Translated by A.P. Strelkova

Acute Symptomatic Epileptic Seizures After Microsurgical Removal of Supratentorial Meningiomas

D.I. Abzalova[1] ✉, A.V. Prirodov[1, 2], M.V. Sinkin[1], P.I. Solovyeva[1], I.I. Goncharova[1]

Department of Emergency Neurosurgery
[1] N.V. Sklifosovsky Research Institute for Emergency Medicine
Sukharevskaya Sq. 3, Moscow, Russian Federation 129090
[2] N.I. Pirogov Russian National Research Medical University
Ostrovitianova Str. 1, Moscow, Russian Federation 117997

✉ **Contacts:** Dilyara I. Abzalova, Junior Researcher, Department of Emergency Neurosurgery, N.V. Sklifosovsky Research Institute for Emergency Medicine. Email: dila1307@yandex.ru

RELEVANCE One of the problems complicating the early postoperative period in patients with supratentorial meningiomas is epileptic seizures, which in 9-16% of cases first develop within the first 7 days after tumor removal (acute symptomatic epileptic seizures).

AIM OF THE STUDY To identify risk factors for the occurrence of acute symptomatic epileptic seizures in the early postoperative period in patients with supratentorial meningiomas and to evaluate the effectiveness of prophylactic antiepileptic therapy.

MATERIAL AND METHODS A prospective, single-blind, randomized, placebo-controlled study was conducted using the sequential, alternate-arm randomization method. The treatment of 102 patients with supratentorial meningiomas was analyzed, in whom the tumor was removed between 01.01.2021 and 30.09.2023 at the N.V. Sklifosovsky Research Institute for Emergency Medicine.

To identify risk factors for the development of acute symptomatic epileptic seizures in patients, we assessed the data of the anamnesis, examination of the patient, electroencephalography before surgery, neuroimaging before and after tumor resection, as well as the characteristics of the intraoperative period, duration and outcomes of hospitalization.

To evaluate the effectiveness of the prophylactic use of antiepileptic drugs, patients were divided into two groups. The first group consisted of 49 patients who took an antiepileptic drug as a prophylaxis of early epileptic seizures. The second group consisted of 53 patients who took a placebo drug. Both groups were divided into two subgroups each depending on the development of an epileptic seizure or its absence after surgery. In the first group, patients with epileptic seizures were considered the main subgroup, the patients without seizures were considered the control. We assessed the placebo group similarly.

RESULTS In the placebo group, a risk factor for the development of acute symptomatic epileptic seizures was the transection of one or more veins, which was necessary to achieve sufficient surgical access, leading to a change in cerebral venous blood flow (p=0.013, odds ratio (OR)=11.43; 95% CI [1.75–74.73]). In both the antiepileptic drug group and the placebo group, risk factors included an increase in the volume of cerebral edema according to postoperative CT scan data compared with preoperative (p=0.05, OR=18.8; 95% CI [2.0–182.7] and p=0.01, OR=12.6; 95% CI [2.36–68.0], respectively), as well as hemorrhagic transformation of the perifocal edema zone (p=0.03, OR=8.75; 95% CI [1.36–56.4] and p=0.02, OR=9.7; 95% CI [2.1–44.6], respectively).

The efficacy of prophylactic use of antiepileptic drugs in reducing the incidence of acute symptomatic epileptic seizures in the first 7 days after surgery was not established (p=0.295, OR=0.533; 95% CI [0.181–1.572]).

CONCLUSION We have identified the following risk factors for the development of acute symptomatic epileptic seizures: an increase in the volume of cerebral edema compared to the preoperative level according to postoperative computed tomography, the development of hemorrhagic transformation of cerebral edema in both groups, and the intersection of one or more veins during surgery (in the placebo group). Confirmation of the efficacy of routine use of antiepileptic drugs for the prevention of acute symptomatic epileptic seizures not received.

Keywords: acute symptomatic epileptic seizures, postoperative seizures, meningioma

For citation Abzalova DI, Prirodov AV, Sinkin MV, Solovyeva PI, Goncharova II. Acute Symptomatic Epileptic Seizures After Microsurgical Removal of Supratentorial Meningiomas. *Russian Sklifosovsky Journal of Emergency Medical Care*. 2024;13(3):353–364. https://doi.org/10.23934/2223-9022-2024-13-3-353-364 (in Russ.)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship The study had no sponsorship

Affiliations

Dilyara I. Abzalova	Junior Researcher, Department of Emergency Neurosurgery, State Budgetary Healthcare Institution N.V. Sklifosovsky Research Institute for Emergency Medicine; http://orcid.org/0000-0002-7217-6940, dila1307@yandex.ru; 40%, collection of primary material, its statistical processing, writing the main text of the article, preparing the text for publication
Aleksander V. Prirodov	Doctor of Medical Sciences, Neurosurgeon, Head of the Neurosurgical Department No. 2, N.V. Sklifosovsky Research Institute for Emergency Medicine, Professor of the Department of Fundamental Neurosurgery, N.I. Pirogov Russian National Research Medical University; http://orcid.org/0000-0003-2444-8136, aprirodov@yandex.ru; 25%, research idea, preparation of article plan, revisions, final approval of text

Mikhail V. Sinkin	Doctor of Medical Sciences, Leading Researcher of the Emergency Neurosurgery Department, Head of the Neurophysiology Laboratory, N.V. Sklifosovsky Research Institute for Emergency Medicine; http://orcid.org/0000-0001-5026-0060, mvsinkin@gmail.com; 25%, research idea, preparation of article plan, revisions, final approval of article text
Polina I. Solovyeva	Junior Researcher, Department of Emergency Neurosurgery, N.V. Sklifosovsky Research Institute for Emergency Medicine; http://orcid.org/0000-0001-6858-6210, psolovyeva@yandex.ru; 7%, collection of primary material according to the study design
Irina I. Goncharova	Candidate of Medical Sciences, Senior Researcher, Department of Anesthesiology, N.V. Sklifosovsky Research Institute for Emergency Medicine; http://orcid.org/0000-0002-5685-4916, irishka_utkina@list.ru; 3%, collection of primary material according to the study design

ACF – anterior cranial fossa
ALV – artificial lung ventilation
antiEP – antiepileptic drug
ASES – acute symptomatic epileptic seizures
CI – confidence interval
CT – computed tomography
EDH – epidural hematoma
EEG – electroencephalography
GOS – Glasgow Outcome Scale
ICH – intracerebral hematoma
KS – Karnofsky scale
MRI – magnetic resonance imaging
OR – odds ratio
PLA – placebo
SAH – subarachnoid hemorrhage

INTRODUCTION

Epileptic seizures are one of the manifestations of brain tissue (BT) damage, which significantly reduces the quality of life of patients with intracranial tumors [1]. Epileptic seizures that occur for the first time in life may develop before surgery, being a manifestation of the disease itself, or after surgery, being a consequence of tumor resection [2]. Postoperative epileptic seizures are divided into early, developing during the first 7 days after surgery, and late, occurring after this period [3]. In 9–16% of patients with supratentorial meningiomas, early de novo epileptic seizures develop for the first time after neurosurgical intervention [3–6]. According to the definition of the International League Against *Epilepsy (ILAE*), seizures that have a close temporal relationship with CNS damage (metabolic, toxic, infectious or structural) are called "acute symptomatic" [7]. In this regard, *de novo epileptic seizures* occurring in the first 7 days after removal of an intracranial tumor should now be designated as acute symptomatic epileptic seizures (ASES). Such standardization of the definition allows for multicenter comparative studies of ASES in patients with different cerebral pathologies.

