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ICU mortality is increased with high admission serum osmolarity in all patients other than those admitted with pulmonary diseases and hypoxia

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Summary at a glance

Increased admission serum osmolarity was associated with increased mortality in all patients except in patients with pulmonary diseases and hypoxia where this was not associated with increased odds for ICU mortality.

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ABSTRACT

Background and objective: High serum osmolarity has been shown to be lung protective. There is lack of clinical studies evaluating impact on outcomes such as mortality. We aimed to examine the effect of serum osmolarity on ICU mortality in critically ill patients

Methods: Data from January 2000 to December 2012 was accessed using the ANZICS CORE database. 509,180 patients were included. Serum osmolarity was calculated from data in the first 24 hours of ICU admission. Predefined subgroups (APACHE III diagnostic codes), including patients with acute pulmonary diagnoses, were examined. The effect of serum osmolarity on ICU mortality was assessed with analysis adjusted for illness severity (serum sodium, glucose and urea component removed) and year of admission. Results are presented as odds ratio (OR) (95% CI) referenced against a serum osmolarity of 290 – 295 mmol/l.

Results: The ICU mortality was elevated at each extremes of serum osmolarity (U-shaped relationship). A similar relationship was found in various subgroups, with the exception of patients with pulmonary diagnoses in whom ICU mortality was not influenced by high serum osmolarity and was different from other non-pulmonary sub-groups ($P < 0.01$). Any adverse associations with high serum osmolarity in pulmonary patients were confined to patients with a $\text{PaO}_2/\text{FiO}_2$ ratio > 200 .

Conclusion: High admission serum osmolarity was not associated with increased odds for ICU death, in pulmonary patients, unlike other subgroup of patients and could be potential area for a future interventional therapy.

Key Words: serum osmolarity, ICU mortality, pulmonary patients, $\text{PaO}_2/\text{FiO}_2$ ratio, APACHE III diagnostic codes, serum sodium, serum glucose, serum urea

Short title: Osmolarity doesn't affect lung mortality

Introduction

Acute respiratory distress syndrome (ARDS) is a common diagnosis in ICU patients, which bears a high mortality rate¹. Unfortunately, lung protective ventilation remains the only accepted efficacious treatment strategy so far². Hence the need for novel therapeutics option is imperative. Hyperosmolarity has been shown to be lung protective in multiple experimental and basic science studies of ARDS³⁻⁷. However, hyperosmolarity has not been associated with better clinical outcomes in patients with lung injury.

Similar to hyperosmolarity, induced hypernatremia has also been shown to be protective in acute lung injury, with proposed mechanisms being a decrease in cellular infiltrate⁸ and preservation of alveolar surfactant⁹. In keeping with this evidence, we observed previously that the phenomenon of increased intensive care unit (ICU) mortality with hypernatremia in an unselected cohort of patients, does not occur in patients with a pulmonary diagnoses, particularly those with $\text{PaO}_2/\text{FiO}_2$ ratios of less than 200¹⁰. These observations may be simply due to the fact that serum sodium is a major contributor to serum osmolarity.

In the current study we investigated the association of osmolarity with ICU mortality in critically ill patients. The research question was whether the mortality rate that is associated with high admission serum osmolarity, would be relatively lower in ICU patients with an acute pulmonary diagnoses.

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Methods

Data from January 2000 to December 2012 was accessed using the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS–APD)¹¹. During the study period patients with recorded sodium, glucose and urea measurements were included. The data included: age, gender, co-morbidities, physiological variables in the first 24 hours, calculated osmolarity (based on serum sodium, glucose and urea – high and low), ICU admission diagnoses, source of admitted patient - both for hospital and ICU, hospital characteristics, date of admission, ICU and hospital mortality rate and Acute Physiology and Chronic Health Evaluation III score (APACHE III). Study population was analysed by subgroups - : pulmonary and non-pulmonary, medical, surgical, cardiac, neurological, liver, sepsis, ventilated (invasive) and non-ventilated categories (based on APACHE codes). Serum osmolarity was calculated from the highest serum sodium, glucose and urea values within initial twenty four hours of ICU admission. Primary outcome was the effect of serum osmolarity on ICU mortality in patients with or without a pulmonary diagnoses, adjusted for illness severity (serum sodium, glucose and urea eliminated) and year of admission in patients with or without a pulmonary diagnoses. Severity of lung disease in pulmonary patients was stratified by admission $\text{PaO}_2/\text{FiO}_2$ ratio cut off of 200.

