Neuro-Psychiatric Predictors of Two-Year Outcome of Epilepsy Surgery in Refractory Epilepsy

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract YES
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found YES
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported YES
Objectives	3	State specific objectives, including any prespecified hypotheses YES
Methods		
Study design	4	Present key elements of study design early in the paper YES
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection YES
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up YES
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable YES
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group YES
Bias	9	Describe any efforts to address potential sources of bias YES
Study size	10	Explain how the study size was arrived at YES
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why YES
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding YES
		(*b*) Describe any methods used to examine subgroups and interactions YES
		(*c*) Explain how missing data were addressed YES
		(*d*) If applicable, explain how loss to follow-up was addressed YES
		(*e*) Describe any sensitivity analyses N/A
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed YES
		(b) Give reasons for non-participation at each stage YES
		(c) Consider use of a flow diagram N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders YES
		(b) Indicate number of participants with missing data for each variable of interest YES
		(c) Summarise follow-up time (eg, average and total amount) YES
Outcome data	15*	Report numbers of outcome events or summary measures over time YES
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included YES
		(*b*) Report category boundaries when continuous variables were categorized YES
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period YES
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses YES

Discussion		
Key results	18	Summarise key results with reference to study objectives YES
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias YES
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence YES
Generalisability	21	Discuss the generalisability (external validity) of the study results YES
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based YES

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Neuro-psychiatric predictors of two-year outcome of epilepsy surgery in refractory epilepsy

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Abstract

Epilepsy surgery is currently the standard treatment for intractable epilepsy. Seizure freedom and discontinuation of antiepileptic drugs are the ultimate goals of epilepsy treatment. This study was carried out to delineate a) possible differences in the success rate of epilepsy surgery 6 and 24 months after surgery; and b) the neuro-psychiatric predictors of a good response to surgery. In this cohort study, 189 intractable epileptic patients who underwent epilepsy surgery were included. We collected neuro-psychiatric data at three time points, i.e. pre-operative and 6 and 24 months after surgery. Surgery outcome was estimated using the Engel class I-IV classification. We found that 6 months after surgery the success rate was 78.8%, while at 24 months the success rate had significantly increased to 88.3%. This success rate was not only reflected by the reduced number of seizures post-surgery, but also by a reduced dosage and use of antiepileptic drugs. Logistic regression analysis showed that a successful outcome of surgery is predicted by having temporal rather than extratemporal lobe epilepsy and less than 9 pre-surgery seizures per month, while a positive familial history of epilepsy, age and dysphoric symptoms the first three months after surgery significantly worsened the outcome of surgery. Duration of illness, age at onset, epilepsy location, type of lesions, and the presence of psychosis were not significant in predicting treatment outcome. These findings have clinical relevance in that a better selection of patients based on the significant predictors will increase the success rate of epilepsy surgery and treatment.

Key words: epilepsy, Engel class, surgery, predictors, dysphoric syndrome

Strengths and limitations of the study

- The authors analyze a large series (n=189) of consecutively admitted patients with refractory epilepsy who underwent epilepsy surgery and delineate the differences in surgical outcome between 6 and 24 months after surgery, clinical predictors of good surgical outcome (Engel class I) and the effects of withdrawal of antiepileptic drugs (AEDs).
- This is a first study that adjusts the results of epilepsy surgery outcome data for changes in AEDs. Moreover, the authors propose that Engel's classification into 4 classes may not be adequate because post-surgery patients allocated to an Engel class who had their AEDs discontinued or reduced differ from those belonging to same Engel class but who had an increased or unchanged AED intake. Therefore, the authors suggest that the Engel class classification should be refined taking into account post-operative changes in AED status.
- The shorter follow-up period (24 months) and the high success rate of epilepsy surgery (the percentage of patients allocated to class I is 88.3%) are limitations of the study.

Introduction

In most state-of-the-art epilepsy units, epilepsy surgery is currently the standard treatment for intractable epilepsy. Generally, the success rate, defined as a seizure free status or Engel class I, is between 62% (1) - 71% (2), as compared to 14% in non-operated cases (1). For example, in the Epilepsy Unit of King Chulalongkorn Memorial Hospital, Bangkok, Thailand, the success rate in cases undergoing epilepsy surgery is 66.7 % as compared to 5% in cases without surgery (3). Clinical experience is that some epilepsy patients who are non-responders to surgery in the first few months after surgery become seizure free and thus responders some months later.

In order to improve the success rate to epilepsy surgery, selection criteria for surgery based on clinical and biological characteristics of responders and non-responders should be delineated. Neurological predictors include type of resection, preoperative aura, presence of postoperation spikes (2), extratemporal resection, simple partial seizure (SPS) (4), long seizure duration, number of seizures per month at baseline, secondarily generalized seizures (SGTCS) and ictal dystonia (5). It is debated whether psychiatric problems may modulate the outcome to epilepsy surgery. Some studies show that preoperative psychiatric diagnoses may predict a negative outcome to epilepsy surgery (6-10). Other studies, however, report that a history of psychiatric diagnosis is not a predictor for surgery outcome (11). It has remained elusive, however, whether clinical variables, such as duration of illness, type of epilepsy, epilepsy location and a familial history of epilepsy may predict a good outcome, and whether a combination of these and other factors may improve the prediction.

To complicate matters, discontinuation of antiepileptic drugs (AEDs) may interfere with surgery outcome. Surgery may allow to taper down or even discontinue AED intake in some patients after epilepsy surgery. On the other hand, tapering down AEDs may cause seizure recurrence in about a third of patients (12). This indicates that when assessing epilepsy surgery outcome one has to take the AED state into account. This may also indicate that Engel's classification into 4 classes is not always adequate. For example, it is obvious that there is a difference between post-surgery patients allocated to an Engel class and who had their AEDs discontinued or reduced and those belonging to same class but who had an increased or unchanged AED intake. One approach is to adjust the Engel classes for post-operative changes in AED state.

This study was carried out to delineate a) the success rate of epilepsy surgery 6 and 24 months after surgery as assessed by means of Engel classes; b) clinical predictors of a good treatment response; and c) the effects of discontinuation or reduction of AEDs on this prediction.

Patients and Methods

This is a cohort study performed at the Comprehensive Epilepsy Unit, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. We included all intractable epilepsy patients who underwent epilepsy surgery and attended the Comprehensive Epilepsy Unit for post-operative evaluations from October 2005 until June 2008. One hundred and eighty-nine subjects were included in this study. We collected data at three different time points, that is pre-operation, and 6 and 24 months after surgery. We collected socio-demographic data; epilepsy-related data and diagnoses (e.g.

duration of illness, familial history, epilepsy location, type of epilepsy, number of seizures per month before surgery, and use of AEDs before surgery); neurosurgical outcome data (number of seizures per month 6 and 24 months after surgery, Engel class, use of AEDs 6 and 24 months after surgery) and psychiatric data (psychosis before epilepsy surgery and dysphoric disorder the first three months after surgery), using semi-structured interviews; neurological, medical and neurosurgical records; 24 hour EEG reports; brain imaging techniques; and the International Neuropsychiatric Interview (M.I.N.I.), in a Thai validated version (13). Dysphoric disorder was defined as an emotional response within the first 3 months after epilepsy surgery characterized by labile mood, crying spells, behavioral outbursts, sleep problems, concentration disorders, and / or irritability. The semistructured interviews were carried out by a trained master degree psychologist and the neurological diagnoses were made by senior neurologists. The study was approved by the Ethics Research Committee at Chulalongkorn University, Department of Medicine, Bangkok, Thailand and all participants gave written informed consent to participate.

Statistics.

We used analyses of contingence tables (χ^2 tests) or Fisher's exact probability test to check differences in the distribution of variables among two or more study groups. Relationships between variables were assessed using Pearson's correlation coefficients. Generalized linear model analysis was used to predict dependent variables by means of different explanatory variables. We used analyses of variance (ANOVA) in order to ascertain differences in continuous variables between two or

more study groups. Multiple post-hoc differences were assessed by means of Tukey's tests. Binary logistic regression analysis was used to define the associations between a dichotomous dependent variable and a set of independent variables. We used the logistic regression coefficients of the explanatory variables in the final equation to estimate odds ratios with confidence intervals. We used the sign test to assess the differences in the Engel classes (considered as ordinal scaled variables) 6 and 24 months after epilepsy surgery. The Sign Test is a nonparametric test statistic which can be employed to test paired samples of ordinally scaled variables and which uses only directional and not magnitude information. The effects of epilepsy surgery on the discontinuation of AEDs were analyzed using the McNemar test, a non-parametric test to analyze differences in repeated measurements of binary data. The surgery effects on the number of seizures and AED use was analyzed using factorial repeated measurement design ANOVA or the Wilcoxon signed rank test, a non-parametric test used to check differences in pairs of data. The results of parametric tests were checked using non parametric tests including Spearman's rank order correlation coefficients and the Kruskal-Wallis test. Data were analyzed using the SPSS Versions 15 and 19. There were no missing values in our data set. Statistical significance was set at α=0.05 (two tailed).

Results

1. Characteristics of Engel classes

Table 1 shows that there was a significant difference in Engel class distribution between the two time points. The Sign Test showed that there were significantly more negative differences than positive differences, indicating that some

patients improved from month 6 to month 24. For example, 6 months after surgery 149 patients were allocated to class I, while 24 months after surgery 167 were allocated to class I. In this paper we will report on the Engel classes 24 months after epilepsy surgery.

Table 2 shows the demographic data of the patients in this study according to Engel's classification. There was a marginal but significant difference in age between the Engel classes. Tukey's post-hoc test showed that patients in Engel class IV were significantly younger than those belonging to class III (p=0.011). There were no significant differences in duration of illness, age at onset or gender between the Engel classes. The number of pre-surgery seizures was significantly lower in patients with Engel class I than in those with Engel class II (p=0.012 by Tukey's post-hoc tests) and class IV (p=0.007), while there was a trend towards a significant difference with class III (p=0.068). There were no significant differences in number of pre-surgery seizures between class II, III and IV. Table 2 shows that the number of post-surgery seizures was significantly different between the 4 classes. This was validated using the Kruskal-Wallis test ($\chi 2$ =150.62, df=3, p<0.001). Tukey's tests showed that all pairwise and post-hoc analyses were significant, e.g. class I from class II (p=0.004), III (p<0.001) and IV (p<0.001), class II from class III (p=0.015) and class IV (p<0.001) and class III from class IV (p<0.001).

There were no significant differences in the ratio focal versus generalized epilepsy between the 4 Engel classes. The number of subjects with temporal lobe epilepsy versus extratemporal lobe epilepsy (i.e. frontal + parietal + occipital + hypothalamic) was significantly different between the Engel classes. Thus, patients belonging to Engel classes III+IV suffered significantly more from extratemporal

lobe epilepsy than those belonging to classes I+II. There were no significant differences in right versus left location between the Engel classes. Thus patients belonging to class I+II did not differ from those belonging to class III+IV ($\chi 2$ =0.01, df=1, p=0.906) and class I subjects did not differ significantly from class IV subjects (phi=0.073, p=0.333). There were no significant associations between Engel classes and type of lesion. Thus, hippocampal sclerosis versus tumors did not differ between class I+II versus class III+IV (phi=0.151, p=0.986). There was no significant association between a positive family history of epilepsy and the Engel classes. The number of subjects with the dysphoric syndrome was significantly higher in subjects with Engel classes III+IV than in those with Engel classes I+II. There was no significant difference in the number of individuals with and without psychoses before surgery between the Engel classes.

2. Effects of epilepsy surgery on number of seizures and intake of antiepileptics

Table 2 shows the number of seizures both before and after epilepsy surgery. RM design ANOVA showed that the number of seizures was significantly reduced by epilepsy surgery (F=6.45, df=1/185, p=0.012). The interaction pattern time X Engel class was significant (F=10.34, df=3/185, p<0.001), showing that epilepsy surgery reduced the number of seizures in class I, II and III, while in class IV the number of seizures further increased after surgery.

Table 3 shows the differences between post-surgery minus pre-surgery use of AEDs as binary responses. The discontinuation of anti-epileptic drugs after surgery is shown as negative ranks, the initiation of new anti-epileptic drug treatments after surgery as positive ranks, while no changes in the treatments after surgery are shown

as ties. McNemar tests for paired data showed that two years after epilepsy surgery phenytoin, carbamazepine, valproic acid gabapentin, topiramate, and clobazam could be discontinued in a significant number of patients, while there were no significant changes in the number of patients treated with phenobarbital, clonazepam, or levetiracetam. The total number of AEDs was significantly lower after surgery than before surgery. RM design ANOVA additionally showed that there was a significant time X Engel class interaction showing that the total number of drugs was reduced in class I but not in the other classes. Table 4 shows that the dosages of all AEDs, except clonazepam were lower 24 months after surgery than before.

3. Prediction of response to epilepsy surgery

The abovementioned effects of epilepsy surgery on the intake of AEDs show that Engel's classification into 4 classes is far from adequate. Thus, it is clear that there is a difference between patients allocated to for example class I and whom had their AEDs discontinued / reduced and those belonging to class I but who had an increased / unchanged AED intake. Therefore, we controlled for changes in AED state in two ways: a) by adjusting statistically for effects of AED state by entering the total number of AEDs prior and after surgery into the analyses; and b) by computing a new index of surgery response based on Engel's classification and the AED state. Toward this end we computed a new score based on Engel classes and the change in AED state from baseline to post-surgery, e.g. decreased intake of drugs: rating=1, unchanged: rating=2 and increased: rating=3. Thus for class I this yields three scores, i.e. 1 (class I and reduced intake), 2 (class I and unchanged drug state) and 3 (class I but increased drug intake). Applied to all 4 classes, this method yields a severity

score ranging from 1-12. There is a significant association between Engel's class classification and this newly presented severity score (Spearman's correlation: r=0.592, p<0.001).

Table 5 shows the outcome of a generalized linear model analysis with this new severity score as dependent variable and the variables listed in Table 2 and the drug state of the patients as predictor variables. A lower severity score was associated with temporal lobe versus extratemporal lobe epilepsy and a negative family history of epilepsy; a worse outcome was predicted by an increased number of seizures before surgery, dysphoric syndrome the first 3 months after surgery and use of gabapentin. Using a threshold value > 9 for the total number of seizures before surgery showed a similar significant effect (Wald=8.99, df=1, p=0.003), suggesting that a threshold value of 9 or more may be used as a predictor variable.

We have also examined the prediction of the Engel classes using the same variables as in Table 5 but considering that the Engel classes are continuous classes or ordinal variables ranging from 1 (for class I) to 4 (for class IV). In order to adjust for the drug state of the patients we have entered the number of AEDs as additional explanatory variables. This model with Engel's scaling as dependent variable showed that the outcome was better when suffering from temporal lobe epilepsy (Wald=20.33, df=1, p<0.001) and having a negative family history (Wald=9.21, df=1, p=0.002), while the total number of pre-surgery seizures (Wald=17.03, df=1, p<0.001), dysphoric syndrome (Wald=7.91, df=1, p=0.005) and use of gabapentin (Wald=8.19, df=1, p=0.004) predicted a worse outcome. In our clinic, neurontin is not the first AED choice for seizure treatment and is used in refractory seizures that failed to respond to treatment with other AEDs. This may show that use of

gabapentin should not be regarded as a real explanatory variable but as a post-hoc adjustment for possible effects of the drug state.

Table 6 shows the results of an automatic stepwise logistic regression analysis with Engel's class I as dependent variable (classes III + IV as reference group) and the variables listed in Table 2 (and number of baseline epileptic seizures > 9, yes or no) as predictors. We found that 5 variables were significantly associated with Engel's class I ($\chi 2$ =32.17, df=5, p<0.001, Nagelkerke=0.404; correctly classified cases=92.5%), i.e. temporal versus extratemporal lobe epilepsy, a negative family history of epilepsy, less than 9 seizures before surgery, age and the presence of dysphoric syndrome.

Discussion

A first major finding of this study is that there were significant differences in surgery outcome between 6 and 24 months after surgery: our success rate at 6 months (78.8%) had significantly increased (88.3%) at 24 months. Already in 1970 it was suggested that some patients may show seizures after surgery that eventually remit some months to years later, i.e. the "running down phenomenon"(4, 14). Previous reports on the effects of epilepsy surgery did not always show comparable results. Elsharkawy's study reported that the prevalence of Engel class I was 76.2% at 6 months, 72.3% at 2 years and 71.1% at 5 years (15). In another study, the prevalence of being completely seizure-free at 12 and 18 years after MTLE/HS surgery was 65% and 62%, respectively (16). The risk of having any recurrence was 22% during the first 24 months and increased 1.4% per year afterwards (16). Some of the long term post-surgical following studies supported the concept that the prognosis may improve

over time, e.g. less memory decline (17). One explanation of these contradictory data is that the running down phenomenon may occur in an initially non-equilibrium period, with an undetermined duration, and that seizures may re-occur after that time point.

A second major finding is that the efficacy of epilepsy surgery was not only reflected by the reduced number of seizures, but also by a reduced use of AEDs. We were able to discontinue one or more AEDs in 48.68% of the patients. This discontinuation rate might be slightly lower than that in previous reports which showed that around 52.6% of the patients can discontinue AEDs at 2 years without seizure recurrence (18). Most studies also reported that AED discontinuation may be a strong predictor for seizure recurrence in post-surgery seizure-free cases (12).

The third major finding of this study is that a good outcome of epilepsy surgery, i.e. being allocated to class I, could be predicted by temporal versus extratemporal lobe epilepsy, less than 9 pre-surgery seizures per month, a negative familial history of epilepsy, younger age and absence of a dysphoric disorder. Temporal lobe epilepsy (TLE) was the most significant predictor of outcome. This finding is consistent with most published papers showing that TLE, both in short term and long term monitoring period (19) and in pediatric and adult patients has a significantly better postoperative outcome than extratemporal lobe epilepsy (ETLE) (20). In pediatric patients, the seizure free rate in TLE was 71.8% versus 59.7% in ETLE, whereas in adult epilepsy the seizure free rate in TLE was 69.4% versus 45.9% in ETLE (20). In ETLE, it is more difficult to localize the epileptogenic focus to a specific cerebral region and to completely remove the epileptogenic region without impairing the eloquent cortex (21).

The second predictor, i.e. number of pre-operative seizures, shows that surgery may not be the best treatment option for patients with many refractory seizures. A high number of pre-surgery seizures might indicate multiple types of seizures, unidentified multiple lesions or severe pathology or other factors negatively modifying surgery outcome. We established that a threshold value of 9 seizures / month best predicted Engel class I membership, while another study delineated that ∃30 seizures / month best predicted a negative outcome (1). These differences between both studies may reflect differences in sensitivity and specificity. Thus, we established that < 9 seizures per month significantly predicts Engel class I versus II+III+IV, while it is obvious that if we had used Engel class I+II+III versus IV the threshold value would be higher.

To the best of our knowledge, this is a first study showing that a positive family history may worsen post-surgery outcome. Epilepsy is familial and risk is increased two- to four-fold in the first-degree relatives of people with epilepsy of unknown cause (22). Twin studies consistently show higher concordance in monozygotic than in dizygotic pairs (23). However, the genes identified so far affect risk in a very small proportion of patients, while most epilepsies occur in the absence of a significant family history (24). In a few clinical studies on epilepsy with or without psychiatric disorders, genetic linkage is regarded to increase risk of poor clinical outcome (25, 26). Thus, a positive family history of epilepsy, occurs more frequently in TLE with postictal psychosis than in TLE alone (25). A positive family history of epilepsy has also a significant negative impact on the quality of life (26).

