ANESTHETIC MANAGEMENT OF EPILEPSY SURGERY: OUR STANDARDIZED ANESTHETIC PROTOCOL AND REVIEW OF THE LITERATURE
EPILEPSY SURGERY, ANESTHETIC MANAGEMENT

Review Article

EPİLEPSİ CERRAHİSİNDE ANESTEZİ YÖNETİMİ: STANDART ANESTEZİ PROTOKOLÜMÜZ VE LİTERATÜRÜN GÖZDEN GEÇİRİLMESİ
EPİLEPSİ CERRAHİSİ, ANESTEZİ YÖNETİMİ

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ABSTRACT

Epilepsy surgery is a therapeutic intervention for patients with medically refractory seizures. Anesthetic considerations epilepsy surgery for refractory epilepsy include ensuring a safe and comfortable perioperative experience for the patient, providing suitable operating conditions for the neurosurgeon, avoiding interference with intraoperative neuromonitoring recordings. Providing the conditions that simultaneously meet these requirements, using general anesthesia remains a significant challenge for the neuroanesthesiologist. The role of anesthesiologist acquires significant

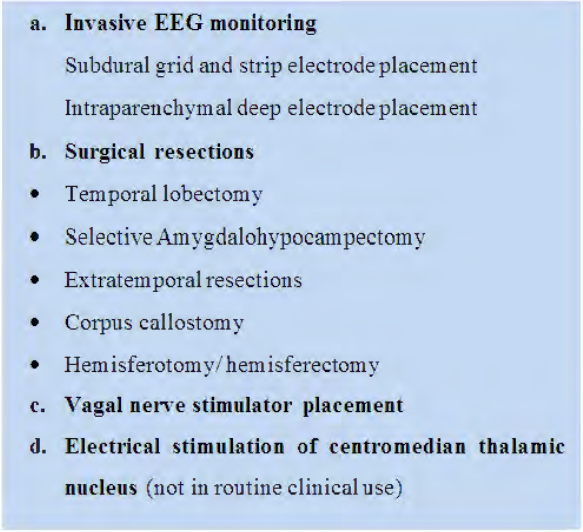
dimensions in management of epilepsy ranging from operative procedure, to the intensive care management of patients with status epilepticus. The knowledge regarding various antiepileptic agents and their potential side effects and interactions with anesthetic agents are of prime concern during surgical procedures for epilepsy.

It requires a skilful and clinically precise handling of such patients during perioperative period by the all team, which is structured by anesthesiologist, neurosurgeon and neurologist. In this study, we aimed to discuss our standardized anesthesia protocol and review of the literaturefor epilepsy surgery.

ÖZET

Epilepsi cerrahisi medikal tedaviye dirençli epilepsi hastaları için tedavi edici bir girişimdir. Dirençli epilepsi için uygulanan epilepsi cerrahisinin anestezisinde önemli olan hastaya operasyon süresince rahat ve güvenli bir deneyim sağlamak, nöroşirürjiyen için uygun cerrahi koşulları oluşturmak, düzgün ve etkin bir intraoperatif nöromonitörleme yapabilmektir. Genel anestezi koşullarını sağlayarak aynı anda bu gereksinimleri karşılamak nöroanestezist için önemli bir sorun olmaya devam etmektedir. Anestezistler, epilepsi cerrahisinde; cerrahi girişimlerde uygulanan anestezi yönetiminden, yoğun bakımda status epileptikusun tedavisine dek birçok aşamada rol almaktadır. Çeşitli antiepileptik ajanlar ve potansiyel yan etkileri ve anestezik maddelerle etkileşimleri konusunda bilgi epilepsiye yönelik uygulanan cerrahi işlemler sırasındaki kaygılarından biridir.
Bu tür hastaların beyin cerrahı ve nörolog içeren bir ekip tarafından becerikli ve klinik olarak hassas bir şekilde ele alınması gerekmektedir.
Bu çalışmada, epilepsi cerrahisinde kliniğimzde uyguladığımız standart anestezi protokolümüz ve bu konuda literatürün gözden geçirilmesi amaçlanmıştır.

