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Hydrochlorothiazide in intensive care unit–acquired hypernatremia: A randomized controlled trial☆,☆☆

Marjolein M.C.O. van IJzendoorn [a,b,*], Hanneke Buter [a], W. Peter Kingma [a], Matty Koopmans [a], Gerjan Navis [b], E. Christiaan Boerma [a]

[a] Department of Intensive Care, Medical Centre Leeuwarden, PO Box 888, 8901 BK Leeuwarden, the Netherlands
[b] Department of Internal Medicine, University Medical Centre Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands

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ABSTRACT

Purpose: Thiazides are suggested as a treatment for intensive care unit (ICU)–acquired hypernatremia (IAH). The primary aim of the study was reducing serum sodium concentration (sNa) in patients with IAH with hydrochlorothiazide (HCT) in comparison to placebo. Secondary end points were a difference in urine sodium concentration (uNa) and duration of severe IAH.

Materials: A monocentric, double-blind, placebo-controlled trial was conducted in 50 patients with IAH and urine potassium + uNa less than sNa in a spot urine sample. Patients were randomized to HCT 25 mg or placebo 1 qd for maximal 7 days. Patients on renal replacement therapy, on medication inducing diabetes insipidus, or with recent use of diuretics were excluded. *IAH* was defined as sNa of at least 143 mmol/L.

Results: At baseline, sNa and uNa were comparable between groups. During the study period, sNa decreased significantly with median 4 mmol/L in both groups, with no significant difference between groups ($P = .32$). Median uNa increased significantly in both groups (46 [16-86] mmol/L in the HCT-group; 20 [10-66]mmol/L in the placebo group), with no difference between groups ($P = .34$). Median duration of sNa of at least 145 mmol/L was 3 days in both groups ($P = .91$).

Conclusion: HCT 25 mg 1 qd did not significantly affect sNa or uNa in patients with IAH.

1. Background

Intensive care unit (ICU)–acquired hypernatremia (IAH) is a common finding with a reported incidence between 3% and 17% [1-8]. IAH has clinical significance because it is associated with prolonged length of stay in the ICU and higher morbidity and mortality [6-8]. IAH is supposed to stem mainly from disturbances in water and sodium homeostasis, including salt overloading and inadequate water administration [9-15]. As such, the traditional approach to reduce serum sodium concentration (sNa) in hypernatremic ICU patients is to reduce sodium intake and enhance (par)enteral water administration. Although this strategy is effective to some extent, it is of note that a systematic reduction in parenteral sodium intake was not associated with a reduction in incidence of IAH [2]. Moreover, water suppletion reduces sNa but does not interfere with potential other underlying mechanisms.

Impairment in renal excretion of cations was identified as one of the contributing factors leading to IAH [15]. To enhance sodium excretion, treatment with hydrochlorothiazide (HCT) has been suggested [9,15]. The expected rise in sodium excretion is due to inhibition of sodium reabsorption in the distal tubule and reduced free water clearance [16]. However, data on the effectiveness of HCT in the specific setting of IAH seem to be missing. To evaluate the effect of HCT treatment on sNa in IAH, a prospective, randomized, placebo-controlled clinical trial was conducted.

2. Materials and methods

2.1. Design and setting

This single-center, prospective, double-blind, randomized, placebo-controlled trial was conducted in a 20-bed mixed medical and surgical ICU in a tertiary teaching hospital. The primary aim of the study was to detect in patients with IAH a difference in reduction of sNa of at least 3 mmol/L after treatment with HCT in comparison to placebo. Secondary end points were the difference in renal sodium excretion, the duration of sNa of at least 145 mmol/L, and fractional sodium excretion (FE_{na}).

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* Corresponding author. Tel.: +31 623595600; fax: +31 58 2866715.
E-mail addresses: vanijzendoorn@kpnmail.nl (M.M.C.O. van IJzendoorn), hanneke.buter@znb.nl (H. Buter), w.p.kingma@znb.nl (W.P. Kingma), matty.koopmans@znb.nl (M. Koopmans), g.j.navis@umcg.nl (G. Navis), e.boerma@chello.nl (E.C. Boerma).

