Epidemiology and Clinical Outcome of ICU-Acquired Dysnatremia in critically ill Medical patients, a Single Center Study

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Abstract: Dysnatremias (hyponatremia and hypernatremia) are commonly encountered in ICU patients and are associated with adverse outcomes including mortality and prolonged LOS, but few studies have specifically investigated the epidemiology of dysnatremia in ICU, especially its association with mortality. **Aim** to assess the prevalence of ICU-acquired dysnatremia in medical ICU patients, and to find out risk factors of dysnatremia and whether it contributes to the risk of mortality and clinical outcome of medical ICU patients. **Methods** We identified 600 consecutive adults (18 years of age or older) admitted to medical ICU between March 2011 to August 2011 who were documented to have normal serum sodium levels (135 to 145 mmol/L) during the first day of ICU admission. ICU acquired hyponatraemia and hypernatraemia were respectively defined as a change in serum sodium concentration to below 135 mmol/L or above 145 mmol/L following day one in the ICU. **Results**: 132 patients (22 %) acquired dysnatremia of them, 111 patients (18.5 %) acquired hyponatremia, and 21 patients (3.5 %) acquired hypernatremia.. Also, the risk of developing hyponatremia is increased with increasing age more than 50 years, presence of fever, administration of hypotonic fluid therapy, use of diuretics, presence of renal impairment and advanced liver disease (RR 2, 2.7, 2.4, 4.8, 2.9, and 2.3 folds;respectively), and that for hypernatremia is increased only with increasing age more than 50 years, presence of fever,and presence of renal impairement (RR 3.23, 1.7, and 1.6 folds; respectively),whereas the use of diuretics, fluid therapy and advanced liver disease had protective effects (RR.2,.6, and.13, respectively). Compared with normonatremic patients, hyponatremia and hypernatremia in general were associated with increased ICU-mortality (RR 2.52, 3.1 folds, respectively),and with increased ICU-LOS (RR 1.8 and 2.1 folds, respectively). **Conclusions** ICU acquired dysnatremia is a common problem in medical ICU with higher prevalence of hyponatremia compared with hypernatremia, and is associated with increased LOS and of ICU mortality.

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1. Introduction

Sodium disturbances (dysnatremias) leading to hyponatremia and hypernatremia are a common problem in adult patients admitted to hospital and intensive care units (ICUs). In fact, the majority of these cases develop after the patient is admitted to the ICU. Because of their incapacitation, lack of access to free water, reliance on intravenous fluid and nutritional support, and the usually serious nature of their underlying disease which often leads to impaired renal water handling, patients in the ICU are at high risk of developing sodium disturbances. In many cases, the occurrence of the dysnatremia acquired in the ICU is largely preventable. Patients in the ICU are well monitored and blood samples are taken frequently. Furthermore, the maintenance of fluid and electrolyte balance is one of the focal points of critical care**[1]**.

The sodium disturbances, hyponatremia and hypernatremia, are among the laboratory abnormalities detected most frequently in patients admitted to intensive care. They are important markers of a critically ill patient's clinical status that often prompt changes to a patient's treatment, and they are associated with an increased risk of death**[2].**

Some studies have consistently demonstrated the common prevalence of acquired sodium disorders in the hospital and intensive care settings, and how it correlates with untoward outcomes. However **Eghitesadi-Araghi *et al.,*** demonstrated that both hypo- and hypernatremia were present on admission or developing during the ICU stay. These changes are independent risk factors for poor prognosis and the two devils; hyponatremia and hypernatremia can show the two faces to the same patients in the ICU **[3].**

A large proportion of medical ICU patients has abnormal values of serum sodium concentration. Some recent studies were done to incorporate serum sodium level in the scoring systems which evaluate the prognosis and risk of mortality in medical ICU patients **[4]**, the most common system is the 2nd version of, APACHE II (Acute Physiology Assessment and Chronic Health Evaluation) introduced in 1985. It generates a point score ranging

from o to 71 based on 12 physiologic variables, age, and underlying health. **[5].**

Few studies have been conducted to assess the prevalence of acquired sodium disturbance in medical ICU patients especially in relation to outcome, therefore, this study was conducted firstly to assess the prevalence of acquired sodium disorders in medical ICU patients who were admitted to medical ICU of Zagazig University within a period of 5 months,secondly to find out the most important factors causing changes in Na balance in the ICU and finally to determine the impact of acquired sodium disorders on the clinical outcome of medical ICU patients.

