Journal of Critical Care 38 (2017) 225–230

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

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

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ARTICLE INFO

Keywords:
Critical care
Hypernatremia
Sodium
Electrolytes
Thiazide diuretics
Hydrochlorothiazide

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}).

☆ Conflicts of interest: None of the authors have conflicts of interest.
☆☆ Financial disclosure: No funding was provided. None of the authors received financial support for contributing to the manuscript.

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http://dx.doi.org/10.1016/j.jcrc.2016.11.035

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