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Interval Change In Anion Gap As A Predictor Of Clinical Outcome In Patients With Shock: A Prospective Observational Study.

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Abstract

Background: An elevated serum anion gap is associated with adverse outcomes in critically ill patients. The prognostic significance of its interval change during early critical care, particularly among patients with shock, has been less well characterized. This study evaluated whether the change in anion gap over the first 24 hours was associated with mortality and duration of intensive care unit (ICU) stay. ***Methods:*** This prospective observational study was conducted in the ICU of Deenanath Mangeshkar Hospital and Research Centre, Pune, from June 2015 to May 2016. Two hundred patients with clinical features of shock requiring vasoactive medication were included. Patients receiving palliative care, those transferred from another hospital, and those with chronic kidney disease or chronic liver disease were excluded. Serum sodium, chloride, and bicarbonate were measured at admission and after 24 hours. Anion gap was calculated as Na − (Cl + HCO3). For consistency with the study's results, delta anion gap (ΔAG) was defined as admission AG minus 24-hour AG; therefore, a negative ΔAG represented a rise in anion gap over 24 hours. Associations with mortality and ICU stay were assessed using Fisher's exact test and chi-square test, with $p<0.05$ considered statistically significant. ***Results:*** Of 200 patients, 137 (68.5%) died. Septic and cardiogenic shock each accounted for 91 patients (45.5%). A negative ΔAG (<0) was observed in 89 patients, of whom 84 (94.38%) died. Mortality was 51.35% (38/74) among patients with ΔAG 0–5 and 40.54% (15/37) among those with ΔAG >5. The association between ΔAG category and mortality was statistically significant ($p<0.001$). Among survivors, ΔAG was also significantly associated with ICU length of stay ($p=0.036$); 40% of survivors with ΔAG <0 remained in ICU for >10 days compared with 11.1% with ΔAG 0–5 and 0% with ΔAG >5. ***Conclusion:*** In this single-centre prospective cohort, a negative 24-hour interval change in anion gap was strongly associated with mortality and longer ICU stay among patients with shock. Serial assessment of anion gap may provide a simple adjunct for early risk stratification. These findings require confirmation in larger, multicentre studies with adjustment for potential confounders.

Keywords: anion gap; delta anion gap; shock; mortality; intensive care unit; critical illness; prognosis.

INTRODUCTION

Shock is a life-threatening physiological state characterized by inadequate systemic tissue perfusion and impaired oxygen delivery. Persistent tissue hypoxia may result in cellular dysfunction, end-organ injury, multiple organ failure, and death.

The serum anion gap (AG) is a calculated marker representing the concentration of unmeasured anions in plasma. It is conventionally calculated as: AG = [Na+] − ([Cl−] + [HCO3−]). In critically ill patients, an increased AG may reflect accumulation of lactate, ketoacids, retained organic acids, or other unmeasured anions and may therefore provide information about the severity of metabolic derangement.

Previous studies have examined the relationship between an elevated initial anion gap and outcomes in critically ill patients. The thesis underlying the present article identified a gap in the literature concerning the prognostic value of the interval change in anion gap during the early course of shock. Lipnick et al. reported an association between the difference in anion gap at critical-care initiation and a prehospital value and mortality in critical illness. The present study instead evaluated the change over the first 24 hours after ICU admission.

The objective was to evaluate whether the 24-hour interval change in anion gap (ΔAG) was associated with mortality in patients with shock and whether it was associated with duration of ICU stay.

MATERIALS AND METHODS

Study design and setting

This was a prospective observational study conducted in the ICU of Deenanath Mangeshkar Hospital and Research Centre, Pune, a tertiary care hospital. The study period was June 2015 to May 2016.

Participants

Patients hospitalized with clinical features of shock requiring vasoactive medication were eligible if they consented to participate. Patients receiving palliative care, patients transferred from an outside hospital, and patients with chronic kidney disease or chronic liver disease were excluded. The final study population comprised 200 patients.

Clinical and laboratory assessment

Age, sex, blood pressure, and relevant underlying illnesses were recorded. Prespecified risk factors included diabetes mellitus, hypertension, ischemic heart disease, malignancy, chronic obstructive pulmonary disease, hypothyroidism, and atrial fibrillation. Blood gas and electrolyte samples were processed in the hospital central laboratory. Sodium and chloride were measured using potentiometric ion-selective electrode methodology on a Prolyte analyzer; pH, bicarbonate, and pCO2 were measured using a GEM Premier 3000 analyzer.