2. Subjects and Methods

The study was conducted from March to August 2011. The primary finding was ICU mortality and reduced length of stay. The hospital is a university hospital with 2090 beds located in Zagazig city, Sharkia Governorate, east of Egypt.

The medical intensive care unit of the Internal Medicine Department includes 44 beds. Patient admission includes cardiac, respiratory, neurological, gastrointestinal, endocrinological, and other miscellaneous medical emergencies

Study design: Observational, descriptive, cross-sectional study including patients with normal serum Na admitted to the medical intensive care unit of the Internal Medicine Department, Faculty of Medicine, Zagazig University in the period from March to August 2011.

Subjects: A total number of 774 patients with different medical disorders was admitted to our medical intensive care unit with documented normal serum sodium on admission during the study period. Patients were included in the study cohort if their ICU stay was longer than one day in duration and they were documented to have exclusively 'normal' serum sodium level with reference range (135 to 145 mmol/L) during the first day of their ICU admission. Hypernatremia was defined as a serum sodium concentration >145 mmol/L. Hyponatraemia was defined as a serum sodium concentration <135 mmol/L.

Exclusion criteria: Subjects with abnormal serum Na level at time of admission or within 24 hours of admission, patients who received renal replacement therapy during their ICU admission, patients who were <18 years of age, those without a valid APACHE II score, and those with missing sodium values were excluded, leaving 600 patients for analysis.

All serum Na values were adjusted for concomitantly measured serum glucose levels. If the glucose level was greater than 100 mg/dL, serum Na values were adjusted upward by 2 meq/L for each 100mg/dL increment in serum glucose **[6].**

History and clinical examination were recorded for all patients especially age, gender, presence of diabetes and other comorbid conditions, temperature, blood pressure, pulse, respiratory rate, Glasgow Coma Score (GCS), and APACHE II score **[5]**.

Laboratory data included CBC, serum albumin, serum ALT, PT, PTT, INR, urea, creatinine, random blood glucose. Arterial blood gases, serum sodium,and potassium. (Estimation was done by **Roche cobas b 121 system**, arterial blood gas and electrolyte analyzer **[7].**

The patients were further classified into three groups: hyponatremic, normonatremic, and hypernatremic according to further changes in their serum sodium levels during ICU stay**.**

Ethical clearance: informed consent from the patients' relatives was taken to participate in the study.

Statistical methods

All data were coded, checked, entered and analyzed using SPSS software version 17; variables are described as means and standard deviations (SDs). methods included the Chi-square test, ANOVA and relative risk (RR) and confidence intervals(CI). A *p* value <0.05 was considered statistically significant [8].

3. Results

This study was conducted for a period of 5 months in the medical ICU of Zagazig University hospitals. The total number of patients admitted in that period, and fulfilling the inclusion criteria, was 600. Out of them, 468 patients (78 %) maintained normal serum Na of (135- 145 meq/l) during their ICU stay. Hyponatremia (Na<135 meq/l, mean±SD 126.34±6.42 meq/l) developed in 111 patients (18.5%), and hypernatrmia (Na>145 meq/l, mean ±SD 151.34±6.42 meq/l) developed in 21 patients (3.5%).

The baseline characteristics of the study population (n=600) are summarized in Table(1), fifty-one percent (n=306) of the patients were female, forty-nine percent (n=294) of the patients were male.

Mortality The overall ICU mortality rate for the study population was 16%. Compared with patients with normal serum sodium levels, mortality was increased for patients with ICU-acquired hyponatremia and hypernatremia (Table 4).

