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Original Article

Effects of epilepsy control following decompressive craniectomy on mortality and morbidity in epileptic patients with malignant MCA infarction

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Abstract

Aim: The present study aims to investigate the effects of seizure or epilepsy formation on mortality and morbidity in epileptic patients after craniectomy.

Material and Methods: The patients were divided into the following groups: Group 1, those who had no seizures, but were routinely treated with 3x100 mg of epanutin daily (n=6), Group 2, those who had at least one or multiple seizures and were initiated a second antiepileptic drug in addition to 3x100 mg of epanutin daily (n=13), and Group 3, those who had multiple seizures and who were sedated or narcotized in addition to being treated with 3x100 mg of epanutin daily (n=7). All patients underwent decompressive craniectomy within a maximum period of 48 hours and their characteristics such as age, gender, localization of infarct, hemiplegia, monoplegia, operation time, Glasgow coma and outcome scales were recorded.

Results: According to the Glasgow Outcome Scale, 1 patient in Group 1, 8 patients in Group 2 and 6 patients in Group 3 died and there was a significant increase in patient losses in Group 2 and Group 3 compared to Group 1 ($p<0.05$). 10 patients continued to live their lives with the support of home-care services and 2 patients with other forms of help.

Conclusion: It was seen that there is a high incidence of seizure and epilepsy in MMCA infarcts after decompressive craniectomy and this significantly increased mortality or dysfunctional recovery if epilepsy could not be brought under control.

Keywords: Decompressive craniectomy; epilepsy; glasgow coma scale; MMCA infarction, mortality

INTRODUCTION

Vascular pathologies are the most common cause of epilepsy and the incidence of vascular epilepsy arising from symptomatic epilepsy varies between 2-15% (1). Stroke is the most important risk factor in the development of epileptic seizures and it is known to be responsible for the subsequent increase in the number of seizures (2,3). Decompressive craniectomy surgery is performed as a result of raised intracranial pressure after vasospasm in hemispheric brain lesions, particularly in cases of cerebral infarct (4). In malignant middle cerebral artery (MMCA) infarctions, an epileptic seizure occurs when brain edema develops with ischemia on the MMCA (5,6). Decompression craniectomy is performed to reduce the intracranial pressure in malignant MMCA infarctions (7) Some researchers have suggested that craniectomy increases the risk of epilepsy in some cases such as traumatic brain injury (8). In a study, it was reported that a quite large cortical lesion created by the decompressive craniectomy performed in patients with MMCA infarction was an important risk factor for more frequent epilepsy seizures (9). Exposure to ischemic edema of a hemisphere increases mortality in malignant MCA infarcts (10). The Glasgow Coma and Outcome Scale is known to be a reliable, effective and objective method for evaluating preoperative and postoperative consciousness of patients before and after decompressive craniectomy surgery (11,12). The present study aims to evaluate the incidence and development of seizures between groups before and after surgery by considering Glasgow Coma and Outcome Scale data in patients with malignant MCA stroke, who underwent decompressive craniectomy in our centers.

MATERIAL and METHODS

This study, which was conducted retrospectively (2019/3-7) with the permission of the local ethics

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committee and necessary permissions from the relevant institutions, was carried out by examining the records of epileptic patients, who had MMCA infarction, and were being treated at the brain and neurosurgery clinics, at the Adiyaman Training and Research Hospital before and after decompressive craniectomy surgery. The study population consisted of 26 patients, who underwent decompressive craniectomy in these five hospitals between March 2010 and June 2018 to reduce the shift due to MMCA infarction. The patients were divided into those who had had no seizures, but were routinely treated with 3x100 mg of epanutin daily, Group 1 (n=6), those who had at least one or multiple seizures and were initiated a second antiepileptic drug in addition to 3x100 mg of epanutin daily, Group 2 (n=13), and those who had multiple seizures and who were sedated or anaesthetized in addition to being treated with 3x100 mg of epanutin daily, Group 3 (n=7). All patients underwent decompressive craniectomy within a maximum period of 48 hours and their characteristics such as age, gender, localization of infarct, hemiplegia, monoplegia, operation time, Glasgow Coma and Outcome Scales were recorded. This was followed by an evaluation of the patients according to these variables or their relations between the groups.

