Impact of Hypernatremia on Patients with Traumatic Brain Injury

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Abstract

Background: Hypernatremia is frequently encountered in the neurocritical intensive care units (ICUs) and its effect can badly affect the mortality.

Objective: To verify whether the occurrence of hypernatremia during the ICU stay increases the risk of death in patients with severe traumatic brain injury (TBI).

Methods: Randomized prospective study; 100 patients with TBI in Neurocritical care units at Cairo University Hospitals. Hypernatremia is defined as serum sodium above 145 mmol/l. Logistic regression models were used to assess independent factors that could affect patients' mortality including hypernatremia, age, desmopressin and Glasgow Coma Score.

Results: We included in the study 100 TBI patients (mean age 35.8 ± 21.3 years); males 86%. Extradural hematoma (EDH) was documented in 27 pts (27%), subarachnoid hemorrhage (SAH) in 20 pts (20%), intracerebral hemorrhage (ICH) in 19 pts (19%), cerebral contusion in 17 pts (17%), brain oedema in 15 pts (15%) & acute subdural hematoma in 2 pts (2%). Glasgow Coma Scores (range 3 to 10); 60 pts were mechanically ventilated; 10% were diabetic & 22% hypertensives. Hypernatremia was documented in 40 pts (40%) of total 100 pts with TBI. The total in-hospital mortality was 36 pts 100 (36%), 10 of them had normal sodium levels all over of their in hospital course and 26 pts were hypernatremic. After adjustment for the baseline risk, the incidence of hypernatremia over the course of the ICU stay was significantly related with increased mortality (hazard ratio 3.2 (p:0.0001). However, there was positive correlation between serum sodium levels and duration of the ICU stay (Spearman correlation coefficient 0.5 and p value 0.002).

Conclusions: Hypernatremia in patients with severe TBI is associated with an increased risk of death and a longer ICU stay. This association is independent of other outcome predictors including age and Glasgow Coma Score. Strategies to prevent hypernatremia in neurocritical ICUs should be encouraged.

Key Words: Hypernatremia – Neurocritical ICU – Traumatic brain injury.

Introduction

HYPERNATREMIA, a water balance disorder encountered in about 6 to 9% of critically ill patients, has been associated with an increased risk of death and complications in some recent retrospective studies in general intensive care units (ICUs). Hypernatremia is associated with many adverse effects including, fever, generalized weakness, confusion, irritability, obtundation, seizures, coma and increased extent of intracerebral hemorrhage [1,2,3].

Patients with severe traumatic brain injury (TBI) have a high risk of developing hypernatremia over the course of their ICU stay, due to the coexistence of predisposing conditions such as impaired sensorium, altered thirst, central diabetes insipidus (CDI) with polyuria, and increased insensible losses. Moreover, these patients often receive mannitol or hypertonic saline solutions, with the aim of reducing cerebral edema and controlling intracranial pressure. In this clinical setting, it is not known, however, whether increased serum sodium (Na) is an independent risk factor for death, or is simply a surrogate marker of illness severity [4-6].

On the other hand, in a recent series of patients from a neuro-ICU, hypernatremia was documented in only 8% of them; moreover, only the more advanced forms of this disorder (that is, serum Na exceeding 160 mmol/l) were associated with increased mortality [6,7]. These conflicting findings leave the question of the true clinical significance of moderate increases in serum Na (for example, between 145 and 160 mmol/l) unresolved.

Aim of the study:

We designed the present study in order to verify whether the occurrence of hypernatremia during
the ICU stay is an independent risk factor of death in patients with TBI.

**Material and Methods**

The study was designed as a prospective analytic study that enrolled 100 patients with TBI admitted to the neurocritical care units at Cairo University Hospitals in the period between (October 2007 and March 2008).

After permission of the local ethics committee and informed consent of patients' relatives of 1st degree, we prospectively collected data concerning demography, clinical and laboratory characteristics, prognostic factors and outcome, which were entered into an electronic database. For each patient, the following data were obtained at admission as age, sex, cause of admission classified by type of trauma, premorbid functional status, acute and chronic comorbidities, brain CT-scan data, Glasgow Coma Score, hemodynamics, respiratory status and mechanical ventilation, blood gases, serum electrolytes, serum glucose, hemoglobin, leukocyte and platelet counts, renal function, and urinary output. Additional data were collected on a daily basis: Serum electrolyte levels (all values, if more than one value was available), serum glucose, administered medications and fluids, including vasopressin and osmotic therapy (defined as the use of 3% or 5% saline or mannitol to treat cerebral edema or raised intracranial pressure), urinary volume, mechanical ventilation, and intracranial pressure (ICP) when available. Finally, data concerning ICU complications, ICU mortality and in-hospital mortality were also collected.

