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Long-Term Mortality of Nonischemic Seizures to Epilepsy After Open Heart Surgery

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Abstract

Objectives: This study aims to investigate the effect of isolated seizures turning into epilepsy on long-term mortality after open heart surgery.

Material and Methods: All patients who underwent cardiopulmonary bypass were analyzed retro-spectively. Patients with generalized or focal new-onset seizures in postoperative period were eligible for the study. Of them, patients with previous neurological disturbances were kept out of the analysis. Postoperative neurological complications including ischemic or hemorrhagic events were also exclud-ed from the study.

Results: Patients with seizure had a substantially higher incidence of operative mortality. Twenty-five epileptic patients (0.88%) were reviewed. Two seizures occurred in 6 patients (24%) in a median of 1 day postoperatively. Three patients (12%) had repeated seizures, 1 (4%) of them had twice. Twenty-four patients (96.0%) were discharged without new-onset neurologic deficit.

Conclusions: The emergence and recurrence of a new postoperative seizure in patients may increase the possibility of death in the postoperative hospital and in the long term.

Keywords: Open heart surgery, seizures, epilepsy, mortality

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Introduction

Neurological complications after cardiac surgery can manifest themselves with very different clinical results. Some of them manifest as stroke, short- and long-term memory dysfunction, delirium, cognitive decline, transient neurological dysfunction, and seizure. All of them involve varying degrees of neurological damage that can affect perioperative outcomes, long-term survival, and quality of life[1,4]. Seizures occurring after cardiac surgery are thought to be the result of focal or global cerebral ischemia from hypoperfusion, particulate or air emboli, metabolic derangements[5]. Different risk factors have been linked to postoperative seizure (PS), including aortic atherosclerosis, cardiopulmonary bypass time, and use of deep hypothermic circulatory arrest[6]. Acute symptomatic seizures, nonepileptic events, and epileptic discharges, whether transient or permanent, related to acute brain injury or metabolic disorders, can also result in mortality and morbidity[5-6]. These new-onset seizures and epilepsy can have a lesser impact on these postoperative outcomes than the other disastrous neurological complications, such as stroke. With this sentence, it is aimed to express neurological events with higher morbidity and mortality, such as ischemic or hemorrhagic stroke. The seizure is the definition of focal or generalized convulsions triggered by specific motor, sensory, or cognitive stimulation of one time[7]. It can be frequently localized and does not seem from one to each other in terms of location and lateralization. Therefore, seizure occurring in the postoperative period is an initial manifestation of epilepsy and essential to make a differential diagnosis from the ischemic background. It can turn to epilepsy with repeated seizures with approximately 2%-3% and also may be generalized or localized[8]. Generalized epileptic discharge can be triggered by the same point and can include cortical and subcortical structures by rapidly engaging. Unlike, focal epileptic status can be limited to one hemisphere of the brain by originating from subcortical structures[7]. A seizure can resolve in the early postoperative period and necessitates no longer medical treatment; otherwise, epilepsy needs electroencephalography and magnetic resonance imaging of the brain to determine recurrency, close follow-up, and long-term medical drug therapy. The present study was managed to elucidate the frequency and prognosis of non-ischemic postoperative seizures, not previously diagnosed, transforming into epilepsy in a cardiac surgical cohort.

Materials and Methods

Preparation of Database

This retrospective study was performed in a high-volume training and research hospital. The study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (decision no: 2021/04-23, date: 15.04.2021). All patients having open-heart surgery were reviewed from hospital records to identify new neurological events in the postoperative period from January 2009 to March 2020 in University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital.

Patients who had a preexisting seizure disorder or those on preoperative anticonvulsant medication or who developed significant stroke or transient ischemic attack in the preoperative period were excluded from this analysis. Postoperative neurological events based on ischemia or hemorrhage were also kept outside the study. Then, variables belonging to the patients with new-onset seizures and epilepsy after the operation were entered prospectively during the hospital stay. The hospital database was also queried to gather additional variables such as electroencephalography, computerized tomography, and diffusion magnetic resonance of the brain. After the discharge from the cardiovascular clinics, cardiac and neurological records in outpatient clinics were examined. Then, the Social Insurance System (SGK) was tested for the survival and date of death of the patients out of the hospital.

Patients who experienced convulsive seizure activity and some of them who turned to epilepsy in the postoperative

period had open-heart surgery with cardiopulmonary bypass while intubated or not. Electroencephalography (EEG) was taken in all patients with seizures or epilepsy in the postoperative intensive care unit. The convulsive activity was confirmed and treated immediately with intravenous or oral antiepileptic drugs by the neurologist. Non-contrast head computed tomography was provided to all hemodynamically stable patients after a seizure event happened for the first time. A delayed computed tomography scan was obtained in extubated patients or in repeated conditions or in those intubated but with achieved right cardiovascular balance. Patients who did not have cardiovascular problems in their transportation to tomography were described. The neurologist arranged antiepileptic medications at discharge and outpatient follow-up.

