ORIGINAL ARTICLE **DOI: https://doi.org/10.18502/fem.v6i2.8715**

Relationship between seizures and metabolic acidosis: a prospective observational study

Yunus Diler[1], Serdar Özdemir[2]*, Ibrahim Altunok[2], Serkan Emre Eroğlu[2]

1. Department of Neurology, University of Health Sciences Ümraniye Training and Research Hospital, Istanbul, Turkey.
2. Department of Emergency Medicine, University of Health Sciences Ümraniye Training and Research Hospital, Istanbul, Turkey.

***Corresponding author:** Serdar Özdemir; **Email:** dr.serdar55@hotmail.com

Published online: 2022-01-17

Abstract: **Objective:** To assess changes in blood gas parameters, such as pH, partial carbon dioxide pressure (PaCO2), bicarbonate (HCO3), base deficit, and lactate values, in patients who present to the emergency care unit after a seizure.

Methods: This is a prospective study on patients who suffered a generalized tonic-clonic seizure. The demographic and biochemical data of the patients and their blood gas parameters were recorded both at the time of presentation to the emergency department and during the follow-up examination.

Results: A total of 68 patients were included in the study. Among the patients, 60.3% (41) were male. The median age of the patients was 43 years (IQR: 29-65.25). The median initial lactate value was 5.7 mmol/L (25th and 75th percentiles: 3.5–8.5 mmol/L). The median follow-up lactate value was 1.8 mmol/L (25th and 75th percentiles: 1.1–2.8 mmol/L). The statistical analysis of the blood gas parameters revealed a statistically significant difference in the pH, PaCO2, base deficit, and lactate values between the initial and follow-up evaluations (P<0.001).

Conclusion: The results of our study suggest that metabolic acidosis with high anion gap may develop due to the increase in the lactate levels as a result of a tonic-clonic seizure.

Keywords: Acidosis; Epilepsy; Lactic Acid; Seizure

Cite this article as: Diler Y, Özdemir S, Altunok I, Emre Eroğlu S. Relationship between seizures and metabolic acidosis: a prospective observational study. Front Emerg Med. 2022;6(2):e20.

1. Introduction

Epilepsy is one of the most common brain diseases affecting more than 70 million people worldwide. It has a complex group of symptoms associated with multiple risk factors and a strong genetic predisposition rather than a single etiological cause. Although relevant medications can suppress seizures in two-thirds of all patients, they are not effective in improving long-term prognosis (1). Metabolic acidosis is a clinical condition characterized by a decrease in serum bicarbonate concentration, a secondary 1 mmHg decrease occurs in arterial partial carbon dioxide pressure (PaCO2) per 1 mmol/L decrease in serum bicarbonate concentration, and the blood pH also decreases. Acute metabolic acidosis may present within a period of few minutes up to a few days, whereas the chronic form may take weeks or years to manifest (2). The acute form of metabolic acidosis is most often caused by the overproduction of organic acids, such as ketoacids and lactic acid, whereas the chronic form is often associated with bicarbonate deficiency and/or impaired kidney function (2). The calculation of the serum anion gap (AG) assists in differential diagnosis by categorizing cases into normal and high AG groups (3). Acute metabolic acidosis may cause mortality and morbidity primarily due to decreased cardiac output, arterial dilation with hypotension, altered oxygen delivery, decreased adenosine triphosphate (ATP) production, predisposition to arrhythmias, and impaired immune response (2). This study aimed to assess changes in blood gas parameters, such as pH, PaCO2, bicarbonate, base deficit, and lactate values in patients who presented to the emergency care unit after a seizure.

2. Methods

2.1. Study design

This observational study was conducted prospectively following the ethics committee approval numbered B.10.1.TKH.4.34.H.GP.0.01/101 obtained from the Clinical Studies Ethics Committee of Ümraniye Hospital, Istanbul, Turkey. Written informed consent was obtained from patients or their relatives.

2.2. Study population

Patients who had experienced a generalized tonic-clonic seizure and presented to the emergency department (ED) of Ümraniye Hospital between December 15th, 2019 and June 15th, 2020 were invited, either directly or through their guardians, to participate in the study, and those who agreed to participate were included in the study. All patients were either still actively seizing at the time of presentation to the ED, or their seizure had stopped near presentation. Patients with severe hepatic dysfunction, those using valproate or 5-

Table 1 Biochemical data of the patients

Biochemical parameter	Median (interquartile range)
Aspartate transaminase (U/L)	28.9 (18.5-30.7)
Alanine transaminase (U/L)	22.3 (13.2-25.0)
Blood urea nitrogen (mg/dL)	29.7 (23.2-39.1)
Creatinine (mg/dL)	0.8 (0.7-1.1)
Sodium (mEq/L)	138.4 (136.2-140.4)
Potassium (mEq/L)	4.2 (3.8-4.5)
Glucose (mg/dL)	114 (97.7-155.0)