For the purpose of the analysis, the presence of hypernatremia was defined as serum Na >145mmol/l on at least two occasions during ICU stay.

**Data analysis:**

Data were statistically described in terms of range, mean ± standard deviation (± SD), frequencies (number of cases) and relative frequencies (percentages) when appropriate. Correlation between various variables was done using Spearman rank correlation equation for non normal variables. Logistic regression was used to determine independent factors for mortality. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

**Results**

**Clinical characteristic of the study population, follow-up and mortality:**

We enrolled 100 patients with severe TBI. The characteristics of the population in our study are summarized in Table (1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35.8±21.3 years</td>
</tr>
<tr>
<td>Sex (M/F) ratio</td>
<td>86/14</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>(10/100) 10%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>(22/100) 22%</td>
</tr>
</tbody>
</table>

Sixty patients were mechanically ventilated, about 15 pts of them underwent tracheostomy. Only 55 patients (55%) suffered from an isolated TBI, while the remaining 45% of the others also had other involvements as limb or thoracic trauma. Twenty three pts experienced seizures, 10 of them had high serum sodium level and the rest of pts had normal serum sodium level. Extrudal hematoma (EDH) was documented in 27 pts (27%), subarachnoid hemorrhage (SAH) in 20 pts (20%), intracerebral hemorrhage (ICH) in 19 pts (19%), cerebral contusion in 17 pts (17%), brain oedema in 15 pts (15%) and acute subdural hematoma (SDH) in 2 pts (2%) Fig. (1).

CT scan at admission showed cerebral swelling with a midline shift in 30% of the patients, and cerebral herniation in about 12% of them. Twenty eight percent underwent neurosurgical emergent procedures after admission to the ICU. Only 10% of the patients were severely hypotensive at admission, but about one-half of them required vasopres sor administration during their ICU stay.
Of the 100 patients, 36 (36%) died in the ICU within 10 days after admission. 30 of the 36 deaths in the ICU occurred within 6 days after admission. The total in-hospital mortality was 36/100 (36%), 10 of them had normal sodium levels all over their in-hospital course and 26 patients were hypernatremic.

The mean serum Na on admission was 139 mmol/l (standard deviation 3.9). Only one patient (1%) had serum Na above 145mmol/l (value 147 mmol/l). Altogether, 40% of the patients during follow-up days were complicated by hypernatremia. In fact, the serum Na in patients with hypernatremia was, on average, 152.6±2.1mmol/l (range 148 to 161).

Polyuria >24 hours was detected in 12% of the 100 subjects and in the instances of ascertained polyuria, the mean urinary output was 4 l/day and the maximum being 9 l/day.

Twelve patients (12%) received desmopressin at least once over the course of their ICU stay. Patients receiving desmopressin had a higher urinary output and serum Na than those not receiving this medication (mean urinary output 3.7±0.6 Vs. 2.5±0.5 l/day, p<0.0001; mean serum Na 148±4.5 Vs. 142±3.4mmol/l, p<0.0001).

Mannitol was administered in 70% (70/100) of the patients for at least 24 hours (1-2gm/kg/d). No hypertonic saline solutions were administered. These interventions did not bear any apparent relation to serum Na or desmopressin administration.

The average of the daily mean serum glucose was 163gm/dl. Hyperglycemia occurred at least once in 30% of the patients during stay in the ICU. There was no significant difference in mean glucose levels and in the mortality rate.

Relation between hypernatremia and ICU mortality:

Hypernatremia was documented in 40 pts (40%) of total 100 pts with TBI, where it occurred in 14 pts in EDH (14/27=52%), 13 pts in SAH (13/20=65%), 8 pts in ICH (8/19=42%) and 5 pts in cerebral contusion (5/17=30%). The overall mortality in the 40 patients that developed hypernatremia was 26 (65%) versus 10 out of 60 pts (16.7%) who had no hypernatremia throughout their ICU course, so mortality was significantly higher in hypernatremic group (p-value 0.000).

Patients who died within the 1st week of their ICU stay had the highest increase in daily average serum Na. In fact, the 19 patients died on day 4 had a mean increase of serum Na of +3.7mmol/l, which was higher than that observed in the same period in the resting patients (+1.5mmol/l; p=0.020).

