Clinical Nutrition 38 (2019) 2639–2644

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Development of hyponatremia in non-critical patients receiving total parenteral nutrition: A prospective, multicenter study

Emilia Gómez-Hoyos [a, *], Ana Ortolá Buigues [a], Maria Dolores Ballesteros Pomar [b], Alfonso Vidal Casariego [b], Yaiza García Delgado [c], Maria Julia Ocón Bretón [d], Angel Luis Abad González [e], Luis Miguel Luengo Pérez [f], Pilar Matía Martín [g], Maria José Tapia Guerrero [h], María Dolores Del Olmo García [i], Ana Herrero Ruiz [j], Julia Álvarez Hernández [k], Diego Bellido Guerrero [l], Sandra Herranz Antolín [m], Carmen Tenorio-Jiménez [n], Maria Victoria García Zafra [o], Francisco Botella Romero [p], María Argente Pla [q], Miguel Angel Martínez Olmos [r], Irene Bretón Lemes [s], Isabelle Runkle De la Vega [g], Daniel De Luis Román [a]

[a] Endocrinology and Nutrition Department, Hospital Clínico Universitario de Valladolid-IEN, Universidad de Valladolid, Valladolid, Spain
[b] Endocrinology and Nutrition Department, Complejo Asistencial Universitario de León, León, Spain
[c] Endocrinology and Nutrition Department, Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain
[d] Endocrinology and Nutrition Department, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain
[e] Endocrinology and Nutrition Department, Hospital General Universitario de Alicante, Alicante, Spain
[f] Endocrinology and Nutrition Department, Hospital Infanta Cristina, Badajoz, Spain
[g] Endocrinology and Nutrition Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos (IDISSC), Madrid, Spain
[h] Endocrinology and Nutrition Department, Hospital Regional Universitario de Málaga, Málaga, Spain
[i] Endocrinology and Nutrition Department, Hospital Universitario Severo Ochoa, Madrid, Spain
[j] Endocrinology and Nutrition Department, Hospital Clínico Universitario de Salamanca, Salamanca, Spain
[k] Endocrinology and Nutrition Department, Hospital Universitario Príncipe de Asturias, Madrid, Spain
[l] Endocrinology and Nutrition Department, Complejo Hospitalario Universitario de Ferrol, Coruña, Spain
[m] Endocrinology and Nutrition Department, Hospital Universitario de Guadarajara, Guadarajara, Spain
[n] Endocrinology and Nutrition Department, Complejo Hospitalario de Jaén, Jaén, Spain
[o] Endocrinology and Nutrition Department, Hospital Universitario Santa Lucia, Cartagena, Spain
[p] Endocrinology and Nutrition Department, Complejo Hospitalario Universitario de Albacete, Albacete, Spain
[q] Endocrinology and Nutrition Department, Hospital Universitario y Politécnico de La Fe, Valencia, Spain
[r] Endocrinology and Nutrition Department, Complejo Hospitalario Universitario de Santiago, Santiago de Compostela, Spain
[s] Endocrinology and Nutrition Department, Hospital Universitario Gregorio Marañón, Madrid, Spain

ARTICLE INFO

Article history:
Received 12 April 2018
Accepted 25 November 2018

Keywords:
Hyponatremia
Total parenteral nutrition
Hyponatremia risk factors
Severe malnutrition

SUMMARY

Background & aims: Hyponatremia is frequent in hospitalized patients, especially in those receiving total parenteral nutrition (TPN). Furthermore, the presence of hyponatremia is associated with increased morbimortality in both groups. The goal of this study is to describe the prevalence of hyponatremia developing during TPN in non-critical patients, and identify risk factors for its appearance.
Methods: This prospective multicenter study involved 19 Spanish hospitals. Noncritically-ill patients prescribed TPN over a 9-month period were studied. Variables analyzed demographic characteristics, prior comorbidities, drug therapy, PN composition, additional iv fluids, and serum sodium levels.
Results: A total of 543 patients were recruited, 60.2% males. Age: 67 (IR 57–76). Of 466/543 who were eunatremic when starting TPN, 18% developed hyponatremia (serum sodium < 135 mmol/L) during TPN. Independent risk factors identified by logistic regression analysis: female (OR 1.74 [95% CI = 1.04–2.92], p = 0.036); severe malnutrition (OR 2.15 [95% CI = 1.16–4.35], p = 0.033); opiates (OR 1.97 [95% CI = 1.10–3.73], p = 0.036); and nausea/vomiting (OR 1.75 [95% CI = 1.04–2.94], p = 0.036).

