How many more seizure remission can we achieve with epilepsy surgeries in a general epilepsy population?

[1]Si-Lei Fong, [1]Kheng-Seang Lim, [2]Khine Yee Mon, [3]Sherrini Ahmad Bazir, [1]Chong-Tin Tan

[1]Neurology Division, Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia
[2]Neuromedical Department, University of Medicine (1), Yangon, Myanmar
[3]Subang Jaya Medical Centre, Kuala Lumpur, Malaysia

Abstract

Background & Objective: We knew that 63.6% of the epilepsy population can be seizure free with the use of anti-epileptic drugs (AED), but are unsure how many more with epilepsy surgeries. We aimed to determine the additional remission rate achieved with epilepsy surgeries in addition to AED. *Methods:* We analysed the seizure outcome among epilepsy patients seen retrospectively over one-year period in University Malaya Medical Centre, Malaysia, which provides all levels (level 1-4) of epilepsy cares, in response to anti-epileptic drug (AED) and epilepsy surgeries. The seizure outcome was categorised into remission and drug-resistant, according to ILAE definition of drug resistance. *Results:* There were 909 patients seen during the study period, majority with focal epilepsy (63.3%), and Chinese (37.4%). Of those, 409 (45.0%) were in seizure remission, 238 (26.2%) had drug-resistant epilepsy and 262 (28.8%) uncertain. Only the remission and drug-resistant groups (N=647) were included in subsequent analysis. The mean age of onset in drug-resistant group was 14.8±12.3 years old, which was significantly younger than the remission group (20.8±16.8, *p*<0.05). There were 40 (54.8%) patients who underwent resective epilepsy surgeries (10 were lesion-negative cases). The seizure freedom rate with epilepsy surgery was 60.0% (n=24). Overall, a total of 59.5% of patients were in seizure remission with AED, with an additional 3.7% with epilepsy surgery.
Conclusion: There were 3.7% of epilepsy patients achieved seizure remission with epilepsy surgeries in a general epilepsy cohort in addition to AEDs.

Keywords: Seizure outcome, anti-epileptic drugs, epilepsy surgery, epilepsy cohort

INTRODUCTION

Epilepsy is one of the commonest neurological disorders affecting up to 70 million people worldwide.[1] The median lifetime prevalence of active epilepsy in developed country was 4.9 per 1,000 population and up to 12.7 per 1, 000 population in developing countries.[1] International League Against Epilepsy's (ILAE) Commission on Outcome Measurement in Epilepsy (COME) established the domains for seizure outcome measurement based on seizure frequency, seizure severity, quality of life, cognitive function and adverse events.[2] These domains are important in assessment of efficacy of treatment or impairment and disabilities.

Over the ensuing years, despite the use of newer anti-epileptic drugs (AED), the overall efficacy of AEDs alone were found to be 63.6%.[3] The remaining 36.3% of patient continued to have seizures. Previous studies on efficacy of AED regimes were performed in Western population.[3-6] In addition, studies of seizure outcome were either based entirely on the patients on AEDs or selected group of patients who underwent epilepsy surgeries in tertiary epilepsy referral centres. Although epilepsy is a global health issue, epilepsy in Asian population differs from Western population in the biological, environmental, psychosocial, economic and cultural aspects.[7] Consequently, the efficacy and responsiveness to AED regimes may differ also between the Asian and Western populations.

Epilepsy surgeries have been increasingly used for patients with drug resistant epilepsies over the years. Among the epilepsy surgery cohort, extensive studies reported a seizure-free rate ranges from 50 to 89% following epilepsy surgeries for temporal lobe epilepsy.[8] However, epilepsy surgery is underutilized worldwide. In United States (USA), epilepsy surgery gap, as defined by the percentage of patients who are eligible for surgery but did not receive surgery, was reported to be as high as 96–99%.[9] In India, Radhakrishnan in 2009 reported only 200 epilepsy surgeries (0.04%) were performed per year despite having over 500,000 potential epilepsy surgery candidates.[10] Although the number of epilepsy surgeries increased to 734 per year in 2016, it is still underutilized.[11] Epilepsy surgery gap is a global issue because most tertiary hospitals especially in the low-middle income countries do not have comprehensive epilepsy surgery program. In Southeast Asia, some countries (3/11, 27%) have no epilepsy surgery services, and only 5/11 (45%) provided stage-4 epilepsy care.[12] In our opinion, knowing the percentage of epilepsy surgical remediable cases and seizure freedom rate in a general epilepsy population are important information especially for hospitals or countries without an epilepsy surgery program. These will guide the policy-maker to estimate the number of epilepsy surgical remediable cases in a city or a country based on the total epilepsy population.