Table (2) shows comparison of the mean values ± SD of scoring system of ICU and duration of stay in ICU among studied groups with statistically significant differences were found among studied groups as regards APACH II score and duration of stay in ICU.

Table (3) shows relative risk of developing hyponatremia in association with age more than 50 years, fever, fluid therapy, diuretics, renal impairment (s.creatinine >1.5 mg / dl), and advanced liver disease

(RR 2, 2.7, 2.4, 4.8, 2.9, 2.3 folds; respectively) and relative risk of developing hypernatremia in association with age more than 50 years, fever and, renal impairment (RR 3.2,1.7,and 1.6 folds, respectively), whereas hypotonic fluid therapy, diuretics, and advanced liver disease had protective effects (RR.2,.6, and.13, respectively).

Table (4) shows the frequency of dysnatremia and mortality in the study. Dysnatremia developed in 22% of patients with mortality of 28%, whereas mortality occurred in 10% of normonatremic patients.

Table (5) shows increased relative risk of mortality, and increased LOS with hyponatremia by 2.5, and 1.8 folds respectively, and with hypernatremia by 3.1, and 2.1 folds, respectively.

Table (1) comparison of the mean values of demographic, laboratory and clinical data of studied groups:

	Normal 468	Hyponatremic 111	Hypernatremic 21	f	*p*
Age (years)	60 ± 8.6	56.6 ± 6.8*	75.1 ± 9.3**	47.4	< 0.001
Male 294 (49%)	240 (81.7)	42 (14.3)	12 (4)	3.5	NS
Female 306 (51%)	228 (74.5)	69 (22.5)	9 (3)	3.4	NS
S.creatinine (mg/dl)	1.2± 1.1	1.48±.9*	1.62±.9*	10.6	< 0.001
Urea (mg/dl)	40.2 ± 24	49.2 ± 37.7	58.9 ± 33	2.2	NS
RBS (mg/dl)	110 ± 73.5	152 ± 67*	171.6 ± 99*	17.3	<0.001
Albumin (g/dl)	3.7 ± 0.84	3±.9	3.2±1	10.8	NS
HB g/dl	11.25 ± 2.1	11.6 ± 1.7	10.3 ± 2.98**	3.42	0.03
HR/m	78.5 ± 10.8	80.7 ± 7.1	78 ± 7.8	2.17	NS
RR/m	17.7 ± 1.3	17.4 ± 1.2	17.6 ± 1.2	1.55	NS
Temp c	37.4 ± 0.8	37.6 ± 0.7	38.1±.8**	3.36	0.035

Hb hemoglobin, HR:heart rate,RBG:random blood glucose,RR:respiratory rate, Temp: temperature. * significant compared to normonatremic, **significant compared to hyponatremic

Table (2) comparison of the mean values ± SD of clinical scoring system and length of stay in ICU in days, among studied groups:

	Normal	Hyponatremic	Hypernatremic	f	*p*
Apache II score	15.3 ± 7.4	22.9 ± 7.2*	24.4 ± 8.3*	15.5	<0.001
LOS	7.7 ±3.1	9.5 ± 4.8*	9.9 ± 5.6*	13.6	<0.001

* Significant compared to normonatremic.

Table (3): The risk of occurrence of hyponatremia and hypernatremia in ICU patients in association with different risk factors.

Variable	Hyponatremic RR (95%Cl)	*P* value	Hypernatremic RR (95%Cl)	*P* value
Age > 50 years	2 (1.33 to 3.23)	<0.001	3.2 (0.96 to 10.79)	.0574
Fever	2.7 (2.0 to 3.80)	<0.001	1.7 (0.58 to 4.83)	.333
Hypotonic IV fluid:	2.4 (1.70 to 3.41)	<0.0001	.2 (0.04 to 0.82)	.02
Diuretics	4.8 (3.37 to 6.86)	<0.0001	.6 (0.18 to 2.07)	.44
Renal impairment	2.9 (2.03 to 4.35)	<0.001	1.6(0.68 to 3.67)	.27
Advanced liver disease	2.3 (1.63 to 3.15)	<0.001	.13 (0.01 to 0.96)	.04

RR: relative risk,CI: confidence interval.