All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Logistic regression was used to study association between ICU mortality and serum osmolarity (categorical variable with 5 mmol/l increments). Multivariate models were adapted for centre, admission date, severity of illness and propensity to be admitted with a pulmonary diagnosis. Modified APACHE III risk of death score was obtained after removing components of sodium, glucose and urea. To adjust for potential differences between patients with a pulmonary diagnosis and those without, propensity score for pulmonary diagnosis was calculated for each patient (using logistic regression model and pulmonary diagnosis as the outcome). The propensity model was generated by stepwise selection method (inclusion cut off

P<0.01). Variables included were: patient source for hospital and ICU, hospital characteristics (level, location and care type), date of admission, age, gender, indigenous status and comorbidities. Results are presented as odds ratios (OR) (95% confidence intervals; CI) referenced for a serum osmolarity of 290 – 295 mmol/l. The methodology used was similar to the previously examined admission serum sodium in ICU patients¹⁰, however besides examining an extended study period (including two additional years of patients information gathering: 2011 and 2012) and a larger cohort of patients, sensitive tests like akaike information criteria for goodness of fit, area under the curve for discrimination and Wald Chi-Square statistic for interaction (all adjusted for site, severity, year & propensity for pulmonary diagnosis) were used to further differentiate between serum osmolarity and serum sodium as a predictor of ICU mortality for the separation of pulmonary and non-pulmonary patients. Southern Adelaide Human Research Ethics Committee South Australia (#285.13) approved the research proposal.

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Results

Patients aged more than 16 years and admitted to one of the 129 adult ICUs (26% rural, 22% metropolitan, 24% tertiary and 28% private) in Australia and New Zealand, and with a valid sodium, glucose and urea data, were included. Most of the hospitals (61%) had bed capacity of less than 300, whereas the rest had more than 300 beds. Initial search of the database for the period ranging from year 2000 to 2012 identified 888,519 patients with valid sodium, glucose and urea measurements. Of these, 509,180 patients meeting the screening criteria were included, and the rest were excluded due to missing mortality data ($n=19751$), missing severity of illness data ($n=75065$), stay in ICU < 4 hours ($n=18236$), age < 16 years ($n=18921$), transfer to another ICU ($n=2133$) and readmission during the same hospital admission ($n=175,233$) (Figure 1).

During the study period there were 55,711 pulmonary and 453,469 non pulmonary patients. The difference between pulmonary and non-pulmonary patient is shown in Table 1. Overall, ICU mortality rate incremented at each extreme of calculated serum osmolality. A similar relationship was observed in the subgroup populations, except patients with pulmonary diagnoses ($n=55,711$), in whom ICU mortality rate did not rise with increasing serum osmolality, and was different from other non-pulmonary sub-groups ($n=453,469$) ($P<0.001$) (Figure 2).

Patients with pulmonary diagnoses were subsequently analysed as those with admission $\text{PaO}_2/\text{FiO}_2$ ratio < 200 ($n=26133$) and ≥ 200 ($n=17787$). The $\text{PaO}_2/\text{FiO}_2$ ratio had a significant interaction with highest serum osmolality ($P<0.001$), suggesting that hyperosmolality associated mortality was further alleviated with hypoxia in greater severity of respiratory failure ($\text{PaO}_2/\text{FiO}_2 < 200$) and any adverse associations with high serum osmolality in pulmonary patients, were confined to patients with a $\text{PaO}_2/\text{FiO}_2$ ratio ≥ 200 (Figure 3). Similar results were seen with hospital mortality.

Serum osmolality was a stronger predictor of ICU mortality than serum sodium for the separation of pulmonary and non-pulmonary patients as evidenced by the akaike information for goodness of fit criteria (lower = better fit) (174223 vs. 174592; $P < 0.001$), area under the curve for discrimination (higher = better discrimination) (0.9154 vs. 0.9148; $P < 0.001$) and the Wald Chi-Square statistic for interaction (higher = increased significance) (196 vs. 149; $P < 0.001$).

