DOI:10.4274/tnd.2023.77012
Turk J Neurol 2023;29:118-125

Original Article / Özgün Araştırma

Evaluation of Thiol-disulfide Homeostasis and Ischemia-modified Albumin Levels in Patients Presenting to the Emergency Department in the Postictal Period

Postiktal Dönemde Acil Servise Başvuran Hastalarda Tiyol-disülfid Homeostazisinin ve İskemi-modifiye Albümin Düzeyinin Değerlendirilmesi

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Abstract

Objective: Epileptic seizures are thought to increase oxidative stress. This study aims to show how thiol-disulfide homeostasis (TDH) and ischemia-modified albumin (IMA) values, which are oxidative stress parameters, affect patients with epileptic seizures.

Materials and Methods: This study is a prospective, clinical trial, case-controlled trial. A total of 51 patients who were admitted to the emergency department with epileptic seizures and 51 healthy volunteers were enrolled in this study. Oxidative stress and lactate values were measured from blood samples that were drawn intravenously from the patient group, and these biomarkers were compared with the healthy control group.

Results: Statistically significant differences were found between patients in the epilepsy and control groups for all IMA values ($P < 0.001$) and for all TDH values except disulfide ($P < 0.001$). Native thiol and total thiol levels were found statistically significantly lower in patients with status epilepticus than in patients with only epileptic seizures ($P < 0.001$).

Conclusion: It has been seen that epileptic attack increases oxidative stress. TDH and IMA levels are affected statistically significantly after epileptic seizure. Especially the decrease in native thiol and total thiol levels is noticeable in patients with status epilepticus.

Keywords: Epilepsy, ischemia-modified albumin, oxidative stress, thiol-disulfide homeostasis

Öz

Amaç: Epileptik nöbetin oksidatif stresi artırdığı düşünülmektedir. Çalışmamızda; oksidatif stres parametresi olan tiyol-disülfit homeostazı (TDH) ve iskemi modifiye albümin (İMA) düzeylerinin epileptik nöbet geçiren hastalarda nasıl etkilendiğini göstermeyi amaçladık.

Gereç ve Yöntem: Prospektif, klinik araştırma ve olgu kontrollü bir çalışma olarak yapıldı. Acil servisimize epileptik atakla gelen 51 hasta ve 51 sağlıklı gönüllü dahil edildi. İntravenöz alınan kan örneklerinden oksidatif stres ve laktat değerleri ölçüldü. Bu biyobelirteçlerin sağlıklı kontrol grubu ile karşılaştırması yapıldı.

Bulgular: Tüm İMA değerleri için ($P < 0,001$) ve disülfit dışındaki tüm TDH değerleri için ($P < 0,001$) epilepsi ve kontrol grupları arasında istatistiksel anlamlı bir farklılık bulunmuştur. Native tiyol ve total tiyol düzeyleri status epileptikus hastalarında sadece epileptik nöbet geçiren hastalara göre istatistiksel olarak anlamlı olarak daha düşük bulundu ($P < 0,001$).

Sonuç: Epileptik atağın oksidatif stresi artırdığı görülmüştür. Epileptik nöbet sonrasında TDH ile İMA düzeyleri istatistiksel olarak anlamlı şekilde etkilenmektedir. Özellikle native tiyol ve total tiyol düzeyindeki azalma status epileptikus hastalarında daha belirgin olmaktadır.

Anahtar Kelimeler: Epilepsi, iskemi-modifiye albümin, oksidatif stres, tiyol-disülfit homeostazı

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Received/Geliş Tarihi: 14.10.2022 **Accepted/Kabul Tarihi:** 10.03.2023

Introduction

Epileptic seizures are temporary signs/symptoms that are induced due to abnormal and extreme synchronous or asynchronous neuronal activity. Epilepsy is a disorder characterized by continuous epileptic seizures (1). Status epilepticus is a neurological emergency that shows long-term attack activity or multiple attacks without a return to a basal state (2). Epilepsy can affect people of all ages and genders (3). A vast majority of patients with epilepsy can lead a normal life with adequate and effective treatment (4). Moreover, epilepsy is responsible for 0.3% of all deaths across the world, according to the Global Burden of Disease Study, which is supported by the World Health Organization, World Bank, Harvard School of Public Health, and the Bill and Melinda Gates Foundation (5).

Oxidative stress has a role in the pathogenesis of several diseases (6). It affects degenerative processes and plays a part not only in epilepsy but also in many brain diseases (7). Oxidative stress is responsible for epilepsy and is considered one of the main mechanisms of increased seizure frequency and recurrent seizure risk (5).