* Corresponding author. Endocrinology and Nutrition Department, Hospital Clínico Universitario de Valladolid, 6ª Oeste, Ramón y Cajal 3, 47003, Valladolid, Spain. Fax: +34 983 33 32 32.
E-mail address: emiliagomezhoyos@gmail.com (E. Gómez-Hoyos).

https://doi.org/10.1016/j.clnu.2018.11.014

Conclusions: Previously eunatremic patients frequently develop hyponatremia while receiving TPN. In this group, severe malnutrition is an independent risk factor for hyponatremia, as well as previously described risk factors: opiates, nausea/vomiting, and female gender.

1. Introduction

Hyponatremia is the most frequently encountered electrolyte disturbance in hospitalized patients [1]. Low serum sodium levels are more frequent in patients receiving parenteral nutrition than in the general hospital population. A recently published retrospective study found that 40% of patients receiving total parenteral nutrition (TPN) developed hyponatremia at some point during hospitalization, versus 25.8% of control subjects who did not receive TPN [2].

The presentation of hyponatremia has been associated with increased morbimortality. In fact, the mortality rate has been found to be higher in patients on TPN than in the general hospital population, specifically in patients on TPN presenting sustained hyponatremia, with low serum sodium levels found in a minimum of 75% of blood tests [2]. Furthermore, of hyponatremia is accompanied by a decrease in mortality, as shown in a metanalysis of retrospective studies [4]. Active therapy correcting hyponatremia has also been prospectively found to reduce hospital length-of-stay [3].

Hyponatremia is induced by a disturbance in water metabolism, almost always as a consequence of non-osmotic Arginine Vasopressin (AVP) secretion, the Human Antidiuretic Hormone or ADH [4]. The secretion of AVP is normally inhibited by descents in plasma osmolality. However, when AVP secretion fails to be inhibited by the presence of plasma hyposmolality, distal nephron water reabsorption is increased (antidiuresis) and hyponatremia can ensue. This non-osmotic AVP secretion can be induced by physiological stimuli (low effective circulating volume, post-surgical stress, pain, nausea or vomiting) or by the non-physiological, inappropriate AVP secretion of the Syndrome of Inappropriate ADH secretion-SIADH. TPN patients could be at an increased risk for development of SIADH, either drug-induced (opiates, antidepressants or pregabalin/gabapentin), or caused by ectopic AVP paraneoplastic secretion [5]. The combination of persistent non-osmotic AVP secretion and increased oral or parenteral fluid intake, frequent in hospitalized patients [6], would result in progressive plasmatic hypoosmolality, and in the induction or exacerbation of hyponatremia. This combination is often found in patients on TPN. Thus, hospitalized patients receiving TPN would be at a high risk for development of hyponatremia.

TPN is indicated in patients that need nutritional support, and in whom the gastrointestinal (GI) tract cannot be used. This situation can be seen following major GI surgery, or in the context of sustained vomiting, GI obstruction and diarrhea [7,8]. Furthermore, physiological non-osmotic stimuli of AVP secretion, such as pain, and nausea, or low effective circulating volumen (i.e extrarenal sodium loss secondary to GI loss) are often present. In this context, the increase in intravenous fluid therapy caused by TPN can induce a descent in serum sodium. Although several predisposing factors (thiazide diuretics, surgery, hypotonic intravenous fluids and AVP-stimulating drugs) have been identified in the general hospital population [9], no studies have directly investigated which factors contribute to hyponatremia acquired while patients are receiving TPN.

The aim of this study is to describe the prevalence of hyponatremia acquired during TPN, and identify its risk factors. Detection of the latter could help identify patients at risk for hyponatremia when initiating TPN, and permit prompt intervention.

