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Levetiracetamas a Brain Tumor Post Operation Seizure Prevention Drug

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Abstract: ***Levetiracetam is a new generation antiepileptic drug that has a small side effect and interaction that is lesser than Fenitoin. The use of this drug covers as prevention for post operation seizure for patients who are at high risk to experience such seizure. This case reports a male, 25 years; with IntraaxialRegio Frontal Sinistratumor with suspect Low grade Glioma and Symptomatic Epilepsy undergoes an Awake Craniotomy to remove the tumor. The patient had experienced 5 episodes of seizures although his condition has been controlled with Fenitoin and Carbamazepine as antiepileptic drug. This case reports 3 repeated seizures occurredwithin16 hours post operation and therefore the antiepileptic drug of Levetiracetam was introduced. After the new drug was administered, seizure was reported absent until the patient was discharged. Seizure post brain tumor surgery is a serious complication, usually caused by the activity of surgery or an emergency medical condition that requires immediate therapy and care. This occurrence is related to the remaining neurological symptoms which may increase the patient's morbidity and decrease the quality of life. Giving the right antiepilepsy drug before and after surgery is expected to increase chances of post-operative seizure for patients who are at high risk, therefore reducing hospitalization duration and reducing cost of hospitalization.***

Keywords: Epilepsy, Fenitoin, Post Operation seizure, Levetiracetam, brain tumor

1. Introduction

Seizure normally occurs at 20-45% of patients with brain tumor which increase pain level and the decrease of patient's life quality.[1] 15-20% of seizure occurs to patients who undergo supratentorial craniotomy. The high occurrence of such seizure leads to the use of antiepileptic drug as a prevention for post-operation seizure to give the patients with brain tumor the more optimal result. Clinical guidance or consensus to select the best antiepileptic medication for prevention of seizure to post-operation patients who undergoes brain tumor operation is not formulated yet, however several case reports used the new generation antiepileptic drug (Levetiracetam) as to prevent post-operation seizure.[1] Patients with glioma were reported to have epilepsy a week post-operation and 48% experience epilepsy during illness.[2] There are many risks that are related to post surgery seizure such as intraparenchymal seizure, young age (<50 years), tumor that is located at front lobe, multiple lesions, partial or total tumor resection craniotomy, history of seizure and the growth rate of tumor.2Post operative seizure could also potentially blindside the evaluations towards post operation complication such as patient's level of consciousness, bleeding complication and the growth of the remaining tumor which can cause cerebral edema. Risk of seizure can also increase chance of patient's mortality due to aspiration, brain hypoxia, brain edema and collapsed. Several cases of post-operation seizure are reported to increase number of depressions, anxiety and suicidal attempts rate. Epilepsy associated with brain tumors is difficult to treat and has an impact on the patient's quality of life. Epilepsy associated with supratentorial brain tumor occurs in 40-60% of cases especially in Low Grade Glioma and glioneuraltumors located in the fronto-temporal lobes or eloquent cortex.[3] Seizure can occur during illness, during surgery, post operation and during chemotherapy.[3] The American Neurological Association (ANA) does not endorse regular consumption of antiepileptic drug as a prevention towards post-operation seizure for patients who has history of seizures, however, such decision needs to be considered again for patients who has history of seizures and at high risk to experience repeated seizures.

2. Case

Male, 25 years old, was diagnosed with tumor at the IntraaxialRegio Frontal Sinistra with a suspect of *Low Grade Glioma* andsymptomatic epilepsy was decided to undergo Awake Craniotomy to resect the tumor. Patient indicated having history of seizure in the past 4 months before being admitted to the hospital with seizure was experienced throughout the whole body for ± 15 minutes in each episode. Patient was conscious before the seizure, unconscious during the seizure and regained his consciousness post seizure. Patient also indicated that he had no history of seizure prior to 4 months, the first time experiencing episodes of seizure and had 5 episodes of seizure before the surgery. The last reported seizure was two weeks prior to the surgery. Patient also indicated to experience intermittent headache at the back of his head once to twice per week. Other symptom that was observed include tremor at the tip of fingers especially when the body is moving. Other symptoms like weakness at joints and muscles, double vision, projectile vomiting, fever, speech difficulty was declared as absence. The patient had frequently visited a Neurologist and had done EEG (Electroencephalogram) with result indicated as "normal" and was given Fenitoin 100mg every 8 hours PO and carbamazepine 200 mg every 8 hours. Patient had not been taking anti seizure drug since two weeks prior and had reported if headache occurred, a 500mg paracetamol was then taken. Other systemic diseases such as hypertension, diabetes, asthma and cardiac-related diseases were absent.