There are various methods for measuring antioxidant/oxidant molecules that can show oxidative stress (8). Thiol molecules are an important part of the antioxidant system. They are organic compounds that can react with free radicals against harmful effects and contain sulfhydryl (-SH) groups (6). Thiol groups revert oxidatively by substantial oxidant molecules. Moreover, composed disulfide bond structures can be reduced to thiol groups again, continuing the thiol-disulfide homeostasis (TDH).

Albumin is another oxidant/antioxidant molecule (9), and its metal binding capacity decreases acute ischemic conditions, and this results in protein ischemia and a metabolic variant of ischemia-modified albumin (IMA) (10). Studies have shown that IMA values in the blood increase in the case of ischemia and injuries, and they are correlated with the severity of the ischemia (9,10).

In epilepsy, every seizure increases oxidative stress, and it is vital to control the disease with an effective treatment. The purpose of this study is to show that the values of TDH and IMA, which are the parameters of oxidative stress, increase in patients with epileptic seizures. The plan is to explore these parameters in patients who were admitted to the emergency department with epileptic seizures and compare the results with the healthy control group. The goal is to show that these oxidative parameters increase and antioxidative parameters decrease in patients with epileptic seizures, which can be used in the emergency department to differentiate epileptic seizures and pseudoseizures. This study aims to demonstrate that oxidative stress is important in the diagnosis, follow-up, and treatment of patients with epileptic seizures.

Materials and Methods

This study is a prospective, case-controlled, clinical trial. It includes patients who were admitted to the emergency department of the training and research hospital due to epileptic seizures within a 6-month time frame between the dates of November 1, 2018, and April 30, 2019. The approval for this study was received from the Ethical Committee of University of Health Sciences Türkiye, Ankara Numune Training and Research Hospital (decision number: 18-2276). Furthermore, detailed, informed consent forms were provided by all participants. In order to protect the rights of the participants in this study, the Helsinki Declaration was followed. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The kits used for measurement in this study were provided free of charge by the authors.

Based on the temporal labels and/or symptoms that are induced as a result of abnormal and extreme electrical activity in the brain, the patients that had generalized tonic-clonic contraction with a loss of consciousness as epileptic seizure were evaluated (1). Status epilepticus is a neurological emergency situation that shows long-term attack activity or multiple attacks without a return to a basal state or an occasional return to a former normal state (2).

By applying the inclusion and exclusion criteria, groups were formed from patients that had a known epilepsy diagnosis or were diagnosed with epilepsy by electroencephalography. The inclusion criteria were as follows: patients who were admitted to the emergency department due to epileptic seizures, those who had a seizure in the emergency department, and those who had continuing epileptic seizures (status epilepticus). Healthy volunteers, who were companions of the patients that were admitted to the hospital, were included as the control group. Fifty-one patients who came to the emergency department for 6 months and met the study criteria were included in this study as the epilepsy group, and 51 healthy volunteers were included as the control group.

The exclusion criteria were as follows: people who did not want to participate, pregnant women, smokers, alcohol consumers, antioxidant drug users, anyone under the age of 18, those who have a history of known malignancy, those with infections, those with Parkinson and Alzheimer's disease, or those with a known chronic disease that may cause oxidative stress (like diabetes mellitus, cardiovascular disease, history of previous cerebrovascular accident, chronic kidney disease, rheumatoid arthritis, and chronic lung disease).

Thiol-disulfide Homeostasis Measurement Method

In order to examine TDH values, blood was drawn intravenously from the patients and put into yellow covered tubes that included ethylenediaminetetraacetic acid (serum/cell resolving gel). Moreover, these blood specimens were centrifuged at 1,500 cycles per minute for 10 minutes in the biochemistry laboratory of the hospital. To determine the total thiol and native thiol levels, the dissolved serums were stored at -80 °C after being divided into Eppendorf tubes until the time of analysis. After collection, all the samples were dissolved simultaneously, and their blood thiol-disulfide parameters were estimated using the Erel and Neşelioğlu method of automated measurement on a Roche Hitachi Cobas c501 automatic analyzer. This is commonly used in this country by Roche Diagnostics Türkiye, and it originated in Switzerland. Thiols are a class of organic compounds containing a -SH consisting of a sulfur atom and a hydrogen atom bonded to a carbon atom. The plasma thiol pool consists mainly of albumin thiols, protein thiols, and small amounts of low molecular weight thiols such as cysteine, cysteinylglycine, glutathione, homocysteine, and gama-glutamylcysteine. Thiols can cause an oxidation reaction through oxidants and form disulfide bonds, which is a covalent bond. The link is also called a