Despite the prevalence of ASES among patients after meningioma resection, there are currently no recommendations on the need for drug prophylaxis and the duration of its implementation [8, 9].

The aim of the study was to identify risk factors for the development of ASES in the early postoperative period in patients with supratentorial meningiomas and to evaluate the effectiveness of prophylactic antiepileptic therapy.

MATERIAL AND METHODS

Following approval by the local ethics committee of the N.V. Sklifosovsky Research Institute for Emergency Care (protocol No. 10-21 dated November 18, 2021), a prospective, single-blind, randomized, placebo-controlled study was conducted using the sequential, alternate-arm randomization method.

The inclusion criteria were:

— a supratentorial meningioma confirmed by neuroimaging methods for the first time (according to magnetic resonance imaging (MRI) with contrast enhancement);

— absence of epileptic seizures before surgery;

— the patient signs informed consent to participate in the study.

The study cohort did not include patients under the following conditions:

— tumor recurrence;

— biopsy of the neoplasm;

— multiple brain tumors;

— Karnofsky scale score below 60% before surgery;

— history of intolerance to antiepileptic drugs (antiEPs);

— refusal to participate in the study.

The exclusion criteria for patients during the study were:

— the patient's refusal to further participate in the study;

— registration of side effects from the administration of antiepileptic drugs (antiEPs);

— confirmation by the results of histological examination of the etiology of the neoplasm, which is different from meningioma.

An analysis of the treatment of 102 patients with supratentorial meningiomas confirmed by postoperative histological examination of the resected tumor was conducted. These patients had their tumors removed between 01.01.2021 and 30.09.2023 at the N.V. Sklifosovsky Research Institute for Emergency Care.

The patients were divided into two groups. The first group (the antiEPs group) consisted of 49 patients who took antiEPs as a prophylaxis of early epileptic seizures. They started taking antiEPs 24 hours before the surgery. The antiepileptic drug used was lacosamide in the form of an oral solution. The dose of the drug was 200 mg per day and was divided into 2 doses (standard therapeutic dose). The second group (the PLA-placebo group) consisted of 53 patients who did not undergo prophylaxis of early epileptic seizures. These patients took 100 ml of 10% glucose solution orally 2 times a day as a placebo. This solution was chosen because of its consistency and taste similar to lacosamide. If ASES developed in this group, short-term antiepileptic therapy with lacosamide was carried out for 7 days after the seizure. When status epilepticus developed, intensive therapy of this condition was initiated, which included intravenous administration of antiEPs, benzodiazepines and anesthetic drugs (depending on the degree of refractoriness of status epilepticus). Both PLA and antiEPs were discontinued on day 8 after surgery, provided that there was no need to continue therapy (serial course of seizures, status epilepticus). Both groups were divided into two subgroups, each depending on the development of ASES or its absence after surgery. In the first group, patients with ASES were considered the main subgroup (PEP ASES "+"), without ASES — the control (antiEPs ASES "—"). The second group (PLA ASES "+" and PLA ASES "—") was assessed similarly. The study design is presented in Fig. 1.

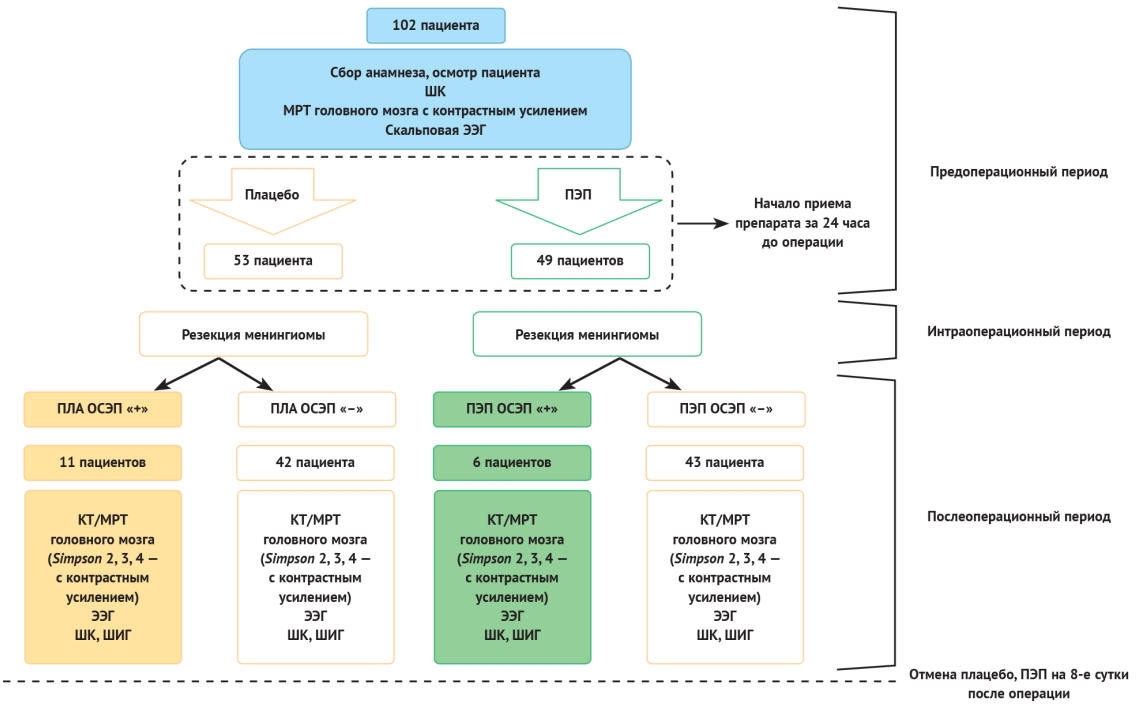

Fig. 1. Study design

Notes: КТ - computed tomography; МРТ - magnetic resonance imaging; ОСЭП- acute symptomatic epileptic seizures; ПЛА - placebo; ПЭП — antiepileptic drugs; ШИГ - Glasgow Outcome Scale; ШК - Karnofsky scale; ЭЭГ - electroencephalography

Quantitative indicators with normal distribution were described using arithmetic means (*M)* and standard deviations (*SD)*, 95% confidence interval (95% CI) boundaries. In the absence of normal distribution, quantitative data were described using the median (*Me)* and lower and upper quartiles (*Q1 – Q3)*.

