

The role of oxidative and antioxidative status in patients with suspected seizures in the emergency department

The role of oxidative and antioxidative status in seizures

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Abstract

Aim: The aim of this study was to investigate the diagnostic value of Total oxidant level (TOS) and Total antioxidant level (TAS) in the differentiation of epileptic seizures and psychogenic nonepileptic seizures (PNES) in adult patients presenting to the emergency department (ED) with complaints of seizures.

Material and Method: This prospective observational study was conducted at Antalya Training and Research Hospital. Patients were categorized into either a pseudoseizure group or a seizure group. Serum TAS and TOS levels were measured spectrophotometrically by colorimetric methods. Thirty and 60 minutes after the onset of symptoms, serum samples were collected for measuring serum albumin, ischemia modified albumin (IMA), TAS and TOS levels. Data were analyzed using SPSS 21.

Results: A total of 110 participants were categorized into either a pseudoseizure group (n=48, 43.6%) or a seizure group (n=62, 56.4%). Regarding 30-minute IMA and TOS, levels were significantly higher in the seizure group (p=0.001 and p<0.001). There was no statistically significant difference between seizure and pseudoseizure groups in terms of 30-minute TAS levels (p=0.16). Regarding 60-minute, IMA and TOS, levels were significantly higher in the seizure group (p<0.001 and p=0.002, p<0.05). There was no statistically significant difference between seizure and pseudoseizure groups in terms of TAS levels (p=0.19). Anion gap and lactate levels were significantly higher in the seizure group (p<0.001).

Discussion: According to the results of our study, serum IMA, anion gap, lactate, and TOS levels increased significantly in patients with seizures compared to patients with pseudoseizures.

Keywords

Seizures; Oxidative status; Anion gap

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Introduction

Epilepsy is a group of neurological disorders characterized by seizure activity [1]. Overactivity is observed in a part or all of the central nervous system as a result of sudden, paroxysmal, high voltage electrical discharges. The term “epilepsy” is used if loss of consciousness, abnormal sensory or motor activity and dysfunction in behavior that can be observed during a seizure are repetitive [2].

Long-term video-Electroencephalography (EEG) monitoring is the gold standard for the diagnosis of seizure activity. Although they are often associated with psychogenic processes rather than abnormal neuronal discharge, pseudoseizure episodes may resemble epileptic seizures [3]. They are common clinical conditions in the ED and require careful differential diagnosis. Universally accepted nomenclature is PNES. The incidence of PNES is unknown. However, in patients admitted to epilepsy monitoring units for unusual or intractable seizures, about 20% to 40% are found to have a diagnosis of PNES rather than epileptic seizures with extended video-EEG monitoring [4].

Human albumin is a negatively charged globular protein and conditions such as ischemia, hypoxia, and acidosis may cause a structural change in N terminal of serum albumin and may change it to ischemia-modified albumin (IMA) [5]. In a previous study increased total oxidant level and decreased total antioxidant level were observed in patients with febrile seizures [6]. A number of animal studies in the literature suggest that oxidative stress may play a role in the etiology of seizure-induced neuronal death [7].

The diagnostic tests that can be used to distinguish epileptic seizures and PNES in EDs are limited [8]. Therefore, new markers are being studied to distinguish between these two clinical entities. The involuntary muscle activity and tonically adducted glottis seen during the generalized tonic-clonic seizure may induce acidosis and hypoxia in these patient populations leading to the increased formation of IMA and total oxidative stress.

In our study, we aimed to determine the role of IMA, TAS and TOS levels, anion gap and lactate levels in the differential diagnosis of patients with suspected seizures or PNES.

Material and Methods

This prospective observational study was performed in a tertiary care facility with 700,000 annual ED patient visits. The study has been approved by the institutional review board. All patients provided written informed consent prior to study participation. A total of 110 patients who were admitted to our ED between February 2014 and April 2015 with seizures or seizure-like symptoms were included in this study. After the definitive diagnosis of all patients by EEG that was performed by a neurologist, patients were divided into 2 groups, namely seizure (n=62) and pseudoseizure (n=48) groups.

Patients known to have generalized tonic-clonic seizure disorder or witnessed tonic-clonic seizure activity by health care providers or relatives and patients who were presented to the ED within 30 minutes were assigned to the seizure group. The exclusion criteria comprised patients younger than 16 years old, any cases of metabolic disease, chronic disease, neurological sequelae, neurological findings following a seizure

with a diagnosis of degenerative and demyelinating disease of the central nervous system and serum albumin level less than 2 g/dL and more than 5.5 g/dL. Patients were also excluded if they had acute and chronic conditions that may affect IMA levels such as trauma, acute ischemic heart disease, mesenteric ischemia, acute cerebrovascular event, pulmonary embolism, and liver disease. As such, 22 cases were excluded.