sulfur–sulfur (SS-) bond or disulfide bridge. Moreover, under oxidative stress conditions, the oxidation of cysteine residues can lead to reversible mixed disulfide formation between protein thiol groups and low molecular mass thiols. The disulfide bonds formed can be reduced back to thiol groups, maintaining dynamic TDH (11). Reducible disulfide bindings are shortened to create free functional thiol groups, and unused reductant sodium borohydride is consumed and extracted with the help of formaldehyde. All thiol groups, including reduced and natural thiol groups, can be determined after the reaction with 5.5-dithiobis-(2-nitrobenzoic) acid. Half of the difference between total thiol and native thiol is recorded as the disulfide content. Furthermore, index 1 value is measured with the ratio of disulfide and native thiol, index 2 value is measured with the ratio of disulfide and total thiol, and index 3 value is measured with the ratio of native thiol and total thiol. Finally, low levels of native thiol, total thiol, and index 3 (native thiol/total thiol) and high levels of disulfide, index 1 (disulfide/native thiol), and index 2 (disulfide/total thiol) indicate the presence of oxidative stress. In epilepsy, which is caused by oxidative stress, oxidative parameters increase and antioxidative parameters decrease. The unit of native thiol, total thiol, and disulfide was recorded as umol/lt (micromole/lt).

Ischemia-modified Albumin Measurement Method

In order to measure the values of IMA, blood samples were drawn from the patients and put into the yellow caped tubes that included EDTA. After 30 minutes, they were centrifuged at 1500 cycles per minute for 10 minutes in the biochemistry laboratory in the hospital, and they were stored at -80 °C. After collection, all the samples were dissolved simultaneously, and the reduced cobalt-albumin binding capacity (IMA level) was measured using the method of Bar-Or. Cobalt binds more to normal albumin than IMA; it also binds to the albumin in the *N*-terminal amino region. Unbound IMA in the serum is measured by the spectrophotometric method. In order to take this measurement, the protein called dithiothretiol (DTT), which reacts with free cobalt and causes a color change, was added to the test tube. Moreover, DTT cannot react with the cobalt that is binding to the albumin, and the amount of unbound free cobalt in the test tube shows IMA levels. The unit for IMA is absorbance unit (ABSU), and the unit for albumin is gr/dl (gram/decilitre). Further, IMA is an oxidative parameter, and high levels of IMA and IMA/Albumin also show oxidative stress.

Statistical Analysis

The research data were analyzed using IBM (International Business Machines) SPSS (Statistical Package for Social Sciences) version 23, and descriptive statistics were presented as mean ± standard deviation, minimum and maximum values, frequency, and percentage. The Mann–Whitney U test was used when parametric assumption was not provided. The one-way analysis of variance was used to compare the variables with normal distribution in groups of three or more, and multiple comparisons were made using the Tamhane test. The Kruskal–Wallis test was used to compare the variables that did not fit the normal distribution in groups of three or more, and multiple comparisons were made using the Dunn test. Yates' correction and Pearson's chi-square test were used to compare categorical variables according to groups, and multiple comparisons were made using the Bonferroni corrected Z-test. The statistical significance level was accepted as $P < 0.05$.

Results

In this study, a total of 51 (50%) volunteers were in the patient group who had epileptic seizures and were admitted to the emergency department, while another 51 (50%) volunteers were in the healthy control group. The average age of each group is given in Table 1, and the median age difference between the patient and control groups is $P < 0.001$. When the participants were evaluated according to age groups, there was heterogeneity between the patient and control groups. In the patient group, the rate of those aged 18–35 was 19.6%, the rate of those aged 36–50 years was 29.4%, the rate of those aged 51–65 was 19.6%, and the rate of those aged 65 and over was 31.4%. In the control group, the rate of those aged 18–35 was 64.7%, the rate of those aged 36–50 years was 27.5%, and the rate of those aged 51–65 was 7.8%, and there was no one over the age of 65.

The distribution of the TDH, IMA, and lactate values for the age groups is provided in Table 2. When the patient and control groups, who were between the ages of 18–35, were examined, no statistically significant difference was observed in native thiol, total thiol, and disulfide values. When the patient and control groups between the ages of 36–50 were examined, a statistically significant difference was observed in the values of native thiol and IMA/Albumin. When other values were examined, no statistically significant difference was observed in the patient and control groups for that age group. When the patient and control groups over 50 years of age were examined, a statistically significant difference was observed in native thiol, total thiol, and IMA/albumin values. When other values were examined, no statistically significant difference was observed in the patient and control groups for that age group.