Comparison of two groups by a quantitative indicator whose distribution differed from normal was performed using the Mann–Whitney *U* test. Comparison of percentages in the analysis of multifield contingency tables was performed using Fisher's exact test (for values of the expected phenomenon less than 10). As a quantitative measure of effect when comparing relative indicators, the odds ratio (OR) with 95% CI was calculated.

RESULTS

PREVENTION OF ACUTE SYMPTOMATIC EPILEPTIC SEIZURES IN THE EARLY POSTOPERATIVE PERIOD

Based on our study, the effectiveness of prophylactic use of antiEPs to reduce the incidence of ASES in the first 7 days after surgery was not established (p = 0.295, Fisher's exact test). The chance of developing ASES with prophylactic use of antiEPs was 1.877 times lower compared to the PLA group, but the indicator was not statistically significant (OR = 0.533; 95% CI [0.181–1.572]).

In order to compare the effectiveness of prophylactic use of antiepileptic therapy, we evaluated patients with ASES in the AEP and PLA groups. Results comparisons patients with ASES presented V Table 1.

When taking PLA, ASESs occurred most frequently on the first day after surgery, while when taking PEPs, they occurred with approximately the same frequency throughout the early postoperative period (Fig. 2). The chance of developing ASES on the first day after surgery was 13-fold lower when taking antiEPs versus PLA (OR=0.075; 95% CI [0.006–0.936]; p =0.05).

RISK FACTORS FOR ASES AFTER SURGICAL REMOVAL OF SUPRATENTORIAL MENINGIOMAS. PREOPERATIVE PERIOD

We assessed possible risk factors for the development of ASES in the preoperative period.

Table 1

Description of the characteristics of the ASES when taking placebo and antiEPs drugs

Evaluated indicator	antiEPs group (n = 49)	PLA group (n = 53)
Frequency of development of ASES	12% (n =6)	21% (n =11)
Semiology of attacks	Focal motor with preserved awareness (n = 1). Bilateral tonic-clonic with focal onset (n = 4). With unspecified debut (n = 1)	Focal motor with preserved awareness (n = 3). Bilateral tonic-clonic with focal onset (n = 8)
The nature of the attacks	Single attack (n = 2). Series of attacks (n =4)	Single attack (n = 3). Series of attacks (n = 8)
Transition of ASES into epileptic status, its nature	Refractory (n = 1). Superrefractory (n =3)	Refractory (n =2).
EEG after ASES	Epileptiform activity (n = 5). Absence of epileptiform activity (n = 1)	Epileptiform activity (n = 4). Absence of epileptiform activity (n = 7)

Notes: ASES - acute symptomatic epileptic seizures; PLA - placebo; antiEPs —antiepileptic drugs; EEG - electroencephalography

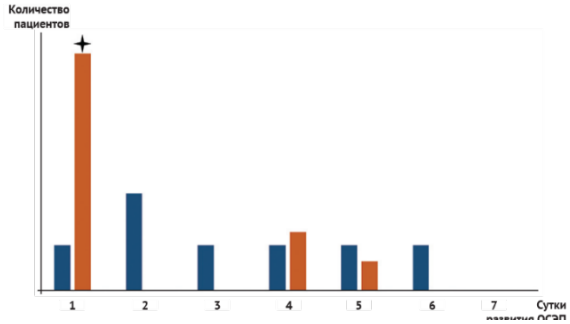

Fig. 2. Timing of acute symptomatic epileptic seizures (ASES) development after surgical treatment in patients with supratentorial meningioma. Patients in the placebo group are indicated with orange color, patients taking a prophylactic antiepileptic drug are indicated with blue color

These included age (p = 0.388, Student's t *-test),* gender (p = 0.905, Pearson's $\chi 2$) of patients, as well as the assessment according to the SC 1 day before surgery (p = 0.201, Mann-Whitney *U*-test), and found that these indicators do not affect the development of ASES. We also analyzed the factors listed in Table 2, but did not find any statistically significant ones among the studied indicators (Table 2).

Table 2

Preoperative risk factors for the development of ASES during resection of supratentorial meningiomas

