SHORT REPORT

Osmolar gap in hyponatraemia: An exploratory study

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Abstract

Hyponatraemia has indeed been extensively studied from multiple angles, including volume status, tonicity, and aetiology; however, the specific consideration of the osmolar gap (OG) within the context of hyponatraemia and its potential impact on their overall outcomes received limited attention in research. The current study represents an effort to address this gap in our understanding.

This prospective exploratory study was conducted on adults aged 14 years and older at the Indus Hospital, Karachi, from 2017 to 2020. The study involved categorising severity of hyponatraemia and volume status. The osmolar gap (OG) was calculated and categorised as either increased (OG>10) or normal (OG<10).

Among the 262 patients included in the study, there were 139 females and 123 males. Elevated OG was observed in 141(53.8%) patients. There were 28 (10.7%) recorded fatalities and majority of these individuals had an elevated OG. These findings underscore the importance for clinicians to consider the osmolar gap when managing patients with hyponatraemia.

Keywords: Hyponatremia, Osmolality, mortality, Osmolar gap (OG).

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Introduction

Hyponatraemic patients have been extensively examined from various perspectives, including volume status, tonicity, aetiology, outcome, and more. However, they have never been scrutinised from the perspective of osmolar gap (OG) until now. Indeed, OG has typically been presumed to be either low or within normal range in such patients.[1] This assumption tends to hold true more frequently when it is not influenced by other factors, such as multiple comorbidities or advanced age.

Osmolar gap (OG) is typically described as difference between the measured osmolality and calculated osmolality. The calculated osmolality is derived from the traditional equation: 2xS.sodium (meq/L) + urea/2.14/2.8 (mg/dl) = RBS/18 (mg/dl).[2]

Conventionally, a cut-off value of 10 is used to determine whether the OG is elevated or not. However, this threshold has remained a subject of ongoing debate.[3]

While there is substantial body of literature on the osmolar gap (OG) in the context of conditions like alcohol poisoning, ketoacidosis, hyperlipidaemia, and paraproteinemia, there is limited available research when it comes to hyponatraemic patients.[4] The scarcity of material on this topic could be attributed, in part, to the preconceived notion among clinicians that hyponatraemia is associated with low or normal OG state.

Hyponatraemia itself does not directly contribute to an increased osmolar gap (OG) because the reduced sodium levels are factored into both calculated and measured osmolality when assessing OG. However, when a substantial OG is detected and it appears to have a notable impact on the patient's outcomes, this should prompt the clinicians to pay closer attention to this particular aspect of the patient's condition.[5]

Regrettably, in our clinical practice, OG has not received widespread attention, and its application has been primarily limited to emergency and critical care settings, where cases of unknown poisoning are frequently encountered. The current study aims to highlight this aspect, shedding light on a situation where an elevated OG may have significance beyond the conventional understanding of this role.

Material, Methods and Results

This observational study was conducted at the Indus Hospital, Karachi campus, from July 2017 to April 2020. The study included all adult patients (aged over 14 years) of any gender who were admitted under the care of various medical specialties, diagnosed with hyponatraemia (S. sodium<135 meq/L) at the time of admission or later during the hospital stay. The sole exclusion criteria applied was the individuals who declined to provide consent. The sample size was determined by considering the prevalence of hyponatraemia, aiming for a statistical power of 95% and setting a significance level (alpha value) at 0.05%.

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Patients' medical histories were documented, followed by thorough examination, with particular attention to assessing their volume status and neurological status, i.e. seizure, ataxia, or altered sensorium.

The severity of hyponatraemia was stratified as mild (S. sodium>130 to 135 meq/L), moderate (S. sodium<130 to >125 meq/L), severe, (S. sodium<125 meq/L). Various laboratoryparameters i.e., serum urea, creatinine, random blood sugar, spot urine sodium, potassium, chloride, serum, and urine osmolality were checked. OG was calculated by subtracting calculated osmolality from measured osmolality. The OG was further categorised as increased (OG>10) or normal (OG<10). Patient outcomes were assessed based on the improvement of sodium level, as well as whether the patient expired during the course of their hospital stay.

Statistical Analysis: Data analysis was conducted using SPSS version 21. Frequency and percentages were computed for all categorical variables, which included gender, comorbidities, severity and tonicity of hyponatraemia, volume status, osmolar gap, and outcome. For quantitative variables, such as age, S. sodium, urea, osmolality, random blood sugar, urine sodium, osmolality, measures of central tendency and dispersion were determined. Chi-Square tests were employed, as needed, to ascertain significant associations between various categorical variables and both the osmolar gap and the patient outcome.

In this study, 262 patients were enrolled, with 139(53.1%) being females and 123(46.9%) males. The mean age of the participants was54.1±16.3 years, and their average serum sodium, osmolality, and osmolar gap (OG) were 124.9±5.9, 295±36.6, and 17.5±32.4, respectively. Notably, 141(53.8%) of the patients had a raised OG, and 28(10.7%) expired during the study (Table.1). **Normal values:** Serum sodium (135 to 145 meq/L), Serum Osmolality275 to 295 mOsm/kg of water, Serum Osmolar Gap <10 mOsm/kg.