The distribution of TDH values for the volunteers is provided in Table 3. The TDH values are calculated as native thiol, total thiol, disulfide [disulfide = (total thiol - native thiol)/2], index 1 (disulfide/native thiol), index 2 (disulfide/total thiol), and index 3 (native thiol/total thiol). Disulfide levels were not different between the study groups ($P > 0.05$). All other TDH values showed a different distribution between the two study groups, and a statistically significant difference was found for TDH levels between the epilepsy and control groups ($P \leq 0.001$). The higher levels of native thiol, total thiol, and index 3 in the control group

Table 1. Average age of volunteers in the groups

	n	$\overline{X}$ ± SD	Median	Minimum-maximum	*P**
Patient	51	51.7 ± 18.7	54	19–92	<0.001
Control	51	33.7 ± 10.7	32	18–57	

*Mann–Whitney U test, $\overline{X}$: Mean, SD: Standard deviation

were found to be statistically significant ($P \leq 0.001$). Moreover, index 1 and index 2 levels in the control group were lower than in the patient group.

The distribution of the IMA and lactate values for the volunteers is shown in Table 4. All IMA values show a different distribution between the two study groups, and a statistically significant difference was found for IMA levels between the epilepsy and control groups ($P \leq 0.001$). It was observed that IMA and IMA/albumin ratio levels increased significantly in the patient group compared with the control group and that albumin levels decreased in the patient group. The increased lactate levels in the patient group were found to be statistically significant. While the blood lactate level was above the normal limit of 1 mmol/l (millimole/liter) in all patients included in the study, a total of 43 patients exceeded the value of 2 mmol/l, which is considered to be a critical limit for most diseases.

Seven of the patients participating in this study were diagnosed with status epilepticus, and samples were taken and evaluated at this state. One of these patients died because the status epilepticus was not controlled (levels for this patient included serum lactate: 3.0 mmol/lt, native thiol: 160.52 umol/lt, total thiol: 220.18 umol/lt, disulfide: 29.83 umol/lt, IMA: 0.865 ABSU, albumin: 4.02 g/dl, index 1: 18.58, index 2: 13.54, index 3: 72.90, and IMA/albumin: 0.21). The mean blood lactate levels in the status epilepticus group were higher than in the patient group. Furthermore, the averages of native thiol, total thiol, index 3, and albumin levels were lower than the averages of the patient group, whereas the averages were higher for disulfide, IMA, IMA/albumin ratios, index 1, and index 2. When patients with an epileptic attack and status epilepticus were compared with each other and the control group, the change in TDH and IMA levels were statistically significant (Table 5). The distribution of the