Indicator and categories	Development of the ASES, *n* (%)		*p*
	ASES "+"	ASES "-"	
Epileptiform activity according to preoperative EEG			
Absence of epileptiform activity	17 (100.0)	81 (95.3)	1.000*
Presence of epileptiform activity	0 (0,0)	4 (4.7)	
Slowing of the activity of the cerebral cortex in the projection of the tumor on preoperative EEG			
No slowdown	13 (76.5)	65 (76.5)	1.000*
Presence of slowdown	4 (23.5)	20 (23.5)	
Tumor lateralization			
Left	5 (29.4)	35 (41.2)	0.559**
Right	9 (52.9)	41 (48.2)	
Left and right	3 (17.6)	9 (10.6)	
Spread of edema to the cerebral cortex			
No involvement of the cerebral cortex by edema	0 (0,0)	4 (4.7)	0.285**
Involvement of the cerebral cortex by edema	14 (82.4)	54 (63.5)	
Absence of cerebral edema	3 (17.6)	27 (31.8)	
Location of meningioma			
Falx	3 (17.6)	7 (8.2)	0.147**
Convexital	7 (41.2)	32 (37.6)	
Greater wing of the sphenoid bone	0 (0,0)	8 (9.4)	
Pyramid of the temporal bone	1 (5.9)	0 (0.0)	
ACF	2 (11.8)	11 (12.9)	
Superior sagittal sinus	1 (5.9)	15 (17.6)	
Lesser wing of the sphenoid bone	2 (11.8)	11 (12.9)	
Tentorium	1 (5.9)	1 (1.2)	
Location of meningioma matrix			
Falx	3 (17.6)	10 (11.8)	0.734**
Convexital	7 (41.2)	32 (37.6)	
Greater wing of the sphenoid bone	1 (5.9)	8 (9.4)	
ACF	2 (11.8)	8 (9.4)	
Superior sagittal sinus	1 (5.9)	15 (17.6)	
Lesser wing of the sphenoid bone	2 (11.8)	11 (12.9)	
Tentorium	1 (5.9)	1 (1.2)	
Frontal lobe lesion			
No frontal lobe damage	5 (29.4)	24 (28.2)	0.922*
Frontal lobe lesion	12 (70.6)	61 (71.8)	
Parietal lobe lesion			
No parietal lobe lesions	11 (64.7)	70 (82.4)	0.100*
Parietal lobe lesion	6 (35.3)	15 (17.6)	
Temporal lobe lesion			
No temporal lobe damage	10 (58.8)	63 (74.1)	0.202*
Temporal lobe lesion	7 (41.2)	22 (25.9)	
Occipital lobe lesion			
No occipital lobe involvement	15 (88.2)	78 (91.8)	0.643*
Occipital lobe lesion	2 (11.8)	7 (8.2)	
Insular lobe lesion			
No insular lesions	16 (94.1)	84 (98.8)	0.307*
Insular lobe lesion	1 (5.9)	1 (1.2)	
Compression of the ventricular system			
No compression of the ventricular system	12 (70.6)	69 (81.2)	0.324*
Compression of the ventricular system	5 (29.4)	16 (18.8)	
Hemorrhage into the tumor stroma			
No bleeding	17 (100.0)	84 (98.8)	1.000*
Hemorrhage into the tumor stroma	0 (0.0)	1 (1.2)	
Hemorrhage into the ventricular system			
No bleeding	17 (100.0)	84 (98.8)	1.000*
Ventricular hemorrhage	0 (0.0)	1 (1.2)	
Presence of petrifications in the tumor structure			
Absence of petrifications	14 (82.4)	71 (83.5)	0.905*
Presence of petrifications	3 (17.6)	14 (16.5)	
Presence of a cystic component in the tumor stroma			
Absence of cysts	15 (88.2)	78 (91.8)	0.643*
Presence of cysts	2 (11.8)	7 (8.2)	
Presence of peritumoral edema			
No swelling	3 (17.6)	26 (30.6)	0.280*
Presence of edema	14 (82.4)	59 (69.4)	
Hemorrhage into the tumor stroma			
No bleeding	17 (100.0)	84 (98.8)	1.000*
Hemorrhage into the tumor stroma	0 (0.0)	1 (1.2)	
Hemorrhage into the ventricular system			
No bleeding	17 (100.0)	84 (98.8)	1.000*
Ventricular hemorrhage	0 (0.0)	1 (1.2)	
Presence of petrifications in the tumor structure			
Absence of petrifications	14 (82.4)	71 (83.5)	0.905*
Presence of petrifications	3 (17.6)	14 (16.5)	
Presence of a cystic component in the tumor stroma			
Absence of cysts	15 (88.2)	78 (91.8)	0.643*
Presence of cysts	2 (11.8)	7 (8.2)	
Presence of peritumoral edema			
No edema	3 (17.6)	26 (30.6)	0.280*
Presence of edema	14 (82.4)	59 (69.4)	

Notes: * — Fisher's exact test; ** — Pearson's χ^2. ASES – acute symptomatic epileptic seizures; ACF – anterior cranial fossa; EEG – electroencephalography

RISK FACTORS FOR ASES AFTER SURGICAL REMOVAL OF SUPRATENTORIAL MENINGIOMAS. INTRAOPERATIVE PERIOD

During statistical analysis on the presented sample, risk factors that can be detected in the intraoperative period in patients operated on for supratentorial meningioma were assessed in the PLA and antiEPs groups (Fig. 3 and 4, respectively). In the PLA group, the risk factor for the development of ASES was the transection of one or more veins, which was forced to be performed to achieve sufficient surgical access, which led to a change in cerebral venous blood flow (p = 0.013). Risk factors for the intraoperative period were not detected in the PEP group.

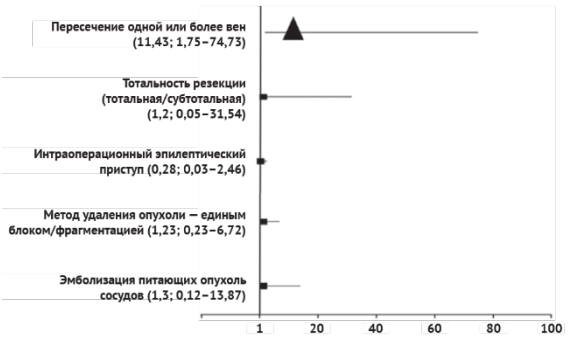

Fig. 3. Forrest plot diagram. Odds ratio of development of acute symptomatic epileptic seizures during the first 7 days after resection of supratentorial meningiomas (intraoperative period) in the placebo group

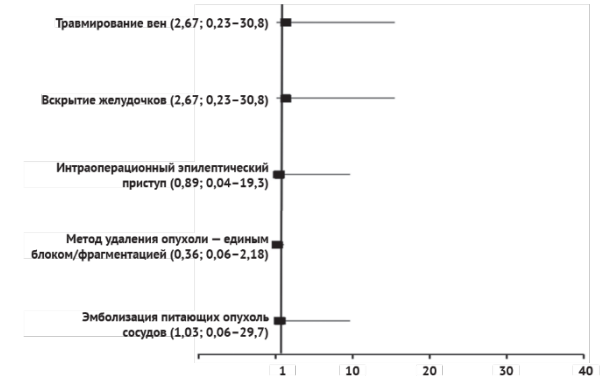

Fig. 4. Forrest plot diagram. Odds ratio of development of acute symptomatic epileptic seizures during the first 7 days after resection of supratentorial meningiomas (intraoperative period) in the group of antiepileptic drugs

The intraoperative period criteria described in Table 3 were also analyzed; however, no statistically significant risk factors for the development of ASES were identified.

Table 3

Statistical significance of differences in intraoperative risk factors for acute symptomatic epileptic seizures in the antiEPs and PLA groups

Factor under study	PEP group, p	PLA group, p
Volume of blood loss, ml	0.255*	0.405*
Operation duration, min	0.067*	0.767*
Intraoperatively identified tumor structure (homogeneous tissue, calcifications, foci of necrosis, hemorrhage)	0.865**	0.301**

Notes: * — Mann–Whitney U-test; ** — Pearson χ^2. antiEPs - antiepileptic drug; PLA – placebo

RISK FACTORS FOR THE DEVELOPMENT OF ASES AFTER SURGICAL REMOVAL OF SUPRATENTORIAL MENINGIOMAS. POSTOPERATIVE PERIOD

When analyzing the postoperative period, we assessed the risk factors for the development of ASES in both groups (Figs. 5 and 6, respectively). In the antiEPs group, we found that the risk factors were an increase in the volume of cerebral edema according to postoperative CT data compared to preoperative (p = 0.05), as well as hemorrhagic transformation of the perifocal edema zone (p = 0.03). In the placebo group, we found the following risk factors for the development of ASES: an increase in the volume of cerebral edema according to postoperative CT data compared to preoperative (p = 0.01), as well as hemorrhagic transformation of the perifocal edema zone (p = 0.02).