Table 2 Results of blood gas analyses performed at the time of presentation to the emergency department and during the follow-up

Variable	Initial analysis	Follow-up analysis	P-value*
	Median (interquartile range)		
pH	7.32 (7.24-7.39)	7.38 (7.34-7.41)	<0.001
$PaCO_2$ (mmHg)	41.55 (37.42-48.025)	43.25 (38.6-47.52)	0.959
HCO_3 (mmol/L)	20.5 (17.3-24.1)	24.4 (22.5-25.4)	<0.001
Base excess (mmol/L)	-4 (-8.1-0.1)	0.85 (-1.6-2)	<0.001
Lactate (mmol/L)	5.7 (3.5-8.6)	1.8 (1.1-2.8)	<0.001

*Wilcoxon test

fluorouracil due to known hepatic encephalopathy or cardiovascular or psychogenic seizures, and cases in which the seizure was not witnessed by an emergency medical service worker were excluded from the study. Patients with incomplete forms due to excessive workload in the emergency room were also excluded. The flowchart of the study is shown in figure 1.

2.3. Data gathering

Demographic data (age and gender), biochemical data (sodium, potassium, blood urea nitrogen, creatinine, aspartate transaminase, alanine transaminase, and glucose levels), and blood gas parameters (pH, PaCO2, bicarbonate, base excess, and lactate levels) were recorded. The blood gas analysis was repeated at a certain time determined by the clinician during the follow-up period when the patients no longer had any additional seizure. The time between the analyses conducted at the time of seizures and during the follow-up was recorded. The difference in the lactate values between these two analyses was calculated as the delta lactate value.

2.4. Statistical analysis

IBM SPSS Statistics for Mac, version 26 (IBM Corp., Armonk, N.Y., USA) software was used for the statistical analysis of the findings obtained in the study. The normality of continuous data was determined using the Kolmogorov-Smirnov test. Continuous data that fit the normal distribution were expressed as mean and standard deviation, whereas continuous data that did not comply with the normal distribution were expressed using median and interquartile range (IQR) values. The Wilcoxon test was used to determine whether there was any difference between the parameters in the two samples in terms of continuous data.

3. Results

A total of 68 patients were included in the study (Figure 1). Among the patients, 60.3% (41) were male and 39.7% (27) were female. The median age of the patients was 43 years (IQR:29-65.25). The biochemical data of the patients obtained as a result of the tests conducted at the time of presentation are summarized in table 1.

The median time between the two blood gas analyses was calculated as 163.5 minutes (IQR: 118.25-247.75). The distribution of the blood pH values of the patients measured at the time of presentation and during follow-up analysis is shown in figure 2, and the distribution of the lactate values of the patients measured at both evaluation times is given in figure 3. The results of the initial and follow-up blood gas analyses are summarized in table 2. There was no correlation between the time elapsed from the initial to the follow-up blood gas analyses and the delta lactate values [Spearman correlation test, (r)=-0.013, P=0.458].

The statistical analysis of the blood gas parameters revealed statistically significant differences in pH, PaCO2, base excess, and lactate values between the initial and follow-up values (P<0.001). On the other hand, no statistically significant difference was found in relation to the bicarbonate values (P=0.959).