Table 2. The distribution of the TDH, IMA, and lactate values for the age groups

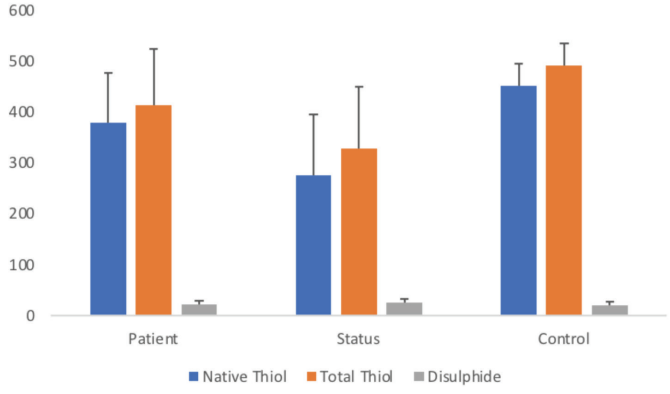
$\overline{X}$ ± SD		Patient (51)			Control (51)			
Age		$\overline{X}$ ± SD	Median	Minimum-maximum	$\overline{X}$ ± SD	Median	Minimum-maximum	*P*
18–35	Native thiol	427.3 ± 81.5	420.4	304.4–569.6	465.0 ± 34.9	466.0	392.9–528.1	0.184**
	Total thiol	475.2 ± 84.3	486.5	343.0–606.0	505.2 ± 37.7	499.7	436.8–577.1	0.301**
	Disulfide	23.9 ± 7.4	23.8	11.6–33.9	20.0 ± 6.0	19.4	5.6–39.0	0.098**
	Index 1	5.7 ± 1.8	5.8	2.8–8.1	4.3 ± 1.3	4.1	1.1–7.8	**0.010****
	Index 2	5.1 ± 1.5	5.2	2.6–7.0	3.9 ± 1.1	3.8	1.1–6.7	**0.012****
	Index 3	89.7 ± 3.0	89.5	85.9–94.6	92.0 ± 2.2	92.3	86.4–97.6	**0.012****
	IMA	0.80 ± 0.07	0.79	0.72–0.95	0.74 ± 0.11	0.72	0.56–1.15	**0.012***
	Albumin	4.1 ± 0.3	4.2	3.4–4.5	4.4 ± 0.1	4.4	4.1–4.6	**0.035***
	IMA/albumin	0.19 ± 0.03	0.18	0.17–0.26	0.74 ± 0.11	0.72	0.59–1.13	**<0.001****
36–50	Native thiol	373.8 ± 93.1	410.3	150.1–446.4	431.8 ± 50.1	445.1	327.8–501.5	**0.029***
	Total thiol	419.4 ± 94.2	455.7	202.6–500.5	472.0 ± 43.2	484.4	391.8–536.9	0.116*
	Disulfide	22.8 ± 5.8	23.4	14.2–34.2	20.1 ± 6.2	20.0	4.8–32.0	0.243**
	Index 1	6.8 ± 3.7	5.5	3.3–17.4	4.8 ± 2.0	4.5	1.0–9.7	0.061*
	Index 2	5.8 ± 2.6	5.0	3.1–12.9	4.3 ± 1.6	4.1	0.9–8.1	0.061*
	Index 3	88.2 ± 5.2	89.9	74.1–93.8	91.2 ± 3.2	91.6	83.6–98.0	0.061*
	IMA	0.79 ± 0.08	0.80	0.63–0.91	0.74 ± 0.06	0.73	0.64–0.93	0.052*
	Albumine	4.2 ± 0.2	4.3	3.8–4.4	4.3 ± 0.1	4.4	3.9–4.5	0.062*
	IMA/albumin	0.19 ± 0.02	0.19	0.14–0.22	0.73 ± 0.07	0.72	0.65–0.93	**<0.001***
Over 50	Native thiol	334.1 ± 113.8	320.7	160.5–526.4	396.7 ± 35.7	399.0	351.5–437.6	**0.044****
	Total thiol	361.4 ± 122.7	361.7	88.9–552.0	440.3 ± 30.4	432.8	413.9–481.7	**0.011****
	Disulfide	21.1 ± 7.5	22.0	4.5–36.2	21.8 ± 10.1	24.1	7.7–31.2	0.868**
	Index 1	9.1 ± 9.7	6.6	0.8–52.4	5.6 ± 2.9	5.8	1.9–8.8	0.360*
	Index 2	6.9 ± 4.7	5.8	0.8–25.5	4.9 ± 2.4	5.2	1.8–7.5	0.360*
	Index 3	86.0 ± 9.5	88.2	48.8–98.3	90.0 ±4.8	89.5	84.9–96.3	0.360*
	IMA	0.85 ± 0.11	0.87	0.43–0.97	0.77 ± 0.10	0.75	0.68–0.91	0.077*
	Albumin	3.9 ± 0.6	4.1	1.3–4.4	4.3 ± 0.1	4.3	4.1–4.5	0.099*
	IMA/albumin	0.23 ± 0.10	0.21	0.10–0.71	0.75 ± 0.09	0.71	0.70–0.89	**0.002***

$\overline{X}$ ± SD: Main ± standard deviation (person count), *Mann–Whitney U test, **t-test for independent samples; if $P \leq 0.05$ is significant, IMA: Ischemia-modified albumin, TDH: Thiol-disulfide homeostasis

TDH, IMA, and lactate values for the patient and control groups is shown in Graphic 1 and 2. Parametric values like native thiol, total thiol, and disulfide are shown in Graphic 1. Non-parametric values like IMA, albumin, IMA/albumin, index 1, index 2, index 3, and lactate are shown in Graphic 2.

Discussion

In this prospective, case-controlled, clinical study, it was observed that antioxidant activity decreased and oxidant activity increased in patients with epileptic seizures compared with the control group and that total seizure activity was associated with oxidative stress. The role of oxidative stress in epilepsy pathogenesis has become a topic explored by many researchers (6,7,10,12,13). The percentage of thiols in plasma tends to decrease with age, both as free thiols and as total forms. Moreover, direct correlations were found between disulfide and total forms of plasma thiols (like this cysteine and homocysteine) and age, whereas native plasma thiols did not show any correlation with age (14). In this study, although age-related TDH and IMA values decreased in both the patient and control groups, it did not create a statistically significant difference for each value. However, the IMA/albumin ratio was statistically significant in the patient group regardless of age.



