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ICU acquired hypernatremia treated by enteral free water – A retrospective cohort study

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ABSTRACT

Purpose: ICU acquired hypernatremia (IAH) is associated with increased morbidity and mortality, however treatment remains controversial. This study aims to determine the effect of enteral free water suppletion in patients with IAH.
Materials and methods: Retrospective single center study in a tertiary ICU. Inclusion criteria: patients with IAH and treatment with enteral free water. Exclusion criteria: patients with renal replacement therapy, diabetic ketoacidosis or hyperosmolar hyperglycaemic state. Primary outcome: change in plasma sodium (in mmol/l) after 5 days treatment. Responders were defined as patients with a decrease in sodium level of 5 mmol/l or more.
Results: In total 382 consecutive patients were included. The median sodium level at the start of water therapy was 149 mmol/l (IQR 147–150). The median volume of enteral water was 4423 ml (IQR 3349–5379 ml) after 5 days and mean sodium decrease was 1.87 mmol/l (SD 4.84). There was no significant correlation between the volume of enteral water and sodium decrease ($r^2 = 0.01$).
Conclusions: Treatment with enteral free water did not result in a clinically relevant decrease in serum sodium level in patients with IAH. In addition, the volume of enteral free water and the use of diuretics was unrelated with sodium change over 5 days.

1. Introduction

Disorders of sodium concentration occur frequently in critically ill patients with a clear shift in incidence in the last 2 decades from hyponatremia to hypernatremia [1,2]. Hypernatremia is often not present on ICU admission but develops during ICU treatment. This so called ICU acquired hypernatremia (IAH), defined as plasma sodium >145 mmol/l, occurs in 4.3%–26% of critically ill patients [3,4]. IAH can be linked to a wide range of symptoms: neurologic due to brain cell shrinkage but also cardiologic due to impaired left ventricular contractility and metabolic due to disturbed glucose utilisation [5]. It is associated with increased morbidity, length of ICU and hospital stay and is identified to be an independent predictor of mortality [3,6,7]. The timing of development of hypernatremia is important, since the acquirement on ICU suggest an iatrogenic- and thus preventable cause. Therefore, already 20 years ago IAH was proposed as an indicator of quality of care [8]. The development of IAH is thought to be multifactorial in critically ill patients with a combination of causes as fever, acute renal failure, polyuria, diarrhoea and infusion of hypertonic solutions in the resuscitation phase [9]. Also, the increasing use over the last decades of hydrocortisone treatment is suggested as a contributing factor [10].

The treatment of IAH is to this date controversial as is shown by a systematic review in 2018, which identified no RCT's on this subject [4]. To our knowledge, only one recent RCT is conducted for treatment of IAH, where hydrochlorothiazide compared to placebo showed no significant effect on serum sodium concentration [11]. The literature published on the treatment of IAH largely has a physiologic rationale of sodium overload or water deficit and therefore consists of correcting free water deficit [12-14]. Treating patients with solute poor or solute free solution poses a clinical dilemma because in patients with IAH hypervolemic hypernatremia is the most common type [15]. Correcting the supposed free water deficit is contributing to an even more positive fluid balance, while this is a risk factor after the resuscitation phase of extubation failure and is associated with mortality [16,17].

The sodium homeostasis in critically ill patients however, could be more complex than previously thought. Recent literature has shown that IAH is not explained by sodium overload or water deficit and

Abbreviations: CAH, Community acquired hypernatremia; IAH, ICU acquired hypernatremia.

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there is evidence of non-osmotic sodium storage in the muscles and skin [18-20]. Nevertheless, it is unclear whether the addition of enteral free water is effective in a complex homeostatic system of sodium regulation in critically ill patients. This study aims to evaluate the effect of enteral free water treatment on serum sodium levels in critically ill patients with IAH.

2. Methods

2.1. Design and setting

We conducted a retrospective single centre study from 2008 to 2019 in a tertiary ICU with mixed medical, surgical and cardiosurgical patients. The local ethical committee (ACWO OLVG) approved the study based on Dutch and European legislation. Informed consent was deemed unnecessary because of the retrospective design.

2.2. Patients

All consecutive adult ICU patients (18 years and older) treated with enteral free water were extracted from the ICU database (MetaVison®, iMDsoft Tel Aviv, Israel). We excluded all patients with a sodium level higher than 145 mmol/l on the day of admission and included all patients treated with enteral free water during the ICU admission for IAH. Patients with renal replacement therapy, diabetic ketoacidosis or hyperosmolar hyperglycaemic state were excluded for the analysis. Total sodium intake in mmol was calculated from enteral feeding and intravenous fluids. Neurosurgical patients or patients with traumatic brain injury are not admitted to this ICU. Enteral free water was administered at the discretion of the attending physician and, in all patients, given by continuous drip via the nasogastric- or postpyloric tube.