Therefore, we aimed to study (1) the AEDs effectiveness in an Asian general epilepsy population, as compared to the Western population, and (2) to determine the additional remission rate achieved with epilepsy surgeries in addition to anti-epileptic drugs (AED) in University Malaya Medical Centre (UMMC, Malaysia), which provides all levels (level 1-4) of epilepsy cares, according to National Association of Epilepsy Care (NACE) guidelines.

METHODS

Sample recruitment and data collection

Our study included patients diagnosed with epilepsy and followed up on a regular basis in University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. This study is approved by Ethics Committee in UMMC (MREC 2019215-7132). Data were collected retrospectively from our epilepsy database which were updated during each clinic visit.

This database contains patients' demography, seizure semiology, seizure type, seizure aetiology, family history of epilepsy, history of febrile seizures. Investigations done and their findings such as scalp EEG, video EEG, magnetic resonant imaging (MRI), computered tomography (CT) brain, positron emitted tomography (PET), single- photon emission computered tomography (SPECT) were recorded.

Appropriate anti- epileptic drug (AED) was started after the diagnosis of epilepsy. Previously tried and current AED regimes were recorded. Patients' seizure control, tolerability to current AED and compliance to AED were recorded during each clinic visit. First AED was further titrated based on seizure control, tolerability or adverse reactions experienced. An AED will be terminated and changed to another AED in the event of (i) failure to achieve seizure control despite optimal dose, (ii) adverse reactions or (iii) other reasons such as financial difficulty. AED dose when it was terminated was recorded. Combination therapy was used when there is partial seizure control with the initial AED or failed to achieve seizure control with monotherapy. Details of epilepsy surgery (if done) were recorded, including the type of epilepsy surgeries and the histopathology of the resected tissues. Seizure control was documented in each clinic visit.

Patients were seen regularly in clinic with a 3 to 6-monthly interval based on seizure control and the need to monitor adverse reactions. Shorter follow up intervals were given to patients post epilepsy surgery and those who needed more frequent review for treatment optimisation.

Inclusion and exclusion criteria

We retrospectively studied the patients diagnosed with epilepsy for 1 year or more, who were seen in our clinic from 4th July 2017 to 3rd July 2018, with at least one year follow up subsequently. We excluded patients who were last seen in clinic before 4th July 2017 and defaulted follow up after that, or non-compliant to AEDs.

Operational definitions

We used the following operational definitions for seizure outcome in our study. Seizure freedom was defined as no seizures in the preceding 12 months or longer from the last clinic visit. Drug-resistance was defined as persistent seizures despite of 2 or more appropriate and adequate AEDs.[13,14] Seizure outcome was defined as uncertain when duration of seizure freedom from last clinic visit was less than 1-year duration or when patient was on monotherapy with AED dosage which was

not optimised yet. An AED regime was defined as monotherapy or combination therapy of 2 or more drugs. First AED was monotherapy with subsequent AED being either a substitution or add-on therapy to the previous AED. Number of AED were counted and regimes which were terminated prematurely before an optimal dose due to side effects or other reasons were not counted.

Statistical analysis

Data were collected using Microsoft Excel and analysed using both Microsoft Excel and SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Differences in continuous variables were tested with student t-tests, and chi-square tests for non-continuous variables.

RESULTS

There were 909 patients were seen during the study period, majority with focal epilepsy (63.3%), and Chinese (37.4%). Of those, 409 (45.0%) were in seizure remission, 238 (26.2%) had drug-resistant epilepsy and 262 (28.8%) uncertain. Only the remission and drug-resistant groups (N=647) were included in subsequent analysis. The mean age of onset in drug-resistant group was 14.8±12.3 years old, significantly younger than the remission group (20.8±16.8 years old, p <0.05). (Table 1)

A total of 59.5% of patients were able to achieve seizure remission with AED with an additional of 3.7 % of patients with epilepsy surgeries (Table 2), of which 39.1%, 16.1%, 3.2%, 0.7%, 0.2% and 0.2% achieved seizure remission with the first, second and subsequent AED regime, respectively. (Table 2)

