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Orijinal Araştırma / Original Article

The Effect of Epileptic Seizure Occurring After Intracranial Hemorrhages on Early Mortality

İntrakraniyal Kanamalar Sonrasında Oluşan Epileptik Nöbetin Erken Dönem Mortalite Üzerine Etkisi

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Abstract

Introduction: Intracranial hemorrhages (ICH) are at high risk for long-term morbidity and morbidity in terms of complications such as epilepsy. In our study, we aimed to determine the effect of epileptic seizure seen after ICH on early mortality and to provide information to the literature.

Material and Method: My study was done retrospectively. A total of 238 patients with a confirmed diagnosis of ICH who met the inclusion criteria were included in the study. In the classification of the seizure as early and late; early seizure up to the 14th day after bleeding; Seizures observed on the 14th day and above were classified as late seizures.

Results: In the demographic data There was no significant difference between the groups in terms of age. Seizure + 57.7% of cases were male; seizure – 52.7% of the cases were male and the groups were not different in terms of gender. When the effect of seizure type on 30-day mortality was examined, it was observed that mortality was significantly higher in cases with late seizures.

Conclusions: We determined that the epileptic seizure seen after ICH has an effect on mortality. Therefore, it is necessary to be careful in terms of mortality in cases with seizures. Especially in cases with late seizures, mortality is higher than in cases with early seizures, so it is necessary to be careful in terms of mortality in cases with late seizures. In addition, we found that the use of antiepileptic drugs did not affect mortality.

Keywords: Epileptic seizure, intracranial hemmorage, mortality, antiepileptic drugs

Öz

Giriş: İntrakraniyal kanamalar (İKK) akut fazda genellikle hematomun ve çevreleyen ödemin nöronal iletim üzerindeki yıkıcı etkisini gösteren epilepsi gibi komplikasyonlar açısından uzun dönem morbidite ve morbidite için yüksek risk altında kalmaktadır. Epileptik nöbet, İKK sonrasında akut ve uzun dönemde sık görülen durumlardan biridir. Çalışmamızda, İKK sonrasında görülen epileptik nöbetin erken dönem mortalite üzerine etkisini tespit edip literatüre bilgi sağlamayı amaçladık.

Gereç ve Yöntem: Çalışmamı retrospektif olarak yapıldı. Çalışmaya dahil edilme kriterlerini karşılayan 238 kesinleşmiş İKK tanılı hasta çalışmaya dahil edildi. Nöbetin erken dönem ve geç dönem olarak sınıflandırmasında; kanama sonrası 14. güne kadar erken nöbet; 14. gün ve üzeri süreçte görülen nöbet ise geç dönem nöbet olarak sınıflandırıldı.

Bulgular: Olguların demografik verilerinde; nöbet + olanlarda yaş ortanca değeri 69,0 yıl; nöbet – olgularda yaş ortanca değeri 69,0 ve tüm olgularda ise yaş ortanca değeri 69 yıl olup; gruplar arasında yaş açısından anlamlı fark tespit edilmedi. Nöbet + olguların %57,7'si erkek; nöbet – olguların %52,7'si erkek olup cinsiyet açısından da gruplar farklı değildi. Nöbet tipinin 30 günlük mortalite üzerine etkisi incelendiğinde ise geç dönem nöbet geçiren olgularda mortalitenin anlamlı olarak yüksek olduğu görüldü

Sonuç: İKK sonrasında görülen epileptik nöbetin mortalite üzerine etkisinin olduğunu tespit ettik. Bu nedenle nöbet geçiren olgularda mortalite açısından dikkatli olmak gerekmektedir. Özellikle geç dönem nöbet görülen olgularda mortalite erken dönem nöbet geçiren olgulara göre daha fazla olduğundan geç dönem nöbet görülen olgularda mortalite açısından dikkatli olmak gerekmektedir. Ayrıca antiepileptik ilaç kullanımının mortalite üzerine etki etmediğini tespit ettik. Daha kapsamlı çalışmalar yapılması ile bu konuda daha net bilgilerin elde edileceğini düşünmekteyiz.

