Desperately needed in Indonesia Basic Epilepsy Surgery Centers with Simple but Reliable presurgical investigations based on Semarang's Experience

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Desperately needed in Indonesia: Basic Epilepsy Surgery Centers with Simple but Reliable pre-surgical investigations, based on Semarang's Experience

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ABSTRACT

Background: Even with optimized anti-epileptic medications, 30% of epilepsy patients will be refractory and this condition leads to cognitive and psychosocial decline, resulting in worse quality of life and higher mortality. With 0,75% prevalence, there are more than 2.0 million epileptic in Indonesia, about 360.000 will be refractory, and half of them are potential candidates for epilepsy surgery (ES). After 17 years since the first ES on July 1999, number of ES increases every year reaching around 50 cases per year. By the end of 2017, the total number reached 615 and most was temporal lobe epilepsy (TLE) cases. Pre-surgical investigations were compared in relation to the seizure free results between the first five-year and the recent twelve-year. Despite the excellent result shown, all of these ES were still performed in Semarang (Diponegoro University), and demographic analysis showed that 80% patients came from Java-Bali area. So that new basic centers capable of performing ES for simple TLE cases are desperately needed to improve treatment for refractory epilepsy cases elsewhere.

Material and methods: Until the end of 2017, there were 615 ES cases, including 514 Temporal Lobe Epilepsies (TLEs). Pre-surgical investigations were grouped as Simple (MRI with specific protocol and routine EEG), Difficult (needs long-term ictal EEG, and /or PET CT), and Complex (needs invasive or intracranial/ subdural grid EEG, and or Electrocorticography/ ECoG during the surgery). For the first five year-period, besides seizure semiology, decision to operate were based on MRI and routine EEG (Simple) in 54 out of 56 (96,4%) TLE cases. One patient had long-term ictal EEG and another had subdural grid EEG implanted, both patients showed visually normal MRI. But for the recent twelve-year, Simple TLEs occupy only 234 out of 458 (51%) TLE cases. Long-term ictal EEG were performed in 161 patients (35,2%), PET study in 39 patients (8,5%), subdural grid EEG in 30 patients (6,5%), and ECoG in 61 patients (13,3%).

Results: As a new ES center performing only simple TLE cases, our surgical results were Class I: 82%, Class II: 11%, and Class III: 7% (9). As a semi advance ES center (after more than 5 years, and only half were simple ES cases), the Class I or seizure free results were 78,7% for simple TLEs, 73,4% for Difficult TLEs, and 65,2% for Complex TLEs. Demographic distribution showed that almost 80% of ES patients came from Java-Bali area, and half of them were from Central Java Province with Semarang as its capital. Patients from other parts of the country were scarce, especially from remotely located islands of East Indonesia.

Conclusion: For the first five year, -as a basic ES center- we relay most on good MRI besides detailed study on seizure semiology and routine EEG. The Class I or Seizure Free result was best in the Simple TLEs with MRI showing discrete unilateral lesion in the temporal lobe. With 17 years experience, and a structured ES program including those patients needed invasive pre-surgical investigations, Semarang is a semi-advance center capable for research and training. This fact should encourage hospitals with micro-neurosurgical capabilities to initiate a new Basic ES Center by sending their neurologist and neurosurgeon to Semarang, so that ES services may become available to PWEs in all part of Indonesia.

Keywords: Epilepsy, Epilepsy Surgery, Temporal Lobe Epilepsy, Epilepsy Surgery Center, Pre-surgical investigation

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INTRODUCTION

Epilepsy is known to affect more than 50 million people around the world, and most of them (almost 80%) are lives in the developing countries.[1] Even with optimized anti-epileptic drug (AED), 30% of those People with Epilepsy (PWE) will continue to have frequent seizures, named Drug Refractory Epilepsy (DRE) and this condition leads to cognitive and psychosocial decline, resulting in worse quality of life and higher mortality.[2-4] Approximately half of these DRE cases are potential candidates for Epilepsy Surgery (ES).[3,5] Complex Partial Epilepsy or once named Psychomotor Epilepsy with seizure focus mostly located in the temporal lobe made up most of these DRE cases.[6] The first randomized controlled trial on DRE cases has shown that in Temporal Lobe Epilepsy (TLE) surgery is superior to optimized

anti epileptic medications, with more than 64% seizure free (SF) with ES compared to only 8% SF with medications.[3] By the end of 2018, with 0.75% prevalence (5, 8), among 267,5 million population (according to the UN World Population Prospect, 2017 revision), there are more than 2 million PWE in Indonesia. Among these, 60% or 1,2 million PWE has localization related or focal epilepsy and 30% of these or 360.000 will be considered as DRE. Half of these DREs are surgically amenable epilepsy syndromes and TLEs occupy most of these DREs.