2. Material and methods

2.1. Study design

The study was observational, non-interventional, multicenter, and prospective. It was approved by the Research Ethics Committee of the Hospital Clínico Universitario de Valladolid. All participants gave written informed consent.

2.2. The population studied

Nineteen Spanish hospitals participated in the study (18/19 are teaching hospitals). The study included all hospitalized noncritically ill patients (i.e., patients not attended in intensive care units) who started TPN as a sole source of nutrition between June 2015 and February 2016. Patients were excluded if they were receiving parenteral nutrition together with enteral nutrition, pregnant, or below 14 years of age.

2.3. The total parenteral nutrition protocol

The TPN formula at all the hospitals was provided as a total nutrient admixture solution containing carbohydrates, proteins, lipids and electrolytes. Both the amount of each macronutrient and electrolyte, and the volume of the formula were prescribed by a physician belonging to the hospital nutrition unit in accordance with the relevant guidelines [7,8]. All patients receiving TPN were seen daily by this physician, who recorded the data of the study variables. Prospective determinations were made of natremia, glycemia, and serum triglyceride levels before TPN and every 3–4 days following its initiation.

2.4. Data collection

Patient data collected included gender, age, prior comorbidity (history of kidney, liver, respiratory or cardiac failure), history of diabetes mellitus, anthropometric data (weight, height, body mass index-BMI-), nutritional assessment by subjective global assessment (SGA) before starting TPN, oncology diagnosis, surgery before TPN, gastrointestinal (GI) losses (diarrhea, intestinal fistulae and/or GI obstruction), presence of pain, of nausea/vomiting and edema/ascites. Other data also recorded included concomitant medication (opiates, antidepressants, angiotensin converting enzyme-ACE-inhibitors, diuretics, non-steroidal anti-inflammatory drugs-NSAIDs-, gabapentin or pregabalin), daily urine output, creatinine level before and during TPN, date of detection of hyponatremia, indication for TPN, dates of initiation and discontinuation of TPN, composition of TPN (energy in kcal, volume in ml, sodium and potassium in mEq, glucose in grams, proteins in grams, lipids in grams, osmolarity in mOsm/L), addition non-PN iv fluids (type and amount), and total osmols received, in mOsm. Osmols were calculated as the sum of urea (50 mmol of urea for every 10 g of proteins administered), sodium chloride (NaCl) and potassium chloride (KCl), with 1 mOsm for every mmol of urea, and 2 mmol for every mmol of NaCl and of KCl [10]. Laboratory tests (glycemia, serum sodium and triglyceride levels) were carried out at the laboratories of each hospital. Serum sodium levels were measured using indirect ion-selective electrolyte methodology.

2.5. Hyponatremia

Hyponatremia was defined as a serum sodium level below 135 mmol/l, after correction for glycemia, when serum triglyceride levels were below 400 mg/dl. Correction for glycemia was done as follows: adding 1.6 mmol/l of serum sodium level for every 100 mg of glycemia over 100 mg/dl up until a glycemia of 400 mg/dl, from which point 4 mmol/l were added for every 100 mg/dl increment in glycemia [11].

2.6. Statistical study

The estimated sample size was 484 patients, assuming a hyponatremia prevalence rate of 28% in patients during TPN (2-tailed significance tests with a 95% CI and a precision of 5%). Continuous variables are described as means ± standard deviation for normally distributed variables or as medians with interquartile range in non-normal distributions. The comparisons between the qualitative variables were made using the Chi-squared test, with Fisher' s correction when necessary. The distribution of the quantitative variables was examined with the Kolmogorov– Smirnov test. The differences between the quantitative variables were analyzed with Student' s t test, using nonparametric tests (Mann–Whitney) when the study variables did not follow a normal distribution. Patients with hyponatremia before starting TPN were excluded from the analyses. We designed multivariate logistic regression models in which the dependent variable was development of hyponatremia during the TPN infusion. Multivariate logistic regression models included significant associations, controlling also for other variables such as age, gender and diuretics. For all calculations, significance was set at $p < 0.05$ for two tails. Statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago IL, USA).