Anahtar Kelimeler: Epileptik nöbet, intrakraniyal kanama, mortalite, antiepileptic ilaç

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INTRODUCTION

The World Health Organization (WHO) defines stroke as "a focal or global deficit that occurs suddenly, lasts for 24 hours or more, or results in death, with no other cause other than a vascular cause".[1] Intracranial hemorrhages (ICC) constitute 10-15% of all strokes and cause morbidity and/or mortality in 60% of cases.[2,3] A case of ICH remains at high risk for long-term morbidity and morbidity in terms of complications such as epilepsy, which generally shows the devastating effect of hematoma and surrounding edema on neuronal transmission in the acute phase.[4,5]

Epileptic seizure is one of the most common acute and long-term conditions after ICH.[6] Seizures that begin after ICH are classically divided into early seizures (from 1-2 hours to 1-2 weeks after bleeding) and late-stage seizures (seizures that occur after 3 weeks or more).[7]

Our study investigating the effect of epileptic seizure seen after ICH on early mortality is one of the few studies conducted on this subject as far as we have researched.[8] In our study, we aimed to determine the effect of epileptic seizure seen after ICH on early mortality and to provide information to the literature.

MATERIAL AND METHOD

Ethics committee approval was obtained from the ethics committee of İzmir Katip Çelebi University Ataturk Research and Training Hospital (with the decision of the ethics committee dated 18.02.2021 and numbered 0071). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Setting

Our study was conducted retrospectively between January 1, 2020 and January 1, 2021. For the study, 238 patients with a confirmed diagnosis of ICH who applied to the emergency department of our hospital and met the inclusion criteria were included in the study.

Study Population

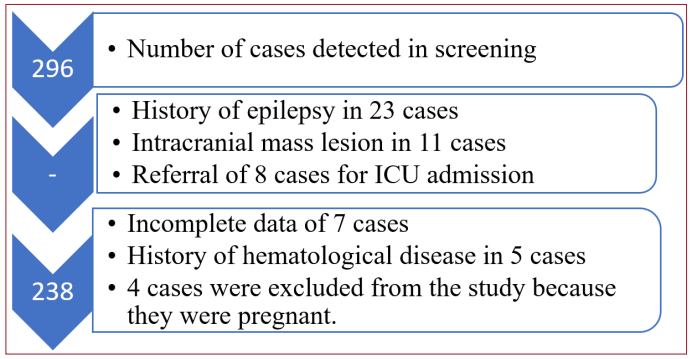
The study was planned to be performed in the emergency department of a tertiary hospital. The number of admissions to the emergency department is an average of 800 patients per day. Our hospital has a bed capacity of 1100 and is one of the largest hospitals in the region. It has units that require all critical interventions, such as aortic dissection, cerebrovascular infarction, coronary angiography laboratory, and is the region's important critical patient care and stroke center.

Patients with a definitive diagnosis of ICH and no history of trauma were included in the study. Patients under the age of 18, pregnant patients and patients with missing data were excluded from these patients. Patients who died without imaging studies, whose outcome could not be followed, and whose medical history was unknown were not included in the study. Patients with a history of any intracranial mass or space-occupying lesion in their medical history, history of epileptic disease and drug use were also excluded from the study.

Patients who were in shock when they applied to our clinic and whose vital data were unstable were not included in the study.

Data collection

For the study, patients were identified by scanning the file and automation system (Enlil Hospital Automation System). "I61.0-9, I63.0-9, I64.0-9, I65.0-9, I66.0-9, I67.0-9 and I68.0-9) ICD10 diagnostic codes from the automation system for ICH used. As a result of the scan, 196 patients were identified. Of the 296 detected cases, 23 had a history of epilepsy, 11 had a history of intracranial space-occupying mass lesion, 8 were referred to another health center due to lack of space in the intensive care unit (ICU), 7 had missing data were not included in the study because 5 of them had a history of hematological disease and 4 of them were pregnant patients.



Study Group

Demographic data of the cases, the way they came to the hospital (outpatient and ambulance), whether they had epileptic seizures, duration of epileptic seizures (prehospital, emergency service and hospitalization service), number of seizures, bleeding sites of the cases (frontal, parietal, temporal, occipital and brain stem). classified) as well as bleeding sites (supratentorial, infratentorial and intraventricular hemorrhages), the glaskow coma scale of the cases (GCS), the National Institutes of Health Stroke Scale score (NIHSS), admission vitals, whether antiepileptic therapy was initiated, response to epileptic medication, hospitalization or discharge status, outcomes, and 30-day mortality were evaluated. The cases of seizures after discharge were obtained from the medical records of the cases (e-pulse system) and mortality information was obtained from the T.C. It was evaluated from the death notification records of the Ministry of Health.

Bleeding areas and epilepsy evaluation of the cases were evaluated by a neurologist and a neurosurgeon. No electroencephalogram (EEG) or test was performed for epilepsy of the cases. A diagnosis of epileptic seizure was made with a complete clinical evaluation. The diagnosis of epilepsy was made according to the ILAE 2007 study (9). In the classification of the seizure as early and late; early seizure up to the 14th day after bleeding; Seizures observed on the 14th day and above were classified as late seizures.