Graphic 1. Parametric values in patient/status/control groups

Oxidative stress increases with age, and as a result, thiol-disulfide levels in plasma decrease.

In this study, antioxidant activity decreased and oxidant activity increased in patients with epilepsy. The levels of native thiol, total thiol, and index 3 showed a statistically significant decrease after epileptic seizures, whereas the levels of index 1 and index 2 showed a statistically significant increase. Disulfide levels were observed to increase in the patient group with epileptic seizures, but this increase was not statistically significant. Index 1 and index 2 are the ratio of disulfide and thiol, and these levels increased in patients with epileptic seizures. This shows that disulfide levels are affected by epileptic activity. Furthermore, it has been shown in the literature that thiol compounds are affected by oxidative stress in many diseases (12,13,15,16,17). These levels are affected by oxidative stress and so thiol compounds decrease in patients with seizures. It is important to control seizures and suppress oxidant activity with an effective antiepileptic treatment (16). In another study by Elmas et al. (6), which examined patients with febrile convulsions, it was shown that native thiol, total thiol, and index 3 levels decreased, while index 1 and 2 levels increased in the group with epileptic seizures. These results support this study; however, in that same study, there was no correlation between total thiol, native thiol, and dynamic disulfide bond levels and seizure frequency or duration of illness, which were evaluated differently. Considering this study along with these other studies, the effect of increased oxidative stress continues even if that stress is removed. Moreover, the changes in oxidant activity seen in patients with status epilepticus in the patient group confirm this study's thesis. Seven patients in the patient group were evaluated in the status epilepticus clinic, and the levels of native thiol, total thiol, and index 3 for status epilepticus patients were lower than the epilepsy patient group averages. The change in native thiol level was found to be statistically significant, and the decrease in the thiol level seen in patients with status epilepticus (including the deceased patient) suggests that it is important for predicting a poor prognosis. In this case, it is vital to control and prevent seizures with antiepileptic treatment and to terminate

Table 3. The distribution of TDH values for volunteers

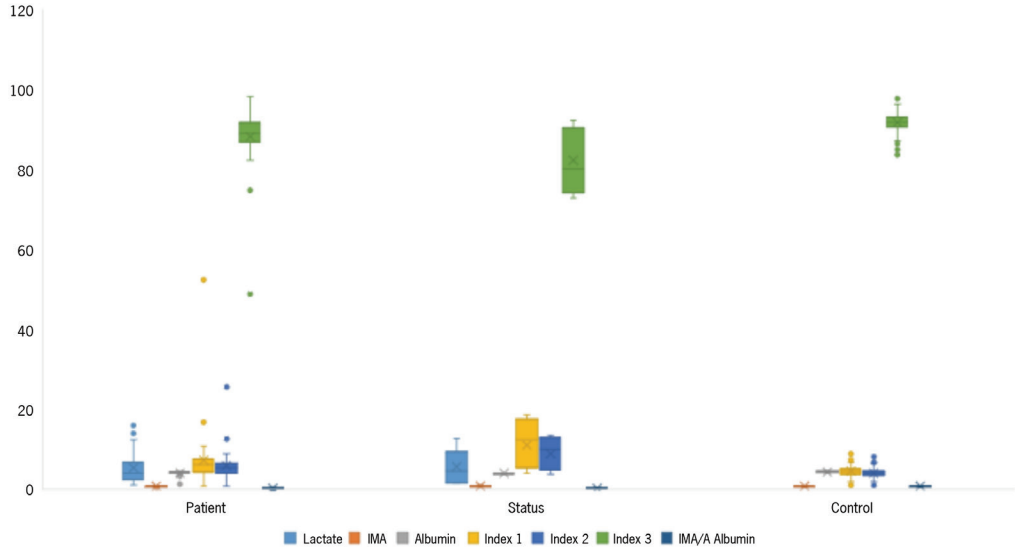
		n	$\overline{X}$ ± SD	Median	Minimum-maximum	*P*
Native thiol	Patient	51	364.1 ± 106.8	383.1	150.2–569.6	<0.001*
	Control	51	450.6 ± 44.5	455.9	327.8–528.2	
Total thiol	Patient	51	400.8 ± 115.4	409.1	88.9–606.0	<0.001*
	Control	51	491.0 ± 43.5	491.5	391.9–577.2	
Disulfide	Patient	51	22.2 ± 7.0	22.8	4.5–36.2	0.145**
	Control	51	20.2 ± 6.3	20.2	4.9–39.1	
Index 1	Patient	51	7.8 ± 7.3	6.2	0.9–52.4	<0.001*
	Control	51	4.6 ± 1.7	4.5	1.0–9.8	
Index 2	Patient	51	6.3 ± 3.8	5.6	0.9–25.6	<0.001*
	Control	51	4.2 ± 1.4	4.1	0.9–8.2	
Index 3	Patient	51	87.4 ± 7.6	88.9	48.8–98.3	<0.001*
	Control	51	91.7 ± 2.8	91.8	83.7–98.0	