Using logistic regression analysis and after adjusting for the effects of the other predictor variables, a younger age appeared to predict Engel class I. There are

only few studies in adults that also examined age as predictor of surgery outcome. Age at surgery significantly contributes to Engel class outcome: in individuals aged less than 50 years, 58% were allocated to Engel class I, while 74% of those who were more than 50 years old and 91% of those who were more than 60 years old were allocated to Engel class I. Srikijvilaikul et al. (27) found no differences in surgical outcome in terms of medication withdrawn between older and younger subjects (threshold value = 50 years old), but more surgical complications in the older group (27). Previous studies in children or teenage showed that early surgical treatment correlated with a better Engel class outcome (28, 29).

The fifth predictor of surgery outcome is dysphoric disorder, i.e. labile and irritable mood emerging within 3 months after surgery, but most often the first 1 to 2 months. While pre-surgery psychiatric factors are identified as predictors of a worse surgery outcome, few studies have examined post-surgery psychiatric predictors. Epilepsy is accompanied by the interictal dysphoric disorder, characterized by intermittent affective symptoms including labile affective symptoms, paroxysmal irritability and outbursts of aggressive behavior (30) (31). The prevalence of interictal dysphoric disorder (and having no depression and dysthymia according to the MINI) is around 48.2% in epilepsy patients (31, 32). There is some evidence suggesting that interictal dysphoric disorder and peri-ictal dysphoric syndrome may be separate syndromes (32). Therefore, it may be hypothesized that dysphoric disorder in the early post-operative period is in fact interictal dysphoric disorder and that in those patients sub-syndromal seizure activity is present despite surgery thereby predicting future clinical seizures. Future research should delineate this symptom complex in association with surgery outcome using the 38-item Interictal Dysphoric Disorder

Inventory (IDDI) (32). Emotional reactivity is a psychosocial stressor increasing circulating glucocorticoid levels causing an increased vulnerability to amygdala kindling (33). Kindling is the process by which repeated minor stimulations (electrical or chemical) of the brain are associated with epileptogenesis and the onset of mood disturbances (34).

Limitations of this study are the lower number of subjects not allocated to Engel class I as a result of the unexpected high success rate of epilepsy surgery in our hospital. As such the results should be interpreted with caution. Future research should validate the predictors delineated in our study and using the IDDI to score severity of the dysphoric syndrome.

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Conflict of interest:

The authors do not report any conflict of interest.

Contributorship

K B. made the study design; KB, LC, ST and MM interpreted the data; KB and MM performed the statistical analyses and wrote the manuscript; LC, ST and KB collected the data.

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Data sharing statement: "There is no additional data available".

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Table 1. Engel class classifications in 189 patients, 6 and 24 months after epilepsy surgery.

Engel classes			**24 months**		
		I	II	III	IV
6 months	I	144	3	1	1
	II	10	3	3	0
	III	0	0	2	0
	IV	13	3	2	4

The distribution of the patients in classes I-IV is significantly different between months 6 and 24 (Sign test: z = -3.17, p=0.002, negative differences = 8, ties = 153).

Table 2. Demographic data and Engel classification 24 months after surgery in 189 patients

Variables / predictors	Engel class I	Engel class II	Engel class III	Engel class IV	*F or O^2	df	p
Age (years)	37.4 (∀9.6)	38.9 (∀9.0)	45.0 (∀7.5)	28.2 (∀8.8)	3.34	3/185	0.0
Duration illness (until surgery) (years)	20.7 (∀10.5)	19.2 (∀11.1)	25.9 (∀15.1)	19. 0 (∀6.9)	0.72	3/185	0.5
Age onset	14.5 (∀9.4)	16.8 (∀6.2)	16.0 (∀7.9)	7.7 (∀14.5)	1.17	3/185	0.3
Gender (% / & ratio)	83 / 84	6 / 3	6 / 2	1 / 4	4.76	3	0.1
Number seizures prior to epilepsy surgery	8.5 (∀13.4)	35.9 (∀70.7)	26.4 (∀30.3)	65.6 (∀124.6)	10.35	3/185	0.
Number of seizures after epilepsy surgery	0.00 (∀0.00)	1.71 (∀1.51)	9.0 (∀9.4)	91.8 (∀137.8)	33.13	3/185	0.
Focal versus generalized epilepsy	160 / 7	9 / 0	8 / 0	4 / 1	0.41	1	0.5

TLE versus ETLE**	157 / 11	7 / 2	7 / 1	0 / 5	20.3***	1	0.
Epilepsy location right left bilateral middle	 83 80 3 1	 6 3 0 0	 3 5 0 0	 3 1 1 0	see text		
Lesion Hippocampal sclerosis Tumor FCD AVM No lesion	 128 28 7 1 3	 7 1 1 0 0	 5 2 0 0 1	 0 2 3 0 0	See text		
Familial history of epilepsia: yes / no	26 / 141	3 / 6	3 / 5	2 / 3	5.8	3	0.1
DD first 3 months after surgery: yes / no	18/ 149	1/ 8	2 / 6	3 / 2	8.4***	1	0.0
Pre-OP psychosis (MINI) yes / no	 7 / 160	 2 / 7	 2 / 6	 0 / 5	2.3***	1	0.1

*F: results of analyses of variance with the 4 Engel groups as categories

*O^2: results of analyses of contigency tables. In cases were we were unable to perform a O^2 test on the 4 Engel categories we have combined groups and examined the differences between Engel class 1 + 2 versus Engel class 3 + 4 (see ***).

**TLE versus ETLE: temporal lobe epilepsia versus extratemporal lobe epilepsy

DD: dysphoric disorder

Table 3. Effects of epilepsy surgery on the discontinuation of anti-epileptic drugs in 189 epilepsy patients

Drug	- ranks	+ ranks	ties	McNemar or Wilcoxon test*	Discontinuation rate
Phenobarbital	7	1	181	0.070	7 / 37
Phenytoin	23	3	163	<0.001	23 / 61
Carbamazepine	25	1	163	<0.001	25 / 133
Valproic acid	16	3	170	0.004	16 / 46
Clonazepam	6	2	181	0.289	6 / 12
Gabapentin	11	2	176	0.022	11 / 20
Lamotrigine	25	4	160	<0.001	25 / 62
Topiramate	13	4	172	0.049	13 / 20
Levetiracetam	26	15	148	0.118	26 / 54
Clobazam	29	10	150	0.003	29 / 58
All drugs	92	13	84	<0.001*	-

The difference between post-surgery minus pre-surgery use of anti-epileptic drugs is shown as the discontinuation of the drugs after surgery (negative ranks), starting new treatments after surgery (positive ranks) or unchanged treatments after surgery (ties)

All analyses are results of McNemar test, except * Wilcoxon test (z=-7.61)

Table 4. Effects of epilepsy surgery on the dosage of anti-epileptic drugs in 189 patients

Drug	- ranks	+ ranks	ties	Wilcoxon test	p
Phenobarbital	12	2	175	-2.684	0.007
Fenytoin	43	6	140	-4.908	<0.001
Carbamazepine	65	15	109	-6.378	<0.001
Valproic acid	27	7	155	-3.066	0.002
Clonazepam	6	3	180	-0.060	0.952
Gabapentin	15	5	169	-2.396	0.017
Lamotrigine	42	13	134	-4.273	<0.001
Topiramate	17	4	168	-3.047	0.002
Levetiracetam	41	22	126	-2.348	0.019
Clobazam	35	12	141	-3.219	<0.001

The differences between post-surgery minus pre-surgery dosages of anti-epileptic drugs is given as reduced dosages (negative ranks), increased dosages (positive ranks) or unchanged dosages (ties) after epilepsy surgery.

Table 5. Results of generalized linear model analysis with the Engel-derived severity score as dependent variable and the listed variables as predictor variables.

Variables	F	df	p	B	SE
TLE versus ETLE*	20.57	1	<0.001	-2.136	0.471
No family history of epilepsy	8.10	1	0.004	-0.953	0.335
Gender	0.69	1	0.406	0.214	0.257
Lesion	0.69	1	0.407	-0.387	0.467
Focal versus generalized	0.00	1	0.946	0.044	0.650
Age	0.05	1	0.822	0.004	0.017
Duration of illness	0.10	1	0.747	0.005	0.015
Number of seizures pre-surgery	16.09	1	<0.001	0.018	0.005
Dysphoric disorder within the first three months after surgery	6.48	1	0.011	0.001	0.001
Use of gabapentin post-surgery	10.00	1	0.002	1.001	0.393
Number of drugs pre-surgery	0.70	1	0.402	-0.112	0.134

*TLE versus ETLE: temporal lobe epilepsia versus extratemporal lobe epilepsy

Table 6. Results of automatic stepwise logistic regression with Engel's class I as dependent variable and the listed variables as predictors

Predictors	Wald	df	p	Odds ratio	95 % CI, lower	95% CI, upper
TLE versus ETLE*	13.08	1	<0.001	21.14	4.05	110.44
Negative family history of epilepsia	5.08	1	0.024	5.58	1.25	24.89
Less than 9 seizures before epilepsy surgery	6.56	1	0.010	6.79	1.57	29.42
Dysphoric disorder first 3 months after surgery	3.96	1	0.047	0.203	0.042	0.977
Age	4.91	1	0.027	0.917	0.850	0.990

*TLE versus ETLE: temporal lobe epilepsia versus extratemporal lobe epilepsy

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Clinical predictors of two-year outcome of resective epilepsy surgery in adults with refractory epilepsy

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Abstract

Objectives: Resective epilepsy surgery is currently a standard treatment for intractable epilepsy. Seizure freedom and discontinuation of antiepileptic drugs are the ultimate goals of epilepsy treatment. This study was carried out to delineate a) possible differences in the success rate of epilepsy surgery 6 and 24 months after surgery; and b) the clinical predictors of a good response to surgery.

Setting: This is a cohort study performed at a tertiary care unit of a University hospital.

Participants: In this cohort study, 189 adults with intractable epilepsy who underwent epilepsy surgery were included. We collected clinical data at three time points, i.e. pre-operative and 6 and 24 months after surgery.

Primary and secondary outcome measures: Engel class I-IV classification was the primary outcome measure of epilepsy surgery. The authors statistically adjusted Engel class I-IV classification for post-operative changes in antiepileptic drugs and used this new classification as a secondary outcome variable.

Results: The success rate was 78.8% 6 months after surgery and increased to 88.3% 24 months after surgery. This success rate was not only reflected by the reduced number of seizures post-surgery, but also by a reduced dosage and use of antiepileptic drugs. Logistic regression analysis showed that a successful outcome of surgery is predicted by having temporal rather than extratemporal lobe epilepsy and less than 9 pre-surgery seizures per month, while a positive familial history of epilepsy, younger age and dysphoric symptoms the first three months after surgery significantly worsened the outcome of surgery. Duration of illness, age at onset, epilepsy location, type of lesions, and the presence of psychosis were not significant in predicting treatment outcome.

Conclusions: These findings have clinical relevance in that a better selection of patients based on the significant clinical predictors will increase the success rate of epilepsy surgery and treatment.

Key words: epilepsy, Engel class, surgery, predictors, dysphoric syndrome

Strengths and limitations of the study

- The authors analyze a large series (n=189) of consecutively admitted patients with refractory epilepsy who underwent epilepsy surgery and delineate the differences in surgical outcome between 6 and 24 months after surgery, clinical predictors of good surgical outcome (Engel class I) and the effects of withdrawal of antiepileptic drugs (AEDs).
- This is a first study that adjusts the results of epilepsy surgery outcome data for changes in AEDs. The authors propose that Engel's classification into 4 classes may not be adequate because post-surgery patients allocated to an Engel class who had their AEDs discontinued or reduced differ from those belonging to same Engel class but who had an increased or unchanged AED intake. Therefore, the authors suggest that the Engel class classification should be refined taking into account post-operative changes in AED status.
- The shorter follow-up period (24 months) is a limitation of the study. The high success rate of epilepsy surgery in this study (i.e. 88.3% at 24 months) may be explained by our strict selection criteria. This cohort comprises 2% MRI-negative epilepsy and >90% temporal lobe surgery patients and, therefore, our findings cannot be readily extrapolated to more heterogeneous cohorts.

Introduction

In most state-of-the-art epilepsy units, resective epilepsy surgery is currently the standard treatment for intractable epilepsy. Generally, the success rate, defined as a seizure free status or Engel class I, is between 62% (1) - 71% (2), as compared to 14% in non-operated cases (1). For example, in the Epilepsy Unit of King Chulalongkorn Memorial Hospital, Bangkok, Thailand, the success rate 24 months after sugery is 66.7% as compared to 5% in cases without surgery (3). Clinical experience is that some epilepsy patients who are non-responders to surgery in the first few months after surgery become seizure free and thus responders some months later.

In order to improve the success rate to epilepsy surgery, selection criteria for surgery based on clinical and biological characteristics of responders and non-responders should be delineated. Neurological predictors include type of resection, preoperative aura, presence of postoperation spikes (2), extratemporal resection, simple partial seizure (4), long seizure duration, number of seizures per month at baseline, secondarily generalized seizures and ictal dystonia (5). It is debated whether psychiatric problems may modulate the outcome to epilepsy surgery. Some studies show that preoperative psychiatric diagnoses may predict a negative outcome to epilepsy surgery (6-10). Other studies, however, report that a history of psychiatric diagnosis is not a predictor for surgery outcome (11). It has remained elusive, however, whether clinical variables, such as duration of illness, type of epilepsy, epilepsy location and a familial history of epilepsy may predict a good outcome, and whether a combination of these and other factors may improve the prediction.

To complicate matters, discontinuation of antiepileptic drugs (AEDs) may interfere with surgery outcome. Surgery may allow to taper down or even discontinue AED intake

in some patients after epilepsy surgery. On the other hand, tapering down AEDs may cause seizure recurrence in about a third of patients (12). This indicates that when assessing epilepsy surgery outcome one has to take the AED state into account. This may also indicate that Engel's classification into 4 classes is not always adequate. For example, it is obvious that there is a difference between post-surgery patients allocated to an Engel class and who had their AEDs discontinued or reduced and those belonging to same class but who had an increased or unchanged AED intake. One approach is to adjust the Engel classes for post-operative changes in AED state.

This study was carried out to delineate a) the success rate of epilepsy surgery 6 and 24 months after surgery as assessed by means of Engel classes; and b) clinical predictors of a good treatment response while adjusting for the effects of discontinuation or reduction of AEDs on this prediction.

Patients and Methods

This is a cohort study performed at the Comprehensive Epilepsy Unit, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. We consecutively included (from October 2005 until June 2008) all intractable epilepsy patients who were selected for epilepsy surgery and attended the Comprehensive Epilepsy Unit for post-operative evaluations. One hundred and eighty-nine subjects were included in this study. We collected data at three different time points, that is pre-operation, and 6 and 24 months after surgery. We collected socio-demographic data, age at onset, duration of illness, familial history of epilepsy, number of seizures per month before and 6 and 24 months after surgery, use of AEDs (type and dosage) before and 6 and 24 months after surgery, using semi-structured interviews performed by a trained master degree research psychologist.

Epilepsy-related characteristics, including epilepsy location and type of epilepsy, were rated by senior neurologists using neurological, medical and neurosurgical records, 24 hour electroencephalogram (EEG) reports and brain imaging techniques, i.e. magnetic resonance imaging (MRI). The post-surgery data at 6 and 24 hours were used to make the Engel class diagnoses in class I (no disabling seizures), class II (almost free of seizures), class III (worthwhile improvement with >50% reduction in disabling seizures), and class IV (no worthwhile improvement). The psychiatric DSM-IV diagnosis psychosis (before surgery) was made by a trained master degree research psychologist using the International Neuropsychiatric Interview (MINI) in a Thai validated version (13). Dysphoric disorder was defined as an emotional response within the first 3 months after epilepsy surgery characterized by labile mood, crying spells, behavioral outbursts, sleep problems, concentration disorders, and / or irritability. The study was approved by the Ethics Research Committee at Chulalongkorn University, Department of Medicine, Bangkok, Thailand and all participants gave written informed consent to participate.

Statistics.

We used analyses of contingence tables (χ^2 tests) or Fisher's exact probability test to check differences in the distribution of variables among two or more study groups. Relationships between variables were assessed using Pearson's correlation coefficients. General and generalized linear model analyses were used to predict dependent variables by means of different explanatory variables. We used analyses of variance (ANOVA) in order to ascertain differences in continuous variables between two or more study groups. Multiple post-hoc differences were assessed by means of Tukey's tests. Binary logistic regression analysis was used to define the associations between a dichotomous dependent

variable and a set of independent variables. We used the logistic regression coefficients of the explanatory variables in the final equation to estimate odds ratios with confidence intervals. We used the sign test to assess the differences in the Engel classes (considered as ordinal scaled variables) 6 and 24 months after epilepsy surgery. The Sign Test is a nonparametric test statistic which can be employed to test paired samples of ordinally scaled variables and which uses only directional and not magnitude information. The effects of epilepsy surgery on the discontinuation of AEDs were analyzed using the McNemar test, a non-parametric test to analyze differences in repeated measurements of binary data. The surgery effects on the number of seizures and AED use was analyzed using factorial repeated measurement design ANOVA or the Wilcoxon signed rank test, a non-parametric test used to check differences in pairs of data. The results of parametric tests were checked using non parametric tests including Spearman's rank order correlation coefficients and the Kruskal-Wallis test. Data were analyzed using the SPSS Versions 15 and 19. There were no missing values in our data set. Statistical significance was set at α=0.05 (two tailed).

Results

1. Characteristics of Engel classes

Table 1 shows that there was a significant difference in Engel class distribution between the two time points. The Sign Test showed that there were significantly more negative differences than positive differences, indicating that some patients improved from month 6 to month 24. For example, 6 months after surgery 149 patients were allocated to class I, while 24 months after surgery 167 were allocated to class I. Twenty three patients who were allocated to Engel classes II, III or IV 6 months after surgery were re-allocated

to Engel class I 24 months after surgery, showing that their status had improved. We have analyzed whether any of the variables listed in Table 2 was associated with this subgroup of patients who had improved, but not one of the variables was significantly significant. In this paper we will report on the Engel classes 24 months after epilepsy surgery.

Table 2 shows the demographic data of the patients in this study according to Engel's classification. There was a marginal but significant difference in age between the Engel classes. Tukey's post-hoc test showed that patients in Engel class IV were significantly younger than those belonging to class III (p=0.011). There were no significant differences in duration of illness and age at onset between the Engel classes. The number of pre-surgery seizures was significantly lower in patients with Engel class I than in those with Engel class II (p=0.012 by Tukey's post-hoc tests) and class IV (p=0.007), while there was a trend towards a significant difference with class III (p=0.068). There were no significant differences in number of pre-surgery seizures between class II, III and IV. Table 2 shows that the number of post-surgery seizures was significantly different between the 4 classes. This was validated using the Kruskal-Wallis test ($\chi 2$ =150.62, df=3, p<0.001). Tukey's tests showed that all pairwise and post-hoc analyses were significant, e.g. class I from class II (p=0.004), III (p<0.001) and IV (p<0.001), class II from class III (p=0.015) and class IV (p<0.001) and class III from class IV (p<0.001).