Statistical Analyzes

It was done using SPSS 28.0 for Windows® statistical program (IBM Inc. Chicago, IL, USA). Number, percentage, mean, standard deviation, median, minimum and maximum were used in the presentation of descriptive data. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov Test. Pearson chi-square test and Fisher's Exact test were used to compare categorical data. T Test was used to compare two independent numerical data and Kruskal Walles Test was used to compare triple numerical data.

In our study, we first performed a regression analysis of the factors that have an effect on mortality from epilepsy. We then included the significant factors in the multiple regression analysis.

Results were considered significant at $p<0.05$, with a 95% confidence interval.

RESULTS

Our study was conducted with 238 people. 186 of these cases did not have seizures after ICH, both before and after hospitalization. Of the 52 cases, 9 had epileptic seizures before the hospital and 43 had epileptic seizures after the hospital, in the early and late period. In this way, the cases were classified as having seizures (seizure +) and non-seizure (seizure -) and data were presented.

In the demographic data of the cases; median age was 69.0 (80.75-58.25) years in those with seizure +; seizure – median age in cases was 69.0 (77.25-58) years and median age in all cases was 69 (78-58) years; There was no significant difference between the groups in terms of age. Seizure + 57.7% of cases were male; seizure – 52.7% of the cases were male and the groups were not different in terms of gender. There was no significant difference between seizure + and - groups in terms of hypertension, diabetes, coronary artery disease and dyslipidemia history. A history of ICH was found to be significantly higher only in cases with seizures + (p=0.044). There was no significant difference between the groups in the way of admission to the hospital, admission hours, admission vital signs, median values of admission GCS and NIHSS scores, and use of anticoagulant/antiaggregant (**Table 1**).

Table 1. Comparison of demographic and disease data of cases according to seizure status

Parametre	All patients (n=238)	Seizure - (n=186)	Seizure + (n=52)	p
Demographic				
Age (years)	69 (78-58)	69.0 (77.25-58)	69.0 (80.75-58.25)	.698**
Gender				.522*
Boy	128 (53.8)	98 (52.7)	30 (57.7)	
Woman	110 (46.2)	88 (47.3)	22 (42.3)	
Hypertension	142 (59.7)	111 (59.7)	31 (59.6)	.992*
diabetes	74 (31.1)	56 (30.1)	18 (34.6)	.428*
Coronary Artery Disease	44 (18.5)	30 (16.1)	14 (26.9)	.074*
ICH disease history	13 (5.5)	9 (4.8)	4 (7.7)	.048*
dyslipidemia	28 (11.8)	23 (12.4)	5 (9.6)	.114*
Disease				
Admission time				.224*
00:00-06:00	76 (31.9)	58 (31.2)	18 (34.6)	
06:00-12:00	58 (24.4)	49 (26.3)	9 (17.3)	
12-00-18:00	29 (12.2)	19 (10.2)	10 (19.2)	
18:00-00:00	75 (31.5)	60 (32.3)	15 (28.8)	
Application Form				.420*
ambulatory	36 (15.1)	30 (16.1)	6 (11.5)	
by ambulance	186 (78.2)	144 (77.4)	42 (80.8)	
Enthusiasm	16 (6.7)	12 (6.5)	4 (7.7)	
Vitals at the Time of Application				
Systolic Blood Pressure	144 (166.25-129)	145.5 (167-130.75)	137.5 (164.25-122)	.101**
Diastolic Blood Pressure	89 (100-77.75)	90 (100-78)	85 (99.5-68.25)	.181**
Heart rate	95 (115-76)	95 (114-78)	98.5 (116.75-76)	.976**
Respiratory rate	16 (18-14)	15 (18-13.75)	16 (20-14)	.242**
GCS	13 (14-12)	13.0 (14.0-12.0)	13.0 (14.0-10.0)	.210**
NIHSS	8 (16-5.75)	8.0 (16.0-5.0)	10.5 (17.5-6.0)	.113**
Anticoagulant/antiaggregant use				.109*
yes	34 (14.3)	23 (12.4)	11 (21.2)	
no	204 (85.7)	163 (87.6)	41 (78.8)	

*: Pearson $\chi 2$ Testi; **: Kruskal Wallis Test used. GCS: Glasgow coma scale, NIHSS: National Institutes of Health Stroke Scale