*: Mann–Whitney U test, **: Unpaired t-test, $\overline{X}$: Mean, if $P \leq 0.05$ is significant, TDH: Thiol-disulfide homeostasis, SD: Standard deviation

the situation with early intervention in the status epilepticus clinic. TDH levels can be considered a useful biomarker in the differential diagnosis of epileptic seizures, treatment, follow-up, status epilepticus, and non-convulsive status.

All IMA values in this study show a different distribution among study groups. A statistically significant difference was found between the IMA levels of the epilepsy and control groups. It was found that the IMA levels and IMA/albumin ratio increase was statistically significant in the epileptic patient group, but the albumin levels decreased. Balta et al. (18) and Abboud et al. (19) showed that plasma IMA levels and the IMA/albumin ratio increased significantly in adult patients who were having seizures similar to those in this study. The study by Kamaşak et al. (10) showed that in patients with generalized tonic-clonic seizures, even without hypoxia markers, plasma IMA levels increased, and these levels were directly proportional to seizure length. In another study, when the IMA values of the group with febrile convulsion and the control group were compared, it was shown that there was a statistically significant difference. It has been shown that if a seizure is prolonged for more than 5 minutes, the level of IMA increases. There is a significant difference between the groups with a seizure lasting more than five minutes and those that last less than that. Serum IMA levels increased as the seizure duration increased, and this fact could be an indicator of status epilepticus (20). In this study, the group with status epilepticus had higher mean blood lactate levels, IMA, and IMA/albumin ratios. Additionally, the mean albumin levels were lower than the averages of the epilepsy group. When patient groups with epileptic attack and status epilepticus were compared, the change in lactate levels was statistically significant. Therefore, IMA levels could be considered a useful biomarker in the differential diagnosis of epileptic seizures to treatment, follow-up, status epilepticus, and a non-convulsive status.

In this study, the increase in lactate levels in the patient group was found to be statistically significant. The mean lactate level in the status epilepticus group was found to be 5.7 mmol/l, which is higher than the patient group. Moreover, lactate levels increased in patients with experimental epilepsy, which is similar to this study (21,22). According to Fauser in Germany, it was shown that blood lactate levels increased after epileptic seizures, which is generally associated with seizure duration, and this supports this study. Elevated lactate levels were transient and were observed for up to 72 hours after a seizure or status epilepticus, while albumin levels remained elevated for 9–14 days (23).



Graphic 2. Non-parametric values in patient/status/control groups

Table 4. The distribution of IMA and lactate values for the volunteers

		n	$\overline{X}$ ± SD	Median	Minimum-maximum	*P*
IMA	Patient	51	0.80 ± 0.10	0.80	0.40–0.90	<0.001*
	Control	51	0.70 ± 0.10	0.70	0.60–1.20	
Albumin	Patient	51	4.1 ± 0.5	4.2	1.3–4.6	<0.001*
	Control	51	4.4 ± 0.1	4.4	3.9–4.6	
IMA/albumin	Patient	51	0.20 ± 0.10	0.20	0.10–0.70	<0.001*
	Control	51	0.70 ± 0.10	0.70	0.60–1.10	
Lactate	Patient	51	5.5 ± 3.9	4.1	1.2–16.0	-
	Control	-	-	-	-	

*: Mann–Whitney U test, $\overline{X}$: Mean, if $P \leq 0.05$ is significant, IMA: Ischemia-modified albumin