Unexpectedly only few patients were not allocated to Engel class I and therefore we were unable to perform Π^2 tests in the 4 study groups. Since the major aim of this study is to delineate the characteristics of a good versus a worse surgery outcome we compared Engel class I versus Engel class II+III+IV using Π^2 tests or Fisher's exact probability tests. There were no significant associations between gender or focal versus secondarily generalized epilepsy and Engel classes I versus II+III+IV. Patients belonging to Engel

classes II+III+IV suffered significantly more from extratemporal lobe epilepsy than those belonging to class I. There was no significant difference in right versus left location between Engel class I versus II+III+IV ($\chi 2$ =0.29, df=1, p=0.591). There was no significant association between Engel class classification and type of lesion, i.e. hippocampal sclerosis versus other or no lesions ($\chi 2$ =1.30, df=1, p=0.25). A positive family history of epilepsy, dysphoric syndrome and pre-operative psychosis were significantly associated with Engel classes II+III+IV.

2. Effects of epilepsy surgery on number of seizures and intake of antiepileptics

Table 2 shows the number of seizures both before and after epilepsy surgery. RM design ANOVA showed that the number of seizures was significantly reduced by epilepsy surgery (F=6.45, df=1/185, p=0.012). The interaction pattern time X Engel class was significant (F=10.34, df=3/185, p<0.001), showing that epilepsy surgery reduced the number of seizures in class I, II and III, while in class IV the number of seizures further increased after surgery.

Table 3 shows the differences between post-surgery minus pre-surgery use of AEDs as binary responses. The discontinuation of anti-epileptic drugs after surgery is shown as negative ranks, the initiation of new anti-epileptic drug treatments after surgery as positive ranks, while no changes in the treatments after surgery are shown as ties. McNemar tests for paired data showed that two years after epilepsy surgery phenytoin, carbamazepine, valproic acid gabapentin, topiramate, and clobazam could be discontinued in a significant number of patients, while there were no significant changes in the number of patients treated with phenobarbital, clonazepam, or levetiracetam. The total number of AEDs was significantly lower after surgery than before surgery. We were able to

discontinue one or more AEPs in 48.68% of the patients, while in 6.88% of the patients we started a new AEP and in 44.44% of the patients AEP intake was unchanged. RM design ANOVA showed that there was a significant time X Engel class interaction indicating that the total number of drugs was reduced in class I but not in the other classes. Table 4 shows that the dosages of all AEDs, except clonazepam were lower 24 months after surgery than before.

3. Prediction of response to epilepsy surgery

The abovementioned changes in the intake of AEDs after epilepsy surgery suggest that Engel's classification should be adjusted to reflect changes in AED status. Thus, it is clear that there is a difference between patients allocated to for example class I and whom had their AEDs discontinued / reduced and those belonging to class I but who had an increased / unchanged AED intake. Therefore, we controlled for changes in AED state in two ways: a) by adjusting statistically for effects of AED state by entering the total number of AEDs prior and after surgery into the analyses; and b) by computing a new index of surgery response based on Engel's classification and the AED state. Toward this end we computed a new score based on Engel classes and the change in AED state from baseline to post-surgery, e.g. decreased intake of drugs: rating=1, unchanged: rating=2 and increased: rating=3. Thus for class I this yields three scores, i.e. 1 (class I and reduced intake), 2 (class I and unchanged drug state) and 3 (class I but increased drug intake). Applied to all 4 classes, this method yields a severity score ranging from 1-12. There is a significant association between Engel's class classification and this newly presented severity score (Spearman's correlation: $r=0.592$, $p<0.001$).

Table 5 shows the outcome of a general linear model analysis with this new severity score as dependent variable and the variables listed in Table 2 and the drug state of the patients as predictor variables. Up to 25.2% in the variance of the severity index was explained by 5 variables ($F=12.32$, $df=5/183$, $p<0.001$): a lower severity score was associated with temporal lobe versus extratemporal lobe epilepsy and a negative family history of epilepsy; a worse outcome was predicted by an increased number of seizures before surgery, dysphoric syndrome the first 3 months after surgery and use of gabapentin. Using a threshold value > 9 for the total number of seizures before surgery showed a similar significant effect ($F=8.99$, $df=1$, $p=0.003$), suggesting that a threshold value of 9 or more may be used as a predictor variable. Entering use of AEDs, total number of AEDs, and dosages of AEDs both before and after surgery (at 24 months) as explanatory variables showed that none of these variables, except gabapentin post-surgery, was significant in explaining the severity index and that entering these drug variables did not change the results. We have also examined the prediction of the Engel classes using the same variables as in Table 5 but considering that the Engel classes are continuous classes or ordinal variables ranging from 1 (for class I) to 4 (for class IV). Generalized linear model analysis showed that this Engel scaling was predicted by 5 variables: the outcome was better when suffering from temporal lobe epilepsy (Wald=20.33, $df=1$, $p<0.001$) and having a negative family history (Wald=9.21, $df=1$, $p=0.002$), while the total number of pre-surgery seizures (Wald=17.03, $df=1$, $p<0.001$), dysphoric syndrome (Wald=7.91, $df=1$, $p=0.005$) and use of gabapentin (Wald=8.19, $df=1$, $p=0.004$) predicted a worse outcome.

Table 6 shows the results of an automatic stepwise logistic regression analysis with Engel's class I as dependent variable (classes III + IV as reference group) and the variables listed in Table 2 (and number of baseline epileptic seizures > 9, yes or no) as predictors.

We found that 5 variables were significantly associated with Engel's class I ($\chi 2$ =31.88, df=5, p<0.001, Nagelkerke=0.401; correctly classified cases=92.8%), namely temporal versus extratemporal lobe epilepsy, a negative family history of epilepsy, less than 9 seizures before surgery, age and the presence of dysphoric syndrome.

Discussion

A first major finding of this study is that there were significant differences in surgery outcome between 6 and 24 months after surgery: our success rate at 6 months (78.8%) had significantly increased (88.3%) at 24 months. Already in 1970 it was suggested that some patients may show seizures after surgery that eventually remit some months to years later, i.e. the "running down phenomenon" (4, 13). Nevertheless, our findings contradict one of the largest series of epilepsy surgery results, showing a gradual decline over time in the estimated proportion of patients who remain seizure free (13). In another study it was reported that the prevalence of Engel class I was 76.2% at 6 months, 72.3% at 2 years and 71.1% at 5 years (14). The prevalence of being completely seizure-free at 12 and 18 years after MTLE/HS surgery was 65% and 62%, respectively (15). A meta-analysis showed seizure control to decline over time especially after 2 years (16). The risk of having any recurrence was 22% during the first 24 months and increased 1.4% per year afterwards (15). Some of the long term post-surgical following studies supported the concept that the prognosis may improve over time, e.g. less memory decline (17). One explanation of these contradictory data is that a running down phenomenon may occur in an initially non-equilibrium period, with an undetermined duration, and that seizures may re-occur after that time point.

The high success rate of epilepsy surgery in our hospital (i.e. 88.3% at 24 months) may be explained by our inclusion criteria, which are based on clinical semiology, 24 hr EEG and MRI to identify subjects with primary epileptogenic lesions. As a consequence this cohort comprises only 2% MRI-negative epilepsy and >90% temporal lobe surgery patients. Therefore, our findings cannot be readily extrapolated to more heterogeneous cohorts including high rates of non-lesional and/or extratemporal epilepsy.

A second major finding is that the efficacy of epilepsy surgery was not only reflected by the reduced number of seizures, but also by a reduced use of AEDs. We were able to discontinue one or more AEDs in 48.68% of the patients, while 13.2% of all patients were free of any AEDs 2 years after surgery. This discontinuation rate might be slightly lower than that in previous reports which showed that around 52.6% of the patients can discontinue AEDs at 2 years without seizure recurrence (18). In another study 28.1% of the patients had discontinued AED treatment 2 years after surgery and had remained seizure free, suggesting that there was no risk of seizure recurrence after discontinuation of AEDs (14). A meta-analysis showed that in patients with all types of surgery, 20% achieved long-term AED discontinuation, 31% remained on polytherapy and 41% were on monotherapy (19). In addition, we found no significant associations between AED discontinuation and seizure freedom. Other studies report that AED discontinuation may be a strong predictor for seizure recurrence in post-surgery seizure-free cases (12). Boshuisen et al. (20), in a study performed on children with intractable epilepsy, found that AED withdrawal did not affect long-term seizure outcome but may unmask incomplete surgical success sooner, identifying children who need continuous drug treatment. One of our analysis showed that use of gabapentin was a significant predictor variable for a worse outcome. In our clinic, however, gabapentin is not the first AED choice for seizure

treatment and is used in refractory seizures that failed to respond to treatment with other AEDs. This may show that use of gabapentin should not be regarded as a real explanatory variable but as a post-hoc adjustment for possible effects of the drug state. The third major finding of this study is that a good outcome of epilepsy surgery, i.e. being allocated to class I, could be predicted by temporal versus extratemporal lobe epilepsy, less than 9 pre-surgery seizures per month, a negative familial history of epilepsy, age and absence of a dysphoric disorder. Temporal lobe epilepsy (TLE) was the most significant outcome predictor. This finding is consistent with most published papers showing that TLE, both in short term and long term monitoring period (21) and in pediatric and adult patients has a significantly better postoperative outcome than extratemporal lobe epilepsy (ETLE) (22). In pediatric patients, the seizure free rate in TLE was 71.8% versus 59.7% in ETLE, whereas in adult epilepsy the seizure free rate in TLE was 69.4% versus 45.9% in ETLE (22). In ETLE, it is more difficult to localize the epileptogenic focus to a specific cerebral region and to completely remove the epileptogenic region without impairing the eloquent cortex (23).

The second predictor, i.e. number of pre-operative seizures, shows that surgery may not be the best treatment option for patients with many refractory seizures. A high number of pre-surgery seizures might indicate multiple types of seizures, unidentified multiple lesions or severe pathology or other factors negatively modifying surgery outcome. We established that a threshold value of 9 seizures / month best predicted Engel class I membership, while another study delineated that more than 30 seizures / month best predicted a negative outcome (1). These differences between both studies may reflect differences in sensitivity and specificity. Thus, we established that < 9 seizures per month

significantly predicts Engel class I versus II+III+IV, while it is obvious that if we had used Engel class I+II+III versus IV the threshold value would be higher.

To the best of our knowledge, this is a first study showing that a positive family history for epilepsy may worsen post-surgery outcome. There is now evidence that the risk to develop epilepsy is significantly increased in the first-degree relatives of people with epilepsy of unknown cause (24). Twin studies consistently show higher concordance in monozygotic than in dizygotic pairs (25). However, the genes identified so far affect risk in a very small proportion of patients, while most epilepsies occur in the absence of a significant family history (26). In a few clinical studies on epilepsy with or without psychiatric disorders, genetic linkage is regarded to increase risk of poor clinical outcome (27, 28). Thus, a positive family history of epilepsy, occurs more frequently in TLE with postictal psychosis than in TLE alone (27). A positive family history of epilepsy has also a significant negative impact on the quality of life (28). The inverse relationship between a family history of epilepsy and Engel class outcome may be explained by mutations in specific genes that are related to a more severe outcome, including drug resistance, and distinct neuroradiological findings as has been observed in benign neonatal epilepsy or benign familial neonatal convulsions (29, 30). However, it is unlikely that single common variants could explain more than 4.4% of outcome variation in newly treated epilepsy (31). Therefore, it should be examined whether multiple common variants may underpin increased resistance to resective epilepsy surgery. There are only few studies in adults that have examined age as a predictor of surgery outcome. In individuals aged less than 50 years, 58% were allocated to Engel class I, while 74% of those who were more than 50 years old and 91% of those who were more than 60 years old were allocated to Engel class I (16). Srikijvilaikul et al. (27) found no differences in surgical outcome in terms of

medication withdrawn between older and younger subjects (threshold value = 50 years old), but more surgical complications in the older group (32). Previous studies in children or teenage showed that early surgical treatment correlated with a better Engel class outcome (33, 34). In our study, however, the absolute differences in age were very small. Therefore, further research should delineate whether age at surgery significantly contributes to Engel class outcome. The fifth predictor of surgery outcome is dysphoric disorder, i.e. labile and irritable mood emerging within 3 months after surgery, but most often the first 1 to 2 months. While pre-surgery psychiatric factors are identified as predictors of a worse surgery outcome, few studies have examined post-surgery psychiatric predictors. Epilepsy is accompanied by the interictal dysphoric disorder, characterized by intermittent affective symptoms including labile affective symptoms, paroxysmal irritability and outbursts of aggressive behavior (35, 36). The prevalence of interictal dysphoric disorder (and having no depression and dysthymia according to the MINI) is around 48.2% in epilepsy patients (36, 37). There is some evidence suggesting that interictal dysphoric disorder and peri-ictal dysphoric syndrome may be separate syndromes (37). Therefore, it may be hypothesized that dysphoric disorder in the early post-operative period is in fact interictal dysphoric disorder and that in those patients sub-syndromal seizure activity is present despite surgery thereby predicting future clinical seizures. Future research should delineate this symptom complex in association with surgery outcome using the 38-item Interictal Dysphoric Disorder Inventory (IDDI) (37). Emotional reactivity is a psychosocial stressor increasing circulating glucocorticoid levels causing an increased vulnerability to amygdala kindling (38). Kindling is the process by which repeated minor stimulations (electrical or chemical) of the brain are associated with epileptogenesis and the onset of mood disturbances (39).

Limitations of this study are the lower number of subjects not allocated to Engel class I as a result of the unexpected high success rate of epilepsy surgery in this cohort. As such the results should be interpreted with caution. Future research should validate the predictors delineated in our study and using the IDDI to score severity of the dysphoric syndrome.

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Conflict of interest:

The authors do not report any conflict of interest.

Contributorship.

K B. made the study design; KB, LC, ST and MM interpreted the data; KB and MM performed the statistical analyses and wrote the manuscript; LC, ST and KB collected the data.

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Table 1. Engel class classifications in 189 patients, 6 and 24 months after epilepsy surgery.

Engel classes			**24 months**		
		I	II	III	IV
6 months	I	144	3	1	1
	II	10	3	3	0
	III	0	0	2	0
	IV	13	3	2	4

The distribution of the patients in classes I-IV is significantly different between months 6 and 24 (Sign test: z = -3.17, p=0.002 negative differences = 28, positive differences = 8, ties = 153).

Table 2. Demographic data and Engel classification 24 months after surgery in 189 patients

Variables / predictors	Engel class I	Engel class II	Engel class III	Engel class IV	*F, χ^2, ψ	df	p
Age (years)	37.4 (±9.6)	38.9 (±9.0)	45.0 (±7.5)	28.2 (±8.8)	3.34	3/185	0.020
Duration illness (years)	23.0 (±10.8)	22.1 (±11.7)	29.0 (±14.7)	20.5 (±6.9)	0.89	3/185	0.444
Age at onset (years)	14.5 (±9.4)	16.8 (±6.2)	16.0 (±7.9)	7.7 (±14.5)	1.17	3/185	0.324
Gender (M / F ratio)	83 / 84	6 / 3	6 / 2	1 / 4	0.69	1	0.407
Number seizures prior to epilepsy surgery	8.5 (±13.4)	35.9 (±70.7)	26.4 (±30.3)	65.6 (±124.6)	10.35	3/185	<0.000
Number of seizures after epilepsy surgery	0.00 (±0.00)	1.71 (±1.51)	9.0 (±9.4)	91.8 (±137.8)	33.13	3/185	<0.000
Focal versus secondarily generalized epilepsy	160 / 7	9 / 0	8 / 0	4 / 1	-0.01**	-	0.764

TLE versus ETLE**	156 / 11	7 / 2	7 / 1	1 / 4	14.36	1	<0.00
Epilepsy location					see text		
right	83	6	3	3			
left	80	3	5	1			
bilateral	3	0	0	1			
middle	1	0	0	0			
Lesion					See text		
Hippocampal sclerosis	128	7	5	0			
Tumor	28	1	2	2			
FCD	7	1	0	3			
AVM	1	0	0	0			
No lesion	3	0	1	0			
Familial history of epilepsia: yes / no	26 / 141	3 / 6	3 / 5	2 / 3	5.70	1	0.017
DD first 3 months after surgery: yes / no	18 / 149	1/ 8	2 / 6	3 / 2	4.77	1	0.029
Pre-operative psychosis: yes / no	7 / 160	2 / 7	2 / 6	0 / 5	0.19**		0.026

*F: results of analyses of variance with the 4 Engel groups as categories

*χ^2: results of analyses of contigency tables. In order to perform χ^2 tests we have combined groups and examined the differences between Engel class I versus Engel class II + III + IV. When we were unable to use χ^2 tests, we have used Fisher's exact probability test with ψ values (**).

TLE versus ETLE: temporal lobe epilepsy versus extratemporal lobe epilepsy

DD: dysphoric disorder

Table 3. Effects of epilepsy surgery on the discontinuation of anti-epileptic drugs in 189 epilepsy patients

Drug	- ranks	+ ranks	ties	McNemar or Wilcoxon test*	Discontinuation rate
Phenobarbital	7	1	181	0.070	7 / 37
Phenytoin	23	3	163	<0.001	23 / 61
Carbamazepine	25	1	163	<0.001	25 / 133
Valproic acid	16	3	170	0.004	16 / 46
Clonazepam	6	2	181	0.289	6 / 12
Gabapentin	11	2	176	0.022	11 / 20
Lamotrigine	25	4	160	<0.001	25 / 62
Topiramate	13	4	172	0.049	13 / 20
Levetiracetam	26	15	148	0.118	26 / 54
Clobazam	29	10	150	0.003	29 / 58
All drugs	92	13	84	<0.001*	-

The difference between post-surgery minus pre-surgery use of anti-epileptic drugs is shown as the discontinuation of the drugs after surgery (negative ranks), starting new treatments after surgery (positive ranks) or unchanged treatments after surgery (ties). Thus "ties" includes patients in which the specific drugs were not changed and patients that were not using this drug.
* All analyses are results of McNemar test, except * Wilcoxon test (z=-7.61)

Table 4. Effects of epilepsy surgery on the dosage of anti-epileptic drugs in 189 patients

Drug	- ranks	+ ranks	ties	Wilcoxon test	p
Phenobarbital	12	2	175	-2.684	0.007
Fenytoin	43	6	140	-4.908	<0.001
Carbamazepine	65	15	109	-6.378	<0.001
Valproic acid	27	7	155	-3.066	0.002
Clonazepam	6	3	180	-0.060	0.952
Gabapentin	15	5	169	-2.396	0.017
Lamotrigine	42	13	134	-4.273	<0.001
Topiramate	17	4	168	-3.047	0.002
Levetiracetam	41	22	126	-2.348	0.019
Clobazam	35	12	141	-3.219	<0.001

The differences between post-surgery minus pre-surgery dosages of anti-epileptic drugs is given as reduced dosages (negative ranks), increased dosages (positive ranks) or unchanged dosages (ties) after epilepsy surgery.

Table 5. Results of general linear model analysis with the Engel-derived severity score as dependent variable and the listed variables as predictor variables.