2.3. Outcome measures

Baseline characteristics were extracted from the ICU database which is routinely updated daily concerning severity of illness data. Primary outcome of the study was the delta sodium, defined as the change in plasma sodium (in mmol/l) after 5 days treatment with enteral free water. In addition, we defined clinically relevant responders arbitrarily as patients with a decrease in sodium level of ≥5 mmol/l over 5 days of treatment with enteral free water. The volume of enteral free water and total sodium administration over the study period were also recorded. In addition, the use of diuretics that are available in this ICU, furosemide and hydrochlorothiazide, was recorded as well to determine their effect on serum sodium level.

2.4. Statistics

Data were extracted from the ICU database and transferred to a SPSS 26.0 database (SPSS® Inc., Chicago Illinois, USA) and analysed using descriptive statistics. Normally distributed data are presented as mean and standard deviation (SD) and skewed data as median and interquartile range (IQR). For the comparison between responders and non-responders we used non-parametric tests, Fischer exact or Mann-Whitney *U* test where appropriate.

3. Results

A total of 409 consecutive patients were identified in the database and after exclusion 382 patients were included in the analysis (Table 1). The median sodium level at the start of water therapy was 149 mmol/l (IQR 147–150). The median total volume of administered enteral free water over 5 days was 4258 [3349–5378] after 5 days and the median decrease in serum sodium level over 5 days was 1.87 mmol (SD 4.84) and median − 2 [IQR -5 - +2]. Fig. 1 shows the distribution of the decrease in serum sodium level, a more or less normal distribution. Fig. 2 shows the scatter plot for the volume of enteral free water (x-axis) and the change in the serum sodium level (y-axis). The correlation coefficient is $r^2 = 0.01$.

We identified 96 responders (a delta sodium of 5 or more mmol/l reduction in serum sodium level over 5 days) and 286 non-responders (less than 5 mmol/l decrease). Sodium at the start of water therapy was median 150 mmol/l (IQR 148–152) in the responders and 148 mmol/l (IQR 147–150) in the non-responders ($p = 0.001$). These groups differ significantly in delta sodium over the study period (responders median − 7 mmol/l vs. non-responders 0 mmol/l). The non-responders only differed significantly for the 'highest SOFA during admission' (mean 10.9, SD 3.4) compared to mean 9.4 (SD 3.4; $p = 0.001$) for the responders. Severity of disease on admission measured by the APACHE IV score was not significantly different for responders compared to non-responders (median 0.34, IQR 0.16–0.57 vs median 0.39, IQR 0.21–0.64; $p = 0.23$). The total volume of enteral free water administered to the responders over the study episode was median 4169 ml and 4277 ml to the non-responders ($p = 0.64$). The sodium intake was comparable as well.

In the patients using furosemide ($N = 349$) on any day in the study episode their median delta sodium was −2.0 [−4 − +1] mmol/l compared to −3.0 [−7.5 − +0.5] mmol/l in patients without furosemide ($p = 0.126$). For patients with hydrochlorothiazide (HCT) treatment ($N = 63$) the median delta sodium was 0.0 mmol/l [−4 − +3] vs. −2.0 [−5 − +1] for patients without HCT ($p = 0.15$).

4. Discussion

This study shows that the administration of enteral free water to critically ill patients with ICU acquired hypernatremia did not result in a clinically relevant decrease in serum sodium level over 5 days. There was no correlation between the volume of administered enteral free water and the change in serum sodium concentration. Moreover, furosemide use was not associated to a more or less extensive decrease in sodium level. The same was true for hydrochlorothiazide.

To our knowledge, this is the first study in critically ill patients to address the treatment of IAH with enteral free water. Although not evidence based, in many ICUs the habit is to treat IAH by enteral free water. The purpose of this treatment is to provide free water which can be easily absorbed by the stomach and intestines, instead of infusing excessive hypotonic intravenous fluids. This was not studied prospectively in critically ill adults. However, in premature infants in neonatal ICU the literature shows limited effect for treatment of hypernatremia with enteral free water and is associated with intestinal morbidity [21,22].