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Patients were included between September 2013 and April 2015. This trial consisted of 2 study arms. HCT (25 mg) or placebo was administered once daily via a nasogastric tube. HCT is not labeled for the use of lowering sNa, but hyponatremia is a well-known adverse effect of this drug. Patients were randomized by a list, generated by a dedicated pharmaceutical trial assistant, in blocks of 6 patients each to distribute patients on HCT or placebo equally during the study period. This randomization list was only available to the pharmaceutical staff responsible for the preparation of the study medication. Criteria for inclusion and exclusion are presented in Table 1. In this study, *IAH* was defined as a sNa of at least 143 mmol/L. This cutoff value was chosen because of the association with inverse outcome of even mild IAH as observed by Darmon et al [7]. The outcome "prevalence of more severe IAH (sNa ≥ 145mmol/L)" was added to investigate if HCT could be beneficial in preventing IAH from becoming more severe compared with placebo. Patients were screened for their eligibility to be enrolled in the study by spot urine samples. Patients were considered eligible in case urine sodium concentration (uNa) plus urine potassium concentration did not exceed sNa. Informed consent was obtained from the patient or next of kin in compliance with applicable laws. The study protocol was approved by the local ethic board and registered at clinicaltrials.gov (NTC01974739) and Eudract (2013-002165-19).

2.2. Data collection

Collected baseline parameters included demographic data, diagnosis and severity of illness on admission, serum electrolyte concentrations, and data concerning renal excretion. Study medication was administered at 6:00 PM, after which collection of 24-hour urine started for the duration of the study period. During the study period, electrolytes were measured routinely 4 times a day by point-of-care testing (ABL800 AutoCheck; Radiometer Pacific Pty Ltd, Australia and New Zealand). Serum creatinine and urea concentrations were routinely measured once daily. FE_{na} was calculated according to Eq. (1). In addition, collected data included fluid balances, dose and kind of administered diuretics, gastric retentions, and severity of illness. All patients with gastric retention greater than 150 mL per 6 hours over a period of more than 24 hours were equipped with a duodenal feeding tube. By protocol, administration of study medication was limited to a maximum of 7 days. Other reasons to end the administration of study medication were a sNa less than 139 mmol/L, the need for (unanticipated) renal replacement therapy, administration of more than 120 mg furosemide per day, and ICU discharge. A certain administered dose of furosemide was allowed to investigate the effect of HCT on IAH in common daily ICU practice. In this daily practice, prescription of other diuretics is very rare. In case sNa exceeded 149 mmol/L, glucose 5% was administered intravenously until sNa returned to less than or equal to 149 mmol/L. Hypokalemia (<3.5 mmol/L) was corrected by a nurse-driven potassium suppletion protocol. All clinical data were automatically stored in a patient data management system from which they were extracted into an anonymized database. No funding was received.

2.3. Statistical analysis

The power analysis was based on data previously collected in patients with sNa of at least 143 mmol/L in our ICU. Main goal was to detect a difference of 3 mmol/L in reduction in sNa between both groups with a power of 80% and α of 5%. Including correction for 2 dropouts per group, 25 patients were needed in both groups. Data were collected and analyzed in SPSS versions 19 and 20 (IBM, Armonk, NY) based on an intention-to-treat principle. Because the majority of variables was not normally distributed, data are expressed as median (interquartile range [IQR]). Analyses were conducted using Mann-Whitney *U* testing for independent variables, Wilcoxon signed rank test for dependent variables, and Fisher exact test to compare percentages. Outcomes were considered significant at $P \leq .05$. Effect sizes were calculated according to Eq. (2).

Eq. (1): Fractional sodium excretion:

$$\text{FEna}\ (\%) = \frac{\text{uNa}}{\text{sNa}} \times \frac{\text{sCreat} \times 0.001}{\text{uCreat}} \times 100,$$

where FEna is fractional sodium excretion, uNa is urine sodium excretion in mmol/L, sNa is serum sodium concentration in mmol/L, sCreat is serum creatinine concentration in μmol/L, and uCreat is urine creatinine concentration in mmol/L.

Eq. (2): Effect size.

$$Z/\sqrt{n},$$

where Z = *Z*-score and n = number of observations

3. Results

3.1. Baseline characteristics

In the inclusion period, 2321 patients were admitted, of which 299 patients developed IAH (Fig. 1). Urine screening was performed in 116 patients. Main reason not to perform a screening spot urine sample was an expected length of stay in the ICU of less than 24 hours. Baseline characteristics did not differ significantly between groups (Table 2). In both groups, the study was terminated prematurely in 1 patient: 1 patient because of hypercalcemia, which was considered a contraindication of HCT, and the other because of the development of diabetes insipidus. Serum creatinine according to laboratory reference values for men and women was elevated in 13 patients in the HCT group and 8 patients in the placebo group (P = .25) [17].