Table (4):Frequency of dysnatremia and mortality.

	Frequency, N (%)	Mortality, N (%)
Normonatremia	468 (78%)	50 (10.67%)
Hyponatremia (1)	111 (18.5%)	30 (27%)*
Hypernatremia (2)	21 (3.5%)	7 (33%)*
Dysnatremia (1)+(2)	132 (22%)	37 (28%)*
Total	600	87 (16%)

*Dysnatremia: hyponatremic and hypernatremic. * significant compared to normonatremic.

Table (5): The risk of increased length of stay and mortality in dysnatremic patients

	Hyponatremic		Hypernatremic	
	RR (95%Cl)	*P* value	RR (95%Cl)	*P* value
mortality	2.5 (1.69 to 3.78)	< 0.001	3.1 (1.61 to 6.03)	0.007
LOS	1.8 (1.11 to 2.8)	< 0.001	2.1(1.31 to 3.52)	< 0.001

4. Discussion

Dysnatremia is associated with substantial morbidity and mortality. The identification of risk factors associated with the development of dysnatremias is important in determining preventive strategies. Data on prevalence and clinical profile of hyponatremias are scarce, especially, in Egypt. We performed this study for evaluation of ICU-acquired sodium disturbances in critically ill medical patients.

We classified patients of the current study into 3 groups according to further changes of serum sodium level during ICU stay: always normonatremia, acquire hyponatremia, and acquire hypernatremia.

In this study, hyponatremia developed in 18.5% of patients.

Goh reported that hyponatremia developed in approximately 30% of patients treated in intensive care unit, and is associated with mortality increase of 7 to 60 % **[9]**. **Upadhyay** in another study obtained that hyponatremia occurred in about 30–40% of hospitalized patients, which is even higher than previous estimates **[10].** This variability of the prevalence in different centers may by due to interventions done to the patient in the ICU and may be due to severity and comorbidity of the original disease that may occur in the ICU**.**

Only 3.5% of our patients developed hypernatremia. **Iwasa, *et al.*, and Ishikawa, *et al.*,** found that hypernatremia was less common than hyponatremia with an incidence of around 1% across the spectrum of all patients**[11,12]**, while **Polderman, *et al.*,** reported that hypernatremia is relatively more common in neurologic and critically ill patients than in the general inpatient population, as water depletion is especially common in the intensive care setting, where a 9% incidence of Na > 150mmol/L has been reported **[13].**

In current study,we identified several patients characteristics that were associated with ICU acquired sodium disturbance, and could potentially be used to help clinicians to identify patients at increased risk. We found higher prevalence of hyponatremia (22.5%) among female patients compared to (14.3%) among male patients, this is in agreement with **Ayus and Arieff** who reported that the risk of developing hyponatremia and its complications is higher in women and children compared with men, and this is because of differences in respect of muscle mass, hormonal and anatomical factors **[14]**. Another study by **Goh** found that hyponatremia affects all races with no sexual predilection exists **[9].**

As regards the factors that may participate in the occurrence of dysnatremia in the current study, we found that the patients aging more than 50 years are at increased risk for development of hyponatremia and hypernatremia than younger patients,this is in agreement with **Goh** who found that hyponatremia is more common in the elderly population because of the increased incidence of co-morbid conditions (e.g, cardiac, hepatic, or renal failure) that can be complicated by hyponatremia **[9].**