Patient also had no history of seizure and no epilepsy history in the family.

On physical examination, his weight was 91 kg; height 170 cm; Body Mass Index (BMI) 31.4 kg/m, Axillary temperature 36.7 ^{o}C; *Numeric Rating Scale* (NRS) still 0/10; NRS moving 0 /10. Fully composmentis, light reflex +/+, isochoric round pupil3mm/3mm; Respiration: breatingrate16 times per menit, Vesicular at both lung fields, rhonchi and wheezing was stated absent, peripheral oxygen saturation 98% at room air. Cardiovascular: pulse rate 71 per minute, blood pressure 130/80 mmHg; Regular heart sounds 1 and 2 single, regular, murmu and gallop were absent; Abdoment: *soepel* or flexible, normal bowel sounds, no swelling in liver and lien, urogenital: spontan urination; Musculoskeletal: good neck muscle flexibility, Mallampati III, complete teeth, Interspinous space is felt right without signs of infection, absence of cranial nerve 12 and nerve 7, Motor and sensory abnormalities are absent. Pathological reflex (-). On further examination it was assessed=: Hematology: WBC 7.57 x10^{3}/µL HGB 15.00 g/dL; HCT 45.40 % (41-53); PLT 340 x 10^{3}µL; Hemostatis function: PPT 10.5 sec (10, 8-14, 4); APTT 27.2 sec (24-36); INR 0.91 (0.9-1.1); Clinical Chemistry: BUN 12.5 mg/dL (8-23); SC 0.8 mg/dL (0.7-1.2); eLFG 124.16.50 (>=90); SGOT 52 U/L (11-33); SGPT 102.40 U/L (11-50); Electrolyte: Na 141 mmol/L and Potassium 4.46 mmol/L; EKG: Normal sinus rhythm, rate 71 times/menit, ST-T *Change* not present; Thorax Imaging (Picture 1): No abnormalities in *Soft tissue*, bones: no abnormalities, sinus pleura sharp left and right, right diaphragm is located higher, left is seen, Heart size is normal, CTR 45 %, Lungs appear without infiltrates/nodes. Rough bronchovascular marking, impression: Heart within normal limits; Head MRI Imaging (figure 2): There is an intraaxialsupratentorial mass with partially well demarcated borders and lobulated edges size ± 5.2 x 5.1 x 4.9 cm at the left frontal lobe cortical-subcortical, with perifocal and *vasogenic*ede main the surrounding, which appears hypointens to isointenseat T1WI, hiperintensat T2WI, danhipo-isointense pada*FLAIR*, danafter giving contrast appears slight slight contrast enhancement at the solid component. Mass is seen pressing left cornu anterior ventricle lateralis and causes *midline shift* as far as ± 1.5 cm to the right sulcus and gyrus outside the lesion appears normal. Ventricle system III, IV, and cistern looks normal. No abnormalities seen in the pons and cerebellum. Orbit, nerves and external eye muscles appear normal. Impessions**:** Solid mass with cystic component inside intraaxialsupratentorialat cortical-subcortical frontal lobe with perifocaland vasogenicedemain the surrounding, which pressesanterior horn of the left lateral ventricaland cause *subfalcineherniation* as far as +/-1.5 cm to the right, giving impression of *primary brain* tumour with suspect *Low GradeAstocytoma*dd / oligodendroglioma. Retention cyst in the left frontal sinus and Ethmoid sinusitis on the right and left sides. Deviation of nasal septum to the right. Hypertrophy of the middle and inferior nasal conchae on the right and left sides.

