4.5</td>
<td>95.5</td>
<td>0</td>
</tr>
<tr>
<td>Protracted vomiting</td>
<td>18.2</td>
<td>81.8</td>
<td>0</td>
</tr>
<tr>
<td>and/or protracted diarrhea*</td>
<td>18.2</td>
<td>81.8</td>
<td>0</td>
</tr>
<tr>
<td>Body temperature &gt; 38°C</td>
<td>4.5</td>
<td>95.5</td>
<td>0</td>
</tr>
<tr>
<td>in the previous 48 h*</td>
<td>18.2</td>
<td>81.8</td>
<td>0</td>
</tr>
<tr>
<td>Bedridden*</td>
<td>50</td>
<td>40.9</td>
<td>9.1</td>
</tr>
<tr>
<td>Thirst*</td>
<td>31.8</td>
<td>68.2</td>
<td>0</td>
</tr>
</tbody>
</table>

Hypotension 4.5 95.5 0
Orthostatic hypotension 4.5 72.7 22.8
Tachycardia and/or orthostatic tachycardia 4.5 95.5 0
Dry mucous 63.6 36.4 0
Positive pinch test 27.3 72.7 0
Dry axillary skin 27.3 72.7 0
Shallow pulse 4.5 95.5 0
Cold extremities 27.3 72.7 0
Dehydration score > 3 45.5 54.5 0

Abbreviations: Patient at Risk of Dehydration: Sum of the Following Starred Variables ≥ 3; Protracted Vomiting: 4 or More Episodes/Day; Protracted Diarrhea: 11 Or More Episodes/Day; Hypotension: Systolic Arterial Blood Pressure (SABP) ≤ 100 Mmhg; Orthostatic Hypotension: SABP in Clinostatism SABP In Orthostatism ≥ 30 Mmhg; Tachycardia: Heart Rate (HR) > 100 Bpm; Orthostatic Tachycardia: Raise In HR > 30 Bpm In Orthostatism; Dehydration Score: Sum Of All The Previous Variables

an hypovolemic state which could be used to create a clinical dehydration score. Additionally, 68.2% of patients had a FENa⁺ < 1%. None of the 22 patients was hypervolemic, even though 1 subject presented peripheral edema (due to venous insufficiency) and 1 had distended neck veins (attributed by the physician to a tricuspid valve dysfunction); none had hepato-jugular reflux, serous effusions or wet lung sounds. The presumptive causes of dehydration are reported in Figure (1).

The median baseline (Na⁺) was 126 mEq/L (min-max 121-130 mEq/L; IQR 123-128 mEq/L). The median weight was 59.0 kg (min-max 38.0-92.0 kg, IQR 53.0-74.0 kg) with an estimated median TBW of 35.4 L (IQR 31.8-44.6 L), while the median BMI was 23.3 kg/m² (19.6-26.8 kg/m²).

Figure 1 Presumptive causes of dehydration. In 3 cases (13.6%) the cause of dehydration remained undefined
Abbreviations: GI Losses: Gastrointestinal Losses; Reduced Access to Water: Bedridden and/or Age ≥ 85 Years; Insensible Losses: Prolonged Fever

Ten patients were considered to be moderately dehydrated and treated using Formula 3 (Group A), while 12 patients were found to be mildly dehydrated and were treated using Formula 4 (Group B).

Although the two expert emergency physicians divided patients according to their grade of dehydration, no statistically significant differences were observed between the two groups in any of the above mentioned variables, apart from cold extremities (60.0% in Group A vs. 0.0% in Group B, \( P\)-value = 0.003). Nevertheless the analysis of the dehydration score reported in Table (2) showed higher scores in patients from Group A, even though the comparison does not reach a full statistical significance (\( P\)-value = 0.051); moreover, the proportion of patients with a score > 3 was also higher in Group A (70.0% vs. 25.0%), even though at a not statistically significant level (\( P\)-value = 0.084).

The median baseline \( \langle \text{Na}^+ \rangle \) was 126 mEq/L in Group A and 127 mEq/L in Group B (\( P\)-value = 0.665). The median amount of Na\(^+\) required for the quantitative correction, computed with Formula 3 and 4 respectively, was 391 mEq in Group A and 230 in Group B, while the median amount of Na\(^+\) actually administered over 24 hours was 412 and 190 mEq (\( P\)-value = 0.0001), respectively; this calculation includes also the K\(^+\) administered, since it produces an increase in the \( \langle \text{Na}^+ \rangle \) identical to the one induced by the same amount of Na\(^+\) [18]. The median volume of fluids infused over 24 hours was 1685 mL in Group A and 1015 in Group B (\( P\)-value = 0.003), with a respective median oral water intake of 770 mL and 850 mL (\( P\)-value n.s.).