Explanatory variables	F	df	p
TLE versus ETLE	16.04	1	<0.001
No family history of epilepsy	5.19	1	0.024
Number of seizures pre-surgery	11.45	1	<0.001
Dysphoric disorder within the first three months after surgery	6.29	1	0.013
Use of gabapentin post-surgery	7.04	1	0.009

TLE versus ETLE: temporal lobe epilepsy versus extratemporal lobe epilepsy

Table 6. Results of automatic stepwise logistic regression with Engel's class I as dependent variable and the listed variables as predictors

Predictors	Wald	df	p	Odds ratio	95 % CI, lower	95% CI, upper
TLE versus ETLE*	12.77	1	<0.001	20.52	3.91	107.60
Negative family history of epilepsia	5.24	1	0.024	5.72	1.28	25.47
Less than 9 seizures before epilepsy surgery	6.40	1	0.011	6.64	1.53	28.77
Dysphoric disorder first 3 months after surgery	4.19	1	0.041	0.19	0.041	0.93
Age	4.90	1	0.027	1.09	1.01	1.18

*TLE versus ETLE: temporal lobe epilepsia versus extratemporal lobe epilepsy

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract YES
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found YES
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported YES
Objectives	3	State specific objectives, including any prespecified hypotheses YES
Methods		
Study design	4	Present key elements of study design early in the paper YES
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection YES
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up YES
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable YES
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group YES
Bias	9	Describe any efforts to address potential sources of bias YES
Study size	10	Explain how the study size was arrived at YES
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why YES
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding YES
		(*b*) Describe any methods used to examine subgroups and interactions YES
		(*c*) Explain how missing data were addressed YES
		(*d*) If applicable, explain how loss to follow-up was addressed YES
		(*e*) Describe any sensitivity analyses N/A
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed YES
		(b) Give reasons for non-participation at each stage YES
		(c) Consider use of a flow diagram N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders YES
		(b) Indicate number of participants with missing data for each variable of interest YES
		(c) Summarise follow-up time (eg, average and total amount) YES
Outcome data	15*	Report numbers of outcome events or summary measures over time YES
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included YES
		(*b*) Report category boundaries when continuous variables were categorized YES
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period YES
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses YES

Discussion		
Key results	18	Summarise key results with reference to study objectives YES
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias YES
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence YES
Generalisability	21	Discuss the generalisability (external validity) of the study results YES
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based YES

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Clinical predictors of two-year outcome of resective epilepsy surgery in adults with refractory epilepsy

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Abstract: 298 words

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Abstract

Objectives: Resective epilepsy surgery is currently a standard treatment for intractable epilepsy. Seizure freedom and discontinuation of antiepileptic drugs are the ultimate goals of epilepsy treatment. This study was carried out to delineate a) possible differences in the success rate of epilepsy surgery 6 and 24 months after surgery; and b) the clinical predictors of a good response to surgery.

Setting: This is a cohort study performed at a tertiary care unit of a University hospital.

Participants: In this cohort study, 189 adults with intractable epilepsy who underwent epilepsy surgery were included. We collected clinical data at three time points, i.e. pre-operative and 6 and 24 months after surgery.

Primary and secondary outcome measures: Engel class I-IV classification was the primary outcome measure of epilepsy surgery. The authors statistically adjusted Engel class I-IV classification for post-operative changes in antiepileptic drugs and used this new classification as a secondary outcome variable.

Results: The success rate was 78.8% 6 months after surgery and increased to 88.3% 24 months after surgery. This success rate was not only reflected by the reduced number of seizures post-surgery, but also by a reduced dosage and use of antiepileptic drugs. Logistic regression analysis showed that a successful outcome of surgery is predicted by having temporal rather than extratemporal lobe epilepsy and less than 9 pre-surgery seizures per month, while a positive familial history of epilepsy, younger age and dysphoric symptoms the first three months after surgery significantly worsened the outcome of surgery. Duration of illness, age at onset, epilepsy location, type of lesions, and the presence of psychosis were not significant in predicting treatment outcome.

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Conclusions: These findings have clinical relevance in that a better selection of patients based on the significant clinical predictors will increase the success rate of epilepsy surgery and treatment.

Key words: epilepsy, Engel class, surgery, predictors, dysphoric syndrome

Strengths and limitations of the study

- The authors analyze a large series (n=189) of consecutively admitted patients with refractory epilepsy who underwent epilepsy surgery and delineate the differences in surgical outcome between 6 and 24 months after surgery, clinical predictors of good surgical outcome (Engel class I) and the effects of withdrawal of antiepileptic drugs (AEDs).
- This is a first study that adjusts the results of epilepsy surgery outcome data for changes in AEDs. The authors propose that Engel's classification into 4 classes may not be adequate because post-surgery patients allocated to an Engel class who had their AEDs discontinued or reduced differ from those belonging to same Engel class but who had an increased or unchanged AED intake. Therefore, the authors suggest that the Engel class classification should be refined taking into account post-operative changes in AED status.
- The shorter follow-up period (24 months) is a limitation of the study. The high success rate of epilepsy surgery in this study (i.e. 88.3% at 24 months) may be explained by our strict selection criteria. This cohort comprises 2% MRI-negative epilepsy and >90% temporal lobe surgery patients and, therefore, our findings cannot be readily extrapolated to more heterogeneous cohorts.

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Introduction

In most state-of-the-art epilepsy units, resective epilepsy surgery is currently the standard treatment for intractable epilepsy. Generally, the success rate, defined as a seizure free status or Engel class I, is between 62% (1) - 71% (2), as compared to 14% in non-operated cases (1). For example, in the Epilepsy Unit of King Chulalongkorn Memorial Hospital, Bangkok, Thailand, the success rate 24 months after sugery is 66.7% as compared to 5% in cases without surgery (3). Clinical experience is that some epilepsy patients who are non-responders to surgery in the first few months after surgery become seizure free and thus responders some months later.

In order to improve the success rate to epilepsy surgery, selection criteria for surgery based on clinical and biological characteristics of responders and non-responders should be delineated. Neurological predictors include type of resection, preoperative aura, presence of postoperation spikes (2), extratemporal resection, simple partial seizure (4), long seizure duration, number of seizures per month at baseline, secondarily generalized seizures and ictal dystonia (5). It is debated whether psychiatric problems may modulate the outcome to epilepsy surgery. Some studies show that preoperative psychiatric diagnoses may predict a negative outcome to epilepsy surgery (6-10). Other studies, however, report that a history of psychiatric diagnosis is not a predictor for surgery outcome (11). It has remained elusive, however, whether clinical variables, such as duration of illness, type of epilepsy, epilepsy location and a familial history of epilepsy may predict a good outcome, and whether a combination of these and other factors may improve the prediction.

To complicate matters, discontinuation of antiepileptic drugs (AEDs) may interfere with surgery outcome. Surgery may allow to taper down or even discontinue AED intake

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in some patients after epilepsy surgery. On the other hand, tapering down AEDs may cause seizure recurrence in about a third of patients (12). This indicates that when assessing epilepsy surgery outcome one has to take the AED state into account. This may also indicate that Engel's classification into 4 classes is not always adequate. For example, it is obvious that there is a difference between post-surgery patients allocated to an Engel class and who had their AEDs discontinued or reduced and those belonging to same class but who had an increased or unchanged AED intake. One approach is to adjust the Engel classes for post-operative changes in AED state.

This study was carried out to delineate a) the success rate of epilepsy surgery 6 and 24 months after surgery as assessed by means of Engel classes; and b) clinical predictors of a good treatment response while adjusting for the effects of discontinuation or reduction of AEDs on this prediction.

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Patients and Methods

This is a cohort study performed at the Comprehensive Epilepsy Unit, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. We consecutively included (from October 2005 until June 2008) all intractable epilepsy patients who were selected for epilepsy surgery and attended the Comprehensive Epilepsy Unit for post-operative evaluations. One hundred and eighty-nine subjects were included in this study. We collected data at three different time points, that is pre-operation, and 6 and 24 months after surgery. We collected socio-demographic data, age at onset, duration of illness, familial history of epilepsy, number of seizures per month before and 6 and 24 months after surgery, use of AEDs (type and dosage) before and 6 and 24 months after surgery, using semi-structured interviews performed by a trained master degree research psychologist.

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Epilepsy-related characteristics, including epilepsy location and type of epilepsy, were rated by senior neurologists using neurological, medical and neurosurgical records, 24 hour electroencephalogram (EEG) reports and brain imaging techniques, i.e. magnetic resonance imaging (MRI). The post-surgery data at 6 and 24 hours were used to make the Engel class diagnoses in class I (no disabling seizures), class II (almost free of seizures), class III (worthwhile improvement with >50% reduction in disabling seizures), and class IV (no worthwhile improvement). The psychiatric DSM-IV diagnosis psychosis (before surgery) was made by a trained master degree research psychologist using the International Neuropsychiatric Interview (MINI) in a Thai validated version (13). Dysphoric disorder was defined as an emotional response within the first 3 months after epilepsy surgery characterized by labile mood, crying spells, behavioral outbursts, sleep problems, concentration disorders, and / or irritability. The study was approved by the Ethics Research Committee at Chulalongkorn University, Department of Medicine, Bangkok, Thailand and all participants gave written informed consent to participate.

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Statistics.

We used analyses of contingence tables (χ^2 tests) or Fisher's exact probability test to check differences in the distribution of variables among two or more study groups. Relationships between variables were assessed using Pearson's correlation coefficients. General and generalized linear model analyses were used to predict dependent variables by means of different explanatory variables. We used analyses of variance (ANOVA) in order to ascertain differences in continuous variables between two or more study groups. Multiple post-hoc differences were assessed by means of Tukey's tests. Binary logistic regression analysis was used to define the associations between a dichotomous dependent

variable and a set of independent variables. We used the logistic regression coefficients of the explanatory variables in the final equation to estimate odds ratios with confidence intervals. We used the sign test to assess the differences in the Engel classes (considered as ordinal scaled variables) 6 and 24 months after epilepsy surgery. The Sign Test is a nonparametric test statistic which can be employed to test paired samples of ordinally scaled variables and which uses only directional and not magnitude information. The effects of epilepsy surgery on the discontinuation of AEDs were analyzed using the McNemar test, a non-parametric test to analyze differences in repeated measurements of binary data. The surgery effects on the number of seizures and AED use was analyzed using factorial repeated measurement design ANOVA or the Wilcoxon signed rank test, a non-parametric test used to check differences in pairs of data. The results of parametric tests were checked using non parametric tests including Spearman's rank order correlation coefficients and the Kruskal-Wallis test. Data were analyzed using the SPSS Versions 15 and 19. There were no missing values in our data set. Statistical significance was set at α=0.05 (two tailed).

Results

1. Characteristics of Engel classes

Table 1 shows that there was a significant difference in Engel class distribution between the two time points. The Sign Test showed that there were significantly more negative differences than positive differences, indicating that some patients improved from month 6 to month 24. For example, 6 months after surgery 149 patients were allocated to class I, while 24 months after surgery 167 were allocated to class I. Twenty three patients who were allocated to Engel classes II, III or IV 6 months after surgery were re-allocated

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to Engel class I 24 months after surgery, showing that their status had improved. We have analyzed whether any of the variables listed in Table 2 was associated with this subgroup of patients who had improved, but not one of the variables was significantly significant. In this paper we will report on the Engel classes 24 months after epilepsy surgery.

Table 2 shows the demographic data of the patients in this study according to Engel's classification. There was a marginal but significant difference in age between the Engel classes. Tukey's post-hoc test showed that patients in Engel class IV were significantly younger than those belonging to class III (p=0.011). There were no significant differences in duration of illness and age at onset between the Engel classes. The number of pre-surgery seizures was significantly lower in patients with Engel class I than in those with Engel class II (p=0.012 by Tukey's post-hoc tests) and class IV (p=0.007), while there was a trend towards a significant difference with class III (p=0.068). There were no significant differences in number of pre-surgery seizures between class II, III and IV. Table 2 shows that the number of post-surgery seizures was significantly different between the 4 classes. This was validated using the Kruskal-Wallis test ($\chi 2$ =150.62, df=3, p<0.001). Tukey's tests showed that all pairwise and post-hoc analyses were significant, e.g. class I from class II (p=0.004), III (p<0.001) and IV (p<0.001), class II from class III (p=0.015) and class IV (p<0.001) and class III from class IV (p<0.001).

Unexpectedly only few patients were not allocated to Engel class I and therefore we were unable to perform Π^2 tests in the 4 study groups. Since the major aim of this study is to delineate the characteristics of a good versus a worse surgery outcome we compared Engel class I versus Engel class II+III+IV using Π^2 tests or Fisher's exact probability tests. There were no significant associations between gender or focal versus secondarily generalized epilepsy and Engel classes I versus II+III+IV. Patients belonging to Engel

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classes II+III+IV suffered significantly more from extratemporal lobe epilepsy than those belonging to class I. There was no significant difference in right versus left location between Engel class I versus II+III+IV ($\chi 2$ =0.29, df=1, p=0.591). There was no significant association between Engel class classification and type of lesion, i.e. hippocampal sclerosis versus other or no lesions ($\chi 2$ =1.30, df=1, p=0.25). A positive family history of epilepsy, dysphoric syndrome and pre-operative psychosis were significantly associated with Engel classes II+III+IV.

2. Effects of epilepsy surgery on number of seizures and intake of antiepileptics

Table 2 shows the number of seizures both before and after epilepsy surgery. RM design ANOVA showed that the number of seizures was significantly reduced by epilepsy surgery (F=6.45, df=1/185, p=0.012). The interaction pattern time X Engel class was significant (F=10.34, df=3/185, p<0.001), showing that epilepsy surgery reduced the number of seizures in class I, II and III, while in class IV the number of seizures further increased after surgery.

Table 3 shows the differences between post-surgery minus pre-surgery use of AEDs as binary responses. The discontinuation of anti-epileptic drugs after surgery is shown as negative ranks, the initiation of new anti-epileptic drug treatments after surgery as positive ranks, while no changes in the treatments after surgery are shown as ties. McNemar tests for paired data showed that two years after epilepsy surgery phenytoin, carbamazepine, valproic acid gabapentin, topiramate, and clobazam could be discontinued in a significant number of patients, while there were no significant changes in the number of patients treated with phenobarbital, clonazepam, or levetiracetam. The total number of AEDs was significantly lower after surgery than before surgery. We were able to

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discontinue one or more AEPs in 48.68% of the patients, while in 6.88% of the patients we started a new AEP and in 44.44% of the patients AEP intake was unchanged. RM design ANOVA showed that there was a significant time X Engel class interaction indicating that the total number of drugs was reduced in class I but not in the other classes. Table 4 shows that the dosages of all AEDs, except clonazepam were lower 24 months after surgery than before.

3. Prediction of response to epilepsy surgery

The abovementioned changes in the intake of AEDs after epilepsy surgery suggest that Engel's classification should be adjusted to reflect changes in AED status. Thus, it is clear that there is a difference between patients allocated to for example class I and whom had their AEDs discontinued / reduced and those belonging to class I but who had an increased / unchanged AED intake. Therefore, we controlled for changes in AED state in two ways: a) by adjusting statistically for effects of AED state by entering the total number of AEDs prior and after surgery into the analyses; and b) by computing a new index of surgery response based on Engel's classification and the AED state. Toward this end we computed a new score based on Engel classes and the change in AED state from baseline to post-surgery, e.g. decreased intake of drugs: rating=1, unchanged: rating=2 and increased: rating=3. Thus for class I this yields three scores, i.e. 1 (class I and reduced intake), 2 (class I and unchanged drug state) and 3 (class I but increased drug intake). Applied to all 4 classes, this method yields a severity score ranging from 1-12. There is a significant association between Engel's class classification and this newly presented severity score (Spearman's correlation: $r=0.592$, $p<0.001$).

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Table 5 shows the outcome of a general linear model analysis with this new severity score as dependent variable and the variables listed in Table 2 and the drug state of the patients as predictor variables. Up to 25.2% in the variance of the severity index was explained by 5 variables ($F=12.32$, $df=5/183$, $p<0.001$): a lower severity score was associated with temporal lobe versus extratemporal lobe epilepsy and a negative family history of epilepsy; a worse outcome was predicted by an increased number of seizures before surgery, dysphoric syndrome the first 3 months after surgery and use of gabapentin. Using a threshold value > 9 for the total number of seizures before surgery showed a similar significant effect ($F=8.99$, $df=1$, $p=0.003$), suggesting that a threshold value of 9 or more may be used as a predictor variable. Entering use of AEDs, total number of AEDs, and dosages of AEDs both before and after surgery (at 24 months) as explanatory variables showed that none of these variables, except gabapentin post-surgery, was significant in explaining the severity index and that entering these drug variables did not change the results. We have also examined the prediction of the Engel classes using the same variables as in Table 5 but considering that the Engel classes are continuous classes or ordinal variables ranging from 1 (for class I) to 4 (for class IV). Generalized linear model analysis showed that this Engel scaling was predicted by 5 variables: the outcome was better when suffering from temporal lobe epilepsy (Wald=20.33, $df=1$, $p<0.001$) and having a negative family history (Wald=9.21, $df=1$, $p=0.002$), while the total number of pre-surgery seizures (Wald=17.03, $df=1$, $p<0.001$), dysphoric syndrome (Wald=7.91, $df=1$, $p=0.005$) and use of gabapentin (Wald=8.19, $df=1$, $p=0.004$) predicted a worse outcome.

Table 6 shows the results of an automatic stepwise logistic regression analysis with Engel's class I as dependent variable (classes III + IV as reference group) and the variables listed in Table 2 (and number of baseline epileptic seizures > 9, yes or no) as predictors.

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We found that 5 variables were significantly associated with Engel's class I ($\chi 2$ =31.88, df=5, p<0.001, Nagelkerke=0.401; correctly classified cases=92.8%), namely temporal versus extratemporal lobe epilepsy, a negative family history of epilepsy, less than 9 seizures before surgery, age and the presence of dysphoric syndrome.

Discussion

A first major finding of this study is that there were significant differences in surgery outcome between 6 and 24 months after surgery: our success rate at 6 months (78.8%) had significantly increased (88.3%) at 24 months. Already in 1970 it was suggested that some patients may show seizures after surgery that eventually remit some months to years later, i.e. the "running down phenomenon" (4, 13). Nevertheless, our findings contradict one of the largest series of epilepsy surgery results, showing a gradual decline over time in the estimated proportion of patients who remain seizure free (13). In another study it was reported that the prevalence of Engel class I was 76.2% at 6 months, 72.3% at 2 years and 71.1% at 5 years (14). The prevalence of being completely seizure-free at 12 and 18 years after MTLE/HS surgery was 65% and 62%, respectively (15). A meta-analysis showed seizure control to decline over time especially after 2 years (16). The risk of having any recurrence was 22% during the first 24 months and increased 1.4% per year afterwards (15). Some of the long term post-surgical following studies supported the concept that the prognosis may improve over time, e.g. less memory decline (17). One explanation of these contradictory data is that a running down phenomenon may occur in an initially non-equilibrium period, with an undetermined duration, and that seizures may re-occur after that time point.

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The high success rate of epilepsy surgery in our hospital (i.e. 88.3% at 24 months) may be explained by our inclusion criteria, which are based on clinical semiology, 24 hr EEG and MRI to identify subjects with primary epileptogenic lesions. As a consequence this cohort comprises only 2% MRI-negative epilepsy and >90% temporal lobe surgery patients. Therefore, our findings cannot be readily extrapolated to more heterogeneous cohorts including high rates of non-lesional and/or extratemporal epilepsy.