Patient was concluded having physical status ASA (*American Society of Anesthesiologists)* III based on anamneses, physical examination and supporting examination with this actual problem at central nervous system: Left frontal lobe intra-axial mass ec suspected low grade glioma + symptomatic epilepsy with consciousness compos mentis with signs of increasing clinical Intracranial Pressure (patient's had seizure 5 times which occurred two weeks prior)and class 1 obesity with BMI 31, 4 kg/m^{2}. Anesthesia technique that is used was *AwakeCraniotomy with ScalpBlock*. Patient was premedicated with Paracetamol 750 mg (oral), Ondasentron 8 mg IV, Fentanyl 25 mcg IV. In the operating room, scalp block was performed using regiment Bupivacaine 0, 25% + Lidocain 1% with volume 3 ml at each site. Intra operation, the patient was given Dexmedetomidine through syringe pump with titration dose 0, 2-0, 4mcg/kg of body weight with target *Richmond Agitation Sedation Scale (*RASS)-2until-3, Paracetamol 1000mg IV, Fentanyl 25 mcg IV, Fenitonin 100 mg, Mannitol 45 gram. Post operation, patient was given analgesic Fentanyl 400 mcg in 24 jam via syringe pump, Paracetamol 1000 mg every 8 jam IV, and ICU care.

At the pre-operating room, an 18 G Intravenous (IV) line was placed in the patient's vein attached to Ringer's lactate with 20 drops per minute. Patient was also informed to fast 8 hours before anesthesia was given. Upon entering the pre-operating room, the patient's vital was examined with compos mentis consciousness, pulse 71 beats / minute, blood pressure 135 / 72 mmHg, breathing rate 20 breaths per minute, spO2 98% room air. Routine preparation such as STATICS, Set Block, emergency medication, emergency equipment outside of operating theatre, operating table was set parallel in horizontal, Vasopressor, Inotropic and a request of post-operation Intensive Care room. Patient's bed was rolled in to the operating room and was attached hemodynamic monitoring tools, oxygenation through nasal cannula 3Liter/min and then Scalp Block was performed. Before incision began, patient was given Fentanyl 25 mcg IV and 15 minutes later operation began. Operation went for 4 hours, 5 minutes with stable hemodynamic (Image 3) with blood pressure fluctuated 110-160/58-80 mmHg, pulse rate 60-90x/min, aspiration rate 18-22x/min, SpO2 98-100 %, nasal cannule 3 Liter per minute. Output: Blood lost 600 ml and Urine 400 ml andfluid replacement: crystalloid solutions 2500 ml.

Patient came into the ICU in a good state of consciousness, hemodynamic upon admitted to ICU: BP 126/68 mmHG, HR 88x/min, RR 18x/min, SpO2 98% with NC 3lpm. During ICU care patient was reported stable, with feelings of pain can be managed by giving Fentanyl 400mcg/24 jam via syringe pump and paracetamol 1000 mg IV. Patient was also given antiepileptic drug Phenytoin 100 mg every 8 hours, Ceftriaxone 2 gram every 24 hours IV, Tranexamic acid 500mg every 8 hours IV. 16 hours in ICU, patient suddenly experiencing whole body seizure for +/-5 minutes and was successfully stopped by giving Propofol. Patient's seizure recurred after 4 hours and seizure was stopped by giving Propofol. Patient had another seizure in the following 3 hours which total episodes of seizure was 3 within 24 hours post operation.

Patient's post-operation laboratory shows normal results: WBC 17.58 x10^{3}/µL HGB 13.70 g/dL; HCT 41.50 % (41-53); PLT 291 x 10^{3}µL, Natrium electrolyte 138 mmol/L, Potassium 3.68 mmol/L; Chloride 104.2 mmol/L. After

evaluating based on post-operation laboratory result and patient's symptoms, it was decided to replace Phenytoin 100mg IV every 8 hours to Levetiracetam 500mg every 12 jam orally. Introducing Levitiracetam to the patient yielded a positive result; patient did not experience seizure within 24 hours the new anti-epileptic drug was introduced, after which the patient was transferred to patient's ward and the seizure was continually monitored. Patient did not show any signs of seizure within 48 hours and was discharged after 4 days of hospitalization.