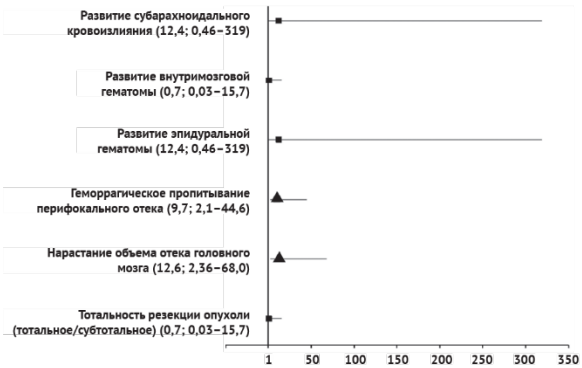

Fig. 5. Forrest plot diagram. Odds ratio of developing acute symptomatic epileptic seizures during the first 7 days after resection of supratentorial meningiomas (postoperative period) when taking placebo

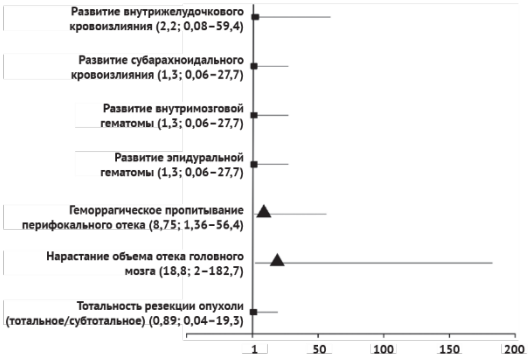

Fig. 6. Forrest plot diagram. Odds ratio of development of acute symptomatic epileptic seizures during the first 7 days after resection of supratentorial meningiomas (postoperative period) when taking antiepileptic drugs

We also assessed the effect of the volume of hemorrhagic impregnation on the development of ASES. It was found that in the PLA group, ASES was more likely to develop with a volume of 3 cm3 or more, and with aniEP - 4.5 cm3 (the method used was the Mann-Whitney *U* -test).

In addition to the above indicators, we also assessed the relationship between ASES and the histological structure of the tumor, but no statistically significant values were found ($p = 0.529$, the method used was Pearson's χ^2).

The criteria of the postoperative period described in Table 4 were also analyzed; however, no statistically significant risk factors for the development of ASES were identified.

Table 4

Risk factors for ASES development during resection of supratentorial meningiomas in the early postoperative period

Risk factor	PEP group, *p*	PLA group, *p*
Change in dislocation, mm	0.195**	0.379**
Residual tumor volume, cm^3	0.509*	0.465*
Volume of postoperative edema, cm^3	0.155*	0.390*
Transverse dislocation after surgery, mm	0.409*	0.409*
Volume of EDH, cm^3	0.594*	0.051*
Volume of ICH, cm^3	0.594*	0.465*
Volume of SAC, cm^3	0.594*	0.051*
Volume of pneumocephalus, cm^3	0.502*	0.693*

Notes: * — Mann–Whitney U -test; ** — Pearson χ^2. IMH - intracerebral hematoma; PLA - placebo; PEP - antiepileptic drug; SAH - subarachnoid hemorrhage; EDH - epidural hematoma

Of the entire study sample, 9 patients in the main and control groups required repeated neurosurgical intervention due to complications. Among them, 4 patients developed ASES after repeated surgery within the first 7 days after primary meningioma resection (Fig. 7).

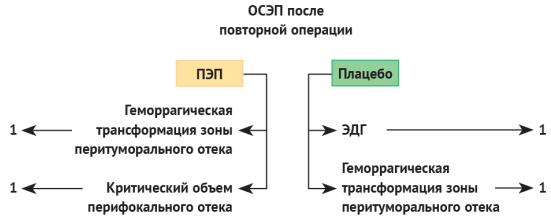

Fig. 7. Reasons for reoperations in patients in the groups of acute symptomatic epileptic seizures "+" that developed after reoperations during the early postoperative period after resection of supratentorial meningioma

FUNCTIONAL OUTCOMES AFTER RESECTION OF SUPRATENTORIAL MENINGIOMAS DEPENDING ON ASES

When analyzing the data, we found that at the end of the early postoperative period, patients with ASES had a worse functional outcome than patients without attacks, despite taking PLA or antiEPs (Table 5).

Table 5

Outcomes of removal of supratentorial meningiomas at the end of the early postoperative period

Indicators	Categories	Development of early epileptic seizures			*p*
		Me	$Q_1 - Q_3$	*n*	
Duration of treatment in intensive care, days	ASES "-"	1.0	1.0–2.0	85	<0.001*
	ASES "+"	3.0	2.0–12.0	17	
Duration of artificial ventilation, days	ASES "-"	0.0	0.0–0.0	85	<0.001*
	ASES "+"	1.0	0.0–9.0	17	
KS, %	ASES "-"	90	90–100	85	<0.001*
	ASES "+"	70	0–90	17	
GOS, score	ASES "-"	4	4–5	85	<0.001*
	ASES "+"	4	1–4	17	

Notes: * — Mann–Whitney U -test. ALV - artificial ventilation; ASES - acute symptomatic epileptic seizures; KS - Karnofsky scale; GOS – Glasgow outcome scale

As can be seen from Table 5, with the development of ASES, patients stayed in the intensive care unit longer after surgery and needed artificial ventilation longer. The score according to the Karnofsky scale and the Glasgow outcome scale

on the 7th day after surgery was also lower in patients who had an epileptic seizure after surgery.

DISCUSSION

RISK FACTORS FOR THE DEVELOPMENT OF ASES AFTER RESECTION OF SUPRATENTORIAL MENINGIOMAS

Meningioma is one of the most common intracranial neoplasms, accounting for 37% of all primary brain tumors [4, 10]. Despite the danger of such a complication of the early postoperative period as ASES, there are currently relatively few studies on this topic in the world literature.