Epilepsy is the common neurological disorder, with a prevalence of about 1%. The antiepileptic drugs (AEDs) play a significant role in treatment of seizure (1). However, for refractory epilepsy, surgical treatment is an option. Epilepsy surgery is varies from invasive electrode placement to the hemispherectomy (**Table 1**).



a. **Invasive EEG monitoring**
   Subdural grid and strip electrode placement
   Intraparenchymal deep electrode placement
b. **Surgical resections**
- Temporal lobectomy
- Selective Amygdalohypocampectomy
- Extratemporal resections
- Corpus callostomy
- Hemisferotomy/hemisferectomy

c. **Vagal nerve stimulator placement**
d. **Electrical stimulation of centromedian thalamic nucleus** (not in routine clinical use)

Table 1**:** *Different types of the surgical management of epilepsy.*

Different types of AEDs are available (**Table 2**).

Drug	Absorption	Protein binding	Half-life Period (h)	Elimination	
Ethosuximide	Fast (%90-95)	0	20-60	%80 hepatic, %20 renal,	¼ alimination without any change, much more fast clearance in pediatric patients
Felbamate		%25	20-23	%50 hepatic, %50 renal	Decreases VPA and DFH clearance
Phenytoin	Slow	%90-93	9-40	Saturable hepatic metabolism	Enzyme induction Half-life depends on concentration
Phenobarbital	Slow	%48-54	72-144	Hepatic (%75) metabolism, ¼ elimination without any change	Enzyme induction, sedation, tolerance and rebound
Gabapentin		%0	5-7	%100 renal	Absorption depends on dose
Carbamazepine	Slow (%75-85)	%70-80	24-45(single dose) 8-24 (chronic)	Hepatic (%95) metabolism active metabolite	Enzyme induction autoinduction
Clonazepam	Fast (%80-90)	%80-90	30-40	Hepatic metabolism	Sedation, tolerance and rebound
Na-Valproate	Fast (%100)	%88-92	7-17 (except chrono form)	Hepatic metabolism active metabolite	Enzyme induction concentration dependent protein-binding
Levetiracetam		%100	7-8	%66 renal, % 34 hidrolize by asetamid groups	Metabolized outside the liver. Inactive metabolite
Oxcarbazepine		%40	8-10	%80-70 liver, remain renal	Major metabolite 10-hydroxy-carbamazepine
Pregabalin		0	6	Renal %95	Do not interact
Tiagabine		96	5-9	%90 Liver	Converted to inactive metabolites with oxidative metabolism
Topiramate		9-17	20-24	%40-70 Renal	Metabolized by the liver also, is increased by enzyme- inducing. Inactive metabolites
Zonisamide		40-60	50-68	%70 Liver	Clearance increases with

Table 2: *Pharmacokinetics of the Antiepileptic Drugs.*

During the all type of epileptic surgeries, anestehiologist is faced with the potential side effects of AEDs and interactions with the anesthetic agents (2).

Anesthesiologist has e key role for the preoperative preparation of these patients for such a complex surgery; and during the surgery, avoiding interference with intraoperative neuromonitoring recordings while keep the patient stable. The knowledge regarding various antiepileptic agents and their potential side effects and interactions with anesthetic agents are of prime concern during surgical procedures for epilepsy surgery. Closely monitoring of the patient, and aware about the complications are main considerations during the perioperative period.

PREOPERATIVE MANAGEMENT OF THE PATIENT FOR EPILEPSY SURGERY

Epileptic patient should carefully prepare for epilepsy surgery. Decision-making in epilepsy surgery is required multidisciplinary approach. Detailed evaluation with long-term video-EEG monitoring, MRI, functional MRI, DTI, Magneto-encephalography, neurophsicologic, and neurocognitive tests are essential (3, 4).

A) Electroencephalography (EEG), Long-term video-EEG monitorization:

EEG is a non-invasive method commonly used for the assessment of epilepsy. However, it is insufficient to determine epileptic focus.

Video EEG with either scalp electrodes or invasive intrac-cranial electrodes is more dedicated recording method used for the electro-anatomo-clinical correlation. While the patient is kept in special rooms prepared for recording under 24 hour surveillance and the seizure is recorded with EEG, seizure symptomsare recorded with the video by changing the doses of antiepileptic drugs if necessary.