A second major finding is that the efficacy of epilepsy surgery was not only reflected by the reduced number of seizures, but also by a reduced use of AEDs. We were able to discontinue one or more AEDs in 48.68% of the patients, while 13.2% of all patients were free of any AEDs 2 years after surgery. This discontinuation rate might be slightly lower than that in previous reports which showed that around 52.6% of the patients can discontinue AEDs at 2 years without seizure recurrence (18). In another study 28.1% of the patients had discontinued AED treatment 2 years after surgery and had remained seizure free, suggesting that there was no risk of seizure recurrence after discontinuation of AEDs (14). A meta-analysis showed that in patients with all types of surgery, 20% achieved long-term AED discontinuation, 31% remained on polytherapy and 41% were on monotherapy (19). In addition, we found no significant associations between AED discontinuation and seizure freedom. Other studies report that AED discontinuation may be a strong predictor for seizure recurrence in post-surgery seizure-free cases (12). Boshuisen et al. (20), in a study performed on children with intractable epilepsy, found that AED withdrawal did not affect long-term seizure outcome but may unmask incomplete surgical success sooner, identifying children who need continuous drug treatment. One of our analysies showed that use of gabapentin was a significant predictor variable for a worse outcome. In our clinic, however, gabapentin is not the first AED choice for seizure

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treatment and is used in refractory seizures that failed to respond to treatment with other AEDs. This may show that use of gabapentin should not be regarded as a real explanatory variable but as a post-hoc adjustment for possible effects of the drug state. The third major finding of this study is that a good outcome of epilepsy surgery, i.e. being allocated to class I, could be predicted by temporal versus extratemporal lobe epilepsy, less than 9 pre-surgery seizures per month, a negative familial history of epilepsy, age and absence of a dysphoric disorder. Temporal lobe epilepsy (TLE) was the most significant outcome predictor. This finding is consistent with most published papers showing that TLE, both in short term and long term monitoring period (21) and in pediatric and adult patients has a significantly better postoperative outcome than extratemporal lobe epilepsy (ETLE) (22). In pediatric patients, the seizure free rate in TLE was 71.8% versus 59.7% in ETLE, whereas in adult epilepsy the seizure free rate in TLE was 69.4% versus 45.9% in ETLE (22). In ETLE, it is more difficult to localize the epileptogenic focus to a specific cerebral region and to completely remove the epileptogenic region without impairing the eloquent cortex (23).

The second predictor, i.e. number of pre-operative seizures, shows that surgery may not be the best treatment option for patients with many refractory seizures. A high number of pre-surgery seizures might indicate multiple types of seizures, unidentified multiple lesions or severe pathology or other factors negatively modifying surgery outcome. We established that a threshold value of 9 seizures / month best predicted Engel class I membership, while another study delineated that more than 30 seizures / month best predicted a negative outcome (1). These differences between both studies may reflect differences in sensitivity and specificity. Thus, we established that < 9 seizures per month

significantly predicts Engel class I versus II+III+IV, while it is obvious that if we had used Engel class I+II+III versus IV the threshold value would be higher.

To the best of our knowledge, this is a first study showing that a positive family history for epilepsy may worsen post-surgery outcome. There is now evidence that the risk to develop epilepsy is significantly increased in the first-degree relatives of people with epilepsy of unknown cause (24). Twin studies consistently show higher concordance in monozygotic than in dizygotic pairs (25). However, the genes identified so far affect risk in a very small proportion of patients, while most epilepsies occur in the absence of a significant family history (26). In a few clinical studies on epilepsy with or without psychiatric disorders, genetic linkage is regarded to increase risk of poor clinical outcome (27, 28). Thus, a positive family history of epilepsy, occurs more frequently in TLE with postictal psychosis than in TLE alone (27). A positive family history of epilepsy has also a significant negative impact on the quality of life (28). The inverse relationship between a family history of epilepsy and Engel class outcome may be explained by mutations in specific genes that are related to a more severe outcome, including drug resistance, and distinct neuroradiological findings as has been observed in benign neonatal epilepsy or benign familial neonatal convulsions (29, 30). However, it is unlikely that single common variants could explain more than 4.4% of outcome variation in newly treated epilepsy (31). Therefore, it should be examined whether multiple common variants may underpin increased resistance to resective epilepsy surgery.

There are only few studies in adults that have examined age as a predictor of surgery outcome. In individuals aged less than 50 years, 58% were allocated to Engel class I, while 74% of those who were more than 50 years old and 91% of those who were more than 60 years old were allocated to Engel class I (16). Srikijvilaikul et al. (27) found no

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differences in surgical outcome in terms of medication withdrawn between older and younger subjects (threshold value = 50 years old), but more surgical complications in the older group (32). Previous studies in children or teenage showed that early surgical treatment correlated with a better Engel class outcome (33, 34). In our study, however, the absolute differences in age were very small. Therefore, further research should delineate whether age at surgery significantly contributes to Engel class outcome.

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The fifth predictor of surgery outcome is dysphoric disorder, i.e. labile and irritable mood emerging within 3 months after surgery, but most often the first 1 to 2 months. While pre-surgery psychiatric factors are identified as predictors of a worse surgery outcome, few studies have examined post-surgery psychiatric predictors. Epilepsy is accompanied by the interictal dysphoric disorder, characterized by intermittent affective symptoms including labile affective symptoms, paroxysmal irritability and outbursts of aggressive behavior (35, 36). The prevalence of interictal dysphoric disorder (and having no depression and dysthymia according to the MINI) is around 48.2% in epilepsy patients (36, 37). There is some evidence suggesting that interictal dysphoric disorder and peri-ictal dysphoric syndrome may be separate syndromes (37). Therefore, it may be hypothesized that dysphoric disorder in the early post-operative period is in fact interictal dysphoric disorder and that in those patients sub-syndromal seizure activity is present despite surgery thereby predicting future clinical seizures. Future research should delineate this symptom complex in association with surgery outcome using the 38-item Interictal Dysphoric Disorder Inventory (IDDI) (37). Emotional reactivity is a psychosocial stressor increasing circulating glucocorticoid levels causing an increased vulnerability to amygdala kindling (38). Kindling is the process by which repeated minor stimulations (electrical or chemical) of the brain are associated with epileptogenesis and the onset of mood disturbances (39).

Limitations of this study are the lower number of subjects not allocated to Engel class I as a result of the unexpected high success rate of epilepsy surgery in this cohort. As such the results should be interpreted with caution. Future research should validate the predictors delineated in our study and using the IDDI to score severity of the dysphoric syndrome.

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Conflict of interest:

The authors do not report any conflict of interest.

Contributorship.

K B. made the study design; KB, LC, ST and MM interpreted the data; KB and MM performed the statistical analyses and wrote the manuscript; LC, ST and KB collected the data.

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Table 1. Engel class classifications in 189 patients, 6 and 24 months after epilepsy surgery.

Engel classes			**24 months**		
		I	II	III	IV
	I	144	3	1	1
6 months	II	10	3	3	0
	III	0	0	2	0
	IV	13	3	2	4

The distribution of the patients in classes I-IV is significantly different between months 6 and 24 (Sign test: z = -3.17, p=0.002, negative differences = 28, positive differences = 8, ties = 153).

Table 2. Demographic data and Engel classification 24 months after surgery in 189 patients

Variables / predictors	Engel class I	Engel class II	Engel class III	Engel class IV	*F, χ^2, ψ	df	p
Age (years)	37.4 (±9.6)	38.9 (±9.0)	45.0 (±7.5)	28.2 (±8.8)	3.34	3/185	0.020
Duration illness (years)	23.0 (±10.8)	22.1 (±11.7)	29.0 (±14.7)	20.5 (±6.9)	0.89	3/185	0.444
Age at onset (years)	14.5 (±9.4)	16.8 (±6.2)	16.0 (±7.9)	7.7 (±14.5)	1.17	3/185	0.324
Gender (M / F ratio)	83 / 84	6 / 3	6 / 2	1 / 4	0.69	1	0.407
Number seizures prior to epilepsy surgery	8.5 (±13.4)	35.9 (±70.7)	26.4 (±30.3)	65.6 (±124.6)	10.35	3/185	<0.001
Number of seizures after epilepsy surgery	0.00 (±0.00)	1.71 (±1.51)	9.0 (±9.4)	91.8 (±137.8)	33.13	3/185	<0.001
Focal versus secondarily generalized epilepsy	160 / 7	9 / 0	8 / 0	4 / 1	-0.01**	-	0.764

TLE versus ETLE**	156 / 11	7 / 2	7 / 1	1 / 4	14.36	1	<0.001
Epilepsy location right left bilateral middle	 83 80 3 1	 6 3 0 0	 3 5 0 0	 3 1 1 0	see text		
Lesion Hippocampal sclerosis Tumor FCD AVM No lesion	 128 28 7 1 3	 7 1 1 0 0	 5 2 0 0 1	 0 2 3 0 0	See text		
Familial history of epilepsia: yes / no	26 / 141	3 / 6	3 / 5	2 / 3	5.70	1	0.017
DD first 3 months after surgery: yes / no	18 / 149	1/ 8	2 / 6	3 / 2	4.77	1	0.029
Pre-operative psychosis: yes / no	7 / 160	2 / 7	2 / 6	0 / 5	0.19**		0.026

*F: results of analyses of variance with the 4 Engel groups as categories
*χ^2: results of analyses of contigency tables. In order to perform χ^2 tests we have combined groups and examined the differences between Engel class I versus Engel class II + III + IV. When we were unable to use χ^2 tests, we have used Fisher's exact probability test with ψ values (**).
TLE versus ETLE: temporal lobe epilepsy versus extratemporal lobe epilepsy
DD: dysphoric disorder

Table 3. Effects of epilepsy surgery on the discontinuation of anti-epileptic drugs in 189 epilepsy patients

Drug	- ranks	+ ranks	ties	McNemar or Wilcoxon test*	Discontinuation rate
Phenobarbital	7	1	181	0.070	7 / 37
Phenytoin	23	3	163	<0.001	23 / 61
Carbamazepine	25	1	163	<0.001	25 / 133
Valproic acid	16	3	170	0.004	16 / 46
Clonazepam	6	2	181	0.289	6 / 12
Gabapentin	11	2	176	0.022	11 / 20
Lamotrigine	25	4	160	<0.001	25 / 62
Topiramate	13	4	172	0.049	13 / 20
Levetiracetam	26	15	148	0.118	26 / 54
Clobazam	29	10	150	0.003	29 / 58
All drugs	92	13	84	<0.001*	-

The difference between post-surgery minus pre-surgery use of anti-epileptic drugs is shown as the discontinuation of the drugs after surgery (negative ranks), starting new treatments after surgery (positive ranks) or unchanged treatments after surgery (ties). Thus "ties" includes patients in which the specific drugs were not changed and patients that were not using this drug.

* All analyses are results of McNemar test, except * Wilcoxon test (z=-7.61)

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Table 4. Effects of epilepsy surgery on the dosage of anti-epileptic drugs in 189 patients

Drug	- ranks	+ ranks	ties	Wilcoxon test	p
Phenobarbital	12	2	175	-2.684	0.007
Fenytoin	43	6	140	-4.908	<0.001
Carbamazepine	65	15	109	-6.378	<0.001
Valproic acid	27	7	155	-3.066	0.002
Clonazepam	6	3	180	-0.060	0.952
Gabapentin	15	5	169	-2.396	0.017
Lamotrigine	42	13	134	-4.273	<0.001
Topiramate	17	4	168	-3.047	0.002
Levetiracetam	41	22	126	-2.348	0.019
Clobazam	35	12	141	-3.219	<0.001

The differences between post-surgery minus pre-surgery dosages of anti-epileptic drugs is given as reduced dosages (negative ranks), increased dosages (positive ranks) or unchanged dosages (ties) after epilepsy surgery.

Table 5. Results of general linear model analysis with the Engel-derived severity score as dependent variable and the listed variables as predictor variables.

Explanatory variables	F	df	p
TLE versus ETLE	16.04	1	<0.001
No family history of epilepsy	5.19	1	0.024
Number of seizures pre-surgery	11.45	1	<0.001
Dysphoric disorder within the first three months after surgery	6.29	1	0.013
Use of gabapentin post-surgery	7.04	1	0.009

TLE versus ETLE: temporal lobe epilepsy versus extratemporal lobe epilepsy

Table 6. Results of automatic stepwise logistic regression with Engel's class I as dependent variable and the listed variables as predictors

Predictors	Wald	df	p	Odds ratio	95 % CI, lower	95% CI, upper
TLE versus ETLE*	12.77	1	<0.001	20.52	3.91	107.60
Negative family history of epilepsia	5.24	1	0.024	5.72	1.28	25.47
Less than 9 seizures before epilepsy surgery	6.40	1	0.011	6.64	1.53	28.77
Dysphoric disorder first 3 months after surgery	4.19	1	0.041	0.19	0.041	0.93
Age	4.90	1	0.027	1.09	1.01	1.18

*TLE versus ETLE: temporal lobe epilepsia versus extratemporal lobe epilepsy

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Clinical predictors of two-year outcome of resective epilepsy surgery in adults with refractory epilepsy: a cohort study

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Abstract

Objectives: Resective epilepsy surgery is currently a standard treatment for intractable epilepsy. Seizure freedom and discontinuation of antiepileptic drugs are the ultimate goals of epilepsy treatment. This study was carried out to delineate a) possible differences in the success rate of epilepsy surgery 6 and 24 months after surgery; and b) the clinical predictors of a good response to surgery.

Setting: This is a cohort study performed at a tertiary care unit of a University hospital.

Participants: In this cohort study, 189 adults with intractable epilepsy who underwent epilepsy surgery were included. We collected clinical data at three time points, i.e. pre-operative and 6 and 24 months after surgery.

Primary and secondary outcome measures: Engel class I-IV classification was the primary outcome measure of epilepsy surgery. The authors statistically adjusted Engel class I-IV classification for post-operative changes in antiepileptic drugs and used this new classification as a secondary outcome variable.

Results: The success rate was 78.8% 6 months after surgery and increased to 88.3% 24 months after surgery. This success rate was not only reflected by the reduced number of seizures post-surgery, but also by a reduced dosage and use of antiepileptic drugs. Logistic regression analysis showed that a successful outcome of surgery is predicted by having temporal rather than extratemporal lobe epilepsy and less than 9 pre-surgery seizures per month, while a positive familial history of epilepsy, younger age and dysphoric symptoms the first three months after surgery significantly worsened the outcome of surgery. Duration of illness, age at onset, epilepsy location, type of lesions, and the presence of psychosis were not significant in predicting treatment outcome.

Conclusions: These findings have clinical relevance in that a better selection of patients based on the significant clinical predictors will increase the success rate of epilepsy surgery and treatment.

Key words: epilepsy, Engel class, surgery, predictors, dysphoric syndrome, mood disorders

Strengths and limitations of the study

- The authors analyze a large series (n=189) of consecutively admitted patients with refractory epilepsy who underwent epilepsy surgery and delineate the differences in surgical outcome between 6 and 24 months after surgery, clinical predictors of good surgical outcome (Engel class I) and the effects of withdrawal of antiepileptic drugs (AEDs).
- This is a first study that adjusts the results of epilepsy surgery outcome data for changes in AEDs. The authors propose that Engel's classification into 4 classes may not be adequate because post-surgery patients allocated to an Engel class who had their AEDs discontinued or reduced differ from those belonging to same Engel class but who had an increased or unchanged AED intake. Therefore, the authors suggest that the Engel class classification should be refined taking into account post-operative changes in AED status.
- The shorter follow-up period (24 months) is a limitation of the study. The high success rate of epilepsy surgery in this study (i.e. 88.3% at 24 months) may be explained by our strict selection criteria. This cohort comprises 2% MRI-negative epilepsy and >90% temporal lobe surgery patients and, therefore, our findings cannot be readily extrapolated to more heterogeneous cohorts.

Introduction

In most state-of-the-art epilepsy units, resective epilepsy surgery is currently the standard treatment for intractable epilepsy. Generally, the success rate, defined as a seizure free status or Engel class I, is between 62% - 71%, as compared to 14% in non-operated cases (1-2). For example, in the Epilepsy Unit of King Chulalongkorn Memorial Hospital, Bangkok, Thailand, the success rate 24 months after sugery is 66.7% as compared to 5% in cases without surgery (3). Clinical experience is that some epilepsy patients who are non-responders to surgery in the first few months after surgery become seizure free and thus responders some months later.

In order to improve the success rate to epilepsy surgery, selection criteria for surgery based on clinical and biological characteristics of responders and non-responders should be delineated. Neurological predictors include type of resection, preoperative aura, presence of postoperation spikes (2), extratemporal resection, simple partial seizure (4), long seizure duration, number of seizures per month at baseline, secondarily generalized seizures and ictal dystonia (5). It is debated whether psychiatric problems may modulate the outcome to epilepsy surgery. Some studies show that preoperative psychiatric diagnoses may predict a negative outcome to epilepsy surgery (6-10). Other studies, however, report that a history of psychiatric diagnosis is not a predictor for surgery outcome (11). It has remained elusive, however, whether clinical variables, such as duration of illness, type of epilepsy, epilepsy location and a familial history of epilepsy may predict a good outcome, and whether a combination of these and other factors may improve the prediction.

To complicate matters, discontinuation of antiepileptic drugs (AEDs) may interfere with surgery outcome. Surgery may allow to taper down or even discontinue AED intake

in some patients after epilepsy surgery. On the other hand, tapering down AEDs may cause seizure recurrence in about a third of patients (12). This indicates that when assessing epilepsy surgery outcome one has to take the AED state into account. This may also indicate that Engel's classification into 4 classes is not always adequate. For example, it is obvious that there is a difference between post-surgery patients allocated to an Engel class and who had their AEDs discontinued or reduced and those belonging to same class but who had an increased or unchanged AED intake. One approach is to adjust the Engel classes for post-operative changes in AED state.

This study was carried out to delineate a) the success rate of epilepsy surgery 6 and 24 months after surgery as assessed by means of Engel classes; and b) clinical predictors of a good treatment response while adjusting for the effects of discontinuation or reduction of AEDs on this prediction.

Patients and Methods

This is a cohort study performed at the Comprehensive Epilepsy Unit, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. We consecutively included (from October 2005 until June 2008) all intractable epilepsy patients who were selected for epilepsy surgery and attended the Comprehensive Epilepsy Unit for post-operative evaluations. One hundred and eighty-nine subjects were included in this study. We collected data at three different time points, that is pre-operation, and 6 and 24 months after surgery. We collected socio-demographic data, age at onset, duration of illness, familial history of epilepsy, number of seizures per month before and 6 and 24 months after surgery, use of AEDs (type and dosage) before and 6 and 24 months after surgery, using semi-structured interviews performed by a trained master degree research psychologist.

Epilepsy-related characteristics, including epilepsy location and type of epilepsy were rated by senior neurologists using neurological, medical and neurosurgical records, 24 hour electroencephalogram (EEG) reports and brain imaging techniques, i.e. magnetic resonance imaging (MRI). The post-surgery data at 6 and 24 hours were used to make the Engel class diagnoses in class I (no disabling seizures), class II (almost free of seizures), class III (worthwhile improvement with >50% reduction in disabling seizures), and class IV (no worthwhile improvement). The psychiatric DSM-IV diagnosis psychosis (before surgery) was made by a trained master degree research psychologist and a senior psychiatrist using the International Neuropsychiatric Interview (MINI) in a Thai validated version (13). Dysphoric disorder was defined as an emotional response within the first 3 months after epilepsy surgery characterized by labile mood, crying spells, behavioral outbursts, sleep problems, concentration disorders, and / or irritability. The study was approved by the Ethics Research Committee at Chulalongkorn University, Department of Medicine, Bangkok, Thailand and all participants gave written informed consent to participate.

Statistics.