Bleeding was detected in the near cranial computed tomography imaging after the cases were admitted to the hospital, and the areas and amounts of bleeding were recorded. In the light of these data; In cases with seizures, the most bleeding was observed in the temporal, parietal and brain stem, respectively; In cases without seizures, it was observed that it was most common in the temporal, brain stem and parietal regions. In addition, while seizure + is not observed in cases with bleeding in other regions; seizure – bleeding was observed in the frontal region, occipital and cerebellar regions of the cases. This situation was found to be statistically significant. When classified as tentorial, there was no significant difference between bleeding sites in terms of seizures. There was no significant difference between the two groups in terms of the amount of bleeding. The relationship in terms of seizures was examined in the cases in which prophylactic antiepileptic treatment was started, and no significant difference was found. Again, no significant difference was found in terms of 7-day or 30-day mortality with the initiation of antiepileptic treatment. In terms of hospitalization, it was observed that the hospitalization status was significantly higher in cases with seizures; Again, it was observed that the rate of exitus in seizure + cases was significantly higher than in seizure - cases. Again, this significant difference was also reached when the 7-day and 30-day mortality data were compared with the seizure + and - groups. While no significant difference was found between the seizure groups in terms of hospitalization; In terms of follow-up times, the median values of the follow-up periods in seizure + cases were the same, but there was a significant difference between quartiles (p<0.001) (**Table 2**).

Table 2. Evaluation of the results of the patients' disease states and outcomes

Parameter	All (n=238)	Seizure - (n=186)	Seizure + (n=52)	p
Bleeding Site				0.003
frontal	14 (5.9)	14 (7.5)	0 (0.0)	
parietal	25 (100.0)	18 (9.7)	7 (13.5)	
temporal	164 (68.9)	121 (65.1)	43 (82.7)	
occipital	5 (2.1)	5 (2.7)	0 (0.0)	
cerebellar	7 (2.9)	7 (3.8)	0 (0.0)	
Brainstem	23 (9.7)	21 (11.3)	2 (3.8)	
Bleeding Site (tentorial)				.365
supratentorial	179 (75.2)	136 (73.1)	43 (82.7)	
infratentorial	12 (5.0)	10 (5.4)	2 (3.8)	
intraventricular	47 (19.7)	40 (21.5)	7 (13.5)	
Amount of Bleeding (mL)	10 (12-8)	10 (12-8)	10 (13.75-8)	.509
Presence of Seizure				-
No Seizure	186 (78.2)	-	186 (78.2)	
Early Seizure	25 (10.5)	-	25 (10.5)	
Late Seizure	27 (11.3)	-	27 (11.3)	
History of Prehospital Seizure				-
yes	9 (3.8)	-	9 (17.3)	
no	229 (96.2)	-	43 (82.7)	
Prophylactic Antiepileptic Use				.109
yes	34 (14.3)	23 (12.4)	11 (21.2)	
no	204 (85.7)	163 (87.6)	41 (78.8)	
Hospitalization Status				0.044
Discharge	5 (2.1)	5 (2.7)	0 (0.0)	
Service Admission	164 (68.9)	134 (72.0)	30 (57.7)	
ICU Admission	58 (24.4)	38 (20.4)	20 (38.5)	
Self-desired exit/treatment refusal	11 (4.6)	9 (4.8)	2 (3.8)	
outcome				<0.001
Discharge	172 (72.3)	145 (78.0)	27 (51.9)	
exit	66 (27.7)	41 (22.0)	25 (48.1)	
Mortality (7 Days)				.001
yes	26 (10.9)	14 (7.5)	12 (23.1)	
no	212 (89.1)	172 (92.5)	40 (76.9)	
Mortality (30 Days)				<0.001
yes	66 (27.7)	41 (22.0)	25 (48.1)	
no	172 (72.3)	145 (78.0)	27 (51.9)	
Hospitalization Time (mean / day)	8 (14-5)	8 (14-5)	11.5 (15-5)	.303
Follow-up Time (average / day)	30 (30-21)	30 (30-30)	30 (30-11.25)	<0.001

*: Pearson $\chi 2$ Testi; **: Kruskal Wallis Test used. ICU: Intensive Care Unit

Table 3. Regression analysis of parameters affecting mortality

Parameter	7 Day Mortality			30 Day Mortality		
	OR (%95 CI)	Wald test	p	OR (%95 CI)	Wald test	p
Gender	0.578 (0.223-1.498)	1.273	0.259	0.527 (0.260-1.067)	3.167	0.075
Age	1.021 (0.984-1.058)	1.212	0.271	1.002 (0.975-1.029)	0.019	0.890
Amount of Bleeding	0.940 (0.810-1.090)	0.676	0.411	0.917 (0.819-1.027)	2.231	0.135
Seizure	0.269 (0.101-0.717)	6.898	0.009	0.249 (0.112-0.553)	11.649	<0.001
Arrival NIHSS	0.862 (0.801-0.928)	15.739	<0.001	0.834 (0.788-0.883)	38.458	<0.001

NIHSS: National Institutes of Health Stroke Scale, OR: Odds Ratio, CI: Confidence interval

When the effect of seizure type on 30-day mortality was examined, it was observed that mortality was significantly higher in cases with late seizures (44% vs 51.9%; p<0.001).