We also found that patients with fever are at increased risk for devolopment of both hyponatremia and hypernatremia,this is in agreement with **Stelfox *et al.*,** who obtained that body temperature disturbances were associated with both ICU acquired hyponatremia and hypernatremia **[15].** Hyponatremia can be explained by profuse sweating associated with fever causing a form of volume depletion–related hyponatremia occurring as a result of loss of sodium and chloride in sweat or may be due to concomitant use of NSAIDs which can cause hyponatremia by inhibiting prostaglandin synthesis and potentiation on the tubular action of vasopressin **[16].** However, hypernatremia may be due to hypovolaemia and dehydration as in dermal losses (excessive sweating) or due to stress associated glucocorticoid excess in stressful situations **[17].**

As regards fluid therapy we found that patients on fluid therapy are at increased risk for development of hyponatremia by. This increased risk may be due to overuse of fluids especially hypotonic fluids and this was in agreement with what has been reported by **Steele *et al.*,** who found that hyponatremia can even develop if excessive near isotonic lactated Ringers is administered in the postoperative period if urine tonicity is higher **[18].**.On the other hand, fluid therapy did not increase the risk of development of hypernatremia, this was in agreement with that reported by others who found that hypernatremia only rarely does it represent salt excess, such as ingestion of salt or infusion of saline or hypertonic fluids **[18,19].**

In present study we found that patients on diuretic therapy are at increased risk for development of hyponatremia, this result is in agreement with other studies which reported that diuretics are associated with risk of hyponatremia through affecting sodium and water homeostasis **[20,21].**

As regards the role of renal impairment in relation to development of dysnatremias, we found that renal impairment increased the risk of acquiring hyponatremia and hypernatremia,this result was in agreement with **Schrier** who reported that, hyponatremia occurs commonly in both acute and chronic renal failure, because the kidneys cannot maximally excrete excess ingested or infused water **[22].** Another study reported that an elevated base line creatinine was associated with 50% increased risk of ICU-acquired hypernatremia which may be a marker

of impaired renal sodium and water regulation or decreased intravascular volume **[15].** This hypernatremia could be explained by either pure water loss in renal disease (e.g., medullary cystic disease), or hypotonic fluid loss as in renal causes e.g (post obstructive diuresis, polyuric phase of acute tubular necrosis, intrinsic renal disease), or hypertonic sodium gain as in hypertonic dialysis **[19].**

In this work, the association of serum sodium levels with the severity of the chronic liver disease in cirrhotic patients was evidenced by the increased relative risk (RR) of hyponatremia in patients with advanced liver disease by 2.27 fold, this was in agreement with **Upadhyay *et al.,*** who reported that hyponatremia occurs even more commonly in cirrhosis, in upwards of 30% to 35% of patients, particularly those with advanced chronic disease **[10].**

On determination of the impact of acquired sodium disorders on the clinical outcome of medical ICU patients, we found that hyponatremia and hypernatremia in general were associated with increased APACHE score, duration of stay in ICU, and increased risk of mortality, this was in agreement with another study which found that the length of stay and mortality in ICU and hospital were increased for patients with ICU acquired hyponatremia and hypernatremia compared with patients with normal serum sodium**[15]**,also in a retrospective one year study from dutch medical ICU, **Polderman *et al.,*** reported 32% hospital mortality for patients with ICU acquired hypernatremia **[13]**, but a third study in medical ICU in Austria, found a relatively higher incidence (39%) of hospital mortality for patients with ICU acquired hypernatremia **[23].**

In general we can conclude that ICU-acquired dysnatremia is a common problem in medical ICU with higher prevalence of hyponatremia compared with hypernatremia and many factors during ICU admission may participate in these acquired dysnatremia in ICU such as fever,comorbid conditions e.g renal impairment, advanced liver disease, diuretics use and, the frequent use of hypotonic fluids. Moreover, the acquired dysnatremia carries a negative impact on the course of original disease, hospital stay and mortality of the patients in ICU.

Frequent serum sodium monitoring is suggested for early detection of dysnatremia, and attention should be paid toward injudicious use of diuretics and hypotonic fluids in ICU. Further studies are needed to address the impact of the severity of dysnatremia on patient outcome, and to determine whether correcting the serum sodium level could improve clinical outcomes in ICU patients.

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