RESEARCH LETTER

Safety and effectiveness of symptomatic hyponatremia treatment according to the European Society of Endocrinology guidelines: a retrospective study

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Introduction Hyponatremia (defined as serum sodium levels below 135 mmol/l) is the most frequent dyselectrolytemia in clinical practice, which may significantly complicate treatment and increase mortality of patients.[1,2] Despite its high prevalence, proper diagnosis and treatment of hyponatremia are still a challenge for many physicians.[3]

Until 2014, the assumed strategy of hyponatremia treatment was a diagnosis-, mechanism-, duration-based approach that was difficult to apply in everyday practice. Some of the important elements of this strategy included the assessment of patient's blood volume and calculation of sodium and potassium deficits, while the treatment depended on whether hyponatremia was acute or chronic, which is sometimes impossible to distinguish.[4-9] Moreover, the previous strategies were focused more on biochemical goals than on the patient's clinical condition, while these parameters may not correlate with one another.

In 2014, the new clinical practice guideline regarding diagnostic approach and treatment of hypotonic hyponatremia in adults was developed.[10] The authors of the guideline proposed an innovative approach based on adjustment of the treatment for the clinical status of the patient and recommended using the 3% saline infusion as the primary treatment of symptomatic patients with hypotonic hyponatremia regardless of the cause. The aim of this retrospective study was to evaluate the safety and utility of the new guideline on diagnosis and treatment of hyponatremia in everyday practice.

Patients and methods We performed a retrospective analysis of 206 patients (142 women, 64 men; mean [SD] age, 74.2 [15.9] years) diagnosed and hospitalized with hyponatremia between September 2014 and October 2015 in the Department of Internal Medicine and Endocrinology at the Medical University of Warsaw (Warsaw, Poland). Based on the diagnostic protocol recommended by the guideline,[10] patients with nonhypotonic hyponatremia (n = 22) and with pseudohyponatremia (n = 3) were excluded from further analysis. The remaining 181 patients with hypotonic hyponatremia were stratified in terms of severity of symptoms into 2 subgroups: 1) the study group with severe/moderately severe symptomatic hyponatremia (n = 16), who received intravenous 150-ml infusions of 3% saline prior to cause-specific treatment and were subsequently analyzed in terms of increase of natremia, improvement of symptoms, and occurrence of adverse events/complications; and 2) the control group without severe/moderately severe symptomatic hyponatremia (n = 165) who received cause-specific treatment without 3% saline infusions.

Severe symptomatic hyponatremia was defined as "any biochemical degree of hyponatremia with presence of severe symptoms including: vomiting, cardiorespiratory distress, abnormal somnolence, seizures, and coma", and moderately symptomatic hyponatremia was defined as "any biochemical degree of hyponatremia with presence of moderately severe symptoms including: nausea without vomiting, confusion, and headache."[10]

The differences in clinical and biochemical parameters were assessed with the Statistica software package v.10 (StatSoft, Tulsa, Oklahoma, United States), using the Fisher exact test, *t* test or Mann–Whitney test, or Kruskal–Wallis analysis of variance as appropriate. Correlations between

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quantitative values were analyzed with the Spearman correlation test.

Results Clinical and biochemical characteristics of study participants are presented in TABLE 1. The study group of patients with symptomatic hyponatremia had a significantly lower mean serum sodium level (P <0.0001) and lower serum osmolality (P <0.0001) as compared with the control group. The study group also had a significantly higher percentage of women (P = 0.04).

The frequency of diagnoses causing hyponatremia was not significantly different between the groups (TABLE 1). Also the prevalence of comorbidities that may have predisposed to hyponatremia independently of the main diagnosis was similar, with the exception of Parkinson disease, which was more frequent in symptomatic patients (P = 0.02).

Out of 16 symptomatic patients, 12 presented with nausea and vomiting, 8 with cardiorespiratory distress, 7 with headache, 6 with confusion, 3 with abnormal somnolence, and 1 experienced seizures followed by coma. The severity of symptoms did not correlate with natremia, but was rather associated with the rate of decrease in the serum sodium level (symptoms were more pronounced in 7 patients with acute hyponatremia).