We used analyses of contingence tables (χ^2 tests) or Fisher's exact probability test to check differences in the distribution of variables among two or more study groups. Relationships between variables were assessed using Pearson's correlation coefficients. General and generalized linear model analyses were used to predict dependent variables by means of different explanatory variables. We used analyses of variance (ANOVA) in order to ascertain differences in continuous variables between two or more study groups. Multiple post-hoc differences were assessed by means of Tukey's tests. Binary logistic

regression analysis was used to define the associations between a dichotomous dependent variable and a set of independent variables. We used the logistic regression coefficients of the explanatory variables in the final equation to estimate odds ratios with confidence intervals. We used the sign test to assess the differences in the Engel classes (considered as ordinal scaled variables) 6 and 24 months after epilepsy surgery. The Sign Test is a nonparametric test statistic which can be employed to test paired samples of ordinally scaled variables and which uses only directional and not magnitude information. The effects of epilepsy surgery on the discontinuation of AEDs were analyzed using the McNemar test, a non-parametric test to analyze differences in repeated measurements of binary data. The surgery effects on the number of seizures and AED use was analyzed using factorial repeated measurement (RM) design ANOVA or the Wilcoxon signed rank test, a non-parametric test used to check differences in pairs of data. The results of parametric tests were checked using non parametric tests including Spearman's rank order correlation coefficients and the Kruskal-Wallis test. Data were analyzed using SPSS. There were no missing values in our data set. Statistical significance was set at α=0.05 (two tailed).

Results

1. Characteristics of Engel classes

Table 1 shows that there was a significant difference in Engel class distribution between the two time points. The Sign Test showed that there were significantly more negative differences than positive differences, indicating that some patients improved from month 6 to month 24. For example, 6 months after surgery 149 patients were allocated to class I, while 24 months after surgery 167 were allocated to class I. Twenty three patients

who were allocated to Engel classes II, III or IV 6 months after surgery were re-allocated to Engel class I 24 months after surgery, showing that their status had improved. We have analyzed whether any of the variables listed in Table 2 was associated with this subgroup of patients who had improved, but not one of the variables was significant. For example, there were no significant associations between improvement in Engel class classification and family history of epilepsy (χ^2=1.16, df=1, p=0.281), temporal versus extratemporal lobe epilepsy (p=0.415 by Fisher's exact probability test) and type of epilepsy (p=0.599 by Fisher's exact probability test). In order to examine possible associations between the improvement in Engel class classification and use of AEDs, we have performed RM design ANOVAs with dosage of AEDs at 6 and 24 months as time factor and improvement in Engel class I classification as factor. We found a significant time X group interaction only for levetiracetam dosage (F=5.47, df=1/187, p=0.02). Logistic regression analysis with use of AEDs (and other variables listed in Table 2) showed that only dosage of levetiracetam was a significant explanatory variable (Wald=10.99, df=1, p=0.001, Nagelkerke=0.110). In the subgroup of patients who had improved at 24 months, the use of levetiracetam showed 1 negative rank, 5 positive ranks and 17 ties, while in those who did not improve there were 16 negative ranks, 5 positive ranks and 166 ties.

Table 2 shows the demographic data of the patients in this study according to Engel's classification. We did not use a p-correction to examine these multiple analyses because these univariate analyses were employed to delineate the possible relevant variables to be used as determinants of independent association with surgery outcome in the ultimate multivariate analyses. There was a marginal but significant difference in age between the Engel classes. Tukey's post-hoc test showed that patients in Engel class IV were significantly younger than those belonging to class III (p=0.011). There were no

significant differences in duration of illness and age at onset between the Engel classes. The number of pre-surgery seizures was significantly lower in patients with Engel class I than in those with Engel class II (p=0.012 by Tukey's post-hoc tests) and class IV (p=0.007), while there was a trend towards a significant difference with class III (p=0.068). There were no significant differences in number of pre-surgery seizures between class II, III and IV. Table 2 shows that the number of post-surgery seizures was significantly different between the 4 classes. This was validated using the Kruskal-Wallis test ($\chi 2$ =150.62, df=3, p<0.001). Tukey's tests showed that all pairwise and post-hoc analyses were significant, e.g. class I from class II (p=0.004), III (p<0.001) and IV (p<0.001), class II from class III (p=0.015) and class IV (p<0.001) and class III from class IV (p<0.001).

Unexpectedly only few patients were not allocated to Engel class I and therefore we were unable to perform Π^2 tests in the 4 study groups. Since the major aim of this study is to delineate the characteristics of a good versus a worse surgery outcome we compared Engel class I versus Engel class II+III+IV using Π^2 tests or Fisher's exact probability tests. There were no significant associations between Engel class I versus II+III+IV and either gender or focal epilepsy versus focal epilepsy with secondarily generalised seizures. Patients belonging to Engel classes II+III+IV suffered significantly more from extratemporal lobe epilepsy than those belonging to class I. There was no significant difference in right versus left location between Engel class I versus II+III+IV (χ^2 =0.29, df=1, p=0.591). There was a weak but significant association between Engel class classification and type of lesion, i.e. hippocampal sclerosis versus other or no lesions (χ^2 =4.94, df=1, p=0.026). A positive family history of epilepsy, dysphoric syndrome and pre-operative psychosis were significantly associated with Engel classes II+III+IV.

2. Effects of epilepsy surgery on number of seizures and intake of AEDs

Table 2 shows the number of seizures both before and after epilepsy surgery. RM design ANOVA showed that the number of seizures was significantly reduced by epilepsy surgery ($F=6.45$, $df=1/185$, $p=0.012$). The interaction pattern time X Engel class was significant ($F=10.34$, $df=3/185$, $p<0.001$), showing that epilepsy surgery reduced the number of seizures in class I, II and III, while in class IV the number of seizures further increased after surgery.

Table 3 shows the differences between post-surgery minus pre-surgery use of AEDs as binary responses. The discontinuation of anti-epileptic drugs after surgery is shown as negative ranks, the initiation of new anti-epileptic drug treatments after surgery as positive ranks, while no changes in the treatments after surgery are shown as ties. McNemar tests for paired data showed that two years after epilepsy surgery phenytoin, carbamazepine, valproic acid gabapentin, topiramate, and clobazam could be discontinued in a significant number of patients, while there were no significant changes in the number of patients treated with phenobarbital, clonazepam, or levetiracetam. The total number of AEDs was significantly lower after surgery than before surgery. We were able to discontinue one or more AEDs in 48.68% of the patients, while in 6.88% of the patients we started a new AED and in 44.44% of the patients AED intake was unchanged. RM design ANOVA showed that there was a significant time X Engel class interaction indicating that the total number of drugs was reduced in class I but not in the other classes. Table 4 shows that the dosages of all AEDs, except clonazepam were lower 24 months after surgery than before.

3. Prediction of response to epilepsy surgery

The abovementioned changes in the intake of AEDs after epilepsy surgery suggest that Engel's classification should be adjusted to reflect changes in AED status. Thus, it is clear that there is a difference between patients allocated to for example class I and whom had their AEDs discontinued / reduced and those belonging to class I but who had an increased / unchanged AED intake. Therefore, we controlled for changes in AED state in two ways: a) by adjusting statistically for effects of AED state by entering the total number of AEDs prior and after surgery into the analyses; and b) by computing a new index of surgery response based on Engel's classification and the AED state. Toward this end we computed a new score based on Engel classes and the change in AED state from baseline to post-surgery, e.g. decreased intake of drugs: rating=1, unchanged: rating=2 and increased: rating=3. Thus for class I this yields three scores, i.e. 1 (class I and reduced intake), 2 (class I and unchanged drug state) and 3 (class I but increased drug intake). Applied to all 4 classes, this method yields a severity score ranging from 1-12. There is a significant association between Engel's class classification and this newly presented severity score (Spearman's correlation: $r=0.592$, $p<0.001$).

Table 5 shows the outcome of a general linear model analysis with this new severity score as dependent variable and the variables listed in Table 2 and the drug state of the patients as predictor variables. Up to 25.2% in the variance of the severity index was explained by 5 variables ($F=12.32$, $df=5/183$, $p<0.001$): a lower severity score was associated with temporal lobe versus extratemporal lobe epilepsy and a negative family history of epilepsy; a worse outcome was predicted by an increased number of seizures before surgery, dysphoric syndrome the first 3 months after surgery and use of gabapentin. Using a threshold value > 9 for the total number of seizures before surgery showed a similar significant effect ($F=8.99$, $df=1$, $p=0.003$), suggesting that a threshold value of 9 or

more may be used as a predictor variable. Entering use of AEDs, total number of AEDs, and dosages of AEDs both before and after surgery (at 24 months) as explanatory variables showed that none of these variables, except gabapentin post-surgery, was significant in explaining the severity index and that entering these drug variables did not change the results.

We have also examined the prediction of the Engel classes using the same variables as in Table 5 but considering that the Engel classes are continuous classes or ordinal variables ranging from 1 (for class I) to 4 (for class IV). Generalized linear model analysis showed that this Engel scaling was predicted by 5 variables: the outcome was better when suffering from temporal lobe epilepsy (Wald=20.33, df=1, p<0.001) and having a negative family history (Wald=9.21, df=1, p=0.002), while the total number of pre-surgery seizures (Wald=17.03, df=1, p<0.001), dysphoric syndrome (Wald=7.91, df=1, p=0.005) and use of gabapentin (Wald=8.19, df=1, p=0.004) predicted a worse outcome.

Table 6 shows the results of an automatic stepwise logistic regression analysis with Engel's class I as dependent variable (classes III + IV as reference group) and the variables listed in Table 2 (and number of baseline epileptic seizures > 9, yes or no) as predictors. We found that 5 variables were significantly associated with Engel's class I (χ^2 =31.88, df=5, p<0.001, Nagelkerke=0.401; correctly classified cases=92.8%), namely temporal versus extratemporal lobe epilepsy, a negative family history of epilepsy, less than 9 seizures before surgery, age and the presence of dysphoric syndrome. These associations remained significant after adjusting (forced entry) for the effects of epilepsy location, type of lesion and focal epilepsy with or without secondarily generalized seizures in logistic regression analyses.

Discussion

A first major finding of this study is that there were significant differences in surgery outcome between 6 and 24 months after surgery: our success rate at 6 months (78.8%) had significantly increased (88.3%) at 24 months. We have performed post-hoc analyses to examine the characteristics of the group of patients who had improved at 24 months. We found that there was only one significant, although weak, predictor, i.e. use of levetiracetam. Thus, in a few patients the increased use of levetiracetam post-surgery may be associated with a better outcome at 24 months, whereas in most of the patients no specific characteristics were detected. Already in 1970 it was suggested that some patients may show seizures after surgery that eventually remit some months to years later, i.e. the "running down phenomenon" (4, 13). Nevertheless, our findings contradict one of the largest series of epilepsy surgery results, showing a gradual decline over time in the estimated proportion of patients who remain seizure free (13). In another study it was reported that the prevalence of Engel class I was 76.2% at 6 months, 72.3% at 2 years and 71.1% at 5 years (14). The prevalence of being completely seizure-free at 12 and 18 years after MTLE/HS surgery was 65% and 62%, respectively (15). A meta-analysis showed seizure control to decline over time especially after 2 years (16). The risk of having any recurrence was 22% during the first 24 months and increased 1.4% per year afterwards (15). Some of the long term post-surgical follow up studies supported the concept that the prognosis may improve over time, e.g. less memory decline (17). One explanation of these contradictory data is that a running down phenomenon may occur in an initially non-equilibrium period, with an undetermined duration, and that seizures may re-occur after that time point.

The high success rate of epilepsy surgery in our hospital (i.e. 88.3% at 24 months) may be explained by our inclusion criteria, which are based on clinical semiology, 24 hr EEG and MRI to identify subjects with primary epileptogenic lesions. As a consequence this cohort comprises only 2% MRI-negative epilepsy and >90% temporal lobe surgery patients. Therefore, our findings may be more difficult to readily extrapolate to more heterogeneous cohorts including high rates of non-lesional and/or extratemporal epilepsy. Nevertheless, the associations of Engel class outcome with the significant predictors (discussed in detail below) were not affected after adjusting for the effects of epilepsy type and etiology in the multivariate analyses.

A second major finding is that the efficacy of epilepsy surgery was not only reflected by the reduced number of seizures, but also by a reduced use of AEDs. We were able to discontinue one or more AEDs in 48.68% of the patients, while 13.2% of all patients were free of any AEDs 2 years after surgery. This discontinuation rate might be slightly lower than that in previous reports which showed that around 52.6% of the patients can discontinue AEDs at 2 years without seizure recurrence (18). In another study 28.1% of the patients had discontinued AED treatment 2 years after surgery and had remained seizure free, suggesting that there was no risk of seizure recurrence after discontinuation of AEDs (14). A meta-analysis showed that in patients with all types of surgery, 20% achieved long-term AED discontinuation, 31% remained on polytherapy and 41% were on monotherapy (19). In addition, we found no significant associations between AED discontinuation and seizure freedom. Other studies report that AED discontinuation may be a strong predictor for seizure recurrence in post-surgery seizure-free cases (12). Boshuisen et al. (20), in a study performed on children with intractable epilepsy, found that AED withdrawal did not affect long-term seizure outcome but may unmask incomplete surgical

success sooner, identifying children who need continuous drug treatment. One of our analysis showed that use of gabapentin was a significant predictor variable for a worse outcome. In our clinic, however, gabapentin is not the first AED choice for seizure treatment and is used in refractory seizures that failed to respond to treatment with other AEDs. This may show that use of gabapentin should not be regarded as a real explanatory variable but as a post-hoc adjustment for possible effects of the drug state.

The third major finding of this study is that a good outcome of epilepsy surgery, i.e. being allocated to class I, could be predicted by temporal versus extratemporal lobe epilepsy, less than 9 pre-surgery seizures per month, a negative familial history of epilepsy, age and absence of a dysphoric disorder. Temporal lobe epilepsy (TLE) was the most significant outcome predictor. This finding is consistent with most published papers showing that TLE, both in short term and long term monitoring period (21) and in pediatric and adult patients has a significantly better postoperative outcome than extratemporal lobe epilepsy (ETLE) (22). In pediatric patients, the seizure free rate in TLE was 71.8% versus 59.7% in ETLE, whereas in adult epilepsy the seizure free rate in TLE was 69.4% versus 45.9% in ETLE (22). In ETLE, it is more difficult to localize the epileptogenic focus to a specific cerebral region and to completely remove the epileptogenic region without impairing the eloquent cortex (23).

The second predictor, i.e. number of pre-operative seizures, shows that surgery may not be the best treatment option for patients with many refractory seizures. A high number of pre-surgery seizures might indicate multiple types of seizures, unidentified multiple lesions or severe pathology or other factors negatively modifying surgery outcome. We established that a threshold value of 9 seizures / month best predicted Engel class I membership, while another study delineated that more than 30 seizures / month best

predicted a negative outcome (1). These differences between both studies may reflect differences in sensitivity and specificity. Thus, we established that < 9 seizures per month significantly predicts Engel class I versus II+III+IV, while it is obvious that if we had used Engel class I+II+III versus IV the threshold value would be higher.

To the best of our knowledge, this is a first study showing that a positive family history for epilepsy may worsen post-surgery outcome. There is now evidence that the risk to develop epilepsy is significantly increased in the first-degree relatives of people with epilepsy of unknown cause (24). Twin studies consistently show higher concordance in monozygotic than in dizygotic pairs (25). However, the genes identified so far affect risk in a very small proportion of patients, while most epilepsies occur in the absence of a significant family history (26). In a few clinical studies on epilepsy with or without psychiatric disorders, genetic linkage is regarded to increase risk of poor clinical outcome (27, 28). Thus, a positive family history of epilepsy, occurs more frequently in TLE with postictal psychosis than in TLE alone (27). A positive family history of epilepsy has also a significant negative impact on the quality of life (28). The inverse relationship between a family history of epilepsy and Engel class outcome may be explained by mutations in specific genes that are related to a more severe outcome, including drug resistance, and distinct neuroradiological findings as has been observed in benign neonatal epilepsy or benign familial neonatal convulsions (29, 30). However, it is unlikely that single common variants could explain more than 4.4% of outcome variation in newly treated epilepsy (31). Therefore, it should be examined whether multiple common variants may underpin increased resistance to resective epilepsy surgery.

There are only few studies in adults that have examined age as a predictor of surgery outcome. In individuals aged less than 50 years, 58% were allocated to Engel class

I, while 74% of those who were more than 50 years old and 91% of those who were more than 60 years old were allocated to Engel class I (16). Srikijvilaikul et al. (27) found no differences in surgical outcome in terms of medication withdrawn between older and younger subjects (threshold value = 50 years old), but more surgical complications in the older group (32). Previous studies in children or teenage showed that early surgical treatment correlated with a better Engel class outcome (33, 34). In our study, however, the absolute differences in age were very small. Therefore, further research should delineate whether age at surgery significantly contributes to Engel class outcome.

The fifth predictor of surgery outcome is dysphoric disorder, i.e. labile and irritable mood emerging within 3 months after surgery, but most often the first 1 to 2 months. While pre-surgery psychiatric factors are identified as predictors of a worse surgery outcome, few studies have examined post-surgery psychiatric predictors. Epilepsy is accompanied by the inter-ictal dysphoric disorder, characterized by intermittent affective symptoms including labile affective symptoms, paroxysmal irritability and outbursts of aggressive behavior (35, 36). The prevalence of inter-ictal dysphoric disorder (and having no depression and dysthymia according to the MINI) is around 48.2% in epilepsy patients (36, 37). There is some evidence suggesting that inter-ictal dysphoric disorder and peri-ictal dysphoric syndrome may be separate syndromes (37). Therefore, it may be hypothesized that dysphoric disorder in the early post-operative period is in fact inter-ictal dysphoric disorder and that in those patients sub-syndromal seizure activity is present despite surgery thereby predicting future clinical seizures. Future research should delineate this symptom complex in association with surgery outcome using the 38-item Interictal Dysphoric Disorder Inventory (IDDI) (37). Emotional reactivity is a psychosocial stressor increasing circulating glucocorticoid levels causing an increased vulnerability to amygdala

kindling (38). Kindling is the process by which repeated minor stimulations (electrical or chemical) of the brain are associated with epileptogenesis and the onset of mood disturbances (39).

Limitations of this study are the shorter follow-up period (24 months) and the lower number of subjects not allocated to Engel class I as a result of the unexpected high success rate of epilepsy surgery in this cohort. As such the results should be interpreted with caution. Future research should validate the predictors delineated in our study and using the IDDI to score severity of the dysphoric syndrome.

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Conflict of interest:

The authors do not report any conflict of interest.

Contributorship.

K B. made the study design; KB, LC, ST and MM interpreted the data; KB and MM performed the statistical analyses and wrote the manuscript; LC, ST and KB collected the data.

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Data sharing statement: No additional data available.

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Table 1. Engel class classifications in 189 patients, 6 and 24 months after epilepsy surgery.

Engel classes			**24 months**		
		I	II	III	IV
6 months	I	144	3	1	1
	II	10	3	3	0
	III	0	0	2	0
	IV	13	3	2	4

The distribution of the patients in classes I-IV is significantly different between months 6 and 24 (Sign test: z = -3.17, p=0.002 negative differences = 28, positive differences = 8, ties = 153).