In general, the treatment for adults with hypernatremia is largely based on the hypothesis of sodium overload or free water deficit [23] and originates from the treatment for community acquired hypernatremia (CAH). However, CAH could have a different etiology than IAH in critically ill patients [4]. It is known that net water loss accounts for the majority of cases in hypernatremia in the general population but in critically ill patients hypervolemic hypernatremia is the most common type [12,15]. In addition, the four currently available formulas to guide infusion therapy (Adrogué-Madias, Barsoum-Levine, Kurtz-Nguyen and a electrolyte-free water clearance formula) do not accurately predict the changes of serum sodium in the individual ICU patient [24].

This study shows a decrease in serum sodium in a some of the included patients (responders). The non-responders showed a significantly higher 'highest SOFA' score during admission but a non-significantly different APACHE IV score on admission. We hypothesise heterogeneity in the population of critically ill patients where a different etiology might need a different therapy. IAH may be a sign of severity of disease, which is supported by the significantly higher 'highest' SOFA score in the non-responders. Also accumulating evidence on a more

Table 1
Baseline characteristics.

	All patients (n = 382)	Responders (n = 96)	Non-responders (n = 286)	P
Age (years)	67 (11.6)	67 (12)	66 (12)	0.61
Male (N)	253 (66%)	58	195	0.17
SOFA score at the start of enteral free water	6 [4–8]	5.0 [4.0–7.0]	6.0 [5.0–8.0]	1.0
SOFA highest on admission	10.5 (3.5)	9.4 (3.4)	10.9 (3.4)	0.001
Type of admission	Medical 271 (71%)	70 (73%)	201(70%)	0.82
	Surgical 111 (29%)	26 (27%)	85 (30%)	
Reason for admission				0.30
General surgery	26 (7%)	7 (7%)	19 (7%)	
Cardiothoracic surgery	71 (19%)	15 (16%)	56 (20%)	
Sepsis	67 (18%)	16 (17%)	51 (18%)	
Pneumonia	80 (21%)	21 (22%)	59 (21%)	
Cardiac	73 (19%)	14 (15%)	59 (21%)	
Neurologic	12 (3%)	6 (6%)	6 (2%)	
Other	53 (14%)	17 (18%)	36 (13%)	
APACHE IV predicted mortality	0.39 [0.19–0.62]	0.34 [0.16–0.57]	0.39 [0.21–0.64]	0.23
ICU mortality	95 (24.9%)	20 (21%)	75 (26%)	0.34
Hospital mortality	139 (36.4%)	35 (36%)	104 (36%)	
Fluid balance day 1–5 in ml	+786 [−1746 − +3865]	924 [−1465 − +3847]	761 [−1821–3883]	0.52
Volume enteral free water (ml)	4258 [3349–5378]	4169 [3579–5102]	4277 [3294–5466]	0.64
Creatinine at the start of enteral free water (umol/l)	74 [55–102]	68 [48–94]	73 [54–101]	0.16
Urea at the start of enteral free water (mmol/l)	11.4 [8–16]	8.8 [6.8–16]	11 [7.5–15.4]	0.29
Sodium at the start of enteral free water (mmol/l)	149 [147–150]	150 [149–152]	148 [147–150]	0.001
Total sodium intake day 1–5 mmol	860 [658–1130]	842 [563–1075]	880 [676–1143]	0.69
Delta Sodium in 5 days mmol/l	-2 [−5 − +2]	−7 [−10 - -6]	0 [−3 − +2]	0.00
With furosemide	N = 349	N = 85	N = 264	1
	−2 [−4 − +1]	−7 [−9.5 - -5]	0 [−2.8 − +2]	0.001
Without furosemide	N = 33	N = 11	N = 22	0.001
	−3 [−7.5 − +0.5]	−9 [−12 - -7]	−0.5 [−3 − +1.3]	

Data presented as mean (SD) or median [IQR]. *P* value represents responders vs non-responders.

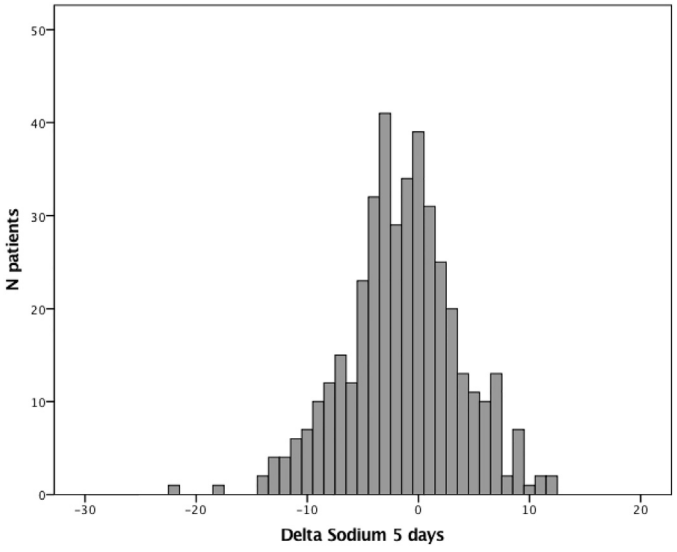

Fig. 1. Distribution plot with on the x-axis the delta sodium after 5 days in mmol and the number of patients on the y-axis.