The effects of age, gender, amount of bleeding, seizure + and admission NIHSS score, which are thought to be effective on mortality, on 7-day and 30-day mortality were investigated. It was observed that the increase in seizure and presentation NIHSS scores had a significant positive effect on both 7-day and 30-day mortality (**Table 3**).

DISCUSION

In this study, we aimed to investigate whether seizures have an effect on early mortality in patients who develop epileptic seizures after ICH. In the data of our study, we found that both the 7-day and 30-day mortality rates of cases with epileptic seizures were significantly higher when compared to cases without seizures.

Similarly, in the study of Szaflarski et al.[10] investigated the incidence of epileptic seizures and the effect of seizures on mortality in stroke patients; reported that seizures in hemorrhagic stroke cases cause a significant increase in 30-day mortality. Again, in a study by Vespa et al.[11] There are data that the presence of seizures in patients after hemorrhagic stroke causes an increase in mortality.

In some studies in the literature, there are publications stating that there is no significant relationship between seizure status and mortality in patients with intracranial hemorrhage. In the study of Claessens et al.[8] it was stated that epileptic seizures were not associated with mortality. In the study of Labovitz et al.[12] it was found that epileptic seizure was not associated with 30-day mortality in both ischemic and hemorrhagic stroke cases. In addition to these, some studies have shown that mortality is reduced in patients with ICH who have had seizures. In the prospective cohort study of Brüning et al.[13] It has been reported that mortality is reduced in ICH patients with seizures. Again, in the study of Mehta et al.[14] It has been reported that mortality is reduced in ICH patients with seizures.

It has been stated that there are many factors affecting mortality in ICH patients. In the study of Claessens et al.[8] high NIHSS score was associated with mortality; In addition, advanced age, high male gender, peripheral vascular disease, and the presence of anticoagulant/antiplatelet drug use were reported to be risk factors for mortality. In our study, we found that high NIHSS scores were associated with mortality; We could not detect a significant relationship between age, gender, location of bleeding and mortality. In this respect, although our study was found to be compatible with the literature in terms of NIHSS, our study did not find any significance in terms of the increased risk of mortality in terms of age, gender and anticoagulant use, and different results were found in the literature. We think that this difference may be due to the number of samples in our study.

There is no clarity in the literature on the use of prophylactic and therapeutic antiepileptic drugs for epilepsy after ICH. In some studies, there are studies reporting that long-term use of antiepileptic drugs benefits neurological recovery and survival. In their study, Claessens et al. reported that it reduced mortality and improved survival, independent of seizure frequency, in cases using antiepileptic drugs for 10 years.[8] In the study of Gilad et al. with patients with ICH; reported positive results in neurological recovery after valproate treatment given to patients.[15] In our study; It was seen that the use of antiepileptic in the cases did not have a significant effect on mortality. We think that more comprehensive and long-term prospective studies on this subject will provide clarity on this issue in the literature.

When the effects of early and late seizures on mortality were examined; Mortality was found to be significantly higher in late-stage seizures at 30-day follow-up. Therefore, as a result of our study; We think that mortality and morbidity will be prevented by making the follow-up periods of seizure patients more carefully and with shorter intervals.

Limitations of study

Our study has several limitations. One of our limitations is that the data obtained because our study was conducted retrospectively were within the scope of the information received by the physicians of the patients. Another limitation of ours is; Although there was not a large enough population to change the study data, the cases that could not be followed up in this process and were excluded due to missing data were still considered as a limitation.

CONCLUSION

We determined that the epileptic seizure observed after ICH had an effect on mortality. Therefore, it is necessary to be careful in terms of mortality in cases with seizures. Especially in cases with late seizures, mortality is higher than in cases

with early seizures, so it is necessary to be careful in terms of mortality in cases with late seizures. In addition, we found that the use of antiepileptic drugs did not affect mortality. We think that with more comprehensive studies, more clear information will be obtained on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: İzmir Katip Çelebi University Non-Interventional Clinical Studys Institutional Review Board (date: 18.02.2021 number: 071).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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