Operative Technique

All patients had the same standard anesthesia protocol, including midazolam, fentanyl, either propofol or thiopental, rocuronium, cisatracurium, or vecuronium. Cardiopulmonary bypass was established with the mean arterial pressure between 70 and 90 mmHg, hematocrit keeping above 25% under moderate hypothermia (32 degrees). Proximal aortic root or aortic arch surgery was performed under 28 degrees of C with antegrade cerebral perfusion maintaining flow at 10 mL/kg. Rewarming was provided until an esophageal temperature of 36 °C with the maximal gradient of 10 °C between the patient and perfusate. Acid-base management was provided with an alpha-stat strategy in all patients. Deairing maneuvers were applied cautiously with the aortic and atrial venting. The primary endpoint was an evaluation of the effect of postoperative seizures turning into epilepsy on postoperative mortality. Secondary endpoints were as follows: the effect of both postoperative seizure and epilepsy on postoperative morbidity and long-term effects of both on anti-epileptic drug therapy were secondary endpoints. The patients were followed up by applying the standard cardiac surgery protocol in the cardiovascular

Study flow chart

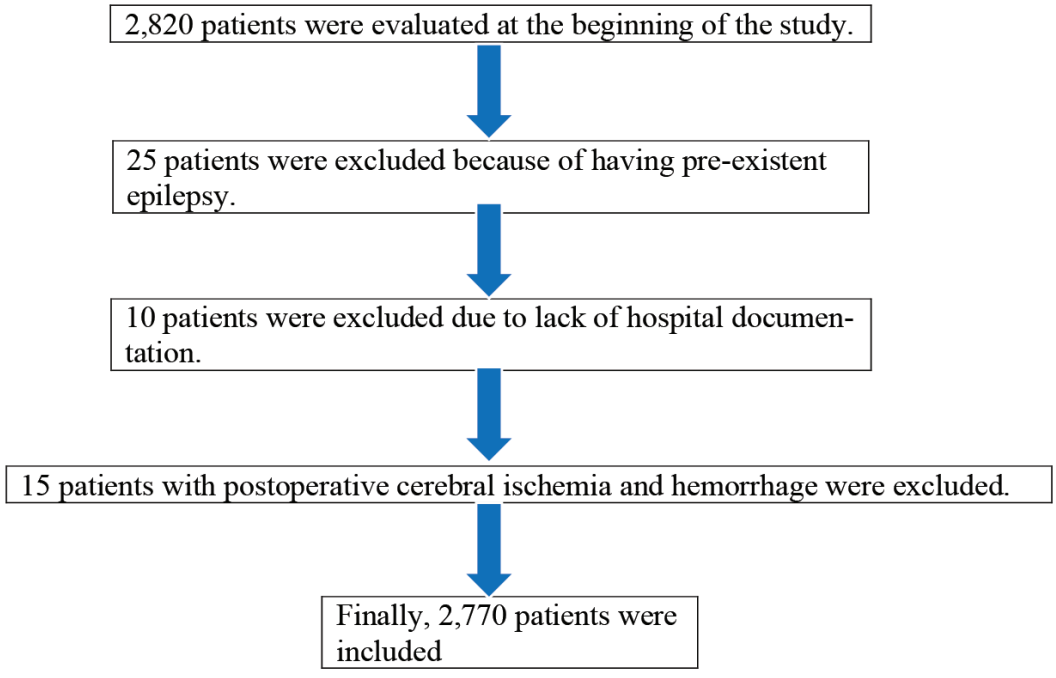

Figure 1. Study flow chart

surgery intensive care unit. All patients were given cefazolin sodium as an antibiotic. We used low doses of tranexamic acid in patients who used various medications due to bleeding in the postoperative period.

Statistical Analysis

The analysis was performed using IBM SPSS Statistics for Mac Version 20 (IBM Corp. Released 2011, Armonk, NY). Numerical variables were summarized as mean ± standard deviation values. Categorical variables were evaluated with cross-table analysis. Comparison of various subgroups was made using c2 test. A $p<0.05$ was considered statistically significant.