Among 191 patients with focal drug-resistant epilepsy, 73 (38.2%) patients were evaluated for epilepsy surgery and 11 (5.8%) refused; whereas the others were undecided for or did not consider presurgical evaluation. There were 40 patients (54.8%) underwent resective epilepsy surgery of which 10 (25.0%) were lesion negative cases and 24 patients (60.0%) were in remission; of which, 12 had anterior temporal lobectomy (ATL), 2 selective amygdalohippocampectomy (SAH) and 10 lesionectomy. For patients with persistent seizures after resective surgery (17, 40.0%), 2 (11.8%) had ATL, 4 (23.5%) SAH and 10 (58.8%) lesionectomy. One patient underwent vagus nerve stimulation (VNS). Among the 32 (43.8%) patients who did not have epilepsy surgery, 8 (25.0%) were planned for surgery, 14 (43.8%) were undecided for or refuse surgery, 6 (18.8%) needed further assessment with intracranial monitoring and 4 (12.5%) were not surgical candidates due to involvement of eloquent cortex or discordant findings after evaluation. Figure 1 illustrated the number of patients with focal drug-resistant epilepsy who underwent surgical evaluation and subsequently achieve seizure freedom post-operatively.

Table 1: Summary of demography and seizure type in different subgroups (N= 647)

Characteristics	Remission (n= 409)	Drug-resistant (n= 238)	*p*-value
Age of onset (years)			
Mean (±SD)	20.7 (±16.8)	14.8 (±12.3)	<0.001
Gender			
Male	219 (53.5%)	125 (52.5%)	0.80
Female	190 (46.5%)	113 (47.5%)	
Ethnic			
Malay	108 (26.4%)	53 (22.3%)	
Chinese	184 (45.0%)	118 (49.6%)	0.59
Indian	110 (26.9%)	64 (26.8%)	
Others	7 (1.7%)	3 (1.3%)	
Seizure type			
Focal	268 (65.5%)	191 (80.3%)	
Generalised	131 (32.0%)	39 (16.4%)	<0.001
Undetermined	10 (2.4%)	8 (3.4%)	

Table 2: Total number of patients achieving seizure freedom in the study cohort (N=647)

Successive anti-epileptic regimes	Total number of patients (n= 409)	%total achieving seizure freedom (n=409)	%of total study cohort (n= 647)	% of total study cohort achieve seizure remission with AED/ surgery
First	253	61.9	39.1	
Second	104	25.9	16.1	
Third	21	5.2	3.2	59.5
Fourth	5	1.2	0.7	
Fifth	1	0.3	0.2	
Sixth	1	0.3	0.2	
Surgery	24	5.9	3.7	3.7

DISCUSSION

Kwan *et al.* (2001) reported that 47% of newly diagnosed epilepsy patients were seizure-free with the first AED.[4] Subsequent studies on this expanded cohort of patients consistently showed that 46%, 49% and 45.7% of patients were able to achieve seizure freedom with their first AED.[3,5,6] Our cohort showed a seizure remission rate of 39.1% with the first AED regime, which is 6.6% lower than the previous studies.[3] The effectiveness with subsequent trial of AED regimes showed similar trend of reduced effectiveness when compared to previous studies. Overall, there were 59.5% seizure remission rate with AED regimes, slightly lower but comparable to previous studies (63.7 to 68.3%).[3,5]

The first challenge in epilepsy management is optimisation of AED regime. In Malaysia and many other Asian countries, only the older generation AEDs are subsidized in government hospital. Despite the emergence of many newer AEDs, these drugs are often more expensive compared to the older generation AEDs and patients need to purchase themselves, which incur