Serum samples for anion gap and lactate measurements were collected at the initial presentation. Thirty and 60 minutes after the onset of symptoms, serum samples were collected for measuring serum albumin, serum IMA, serum TAS and serum TOS levels and serum samples were collected following centrifuge at 1200g for 10 minutes. Serum samples were stored at -80 °C until analyzed. IMA levels were expressed as absorbance units (ABSU). TOS was measured spectrophotometrically by colorimetric methods. The results were expressed as hydrogen peroxide equivalent per liter ($\mu\text{mol H}_2\text{O}_2$ Equiv. /L). TAS was measured by colorimetric measurement method and expressed as micromolar Trolox equivalent per liter ($\mu\text{mt Eq/L}$) [5].

Demographic properties, history of any psychiatric illness, presence of urinary incontinence, tongue biting, postictal period, presence of trauma, event triggering the situation were collected.

Statistical analysis

Power analyses were made with NCSS PASS-2008 home power analysis and sample size. The sample size and power were calculated according to the previous similar studies by taking mean values, standard deviation, $\alpha=0.05$, and $\beta=0.20$ ($1-\beta=0.80$). As a result, the power was determined as 0,82100. According to these results, we included 110 patients in this study. The data obtained from this study were analyzed using SPSS 21 (Statistical Package for the Social Sciences). Mean, median, standard deviation, and frequency values were used for descriptive statistics of the data. The distribution of variables was determined with the Kolmogorov-Smirnov test. The comparison of the two groups was performed using the Mann-Whitney-U test for non-normally distributed variables and the Chi-square for categorical data. ROC analysis was performed for sensitivity and specificity calculations. A p-value of <0.05 was considered statistically significant.

Results

A total of 110 participants were categorized into either a pseudoseizure group (n=48, 43.6%) or a seizure group (n=62, 56.4%). The mean ages of the groups were as follows: 45.55 ± 20.2 years in the seizure group, 32.19 ± 13.1 years in the pseudoseizure group respectively. Gender characteristics of the groups were as follows: 21 (33.9%) female and 41 (66.1%) male in the seizure group, 30 (62.5%) female and 18 (37.5%) male in the PNES group.

Regarding 30-minute IMA, TAS, and TOS levels in the seizure and pseudo seizure groups, IMA and TOS levels were significantly higher in the seizure group ($p=0.001$ and $p <0.001$). There was no statistically significant difference between seizure and pseudo seizure groups in terms of 30-minute TAS levels ($p=0.16$). Regarding 60-minute IMA, TAS, and TOS levels in the seizure and pseudoseizure groups, IMA and TOS levels were significantly higher in the seizure group ($p <0.001$ and $p=0.002$,

Table 1. Thirty and 60-minute analyses of seizure and pseudo-seizure groups

	Seizure (n=62) Mean ± SD	Pseudoseizure(n=48) Mean ± SD	P
30-minute analysis			
IMA (ABSU)	0.523±0.060	0.494±0.037	<0.001
TAS (µmt Eq/L)	1.407±0.300	1.403±0.202	0.162
TOS (H ₂ O ₂ Eq/L)	7.061±3.870	4.531±2.65	<0.001
60-minute analysis			
IMA (ABSU)	0.531±0.061	0.496±0.033	<0.001
TAS (µmt Eq/L)	1.475±0.312	1.391±0.264	0.195
TOS (H ₂ O ₂ Eq/L)	6.951±3.811	4.963±3.521	<0.002
* Student's t-test, SD: standard deviation			

Table 2. The comparison of lactate and anion gap levels between seizure and pseudoseizure groups

	Seizure (n=62) Mean ± SD	Pseudoseizure(n=48) Mean ± SD	p
Lactate (mmol / L)	3.44±2.90	1.63±0.82	<0.001
Anion gap (mEq / L)	12.05±5.69	11.70±15.90	0.002
* Student's t-test, SD: standard deviation			

Table 3. The analysis of accompanying symptoms in seizure and pseudoseizure groups

	Seizure (n=62)	Pseudoseizure (n=48)	P
Psychiatric disorder diagnosis, n (%)	5 (8.1%)	20 (41.7%)	<0.001*
Urinary incontinence, n (%)	11 (17.7%)	2 (4.2%)	0.029*
Tongue biting, n (%)	19 (30.6%)	1 (2.1%)	<0.001*
Postictal symptoms, n (%)	49 (79.0%)	0 (0.0%)	<0.001*
* Chi-square test			

p<0.05). There was no statistically significant difference between seizure and pseudoseizure groups in terms of TAS levels (p=0.19) (Table 1).