3. Results

The study included 543 patients, with a median of 19 patients per hospital (IR 10–45). The median age of the population studied was 65 (IR 57–76) years, and 327 subjects (60.2%) were males. Of the 543 patients, 128 (23.6%) presented a prior comorbidity, 88 (16.2%) a history of diabetes mellitus and 306 (56.4%) an oncological diagnosis. Nutritional status as assessed by SGA was as follows: 192 (36.2%) presented severe malnutrition (SGA C), 177 (33.3%) moderate malnutrition (SGA B) and 162 (30.5%) were normally nourished (SGA A). Mean BMI was 24.7 (±5) kg/m^2. Before TPN, 317 (58.7%) patients had undergone surgery.

The most frequent indications for PN were bowel rest (36.5%), paralytic ileus (21.2%), bowel obstruction (13.1%), oral mucositis (6.3%), vomiting (5.9%), diarrhea (2.6%) or various causes (14.4%). Of the 543 patients, 230 (42.4%) were receiving diuretics (97% furosemide), 169 (31.1%) opiates, 14 (2.6%) pregabalin or gabapentin, 31 (5.7%) antidepressants, 115 (21.2%) NSAIDs and 68 (12.5%) ACE-inhibitors.

The median duration of PN was 8 (IR 6–12) days. The osmolarity, volume, energy, macronutrients, and electrolytes of the parenteral nutrition administered are presented in Table 1. A total of 479 (89.8%) patients received additional iv fluids at some time during their TPN. This additional fluid was isotonic saline in 69.1%, hypotonic solutions (hypotonic saline and/or dextrose) in 11.2%. Both isotonic saline and hypotonic solutions were administered in 19.7%. The daily median volume of the additional iv fluid was 800 (IR 500–1203) ml, contributing a median of 101.3 (IR 65.4–149.8) mEq of sodium daily. The final total volume, osmoles and amount of sodium received by patients daily (NTP plus additional fluids) were: 2649 (IR 2239–3150) ml, 859 (IR 745–981) mOsm and 172.4 (IR 1.9–3.7) mEq respectively. During the period of TNP infusion, 329 (60.6%) patients reported pain, 258 (47.8%) presented nausea or vomiting and 297 (54.7%) presented GI losses. Edema and/or ascites were detected in 114 (21%).

Eighteen percent of patients without prior hyponatremia developed low serum sodium following initiation of TPN. Those patients developing hyponatremia did so within 4 (IR 2–7) days of starting TPN. Serum sodium at diagnosis of hyponatremia was 133 (±1.52) mmol/L, with a minimum level of 126 mmol/L and a maximum of 134 mmol/L. The distribution of patients with hyponatremia by range of natremia was: 2 (1.2%) with natremia <125 mmol/L, 11 (6.8%) with natremia between 125 and 129 mmol/L and 149 (92%). The creatinine level before the beginning TPN was 0.66 (IR 0.50–0.66) mg/dl and during TPN was 0.48 [0.61–0.80] mg/dl, only a 7,4% presented a creatinine level > 1.2 mg/dl. Medium daily urine output during the administration of TNP was 1830 [1527–2234] ml/day and in no patient was the development of oliguria or low urine output (urine output < 500 ml/day) observed.

Table 2 shows the characteristics of the patients who developed hyponatremia and those without hyponatremia during the period of TPN administration. Hyponatremia was significantly more frequent in women, in those with prior severe malnutrition, low BMI, GI losses, nausea/vomiting, and edema/ascites, as well as in those receiving opiates and antidepressants. Table 3 shows the logistic regression data for the risk of developing hyponatremia during TPN. Female gender, severe malnutrition, opiates and nausea/vomiting were all significantly associated with development of hyponatremia following adjustment for the other variables.

4. Discussion

Close to a fifth (18%) of previously normonatremic patients developed de novo hyponatremia during TPN. This represents a higher prevalence than that previously described by Waikar et al., in a prospective study of a general hospital population, in which 5.2% of patients admitted with a normal serum sodium developed hyponatremia during their hospital stay. Thus, parenteral nutrition

Table 1
Description of osmolarity, volume, energy, macronutrients, and electrolytes of the parenteral nutrition administered.