After 24 hours of treatment the \( \langle \text{Na}^+ \rangle \) was significantly higher in both groups compared to baseline values (\( P\)-value = 0.007 in Group A and 0.005 in Group B); however, no statistically significant difference was observed between the two groups either in the after-treatment \( \langle \text{Na}^+ \rangle \) (medians 132 mEq/L in Group A vs. 134 mEq/L in Group B, \( P\)-value = 0.355) and in the correction rate (median \( \Delta \langle \text{Na}^+ \rangle \) = 5 mEq/L/24h in Group A vs. 6 mEq/L/24h in Group B, \( P\)-value = 0.791). Out of the whole sample, 59.1% of patients showed a correction rate within the optimal range (50.0% in Group A vs. 66.6% in Group B), 22.7% experienced a low degree of correction (30.0% in Group A vs. 16.7% in Group B), 18.2% a low risk overcorrection (20.0% in Group A vs. 16.7% in Group B), while none showed a high risk overcorrection. Eventually, the 24-hour diuresis was not statistically different between groups (1400 mL in Group vs. 1425 mL in Group B, \( P\)-value = 0.908).

The median \( \langle \text{copeptin} \rangle \) was 38.05 pmol/L [min-max 1.30-592.00 pmol/L; IQR 9.71-100.95 pmol/L]. The regression analysis showed no clear relationship between \( \langle \text{copeptin} \rangle \) and \( \langle \text{Na}^+ \rangle \) at baseline (\( R^2 = 0.059; \ P\)-value = 0.330). The \( \langle \text{copeptin}\rangle \)-to-\( \langle \text{Na}^+ \rangle \) ratio was also computed: the median was 0.82 pmol/mEq (min-max 0.01-51.93 pmol/mEq; 0.32-3.55 pmol/mEq), and 59.1% of patients had a ratio > 0.30 pmol/mEq. Eventually, the difference in \( \langle \text{copeptin} \rangle \) between the two groups was not statistically significant (16.50 pmol/L in Group A vs. 9.13 pmol/L in Group B, \( P\)-value = 0.051).

After 24 hours, the physical findings suggestive of hypovolemia or dehydration were almost completely cleared. Particularly, only 1 patient still had cold extremities and 1 had a dry axillary skin, while 5 subjects still presented dry mucosae (no statistically significant differences were found between the two groups of treatment).

None of the patients experienced adverse events related to the treatment during their stay in the ED (neither neurological impairment nor fluid overload). Out of the 22 patients, 3 were lost to follow-up (13.7%), 5 died within 30 days from ED discharge (22.7%), 14 (63.6%) were reached by the phone call: their median \( \langle \text{Na}^+ \rangle \) at follow-up was 134 mEq/L (IQR 128-137 mEq/L). No statistically significant differences were found between groups in follow-up data.

**DISCUSSION**

Hyponatremia is the most frequent electrolyte disorder encountered in clinical practice. Although it is associated with poor outcomes and prolonged hospitalization [7], hyponatremia is still undertreated especially in the ED.

The aim of this study was to investigate efficacy and safety of the quantitative treatment of hypovolemic hyponatremia during the first 24 hours spent in an ED Observation Unit. The specific setting of our study is the reason why we chose to assess patients' volume status at baseline through clinical parameters only: in an emergency medicine context, where time and resources usually lack, the physician has to rely on simple and readily available tools to correctly diagnose and treat hyponatremia. The Literature has been critical of the diagnostic accuracy of a clinical approach alone [12,22], but in real-life experience the emergency physician can usually base his decisions only on historical and physical findings, with a few additional laboratory elements (such as FENa\(^-\)), before starting the treatment.

The role of copeptin in hyponatremia has been widely investigated [28,29]. The results obtained from our sample confirmed the wide variability of the \( \langle \text{copeptin} \rangle \) (IQR 9.71-100.95) already described in the Literature [29]. Additionally, the fact that our regression analysis did not show any relationship between \( \langle \text{copeptin} \rangle \) and \( \langle \text{Na}^+ \rangle \) (which is directly related to plasma osmolality) and that only 59.1% of our hypovolemic patients had a \( \langle \text{copeptin}\rangle \)-to-\( \langle \text{Na}^+ \rangle \) ratio > 0.30 pmol/mEq urges us to claim that copeptin is not helpful in the initial evaluation of hypotremic patients in the ED. This could be due to the fact that the \( \langle \text{copeptin} \rangle \) increases in several acute conditions and in stressing situations; both these eventualities are almost always present in the ED setting. The difference (as well as not statistically significant) observed between the two groups in the \( \langle \text{copeptin} \rangle \) could be an interesting finding but has probably no potential clinical impact, especially since a ROC curve demonstrate a poor diagnostic performance (data not shown).