647 Epilepsy

459 Focal epilepsy
(70.9%)

191 Drug-resistant epilepsy
(41.6%)

73 Surgical evaluation
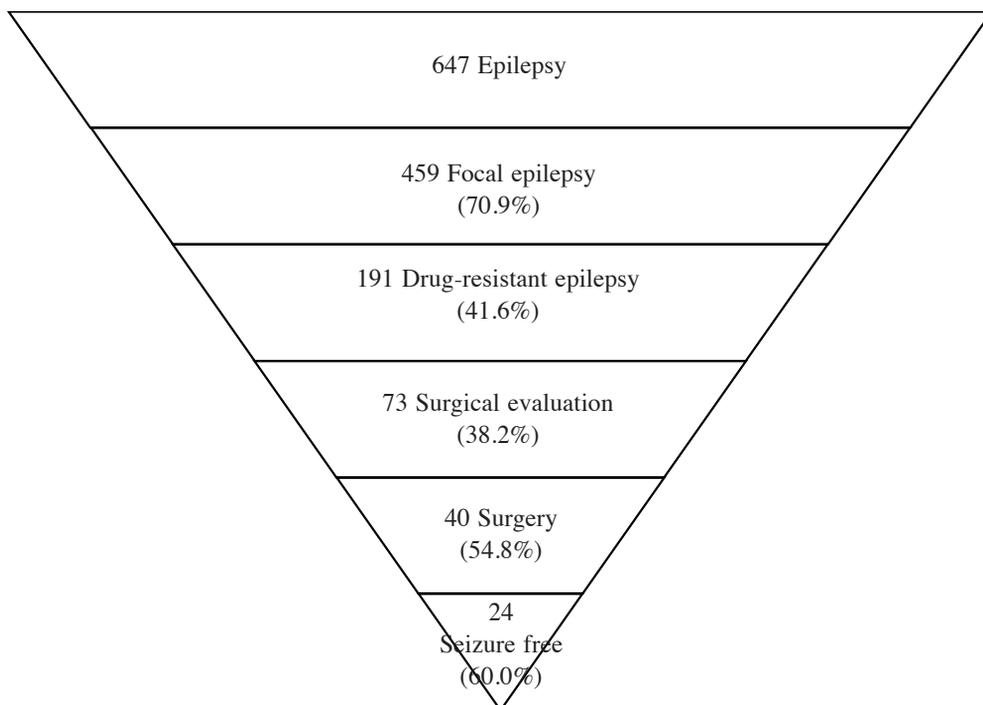(38.2%)

40 Surgery
(54.8%)

24
Seizure free
(60.0%)

Figure 1. Number of epilepsy patients who underwent surgical evaluation and achieve seizure freedom

substantial financial burden. When the options of more affordable older generation AEDs were exhausted due to adverse events, intolerability or inadequate efficacy, the cost factor became the main restriction in epilepsy management when newer AEDs are considered, especially in resource-limited country.[15]

The other major challenge in optimizing AED regimes is patient preference. Some patients were reluctant to increase AED dosage due to fear of side effects. This is probably due to previous experience of AED side effects, cultural belief of long-term treatment causing irreversible organ damage and underestimating the impacts of uncontrolled seizure. Seizure frequency is one of the most important predictors for lower quality of life (QOL) in patients with epilepsy.[16-18] Seizure-free patients often achieve health-related quality of life (HRQOL) similar to general population.[19] However, there were studies reported that comorbidity such as depression and adverse events from AEDs were more important predictors than seizure control for poor quality of life among patients with drug-resistant epilepsy.[20-22] In clinical practice, some patients despite having frequent seizures have relatively unaffected quality of life. These include those with brief, infrequent and less severe seizures or those with aura or nocturnal seizures only, which we defined as *acceptable drug resistant*.

Epilepsy surgery should be considered in patients with drug-resistant epilepsy after appropriate evaluation. The percentage of seizure freedom after resection surgery in patients with concordant data ranges between 60 to 70%.[23,24] However, this figure is based on the cohort of patients who underwent epilepsy surgeries. Our study showed that epilepsy surgeries offer an additional 3.7% chances only to achieve seizure freedom aside from using AEDs alone. There were up to 61.7% of patients with drug-resistant epilepsy were not evaluated for epilepsy surgery. Some of these patients had acceptable drug-resistant epilepsy, as defined earlier. However, there were a small proportion of patients (5.8%) who refused VEM despite frequent disabling seizures in our cohort due to fear of surgical complications or lack of family or financial support. In addition, there were also logistic factors such as lack of funding, facilities or expertise that resulted in underutilization of epilepsy surgeries.[12] Similarly in the European population, only 17% out of the 40% of patients with epilepsy presurgical evaluation had epilepsy surgery.[25] In our study, the low percentage of

seizure remission with epilepsy surgery in an epilepsy cohort as a whole is supportive of the underutilisation of epilepsy surgery.