	Total daily intake	Weight (kg)-adjusted daily intake
Energy (Kcal)	1592.2 (1429.4–1749.6)	25.9 (23.5–28.4)
Proteins (g)	77 (68–91)	1.3 (0–5)
Glucose (g)	187 (165.7–201.2)	3 (2.7–3.3)
Lipids (g)	51.3 (48–60)	0.9 (0,7–1)
Volume (ml)	1967.2 (1669.0–2167.7)	31.2 (26.4–35.6)
Potassium (mEq)	60 (53.7–70)	1 (0.8–1.2)
Sodium (mEq)	77.5 (70.5–95.1)	1.3 (1.1–1.5)
Osmolarity (mOm/L)	1134.1 ± 263.3	

Data are described as medians (interquartile range) or as means +/+ standard deviation. Kcal, Kilocalories; g, grams; ml, milliliters; mEq, milliequivalent; mOsm, milliosmol; L, liter; Kg, Kilograms.

Table 2
Characteristics of patients according to the development of hyponatremia during total parenteral nutrition (TPN) infusion.

Development of hyponatremia during TPN infusion			
Variable	YES	NO	p value
No.patients	85 (18.2)	381 (81.8)	
Age (years)	69 (58.5–76.5)	66.5 (57–75)	NS
Female Gender	48 (56.5)	141 (37)	0.001
Oncology diagnosis	56 (61.2)	204 (53.5)	NS
Prior comorbidity	20 (23.5)	67 (17.6)	NS
Diabetes Mellitus	15 (17.6)	63 (16.5)	NS
Surgery	45 (52.9)	204 (63.5)	NS
BMI (Kg/m^2)	23.9 ± 5.2	25.3 ± 4.9	0.033
SGA			
Normally nourished	17 (20)	132 (35.6)	
Moderate malnutrition	29 (34.1)	122 (32)	
Severe malnutrition	39 (45.9)	117 (30.7)	0.009
Pain	56 (65,9)	230 (60,4)	NS
Nausea/Vomiting	54 (63.5)	169 (44.4)	0.001
Edema/ascites	25 (29.5)	67 (17.6)	0.013
GI losses	57 (76.1)	197 (51.7)	0.01
Antidepressant	9 (10.6)	16 (4.2)	0.029
Opiates	38 (44.7)	102 (26.8)	0.001
Diuretics	43 (50.6)	149 (39.1)	NS
NSAIDs	15 (17.6)	87 (22.8)	NS
ACE-inhibitors	13 (15.3)	45 (11.8)	NS
Gapentin or pregabalin	2 (2.4)	12 (3.1)	NS
Total Osmol (mOsm)/day	848.9 (731.1–975.5)	860.5 (746.2–989.7)	NS
Total volume (ml)/day	2632 (2246–3159)	2650 (2250–3158)	NS
Total sodium (mEq)/day	174 (118–225)	161 (100–217)	NS

Data are described as medians (interquartile range), as means ± standard deviation or as n (%). NS, not significant; BMI, body mass index; SGA, subjective global assessment; GI, gastrointestinal losses; NSAIDs, non-steroidal anti-inflammatory drugs; ACE, angiotensin converting enzyme; mOsm, milliosmol; ml, milliliters; mEq, milliequivalent.

Table 3
Logistic regression analysis: adjusted risk of presenting hyponatremia during total parenteral nutrition (TPN) infusión.

	B	Odds Ratio	95% CI		p value
			Lower	Upper	
Age	0.01	1.01	0.99	1.03	NS
Female Gender	0.53	1.74	1.04	2.92	0.036
SGA					
Normally nourished					NS
Moderate malnutrition	0.51	1.66	0.83	3.32	NS
Severe malnutrition	0.76	2.15	1.16	4.35	0.033
BMI	0.45	1.56	0.85	2.88	NS
Nausea/vomiting	0.56	1.75	1.04	2.94	0.036
GI losses	0.44	1.55	0.90	2.93	NS
Edema/ascites	0.32	1.38	0.73	2.59	NS
Opiates	0.79	1.97	1.10	3.73	0.035
Antidepressant	0.83	2.30	0.88	5.98	NS
Diuretics	0.38	1.46	0.84	2.57	NS

NS, not significant; CI, confidence interval; BMI, body mass index; SGA, subjective global assessment.

patients per se are at a high risk for development of hyponatremia. Severe malnutrition was found to be a risk factor for development of hyponatremia when receiving PN. The total fluid volume administered and the total amount of sodium received were not.