Patients, who were diagnosed with MMCA infarctions in their neurological and radiological examinations in the emergency departments, intensive care units, and neurological clinics were included in the study. Multiple localization infarction, in-vehicle and out-of-vehicle traffic accidents, falling from a height, intracerebral hematoma and epileptic seizures due to various causes were determined as our study exclusion criteria and all patients with these characteristics were excluded from the study. The anterior-posterior X-ray, computed tomography, magnetic resonance imaging and digital subtraction angiography examinations of all patients included in the study were performed, and an enhanced assessment of the infarct margins of the patients was ensured.

Statistical Analysis

The SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used in the statistical analysis of the variables. The conformity of the univariate data to the normal distribution was evaluated by the Shapiro-Wilk test. The one-way ANOVA (Robust Statistics: Brown-Forsythe), a parametric test, was used for the comparison of more than two groups according to quantitative variables, while the Kruskal-Wallis H Test, a non-parametric test, was used with the Monte Carlo results and the Dun's test was used for the Post Hoc analysis. The Wilcoxon signed -ranks test was used with the Monte Carlo results in the comparison of the pre- and postoperative results. The Fisher-Freeman-Halton test was used with the Monte Carlo simulation results in the comparison of the categorical variables and the column ratios of the significant results were compared and expressed according to the Benjamini-Hochberg corrected p-value results. The Neural Network (Multilayer Perceptron) was used to find and estimate the variable that had the highest significance for the groups. The Gradient Descent was used for the optimization algorithm, the hyperbolic tangent for the hidden layer activation function, and the softmax for the layer activation function. The mini-batch method was used for the training data selection and it was adjusted as 100% for the Training set and as 0% for the Testing set. The quantitative data were shown as Mean±SD. (Min/Max) and Median (Min/Max), and the categorical variables were shown as n (%) in the tables. The variables were analyzed at the 95% confidence level and a p-value lower than 0.05 was considered as significant.

RESULTS

A total of 27 epileptic patients with malignant MCA stroke, who had undergone decompressive craniectomy, were recorded between March 2010 and June 2018. Of the patients, 51.8% were female, and 42.8% were male and the age range was 58-75. While 44.4% of the patients were operated on for left MCA infarction, 55.6% were operated on for right MCA infarction. The decompressive craniectomy was performed on average 22 hours after the admission of the patients to the relevant centers.

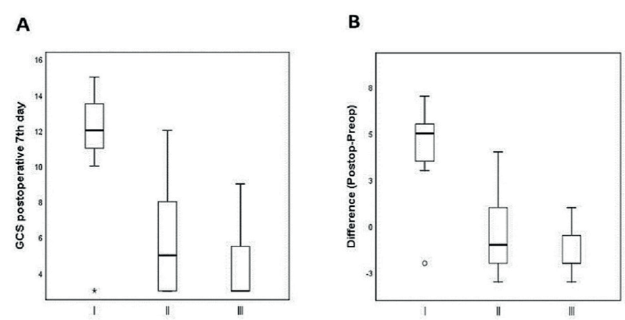

Figure 1. A) Postoperative GCS results and B) pre- and post-operative changes of epileptic patients undergoing decompressive craniectomy

This average time was determined as 22 hours in Group 1, 24 hours in Group 2 and 21 hours in Group 3. All patients had preoperative motor sensory loss, and hemiplegia was detected in 85.7% of patients in Group 1, 84.6% in Group 2, and 85.7% in Group 3. In addition, monoplegia was observed in 14.3% of the patients in Group 1, 7.7% in Group 2 and 42.9% in Group 3. Considering the mortality rates of all patients, 14.3% of patients in Group 1, 69.2% of patients in Group 2, and 85.7% of patients in Group 3 died despite the implementation of decompressive craniectomy (p<0.05) (Figure 2). There was a statistically significant difference between the groups, and the survival rates of the patients in Group 2 and Group 3 decreased significantly compared to Group 1 (p<0.05) (Table 1).