3.2. Primary and secondary end points

Main results are shown in Tables 3 and 4 and Figs. 2 and 3. On the last day of the study, median sNa was 141 (137-147) mmol/L in patients treated with HCT and 144 (139-146) mmol/L in patients treated with

Table 1
Inclusion and exclusion criteria

Inclusion	Exclusion
ICU-acquired serum sodium concentration ≥ 143 mmol/L	Serum sodium concentration on ICU admission ≥143 mmol/L
Expected ICU stay >24 h	Central or nephrogenic diabetes insipidus
18 y of age or above	Severe hypokalemia
Indication of incapacity for renal sodium excretion: urine sodium + urine potassium < serum sodium concentration	Administration of lithium, amphotericin B, or agents affecting vasopressin receptors
	(Anticipation of) renal replacement therapy
	Diuresis <400 mL/d
Informed consent	Use of HCT <48 h previous to urine screen
	Use of loop diuretics <12 h previous to urine screen
	Intolerance to thiazides
	Pregnancy

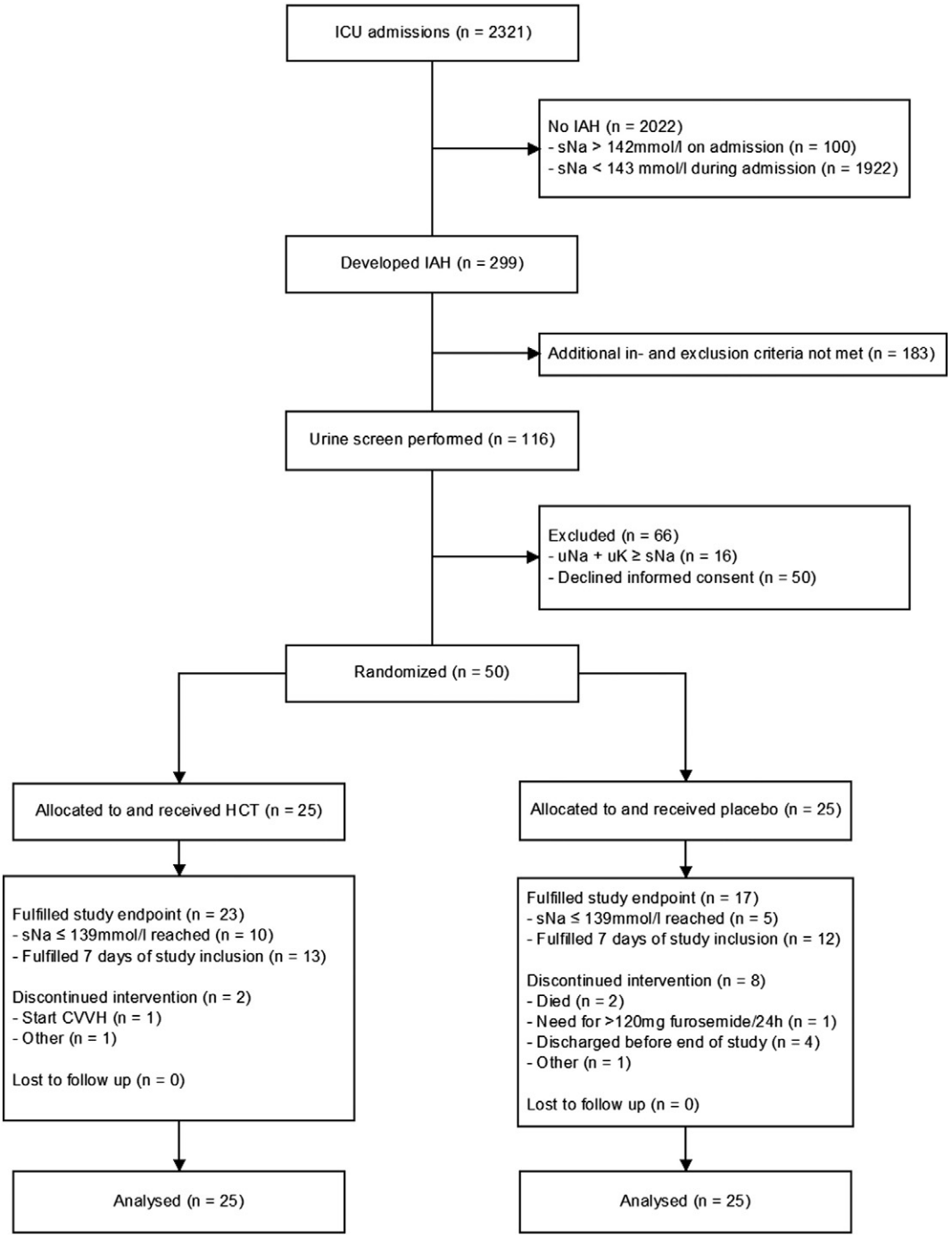

Fig. 1. Flow diagram study enrolment. uK indicates urine potassium concentration in mmol/L; CVVH, continuous venovenous hemofiltration.