Patients with elevated OG exhibited higher osmolality than those with normal OG (312 vs. 270 mOs/L, p=0.019). Additionally, positive and statistically significant connection were observed between OG and hypertonicity, volume status, patient outcomes, and age, with p-values below 0.001, 0.008, 0.07, and 0.038, respectively. Furthermore, there were positive and statistically significant associations between OG and hypertonicity, volume status, patient outcomes, and age, with p-values of <0.001, 0.008, 0.07, and 0.038, respectively. However, no noticeable relation discernible associations were noted

Table-1: Characteristics of patients admitted with Hyponatremia (n=262).

	n (%)
Gender	
Male	123 (46.9)
Female	139 (53.1)
Comorbid	
DM	142 (54.2)
HTN	177 (67.6)
IHD	68 (26)
CKD	171 (65.3)
AKI	30 (11.5)
Tonicity of Hyponatraemia	
Hypotonic	81 (30.9)
Normotonic	66 (25.2)
Hypertonic	115 (43.9)
Severity of Hyponatremia	
Mild	85 (32.4)
Moderate	102 (38.9)
Severe	75 (28.6)
Osmolar Gap	
Raised	141 (53)
Normal	121 (46)
Symptoms of hyponatraemia	38 (14.5)
Outcome	
Discharge	234 (89.3)
Expired	28 (10.7)

DM (Diabetes Mellitus), HTN (Hypertension), IHD (ischaemic heart disease), CKD (chronic kidney disease), AKI (Acute Kidney injury).

Table-2: Co-relation of Lab Parameters with OG.

Lab Parameters	OG(>10) n (%)	OG(<10) n (%)	Total (100%)	*p*-value
Gender				
Male	68 (55.3)	55 (44.7)	123	0.71
Female	73 (52.5)	66 (47.5)	139	
Total	141 (53.8)	121 (46.2)	262	
Volume Status				
Normovolaemic	43 (63.2)	25 (36.8)	68	0.008
Hypovolaemic	58 (44.3)	73 (55.7)	131	
Hypervolaemic	40 (63.5)	23 (36.5)	63	
Total	141(53.8)	121(46.2)	262	
Tonicity				
Hypotonic	12 (14.8)	69 (85.2)	81	0.001
Normotonic	31 (47)	35 (53)	66	
Hypertonic	98 (85.2)	17 (14.8)	115	
Total	141 (53.8)	121 (46.2)	262	
Severity of Hyponatraemia				
Mild	47 (55.3)	38(44.7)	85	0.94
Moderate	54 (52.9)	48 (47.1)	102	
Severe	40 (53.3)	35 (46.7)	75	
Total	141 (53.8)	121 (46.2)	262	
Symptomatic Hyponatraemia				
Yes	16 (42.1)	22 (57.9)	38	0.15
No	125 (55.8)	99 (44)	224	
Total	141 (53.8)	121 (46.2)	262	
Outcome				
Discharged	120 (51.3)	114 (48.7)	234	0.02
Expired	21 (75)	7 (25)	28	
Total	141 (53.8)	121 (46.2)	262	

OG (Osmolar Gap)

between OG and gender, symptomatic hyponatraemia, of the severity of hyponatraemia. Notably, a significant majority of the patients who did not survive during the study 28(10.7%) had elevated OG 21(75%), and this finding was statistically significant, with a *p*-value of 0.017. (Table 2).

Discussion

In clinical practice, traditionally an elevated OG is primarily associated with detection of alcohol poisoning in emergency situation. However, it is now widely recognised that an increase in OG can result from factors beyond the ingestion of toxic alcohols.[6] In this prospective study of 262 hyponatraemic patients with various medical conditions and different levels of hyponatraemia, Osmolar gap was observed to be significantly elevated irrespective of the severity of hyponatraemia. Sadly, 28 (10.7%) patients could not survive, and it is worth noting that a significant number of them had elevated OG levels.

When dealing with patients exhibiting elevated OG levels, it's important not to narrow our focus to a single possibility or develop tunnel vision. An intriguing case report serves as an example, involving a diabetic patient using Metformin who displayed a notably high OG. Initially, the investigation primarily centred on the potential of alcohol poisoning. However, upon further examination, it was revealed to be a case of Metformin-associated lactic acidosis (MALA). MALA is a type-B lactic acidosis and its presence in critically ill patients increases mortality to a significant level.[6,7] Likewise, when in cases of ketoacidosis in patients who have alcohol overdose and an elevated OG, it is crucial not to automatically assume that the elevated OG is solely due to alcohol. It's not an uncommon to observe ketoacidosis or lactic acidosis along with an elevated OG in patients who have experienced alcohol overdose.[8]

The administration of contrast agents for both investigative and therapeutic purposes can elevate serum osmolality and potentially lead to acute kidney injury (AKI). In these cases, OG levels may be elevated and serve as an indicator of early warning sign of AKI. This phenomenon was observed in a study focused on contrast-induced AKI, where OG was assessed in all patients, revealing a significant association between elevated OG and the development of AKI.[9]

One of the reasons of apparently unexplainable raised OG among hyponatraemic patients is insoluble osmoles seen in critically ill patients. These osmoles come out of the cells in these severely ill patients, a phenomenon called sick cell syndrome.[10]

In the chronic kidney disease (CKD) dialysis population, OG has shown potential as a predictive tool for dialysis disequilibrium syndrome (DDS). A statistically significant difference in OG levels between pre-haemodialysis and post-haemodialysis stages has also been noted. Their findings suggested that OG could be used as a surrogate marker for dialysis adequacy, particularly based on the elevation of pre-dialysis OG levels normalising after dialysis.[11]

In the current study, no statistically significant association between OG and CKD was identified. This lack of significance could potentially be attributed to the variable degrees of hyponatraemia present in the patient population, which may have influenced the results.The presence of an elevated OG in a substantial number of patients and its statistically significant association with mortality is indeed a noteworthy finding. It calls for our attention to this often-underappreciated aspect of clinical assessment.

Conclusion

A significant number of patients with hyponatraemia are observed to have an elevated OG, and it is noteworthy that mortality rates tend to be higher among individuals with an elevated OG.

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Author Contribution:
SS: Concept, design, abstract, introduction, discussion, conclusion.
DK: Methodology.
SF: Discussion.
FR: Proofread, conclusion.
MOA: Referencing.
AR: Data analysis, results.