The decision regarding the number of saline infusions administered to symptomatic patients was based on the severity or improvement of symptoms rather than on baseline serum sodium levels. Subsequently, 9 patients received 1 infusion; 3 patients, 2 infusions; 3 patients, 3 infusions, and 1 patient, 4 infusions during the first 24 hours after admission. Normal saline solution (500–1000 ml) was administered to 5 patients before their admission to the department. In each case, a slight reduction in the sodium level was noted afterwards, and all of these patients subsequently received saline infusion (Supplementary material online, *Figure S1*).

We observed a gradual increase of natremia in all patients who received saline. The mean (SD) increase in serum sodium levels after administration of 1 infusion was 3.1 mmol/l (1.4), and during the first 24 hours of hospitalization it was 8.3 mmol/l (2.6). The increase in serum sodium levels correlated positively with the number of infusions received: r_s = 0.881, P <0.0001 after 24 hours. In 3 patients, the rate of serum sodium correction exceeded the recommended 10 mmol/l in the 24-hour period: in 2 patients by 1 mmol/l, and in 1—by 2 mmol/l. All of them received 3 saline infusions during the first 24 hours.

In 15 patients from the study group, an increase of natremia was associated with overall improvement without reported side effects of the treatment. The symptoms noted with the fastest observable improvement (within the first 24 hours) were nausea or vomiting and confusion.

On the sixth day of hospitalization, 1 patient from the study group died. The patient was a 92-year-old woman diagnosed with respiratory failure during the course of severe pneumonia. Her initial sodium concentration was the highest in the entire group (121 mmol/l). Although after the first and only infusion of saline the serum sodium concentration increased to 124 mmol/l, the patient's general condition failed to improve.

Discussion Our study served to evaluate the safety and utility of the clinical practice guideline on diagnostic approach and treatment of hypotonic hyponatremia in everyday practice.

The novel classification of hyponatremia based on symptom severity, as proposed by the guideline, is indicative of the risk of brain edema. Accordingly, the treatment should be more aggressive for more severe symptoms, assuming that the risk of brain edema outweighs the risk of osmotic demyelination syndrome.[11,12] In our study, we found no significant differences in the causes of hyponatremia or in the prevalence of comorbidities between symptomatic and asymptomatic patients, suggesting that the approach based on symptom severity might be better than the previous cause- and mechanism-based strategies for the identification of patients with risk of brain edema.[4]

However, the authors of the guideline point out a major limitation of the proposed classification, which is the identification of patients with acute hyponatremia whose condition, despite initially presenting as clinically asymptomatic, may deteriorate rapidly.[10] We did not face such a situation in the present study, and none of the asymptomatic patients required 3% saline infusions during the hospitalization. Nevertheless, we found that in the symptomatic group the severity of symptoms reflected the rate of decline in sodium concentrations, and the symptoms were more pronounced in patients with acute hyponatremia. Therefore, in each case of hyponatremia an attempt should be made to determine its etiology and duration.

The second limitation of the proposed classification is that none of the symptoms of hyponatremia is disease- or cause-specific.[1,3] This problem was apparent in our study in the case of the patient presenting with abnormal somnolence whose condition did not improve despite saline treatment, and who then presented with growth of natremia, and subsequently died. In this case, the presented symptoms were associated with respiratory failure during the course of severe pneumonia. Therefore, the patient's death should be explained by a serious disease rather than inadequate manipulation of serum sodium concentrations.

The remaining 15 patients treated with saline presented with a gradual alleviation of symptoms parallel to the increase of natremia. The fastest overall improvement was observed in patients who received 3 or 4 infusions. It is worth noting that in 3 patients the rate of sodium increase exceeded the suggested safety limit (10 mmol/l) during the first 24 hours. Although none of them

TABLE 1 Clinical and biochemical characteristics of 181 patients with hypotonic hyponatremia