Surgery for Epilepsy (ES) was started at Diponegoro University Hospital in Semarang on December 1999. For the first five years (2000-2005) only simple TLE cases were operated based on seizure semiology and the presence of obvious unilateral temporal or hippocampal lesions on MRI concordant with the semiology. There were about 10 ES cases every year, and totally 56 ES were performed during this period. During the last twelve years (2006-2017) the number of ES increased to about 40-50 cases per year (Figure 1). By the end of 2017, number of ES reached 615 cases and 514 or 83,6% was TLEs (Figure 2)

Despite the excellent results of ES as shown elsewhere including those reported from Semarang, there is still under utilization of ES as an effective method to abolish seizure. India with over one billion population had more than 1200 ES performed at two major centers,[4] while Malaysia with around 30 million population and estimates of 3000 ES candidates yet only about 100 ES were performed in one center.[1] There are still so many developing countries in Asia and Africa without any center performing ES.[5] Indonesia with about 180.000 ES candidates currently has only one ES center with about 615 ES cases for the past 17 years. Demographic distribution of those PWE underwent ES at this single center were also studied for the purpose of planning new centers in the near future.

There is common opinion that ES is expensive and needs so many sophisticated pre-surgical investigations. Unavailability of many advanced diagnostic modalities such as Single Photon Emission CT (SPECT), Positron Emission Tomography (PET), or Magneto- encephalography (MEG) are discouraging for any intention to start ES. The reasons behind the unavailability of ES in many developing worlds and the desperate need to starts many new ES centers in Indonesia will be discussed based on Semarang's experience.

MATERIAL AND METHOD

During the first five-year, in 54 out of 56 (96,4%) ES cases, the epileptic temporal side were decided based on the presence of unilateral lesion on MRI concordant with the seizure semiology. without any difficult or sophisticated pre-surgical evaluations. The other two cases needed long-term ictal Video-EEG in one and subdural grid implantation in the other one, besides seizure semiology and MRI studies. The results were categorized according to Engel's classification and showed that 82% patients were Seizure Free (SF).[3] But for the recent twelve-year, these simple pre-surgical evaluations were performed in about half of these cases (51%). The rest of ES cases needed either long-term ictal Video-EEG, Positron Emission Topography (PET) scan with Fluoro-Deoxy Glucose (FDG), and even invasive investigations such as subdural grid EEG evaluation for pre-surgical evaluation and/ or Electro-Cortico-Graphy (ECoG). Until the end of 2017 there were totally 615 ES, including 514 TLEs, ages between 1 to 51 year-old.

In TLEs, the surgery is standardized Anterior Temporal Lobectomy or Selective Amygdalo-Hippocampectomy, so that all pre-surgical investigations were aimed to finding out the epileptic side of the temporal lobe. According to the pre-surgical investigation considered as obligatory to confirm the epileptic temporal side, all TLE patients were divided into three groups. Simple (group A) means that the decision for ES was simply based on the presence of unilateral temporal or hippocampal lesion on MRI concordant with seizure semiology (such as prodromal sign or aura, direction of the eye and the head turn and the side of the dystonic arm). Difficult (group B) means that the MRI was visually normal, or there were bilateral lesions, or there were discordance between seizure semiology and the lesions on MRI. These patients need long-term-ictal video EEG and/ or Positron Emission CT scan with Fluoro-Deoxy Glucose. Invasive (group C) means those patients who need pre-surgical invasive intracranial EEG monitoring and those who need Electro-Cortico-Graphic (ECoG) study during the surgery.

RESULTS

Among the 514 TLE cases, 56 cases were operated during the first 5 years after developing ES. During this early phase, 54 out of 56 cases (96.4%) were simple TLEs. The other 2 cases needed long-term ictal EEG and subdural EEG respectively.

During the last 12 years 458 TLEs were operated, and only 234 (51%) cases were simple TLEs. The ather half needs more difficult pre-surgical investigations such as long-term ictal EEG in 161 (35%), FDG-PET studies in 39 (8,5%), and invasive subdural grid EEG in 30 (6,5%). Invasive EEG monitoring

during resection of the epileptogenic focus (Electrocorticography or ECoG) were performed in 61 or 13,3% (Figure 3).

Demographic distribution of the patients showed that from total 615 ES performed, 225 (36,6%) patients were from Central Java (vicinity of Semarang), and 255 (41,5%) patients were from nearby provinces of the same Island (Jakarta, West Java, East Java, and Bali). The others came from Southern Sumatra (47), Northern Sumatra (24), Kalimantan or Borneo (30), Sulawesi or Celebes (6), Moluccas (6), and Papua (7). (Figure 4)

DISCUSSION

The first randomized controlled trial on ES for refractory TLE published at New England Journal of Medicine in 2001[1] had shown that surgery is superior with 64% SF result, compared to optimized medical treatments with 8% SF result. The most recent RCT from AIIMS in Delhi showed a clear benefit of ES in children with DRE, with 77% SF compared to only 7% in non-surgery group.[4]

Introducing a new therapeutic modality for epilepsy needs some time and a great effort to educate the patients and even the medical societies previously involved in the management of epilepsy. As a new and effective treatment to abolish seizure in DRE cases, ES should be started with good selection of surgical candidates, which may yield a good result, and near zero surgical morbidity. That is why we select simple TLE cases with classic TLE semiology concordant with the presence of obvious unilateral temporal lobe lesion on MRI for the first five years (1999-2005).[2] The possibility of doing ES with only good MRI performed with specific TLE protocol, routine EEG and detailed seizure semiology had also been shown by several other centers.[9,10,15,16,17,18] In unilateral mesial temporal or hippocampal sclerosis without contralateral pathology, standard Anterior Temporal Lobectomy or Selective Amygdalo-hippocampectomy can be performed safely with good result without any other investigation for seizure localization or memory localization.[8,18,19] The excellent results as shown by seizure free rates in 82% had to be shown to the patients and his or her family, and also to the medical society as well, especially neurological society.