placebo ($P = .30$). In comparison to baseline, median sNa decreased significantly over time by 4 mmol/L in both groups ($P < .01$). However, the decrease in sNa over time, which was the primary end point, was not different between groups ($P = .47$). If groups were divided into quartiles based on their sNa at study start (<144, 144-145, 146-147, or >147 mmol/L), still no differences in decrease of sNa occur. Median uNa at the end of the study was 110 (70-124) mmol/L in the HCT group and 84 (52-126) mmol/L in the placebo group ($P = .40$). In comparison to baseline, median uNa increased significantly over time by 46 (26-86) mmol/L in patients treated with HCT and 36 (9-78) mmol/L in patients on placebo ($P < .01$). However, this increase did not differ between groups ($P = .70$). Median duration of sNa of at least 145 mmol/L was 3 days in both groups ($P = .91$).

Median FE_{na} at baseline was 0.44% (0.17%-1.09%) in the HCT group and 0.36% (0.19%-0.89%) in the placebo group ($P = .69$). At the end of the study, median FE_{na} was 1.23% (0.62%-2.12%) in the HCT group and 0.89% (0.44%-1.28%) in the placebo group ($P = .09$). Median increase in FE_{na} over time was 0.96% (0.14%-1.47%) in the HCT group, which is a relative increase of 257% (27%-487%). This increase in the placebo group was 0.40% (−0.01% to 0.90%), which is a relative increase of 125% (−2% to 298%) ($P < .01$). However, there was no significant difference in both absolute ($P = .53$) and relative ($P = .19$) increase in FE_{na} between groups. Effect sizes of both HCT and placebo on decrease of sNa and increase of uNa and FE_{na} did not exceed 0.5. Median serum glucose concentrations were on most study days between 7 and 7.5 mmol/L and did not differ between groups.

Table 2
Baseline characteristics

Variables	HCT (n = 25)	Placebo (n = 25)	P-value
Age, years	65 [58–71]	67 [57–77]	0.58
Male, n (%)	21 (84)	15 (60)	0.06
BMI	27.3 [25–31.2]	27.6 [22.4–34.4]	0.99
Reason for ICU-admission, n (%)			
(Complications after) cardiothoracic surgery	2 (8)	5 (20)	0.20
Post resuscitation	2 (8)	3 (12)	
Sepsis	6 (24)	10 (40)	
Respiratory failure	8 (32)	5 (20)	
Miscellaneous	7 (28)	2 (8)	
APACHE IV-score on admission	93 [73–119]	78 [67–99]	0.07
SOFA-score on admission	8 [8–11]	8 [5–11]	0.20
SOFA-score on study start	6 [4–9]	5 [3–7]	0.10
Days until study inclusion	5 [3–7]	8 [5–15]	0.14
Serum [Na^+] on admission, mmol/l	138 [134–139]	138 [136–141]	0.40
Serum [Na^+] on study start, mmol/l	146 [145–148]	146 [144–150]	0.96
Serum [creat] on study start, μmol/L	84 [72–148]	81 [69–108]	0.10
Serum [urea] on study start, mmol/l	14 [9–23]	13 [10–16]	0.14
Urine osmolality on study start, mosm/kg	613 [473–804]	570 [506–710]	0.68
Urine [Na^+] in screening sample, mmol/l	25 [10–62]	20 [10–66]	0.80
Urine [K^+] in screening sample, mmol/l	40 [29–49]	36 [28–50]	0.89
Urine [Na^+] on study start, mmol/l	48 [23–80]	39 [21–82]	0.60
Fluid balance on study start, L	2.3 [−1.2–7.1]	1.1 [−2.2–4]	0.16
Duration of study, days	7 [4–7]	6 [4–7]	0.64
Total ICU length of stay, days	21 [13–30]	24 [14–35]	0.53

No adverse effects of study medication were reported. During or shortly after the study period, 4 patients died, of which 3 were in the placebo group. All cases were reported to the local ethical board, who decided that it was most unlikely that these deaths were related to the study protocol.