3. Discussion

Patient was known to have a high risk of seizure based on the type of tumor, tumor's location, previous history of seizure before surgery and patient's age who is less than 50 years old.2Several previous researches indicated that that *Low Grade Glioma o*ften linked to refractory epilepsy, tumor's location that is located in the frontal lobe and supratentorial has many connections to area which has epileptogenic which makes it a higher risk to experience seizure.4Patient before surgery had history of epilepsy which was controlled by two types of antiepileptic drug (Fenitoin 100 mg every 8 hours, taken orally and Carbamazepine 200 mg every 8 jam, taken orally)and patient has not consumed antiepileptic drug for the previous two weeks due to absence of seizure. During EEG, patient showed normal result and therefore was diagnosed with epileptic symptomatic because of the brain damage caused by tumor. During his 4 months period of illness, brain damage due to tumor, patient had had 5 seizures. During operation, patient received antiepileptic given through IV (Fenitoin 100 mg), and keep on receiving Fenitoin 100mg every 8 hours. However, 16 hours post operation, patient suddenly had total body seizure ± 5 minutes and had to be stopped by giving propofol. During his seizure, patient was not conscious and regained his consciousness after the seizure ended. After the third seizure, patient was decided to change his antiepileptic drug to new generation (Levetiracetam)and stopped the ongoing antileptic drug (Fenitoin). The change of antiepileptic drug was considered an effective decision in controlling seizure in patient. This was evident after Levetiracetam was administered with dosage 500mg every 12 hours, it was capable to lower down number of seizures post-operation jam (figure 4) and patient was returned home after 4 days of hospital care.

In 2014, *The International League Against Epilepsy (ILAE)* defined Epilepsy as a brain diseases which was characterized by one of this following conditions: 1) at least two unprovoked seizures which occurs more than 24 hours; 2) An unprovoked seizure which may cause relapse (at least 60%) after two seizures without other conditions in the next 10 years; 3) a diagnose from epileptic syndrome. Anti-epilepsy therapy is a main treatment for patients with epilepsy. This criteria has successfully been applied to control seizure in 70% of patients using 1 to 3 anti-epilepsy drug. Side effects may arise in 60% of patients and among 4% terminating the drug consumption. The new generation anti-epileptic drug has a milder side effect and a more minimum drug interaction compared to its previous generation.4

There are two generations of antiepileptic drug: first generation (previous); fenitoin, fenobarbital, carbamazepine, asam valproate, zonisamide, danclobazam, and second generation (new): gabapentin, topiramate, lamotrigine, levetiracetam, rufinamide, Vigabatrin, oxcarbazepine, perampanel, dan lacosamide.5 Based on*ILAE*, antiepileptic drug wasdivided into 3 classes: Class A: levetiracetam, carbamazepine, fenitoin, danzonidsamide; Class B: asam valproate; Class C: gabapentin, lamotrigine, oxcarbazepine, fenobarbital, topiramatedan vigabatrin.[5]

Phenytoin is an antiepileptic drug that had been used in the past 8 decades. Phenytoin was normally used for tonic-clonicseiqure or partial seizure. Phenytoin needs 20 minutes to reach plasma concentration to produce desired pharmacologic response; to block sodium ion channel and lengthen refractory nerve cell[6]. Phenytoin absorption in digestive system 30-97%. Initial dose phenytoin 3-4 mg /kg. Phenytoin works slow when given Intramuscular (IM) therefore given through IM is not recommended. Concentration in the plasma to reach the desired dosage is quite small, which is around10 to 20 µg/mL, this causes side effects such nystagmus, diplopia, vertigo, danataxia. Other than that, phenytoin often gives allergic reaction, megaloblastic anemia. Metabolism of phenytoin that happen in the liver needs sitokrom P450, which is also needed in chemotherapy, corticosteroid, *Proton Pump Inhibitori*, Histamin H2-blocker, benzodiazepine drug family, Macrolite antibiotic, andanti depressant. Fenitoinforms a bond with albumin about 90% and it reaches the peak in the plasma after 4-8hours.6In 2005, before the new generation of antiepieptik drug was released; Fenitoin was widely used by many neurosurgeons due to its ability to not interfering with patient's consciousness. However, since 2016 based on survey, 85% of neurosurgeons in the United States preferred Levetiracetam compared toFenitoin.7This is because Fenitoin needs more stable concentration amount in the plasma to reach the required dosage and therefore required giving the drug ± 1 week before the surgery to reach a stable concentration dosage. Therefore when seizure happened, it was considered late to reach effective plasma concentration for a therapy to works. This is not the case of new generation of anti-epileptic drug which has a shorter amount of loading dosage. Other previous generation of anti-epileptic drug such as fenitoin, carbamazepine, valproate acid has shown interactions with each other which present a challenge to consume the drug at the same time.