In a study of patients without a history of epileptic seizures after removal of supratentorial meningioma, *Jian Fernandes Seyedi et al* . found that 47% of them developed an epileptic seizure within the first week, 21% between the 8th and 90th days, and 32% within 3 months after surgery [11]. We previously conducted a 3:1 retrospective case-control study of 133 patients who underwent surgical removal of supratentorial meningioma. In 10% (n = 14) of these patients, ASES was recorded in the early postoperative period. We were also the first to determine the incidence of ASES by days after surgery. Most often, ASES occurred on the first day after meningioma removal—in 50% of patients [12]. Taking these data into account, in the prospective part of the study we assessed the effect of antiEPs not only on the overall frequency of ASES during 7 days after surgery, but also separately for each day of the early postoperative period. It was found that when using antiEPs, the frequency of ASES during the first week does not decrease, but there is a tendency for the prophylactic use of antiEPs to be effective on the first day after surgery.

Previously, studies have been published devoted to the study of risk factors for the development of ASES in patients with supratentorial meningiomas. Thus, *Marco Skardelly et al*. identified only one factor that can cause the development of ASES - convexital location of the meningioma [13]. At the same time, *W.C. Chen* identified several factors that can lead to the development of ASES: male gender, parasagittal location of the tumor and the presence of motor deficit before surgery, as well as a number of postoperative changes - the development of venous infarction, an increase in the volume of cerebral edema, the appearance of intracranial hemorrhages and hydrocephalus [14]. *B. Brokinkel et al*. also distinguished between preoperative and postoperative criteria that lead to the development of ASES. The first group, like the authors of earlier works, includes parasagittal location of meningioma, but also heterogeneous accumulation of contrast agent, presence of intratumor calcifications and Karnofsky score below 80%. At the same time, among postoperative risk factors for development of ASES, *B. Brokinkel et al*. highlight intracranial hemorrhage and hydrocephalus [6]. Researchers *I. Islim et al*. identified 2 risk factors for development of ASES — compression of the frontal and parietal lobes of the brain by meningioma and, as a consequence, dislocation of midline structures [15]. In our retrospective study, we identified the following risk factors for ASES: hemorrhagic transformation of the edema-ischemia zone in the first 7 days after surgery, as well as an increase in cerebral edema compared to the preoperative level [12].

In a prospective study that included the antiEPs and PLA groups, we did not establish a relationship between the volume and localization of meningioma and the development of ASES after surgery. We found that ASES more often develops with hemorrhagic transformation of the perifocal edema zone and an increase in its volume compared to preoperative. In the PLA group, we identified one more risk factor - intraoperative change in cerebral venous blood flow due to forced intersection of one or more cerebral veins.

Partial or complete cessation of blood flow in the structures of the venous system of the brain can lead to the formation of an ischemic focus [16]. In this case, hemorrhagic impregnation of the formed ischemic zone occurs in 30–40% of patients with venous infarction [17].

Currently, the pathophysiological process that leads to the development of clinical and morphological manifestations of venous infarction has been described. It consists in the fact that changes in blood flow in the cerebral veins lead to an increase in venous and capillary pressure and, as a consequence, to a decrease in cerebral perfusion. In turn, cerebral hypoperfusion leads to ischemia of the brain substance, which is manifested by cytotoxic edema and damage to the blood-brain barrier with the subsequent development of vasogenic edema. An increase in pressure in the cerebral venous system can lead to hemorrhagic impregnation of the ischemic focus [18]. In the clinical picture of venous infarction of the brain, epileptic seizures (39.3%), headache (88.8%) and motor neurological deficit (37.2%) most often develop [19].

A number of authors suggest that there is a relationship between the high degree of malignancy of meningioma and ASES [20, 21]. *Islim et al* . did not find such a pattern in their work [15]. We also did not establish this relationship in either retrospective or prospective studies.

When studying the semiology of ASES, *B. Brokinkel et al*. found that most often they are focal without secondary generalization - in 51%, secondarily generalized - in 32%, with an unknown onset - in 17% of patients [6]. In the group of patients we studied, bilateral tonic-clonic seizures with focal onset occurred most often - in 70% of patients. Also, in our sample, ASES were most often serial in nature.

USE OF ANTIEPS FOR THE PREVENTION OF ASES IN PATIENTS WITH SUPRATENTORIAL MENINGIOMA

Tsuji et al. conducted a study in 1993, prospectively analyzing 20 patients operated on for supratentorial meningioma. All patients were given perioperative antiEP (valproic acid), and only 2 patients developed ASES in the early postoperative period, which was considered by the authors as evidence of the effectiveness of such a therapy regimen [22]. A similar study was conducted by *Gazzeri et al*., using antiEP for prophylactic purposes in 30 patients with anterior cranial fossa (ACF) meningioma. The authors did not specify the name or doses of the drugs used. ASES developed in only 1 patient, which was considered by the scientists as evidence of the effectiveness of the drugs used [23].

Sughrue et al. in their retrospective study evaluated patients taking antiEPs for prophylactic purposes with patients in the control group, which consisted of 51 out of 180 people. ASES developed in only 1 patient in the control group. Given these results, the authors express doubts about the need for prophylactic use of antiEPs in the perioperative period of meningioma resection, since they believe that the incidence of ASES in the population is extremely low, and the risks of its occurrence are much lower than the likelihood of side effects from the use of antiEPs [24].

Wirsching et al. in their retrospective study compared the incidence of ASES in patients with and without prophylactic antiepileptic therapy. Of 535 patients, 244 received antiEPs in the perioperative period. Phenytoin was the most commonly used drug, but carbamazepine, levetiracetam, and valproic acid were also used in 24% of patients in the study group. The researchers found no difference in the occurrence of ASES in the two groups, so they do not recommend the routine use of antiEPs for prophylactic purposes in the perioperative period in patients with meningiomas. [2]

Lee et al. conducted a prospective study in which 189 patients without a history of epileptic seizures received intravenous phenytoin as a prophylactic antiepileptic therapy during the perioperative period, 185 patients formed the PLA group. In patients of the main group, the drug was administered 15–20 minutes before the end of the main stage of resection and continued for 3 days after surgery. During the first 3 days after surgical treatment of meningiomas, ASES developed in 9 patients (4.9%) of the main group and in 2 patients (1.1%) of the control group, however, no statistically significant difference in the development of ASES was found [25].

Behari et al. in turn studied the possible complications of surgical treatment of giant meningiomas. Of the 20 patients analyzed, 13 had no history of epileptic seizures, but despite this they received perioperative antiepileptic therapy on an equal basis with other patients. The antiEPs used was phenytoin. The authors noted the absence of ASES after surgery in all groups, which they assessed as effective prophylactic use of phenytoin in patients with giant meningiomas [26].