The anion gap and lactate levels measured at admission were significantly higher in the seizure group (p <0.001) (Table 2). Regarding the analysis of accompanying symptoms and background history between seizure and pseudoseizure groups, the diagnosis of psychiatric disorder was significantly higher in the pseudoseizure group (41.7% vs 8.1%, p <0.001). In the seizure group, the incidence of urinary incontinence (17% vs 4.2%, p=0.02), tongue biting (30.6% vs 2.1%, p<0.001) and postictal period (79% vs 0%, p<0.001) was significantly higher (Table 3). In the seizure group, 7 (11.3%) patients were hospitalized, 52 (83.9%) patients were discharged with the suggestion to take the current treatment, new medications were suggested only to 2 (3.2%) patients and 1 (1.6%) patient was referred to the psychiatric outpatient clinic because of medication non-compliance. In the pseudoseizure group, 21 (43.8%) patients were discharged with the current treatment, new medications were added in 2 (3.2%) patients and 27 (56.3%) patients were referred to the psychiatric outpatient clinic.

The ROC curve analysis of 30-minute IMA, TOS, lactate, anion

gap levels for predicting the discrimination between seizure (n= 62) and pseudoseizure (n= 48) groups revealed an area under the curve of 0.68 (95% CI, 0.58-0.78, p = 0.01), 0.71 (95% CI, 0.62-0.78, p<0.001) 0.74 (95% CI, 0.63-0.83 p<0.001) and 0.66 (%95CI, 0.56-0.76 p<0.001) respectively (Figure 1). IMA, TOS, lactate, and anion gap had a sensitivity of 27%, 35%, 46%, 67% and specificity of 85%, 93% and 80% and 64% at 0.53 ABSU, 9.63 µmt Eq/L, 2.25 mmol/L and 10.5 respectively.

The ROC curve analysis of 60-minute IMA and TOS levels for predicting the discrimination between seizure and pseudoseizure groups revealed an area under the curve of 0.697 (95% CI, 0.59-0.80, p<0.001) and 0.67 (95% CI, 0.57-0.78, p=0.002). A cut-off value of 0.55 for IMA and 11.35 for TOS had a sensitivity and specificity of 11%, 21% and 95%, 91% respectively (Figure 2).

Discussion

According to the results of this study, serum IMA and TOS levels were increased in patients with generalized seizure activity 30 and 60 minutes after the event. As expected, lactate levels and anion gap were higher in seizure patient group.

Seizures constitute a major part of the ED admissions due to neurological disorders. In a study conducted in the United States, they accounted for 1% of all ED admissions [9]. Pseudoseizure episodes, which resemble epileptic seizure and which are due to psychogenic processes rather than a neuronal discharge, are common clinical conditions in the EDs and require careful differential diagnosis [3]. As they are mostly diagnosed in epilepsy centers or neurology clinics, sufficient data has not been yet obtained to determine its prevalence in the ED. Ten to 45 percent of patients who were referred to specialty epilepsy services as having intractable epilepsy are diagnosed with pseudo seizures. Although video-EEG is the gold standard in terms of discrimination of these two clinical conditions, this is not always possible in the ED setting.

There are not enough biochemical markers in clinical practice to determine whether the patient, especially those who were not witnessed, had actually an epileptic seizure or a PNES. Üzel et al. [5] reported serum IMA levels were significantly increased in adult patients who experienced seizures. They have postulated that serum IMA can be a useful serum marker in the differential diagnosis of epileptic seizures. In another study by Kocaoglu et al. [10] reported in children presenting with seizures, they determined that IMA could be used for the verification of diagnosis and severity of seizures. Our result was compatible with the previous studies, as statistically significant difference was found between seizure and pseudo seizure groups in terms of 30 and 60-minute IMA levels.

There are numerous studies that showed an increase in serum levels of IMA in myocardial ischemia, end-stage renal failure, acute intestinal ischemia, acute cerebrovascular events, peripheral vascular disease and pregnancy [11]. Unfortunately, IMA is a non-specific marker that increases in oxidative stress situations caused by ischemia.