Table 2. Demographic data and Engel classification 24 months after surgery in 189 patients

Variables / predictors	Engel class I	Engel class II	Engel class III	Engel class IV	*F, χ^2, ψ	df	p
Age (years)	37.4 (±9.6)	38.9 (±9.0)	45.0 (±7.5)	28.2 (±8.8)	3.34	3/185	0.020
Duration illness (years)	23.0 (±10.8)	22.1 (±11.7)	29.0 (±14.7)	20.5 (±6.9)	0.89	3/185	0.444
Age at onset (years)	14.5 (±9.4)	16.8 (±6.2)	16.0 (±7.9)	7.7 (±14.5)	1.17	3/185	0.324
Gender (M / F ratio)	83 / 84	6 / 3	6 / 2	1 / 4	0.69	1	0.406
Number seizures prior to epilepsy surgery	8.5 (±13.4)	35.9 (±70.7)	26.4 (±30.3)	65.6 (±124.6)	10.35	3/185	<0.000
Number of seizures after epilepsy surgery	0.00 (±0.00)	1.71 (±1.51)	9.0 (±9.4)	91.8 (±137.8)	33.13	3/185	<0.000
Focal versus focal with secondarily generalized seizures	160 / 7	9 / 0	8 / 0	4 / 1	-0.01**	-	0.764

TLE versus ETLE**	156 / 11	7 / 2	7 / 1	1 / 4	14.36	1	<0.00
Epilepsy location					see text		
right	83	6	3	3			
left	80	3	5	1			
bilateral	3	0	0	1			
middle	1	0	0	0			
Lesion					See text		
Hippocampal sclerosis	128	7	5	0			
Tumor	28	1	2	2			
FCD	7	1	0	3			
AVM	1	0	0	0			
No lesion	3	0	1	0			
Familial history of epilepsia: yes / no	26 / 141	3 / 6	3 / 5	2 / 3	5.70	1	0.017
DD first 3 months after surgery: yes / no	18 / 149	1/ 8	2 / 6	3 / 2	4.77	1	0.029
Pre-operative psychosis: yes / no	7 / 160	2 / 7	2 / 6	0 / 5	0.19**		0.026

*F: results of analyses of variance with the 4 Engel groups as categories

*χ^2: results of analyses of contigency tables. In order to perform χ^2 tests we have combined groups and examined the differences between Engel class I versus Engel class II + III + IV. When we were unable to use χ^2 tests, we have used Fisher's exact probability test with ψ values (**).

TLE versus ETLE: temporal lobe epilepsy versus extratemporal lobe epilepsy

DD: dysphoric disorder

Table 3. Effects of epilepsy surgery on the discontinuation of anti-epileptic drugs in 189 epilepsy patients

Drug	- ranks	+ ranks	ties	McNemar or Wilcoxon test*	Discontinuation rate
Phenobarbital	7	1	181	0.070	7 / 37
Phenytoin	23	3	163	<0.001	23 / 61
Carbamazepine	25	1	163	<0.001	25 / 133
Valproic acid	16	3	170	0.004	16 / 46
Clonazepam	6	2	181	0.289	6 / 12
Gabapentin	11	2	176	0.022	11 / 20
Lamotrigine	25	4	160	<0.001	25 / 62
Topiramate	13	4	172	0.049	13 / 20
Levetiracetam	26	15	148	0.118	26 / 54
Clobazam	29	10	150	0.003	29 / 58
All drugs	92	13	84	<0.001*	-

The difference between post-surgery minus pre-surgery use of anti-epileptic drugs is shown as the discontinuation of the drugs after surgery (negative ranks), starting new treatments after surgery (positive ranks) or unchanged treatments after surgery (ties). Thus "ties" includes patients in which the specific drugs were not changed and patients that were not using this drug.
* All analyses are results of McNemar test, except * Wilcoxon test (z=-7.61)

Table 4. Effects of epilepsy surgery on the dosage of anti-epileptic drugs in 189 patients

Drug	- ranks	+ ranks	ties	Wilcoxon test	p
Phenobarbital	12	2	175	-2.684	0.007
Fenytoin	43	6	140	-4.908	<0.001
Carbamazepine	65	15	109	-6.378	<0.001
Valproic acid	27	7	155	-3.066	0.002
Clonazepam	6	3	180	-0.060	0.952
Gabapentin	15	5	169	-2.396	0.017
Lamotrigine	42	13	134	-4.273	<0.001
Topiramate	17	4	168	-3.047	0.002
Levetiracetam	41	22	126	-2.348	0.019
Clobazam	35	12	141	-3.219	<0.001

The differences between post-surgery minus pre-surgery dosages of anti-epileptic drugs is given as reduced dosages (negative ranks), increased dosages (positive ranks) or unchanged dosages (ties) after epilepsy surgery.

Table 5. Results of general linear model analysis with the Engel-derived severity score as dependent variable and the listed variables as predictor variables.

Explanatory variables	F	df	p
TLE versus ETLE	16.04	1	<0.001
No family history of epilepsy	5.19	1	0.024
Number of seizures pre-surgery	11.45	1	<0.001
Dysphoric disorder within the first three months after surgery	6.29	1	0.013
Use of gabapentin post-surgery	7.04	1	0.009

TLE versus ETLE: temporal lobe epilepsy versus extratemporal lobe epilepsy

Table 6. Results of logistic regression with Engel's class I as dependent variable and the listed variables as predictors

Predictors	Wald	df	p	Odds ratio	95 % CI, lower	95% CI, upper
TLE versus ETLE*	12.77	1	<0.001	20.52	3.91	107.60
Negative family history of epilepsia	5.24	1	0.024	5.72	1.28	25.47
Less than 9 seizures before epilepsy surgery	6.40	1	0.011	6.64	1.53	28.77
Dysphoric disorder first 3 months after surgery	4.19	1	0.041	0.19	0.041	0.93
Age	4.90	1	0.027	1.09	1.01	1.18

*TLE versus ETLE: temporal lobe epilepsy versus extratemporal lobe epilepsy

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract YES
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found YES
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported YES
Objectives	3	State specific objectives, including any prespecified hypotheses YES
Methods		
Study design	4	Present key elements of study design early in the paper YES
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection YES
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up YES
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable YES
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group YES
Bias	9	Describe any efforts to address potential sources of bias YES
Study size	10	Explain how the study size was arrived at YES
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why YES
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding YES
		(*b*) Describe any methods used to examine subgroups and interactions YES
		(*c*) Explain how missing data were addressed YES
		(*d*) If applicable, explain how loss to follow-up was addressed YES
		(*e*) Describe any sensitivity analyses N/A
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed YES
		(b) Give reasons for non-participation at each stage YES
		(c) Consider use of a flow diagram N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders YES
		(b) Indicate number of participants with missing data for each variable of interest YES
		(c) Summarise follow-up time (eg, average and total amount) YES
Outcome data	15*	Report numbers of outcome events or summary measures over time YES
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included YES
		(*b*) Report category boundaries when continuous variables were categorized YES
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period YES
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses YES

Discussion		
Key results	18	Summarise key results with reference to study objectives YES
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias YES
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence YES
Generalisability	21	Discuss the generalisability (external validity) of the study results YES
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based YES

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Clinical predictors of two-year outcome of resective epilepsy surgery in adults with refractory epilepsy: a cohort study

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Abstract: 246 words

Text: 3979 words

Abstract

Objectives: Resective epilepsy surgery is currently a standard treatment for intractable epilepsy. Seizure freedom and discontinuation of antiepileptic drugs are the ultimate goals of epilepsy treatment. This study was carried out to delineate a) possible differences in the success rate of epilepsy surgery 6 and 24 months after surgery; and b) the clinical predictors of a good response to surgery.

Setting: This is a cohort study performed at a tertiary care unit of a University hospital.

Participants: In this cohort study, 189 adults with intractable epilepsy who underwent epilepsy surgery were included. We collected clinical data at three time points, i.e. pre-operative and 6 and 24 months after surgery.

Primary and secondary outcome measures: Engel class I-IV classification was the primary outcome measure of epilepsy surgery. The authors statistically adjusted Engel class I-IV classification for post-operative changes in antiepileptic drugs and used this new classification as a secondary outcome variable.

Results: The success rate was 78.8% 6 months after surgery and increased to 88.3% 24 months after surgery. This success rate was not only reflected by the reduced number of seizures post-surgery, but also by a reduced dosage and use of antiepileptic drugs. Logistic regression analysis showed that a successful outcome of surgery is predicted by having temporal rather than extratemporal lobe epilepsy and less than 9 pre-surgery seizures per month, while a positive familial history of epilepsy, younger age and dysphoric symptoms the first three months after surgery significantly worsened the outcome of surgery. Duration of illness, age at onset, epilepsy location, type of lesions, and the presence of psychosis were not significant in predicting treatment outcome.

Conclusions: These findings have clinical relevance in that a better selection of patients based on the significant clinical predictors will increase the success rate of epilepsy surgery and treatment.

Key words: epilepsy, Engel class, surgery, predictors, dysphoric syndrome, mood disorders

Strengths and limitations of the study

- The authors analyze a large series (n=189) of consecutively admitted patients with refractory epilepsy who underwent epilepsy surgery and delineate the differences in surgical outcome between 6 and 24 months after surgery, clinical predictors of good surgical outcome (Engel class I) and the effects of withdrawal of antiepileptic drugs (AEDs).
- This is a first study that adjusts the results of epilepsy surgery outcome data for changes in AEDs. The authors propose that Engel's classification into 4 classes may not be adequate because post-surgery patients allocated to an Engel class who had their AEDs discontinued or reduced differ from those belonging to same Engel class but who had an increased or unchanged AED intake. Therefore, the authors suggest that the Engel class classification should be refined taking into account post-operative changes in AED status.
- The shorter follow-up period (24 months) is a limitation of the study. The high success rate of epilepsy surgery in this study (i.e. 88.3% at 24 months) may be explained by our strict selection criteria. This cohort comprises 2% MRI-negative epilepsy and >90% temporal lobe surgery patients and, therefore, our findings cannot be readily extrapolated to more heterogeneous cohorts.

Introduction

In most state-of-the-art epilepsy units, resective epilepsy surgery is currently the standard treatment for intractable epilepsy. Generally, the success rate, defined as a seizure free status or Engel class I, is between 62% - 71%, as compared to 14% in non-operated cases (1-2). For example, in the Epilepsy Unit of King Chulalongkorn Memorial Hospital, Bangkok, Thailand, the success rate 24 months after sugery is 66.7% as compared to 5% in cases without surgery (3). Clinical experience is that some epilepsy patients who are non-responders to surgery in the first few months after surgery become seizure free and thus responders some months later.

In order to improve the success rate to epilepsy surgery, selection criteria for surgery based on clinical and biological characteristics of responders and non-responders should be delineated. Neurological predictors include type of resection, preoperative aura, presence of postoperation spikes (2), extratemporal resection, simple partial seizure (4), long seizure duration, number of seizures per month at baseline, secondarily generalized seizures and ictal dystonia (5). It is debated whether psychiatric problems may modulate the outcome to epilepsy surgery. Some studies show that preoperative psychiatric diagnoses may predict a negative outcome to epilepsy surgery (6-10). Other studies, however, report that a history of psychiatric diagnosis is not a predictor for surgery outcome (11). It has remained elusive, however, whether clinical variables, such as duration of illness, type of epilepsy, epilepsy location and a familial history of epilepsy may predict a good outcome, and whether a combination of these and other factors may improve the prediction.

To complicate matters, discontinuation of antiepileptic drugs (AEDs) may interfere with surgery outcome. Surgery may allow to taper down or even discontinue AED intake

in some patients after epilepsy surgery. On the other hand, tapering down AEDs may cause seizure recurrence in about a third of patients (12). This indicates that when assessing epilepsy surgery outcome one has to take the AED state into account. This may also indicate that Engel's classification into 4 classes is not always adequate. For example, it is obvious that there is a difference between post-surgery patients allocated to an Engel class and who had their AEDs discontinued or reduced and those belonging to same class but who had an increased or unchanged AED intake. One approach is to adjust the Engel classes for post-operative changes in AED state.

This study was carried out to delineate a) the success rate of epilepsy surgery 6 and 24 months after surgery as assessed by means of Engel classes; and b) clinical predictors of a good treatment response while adjusting for the effects of discontinuation or reduction of AEDs on this prediction.

Patients and Methods

This is a cohort study performed at the Comprehensive Epilepsy Unit, King Chulalongkorn Memorial Hospital, Bangkok, Thailand. We consecutively included (from October 2005 until June 2008) all intractable epilepsy patients who were selected for epilepsy surgery and attended the Comprehensive Epilepsy Unit for post-operative evaluations. One hundred and eighty-nine subjects were included in this study. We collected data at three different time points, that is pre-operation, and 6 and 24 months after surgery. We collected socio-demographic data, age at onset, duration of illness, familial history of epilepsy, number of seizures per month before and 6 and 24 months after surgery, use of AEDs (type and dosage) before and 6 and 24 months after surgery, using semi-structured interviews performed by a trained master degree research psychologist.

Epilepsy-related characteristics, including epilepsy location and type of epilepsy were rated by senior neurologists using neurological, medical and neurosurgical records, 24 hour electroencephalogram (EEG) reports and brain imaging techniques, i.e. magnetic resonance imaging (MRI). The post-surgery data at 6 and 24 hours were used to make the Engel class diagnoses in class I (no disabling seizures), class II (almost free of seizures), class III (worthwhile improvement with >50% reduction in disabling seizures), and class IV (no worthwhile improvement). The psychiatric DSM-IV diagnosis psychosis (before surgery) was made by a trained master degree research psychologist and a senior psychiatrist using the International Neuropsychiatric Interview (MINI) in a Thai validated version (13). Dysphoric disorder was defined as an emotional response within the first 3 months after epilepsy surgery characterized by labile mood, crying spells, behavioral outbursts, sleep problems, concentration disorders, and / or irritability. The study was approved by the Ethics Research Committee at Chulalongkorn University, Department of Medicine, Bangkok, Thailand and all participants gave written informed consent to participate.

Statistics.

We used analyses of contingence tables (χ^2 tests) or Fisher's exact probability test to check differences in the distribution of variables among two or more study groups. Relationships between variables were assessed using Pearson's correlation coefficients. General and generalized linear model analyses were used to predict dependent variables by means of different explanatory variables. We used analyses of variance (ANOVA) in order to ascertain differences in continuous variables between two or more study groups. Multiple post-hoc differences were assessed by means of Tukey's tests. Binary logistic

regression analysis was used to define the associations between a dichotomous dependent variable and a set of independent variables. We used the logistic regression coefficients of the explanatory variables in the final equation to estimate odds ratios with confidence intervals. We used the sign test to assess the differences in the Engel classes (considered as ordinal scaled variables) 6 and 24 months after epilepsy surgery. The Sign Test is a nonparametric test statistic which can be employed to test paired samples of ordinally scaled variables and which uses only directional and not magnitude information. The effects of epilepsy surgery on the discontinuation of AEDs were analyzed using the McNemar test, a non-parametric test to analyze differences in repeated measurements of binary data. The surgery effects on the number of seizures and AED use was analyzed using factorial repeated measurement (RM) design ANOVA or the Wilcoxon signed rank test, a non-parametric test used to check differences in pairs of data. The results of parametric tests were checked using non parametric tests including Spearman's rank order correlation coefficients and the Kruskal-Wallis test. Data were analyzed using SPSS. There were no missing values in our data set. Statistical significance was set at α=0.05 (two tailed).

Results

1. Characteristics of Engel classes

Table 1 shows that there was a significant difference in Engel class distribution between the two time points. The Sign Test showed that there were significantly more negative differences than positive differences, indicating that some patients improved from month 6 to month 24. For example, 6 months after surgery 149 patients were allocated to class I, while 24 months after surgery 167 were allocated to class I. Twenty three patients

who were allocated to Engel classes II, III or IV 6 months after surgery were re-allocated to Engel class I 24 months after surgery, showing that their status had improved. We have analyzed whether any of the variables listed in Table 2 was associated with this subgroup of patients who had improved, but not one of the variables was significant. For example, there were no significant associations between improvement in Engel class classification and family history of epilepsy (χ^2=1.16, df=1, p=0.281), temporal versus extratemporal lobe epilepsy (p=0.415 by Fisher's exact probability test) and type of epilepsy (p=0.599 by Fisher's exact probability test). In order to examine possible associations between the improvement in Engel class classification and use of AEDs, we have performed RM design ANOVAs with dosage of AEDs at 6 and 24 months as time factor and improvement in Engel class I classification as factor. We found a significant time X group interaction only for levetiracetam dosage (F=5.47, df=1/187, p=0.02). Logistic regression analysis with use of AEDs (and other variables listed in Table 2) showed that only dosage of levetiracetam was a significant explanatory variable (Wald=10.99, df=1, p=0.001, Nagelkerke=0.110). In the subgroup of patients who had improved at 24 months, the use of levetiracetam showed 1 negative rank, 5 positive ranks and 17 ties, while in those who did not improve there were 16 negative ranks, 5 positive ranks and 166 ties.

Table 2 shows the demographic data of the patients in this study according to Engel's classification. We did not use a p-correction to examine these multiple analyses because these univariate analyses were employed to delineate the possible relevant variables to be used as determinants of independent association with surgery outcome in the ultimate multivariate analyses. There was a marginal but significant difference in age between the Engel classes. Tukey's post-hoc test showed that patients in Engel class IV were significantly younger than those belonging to class III (p=0.011). There were no

significant differences in duration of illness and age at onset between the Engel classes. The number of pre-surgery seizures was significantly lower in patients with Engel class I than in those with Engel class II ($p=0.012$ by Tukey's post-hoc tests) and class IV ($p=0.007$), while there was a trend towards a significant difference with class III ($p=0.068$). There were no significant differences in number of pre-surgery seizures between class II, III and IV. Table 2 shows that the number of post-surgery seizures was significantly different between the 4 classes. This was validated using the Kruskal-Wallis test ($\chi 2 =150.62$, $df=3$, $p<0.001$). Tukey's tests showed that all pairwise and post-hoc analyses were significant, e.g. class I from class II ($p=0.004$), III ($p<0.001$) and IV ($p<0.001$), class II from class III ($p=0.015$) and class IV ($p<0.001$) and class III from class IV ($p<0.001$).

Unexpectedly only few patients were not allocated to Engel class I and therefore we were unable to perform Π^2 tests in the 4 study groups. Since the major aim of this study is to delineate the characteristics of a good versus a worse surgery outcome we compared Engel class I versus Engel class II+III+IV using Π^2 tests or Fisher's exact probability tests. There were no significant associations between Engel class I versus II+III+IV and either gender or focal epilepsy versus focal epilepsy with secondarily generalised seizures. Patients belonging to Engel classes II+III+IV suffered significantly more from extratemporal lobe epilepsy than those belonging to class I. There was no significant difference in right versus left location between Engel class I versus II+III+IV ($\chi^2 =0.29$, $df=1$, $p=0.591$). There was a weak but significant association between Engel class classification and type of lesion, i.e. hippocampal sclerosis versus other or no lesions ($\chi^2 =4.94$, $df=1$, $p=0.026$). A positive family history of epilepsy, dysphoric syndrome and pre-operative psychosis were significantly associated with Engel classes II+III+IV.

2. Effects of epilepsy surgery on number of seizures and intake of AEDs

Table 2 shows the number of seizures both before and after epilepsy surgery. RM design ANOVA showed that the number of seizures was significantly reduced by epilepsy surgery ($F=6.45$, $df=1/185$, $p=0.012$). The interaction pattern time X Engel class was significant ($F=10.34$, $df=3/185$, $p<0.001$), showing that epilepsy surgery reduced the number of seizures in class I, II and III, while in class IV the number of seizures further increased after surgery.