By logistic regression analysis of independent factors for mortality in the studied population, hypernatremia and renal impairment were the independent factors for mortality (p value 0.0001 and 0.03 respectively). Hypernatremia was associated with a threefold increase in the hazard of ICU death even after adjustment for baseline risk [hazard ratio=3.20 (95% confidence interval: 1.6 to 6.5; p=0.0001)].

There was a positive correlation with sodium levels and duration of the ICU stay as Pearson correlation coefficient was 0.5 and the p value was 0.002, and so the higher serum sodium levels the longer the ICU stay.

Discussion

This study shows that, in the immediate post-TBI period, mild hypernatremia is associated with an increased risk of death, although, in a proportion of the patients, this association is due to the occurrence of central diabetes insipidus (CDI), a marker of the extension and severity of brain injury [9]. In this study we couldn't use criteria of Agha and colleagues to define CDI in the immediate post-TBI as serum Na >145 mmol/l in the presence of both polyuria (>3.5 l/day) and diluted urine (osmolality <300 mOsm/l), as data on urine osmolality was not routinely measured. Our analyses, however, showed a CDI incidence of 12% (12/100); that is, comparable to the range of 15 to 26% documented by the previous studies on the subject [10-12]. This concordant finding suggests that in our series CDI was correctly classified. In another small series of TBI patients the incidence of CDI was much lower [13], probably owing to the exclusion of patients with incomplete data. Similarly to those studies, we found that CDI is associated with an increase in the severity of brain injury 10 and in the risk of death [13]. Finally, our analysis was adjusted for several factors potentially capable of confounding the relation between hypernatremia, CDI and mortality; namely, the use of hypertonic saline solution, intravenous mannitol, serum glucose levels, and the incidence of hyperglycemia [14,15].

Our results confirm the recent finding from Umberto, Venkatesh studies that confirmed that hypernatremia is an independent risk indicator of death [16].
The incidence of hypernatremia in our study (40%) is higher than that reported by Qureshi and colleagues (19%) [17] and that reported by Wartenberg and colleagues (22%) [18]. The latter two series, however, included patients with subarachnoid hemorrhage rather than with TBI; moreover, the study by Qureshi and colleagues defined hypernatremia by serum Na at admission or on day 3, and the study by Wartenberg defined hypernatremia as serum Na >150 mmol/l. Another study from a very large dataset (The Traumatic Coma Data Bank) reported an occurrence of electrolyte abnormalities in patients affected by TBI as high as 59%, with a peak incidence in the first 24 to 96 hours [19].

The definition of hypernatremia in our study refers to the first 14 days of ICU stay, and it is robust since it requires that at least two values of serum Na be >145 mmol/l in all patients receiving multiple daily determinations of serum sodium. Van Beek and colleagues recently examined the relation between serum Na and outcome using data from the IMPACT database [20]. Their analysis took into consideration only serum Na values at admission, however, not those obtained during the ICU stay. At variance with what is observed during the ICU stay, patients with TBI show hypernatremia only rarely at admission, which in fact was detected only in 5% of the patients of the IMPACT study and 1% in our study. In that setting Van Beek and colleagues defined high serum Na as Na levels above the 75th percentile, corresponding to 142 mmol/l [20] that is, a level lower than the standard cut-off value currently used for defining hypernatremia.

Finally, the relation between hypernatremia and mortality has been already documented in studies mostly dealing with patients in general ICUs [1,2], and not specifically including TBI patients. Even on the basis of the more recent literature, unfortunately based on retrospective studies only [1,3], it is not however possible to definitely exclude the possibility that hypernatremia in the ICU could simply be regarded as a surrogate marker of illness severity, rather than as an independent predictor of mortality. In the case of patients with TBI the interpretation of the relation between high serum Na levels and outcome is made even more difficult by the presence of peculiar interfering factors—such as for example CDI, and the use of hypertonic saline to control cerebral edema and elevated ICP [22,23]. In our study we did not use hypertonic saline and only 12% of patient diagnosed as CDI so we can say that the occurrence of hypernatremia is related to the severity of illness and could be an independent risk factor of mortality.

Conclusions:
Hypernatremia is associated with an increased risk of death in patients with severe TBI and a longer ICU stay. This association is independent of other outcome predictors, including age, Glasgow Coma Score and so Strategies to prevent hypernatremia in ICU should be encouraged.

References