The serum anion gap was calculated using the traditional equation:

$AG = Na^+ - (Cl^- + HCO_3^-)$

Definition of delta anion gap

Anion gap was measured at admission and again after 24 hours. To preserve the interpretation used throughout the thesis results, ΔAG was defined as:

ΔAG = AG at admission − AG at 24 hours

Accordingly, a negative ΔAG indicates that the anion gap increased during the first 24 hours, whereas a positive ΔAG indicates that the anion gap decreased. ΔAG was categorized as <0, 0–5, or >5.

Outcomes

The primary outcome was in-hospital mortality. A secondary outcome was duration of ICU stay, categorized as 0–5 days, 5–10 days, or >10 days. The analysis of ICU duration was performed among patients who survived.

Statistical analysis

Data were compiled and analyzed using SPSS version 20. Quantitative variables were described as mean ± standard deviation and categorical variables as frequencies and percentages. Student's t-test was used for comparison of independent group means. Fisher's exact test was used to assess associations involving mortality, risk factors, types of shock, and ICU stay categories. Chi-square testing was used to evaluate the association between ΔAG category and mortality. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 200 patients fulfilled the study eligibility criteria and were included in the analysis. Overall mortality was 137/200 (68.5%).

Baseline characteristics

Characteristic	n	%
Age ≤20 years	2	1.0
Age 21–30 years	4	2.0
Age 31–40 years	11	5.5
Age 41–50 years	8	4.0
Age 51–60 years	50	25.0
Age 61–70 years	39	19.5
Age 71–80 years	62	31.0
Age >80 years	24	12.0
Male sex	136	68.0
Female sex	64	32.0

The largest age group was 71–80 years (62/200, 31.0%), followed by 51–60 years (50/200, 25.0%). Males constituted 68.0% of the cohort.

Underlying medical illnesses

Risk factor	n	%
Diabetes mellitus	128	64.0
Hypertension	128	64.0
Ischemic heart disease	52	26.0
Malignancy	17	8.5
COPD	11	5.5
Atrial fibrillation	8	4.0
Hypothyroidism	6	3.0

Type of shock

Type of shock	n	%
Septic shock	91	45.5
Cardiogenic shock	91	45.5
Hypovolemic shock	9	4.5
Traumatic shock	4	2.0
Neurogenic shock	3	1.5
Hypoadrenal shock	2	1.0

Mortality according to age and sex

Age group	Deaths / total	Mortality %
≤20	1/2	50.0
21–30	1/4	25.0
31–40	7/11	63.6
41–50	8/8	100.0
51–60	30/50	60.0
61–70	23/39	59.0
71–80	51/62	82.3
>80	16/24	66.7

The association between age group and mortality was statistically significant (p=0.010). Mortality was 72.1% among males and 60.9% among females; the association with sex was not statistically significant (p=0.142).

Mortality according to underlying illness

Risk factor	Deaths / total	Mortality %	p-value
Diabetes mellitus	80/128	62.5	0.017
Hypertension	83/128	64.8	0.156
Ischemic heart disease	37/52	71.2	0.729
Malignancy	12/17	70.6	0.999
COPD	10/11	90.9	0.178
Hypothyroidism	2/6	33.3	0.080
Atrial fibrillation	5/8	62.5	0.999

Mortality according to type of shock

Type of shock	Deaths / total	Mortality %
Septic	61/91	67.0
Cardiogenic	70/91	76.9
Neurogenic	1/3	33.3
Traumatic	4/4	100.0
Hypoadrenal	0/2	0.0
Hypovolemic	1/9	11.1

Mortality differed

Delta anion gap and mortality

ΔAG category	Deaths	Survivors	Total	Mortality %
<0	84	5	89	94.38
0–5	38	36	74	51.35
>5	15	22	37	40.54
Total	137	63	200	68.50

A negative ΔAG was strongly associated with mortality. Mortality was 94.38% in patients with ΔAG <0 compared with 51.35% in those with ΔAG 0–5 and 40.54% in those with ΔAG >5 (chi-square test, p<0.001).

Delta anion gap and ICU length of stay among survivors

ΔAG category	<5 days	5–10 days	>10 days	Total
<0	2	1	2	5
0–5	11	21	4	36
>5	12	10	0	22
Total	25	32	6	63

Among survivors, ΔAG category was significantly associated with ICU length of stay (p=0.036). Forty percent of survivors with ΔAG <0 stayed in ICU for >10 days, compared with 11.1% with ΔAG 0–5 and none with ΔAG >5.