Table 5. The distribution of the TDH, IMA, and lactate values for the status epilepticus/epileptic seizure/control groups

		n	$\overline{X}$ ± SD	Median	Minimum-maximum	*P*
Native thiol	Status epilepticus	7	275.7 ± 120.0[b]	293.3	150.1–451.7	**<0.001****
	Epileptic seizure	44	378.1 ± 98.9[b]	400.6	150.2–569.6	
	Control	51	450.5 ± 44.5[a]	455.9	327.8–528.1	
Total thiol	Status epilepticus	7	327.2 ± 121.4	365.8	202.6–517.5	**<0.001****
	Epileptic seizure	44	412.4 ± 111.4[b]	432.8	88.9–606.0	
	Control	51	491.0 ± 43.5	491.4	391.8–577.1	
Disulfide	Status epilepticus	7	25.7 ± 7.8	26.2	14.2–36.2	0.107**
	Epileptic seizure	44	21.5 ± 6.7	22.7	4.5–34.2	
	Control	51	20.2 ± 6.3	20.2	4.85–39.0	
Index 1	Status epilepticus	7	11.1 ± 5.7	12.3	4.1–18.5[b]	**<0.001*****
	Epileptic seizure	44	7.2 ± 7.4	6.1	0.9–52.4[b]	
	Control	51	4.5 ± 1.6	4.4	1.0–9.7[a]	
Index 2	Status epilepticus	7	8.8 ± 3.8	9.9	3.8–13.5[b]	**<0.001*****
	Epileptic seizure	44	5.8 ± 3.6	5.4	0.8–25.5[b]	
	Control	51	4.1 ± 1.3	4.1	0.9–8.1[a]	
Index 3	Status epilepticus	7	82.3 ± 7.7	80.1	72.9–92.3[b]	**<0.001*****
	Epileptic seizure	44	88.2 ± 7.3	89.1	48.8–98.3[b]	
	Control	51	91.7 ± 2.7	91.7	83.6–98.0[a]	
IMA	Status epilepticus	7	0.86 ± 0.06	0.86	0.70–0.90[b]	**<0.001*****
	Epileptic seizure	44	0.81 ± 0.09	0.81	0.40–0.90[b]	
	Control	51	0.74 ± 0.10	0.73	0.50–1.10[a]	
Albumin	Status epilepticus	7	3.9 ± 0.2	3.9	3.4–4.1[b]	**<0.001*****
	Epileptic seizure	44	4.1 ± 0.5	4.2	1.3–4.6[b]	
	Control	51	4.4 ± 0.1	4.4	3.99–4.6[a]	
IMA/albumin	Status epilepticus	7	0.22 ± 0.02	0.21	0.1–0.2[b]	**<0.001*****
	Epileptic seizsure	44	0.20 ± 0.08	0.19	0.10–0.70[b]	
	Control	51	0.74 ± 0.09	0.72	0.59–1.13[a]	
Lactate	Status epilepticus	7	5.7 ± 3.6	4.5	1.5–12.7	0.904*
	Epileptic seizure	44	3.2 ± 3.8	3.9	1.2–16	

$\overline{X}$ ± SD: Main ± standard deviation; n: Person count, *: Mann–Whitney U test, **: One-Way analysis of variance, ***: Kruskal–Wallis test; [a, b]: There is no difference between groups with the same letter, if $P \leq 0.05$ is significant, IMA: Ischemia-modified albumin, TDH: Thiol-disulfide homeostasis

Conclusion

This study showed that oxidative stress parameters increased in patients with epileptic seizures who were admitted to the emergency department through the measurement of TDH, IMA, and lactate values. It was shown that these antioxidant parameters had a statistically significant decrease in patients with epileptic seizures. However, the oxidant parameters increased. In patients with status epilepticus, oxidative parameters, like disulfide, IMA, and index 1 and 2 levels, were higher than in patients with only epileptic seizures. This suggests that TDH is meaningful in predicting a poor prognosis. In daily practice, blood lactate levels are used to distinguish between epileptic and non-epileptic seizures. The statistically significant results of native thiol, disulfide, and IMA values evaluated in this study in patients with epileptic seizures and also in patients with status epilepticus show that these parameters can also be used to differentiate epileptic and non-epileptic seizures. IMA/albumin ratio can be used together with lactate as a safer parameter in differentiating epileptic attacks regardless of age. This study is valuable in that there are no other studies in the literature comparing these oxidative stress parameters in epileptic seizures and status epilepticus.

Ethics

Ethics Committee Approval: The approval for this study was received from the Ethical Committee of University of Health Sciences Türkiye, Ankara Numune Training and Research Hospital (decision number: 18-2276).

Informed Consent: Informed consent forms were provided by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.G., Design: İ.G., A.B.E., H.Ş.K., Data Collection or Processing: İ.G., A.K., Analysis or Interpretation: A.K., Ö.E., S.N., Literature Search: İ.G., A.B.E., H.Ş.K., Writing: İ.G., A.B.E., H.Ş.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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