Table 1. Analysis of the demographical and functional data of the epileptic patients, who underwent decompressive craniectomy

	I (n=7)	II (n=13)	III (n=7)	P	Pairwise Comparison I-II	I-III	II-III
	Mean±SD. (Min/Max)	Mean±SD. (Min/Max)	Mean±SD. (Min/Max)				
Age	65.86±5.98 (58 / 75)	67.69±4.89 (60 / 80)	67.43±4.20 (61 / 74)	**0.738** [a]	ns.	ns.	ns.
	n (%)	**n (%)**	**n (%)**				
Gender							
Female	3 (42.9)	7 (53.8)	4 (57.1)	**0.999** [ff]	ns.	ns.	ns.
Male	4 (57.1)	6 (46.2)	3 (42.9)				
Place of lesion							
Right MCA	4 (57.1)	6 (46.2)	5 (71.4)	**0.698** [ff]	ns.	ns.	ns.
Left MCA	3 (42.9)	7 (53.8)	2 (28.6)				
GOS							
Death	1 (14.3)	8 (61.5) [I]	6 (85.7) [I]	**0.015** [ff]	**0.043**	**0.008**	ns.
Vegetative	0 (0)	2 (15.4)	1 (14.3)		ns.	ns.	ns.
Disability	4 (57.1)	3 (23.1)	0 (0)		ns.	ns.	ns.
Healing	2 (28.6)	0 (0)	0 (0)		ns.	ns.	ns.
Hemiplegia							
Absent	1 (14.3)	2 (15.4)	1 (14.3)	**0.999** [ff]	ns.	ns.	ns.
Present	6 (85.7)	11 (84.6)	6 (85.7)		ns.	ns.	ns.
Monoplegia							
Absent	6 (85.7)	12 (92.3)	4 (57.1)	**0.192** [ff]	ns.	ns.	ns.
Present	1 (14.3)	1 (7.7)	3 (42.9)		ns.	ns.	ns.
Mortality							
Live	6 (85.7) [II, III]	4 (30.8)	1 (14.3)	**0.014** [ff]	**0.019**	**0.008**	ns.
Ex	1 (14.3)	9 (69.2) [I]	6 (85.7) [I]		**0.019**	**0.008**	ns.

[a]One way ANOVA (Robuts Statistic :Brown-Forsythe), [ff] Fisher Freeman Halton (Monte Carlo); Post Hoc Test: Benjamini-Hochberg Correction, [k] Kruskal Wallis Test (Monte Carlo Post Hoc Test : Dunn's Test, [w] Wilcoxon Signed Ranks Test (Monte Carlo), SD: Standard Deviation, Min: Minimum, Max: Maximum, ns.: not significant

Table 2. Pre- and postoperative analysis of the GCS data of epileptic patients, who underwent decompressive craniectomy

	I (n=7)	II (n=13)	III (n=7)	P	Pairwise Comparison I-II	I-III	II-III
	Mean±SD. (Min/Max)	Mean±SD. (Min/Max)	Mean±SD. (Min/Max)				
Time (hour)	22 (15 / 40)	24 (8 / 40)	21 (10 / 35)	**0.923** [k]	ns.	ns.	ns.
GCS							
Preoperative	8 (5 / 8)	6 (4 / 8)	6 (4 / 8)	**0.052** [k]	ns.	ns.	ns.
Postoperative (7th day)	12 (3 / 15)	5 (3 / 12)	3 (3 / 9)	**0.005** [k]	**0.047**	**0.012**	ns.
Change (Postop-Preop)	5 (-2 / 7)	-1 (-3 / 4)	-2 (-3 / 1)	**0.003** [k]	**0.037**	**0.009**	ns.
P-value for Preop and Postop GCS	**0.032** [w]	**0.760** [w]	**0.091** [w]				

[a] One way ANOVA (Robuts Statistic :Brown-Forsythe), [ff] Fisher Freeman Halton (Monte Carlo); Post Hoc Test: Benjamini-Hochberg Correction, [k] Kruskal Wallis Test (Monte Carlo); Post Hoc Test : Dunn's Test, [w] Wilcoxon Signed Ranks Test (Monte Carlo), SD: Standard Deviation, Min: Minimum, Max.: Maximum, ns.: not significant

Table 3. The Neural Network analysis of the significance changes of intergroup parameters after decompressive craniectomy

Variable Importance		Sample (Holdout)	Predicted			
Independent Variable	**Normalized Importance**		**I**	**II**	**III**	**Percent Correct**
Change	100.0%	**Training (%100)**				
GCS postoperative 7th day	72.9%					
Age	68.4%	**I**	6	1	0	**85.7%**
GCS	52.4%					
Monoplegia	45.8%	**II**	0	11	2	**84.6%**
Hemiplegia	42.3%					
Place of Lesion	29.7%	**III**	0	0	7	**100.0%**
GCS Preoperative	25.5%					
Time (hour)	21.7%					
Mortality	8.8%	**Overall Percent**	22.2%	44.4%	33.3%	**88.9%**
Gender	6.5%					