Hospitalized patients often present conditions that interfere with aquaresis, such as pain, nausea, postsurgical stress and hyponatremia-inducing medications. When the above are combined with excess fluid intake, the kidney's capacity to eliminate free water may be insufficient to prevent the development or worsening of hyponatremia [6]. In fact, published reports indicate that the mean serum sodium of inpatients is 5–6 mmol/L less than what is observed in outpatients [12]. Our study has found that TPN patients are at a high risk for development of hyponatremia, with 18% of previously eunatremic patients developing it during TPN, as compared with 5.2% of the general hospitalized population, as previously described [1]. A prior retrospective study found an even higher prevalence of de novo hyponatremia in TPN patients than in our current study, with 28% of 222 patients developing hyponatremia during TPN [13]. A possible explanation for this discrepancy could be the greater degree of homogeneity of the patients studied in the retrospective analysis, that was performed in a single center. In any event, our results indicate that TPN patients are at an increased risk for development of hyponatremia than the general hospitalized population.

Severe malnutrition was the most important risk factor for development of hyponatremia during TPN in our study population. Although nausea or vomiting, gender female, and opiates were all associated with hyponatremia development, the OR for hyponatremia was lower in all of these cases. Up until now, malnutrition has not been considered to be a risk factor for hyponatremia. However, when studying 8.888 patients on hemodialysis, Dekker et al. found that malnutrition was an independent risk factor for hyponatremia, with an OR of 1.49 (95% CI = 1.30–1.70) [14]. In our study, the risk for hyponatremia in severely malnourished subjects

was even higher, with an OR of 2.15 (95% CI = 1.16–4.35). In fact, no previously normonatremic patients who were normally nourished or who displayed moderate malnutrition developed hyponatremia during TPN. One possible explanation for this relationship could be include the altered body fluid distribution characteristic of disease-associated malnutrition. Catabolism of organic phosphates in the intracellular compartment (IC) could result in the excretion of inorganic phosphate and potassium into the extracellular compartment (EC), accompanied by a concomitant water shift from the IC to the EC [15]. An increased water shift from the IC to the EC could also be explained by defective cell membrane integrity, allowing movement of intracellular solutes to the extracellular liquid compartment [16]. Furthermore, malnourished patients often present disease-associated inflammation, and elevated pro-inflammatory cytokines [17,18]. IL-1Beta and IL-6 have been shown to stimulate non-osmotic AVP secretion [19,20]. Thus, inflammation per se could help explain the greater risk for hyponatremia found in malnutrition [21]. In any event, this prospective study, together with what has been describing by Dekker et al. [14] establish severe malnutrition as a risk factor for hyponatremia.

We found that diuretic use was not associated with an increased in the prevalence of TPN- associated hyponatremia, in divergence with prior studies [9]. However, the diuretic-treated patient were on furosemide therapy, whereas in the study of Hoorn et al., patients developing diuretic-induced hyponatremia were primarily on thiazide [9]. Furosemide can cause hypovolemic hyponatremia and sodium depletion. However, in our patients, the high amount of sodium and fluids administered would prevent this diuretic-induced complication. Surgery was also found by Hoorn et al. [9] to be a risk factor for the development of hyponatremia, which was not the case in our series. This divergence could be explained by the fact that our patients were not in the immediate post-operative period. Thus, they were not candidates for post-surgical hyponatremia.

We found that TPN-associated hyponatremia was more frequent in women, in patients who take opiates and in those with nausea or vomiting. Both thiazide-induced [22] and post-surgical hyponatremia [23] have also been found to be more frequent in women. In fact, the extracellular compartment of women contains relatively more liquid than in the case of men [24]. Additionally, AVP exerts a greater effect on the distal nephron in women than in men, thus explaining more marked antidiuresis in the former [25]. Regarding nausea/vomiting-associated and opiates hyponatremia, both induce non-osmotic AVP secretion [26,27]. In the last case, the AVP secretion is nonphysiological or inappropriate (SIADH) [26].