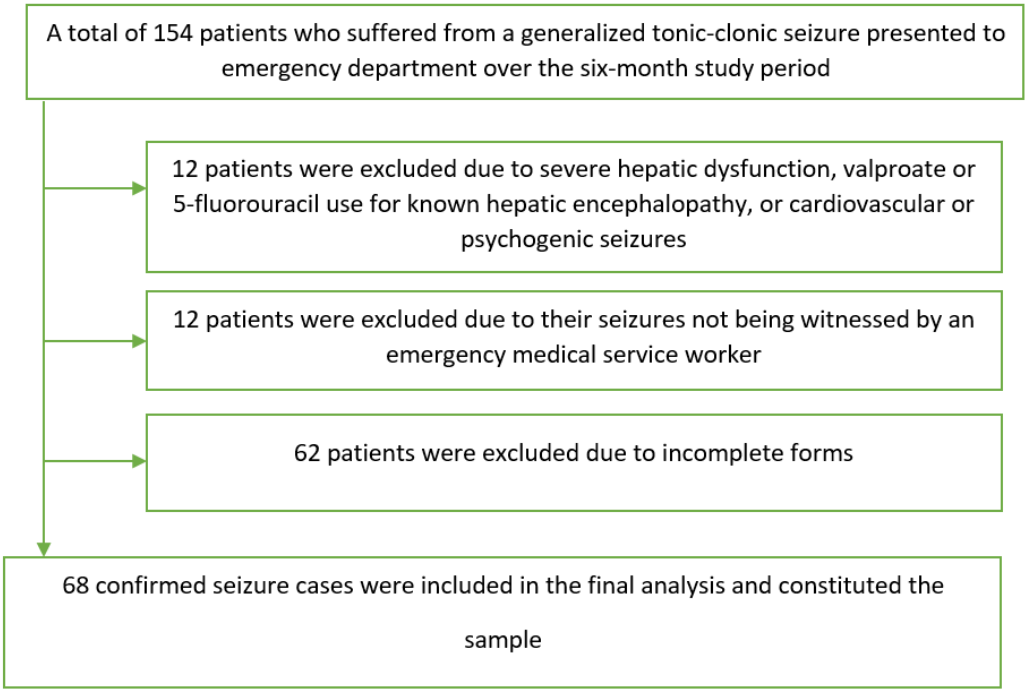

Figure 1 Flowchart of the study

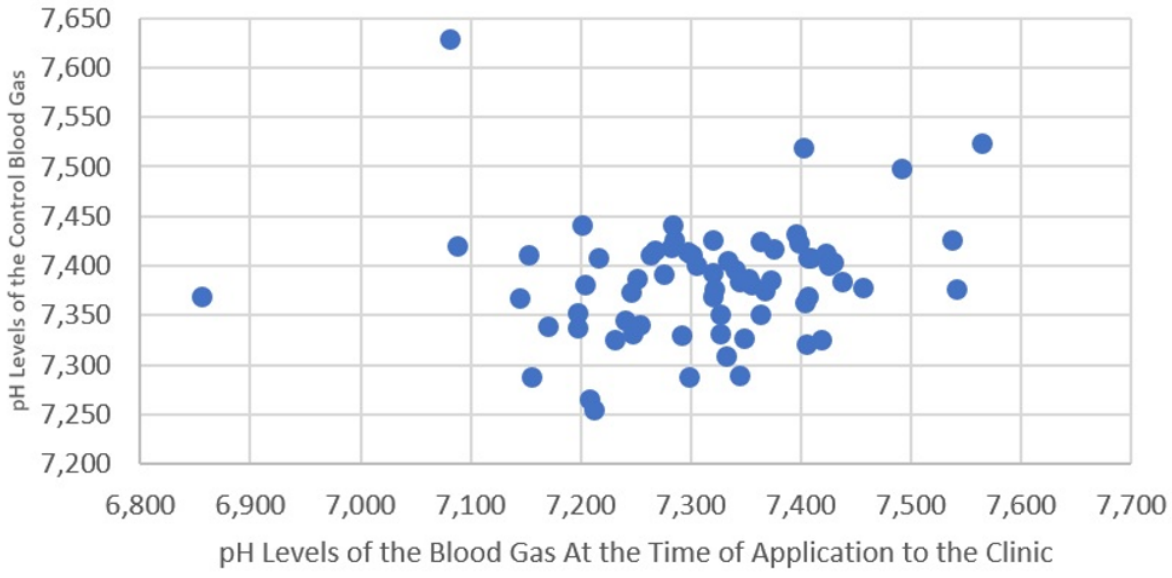

Figure 2 Distribution of the blood pH values of the patients measured at the time of presentation and during the follow-up

4. Discussion

This study showed that metabolic acidosis with high AG and lactatemia developed in patients presenting to our ED after suffering from a seizure, and that these two conditions regressed after a median of 163.5 minutes. We believe that metabolic acidosis developed in these patients due to the formation of lactate, which is an anaerobic respiratory product generated due to the inability of seizure cases to respond to tissue hypoxia, as well as the increased oxygen demand.

Lactate is a byproduct of glycolysis. Glucose decomposes to form pyruvate through the glycolytic route, and pyruvate may undergo the Krebs cycle and enter the electron transfer chain in the presence of sufficient oxygen. However, pyruvate cannot enter the Krebs cycle in the absence of oxygen (4). It is metabolized to lactate to maintain glycolysis and limited ATP production (4). Increased serum lactate levels cause lactatemia and metabolic acidosis with high AG (3). Sepsis, cardiogenic shock, heart failure, severe hypoxia, liver failure, and intoxication are the most common causes of an increase