Neural Network (Multilayer Perceptron), Hidden layer activation function: Hyperbolic tangent, Output layer activation function: Sofrmax, Dependent Variable: Groups

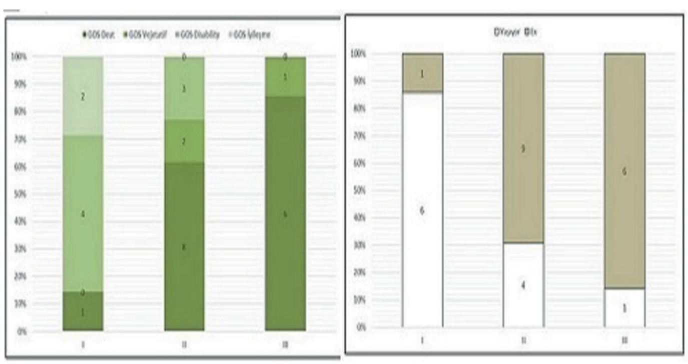

Figure 2. The inter-group A) Graphical demonstration of GCS changes B) Demonstration of mortality of epileptic patients who underwent decompressive craniectomy

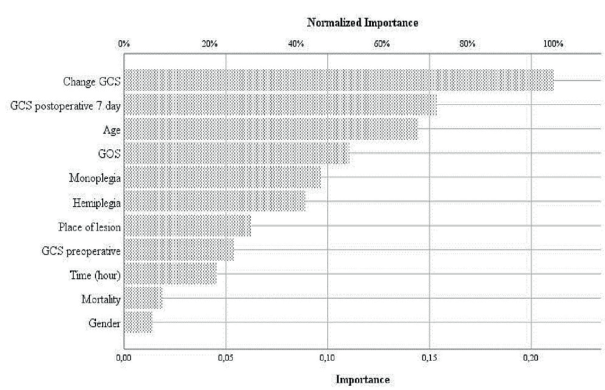

Figure 3. Schematic representation of inter-group significance change of the study data after decompressive craniectomy

According to the Glasgow Outcome Scale, 1 patient in Group 1, 8 patients in Group 2 and 6 patients in Group 3 died, and there was a significant increase in patient losses in Group 2 and Group 3 compared those in to Group 1 (p<0.05). In addition, 10 patients continue to live their lives with the support of home-care services and 2 patients with other forms of help. The mean duration of hospital stay of the patients was 28 days (Table 1) (Figure 2).

According to the Glasgow Coma Scale (GCS), the preoperative GCS data of all patients were recorded as 8 and below. The mean GCS values of the patients after decompressive craniectomy were 12 in Group 1, in which no patient had seizures, 5 in Group 2, in which patients had single or multiple seizures, and 3 in Group 3, in which sedation or narcotization were used in an attempt to bring epilepsy under control. The pre- and postoperative GCS results of the patients in Group 1 significantly increased compared to the preoperative levels (p<0.05). However, no statistically significant results could be recorded for the patients in Group 2 and Group 3 for the same condition (p>0.05). The postoperative GCS results of Group 2 and Group 3 patients significantly decreased compared to those in Group 1, in which epileptic conditions could be kept under control (p<0.05). However, no statistical significance was observed in the evaluation of the same comparison based on the preoperative GCS results (p>0.05) (Table 2) (Figure 1). When the statistical evaluations of the pre- and postoperative GCS results within the groups were taken into consideration, the change in Group 2 and Group 3 was negative compared to the change in Group 1 (p<0.05) (Tables 2 and 3) (Figures 1 and 3).

DISCUSSION

In this study, it has been shown that caesarean section and laparoscopic cholecystectomy together can be performed safely in 12 patients. Caesarean section and laparoscopic cholecytectomy can be performed simultaneously, especially in patients with complicated gallstones or recurrent symptoms. Gallbladder-related problems in pregnant women are associated with increased maternal and infant morbidity and mortality. It has been shown in various studies that invasive procedures such as laparoscopic cholecystectomy and ERCP can be performed safely in patients with complicated gallstones during pregnancy (5,6). On the other hand, approximately 5% of 9714 pregnant women who underwent cholecystectomy developed maternal and infant morbidity. In this study, cholecystectomies performed during pregnancy were found to be associated with longer hospitalization and increased cost than non-pregnant patients (7).