There are many markers and different methods for measuring these markers to evaluate oxidative stress and antioxidant state. In the literature, measurements of various biomarkers indicating oxidative damage and antioxidant defense system to study the pathophysiology of diseases associated with

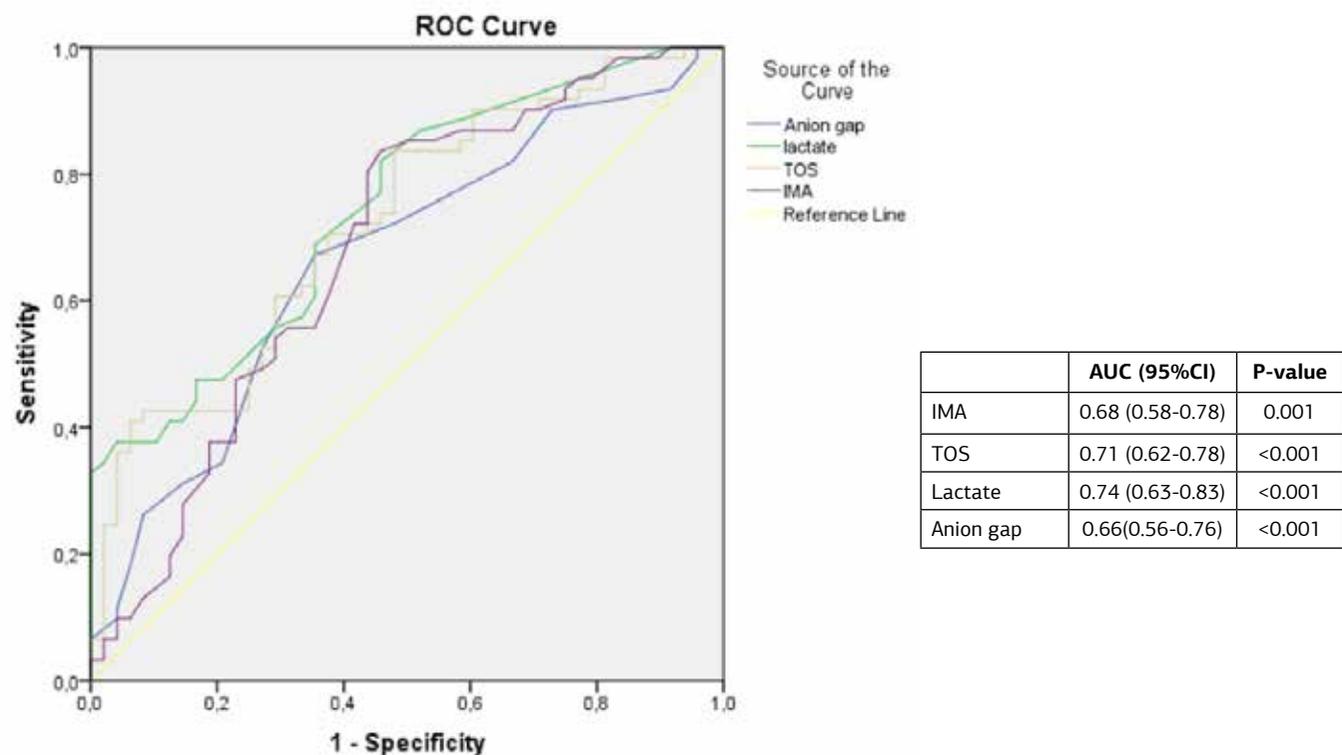


Figure 1. Comparison of ROC curves for IMA, TOS, lactate and Anion gap.

