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Research Article

Does hypernatremia impact mortality in Toxic Epidermal Necrolysis?

Wird die Mortalität bei Toxisch Epidermaler Nekrolyse durch eine Hypernatriämie beeinflusst?

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Abstract

Introduction: In-hospital hypernatremia is associated with increased mortality rates. We want to elucidate the impact of in-hospital acquired hypernatremia in mortality of Toxic Epidermal Necrolysis (TEN).
Purpose: Is there an association between hypernatremia and mortality in patients with TEN?
Method: Retrospective study of 25 patients with TEN. Laboratory electrolyte results, diuresis and survival were analyzed. Patients were separated in two groups without (Group A) or with (Group B) hypernatremia.
Results: In Group A 10 patients with a TBSA of 74±25% (mean ± standard deviation), and a SCORTEN-Score of 2.7±0.9 were summarized. Diuresis within the first 10 days after admission was 1±0.3 ml/kg/hour. In Group B 15 patients with a TBSA of 76±19%, and a SCORTEN-Score of 3.5±1 were included. Diuresis within the first 10 days after admission was 1.4±0.4 ml/kg/hour. Hypernatremia occurred on day 3.3±2.4 after admission and persisted for 5.3±2.9 days. Statistical analysis showed a significantly higher diuresis (p=0.007) and SCORTEN-Score (p=0.04) in the hypernatremic patients. One normonatremic and 8 hypernatremic patients died during ICU-stay (overall mortality rate 36%). A significantly higher mortality rate was found in Group B (odds ratio: 13,5; 95% confidence interval: 1.34–135.98; p=0.01) during ICU-stay.
Conclusion: TEN patients with an in-hospital acquired hypernatremia have an increased mortality risk. Close electrolyte monitoring is advisable in these patients.

Keywords: Toxic Epidermal Necrolysis, hypernatremia, intensive care

Zusammenfassung

Einleitung: Hypernatriämien gehen bei schwerstkranken Patienten mit einer erhöhten Mortalität einher. Die kausalen Zusammenhänge sind noch weitgehend unklar. Ziel dieser Studie war es festzustellen, ob hypernatriäme Patienten mit einer Toxisch Epidermalen Nekrolyse (TEN) eine erhöhte Mortalität aufweisen.
Material und Methoden: Retrospektive Studie an 25 TEN-Patienten. Es erfolgte die Differenzierung in normonatriäm (Gruppe A) und hypernatriäm (Gruppe B). Neben dem Serum-Natrium-Verlauf wurden die tägliche Diuresemenge und die Mortalitätsrate analysiert.
Ergebnisse: In Gruppe A konnten 10 Patienten mit einer Epidermolyse von 74±25% der Köperoberfläche (KOF) und einem SCORTEN von 2,7±0,9 eingeschlossen werden. Die Diurese innerhalb der ersten 10 Tage betrug 1±0,3 ml/kg/Stunde. In Gruppe B wurden 15 Patienten mit einer Epidermolyse von 76±19% der KOF und einem SCORTEN von 3,5±1 eingeschlossen. Die durchschnittliche Diurese innerhalb der ersten 10 Tage betrug 1,4±0,4 ml/kg/Stunde. Eine Hypernatriämie wurde am 3. ±2 Tage nach der stationären Einweisung manifest und persistierte für 5±3 Tage. Die statistische Analyse ergab eine signifikant höhere Diurese (p=0,007) und SCORTEN (p=0,04) in Gruppe B. Ein

normonatriämer and 8 hypernatriäme Patienten verstarben auf der Intensivstation. In Gruppe B wurde eine signifikant höhere Mortalität berechnet (Odds Ratio: 13,5; 95% Konfidenz-Intervall: 1,34–135,98; p 0,01).
Schlussfolgerung: Hypernatriäme Patienten, welche an einer TEN erkrankt sind, haben ein erhöhtes Mortalitätsrisiko. Eine engmaschige Kontrolle der Elektrolyte erscheint daher empfehlenswert.