Conservative treatment of symptomatic gallbladder stones and postponement of cholecystectomy cause symptomatic and complicated early postpartum period. In a study conducted by Veerappan A et al 56 patients with complicated gallbladder disease during pregnancy reported that 58% of those treated conservatively became symptomatic in the postpartum period. 82% of them became symptomatic in the first three months postpartum period (4). Jorge AM et al found that 75% of 53 patients with symptomatic gallstones during pregnancy required cholecystectomy for recurrent symptoms within the first three months postpartum (8).

Laparoscopic cholecystectomy with caesarean section first described in 1997 by Pelosi MA et al (9). In this case, all trocars were placed under direct vision and the abdomen was closed. Two years later, hand-assisted laparoscopic cholecystectomy was described by the same authors (10). In the following years, there are studies in the literature in the form of case reports suggesting that cholecystectomy can be performed with cesarean section (11,12).

Mushtaque M et al (13) performed cholecystectomy in 32 cases with a mini-subcostal incision at the same time by cesarean section. Patients postoperative 5-7. days were discharged. The authors advocated that two operations be performed simultaneously instead of separate operations. However, since laparoscopic cholecystectomy is a minimally invasive procedure, it is wise to perform laparoscopic cholecystectomy simultaneously with caesarean section. In our study, the fact that the duration of hospitalization did not exceed two days MMCA refers to brain edema that develops due to the ischemic lesion volume of the MCA region infarction. MMCA accounts for approximately 10% of supratentorial strokes and clinical worsening occurs if it is not intervened within the first 24-48 hours (13). The development of postoperative epilepsy after decompressive craniectomy in non-traumatic situations is considered a major problem and the initiation of prophylactic antiepileptic drug therapy in these patients is a frequently used method in neurosurgery irrespective of whether the patients have a history of seizure or not. There are very few studies on high seizure incidence or epilepsy in patients undergoing decompressive craniectomy after MMCA infarction (9). In the present study, the preoperative and postoperative evaluations of patients, who were both epileptic and had MMCA infarction without traumatic or other causes and had undergone decompressive craniectomy were retrospectively evaluated. In the present study, the pre- and postoperative evaluations were made for patients, who had both epilepsy and MMCA infarcts and who had undergone decompressive craniectomy, excluding traumatic and other causes. In addition, risk factors for epilepsy, seizure number, and side, the incidence of epilepsy, seizure onset timing, and effects of epilepsy or seizure on mortality and patient's quality of life were evaluated in the study. In this respect, the present study is one of the most extensive studies in the literature.

Studies have reported that decompressive craniectomy is beneficial in neurosurgical conditions that cause an increase in intracranial pressure, and MMCA infarctions constitute 1% of all infarction cases (14-16). As a result of infarction, brain edema, and brain herniation can lead to an 80% mortality rate and surgical intervention is required within a maximum period of 24-48 hours upon identification of an ischemic lesion covering 50% of the middle cerebral artery region in the CT imaging (17). In this study, the time when the decompression craniectomy was performed and the clinical outcomes after MMCA infarction were analyzed to evaluate the importance of surgical timing. In a recent study, it was reported that the age of a patient, the dominant hemisphere, the time of surgery, and the pathologies that occurred before and after surgery were the factors affecting mortality and morbidity in MMCA infarction (10). In addition, cytotoxic edema occurs due to oxygen deficiency, which develops rapidly due to MMCA infarction and has destructive effects, and this cytotoxic edema disrupts the cell membrane and blood-brain barrier after approximately 24 hours and turns into vasogenic edema. When this process cannot be prevented, intracranial pressure deteriorates and eventually, a process leading up to herniation occurs (18,19). In the present study, all patients with diffuse edema and shifts were operated on within the following 22 hours, considering the mechanism of edema formation and the advanced age of the patients. Post-stroke craniectomy application due to MMCA infarction was found to be 22 hours in Group 1, 24 hours in Group 2 and 21 hours in Group 3. In a study evaluating the incidence of epilepsy seizures after craniectomy, it was seen that women had more seizures than men. In addition, an increased tendency to post-stroke seizures or susceptibility to epilepsy was seen in postoperative studies on both female and male patients (20). In the present study, 51.8% of the patients were female and 42.8% were male. However, no significant relationship could be found between gender and epileptic seizure and mortality after craniectomy.