B) Neroimaging

i- Magnetic resonance Imaging is a more specific technique than computer tomography (CT). Today, it is not used to diagnose and follow up the epilepsy other than the conditions when calcifications are required to be shown. Another use of CT in operative epilepsy is the postoperative imaging of the intracranial electrodes Magnetic Resonance Spectroscopy introduces findings in terms of etiology in temporal lobe epilepsy.

ii- Diffusion tensor imaging (DTI) is one of the high resolution imaging techniques recently used in epilepsy high resolution. It allows the mapping of white matter organization and abnormalities in patients with suspected focal cortical dysplasia.

iii- Functional imaging techniques: It is used especially when EEG findings recorded surface electrodes in MRI are not sufficient in patients not having lesions and it allows mapping ictal hyperfusion.

Ictal and interictal SPECT findings may be compared, aligned and assessed together with MRI.

Fluorodeoxyglucose-PET' (FDG- PET) administered in interictal period is a widespread used PET study; it measures regional glucose metabolism and localizes hypo-metabolic areas. α-methyl-L-tryptophan-PET (AMT-PET) is used to distinguish epileptogenic lesion from non-epileptogenic lesions in tuber sclerosis and multifocal cortical dysplasia; further it allows mapping of residual epileptogenic region in ineffective operations. Flumazenil-PET could yield correlated findings in invasive records and image epileptogenic zone without overflowing MRI boundaries.

Magneto encephalography (MEG): It is technique used for mapping irritative zone by recording magnetic zone occurred interictal epileptiform activity (magnetic dipoles). Currently it is used in limited epilepsy surgeries as its clinical value is not determined completely.

Functional MRI: It relies on evaluation of cerebral blood flow by utilizing paramagnetic deoxihemoglobin. It is promising technique in preparation for epilepsy surgery in children. For patients uncooperative to fMRI paradigms due to age and cognitive levels, fMRI applications are being developed under sedation. The use of functional MRI in epilepsy and pediatric can be summed up as localization of epileptic focus, localization of sensorimotor cortex and activation of visual and auditory cortex.

C) Neuropsychological and cognitive assessment

Every epilepsy surgery patient must be neuropsychologically assessed. The objective is to determine the level of pre-operative cognitive functions, understand relation between epileptogenic lesion and cortex and determine functional deficit that may arise post operatively. Neuropsychological assessment and semiological and electrographic and radiological findings are assessed together for lateralization and localization.

Wada test

Wada test used for lateralization of language and memory functions have recently given way to fMRI applications as it is an invasive method and it bears cooperation difficulties relatively. Injecting sodium amital from carotid artery creates temporary neurological deficit. It is an invasive method and fMRI is used more often instead of WADA test.

PREOPERATIVE ANESTHETIC EVALUATION FOR AEDs RELATED SIDE EFFECTS

Main characteristics of the antiepileptics commonly used in the anesthetic practice are summarized in Table 2. New antiepileptics such as lamotrigine, vigabatrin, oxcarbazepine, topiramate, gabapentin, pregabalin, levetiracetam, zonisamide, lacosamide are commercially available.

All antiepileptic drugs are available in oral and/or IV form. There also available exists intravenous forms of diphenylhydantoin and levatiracetam. Knowing such forms are of particular importance in terms of implementation during surgery. If it is planned to give the patient non-intravenous form antiepileptic agent, nasogastric tube should be placed before surgical area is covered.

Since all antiepileptics related to anesthetics may cause metabolic disordersin the perioperative period, bleeding disorders, electrolyte disturbances and hypotension and in this respect; it is important to monitor the patients being treated with multiple antiepileptics.

It has been shown that in patients with long-term useof phenytoin and carbamazepine, the need of perioperative opioid reduces and patients develop

resistance against hepatic enzyme induction, seconder non-depolarizing neuromuscular agents (6). In addition, with phenytoin bolus injection, neuromuscular blockade period prolongs. In this respect, the safest muscle relaxant agent is cisatracurium and it is used during epilepsy surgery as infusion in our clinic (7).

All antiepileptic agents reduce minimal alveolar concentration of inhalated anesthetics. Enflurane, sevoflurane, metohexiton, flumazenil, tramadol, etomidate, high-dose opioids,local anesthetic scan triggerseizure activity (8,9).

All antiepileptic agents may cause bleeding and clotting disorders. Valproic acid is also of importance in terms of these side effects, even if the test results are normal as it may result in increased bleeding during surgery. In particular, in patients using multipleAEDs, unexplained perioperative bleeding like a leakagecan be detectedand this condition should be treated. Even if liver function tests of these patients are normal, intravenous vitamin K is administered at our clinic, as their reserves are insufficient. During the surgery, the patients are treated with freshly frozen plasma and thrombocytes when necessary.