Schlüsselwörter: Toxisch Epidermale Nekrolyse, Hypernatriämie, Intensivmedizin

Introduction

Toxic Epidermal Necrolysis (TEN) is a rare disease with an incidence of approximately 1–2 per million/year [1], [2]. Prodromi are unspecific symptoms like fever and malaise. TEN is clinically diagnosed by cutaneous erythema, progressive blistering, epidermolysis (>30% Total Body Surface Area (TBSA)), mucosal erosions, and/or ophthalmic affection. The cutaneous eruption is characterized by the Nikolsky sign, which is defined as epidermolysis with mobility of the affected epidermis upon healthy skin and epidermal detachment on the slightest friction [3]. Skin biopsy is the only reliable method to confirm the diagnosis of TEN (separation of the epidermo-dermal junction) in correlation with the macroscopic clinical presentation of the skin [4]. Burn center treatment is recommended in TEN-patients, because of the extensive cutaneous defects [5].
High mortality rates of TEN have been reported (14 to 70%) [6], [7], [8], [9]. The independent predictors of mortality in TEN are Age (>40 years), heart rate (>120/min), presence of malignant tumors, initial epidermolysis (>10% affected surface area), serum urea (>10 mmol/l), serum bicarbonate (<20 mmol/l), and serum glucose (>14 mmol/l). These variables are described by Bastuji-Garin et al. after evaluating epidemiologic and diagnostic parameters [10].
Hypernatremia (>145 mmol/) is a common electrolyte disorder characterized by a deficit of total-body water relative to total-body sodium [11]. Hypernatremia can result from water loss, or hypertonic sodium gain. It is almost never found in an alert patient with a normal thirst mechanism and access to water. The two main defense mechanisms against hypernatremia are thirst and stimulation of vasopressin release [12]. Hypernatremia can be classified according to the patient's volume status (hypovolemia, euvolemia, hypervolemia). In hypovolemic hypernatremia free water loss exceeds sodium loss, whereas patients with an euvolemic hypernatremic state have pure water loss without signs of hypovolemia. Hypervolemic hypernatremia, caused by a pure sodium overload is rare and frequently caused iatrogenically, by excessive sodium administration, overcorrection of hyponatremia, hypertonic dialysate, and hypertonic enteral or parenteral hyperalimentation. Noniatrogenic etiologies include various mineralocorticoid deficiencies, salt water neardrownings, ingestion of improperly prepared infant formula, and ingestion of salt tablets. Free water loss can result from extrarenal (i.e. sweating, burns, diarrhea, skin diseases) or renal (diuretics, severe osmotic diuresis, severe glucosuria in diabetics, or elevated urea in postobstructive diuresis) causes [12]. It is difficult to distinguish whether these high mortality rates are caused by the hypernatremia itself, the underlying disease process, or the sequelae of hypernatremia treatment [13].
In non-TEN critically ill patients an acquired hypernatremic state appears to be associated with increased mortality rates (range from 31% to 66%) [13], [14], [15], [16], [17], [18], [19]. We present a retrospective study to elucidate the impact of in-hospital acquired hypernatremia on mortality.

Materials and methods

Fifty-two patients with a severe cutaneous drug reaction were treated during the past 10 years. Twenty-five patients with TEN (epidermolysis >30% TBSA) were identified retrospectively. Patients with an epidermolysis <30% TBSA were excluded from this study, because of the lower severity of illness and to provide a better comparability in with previous studies in the TEN group. Hemodynamic monitoring was realized by continuous invasive blood pressure measurement. To achieve a balanced fluid regimen, urinary output, mean arterial blood pressure, and blood gas analysis were performed every 1–3 hours. Transdermal water loss (epidermolytic skin) was calculated with 40 ml/%-TBSA/day. Amount and type of infusate (Ringer's solution, glucose 5%) and/or diuretics (e.g. Furosemid) were adjusted to individual requirements. Hypernatremia was defined at serum sodium levels ≥146 mmol/l. Hypernatremia was treated immediately with an increased infusion rate of electrolyte free water (glucose 5%).
Statistics were performed with SPSS® 15.0 (SPSS Inc., Chicago, USA). To estimate significance Mann-Whitney-U- or CHI-square-test were performed. Results are written in mean value ± standard deviation. Survival was calculated using Kaplan-Meier method; logrank (Mantel-Cox) analysis was used to calculate statistical significance.

Results

25 (17 female; 8 male) patients with a mean age of 59±18 years, a mean epidermolysis surface of 76.4±19%,

Table 1: Patients characteristics divided in Group A (without hypernatremia) and Group B (with hypernatremia). 10-days-diuresis [ml/kg/hours], serum sodium level on admission [mmol/l], age [years], TBSA [%], SCORTEN-Score, mean amount of daily administered furorese [mg/day], mean daily infusion-diuresis-ratio (IDR) [ml] for two periods (day 1 to 4 and day 1 to 10) of each subgroup is displayed with values for mean, standard deviation (SD), minimum, maximum and p-value.

	Group A	Group B	p-value
Number of patients	10	15	
Age [years]	57±18	60±18	n.s.
Epidermolysis [%-TBSA]	74±22	76±19	n.s.
SCORTEN [count]	2.7±0.9	3.5±1	0.04
Diuresis [ml/kg/h]	1±0.3	1.4±0.4	0.007
Serum Sodium (admission) [mmol/l]	135±5	142±5	0.004
Furorese [mg]	11±13	14±10	n.s.
IDR (day 1 to 4) [ml]	1,440±601	1,737±748	n.s.
IDR (day 1 to 10) [ml]	1,528±742	1,930±618	n.s.