4. Discussion

In this study, patients treated with 25 mg HCT once daily did not show a difference in the reduction of sNa compared with patients treated with placebo. In addition, no significant differences in renal sodium excretion, the duration of sNa of at least 145 mmol/L, and FE_{na} were observed. However, in both groups, sNa decreased and uNa increased compared with baseline.

These results do not seem to be in line with previous literature in which thiazides are suggested as treatment for IAH [9,15]. However, the recommendation to use thiazides for IAH do not seem to be based on solid data in the specific ICU setting. In general, such recommendations are based upon the presumed mechanisms of action and extrapolated from non-ICU patient populations. Indeed, in our study, a low renal cation excretion was found in 86% of all patients with IAH, whereas fluid balances were positive. This suggests a potential role of abnormal cation handling by the kidney in critically ill patients in the development of IAH. The question is why we did not observe a sodium-lowering effect of thiazides in our study. This effect was expected because of both the pharmacodynamics of thiazides and the various publications describing thiazide-induced hyponatremia in non-ICU patients [18-32].

When analyzing this discrepancy, several factors have to be taken into account. Firstly, the mechanisms of action of HCT could be altered in critically ill patients. HCT belongs to the group of thiazides. These drugs increase renal sodium and chloride excretion by blocking the sodium-chloride cotransporter (SCC), thereby interfering with reabsorption of these ions. The main site of action is the distal tubule [16,18,22,33]. Under normal circumstances, only 5% of filtrated sodium is reabsorbed in the distal tubule against 70% in the proximal tubule and 20% to 25% in Henle's loop. Nevertheless, blocking sodium reabsorption in the distal tubule is potentially effective because less compensating mechanisms to undo this effect are present [16]. However, our study population was characterized by a high incidence of acute kidney injury (AKI). Thirteen of 25 patients on HCT had elevated serum creatinine values after the initial fluid resuscitation, whereas serum creatinine even underestimates the incidence of AKI [34]. Reduction of glomerular filtration rate is a hallmark of AKI [35]. As a consequence, the absolute sodium content per time in the distal tubule may be diminished, conceivably interfering with the net effect of sodium reabsorption blocking agents.

Factors influencing thiazides-induced reduction in sNa are extensively described in light of thiazide-induced hyponatremia and include

Table 3
Main study results at last day of study inclusion

Variables	HCT (n = 25)	Placebo (n = 25)	*P* value
Decrease in serum [Na^+], mmol*	4 (1-9)	4 (2-6)	.47
Serum [Na^+], mmol/L	141 (137-147)	144 (139-146)	.32
Increase in urine [Na^+], mmol	46 (26-86)	36 (9-78)	.31
Urine [Na^+], mmol/L	110 (70-124)	84 (52-126)	.34
Serum [creat], μmol/L	76 (46-147)	68 (58-83)	.49
Serum [urea], mmol/L	13 (8-21)	11 (8-12)	.27
Fluid balance at last day of study, L	−1.3 (−5.2 to 3.7)	−1.4 (−6.2 to 2.9)	.65
Mean dose of loop diuretics per study day, n, mg	13, 3 (0-13)	15, 6 (0-16)	.45

Data are expressed as median (IQR) unless stated otherwise. *P* value < .05 is considered as statistically significant. Fluid balance corrected for insensible loss of 500 mL/d since ICU admission. Dose of loop diuretics: total amount of administered furosemide during study period/days of inclusion.
* Primary end point.

Table 4
Decrease in serum sodium concentration compared with baseline, divided on serum initial sodium concentration

sNa at study start	HCT (n = 25)	Placebo (n = 25)	*P* value
<144 mmol/L, n	4.5 (0.75–9.25), 6	3 (2.25–6.75), 4	.76
144-145 mmol/L, n	4 (0–9), 11	5 (0.5–7), 9	.82
146-147 mmol/L, n	8 (1–11), 5	4 (1–5), 7	.11
>147 mmol/L, n	2 (1-.), 3	5 (1–6), 5	1