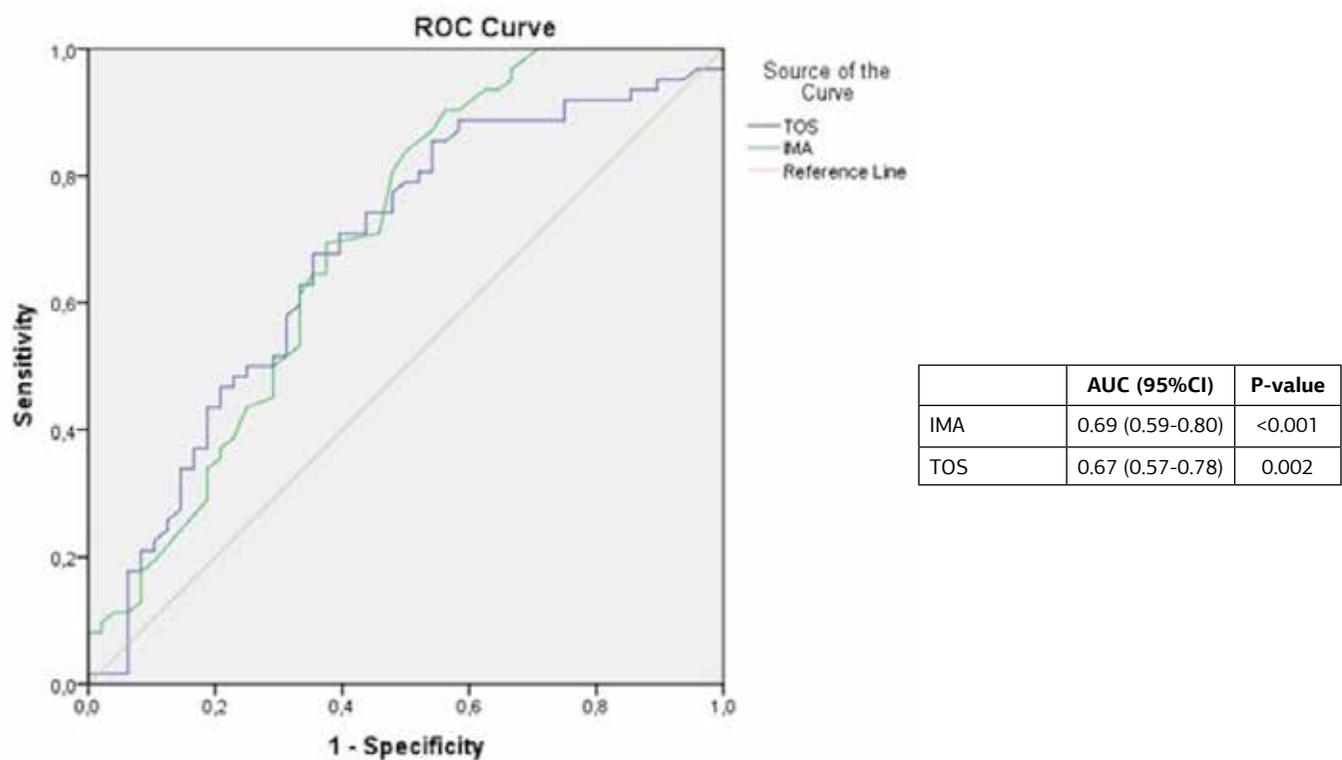


Figure 2. Comparison of ROC curves for IMA and TOS. AUC, area under the ROC, IMA, TOS.

oxidative stress were performed. Recently, the level of serum lipid peroxidation has been shown to determine TOS. TAS is a useful indicator of antioxidant activity in the serum. In our study, we measured TAS and TOS levels in patients with seizures and pseudoseizures to measure the usability of TAS and TOS levels in patients with seizures. In a previous study, increased total oxidant level and decreased total antioxidant level were observed in patients with febrile seizures [6]. In another animal study, it is postulated that oxidative stress may play a role in the etiology of seizure-induced neuronal death [7]. The increased TOS activity found in our seizure group supports the previous studies.

In a study by Bakes and colleagues [12], including 49 patients and 40 controls, they have determined that anion gap is high in patients with generalized seizures and that high anion gap can be used in the differential diagnosis of patients with altered consciousness. In our study, a significant difference was detected between the groups in terms of seizures and pseudoseizures.

Lactic acid is one of the most common causes of metabolic acidosis associated with mortality. In relation to this, changes in lactate levels can be seen after generalized seizures. Seizure-associated lactate elevation is a temporary phenomenon and lactate levels tend to decrease quickly with the termination of the seizure. Lactate levels that do not tend to fall 1-2 hours after seizure should suggest another etiology with epilepsy and further investigations should be made in this direction [12]. In a study by Hazourd and colleagues [13], they determined that high levels of lactate might be due to aerobic and anaerobic metabolism that occurs due to muscle contraction in tonic-clonic phase in patients with altered consciousness. In our study, lactate levels in patients with seizures were also significantly higher compared to patients with pseudoseizures.

According to the results of our study, as serum IMA, anion gap, lactate, and TOS levels were increased significantly in patients with seizures compared to patients with pseudoseizures, we believe that these laboratory markers can be utilized in the differential diagnosis of patients with seizures and pseudoseizures.

Limitations of the study

As it is not possible to perform in an emergency setting, video-EEG could not be performed in all of the patients in pseudoseizure and seizure groups. All patients with pseudoseizures were evaluated by neurologists and video-EEG was scheduled only for patients with suspected clinical history and neurological examination. IMA is affected by many medical conditions creating tissue oxidative stress. The conditions causing tissue oxidative stress other than our exclusion criteria may also have affected the serum IMA levels.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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