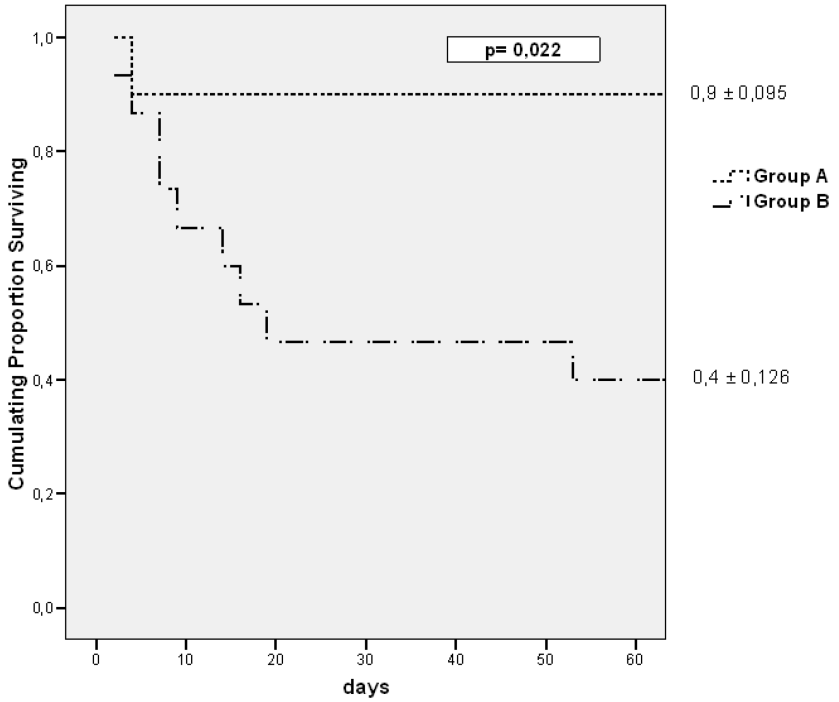

Figure 1: Survival curves according to the TEN patients with an in-hospital acquired hypernatremic state. The probability of hospital mortality over time was determined using Kaplan-Meier survival analysis. Logrank (Mantel-Cox) analysis evidenced a significant difference between Group A (normonatremic) and Group B (hypernatremic) curves.

and a mean SCORTEN-Score of 3.2±1 were included. Mean urinary output was 1.2±0.4 ml/hour within the first 10 days after admission. Patients were separated into two groups: Group A (without) and Group B (with) in-hospital acquired hypernatremia.

In Group A, 10 patients (5 female; 5 male) were summarized. Mean age, affected TBSA, SCORTEN, diuresis, serum sodium level (on admission), amount of furorese and daily infusion-diuresis-ratio (IDR) (for day 1 to 4 and day 1 to 10) are given in Table 1. Four patients showed a mucosal involvement. Mean creatinine (10 days after admission) was 65±27 µmol/l. Six patients (60%) did not receive any diuretic medication. There was no elevated serum sodium level in Group A within the first 10 days after admission.

In Group B 15 patients (12 female; 3 male) were included. Mean age, affected TBSA, SCORTEN, diuresis, serum sodium level (on admission), amount of furorese and daily IDR (for day 1 to 4 and day 1 to 10) are given in Table 1. Five patients showed a mucosal involvement. Mean creatinine (10 days after admission) was 93±49 µmol/l. Four patients (27%) did not receive any diuretic medication. Hypernatremia occurred on day 3.3±2.4 after admission and persisted for 5.3±2.9 days.

No significant differences in age, sex, affected TBSA, mucosal involvement and daily amount of furorese applied (over a 10-days-period) and daily IDR were found between Group A and Group B. Statistical analysis showed a significantly higher mean creatinine within 10 days after admission (p=0.025), higher diuresis (p=0.007), higher mean serum sodium levels on admission (p=0.004), and a higher SCORTEN-Score (p=0.04) in Group B (Table 1).

One normonatremic and 8 hypernatremic patients died during ICU-stay (overall mortality 36%). A significantly higher mortality rate was found in Group B (odds ratio: 13,5; 95% confidence interval: 1.34–135.98; p=0.01) during ICU-stay (Figure 1). 4 patients died in a septic state due to pneumonia, 2 patients died after myocardial infarction, and 1 patient died due to a pulmonary embolism. The remaining 2 patients died of multi-organ failure for which no pathologic mechanism could be identified.