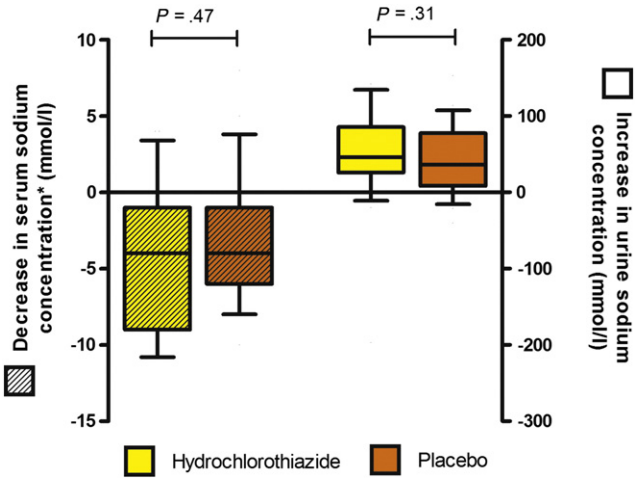

Fig. 2. Decrease in serum sodium concentration and increase in urine sodium concentration compared with baseline. *Primary end point.

impairment of free-water clearance and excessive anti-diuretic hormone (ADH) activity [20,23-27,30,31,36-37]. In the acute phase of critical illness, ADH activity is enhanced. Apart from blocking the SCC, the sNa-lowering effect of thiazides may additionally be attributed to a direct effect of thiazide diuretics on the plasma membrane expression of aquaporin 2 [30]. However, this is associated with water-intake–mediated weight gain, hampered by limited water excess of our patients, and expressed by the negative fluid balances at the end of the study.

Lastly, thiazide resistance, a compensatory mechanism by blocking of the thiazide-sensitive SCC, could have played a role [38]. However, so far, no data on thiazide resistance in relation to critical illness have been reported.

Our study has several limitations. We restricted our protocol to one particular thiazide and one specific dosage regimen of HCT. Based on the power analysis, our sample sizes were small but appropriate. However, these samples could have been too small to detect a relatively small difference in patients with borderline hypernatremia. On the other hand, the courses of sNa during the entire study duration seem to be similar. Many types of thiazides were developed differing mainly by their potency, but dose-response curves and chloruretic effects are comparable [22]. Although higher doses of HCT are considered safe and prescribed for other indications, no additional effect on electrolyte excretion could be expected [21]. However, patients with impaired renal function possibly need a higher dose of HCT to evoke an effect at its site of action in the kidney. HCT has a half-life of approximately 9 hours, so administering it twice daily could potentially enhance sodium excretion [28,32]. In our protocol, duration of treatment was limited to 7 days. This should be long enough to result in both lowering sNa and enhancing renal sodium excretion [19,21-23,28,37]. Based on the medication verification system in our patient data management system, only 2 patients missed 2 doses of medication, concerning 1 patient in both study groups. Adequate administration of study medication seems likely because only few patients had gastric retentions, of which all were fed by duodenal tube. Bypassing the stomach does not influence absorption of HCT because most resorption takes place in the duodenum and upper jejunum [19]. Administering HCT in our study was limited to patients with impaired renal sodium excretion. Therefore, its effect in patients without impaired renal sodium excretion needs further investigation. The use of loop diuretics is almost inevitable in the ICU setting and may interfere with HCT sodium reabsorption [39]. We carefully limited the use of loop diuretics by protocol, and its use was well balanced between groups. Finally, it is possible that IAH is not related to sodium intake or water balance, but so far, no data were available to establish this assumption.

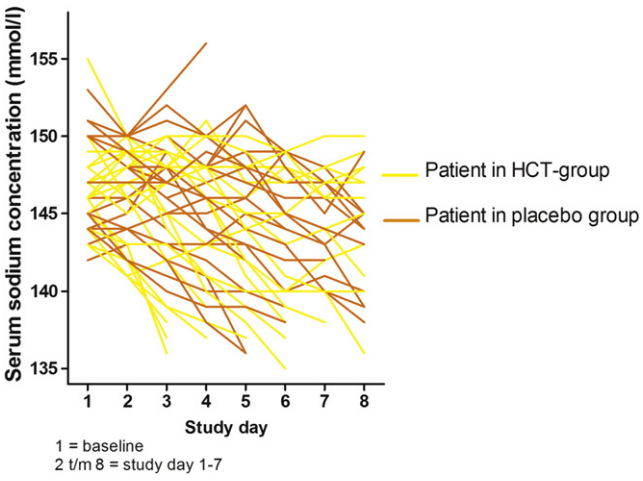

Fig. 3. Course of serum sodium concentration during study period, both groups.

5. Conclusions

In this single-center, randomized, placebo-controlled clinical trial, we could not identify a significant effect of enterally administered HCT 25 mg 1 qd on serum sodium reduction or renal sodium excretion in critically ill patients with IAH. These results warrant further investigations to unravel the etiology of impaired renal sodium excretion in IAH and the potential for therapeutic interventions.

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