Islim et al. retrospectively analyzed 283 patients with meningioma. 215 patients had no history of seizures before surgery, of which 13% (n = 29) developed early and delayed seizures. The average follow-up period was 12 months. The authors found that 9 patients developed ASES. Taking into account this fact, as well as the identified risk factors for the development of ASES, the researchers concluded that prophylactic use of antiEPs in the perioperative period and for at least a year after surgery is recommended for patients without epileptic seizures before meningioma resection, as well as at least 1 of 2 criteria - convexital location of the tumor and compression of the frontal or parietal lobes of the brain [15].

Cai et al. retrospectively reviewed the medical records of 517 patients with supratentorial meningioma without epileptic seizures before surgery. The scientists identified ASES in 5.8% of patients (n = 30). Valproic acid was used as a prophylactic antiEPs, and levetiracetam was added to the therapy if 2 or more seizures or epileptic status developed. Using this population as an example, the

authors found a decrease in the likelihood of ASES in patients with convexital and parasagittal meningioma with prophylactic use of antiEPs [27].

Yang et al. retrospectively evaluated the effect of valproic acid on the prevention of ASES in patients with supratentorial meningioma. Of 148 patients without epileptic seizures before surgery, 68 patients received perioperative antiEPs, of whom 24 developed ASES. In the control group, ASES was observed in only 7 patients. Based on this, the authors concluded that valproic acid is ineffective for the prevention of ASES [28].

Given the lack of standards for prophylactic antiepileptic therapy in resection of supratentorial meningiomas, the small number of prospective studies on this topic, and the change in the spectrum of the most commonly used antiEPs over time, we decided to conduct a single-blind, randomized, placebo-controlled study to study this issue in more detail. We were the first to use lacosamide as an antiEPs for the prevention of ASES in resection of supratentorial meningiomas and found that antiEPs reduce the incidence of ASES in the first day after surgery, but do not affect the total number of seizures during the early postoperative period. No side effects that would require discontinuing lacosamide were registered among patients.

LIMITATIONS OF THE STUDY

The limitation of the study is the small sample size of patients in the main group due to the low incidence of the complication of surgical resection of supratentorial meningiomas that we studied. Another feature of our study is that the preoperative neuroimaging study was MRI of the brain with contrast enhancement, and the postoperative control study was CT of the brain with or without contrast enhancement depending on the degree of meningioma removal according to the *Simpson scale*. This relates to the methodology.

CONCLUSION

We established risk factors for the development of acute symptomatic epileptic seizures: transection of 1 or more cerebral veins during surgery in the placebo group, an increase in the volume of cerebral edema according to postoperative computed tomography compared with preoperative data, and hemorrhagic transformation of the perifocal edema zone in both groups. The effectiveness of routine prophylactic use of antiepileptic drugs in patients with supratentorial meningiomas has not been established. In our sample, when taking lacosamide at a dose of 200 mg per day, the odds ratio for the development of acute symptomatic epileptic seizures during the first week after meningioma removal was 1.877 times lower compared with the placebo group, but the differences are not statistically significant (p = 0.295, Fisher's exact test). We confirmed that disease outcomes at the end of the early postoperative period are worse with the development of acute symptomatic epileptic seizures, regardless of the use of an antiepileptic drug or its absence.

Thus, we did not obtain confirmation of the effectiveness of routine use of lacosamide for the prevention of acute symptomatic epileptic seizures in patients with supratentorial meningiomas in the period from the day before surgery to the 7th day after it.

CONCLUSIONS

1. Risk factors for the development of acute symptomatic epileptic seizures during removal of supratentorial meningiomas are transection of 1 or more cerebral veins during surgery in the placebo group (OR=11.43; 95% CI [1.75–74.73]), increase in the volume of cerebral edema according to postoperative CT data compared to preoperative (OR=12.6; 95% CI [2.36–68.0] and (OR=18.8; 95% CI [2–182.7] in the control and main groups, respectively), as well as hemorrhagic transformation of the perifocal edema zone (OR=9.7; 95% CI [2.1–44.6] and (OR=8.75; 95% CI [1.36–56.4] in the control and main groups, respectively).

2. Routine prophylactic antiepileptic therapy of acute symptomatic epileptic seizures in the early postoperative period of removal of supratentorial meningiomas with lacosamide did not show its effectiveness in reducing the frequency of seizures during the entire early postoperative period (OR=0.533; 95% CI [0.181–1.572]). However, a decrease in the incidence of acute symptomatic epileptic seizures on the first day after surgery was established with prophylactic use of antiEPs (OR=0.075; 95% CI [0.006–0.936]).