There is a common opinion that ES is expensive and needs so many difficult and sophisticated pre-surgical diagnostic assessments. Our experience shows that more than 50% of ES were simple TLEs that needs only understanding detailed seizure semiology and good MRI with specific protocol showing unilateral temporal or hippocampal lesion. MRI had been shown to be the best imaging modality to show structural lesions related to epilepsy such as hippocampal sclerosis, benign glioneuronal tumors, vascular malformations, and malformations of cortical developments.[20,21,22,23] Visual MRI might identify hippocampal sclerosis in 80-90% patients, and almost 90% if the patients will be seizure free after surgery.[24,25,26] Our own study on MRI in 100 cases of refractory TLEs had shown the presence of epileptogenic lesion in 79% cases, and Hippocampal sclerosis was found in 59%.[27] So that it is justified to perform MRI studies in medically refractory TLE or other focal epilepsy cases.[27] Quantitative MRI studies (hippocampal volumetry or T2 relaxometry) further improve the sensitivity to detect epileptic temporal lobe.[28,29]

All cases with discrete MRI lesions, if correspond well with the seizure semiology, will be good cases for any new center willing to start ES, since these cases has good indications for ES and the result will be excellent as described by Sujoy and Chandra.[10,18] The difficult cases which needs more sophisticated pre-surgical evaluations such as long-term ictal video EEG, PET-CT studies, or even invasive intracranial electrodes implantation might be referred to our center in Semarang for further evaluations. As shown in the last 12 years period, the other half of our ES cases were the more difficult epilepsy cases with normal MRI, cases with bilateral sclerosis, or those with extra-temporal epileptogenic zone close to the eloquent area of the brain. Long-term ictal EEG were decisive for 35% of our ES cases, while FDG-PET scan was decisive in 8,5% to finding out the epileptic temporal lobe. Routine interictal EEG with 30 minutes recording doesn't help much since 60% shows bilateral interictal discharges despite good outcome after unilateral temporal lobectomy.[31,32,33] Interictal discharges may also incorrectly lateralize the temporal foci in 10-20% patients.[24,34] That is why long-term ictal EEG is an important pre-surgical evaluation in about 35% of our ES cases. Using long-term ictal EEG, accurate localization of the epileptogenic foci is possible in 65-70% of TLE cases.[35,36]

Absence of hospitals or medical facilities performing epilepsy surgery is one of the main reasons behind the lack of awareness among referring physicians and even neurologist about the benefit of ES. Despite lack of understanding of ES, absence of exposure or contact with any ES case creates overwhelmed fears about surgery and its complications. This is the main reason for non-referral or delayed referral of refractory epilepsy cases indicated for evaluations regarding the possibility of ES. More than 90 % DREs who were finally having ES at our center were self-referred. They knew about ES from the mass media, including the Internet and

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the so-called 'social media', hearing about other patient's ES experience. Data from our 536 ES cases shows the mean duration of suffering of repeated seizures before ES was about 15 years.[18] But these patients were considered to be the more fortunate ones compared to those who never heard about ES and having seizures during their lifetime. It seems that as an effective method to abolish seizures, ES is much less promoted and even not known for many physicians. On the other hand, all new and expensive AEDs are extensively marketed and sponsored by pharmaceutical companies, in spite of the fact that the chance of new AEDs including Levetiracetam to control seizures in these patients is at best around 16%, as compared to 70-90% with ES.[37,38]

Demographic distribution of those DRE patients who finally came for ES in Semarang showed that almost 80% were from Java and Bali areas, and almost half of these were from Central Java. The fact that there were many other large University-affiliated Academic Hospitals with micro-neurosurgical facilities in Java (Jakarta, Bandung, Malang, Surabaya, and Jogjakarta) and at least one in each large islands of the Indonesian archipelago (2 in Sumatra, one in Kalimantan and one in Sulawesi), it imperative for neurologist and neurosurgeon at those centers to initiate plan to start ES with simple TLEs as we did for the first five years.[9] The problem in developing a new ES center is not in the surgical technique, but in pre-surgical evaluation. The neurologist and the epilepsy surgeon should not make any mistake differentiating pseudo seizures from true seizure, and the ES candidate have had enough and reliable AED trials.[39,40] Besides standard micro neurosurgical facilities, the neurosurgeon should be well trained to perform a standard Anterior Temporal Lobectomy, including Amygdalo-hippocampectomy. How much training needed is debatable, optimal training for one year is desirable, but a six months intensive training in a center with structured ES programs, such as in Semarang might be considered.[39,40,41]

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