Discussion

Adjusted ICU mortality, increased at both extremes of osmolality. However, in contrast, this relationship was not evident among patients admitted with acute pulmonary diagnoses. Unlike patients without pulmonary diagnoses, high serum osmolality in the first 24 hours of ICU admission was not associated with increased mortality in patients with acute pulmonary diagnoses. This discrepancy was more obvious in patients with severe derangement in oxygenation (admission $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 200).

To our knowledge this is the first clinical data consistent with the lung protective effects of hyperosmolality found in lab studies^{3-7,12-15}. The postulated mechanisms include a decrease in the expression of endothelial leukocyte adhesion molecules^{3,4}, attenuation of neutrophil lung sequestration⁵, blockade of pro-inflammatory effects of lipopolysaccharide^{4,6}, and remodelling of the endothelial barrier and the actin cytoskeleton, to enhance barrier properties and blockade of pro-inflammatory P-selectin expression⁷. Hyperosmolality can also up-regulate or down-regulate the transient receptor potential 4 ion channel, which plays a critical role in lung vascular mechanotransduction¹⁶. Activation of these channels particularly during hypo-osmolality¹⁷⁻²¹, can result in endothelial calcium influx and a rise in pulmonary vascular permeability¹⁶. Perhaps hyperosmolality can suppresses these channels, leading to a decrease in pulmonary vascular permeability, which may be beneficial in patients with lung injury. In our study, patients with hypoxia had the maximum benefit from high serum osmolality.

Administration of hypertonic saline leads to hyperosmolarity with effective hypertonicity and has been shown to rescue T cell suppression from trauma-induced anti-inflammatory mediators²², suppress neutrophil activation²³⁻²⁵ and decrease macrophage migration²⁶, preserve alveolar surfactant⁹, and attenuate pulmonary neutrophil sequestration^{8,23,27-31}; thereby ameliorating lung injury²³.

Serum sodium is a major contributor to serum osmolarity. In our study, osmolarity was a stronger predictor of ICU mortality than serum sodium for the separation of pulmonary and non-pulmonary patients. However, inducing hypernatremia is the most common, safe and feasible means of achieving hyperosmolarity in the clinical setting. There have been concerns around the *association* of hypernatremia and mortality in unselected cohort of patients³²⁻³⁷. However, based on our results¹⁰, previous animal studies^{8,9,27-31} and provided the hypernatremia is induced safely (i.e. shift of less than 12mmol in 24 hours), we anticipate there will be protective effect of hypernatremia in patients with acute lung injury. There are indirect clinical evidence to support this, in a study examining hypertonic resuscitation in patients with shock after blunt trauma showed improved ARDS-free survival among patients at risk for ARDS with massive transfusion³⁸. Similarly in a study examining resuscitation of pre-hospital post traumatic hypotension, acute lung injury was less common with hypertonic saline/dextran than with normal saline³⁹. The current study adds to the hypothesis that inducing hyperosmolarity by carefully inducing hypernatremia will result in amelioration of acute lung injury in critically ill patients. This hypothesis needs to be tested in a prospective controlled study.

Strengths and limitations

The study examined data from a large cohort of patients (n=509,180), derived from large multinational database. This minimizes bias and improves external validity of the study. The ANZICS database is routinely subjected to internal validation

processes and on-site audits by trained ANZICS auditors, suggesting that the calculated serum osmolarity values are likely valid. However, there are some limitations. Few patients had to be excluded because of missing data; however, they represented only 11% of the screened population. Being a retrospective study, interventions to induce high/low serum osmolarity before ICU admission could not be accounted for. Also data around subsequent changes in serum osmolarity (and its potential effect on outcomes) was not available. This should be evaluated in future studies. The broad category of 'pulmonary diagnoses' includes a range of pulmonary conditions, while hyperosmolarity may only benefit patients with lung injury. To study these patients (as these data are not routinely collected), we examined patients presenting with a pulmonary diagnoses and with hypoxia ($\text{PaO}_2/\text{FiO}_2 \leq 200$) in the first 24 hours using an interaction model, which revealed reduced risk of mortality with hyperosmolarity. Effect of hyperosmolarity in patients with ARDS should be a evaluated in future study. Finally although serum sodium has been previously examined as a predictor of ICU mortality and its differential effect on patients with respiratory diagnosis¹⁰, serum osmolarity has never been examined in ICU patients.