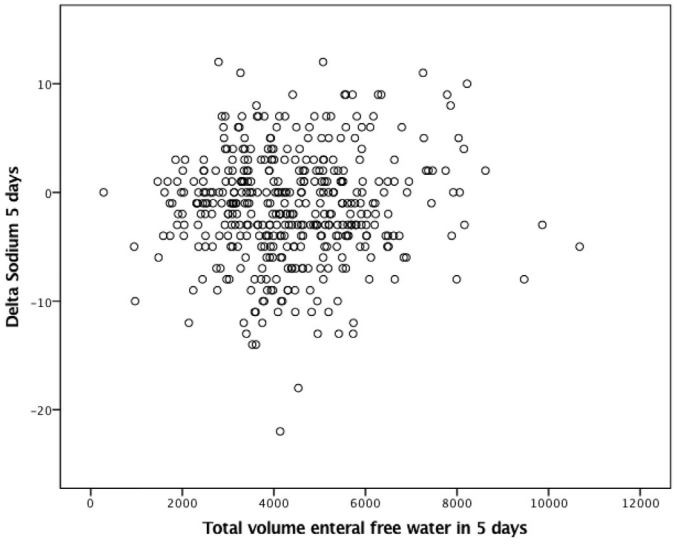

Fig. 2. Scatter plot for the volume of enteral free water in ml (x-axis) and the change in the serum sodium level in mmol (y-axis).

complex sodium homeostasis irrespective of volume status disturbs the old view on too much salt or too little water even more [18-20].

The concomitant use of diuretics did not lead to a decrease, nor to an increase in serum sodium. This is in concordance with a previously published paper that shows that hydrochlorothiazide in critically ill patients did not reduce serum sodium concentration [11]. This could be explained by an impaired renal sodium excretion in spite of positive fluid balances. Moreover, there could be different pharmacokinetics and pharmacodynamics in critically ill patients. We found a trend but not a significant difference in total sodium intake in responders comparing to non-responders, however, precise water and sodium balances could not be calculated because urinary sodium values were not recorded. Additional studies should be performed to investigate the effect of enteral free water treatment in combination with diuretics on serum sodium.

The association with IAH and morbidity and mortality has been shown previously, it is however difficult to determine if this is can be attributed to hypernatremia or the underlying disease. A study by Hoorn et al. showed that patients with IAH were generally sicker already on admission with a higher APACHE II score [7]. Moreover, co-existing with hypernatremia could be a chloride- and fluid overload, which are by themselves associated with detrimental outcomes [25]. Since prospective studies are lacking, it is unclear if treating IAH could improve

outcomes. Some authors suggest that hypernatremia is linked to the immune system and storage of sodium in the skin could facilitate antimicrobial host defense to serve as protection [26]. Treating this hypernatremia, which could be an immunological defense mechanism in inflammatory states such as infection could harm instead of help critically ill patients [27]. In addition, intracellular osmolyte formation may need hypertonic extracellular fluid to maintain cell integrity. Future research should clarify these hypotheses.

This study is limited by the retrospective design and the single-center approach. Also, the delta sodium of 5 mmol/l was an arbitrarily chosen value. It is unknown whether the provision of a larger volume of enteral free water or longer treatment could result in a lower serum sodium. In addition, taking into account the volume of distribution of free water, large volumes are probably necessary to have any effect on IAH. This is could result in even more detrimental clinical outcomes since a positive fluid balance after resuscitation phase is associated with mortality. [16,17]. In the present study no correlation was present between the volume of enteral free water administered and the change in serum sodium concentration. Nevertheless, we report unique data on the absence of effect of treatment on hypernatremia in critically ill patients. A prospective study on enteral free water treatment for IAH is needed to confirm these results.

5. Conclusions

Treatment with enteral free water did not result in a clinically relevant decrease in serum sodium level in critically ill patients with hypernatremia. Furosemide and hydrochlorothiazide did not determine the changes of serum sodium during ICU stay in patients with IAH. In addition, the volume of enteral free water was unrelated with the change of sodium over 5 days.

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None

Authors' contributions

P.H.J. van der Voort and E.A.J. de Vos contributed equally to this work.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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