Table 3 shows the differences between post-surgery minus pre-surgery use of AEDs as binary responses. The discontinuation of anti-epileptic drugs after surgery is shown as negative ranks, the initiation of new anti-epileptic drug treatments after surgery as positive ranks, while no changes in the treatments after surgery are shown as ties. McNemar tests for paired data showed that two years after epilepsy surgery phenytoin, carbamazepine, valproic acid gabapentin, topiramate, and clobazam could be discontinued in a significant number of patients, while there were no significant changes in the number of patients treated with phenobarbital, clonazepam, or levetiracetam. The total number of AEDs was significantly lower after surgery than before surgery. We were able to discontinue one or more AEDs in 48.68% of the patients, while in 6.88% of the patients we started a new AED and in 44.44% of the patients AED intake was unchanged. RM design ANOVA showed that there was a significant time X Engel class interaction indicating that the total number of drugs was reduced in class I but not in the other classes. Table 4 shows that the dosages of all AEDs, except clonazepam were lower 24 months after surgery than before.

3. Prediction of response to epilepsy surgery

The abovementioned changes in the intake of AEDs after epilepsy surgery suggest that Engel's classification should be adjusted to reflect changes in AED status. Thus, it is clear that there is a difference between patients allocated to for example class I and whom had their AEDs discontinued / reduced and those belonging to class I but who had an increased / unchanged AED intake. Therefore, we controlled for changes in AED state in two ways: a) by adjusting statistically for effects of AED state by entering the total number of AEDs prior and after surgery into the analyses; and b) by computing a new index of surgery response based on Engel's classification and the AED state. Toward this end we computed a new score based on Engel classes and the change in AED state from baseline to post-surgery, e.g. decreased intake of drugs: rating=1, unchanged: rating=2 and increased: rating=3. Thus for class I this yields three scores, i.e. 1 (class I and reduced intake), 2 (class I and unchanged drug state) and 3 (class I but increased drug intake). Applied to all 4 classes, this method yields a severity score ranging from 1-12. There is a significant association between Engel's class classification and this newly presented severity score (Spearman's correlation: $r=0.592$, $p<0.001$).

Table 5 shows the outcome of a general linear model analysis with this new severity score as dependent variable and the variables listed in Table 2 and the drug state of the patients as predictor variables. Up to 25.2% in the variance of the severity index was explained by 5 variables ($F=12.32$, $df=5/183$, $p<0.001$): a lower severity score was associated with temporal lobe versus extratemporal lobe epilepsy and a negative family history of epilepsy; a worse outcome was predicted by an increased number of seizures before surgery, dysphoric syndrome the first 3 months after surgery and use of gabapentin. Using a threshold value > 9 for the total number of seizures before surgery showed a similar significant effect ($F=8.99$, $df=1$, $p=0.003$), suggesting that a threshold value of 9 or

more may be used as a predictor variable. Entering use of AEDs, total number of AEDs, and dosages of AEDs both before and after surgery (at 24 months) as explanatory variables showed that none of these variables, except gabapentin post-surgery, was significant in explaining the severity index and that entering these drug variables did not change the results. We have also examined the prediction of the Engel classes using the same variables as in Table 5 but considering that the Engel classes are continuous classes or ordinal variables ranging from 1 (for class I) to 4 (for class IV). Generalized linear model analysis showed that this Engel scaling was predicted by 5 variables: the outcome was better when suffering from temporal lobe epilepsy (Wald=20.33, df=1, p<0.001) and having a negative family history (Wald=9.21, df=1, p=0.002), while the total number of pre-surgery seizures (Wald=17.03, df=1, p<0.001), dysphoric syndrome (Wald=7.91, df=1, p=0.005) and use of gabapentin (Wald=8.19, df=1, p=0.004) predicted a worse outcome.

Table 6 shows the results of an automatic stepwise logistic regression analysis with Engel's class I as dependent variable (classes III + IV as reference group) and the variables listed in Table 2 (and number of baseline epileptic seizures > 9, yes or no) as predictors. We found that 5 variables were significantly associated with Engel's class I (χ^2 =31.88, df=5, p<0.001, Nagelkerke=0.401; correctly classified cases=92.8%), namely temporal versus extratemporal lobe epilepsy, a negative family history of epilepsy, less than 9 seizures before surgery, age and the presence of dysphoric syndrome. These associations remained significant after adjusting (forced entry) for the effects of epilepsy location, type of lesion and focal epilepsy with or without secondarily generalized seizures in logistic regression analyses.

Discussion

A first major finding of this study is that there were significant differences in surgery outcome between 6 and 24 months after surgery: our success rate at 6 months (78.8%) had significantly increased (88.3%) at 24 months. We have performed post-hoc analyses to examine the characteristics of the group of patients who had improved at 24 months. We found that there was only one significant, although weak, predictor, i.e. use of levetiracetam. Thus, in a few patients the increased use of levetiracetam post-surgery may be associated with a better outcome at 24 months, whereas in most of the patients no specific characteristics were detected. Already in 1970 it was suggested that some patients may show seizures after surgery that eventually remit some months to years later, i.e. the "running down phenomenon" (4, 13). Nevertheless, our findings contradict one of the largest series of epilepsy surgery results, showing a gradual decline over time in the estimated proportion of patients who remain seizure free (13). In another study it was reported that the prevalence of Engel class I was 76.2% at 6 months, 72.3% at 2 years and 71.1% at 5 years (14). The prevalence of being completely seizure-free at 12 and 18 years after MTLE/HS surgery was 65% and 62%, respectively (15). A meta-analysis showed seizure control to decline over time especially after 2 years (16). The risk of having any recurrence was 22% during the first 24 months and increased 1.4% per year afterwards (15). Some of the long term post-surgical follow up studies supported the concept that the prognosis may improve over time, e.g. less memory decline (17). One explanation of these contradictory data is that a running down phenomenon may occur in an initially non-equilibrium period, with an undetermined duration, and that seizures may re-occur after that time point.

The high success rate of epilepsy surgery in our hospital (i.e. 88.3% at 24 months) may be explained by our inclusion criteria, which are based on clinical semiology, 24 hr

EEG and MRI to identify subjects with primary epileptogenic lesions. As a consequence this cohort comprises only 2% MRI-negative epilepsy and >90% temporal lobe surgery patients. Therefore, our findings may be more difficult to readily extrapolate to more heterogeneous cohorts including high rates of non-lesional and/or extratemporal epilepsy. Nevertheless, the associations of Engel class outcome with the significant predictors (discussed in detail below) were not affected after adjusting for the effects of epilepsy type and etiology in the multivariate analyses.

A second major finding is that the efficacy of epilepsy surgery was not only reflected by the reduced number of seizures, but also by a reduced use of AEDs. We were able to discontinue one or more AEDs in 48.68% of the patients, while 13.2% of all patients were free of any AEDs 2 years after surgery. This discontinuation rate might be slightly lower than that in previous reports which showed that around 52.6% of the patients can discontinue AEDs at 2 years without seizure recurrence (18). In another study 28.1% of the patients had discontinued AED treatment 2 years after surgery and had remained seizure free, suggesting that there was no risk of seizure recurrence after discontinuation of AEDs (14). A meta-analysis showed that in patients with all types of surgery, 20% achieved long-term AED discontinuation, 31% remained on polytherapy and 41% were on monotherapy (19). In addition, we found no significant associations between AED discontinuation and seizure freedom. Other studies report that AED discontinuation may be a strong predictor for seizure recurrence in post-surgery seizure-free cases (12). Boshuisen et al. (20), in a study performed on children with intractable epilepsy, found that AED withdrawal did not affect long-term seizure outcome but may unmask incomplete surgical success sooner, identifying children who need continuous drug treatment. One of our analysis showed that use of gabapentin was a significant predictor variable for a worse

outcome. In our clinic, however, gabapentin is not the first AED choice for seizure treatment and is used in refractory seizures that failed to respond to treatment with other AEDs. This may show that use of gabapentin should not be regarded as a real explanatory variable but as a post-hoc adjustment for possible effects of the drug state.

The third major finding of this study is that a good outcome of epilepsy surgery, i.e. being allocated to class I, could be predicted by temporal versus extratemporal lobe epilepsy, less than 9 pre-surgery seizures per month, a negative familial history of epilepsy, age and absence of a dysphoric disorder. Temporal lobe epilepsy (TLE) was the most significant outcome predictor. This finding is consistent with most published papers showing that TLE, both in short term and long term monitoring period (21) and in pediatric and adult patients has a significantly better postoperative outcome than extratemporal lobe epilepsy (ETLE) (22). In pediatric patients, the seizure free rate in TLE was 71.8% versus 59.7% in ETLE, whereas in adult epilepsy the seizure free rate in TLE was 69.4% versus 45.9% in ETLE (22). In ETLE, it is more difficult to localize the epileptogenic focus to a specific cerebral region and to completely remove the epileptogenic region without impairing the eloquent cortex (23).

The second predictor, i.e. number of pre-operative seizures, shows that surgery may not be the best treatment option for patients with many refractory seizures. A high number of pre-surgery seizures might indicate multiple types of seizures, unidentified multiple lesions or severe pathology or other factors negatively modifying surgery outcome. We established that a threshold value of 9 seizures / month best predicted Engel class I membership, while another study delineated that more than 30 seizures / month best predicted a negative outcome (1). These differences between both studies may reflect differences in sensitivity and specificity. Thus, we established that < 9 seizures per month

significantly predicts Engel class I versus II+III+IV, while it is obvious that if we had used Engel class I+II+III versus IV the threshold value would be higher.

To the best of our knowledge, this is a first study showing that a positive family history for epilepsy may worsen post-surgery outcome. There is now evidence that the risk to develop epilepsy is significantly increased in the first-degree relatives of people with epilepsy of unknown cause (24). Twin studies consistently show higher concordance in monozygotic than in dizygotic pairs (25). However, the genes identified so far affect risk in a very small proportion of patients, while most epilepsies occur in the absence of a significant family history (26). In a few clinical studies on epilepsy with or without psychiatric disorders, genetic linkage is regarded to increase risk of poor clinical outcome (27, 28). Thus, a positive family history of epilepsy, occurs more frequently in TLE with postictal psychosis than in TLE alone (27). A positive family history of epilepsy has also a significant negative impact on the quality of life (28). The inverse relationship between a family history of epilepsy and Engel class outcome may be explained by mutations in specific genes that are related to a more severe outcome, including drug resistance, and distinct neuroradiological findings as has been observed in benign neonatal epilepsy or benign familial neonatal convulsions (29, 30). However, it is unlikely that single common variants could explain more than 4.4% of outcome variation in newly treated epilepsy (31). Therefore, it should be examined whether multiple common variants may underpin increased resistance to resective epilepsy surgery.

There are only few studies in adults that have examined age as a predictor of surgery outcome. In individuals aged less than 50 years, 58% were allocated to Engel class I, while 74% of those who were more than 50 years old and 91% of those who were more than 60 years old were allocated to Engel class I (16). Srikijvilaikul et al. (27) found no

differences in surgical outcome in terms of medication withdrawn between older and younger subjects (threshold value = 50 years old), but more surgical complications in the older group (32). Previous studies in children or teenage showed that early surgical treatment correlated with a better Engel class outcome (33, 34). In our study, however, the absolute differences in age were very small. Therefore, further research should delineate whether age at surgery significantly contributes to Engel class outcome.

The fifth predictor of surgery outcome is dysphoric disorder, i.e. labile and irritable mood emerging within 3 months after surgery, but most often the first 1 to 2 months. While pre-surgery psychiatric factors are identified as predictors of a worse surgery outcome, few studies have examined post-surgery psychiatric predictors. Epilepsy is accompanied by the inter-ictal dysphoric disorder, characterized by intermittent affective symptoms including labile affective symptoms, paroxysmal irritability and outbursts of aggressive behavior (35, 36). The prevalence of inter-ictal dysphoric disorder (and having no depression and dysthymia according to the MINI) is around 48.2% in epilepsy patients (36, 37). There is some evidence suggesting that inter-ictal dysphoric disorder and peri-ictal dysphoric syndrome may be separate syndromes (37). Therefore, it may be hypothesized that dysphoric disorder in the early post-operative period is in fact inter-ictal dysphoric disorder and that in those patients sub-syndromal seizure activity is present despite surgery thereby predicting future clinical seizures. Future research should delineate this symptom complex in association with surgery outcome using the 38-item Interictal Dysphoric Disorder Inventory (IDDI) (37). Emotional reactivity is a psychosocial stressor increasing circulating glucocorticoid levels causing an increased vulnerability to amygdala kindling (38). Kindling is the process by which repeated minor stimulations (electrical or

chemical) of the brain are associated with epileptogenesis and the onset of mood disturbances (39).

Limitations of this study are the shorter follow-up period (24 months) and the lower number of subjects not allocated to Engel class I as a result of the unexpected high success rate of epilepsy surgery in this cohort. As such the results should be interpreted with caution. Future research should validate the predictors delineated in our study and using the IDDI to score severity of the dysphoric syndrome.

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Conflict of interest:

The authors do not report any conflict of interest.

Contributorship.

K B. made the study design; KB, LC, ST and MM interpreted the data; KB and MM performed the statistical analyses and wrote the manuscript; LC, ST and KB collected the data.

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Table 1. Engel class classifications in 189 patients, 6 and 24 months after epilepsy surgery.

Engel classes			**24 months**		
		I	II	III	IV
6 months	I	144	3	1	1
	II	10	3	3	0
	III	0	0	2	0
	IV	13	3	2	4

The distribution of the patients in classes I-IV is significantly different between months 6 and 24 (Sign test: z = -3.17, p=0.002 negative differences = 28, positive differences = 8, ties = 153).

Table 2. Demographic data and Engel classification 24 months after surgery in 189 patients

Variables / predictors	Engel class I	Engel class II	Engel class III	Engel class IV	*F, χ^2, ψ	df	p
Age (years)	37.4 (±9.6)	38.9 (±9.0)	45.0 (±7.5)	28.2 (±8.8)	3.34	3/185	0.020
Duration illness (years)	23.0 (±10.8)	22.1 (±11.7)	29.0 (±14.7)	20.5 (±6.9)	0.89	3/185	0.444
Age at onset (years)	14.5 (±9.4)	16.8 (±6.2)	16.0 (±7.9)	7.7 (±14.5)	1.17	3/185	0.324
Gender (M / F ratio)	83 / 84	6 / 3	6 / 2	1 / 4	0.69	1	0.406
Number seizures prior to epilepsy surgery	8.5 (±13.4)	35.9 (±70.7)	26.4 (±30.3)	65.6 (±124.6)	10.35	3/185	<0.000
Number of seizures after epilepsy surgery	0.00 (±0.00)	1.71 (±1.51)	9.0 (±9.4)	91.8 (±137.8)	33.13	3/185	<0.000
Focal versus focal with secondarily generalized seizures	160 / 7	9 / 0	8 / 0	4 / 1	-0.01**	-	0.764

TLE versus ETLE**	156 / 11	7 / 2	7 / 1	1 / 4	14.36	1	<0.00
Epilepsy location					see text		
right	83	6	3	3			
left	80	3	5	1			
bilateral	3	0	0	1			
middle	1	0	0	0			
Lesion					See text		
Hippocampal sclerosis	128	7	5	0			
Tumor	28	1	2	2			
FCD	7	1	0	3			
AVM	1	0	0	0			
No lesion	3	0	1	0			
Familial history of epilepsia: yes / no	26 / 141	3 / 6	3 / 5	2 / 3	5.70	1	0.017
DD first 3 months after surgery: yes / no	18 / 149	1/ 8	2 / 6	3 / 2	4.77	1	0.029
Pre-operative psychosis: yes / no	7 / 160	2 / 7	2 / 6	0 / 5	0.19**		0.026

*F: results of analyses of variance with the 4 Engel groups as categories

*χ^2: results of analyses of contigency tables. In order to perform χ^2 tests we have combined groups and examined the differences between Engel class I versus Engel class II + III + IV. When we were unable to use χ^2 tests, we have used Fisher's exact probability test with ψ values (**).

TLE versus ETLE: temporal lobe epilepsy versus extratemporal lobe epilepsy

DD: dysphoric disorder

Table 3. Effects of epilepsy surgery on the discontinuation of anti-epileptic drugs in 189 epilepsy patients

Drug	- ranks	+ ranks	ties	McNemar or Wilcoxon test*	Discontinuation rate
Phenobarbital	7	1	181	0.070	7 / 37
Phenytoin	23	3	163	<0.001	23 / 61
Carbamazepine	25	1	163	<0.001	25 / 133
Valproic acid	16	3	170	0.004	16 / 46
Clonazepam	6	2	181	0.289	6 / 12
Gabapentin	11	2	176	0.022	11 / 20
Lamotrigine	25	4	160	<0.001	25 / 62
Topiramate	13	4	172	0.049	13 / 20
Levetiracetam	26	15	148	0.118	26 / 54
Clobazam	29	10	150	0.003	29 / 58
All drugs	92	13	84	<0.001*	-

The difference between post-surgery minus pre-surgery use of anti-epileptic drugs is shown as the discontinuation of the drugs after surgery (negative ranks), starting new treatments after surgery (positive ranks) or unchanged treatments after surgery (ties). Thus "ties" includes patients in which the specific drugs were not changed and patients that were not using this drug.
* All analyses are results of McNemar test, except * Wilcoxon test (z=-7.61)

Table 4. Effects of epilepsy surgery on the dosage of anti-epileptic drugs in 189 patients

Drug	- ranks	+ ranks	ties	Wilcoxon test	p
Phenobarbital	12	2	175	-2.684	0.007
Fenytoin	43	6	140	-4.908	<0.001
Carbamazepine	65	15	109	-6.378	<0.001
Valproic acid	27	7	155	-3.066	0.002
Clonazepam	6	3	180	-0.060	0.952
Gabapentin	15	5	169	-2.396	0.017
Lamotrigine	42	13	134	-4.273	<0.001
Topiramate	17	4	168	-3.047	0.002
Levetiracetam	41	22	126	-2.348	0.019
Clobazam	35	12	141	-3.219	<0.001

The differences between post-surgery minus pre-surgery dosages of anti-epileptic drugs is given as reduced dosages (negative ranks), increased dosages (positive ranks) or unchanged dosages (ties) after epilepsy surgery.

Table 5. Results of general linear model analysis with the Engel-derived severity score as dependent variable and the listed variables as predictor variables.

Explanatory variables	F	df	p
TLE versus ETLE	16.04	1	<0.001
No family history of epilepsy	5.19	1	0.024
Number of seizures pre-surgery	11.45	1	<0.001
Dysphoric disorder within the first three months after surgery	6.29	1	0.013
Use of gabapentin post-surgery	7.04	1	0.009

TLE versus ETLE: temporal lobe epilepsy versus extratemporal lobe epilepsy

Table 6. Results of logistic regression with Engel's class I as dependent variable and the listed variables as predictors

Predictors	Wald	df	p	Odds ratio	95 % CI, lower	95% CI, upper
TLE versus ETLE*	12.77	1	<0.001	20.52	3.91	107.60
Negative family history of epilepsia	5.24	1	0.024	5.72	1.28	25.47
Less than 9 seizures before epilepsy surgery	6.40	1	0.011	6.64	1.53	28.77
Dysphoric disorder first 3 months after surgery	4.19	1	0.041	0.19	0.041	0.93
Age	4.90	1	0.027	1.09	1.01	1.18

*TLE versus ETLE: temporal lobe epilepsy versus extratemporal lobe epilepsy