DISCUSSION

The principal finding of this study was the strong association between the 24-hour interval change in anion gap and outcome in patients with shock. Patients whose anion gap increased over the first 24 hours (negative ΔAG using the study's definition) had markedly higher mortality than patients whose anion gap remained stable or decreased.

The overall mortality in the cohort was 68.5%. Septic and cardiogenic shock were the predominant shock categories, each accounting for 45.5% of the cohort. Cardiogenic shock had a mortality of 76.9% and septic shock 67.0%. The high mortality in this cohort is consistent with the severe physiological derangement expected in patients requiring vasoactive medication, although direct comparison with other cohorts is limited by differences in case mix and study design.

The association between negative ΔAG and mortality is biologically plausible. A rising anion gap during early shock may reflect persistence or worsening of unmeasured anions associated with tissue hypoperfusion, lactate generation, impaired clearance, or other metabolic disturbances. The thesis also notes previous work showing that an elevated initial anion gap is associated with adverse outcomes in critically ill patients. The present study extends that concept by examining the direction of change over 24 hours rather than a single baseline measurement.

The association with ICU length of stay among survivors provides additional support for ΔAG as a potential marker of ongoing illness severity. In this study, 40% of survivors with ΔAG <0 stayed in ICU for more than 10 days, whereas no survivor with ΔAG >5 remained for more than 10 days. This finding should be interpreted cautiously because the survivor subgroup was small, particularly in the ΔAG <0 category.

Diabetes mellitus was the only underlying illness showing a statistically significant association with mortality in the thesis analysis (p=0.017). Other comorbidities had high observed mortality in some categories, particularly COPD, ischemic heart disease, and malignancy, but their associations were not statistically significant. The small numbers in several subgroups limit the reliability of these estimates.

The study excluded patients with chronic kidney disease and chronic liver disease because these conditions can influence anion gap interpretation, particularly through alterations in albumin and accumulation or clearance of unmeasured anions. This improves internal consistency of the biomarker assessment but limits generalizability to patients with these common comorbidities.

Strengths

- Prospective observational design with serial measurement of the same biomarker.
- Assessment of anion gap at admission and after a defined 24-hour interval.
- Clinically relevant outcomes of mortality and ICU length of stay.
- Exclusion of chronic kidney and liver disease, which may confound anion gap interpretation.

Limitations

- The study was single-centre and included only 200 patients.

- The study was conducted over one year and included a heterogeneous shock population.
- Treatment protocols were not standardized across clinicians, which may have introduced confounding.
- No multivariable analysis was reported, so the independent prognostic contribution of ΔAG after adjustment for age, shock type, comorbidities, lactate, and other severity markers cannot be established.
- Several shock subgroups were very small, making mortality estimates such as 100% mortality in traumatic shock unstable.
- Because the raw master dataset and individual patient-level anion-gap values were not included in the thesis text supplied for conversion, additional diagnostic accuracy analyses such as ROC curves, sensitivity, specificity, and adjusted odds ratios were not added.

CONCLUSION

In this prospective observational cohort of 200 patients with shock, a negative 24-hour interval change in anion gap—indicating an increase in anion gap from admission to 24 hours—was strongly associated with mortality and was also associated with longer ICU stay among survivors. Serial ΔAG assessment may therefore serve as a simple adjunct to clinical assessment and established markers of shock severity. However, the observed association should not be interpreted as proof of independent predictive performance or causality. Larger, multicentre studies incorporating lactate, albumin, organ dysfunction scores, and multivariable modeling are warranted before routine prognostic use of ΔAG can be recommended.

DECLARATIONS

Ethics approval and consent

The thesis documents prospective observational research with informed consent procedures and patient information materials. The source thesis states that participation was voluntary and that patient information would be kept confidential. The exact ethics committee approval number/date was not available in the supplied thesis text and has therefore not been invented in this manuscript.

Funding

Not reported in the supplied thesis.

Conflict of interest

Not reported in the supplied thesis.

Data availability

The thesis states that the study data were compiled in a master chart. The individual-level master chart was not included in the supplied document text used for this conversion.

Author contributions

Not specified in the supplied thesis; should be completed according to the actual contributions of all authors before journal submission.

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