The findings of this study reflected the overall seizure outcome in our centre which cares for general epilepsy population and receives drug-resistant epilepsy referrals from the country. Although we would expect a larger number of patients with drug-resistant epilepsy in our centre due to the referrals, our result showed that the remission rate is comparable to previous studies. Being a multi ethnic country with Malay being the major ethnic in our country, the Chinese patients in our cohort may be overrepresented. Further studies with wider coverage need to be done to ascertain the seizure outcome in our epilepsy population in Malaysia. We realize that the findings is dependent on referral and treatment patterns, and reports from different regions would provide a more comprehensive picture.

In conclusion, there were additional 3.7% of epilepsy patients achieved seizure remission with epilepsy surgeries in a general epilepsy cohort in addition to AEDs. Tolerable drug-resistant epilepsy and patient- related factors such as fear and misconception for epilepsy surgery were the main challenges faced in improving the utilisation of epilepsy surgery.

DISCLOSURE

REFERENCES

1. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. *Epilepsia* 2010;51:883-90.
2. Baker GA, Camfield C, Camfield P, *et al*. Commission on Outcome Measurement in Epilepsy, 1994-1997: final report. *Epilepsia* 1998;39:213-31.
3. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: A 30-Year Longitudinal Cohort Study. *JAMA Neurol* 2018;75:279-86.
4. Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. *Epilepsia* 2001;42:1255-60.
5. Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. *Neurology* 2012;78:1548-54.
6. Mohanraj R, Brodie MJ. Diagnosing refractory epilepsy: response to sequential treatment schedules. *Eur J Neurol* 2006;13:277-82.

7. Tan CT. Differences in epilepsy and seizures between Asia and the West. *Neurol Asia* 2007:59-60.

8. Tellez-Zenteno JF, Dhar R, Wiebe S. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain* 2005;128:1188-98.

9. Schiltz NK, Fernandez-Baca Vaca G. Epidemiologist's view: Addressing the epilepsy surgery treatment gap with minimally-invasive techniques. *Epilepsy Res* 2018;142:179-81.

10. Radhakrishnan K. Challenges in the management of epilepsy in resource-poor countries. *Nat Rev Neurol* 2009;5:323-30.

11. Rathore C, Radhakrishnan K. Epidemiology of epilepsy surgery in India. *Neurol India* 2017;65:S52-s9.

12. Thuy Le MA, Fong SL, Lim KS, *et al*. Underutilization of epilepsy surgery in ASEAN countries. *Seizure* 2019;69:51-6.

13. Kwan P, Arzimanoglou A, Berg AT, *et al*. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;51:1069-77.

14. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314-9.

15. Radhakrishnan A. Bridging the treatment gap in epilepsy-is there an emerging trend in the use of newer antiepileptic drugs? *Neurol India* 2016;64:1140-2.

16. Bautista RE, Glen ET. Seizure severity is associated with quality of life independent of seizure frequency. *Epilepsy Behav* 2009;16:325-9.

17. Leidy NK, Elixhauser A, Vickrey B, Means E, Willian MK. Seizure frequency and the health-related quality of life of adults with epilepsy. 1999. *Neurology* 2001;57:S69-73.

18. Zhao Y, Wu H, Li J, *et al*. Quality of life and related factors in adult patients with epilepsy in China. *Epilepsy Behav* 2011;22:376-9.

19. Stavem K, Loge JH, Kaasa S. Health status of people with epilepsy compared with a general reference population. *Epilepsia* 2000;41:85-90.

20. Luoni C, Bisulli F, Canevini MP, *et al*. Determinants of health-related quality of life in pharmacoresistant epilepsy: Results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. *Epilepsia* 2011;52:2181-91.

21. Park SP, Song HS, Hwang YH, Lee HW, Suh CK, Kwon SH. Differential effects of seizure control and affective symptoms on quality of life in people with epilepsy. *Epilepsy Behav* 2010;18:455-9.

22. Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology* 2004;62:258-61.

23. Engel J, Jr. Surgery for seizures. *N Engl J Med* 1996;334:647-52.

24. West S, Nolan SJ, Newton R. Surgery for epilepsy: a systematic review of current evidence. *Epileptic Disord* 2016;18:113-21.

25. Boon P, Ryvlin P, Wheless JW, Kawai K. Treating drug resistant epilepsy- why are we waiting? *European Neurological Review* 2015;10:171-5.