Results

A total of 2,820 patients had cardiac surgery during the study period. Twenty-five of them had postoperative seizures (0.90%). Preoperative characteristics are given in Table 1. The seizure group had a significantly greater percentage of male gender, a greater percentage of Canadian Cardiovascular Society class, worse renal function, a higher percentage of valvular heart disease and chronic obstructive pulmonary disease. Postoperative morbidity and mortality are demonstrated in Table 2. Patients with seizure group had a substantially higher incidence of operative mortality (4 of 25, 16% vs. 123 of 2,745, 4.4% p=0.0026). Considering the 30-day status of the seizure group, it is seen that the occurrence of deaths is more (4 of 25, 16% vs. 42 of 2,745, 1.5% p=0.0026) after open heart surgery. When we assessed the long-term mortality, we saw that there was a statistically significant elevation in the seizure group. (7 of 25, 28% vs. 145 of 2,745, 5% p=0.0004). Whereas, there was no statistically significant difference in 1-year mortality between the results of both

Table 1. Preoperative characteristics

Variables	All patients (n=2,770)	Seizures (n=25)	Non-seizures (n=2,745)	p-value
Age, years (mean ± SD)	68.20±12.21	72.64±11.4	67.13±18.3	0.051
Males	1,805 (65.1)	15 (60.0)	1,790 (65.2)	0.649
Elective	1,670 (60.2)	13 (52.0)	1,657 (60.3)	0.525
Urgent/emergency	1,150 (41.5)	12 (48.0)	1,138 (41.4)	0.484
Reoperation	315 (11.3)	1 (4)	314 (11.4)	0.243
CCS class 3/4	628 (22.6)	10 (40.0)	618 (22.5)	0.09988
EF %	45±13.8	50±15.1	52±11.8	0.097
Creatinine mg/dL	1.32±1.64	1.45±5.64	1.26±1.53	0.908
CAD	1,184 (42.7)	8 (32.0)	1,176 (42.8)	0.485
Valvular disease	1,466 (52.9)	11 (44.0)	1,455 (53.0)	0.514
MI	141 (0.5)	3 (12.0)	138 (0.50)	0.045
PAD	705 (25.0)	1 (4)	704 (25.6)	0.039
CHF	591 (21.3)	2 (8)	589 (21.4)	0.174
COPD	168 (6)	3 (12)	165 (6)	0.045
Diabetes mellitus	705 (25)	4 (16)	701 (25.5)	0.396
DIALYSIS	59 (2.1)	2 (8)	57 (2)	0.313
Cardiogenic shock	168 (6)	2 (8)	166 (6)	0.315
AF	338 (14)	4 (16)	334 (12.1)	0.548

AF: Atrial fibrillation, CCS: Canadian Cardiovascular Society, CAD: Coronary artery disease, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, EF: Ejection fraction, SD: Standard deviation, n: Number

groups. (0 of 25, 0% vs. 41 of 2,745, 1.4% p=0.3173). In the seizure group, the rate of patients who were revised for bleeding was statistically significantly higher (3 of 25, 12% vs. 132 of 2,745, 4.8% p=0.045). Frequencies of patients with prolonged intubation more than 3 days, dialysis patients and reoperated patients were not significantly different between the two groups.

Twenty-five epileptic patients (0.90%) were reviewed. Two seizures occurred in six patients (24%) in a median of 1 day postoperatively. Only one of three patients who had recurrent seizures had two attacks. Three patients (12%) had repeated seizures, one (4%) of them had twice. All seizures were classified as generalized tonic-clonic. Head computed tomography was performed in 21 patients (84%). Head computed tomography of these patients was not taken preoperatively. Computed tomography scans were performed on patients who had a postoperative attack. Twenty-four patients (96.0%) were discharged without new-onset neurologic deficit.

Discussion

The frequency of seizure in adults during lifetime it is about 8%-10%. Of them, 2%-3% turn into epilepsy[9]. Initially, it is essential to assess the predisposing factors such acute systemic disorders or acute brain damage. The relationship between the brain injury and cardiopulmonary bypass is highly relevant[10]. Hypoperfusion, atheroembolism, transient coagulation disorder and preexisting vascular disease, or a combination of these factors are responsible for the acute brain damage. Major of minor brain damage results in various clinical scenarios including stroke, cognitive changes, encephalopathy, delirium or seizure. Seizures occur after abnormal electrical discharge of the brain mostly related to the hypoperfusion. Unfortunately, some of them cause lifelong epilepsy, resulting in taking daily anti-epileptic drug in addition to cardiac pills[10].