New generation of antiepileptic drug such as Levetiracetamis excreted from the body without going through the liver process therefore the risk of drug interaction is lower compared to the previous generation. Levetiracetam is also known to have a low bond with protein. Levetiracetam can form a bond and modulate SV2A activity in brain neurons which cause slowing down the release of neurotransmitter glutamate. Levetiracetamis absorbed quickly and reach peak plasma concentration within 1 hour. Food does not interfere with levels of absorption, however could reduce maximum concentration observed (C-max) to about 20% and delay time of maximum concentration observed *(*T-max) to about 1, 5 hours. Bioavailability of levetiracetam tablet reaches 100%, and possesses the same bioequivalence in terms of absorption

and when consumed with water. Oral Levetiracetam is also bioequivalent with injection, in which Levetiracetam oral has C-max, C-min, dankadarsistemik total yang samadenganlevetiracetaminjeksi yang diberikanperinfusdurasi 15 menit. Because of that, oral Levetiracetamis equally good with levetiracetam injection, having the same qualities, efficacy and safety. Levetiracetam is eliminated through renal. Levetiracetaminside the human body is metabolized in a specific limit. The main Metabolic route is through enzymatic hydrolysis in acetamide group. Metabolic result of carboxylic acid, is ucb L057, and inactive. A research that was done in 82 patients, 2.4% of those receiving Levetiracetam experiences side effct and needs further medication. [5]Levetiracetem also has the capability to increase sensitivity towards chemotherapy drugs, anti-nauseous and neuroprotective effct.4Because of these, neurosurgeons prefer Levetiracetam compared to Fenitointo prevent post craniotomy seizure or post brain surgery.

Patients at the perioperative which has *Low Grade Glioma*has a high risk of having post-operative seizure and can be prevented by giving anti-epileptic drug. In a retrospective research done in Duke University Hospital between May 2010 - December 2011, only 12 out of 165 patients who underwent the operation and had seizure (10 general seizure, and 2 partial seizure). Before the operation, 88 of them had seizure, after being administered with Levepiracetam 1000-3000mg/day post operation for 7 days show a significant reduction when compared to patient who did not receive anti-epileptic drug.5According to research done by Luchi, et al (2015), in comparing research results in the usage of Levetiracetam and Fenitoinas prevention drug to post operation seizure in craniotomy to resect brain tumor. These 147 patients received randomized trial (74 patients received levetiracetamand73 patients received fenitoin) and were monitored for 7 days post operation. Result shows that seizure was reported absent during the operation, however there are 12 from 147 patients in the trial who had seizure within 7 days; 1.4% in those who received Levetiracetamdan 14.1 % in the group who received Fenitoin.1

Post tumor operation seizure is widely occurring incidence and a serious complication as result of brain tumour operation, which is usually related to the high risk of neurological sequelae and medicine from the surgery itself. This would give clinicians to give treatment to terminate the seizure so that effects such as infection due to aspiration, wounds caused by patients falling out of bed, decrease of consciousness and brain swelling. Repeating seizure which occur after tumor resection is not a sign of symptomatic seizure, but it is a sign of chronic condition such as epilepsy[8, 9] Post operation surgery happened in 34 cases out of 679 cases (around 5.1%) in which 17 patients experience multiple seizure and 14 patients experience single general seizure. More than half of patients who had seizure in the first 3 days post operation and 29 cases out of 34 cases experience seizure in thefirst 7 days.9

Post operation seizure often be the cause to perform the surgery again to correct post-operative wounds. Post operation seizure could be prevented and overcame by giving antiepileptic drug which in turn will reduce numbers of occurrence and therefore giving a better patients care and reducing hospitalization time and cost can be lowered.