This study offers a novel and robust evidence for association between hyperosmolarity and amelioration of mortality risk in patients with pulmonary diseases. Induction of hyperosmolarity could be a potential intervention that needs to be studied further.

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Disclosure statement

Parts of this study were presented at the Annual Meeting of Australian and New Zealand Intensive Care Society (ANZICS) in 2014. Part of the methodology used in the manuscript similar to the previously examined serum sodium with ICU mortality in 2014.

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Figure Legend

Figure 1: Consort diagram of subjects examined in this study.

The study methodology is similar to the previously examined outcomes with serum sodium¹⁰

Figure 2: Adjusted odds ratio (shaded lines are 95% confidence intervals) of ICU mortality relative to 290 – 295 mmol/l for different categories of highest serum osmolarity in the first 24 hours in patients with pulmonary (dotted) or without pulmonary diseases (solid). The relationship between osmolarity and ICU mortality was significantly different between pulmonary and non-pulmonary patients ($P < 0.001$) in the first 24 hours of ICU admission.

Figure 3: Adjusted odds ratio (shaded lines are 95% confidence intervals) of ICU mortality relative to 290 – 295 mmol/l for different categories of highest serum osmolarity in the first 24 hours in pulmonary patients with $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 200 (dotted) and $\text{PaO}_2/\text{FiO}_2$ ratio > 200 (solid). The relationship between osmolarity and ICU mortality was significantly different in pulmonary patients between those with $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 200 and $\text{PaO}_2/\text{FiO}_2$ ratio > 200 ($P < 0.001$) in the first 24 hours of ICU admission.

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Table 1: Characteristics and outcomes of patients with non-pulmonary or pulmonary admission diagnoses

	Non-pulmonary (n =453,469)	Pulmonary (n=55711)	p-value
Age, mean (SD*)	61.6 (18.2)	61.7 (17.9)	0.30
Male gender, number (%)	26,8666 (59)	30,154 (54)	<0.001
APACHE [†] II score, mean (SD)	15.9 (7.6)	18.7 (7.8)	<0.001
APACHE [†] III score, mean (SD)	52.8 (27.7)	59.6 (27.0)	<0.001
SAPS [‡] II, mean (SD)	31.0 (16.2)	34.9 (15.6)	<0.001
ICU [§] LOS (hrs), median (IQR [¶])	43.4 [22.5-85.7]	76.4 [39.4-161]	<0.001
Physiological variables (first 24 hours)			
Highest MAP ^{**} , mean (SD)	98.1 (16.0)	100.0 (16.5)	<0.001
Highest heart rate, mean (SD)	99.6 (21.8)	113.0 (23.2)	<0.001
Highest temperature (°C), mean (SD)	37.3 (0.8)	37.5 (0.9)	<0.001
Highest sodium (mmol/l), mean (SD)	140.0 (4.5)	139.0 (4.9)	<0.001
Lowest sodium (mmol/l,) mean (SD)	137.0 (4.6)	137. 0 (5.1)	<0.001
Highest glucose (mmol/l), mean (SD)	9.7 (4.9)	10.2 (4.8)	<0.001
Lowest glucose (mmol/l,) mean (SD)	6.6 (3.1)	6.8 (3.2)	<0.001
Highest urea (mmol/l,) median (IQR)	6.2 (4.5-9.5)	7.6 (5.0-12.1)	<0.001
Lowest PaO ₂ /FiO ₂ ratio mean (SD)	293 (148)	197 (115)	<0.001
ICU mortality, number (%)	32632 (7)	7351 (13)	<0.001
Hospital mortality, number (%)	50985 (11)	11392 (20)	<0.001

Some previously reported variable outcomes remained unchanged since 2014¹⁰

* Standard deviation, [†] Acute Physiology and Chronic Health Evaluation, [‡] Simplified Acute Physiology Score, [§] Intensive Care Unit, ^{||} Length of stay, [¶] Interquartile range, ^{**} Mean arterial pressure

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Exclusion of patients

- Missing mortality data (n= 19751)
- Missing severity of illness data (n=75065)
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- Age < 16 years (n=18921)
- Transfer to another ICU (n=2133)
- Readmission due to same hospital admission (n=175,233)

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