The total amount of administered sodium and liquids did not influence the development of hyponatremia during TPN. This finding should not come as a surprise, as similar results were found in a previous retrospective study [13]. A normally functioning kidney (normal renal function or non-oliguric renal failure) needs 50 mOsm of solute to eliminate every liter of water. Protein-derived urea provides sufficient osmols in urine to assure the elimination of free water when added to the osmols from NaCl and KCl, even when the quantity of sodium administered is low unless underlying antidiuresis is present [10]. In our study, the total osmols administered were 859 (IR 745–981) mOsm/day, when including all ions and urea. A normally functioning kidney would thus be able to eliminate up to 17 L of free water when receiving this quantity of osmols [10]. Therefore, only patients receiving over 17 L a day would develop hyponatremia, unless AVP-mediated antidiuresis was present.

The present study is not exempt from limitations. First, the blood samples were not centralized, and serum values were thus determined in different laboratories. Secondly, the study did not include a non-TPN control group with which to compare our study population. Thirdly, the determination of natremia at 3–4 days after the beginning of TPN could imply a delay of 2–3 in the diagnosis of hyponatremia. Future studies are needed to better characterize hyponatremia-associated malnutrition, measuring pro-inflammatory cytokine levels, and further studying body fluid distribution. Furthermore, studies should be directed towards the description and analysis of optimum therapy for TPN- associated hyponatremia.

In conclusion, TPN patients are at a high risk for the development of hyponatremia. Severe malnutrition was found to be the most important risk factor for its presentation. Additional risk factors were female gender, nausea/vomiting, and opiate administration. Neither the quantity of sodium nor that of fluids administered played a role in the development of hyponatremia. Patients presenting risk factors should be closely monitored for hyponatremia development following the initiation of TPN.

Conflicts of interest and funding resources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Authors declare no conflicts of interest. Dr. Isabelle Runkle has worked in an advisory capacity for Otuska, and given talks sponsored by Otsuka.

CRediT authorship contribution statement

Emilia Gómez-Hoyos: Conceptualization, Writing - review & editing, Formal analysis, Writing - original draft. **Ana Ortolá Buigues:** Writing - review & editing, Formal analysis. **Maria Dolores Ballesteros Pomar:** Writing - review & editing. **Alfonso Vidal Casariego:** Writing - review & editing. **Yaiza García Delgado:** Writing - review & editing. **Maria Julia Ocón Bretón:** Writing - review & editing. **Angel Luis Abad González:** Writing - review & editing. **Luis Miguel Luengo Pérez:** Writing - review & editing. **Pilar Matía Martín:** Writing - review & editing. **Maria José Tapia Guerrero:** Writing - review & editing. **María Dolores Del Olmo García:** Writing - review & editing. **Ana Herrero Ruiz:** Writing - review & editing. **Julia Álvarez Hernández:** Writing - review & editing. **Diego Bellido Guerrero:** Writing - review & editing. **Sandra Herranz Antolín:** Writing - review & editing. **Carmen Tenorio-Jiménez:** Writing - review & editing. **Maria Victoria García Zafra:** Writing - review & editing. **Francisco Botella Romero:** Writing - review & editing. **María Argente Pla:** Writing - review & editing. **Miguel Angel Martínez Olmos:** Writing - review & editing. **Irene Bretón Lemes:** Writing - review & editing. **Isabelle Runkle De la Vega:** Writing - review & editing. **Daniel De Luis Román:** Conceptualization, Writing - review & editing.

Acknowledgements

The Spanish Society of Endocrinology and Nutrition provided help with the publicity of the study among Spanish Nutrition specialist.

References

[1] Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. Am J Med 2009;122:857–65.
[2] Gomez Hoyos E, Cuesta M, Del Prado-Gónzalez N, Matía P, Perez Ferre N, De Luis DA, et al. Prevalence of hyponatremia and its associated morbimortality in hospitalized patients receiving parenteral nutrition. Ann Nutr Metab 2017;71:1–7.
[3] Dasta JF, Chiong JR, Christian R, Lin J. Evaluation of costs associated with tolvaptan-mediated hospital length of stay reduction among US patients with the syndrome of inappropriate antidiuretic hormone secretion, based on SALT-1 and SALT-2 trials. Hosp Pr Minneap 2012;40(1):7–14.
[4] Verbalis JG. Disorders of body water homeostasis. Best Pract Res Clin Endocrinol Metab 2003;17(4):471–503.