4. Conclusion

Administration of antiepileptic drug to prevent seizure for post operative tumor who are at high risk have its clinical benefits. Levetiracetamis a new generation anti-epilepsy drug that is effective to prevent incidence of post-operation seizure for patients who were previously given Fenitoin. The effectiveness of Levetiracetam is better compared to Fenitoin and the side effect and drug interaction of Levetiracetam is more minimal compared to Fenitoin. Seizure prevention at post operation results in faster recovery time therefore hospitalization cost can also be lowered.

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Attachment

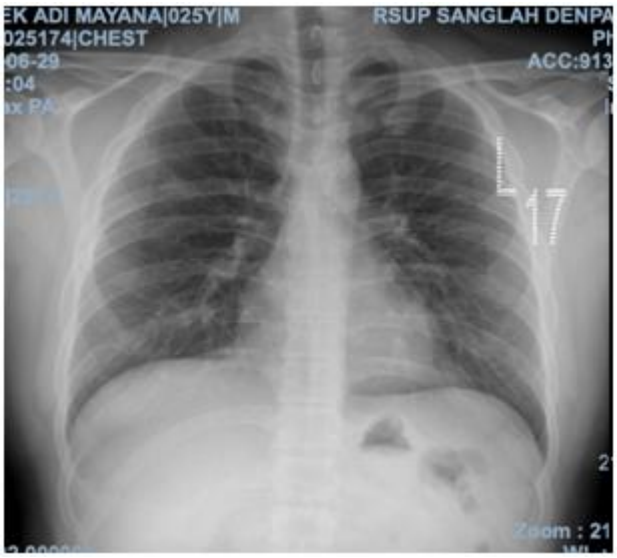

Image 1: Anteriorposterior Chest X-Ray

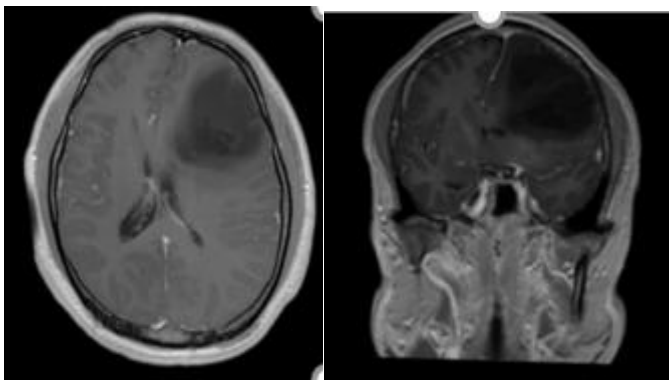

Image 2: MRI

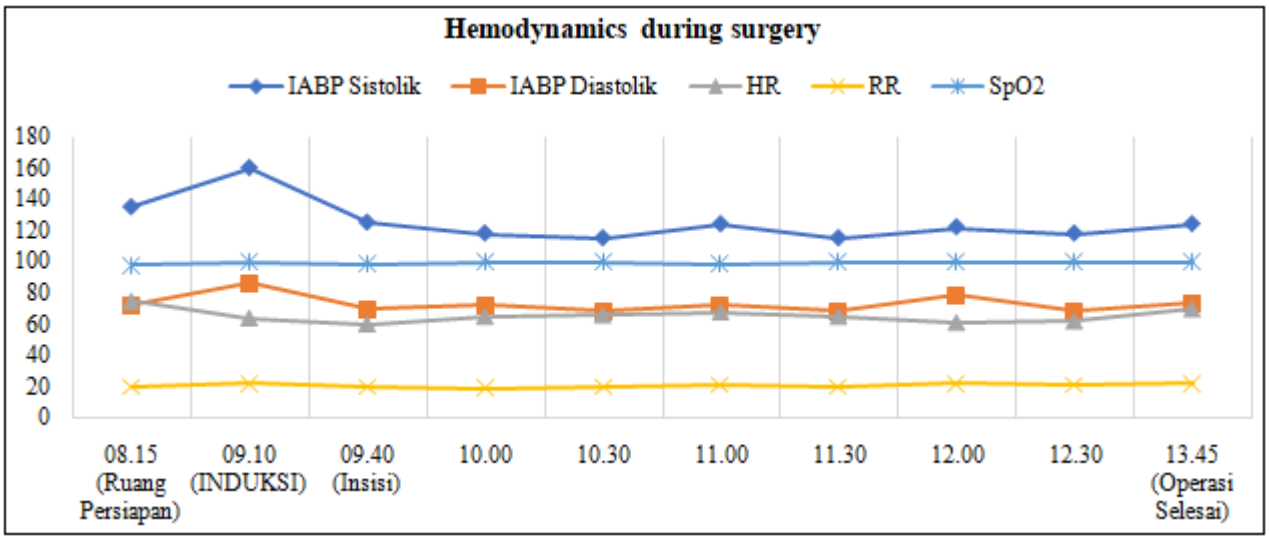

Image 3: HemodynamicDuring Surgery

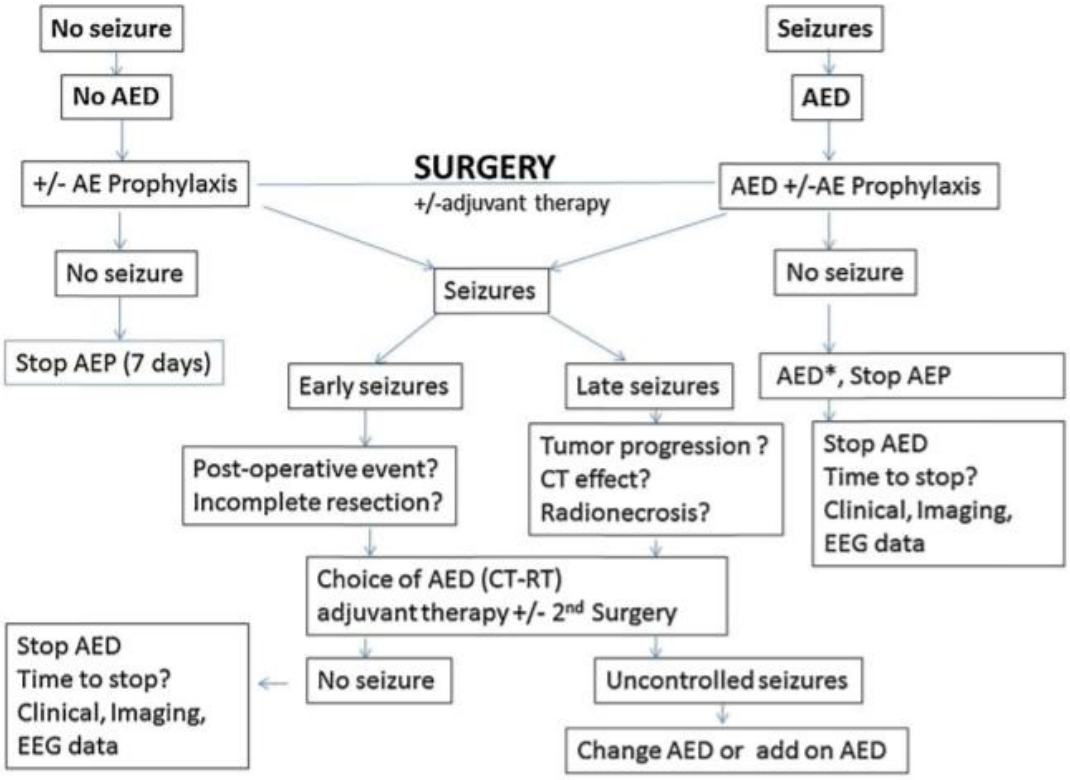

Image 4: Postoperative seizure management flowchart