Due to gabapentin and pregabaline analgesic effects, it is often used in anesthesia to reduce postoperative use of analgesic as well as antiepileptic use. However, in perioperative period, use ofanesthetic may require titrating and cause late extubation(10). In our clinic, patients using preoperative gabapentin, morphine dose is administered after the patient is extubated in postoperative analgesia.

Topiramateis an agent used inmultiple antiepileptic therapies, and directly related metabolic acidosis (11). However, these patients should be evaluated with blood gas and metabolic acidosis during preoperative assessment if possible. If blood gas is not taken out, monitoring depth and rate of respiration per minute at least should provide an insight in terms of patient's metabolic status.In our clinic, topiramate is cut under supervision of ourepileptologists during preoperative period and blood gas analysis is evaluated with acid-base status of the patient.

ANESTHETIC PRINCIPLES FOR EPILEPSY SURGERY

Anesthetic management is included the perioperative period. This period starts with the preoperative evaluation through postoperative follow-up;

a) Preoperative assessment and patient preparation (anesthesia preparation with neuromonitoring, Neuropsychological tests, psychosocial assessment, MRI, fMRI, etc.)
b) Intraoperative monitorization in anesthesia
c) Anesthesia technic (anesthesia, maintenance of anesthesia, anesthesia during neuromonitoring management, safe extubation)
d) Postoperative follow up in PACU, NICU and patient room.

While preoperative anesthesia examination, patient's routine preparation and also antiepileptics and their side effects should be analyzed. If its possible antiepileptic blood levels should be controlled. Bleeding, coagulation time should be controlled and treated if necessary. Respiratory rate and pattern can give idea about acid bases status. Blood gases must be monitor. In our clinic, laboratory examination is done for respiratory (chest graphy), cardiac (ECG), renal (BUN, creatinin, urine analyses), thyroid (free T3, T4, TSH), liver and pancreatic (lipid profile, SGOT, SGPT, GGT, ALP, pancreatic amylase, lipase) functions. Lipid profile and pancreatic function are documented for the propofol infusion related side effects (12).

Anesthesia and intraoperative monitoring

Studies of the agents used during MEP and SSEP monitoring show that all anesthetic agents affect signals negatively. However, total intravenous aesthesia using by propofol and remifentanil is better. Neuromuscular agent cannot be applied if MEP monitored. Although it is affected less by the use of muscle relaxants, SSEP is affected by changes in the patient's body temperature, the anesthesia depth, and changes in blood pressure. Stable and deep anesthesia, control of heart rate and blood pressure, and stable hemodynamics are essential during SSEP monitoring. Minor changes in the blood pressure may rapidly change the signal; thus, the perfusion pressure must be kept stable (13). In our clinic, we routinely use total intravenous anesthesia with propofol and remifentanil. Cisatracurium infusion is continued during the epilepsy surgery until the end of lesion resection.

Electrocorticography is used to determine the area of epileptiform activity. When the general anesthesia applied for epilepsy surgery, all the volatile agents, intravenous hypnotics, and benzodiazepines affect spikes negatively (14). Therefore, before the lesion is excised, the doses of anesthetic agents must be decreased and the patient should be under surface anesthesia, if possible. However, the patient's reflexes, such as moving, straining and couching, must be suppressed with muscle relaxants. Methohexital, etomidate and alfentanil increase the spikes, but it is conflicted (14). To ensure safety, precautions must be taken in case the patient experiences seizures during direct cortical stimulation (**Fig. 1**).

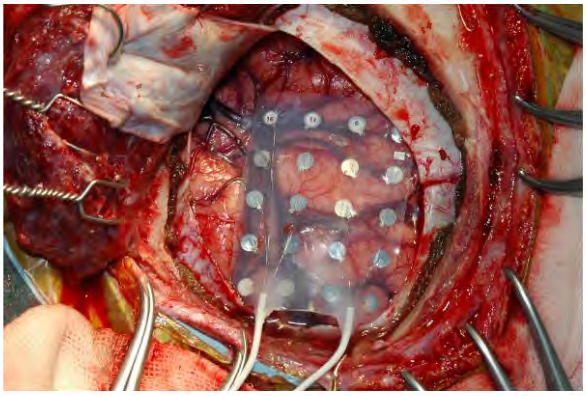


Figure 1. *Intraoperative cortical mapping during epilepsy surgery.*

Iced water should be ready in nurses table in case of emerge. If seizure is occurred related with the stimulation, stimulation should be stopped, surgical area should be washed with iced water, and intravenous propofol or antiepileptic agents can be applied if seizure cannot be controlled. Anesthesiologist should be prepared the mounth following the endotracheal intubation for to avoid the damage of teeth and tongue cause of the biting related with the stimulation. In our clinical experience, generally iced water is effective for seizure control. Additionally bolus dose of propofol also can be used, if required.