Discussion

TEN is a rare, but life-threatening, exfoliative dermatitis, affecting the skin and mucous membranes. The large open surface caused by epidermolysis, leads to an enormous transdermal fluid loss of up to 4 liters per day [8]. In TEN, fluid regimen cannot be performed in a standardized way. The type and the amount of infusate need to be adjusted to individual parameters such as the extent of epidermolysis, body weight, and co-morbidities such as renal insufficiency, chronic or acute pulmonary disease and cardiac dysfunction. A well balanced infusion-diuresis-ratio has to be achieved and monitored vigilantly. Bastuji-Garin et al. described a scoring system (SCORTEN) that enables the physician to determine the severity of the illness and risk of death on admission of TEN patients [10]. Age, tachycardia, presence of malignancy, initial epidermolysis, serum urea, serum bicarbonate, and serum glucose have been shown to predict mortality in TEN [10]. In-hospital acquired hypernatremia is a common electrolyte disorder and is frequently caused iatrogenically [12], [20], [21]. Hypernatremia (>146 mmol/l) is a reliable marker for systemic dehydration [16]. Even a short period of hypernatremia may lead to an induction of apoptosis apart from its neurologic effects [22], [23]. Serum sodium is easy to evaluate in an ICU setting by blood gas analysis and provides additional information about the patients' systemic fluid status [24]. Patients admitted to an ICU have a higher incidence of hypernatremia compared to general hospital population and there is a strong correlation in peak serum sodium level and mortality [16].

In the study of Bastuji-Garin et al. [10] serum sodium imbalance (hypo- and hypernatremia) was shown to have a significant univariate association to patients' survival. Multivariate analysis failed to prove a hypernatremic state as an independent predictor of death. Hence, serum sodium imbalance was not included in the SCORTEN-formula.

The aim of our study was to elucidate the impact of hypernatremia in the mortality of TEN patients. Individuals with an epidermolytic surface <30% TBSA were excluded from this study. There was a significantly higher mean serum sodium level at admission in Group B (with hypernatremia), but only 2 individuals showed abnormally high values (>146 mmol/l). The other Group B patients showed normal serum sodium levels at admission. In-hospital acquired hypernatremia (Group B) occurred on day 3.3±2.4 after admission. The mean daily IDR for the two analyzed periods (day 1 to 4 and day 1 to 10) was higher in the hypernatremic subgroup, but statistical analysis did not show any significance. We registered a mortality rate of 36% in all analyzed TEN-patients, which is at the lower range of prior reported studies [6], [8], [9], [25]. Only 1 normonatremic individual died within 60 days after admission. 13 patients (52%) developed a hypernatremic state during Burn Unit stay. We registered a significantly higher mortality in hypernatremic patients than in normonatremic patients (Figure 1). The mortality rate of hypernatremic TEN patients (60%) was comparable to the results of other hypernatremic non-TEN studies (31% to 66%) [13], [14], [15], [16], [17], [18], [19].

We assume that patients with a TEN have an increased risk of systemic dehydration. One explanation may be the amount of transdermal fluid loss (epidermolysis >30% TBSA) and the painful limitation of oral feeding and fluid uptake due to erosive mucous membrane lesions. On the other hand, termination of the patient's prior medication at admission – as an elementary step in TEN treatment – can provoke alterations in urinary output. In our study a significantly higher diuresis was detected in patients with hypernatremia (Group B), but no larger amount of administered diuretics was registered. A hypernatremic state in TEN patients is a symptom, which may provoke severe complications such as an increased mortality. The reason for increased mortality in hypernatremic patients could not be identified in our study. Even previous studies, focused on hypernatremia and mortality, could not elaborate the specific mechanisms by which hypernatremia leads to increased mortality [13], [14], [15], [16], [17], [18], [19], [26]. There was a significantly higher SCORTEN at admission in Group B, which indicates an increased severity of illness in these patients compared to normonatremic patients.

We conclude that even in specialized Burn Units the incidence of hypernatremia in TEN patients is unavoidable. In case of a hypernatremic state early intervention is obligatory. Short interval blood gas analysis is advisable to register water imbalances early. An arterial line offers easy electrolyte control besides continuous blood pressure monitoring as well as control of pulmonary gas exchange parameters. In a life-threatening disease like TEN we strongly recommend this approach to optimize hemodynamic monitoring. Early transferral of TEN patients to regional Burn Units for critical care management and optimized wound care has been shown to have a positive effect on survival [5].

Limitations

In this retrospective study we analyzed only a small population of hypernatremic TEN patients. There was no standardized protocol for fluid administration protocol after admission. The collected values and findings only have an empiric character and should be investigated by prospective randomized clinical trials.

Competing interests

The authors declare that they have no competing interests.

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