We decided to exclude from the study patients with severe hypovolemia or shock because, in such cases, fluid resuscitation is mandatory regardless of the \( \langle \text{Na}^+ \rangle \) values; the infusion of saline solutions, in fact, must be continued until euvolemia and blood pressure are restored even though this treatment can be associated with an increased risk of overly rapid correction and ODS [5,31].

In our study, the quantitative treatment was started with different desired correction rates according to the grade of...
dehydration established by two expert emergency physician. Their task was to clinically differentiate patients whose therapeutic priority was fluid replacement from those whose therapeutic priority was Na+ replacement. Therefore, 10 patients with moderate dehydration were treated by setting the desired correction rate at 12 mEq/L/24h in order to ensure the administration of larger amounts of fluids; the remaining 12 patients with mild dehydration were treated with a desired correction rate of 6 mEq/L/24h in order to ensure a proper solute replacement. The two groups thus created were then compared in order to evaluate efficacy and safety of these two different therapeutic strategies.

The two expert emergency physician allocated patients according to their clinical judgment. The only significant difference highlighted between groups during the ex-post analysis was observed in the frequency of cold extremities. However, patients with moderate dehydration presented more items of a dehydration score proposed for this study and 70.0% of them had a score > 3 (vs. 25.0% of the other group).

No statistically significant differences were found between the two groups in after-treatment data: although the formula provided a significantly higher amount of Na+ in Group A patients, they obtained similar correction rates, similar after-treatment $\Delta$(Na+) and, above all, similar correction kinetics outcomes. In this regard, 59.1% of all patients obtained an optimal correction over 24 hours, which reached a percentage of 66.6% in the group with a desired correction rate of 6 mEq/L/24h. Unexpectedly, the percentage of low degree corrections was higher in Group B, although this did not reach a statistically significant level. On the other hand, no patient from both groups experienced a high risk overcorrection. However, the deviation between the expected and measured after-treatment $\Delta$(Na+) was consistent, and the fact that the administration of higher amounts of Na+ did not implicate higher correction rates could be related to many external factors that the formula does not include, such as previous diuretic therapy, AVP secretion, RAA axis activation and water and Na+ urine excretion during the first hours of correction. Anyway, our results suggest that such a therapeutic approach can be used both effectively and safely in an ED, since, although the percentage of optimal corrections did not meet our expectations, only 2 patients the treatment was completely ineffective (< 2 mEq/L/24 h) and only in 4 patients it caused minimal over corrections, even though 10 patients were treated with a formula set on a higher target. The main implication of this finding is that hypovolemic patients presenting a contextual hyponatremia can be treated in the ED by infusing a volume of isotonic fluid larger than the one predicted with the Adrogué-Madias formula set on the target suggested by international recommendations (6 mEq/L/24h) with a negligible risk of inducing a potentially harmful overcorrection. In such patients, in fact, the infusion of fluids and electrolytes is followed by an increase in water and Na+ urine excretion leading to a slow increase in the (Na+). Nonetheless, two specific circumstances must be promptly excluded during the first hours of correction. AVP release is deeply involved in the development of both: in fact, in SIADH cases in which euvolemia is not readily apparent and hypovolemia is suspected, a persistent AVP release can lead to water retention and a paradoxical increase in the $\Delta$(Na+) (this must be suspected when the $\Delta$(Na+) significantly increases during treatment); on the other hand, once volume has been restored, some patients can experience an unexpected raise in the (Na+) due to a rapid inhibition of the previous appropriate AVP release with a sudden increase in free water excretion (this must be suspected when urine output suddenly raises).

The main limits of this work are the sample size, the lack of randomization and the unblinded design. Moreover, we can provide no data about patients presenting absolute (Na+) values < 120 mEq/L, since, even though we did not list among exclusion criteria a minimal (Na+), none of those who met the inclusion criteria had such a low (Na+) value.

CONCLUSIONS

The therapeutic priority in hypovolemic patients with an associated hyponatremia is usually fluid rather than Na+ replacement. However, a prompt volume restoration could be sometimes dampened by the emergency physician’s concern of administering excessive amounts of Na+ and inducing overly rapid corrections and ODS. Our results suggest that, as long as the baseline (Na+) is not particularly low (e.g. < 120 mEq/L), the risk of obtaining a dangerous correction rate is low, probably because body homeostasis is promptly restored by volume expansion and intervenes to compensate for the exceeding amount of Na+-administered. Monitoring $\Delta$(Na+) and urine output during the first hours of treatment is essential in order to exclude negative outcomes (inefficacy and poor safety, respectively). There is some evidence that copeptin is not helpful in the first evaluation of hyponatremia in the ED. Eventually, the absence of a gold standard test to define patients’ volume status remains an unmet clinical need.

REFERENCES

9. Greenberg A, Verbalis JG, Amin AN, Burst VR, Chiodo JA, Chong...