Anesthesia:

The methodto be appliedduring anesthesia is standardneuroanaesthetic approach. However some points need attention. What is required in anesthesia approach is to determine the use of intraoperative neuromonitoring. In our clinic, depending on the resective area functions variable neuro-monitoring methods are applied during epilepsy surgeries (7).

Inductionand maintenance of anesthesia in patients is the same as the standard protocol of neurosurgery. Anesthesia induction is made with sodium thiopental due to positive intracranial effects and as it provides more stable hemodynamics.

In addition, bolus dose of fentanylandcisatracurium asmuscle relaxantagent are used. Long-term use of antiepileptics influenced action times of all non-depolarizing muscle relaxant agents. As elimination is different, the least affected agent is cisatracurium in this case. If mappingis madeduring surgery, it may be suitable to administer cisatracurium as infusion as doses ofthe anesthetic drug may be required to reduce. Remifentanil and propofol combination are infused in maintaining anesthesia.

Total intravenousanesthesia is applied manually controlled ortarget controlled. Although it is known that remifentanil infusion changes wave activity at epileptic focus, it is preferred especially if it is recorded due to short action time (15).During recording, negative effect ofpropofol is higher and propofol is discontinued before recording. In the meantime, anesthesia is continued using by increased remifentanil dosesand cisatracurium infusion. If cisatracurium is not to be used, nerve muscle stimulator must be used and when 2 or more response is received for quadruple stimulant, repeating dose should be administered.

Patient should be questioned for peroperative awareness following the surgery. During this period, depth of anesthesia can be evaluated by evoked potential, which is already monitored by epileptologists.

Use of inhalation agents is not recommended if neromonitoring is to be made (16,17). These agents affect records negatively during neromonitoring. During operation, especially if corticalstimulation is mad, seizure risk of the patientduring stimulation is high and ice water washing of surgical area and application of antiepileptic and/or anesthetic agents may be required (18). In recent years, efficiency of propofol bolus in this case has become prominent (19,20). However, during awake craniotomy, it is required to wash surgical area of the spontaneously breathing patient with ice water. In addition, airline safety should be ensured.

Postoperative Follow-up:

In perioperative period, anesthetic agents affect AEDs pharmacokinetically and pharmacodynamically and cause frequent reduction of antiepileptic levels of blood. Perioperative liquid sifts also contribute to this. When surgical manipulation is added, seizure frequency in these patients increased. If antiepileptics are available during surgery, they should be administered intravenously, if not, with the help of nasogastric at prescribed time. In these patients, certain anesthesiologists administer loading dose epdantoin besides antiepileptics. In our clinic, antiepileptic doses are continued to be in use and epdantoin is given in case of seizure in post-operative period.

Any pain, nausea, vomiting, chills, fever and metabolic disorders that may trigger seizure in patientsin the postoperative period should be prevented. An effective pain control should be provided in patient, body temperature should be kept at normal limits and close metabolic monitorization should be done. For this purpose, a combination of paracetamol and morphine is used in our clinic and Cranial block surgery is applied with bupivacaine.

Postoperative nausea and vomiting is provided with the application of ondansetron during closure of the dura. Shivering is a common side effect especially after total intravenous anesthesia. In our clinic, meperidin is used to therapy the patients with normal body temperature.

All antiepileptic agents may affect bleeding and clotting time, caution should be taken in patients using valproic acid in terms of postoperative bleeding.

Conclusion:

Epilepsy surgery requires the teamwork. Neurosurgeon, epileptologist and anesthesiologist have very important roles for success results. Anesthetic management of epileptic patient has a key role for effective neuromonitoring and success of the surgery, and anesthesiologist should be aware about AEDs, and their side effects for perioperative patient safety.

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