[5] Hoorn EJ, Zietse R. Hyponatremia revisited: translating physiology to practice. Nephron Physiol 2008;108(3):46–59.
[6] Anderson RJ, Chung HM, kluge R, Schrier RW. Hyponatremia: a prospective analysis of its epidemiology and the pathogenetic role of vasopressin. Ann Intern Med 1985;102(2):164–8.
[7] American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. Clinical guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. J Parenter Enteral Nutr 2009;33:255–9.
[8] Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, et al. ESPEN guidelines on parenteral nutrition: intensive care. Clin Nutr 2009;28(4):387–400.
[9] Hoorn EJ, J.L, Zietse R. Development of severe hyponatremia in hospitalized patients: treatment-related risk factors and inadequate management. Nephrol Dial Transplant 2006;21:70–6.
[10] Berl T. Impact of solute intake on urine flow and water excretion. J Am Soc Nephrol 2008;19:1076–8.
[11] Hillier A, Abbot R, Barrett B. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med 1999;106:399–403.
[12] Owen JA, Campbell DG. A comparison of plasma electrolyte and urea values in healthy persons and in hospital patients. Clin Chim Acta 1968;22:611–8.
[13] Gómez Hoyos E, Fernández-Peña S, Cuesta M, Ortolá A, Matía P, Pérez-Ferre N, et al. Hyponatremia in patients receiving parenteral nutrition: the importance of correcting serum sodium for total proteins. The role of the composition of parenteral nutrition in the development of hyponatremia. Eur J Clin Nutr 2017. https://doi.org/10.1038/s41430–017 – 0026–5.
[14] Dekker MJE, Marcelli D, Canaud B, Konings CJAM, Leunissen KM, Levin NW, et al. Unraveling the relationship between mortality, hyponatremia, inflammation and malnutrition in hemodialysis patients: results from the international MONDO initiative. Eur J Clin Nutr 2016;70(7):779–84.
[15] Cherney DZ, Zevallos G, Oreopoulos D, Halperin ML. A physiological analysis of hyponatremia: implications for patients on peritoneal dialysis. Perit Dial Int 2001;21(1):7–13.
[16] Gill GV, Osypiw JC, Shearer E, English PJ, Watson ID. Critical illness with hyponatraemia and impaired cell membrane integrity – the 'sick cell syndrome' revisited. Clin Biochem 2005;38(11):1045–8.
[17] Anker SD, Coats AJ. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. Chest 1999;115:836–47.
[18] Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, et al., International Consensus Guideline Committee. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. J Parenter Enteral Nutr 2010;34(2):156–9.
[19] Papanicolaou DA, Wilder RL, Manolagas SC, Chrousos GP. The pathophysiologic roles of interleukin-6 in human disease. Ann Intern Med 1998;128:127–37.
[20] Swart RM, Hoorn EJ, Betjes MG, Zietse R. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. Nephron Physiol 2011;118(2):45–51.
[21] Ohta M, Ito S. Hyponatremia and inflammation. Rinsho Byori 1999;47:408–16.
[22] Hwang KS, Kim G-H. Thiazide-induced hyponatremia. Electrolytes Blood Press 2010;8(1):51.
[23] Tejedor A, Alexandru S, Tejedor Bravo M. Hiponatremia postquirúrgica. Nefrología 2011;2(6):35–47.
[24] Grikiniene J, Volbekas V, Stakisaitis D. Gender differences of sodium metabolism an hyponatremia as an adverse drug effect. Med Kaunas 2004;40(10):935–42.
[25] Ayus JC, Wheeler JM, Arief AL. Postoperative hyponatremic encephalopathy in menstrual women. Ann Intern Med 1992;117:891–7.
[26] Liamis G, Millionis H, Elisaf M. A review of drugs-induced hyponatremia. Am J Kidney Dis 2008;52:144–53.
[27] Rowe JW, Shelton RL, Helderman JH. Influence of the emetic reflex on vasopressin release in man. Kidney Int 1979;16:729–35.