Variable			Symptomatic patients (n = 16)	Asymptomatic patients (n = 165)	*P* value
Demographic and biochemical parameters, mean (SD) [except age]					
Sex, female/male, n			15/1	113/52	0.04
Age, y			81.0 (11.8)	74.1 (15.8)	NS
Serum Na, mmol/l			115.6 (4.3)	128.0 (5.8)	<0.0001
Urinary Na, mmol/l			64.1 (35.0)	58.13 (33.1)	NS
Serum osmolality, mmol/kg H_2O			248.7 (12.2)	275.1 (15.4)	<0.0001
Urinary osmolality, mmol/kg H_2O			372.4 (131.7)	292.4 (137.2)	NS
Glucose, mmol/l			6.6 (1.4)	7.4 (2.5)	NS
Triglycerides, mmol/l			0.84 (0.34)	1.22 (0.6)	NS
Creatinine, µmol/l			84.7 (48.9)	123.2 (97.9)	NS
Total protein, g/dl			6.35 (0.9)	6.5 (0.8)	NS
TSH, mIU/l			1.8 (0.9)	3.1 (8.5)	NS
Length of hospital stay, d			11.1 (7.4)	10.7 (7.7)	NS
Mechanism of hypotonic hyponatremia[a], n (%)					
With decreased extracellular volume	Nonrenal sodium loss	Gastrointestinal loss	2 (12.5)	8 (4.8)	NS
	Renal sodium loss	Diuretics	3 (18.8)	32 (19.4)	NS
		Primary adrenal insufficiency	–	1 (0.6)	NS
	Third spacing	Acute pancreatitis	–	1 (0.6)	NS
With normal extracellular volume	SIADH	Malignancies	–	15 (9.2)	NS
		Pulmonary disorders	6 (37.5)	35 (21.2)	NS
		Disorders of CNS	–	21 (12.8)	NS
		Drugs	–	6 (3.6)	NS
	Secondary adrenal insufficiency		1 (6.2)	3 (1.8)	NS
	Hypothyroidism		–	3 (1.8)	NS
With increased extracellular volume	Heart failure		3 (18.8)	34 (20.6)	NS
	Liver failure		1 (6.2)	6 (3.6)	NS
Comorbidities[b], n (%)					
Hypertension/heart failure			8 (50.0)	48 (29.1)	NS
Renal failure			1 (6.25)	20 (12.1)	NS
Diabetes			2 (12.5)	17 (10.3)	NS
COPD/asthma			–	12 (7.3)	NS
Hypothyroidism			–	8 (4.8)	NS
Neurological diseases	Cerebrovascular disease		2 (12.5)	14 (8.5)	NS
	Epilepsy		–	8 (4.8)	NS
	Parkinson disease		2 (12.5)	3 (1.8)	0.02
	Depression		–	4 (2.4)	NS
Malignancies			–	8 (4.8)	NS

a Classification according to the clinical practice guideline[10]
b Diseases that may predispose to hyponatremia independently of the main diagnosis

A *P* value of less than 0.05 is considered statistically significant.

Abbreviations: CNS, central nervous system; COPD, chronic obstructive pulmonary disease; NS, not significant; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TSH, thyroid-stimulating hormone

developed osmotic demyelination syndrome, we caution that the rate of rise in serum sodium levels with this treatment is difficult to predict. Because physicians tend to treat symptomatic hyponatremia too aggressively, the gradual alleviation of symptoms during the following days should be reinforced and, if possible, the 3% saline infusions should be distributed and divided slowly over the first days of treatment.

Our study has 2 major limitations: it has a retrospective design and the number of patients treated with 3% saline infusion is small. It is, however, the first study to analyze the utility of the proposed guideline, and is representative for a larger number of internal medicine departments where patients with hyponatremia are treated.

In conclusion, in this study we found that the classification of hyponatremia based on

the severity of symptoms, as proposed by the clinical practice guideline, is useful and easy to follow in clinical practice. Treatment of patients with moderate/severe symptoms of hyponatremia with infusions of 3% saline was proved to be effective in terms of improvement of patients' condition as well as normalization of natremia. The treatment was also safe in terms of related complications or adverse effects. However, further prospective studies are required to confirm these observations.

Supplementary material online Supplementary material online is available with the online version of the article at www.pamw.pl.

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