After one episode of seizure, it is required to determine recurrence of the convulsion that determines which part of the brain is damaged. Some seizures can resolve spontaneously with the triggering factors that are eliminated. They occur as transient due to abnormal excessive activity neuronal activity of the brain. Acute seizures can result in permanent focal or generalized variation. Focal seizure originates from one part of the brain hemispheres. Unlikely, generalized seizures rapidly engage the whole brain. Minority of these seizures can transform to epilepsy. The current definition of epilepsy includes "a probability of further seizures similar to the general recurrence risk after two unprovoked seizures (at least 60%) occurring over the next 10 years"[11]. Evidence should be supported by diagnostic work-up such as electroencephalogram and magnetic resonance imaging of the brain[12]. After cardiac surgery, the seizure remains uncertain. Although seizures and epilepsy have been studied in detail, there is little consensus on the etiology, incidence, and long-term prognosis of this event after

Table 2. Postoperative morbidity and mortality

Variables	All patients (n=2,770)	Seizures (n=25)	Non-seizures (n=2,745)	p-value
Operative mortality	127 (4.5)	4 (16)	123 (4.4)	0.002
30-day mortality	46 (1.6)	4 (16)	42 (1.5)	0.002
1-year mortality	41 (1.4)	0 (0)	41 (1.4)	0.317
Lon-term mortality (≥1.5 years)	152 (5.4)	7 (28)	145 (5.2)	0.0004
Reoperation	215 (7.7)	1 (4)	214 (7.7)	0.471
Intubation >72 h	324 (11.6)	3 (12)	321 (11.6)	0.866
Dialysis	59 (2.1)	2 (8)	57 (2.0)	0.313
Revision for bleeding	135 (4.8)	3 (12)	132 (4.8)	0.045

n: Number

cardiovascular surgery[13]. The pathogenesis of seizures is probably multifactorial, it is generally accepted that solid or gaseous intraoperative microembolization, as well as cerebral inflammation and edema, plays an important role[6]. Nevertheless, systemic inflammation therefore might be a potential factor leading to abnormal EEG findings, delirium and seizures. Systemic inflammatory response also has been observed after cardiopulmonary bypass[14]. Seizures and epilepsy will have independent results in open cardiac surgery operations on impaired brain function in elderly brains[15]. Preoperative renal dysfunction, valvular surgery, advanced age, long-term cardiopulmonary bypass, previous cardiac surgery, and peripheral vascular disease appear as increasing risk factors for a seizure[6]. Non-convulsive seizures may also be associated with altered cognition and altered cognition occurs commonly after cardiac surgery. While it has been described that clinically evident seizures occur in 1%-4% of patients after cardiac surgery[6], it is unknown whether non-convulsive seizures also occur at a higher frequency in this population. In our study group, the rate of detecting seizures was approximately 0.9%. It has also been suggested that post-cardiac surgery seizures are associated with longer mechanical ventilation, longer length of stay in hospital, and overall increased morbidity and mortality[16]. It is remarkable that the long-term mortality of the seizures group was high. However, no difference was found in the death rates in the first year in both groups. There is a need for a more analytical assessment of death. Although there is no difference in terms of mortality in both groups in the first year, the mortality rate is increasing in the long-term seizures group. The reasons for this need to be investigated further. This is one of the shortcomings of our study. Similar to the study of Goldstone et al.[6], death was more common in the seizures group in our study. Is there a cardiovascular effect that we do not know about in the long-term seizures group? We do not know that. A very high proportion of seizures, especially for critically preoperative status of open-heart surgery patients, is non-convulsive in nature and can only be detected using continuous video-electroencephalographic (cEEG) monitoring. Non-convulsive seizures can be detrimental to cerebral function and may cause injury. Detection of non-convulsive seizures can be missed in cardiac surgery intensive care. This is the second missing point of our study. Seizures occur infrequently after cardiac surgery and are generally associated with a good prognosis[17]. Prophylactic continuous EEG monitoring is unlikely to be cost-effective in this population. Detection of seizures after open-heart surgery and their short, medium, and long-term results on death should be evaluated in more detail. Therefore, there is always the possibility of having more patients than diagnosed attack patients. It is certain that future studies with a higher number of cases will contribute to the subject[18].

Study Limitations

This study had some limitations. This study was designed as a retrospective study. Continuous EEG monitoring was not available in all postoperative patients, so we cannot rule out that some brief, self-limiting or non-convulsive seizures were overlooked.

Conclusion

Our series is a study examining the incidence of seizures, especially after cardiac surgery, and the effect of seizure on morbidity-mortality in a large case group. The heterogeneity of the literature on this subject requires prospective, multi-center studies.

Ethics

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital Ethics Review Board in accordance with the Declaration of Helsinki (decision no: 2021/04-23, date: 15.04.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: K.K., A.G.K., Design: K.K., A.G.K., Data Collection and/or Processing: K.K., A.G.K., Analysis and/or Interpretation: K.K., A.G.K., Writing: K.K., A.G.K.

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

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