REFERENCES

1. Ersoy TF, Ridwan S, Grote A, Coras R, Simon M. Early postoperative seizures (EPS) in patients undergoing brain tumor surgery. *Sci Rep* . 2020;10(1):13674. PMID: 32792594 https://doi.org/10.1038/s41598-020-70754-z
2. Wirsching HG, Morel C, Gmür C, Neidert MC, Baumann CR, Valavanis A, et al. Predicting outcome of epilepsy after meningioma resection. *Neuro Oncol* . 2016;18(7):1002–1010. PMID: 26683139 https://doi.org/10.1093/neuonc/nov303
3. Islim A, Ali A, Bagchi A, Ahmad MU, Mills SJ, Chavredakis E, et al. Postoperative Seizures in Meningioma Patients: Improving Patient Selection for Antiepileptic Drug Therapy. *J Neurooncol* . 2018;140(1):123–134. PMID: 29959695 https://doi.org/10.1007/s11060-018-2941-2
4. Harvard SC, Rolston JD, Englot DJ. Seizures in meningioma. In: ed. McDermott MW. *Meningiomas* . Pt. 2. Elsevier; 2020. pp. 187–200. (Handbook of Clinical Neurology. Vol. 170).
5. Baumgarten P, Sarlak M, Monden D, Spyrantis A, Bernatz S, Gessler F, et al. Early and Late Postoperative Seizures in Meningioma Patients and Prediction by a Recent Scoring System. *Cancers (Basel)* . 2021;13(3):450. PMID: 33504023 https://doi.org/10.3390/cancers13030450
6. Brokinkel B, Hinrichs FL, Schipmann S, Grauer O, Sporns PB, Adeli A, et al. Predicting postoperative seizure development in meningiomas – Analyzes of clinical, histological and radiological risk factors. *Clin Neurol Neurosurg.* 2021;200:106315. PMID: 33092928 https://doi.org/10.1016/j.clineuro.2020.106315
7. Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. *Epilepsy* . 2010;51(4):671–675. PMID: 19732133 https://doi.org/10.1111/j.1528-1167.2009.02285.x
8. Delgado-López PD, Martín-Alonso J. Prophylactic anticonvulsant therapy in high-grade glioma: A systematic review and meta-analysis of longitudinal studies. *Neurocirugia (Astur: Engl Ed)* . 2020;31(6):268–278. PMID: 32265156 https://doi.org/10.1016/j.neucir.2020.02.003
9. Delgado-López PD, Ortega-Cubero S, González Bernal JJ, Cubo-Delgado E. Profilaxis antiepiléptica en meningiomas: revisión sistemática y metaanálisis. *Neurology (Engl Ed).* 2020 Sep 4:S0213-4853(20)30225-5. PMID: 32896461 https://doi.org/10.1016/j.nrl.2020.06.014 Online ahead of print.
10. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011–2015. *Neuro Oncol*. 2018;20(Suppl 4):iv1-iv86. PMID: 30445539 https://doi.org/10.1093/neuonc/noy131
11. Seyedi JF, Pedersen CB, Poulsen FR. Risk of seizures before and after neurosurgical treatment of intracranial meningiomas. *Clin Neurol Neurosurg.* 2018;165:60–66. PMID: 29316494 https://doi.org/10.1016/j.clineuro.2018.01.002
12. Abzalova DI, Sinkin MV, Yakovlev AA, Prirodov AV, Guekht AB. Risk factors for de novo generalized tonic-clonic seizures in patients with supratentorial meningiomas after neurosurgical treatment. *S. S. Korsakov Journal of Neurology and Psychiatry*. 2023;123(10):69–74. (In Russ.). https://doi.org/10.17116/jnevro202312310169
13. Skardelly M, Rother C, Noell S, Behling F, Wuttke TV, Schittenhelm J, et al. Risk Factors of Preoperative and Early Postoperative Seizures in Patients with Meningioma: A Retrospective Single-Center Cohort Study. *World Neurosurg.* 2017;97:538–546. PMID: 27777150 https://doi.org/10.1016/j.wneu.2016.10.062
14. Chen WC, Magill ST, Englot DJ, Baal JD, Wagle S, Rick JW, et al. Factors Associated with Pre- and Postoperative Seizures in 1033 Patients Undergoing Supratentorial Meningioma Resection. *Neurosurgery*. 2017;81(2):297–306. PMID: 28327947 https://doi.org/10.1093/neuros/nyx001
15. Islim AI, McKeever S, Kusu-Orkar TE, Jenkinson MD. The role of prophylactic antiepileptic drugs for seizure prophylaxis in meningioma surgery: A systematic review. *J Clin Neurosci* . 2017;43:47–53. PMID: 28625584. https://doi.org/10.1016/j.jocn.2017.05.020.
16. Idiculla PS, Gurala D, Palanisamy M, Vijayakumar R, Dhandapani S, Nagarajan E. Cerebral venous thrombosis: a comprehensive review. *Eur Neurol* . 2020;83(4):369–379. PMID: 32877892 https://doi.org/10.1159/000509802
17. Zhang S, Zhao H, Li H, You C, Hui X. Decompressive craniectomy in hemorrhagic cerebral venous thrombosis: clinicoradiological features and risk factors. *J Neurosurg* . 2016;127(4):709–715. PMID: 27767398 https://doi.org/10.3171/2016.8.JNS161112
18. Piazza G. Cerebral Venous Thrombosis. *Circulation*. 2012;125(13):1704–1709. PMID: 22474313 https://doi.org/10.1161/CIRCULATIONAHA.111.067835
19. Ferro JM, Canhão P, Stam J, Bousser MG, Barinagarrementeria F; ISCVT Investigators. Prognosis of cerebral vein and dural sinus thrombosis: results of the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT). *Stroke*. 2004;35(3):664–670. PMID: 14976332 https://doi.org/10.1161/01.STR.0000117571.76197.26
20. Wang YC, Chuang CC, Tu PH, et al. Seizures in surgically resected atypical and malignant meningiomas: Long-term outcome analysis. *Epilepsy Res* . 2018;140:82–89. PMID: 29289807 https://doi.org/10.1016/j.eplepsyres.2017.12.013
21. Chozick BS, Reinert SE, Greenblatt SH. Incidence of seizures after surgery for supratentorial meningiomas: A modern analysis. *J Neurosurg* . 1996;84(3):382–386. PMID: 8609547 https://doi.org/10.3171/jns.1996.84.3.0382
22. Tsuji M, Shinomiya S, Inoue R, Sato K. Prospective Study of Postoperative Seizure in Intracranial Meningioma. *Jpn J Psychiatry Neurol.* 1993;47(2):331–334. PMID: 8271585 https://doi.org/10.1111/j.1440-1819.1993.tb02094.x
23. Gazzeri R., Galarza M., Gazzeri G. Giant olfactory groove meningioma: ophthalmological and cognitive outcome after bifrontal microsurgical approach. *Acta Neurochir (Wien)* . 2008;150(11):1117–1125. PMID: 18936875 https://doi.org/10.1007/s00701-008-0142-z
24. Sughrue ME, Rutkowski MJ, Chang EF, Shangari G, Kane AJ, McDermott MW, et al. Postoperative seizures following the resection of convexity meningiomas: are prophylactic anticonvulsants indicated? *J Neurosurg*. 2011;114(3):705–709. PMID: 20578801 https://doi.org/10.3171/2010.5.JNS091972

25. Lee ST, Lui TN, Chang CN, Cheng WC, Wang DJ, Heimburger RF, et al. Prophylactic anticonvulsants for prevention of immediate and early postcraniotomy seizures. *Surg Neurol*. 1989;31(5):361–364. PMID: 2711309 https://doi.org/10.1016/0090-3019(89)90067-0
26. Behari S, Giri PJ, Shukla D, Jain VK, Banerji D. Surgical strategies for giant medial sphenoid wing meningiomas: a new scoring system for predicting the extent of resection. *Acta Neurochir (Wien)* . 2008;150(9):865–877. PMID: 18754074 https://doi.org/10.1007/s00701-008-0006-6
27. Cai Q, Wu Y, Wang S, Huang T, Tian Q, Wang J, et al. Preoperative antiepileptic drug prophylaxis for early postoperative seizures in supratentorial meningioma: a single-center experience. *J Neurooncol.* 2022;158(1):59–67. PMID: 35434765 https://doi.org/10.1007/s11060-022-04009-4
28. Yang M, Cheng YR, Zhou MY, Wang MW, Ye L, Xu ZC, et al. Prophylactic antiEPs Treatment for Patients with Supratentorial Meningioma Does Not Reduce the Rate of Perioperative Seizures: A Retrospective Single-Center Cohort Study. *Front Oncol* . 2020;10:568369. PMID: 33344228 https://doi.org/10.3389/fonc.2020.568369 eCollection 2020 .

Received on 27/05/2024
Review completed on 05/27/2024
Accepted on 05/06/2024