It was assumed that major residual lesions were avoided due to intracranial hypertension and further deterioration of ischemic penumbras in craniectomies performed a short time after stroke due to MMCA infarction, but no significant difference was observed between the volumes remaining in epilepsy and non-epilepsy patients (5,21). In another craniectomy study, the dominant parts of the hemisphere were affected in patients, who survived pre- and post-surgery and the patients were reported to have faced severe disability (22). Preoperative motor sensory loss was observed in all patients, who were included in the study, hemiplegia was detected in 85.7% of the patients in Group 1, 84.6% of the patients in Group 2, and 85.7% of the patients in Group 3. Monoplegia was also seen in 14.3% of the patients in Group 1, 7.7% of the patients in Group 2, and 42.9% of the patients in Group 3. In the literature, epilepsy was reported to occur after decompressive craniectomy, and it was not determined whether the resection of the cortex infarction might be due to epilepsy (6). Of the patients included in the study, 44.4% were operated on for left MCA infarction and 55.6% for right MCA infarction, while mortality rates showed no change between the intra-group and inter-group.

In the study by Bansal et al. (2015) (13), the recovery rates after decompressive craniectomy in patients under 60 years of age were reported to be significantly higher than in patients over 60 years of age. In the same study, they stated that the presence of stroke on the right or left side of the brain did not make a significant difference in terms of recovery rates after craniectomy (13). The age range of the patients included in the study was determined as 58-75 and 44.4% of the patients were operated on for left MCA infarction and 55.6% for right MCA infarction; there was no statistically significant difference in both cases. The present study represents a mixed-age population and the results obtained are consistent with the literature.

The development of seizures after decompressive craniectomy, one of the major risk factors for seizures or epilepsy in MMCA infarction cases, is said to be related to the volume of stroke and the extent of cortical involvement (23). In a study where decompressive craniectomy was performed after MMCA infarction, researchers observed that 6 of 15 patients, who underwent craniectomy, and 2 of 4 survivors who did not undergo craniectomy, had seizures (24). In a study that included patients who underwent decompressive craniectomy, the mortality rate of patients undergoing craniectomy under the age of 60 was reported to be 18%, while this ratio was 33% for patients over 60 years of age (20). According to the findings of the present study, 14.3% of patients in Group 1, 69.2% of patients in Group 2 and 85.7% of patients in Group 3 died despite the implantation of decompressive craniectomy ($p<0.05$). There was a statistical difference between the groups and the survival rates of the patients in Group 2 and Group 3 were significantly reduced compared to patients in Group 1 ($p<0.05$). In addition, 10 patients continued to live their lives with the support of home- care services and 2 patients with other forms of help. Consistent with the literature data, the low survival rate recorded in this study of patients, where seizures or epilepsy could not be brought under control, should be noted. An important inflammatory response develops after MCA infarctions, and it was shown to play an important role in the development of seizures or epilepsy (25). The lack of inflammatory response analyses before and after decompressive craniectomy can be considered a limitation of this study. As a third risk factor, MMCA infarction involves the temporal lobe, which is located in the motor cortex and often in seizures or epilepsy (5). A further limitation of the present study is that although the lesion regions were distinguished, the lobe and area where epilepsy or seizure development occurred could not be determined.

Studies have reported that seizures will occur earlier if postoperative seizure prophylaxis is not applied in patients with MMCA infarction. Together with the prophylactic treatment, seizures and epilepsy produce different prognostic results after craniectomy (26). A recent study emphasized the importance of initiating prophylactic treatment protocols following decompressive craniectomy after MMCA infarction (27). In the present study, the mean GCS values of the patients after decompressive craniectomy were 12 in Group 1, in which no patient had seizures, 5 in Group 2, in which patients had single or multiple seizures, and 3 in Group 3, in which attempts were made to bring epilepsy under control with sedation or narcotization. The pre- and postoperative GCS results of the patients in Group 1 significantly increased compared to the preoperative levels ($p<0.05$).

CONCLUSION

In conclusion, when the intra-group and inter-group evaluation was performed based on GCS scores, this study confirmed the high incidence of seizures and epilepsy after decompressive craniectomy in MMCA infarcts. It was observed that the exposure of patients to anticonvulsant prophylaxis, where these patients were already epileptic, significantly increased mortality or dysfunctional recovery, if epilepsy could not be brought under control. However, considering that epilepsy may affect the quality of life of these patients, performing decompressive craniectomy as early as possible and controlling seizure formation due to epilepsy may be both effective and important.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: Adiyaman University Ethics Committee, Date; 16.04.2019; Number: 2019/3-7.

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