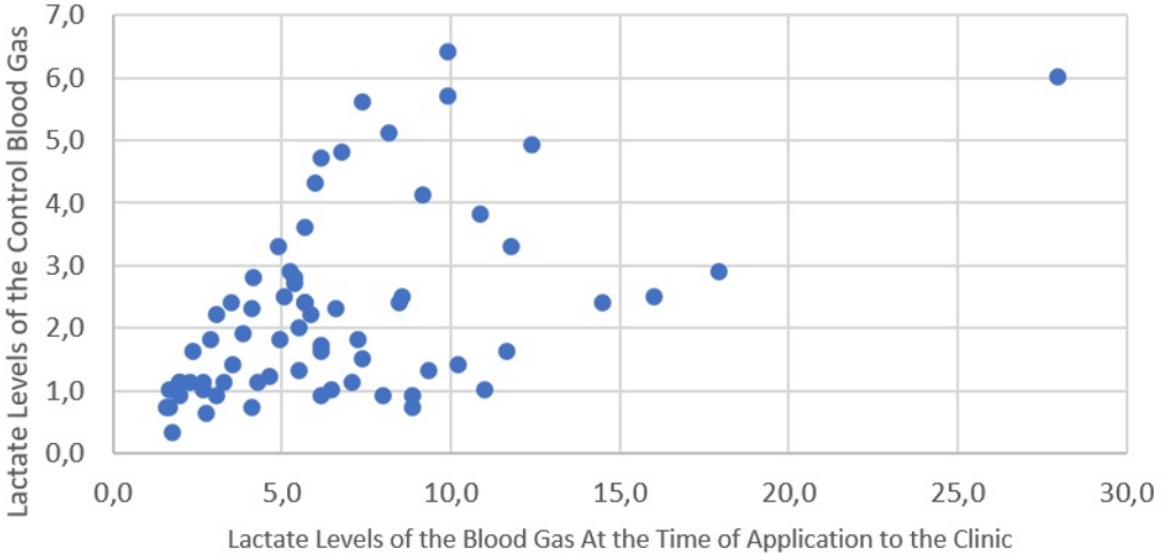

Figure 3 Distribution of the lactate values of the patients measured at the time of presentation and during the follow-up

in lactate levels (3). Therefore, lactate is used by clinicians as a marker of tissue hypoxia (3).

Lactate levels less than 2 mmol/L are accepted to be normal, and those above 2 mmol/L are considered to indicate lactatemia (5,6). On the other hand, lactate values equal to 4 mmol/L or higher are defined as high lactate levels. Among other conditions that are indicative of lactic acidosis, pH values equal to or less than 7.35, partial PaCO2 values equal to or less than 42 mmHg, and lactate levels more than 2 mmol/L can be pointed out (5,6).

Orringer et al. first demonstrated the relationship between pH, lactate and seizures in a study evaluating eight patients in 1977 (7). The authors reported that the lactate levels decreased by 50% in the first hour of the postictal phase (7). In a more recent study conducted in the ER, Matz et al. showed that the lactate levels were above 2.45 mmol/L for up to two hours in 73% of patients. Thus, the authors suggested that lactate could be used in differential diagnosis in stroke cases presenting with a loss of consciousness (8). In another emergency department study, Bakes et al. reported that the decrease in bicarbonate value and the increase in the serum AG might be related to the shifts of anions due to seizure-related lactic acidosis (9). Süße et al. demonstrated that the intracerebral lactate levels in cerebrospinal fluid moderately increased in 28% of postictal patients who underwent diagnostic lumbar puncture, even hours after the seizure (10). Conradsen et al. observed that muscle contractions experienced during tonic-clonic seizures were not synchronous like physiological contractions and the former required more energy than the latter. The authors suggested that this might be the reason for the high lactate levels in this group of patients (11).

In the current study, the median lactate values of the patients at the time of presentation to our ED with a seizure was found to be 5.7 mmol/L, which revealed a severe increase in lactate levels. Additionally, the median initial pH value of the patients was determined to be 7.32 indicating that the patients had acidosis at the time of presentation to our ED. The median lactate levels of the patients decreased to 1.8 mmol/L after treatment and their pH values were found to be within the normal range, suggesting that lactic acidosis was associated with seizures.

5. Limitations

The most important limitations of our study were that the seizures of the patients could not be observed by the researchers and the duration of the seizures was not recorded. Thus, all seizures have been recorded as generalized tonic-clonic seizure by researchers. The blood gas analyses of the patients were performed when they arrived at the hospital. Secondly, although our study was designed prospectively, there were patients with incomplete forms due to the overcrowded nature of the ER, which was an important reason for the limited sample size. Thirdly, the duration of the seizure or the number of seizures could not be recorded. These could have impacted the result of the study. Lastly, our study had a single-center design, and therefore our results cannot be generalized to other healthcare institutions. We recommend multicenter studies in larger populations to increase the generalizability of data and confirm our findings.

6. Conclusion

This study revealed that metabolic acidosis with high AG might develop due to the elevation in lactate levels after a tonic-clonic seizure. Clinicians should pay attention to the adverse effects of metabolic acidosis, especially in patients presenting with seizures and those with metabolic risk fac-

tors.

7. Declarations

7.1. Acknowledgment

None.

7.2. Authors' contribution

All authors are responsible for conception, design of the study, data collection, data analysis, and assembly. The manuscript was written and approved by all authors.

7.3. Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

7.4. Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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