Seizure: European Journal of Epilepsy 64 (2019) 23–28

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Substitution has better efficacy than add-on therapy for patients with focal epilepsy after their first antiepileptic drug treatments fail

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ARTICLE INFO

Keywords:
Epilepsy
Antiepileptic drugs
Substitution
Add-on
Outcomes

ABSTRACT

Purpose: This study is to compare the efficacy of substitution with add-on therapy in patients with focal epilepsy, whose first monotherapy has failed after receiving usual treatments.

Methods: This is a prospective, long-term, non-randomized observational cohort study. Data were collected from Wenzhou Epilepsy Follow Up Registry Database. Focal epilepsy patients from January 2003 to June 2015, whose first monotherapy had failed, were registered. The total observation period was three years. The major outcome measure was seizure remission rate. The secondary outcome measures included retention rates and incidences of intolerable adverse events.

Results: A total of 596 patients were included, among them 209 received substitution therapy, and 387 received add-on therapy. Seizure remission rates were 56.5% by substitution therapy and 39.0% by add-on therapy, respectively ($p = 0.025$). Retention rate was 49.3% by substitution therapy, and 36.2% by add-on therapy ($p = 0.031$). Incidence of intolerable adverse events for substitution and add-on was 4.8% and 7.2%, respectively ($p = 0.243$). There were 457 patients who failed to the first monotherapy due to lack of efficacy. In these patients, seizure remission rates of substitution and add-on were 51.0% and 38.1%, respectively ($p = 0.171$). Retention rates were 48.1% and 36.0%, respectively ($p = 0.136$). And, incidences of intolerable adverse events were 2.9% and 6.8%, respectively ($p = 0.137$).

Conclusion: The seizure remission rate and retention rate of substitution therapy are better than those of add-on therapy for focal epilepsy patients whose first monotherapy fails.

1. Introduction

Monotherapy is generally recognized as the first-line treatment option for patients with newly diagnosed epilepsy [1,2]. After monotherapy, 70–80% patients will be seizure-free and 60–70% can stop receiving treatment through 2–5 years of standard rational first monotherapy [3–5]. While, there are still 30–40% patients who cannot get seizure free by first monotherapy due to inadequate control, intolerable side effect, and some other reasons [6]. Moreover, the chance of seizure free will distinctly decline after failure of monotherapy. In addition, studies by Brodie et al [3] and Schiller et al [4] showed that more than 10% patients could get seizure-free upon receiving the second antiepileptic drug (AED) [2]. Thus, the strategy after failure of the first AED is also important.

It is reported that monotherapy has few adverse effects and sometimes has better seizure control [7–11]. Monotherapy have many advantages, such as no drug interactions, easy evaluation of efficacy and adverse effect, simple strategy, and good compliance. New AEDs have been developed and the safety of medication has been largely improved through the change of pharmacokinetics and mechanism of drug action. Several researchers have discussed the concept of 'rational polytherapy'. They suggest that rational polytherapy may be better than monotherapy or irrational polytherapy [5,12,13] and adding of a second drug may increase the chance of seizure-free [14].

Both of monotherapy and combination therapy have advantages. However, the efficacy comparison between substitution and add-on therapy for patients with newly diagnosed focal epilepsy, whose first AED failed, has not been done so far. In order to resolve this problem, we performed a prospective, long-term, non-randomized observational cohort study.

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https://doi.org/10.1016/j.seizure.2018.11.018
Received 18 July 2018; Received in revised form 27 November 2018; Accepted 29 November 2018

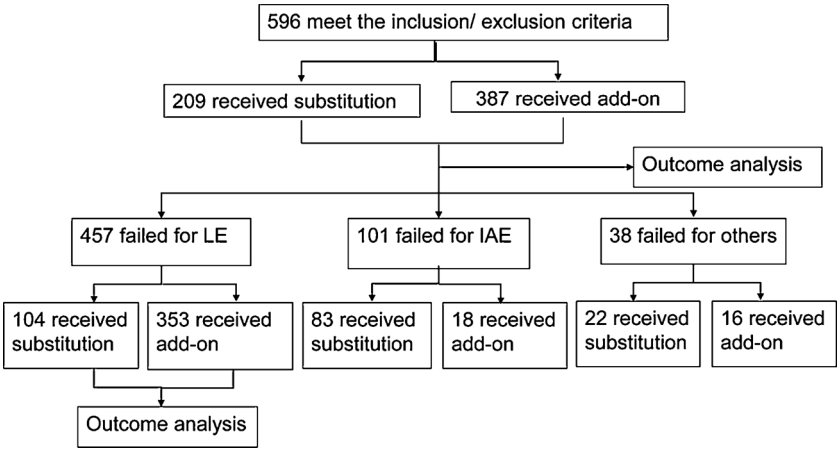

Fig. 1. The study flow chart. LE, lack of efficacy; IAE, intolerable adverse event.

2. Materials and methods

2.1. Study design

We conducted a prospective, observational, long-term, non-randomized cohort study. Patients with focal epilepsy, who received first AED monotherapy but failed, were enrolled. Patients were further grouped based on the failure reasons of first AED monotherapy, including lack of efficacy, adverse effects, others (such as pregnancy, poor economic conditions, non-compliance). Effectiveness comparison was performed between patients receiving substitution and add-on therapy, all of their treatments failed due to lack of efficacy.

2.2. Patients

The patient data were obtained from Wenzhou Epilepsy Follow Up Registry Database (WEFURD) during January 2003 to June 2015. WEFURD was established by epilepsy team of Wenzhou Medical University in January 2003. It was also registered in the World Health Organization (WHO) Registry Network (registration number: ChiCTR-OCH-14004616). Informed consents were obtained from every patient and the study was approved by the ethics review board of the First Affiliated Hospital of Wenzhou Medical University.

Patients meeting the following criteria were included: (i)diagnosis of symptomatic or cryptogenic focal epilepsy according to the classification of epilepsy and epileptic syndromes by the International League Against Epilepsy in 1981 [15] and 1989 [16]; (ii) at least two unprovoked seizures in the preceding year; (iii) unsuccessful treatment with a suitable first AED monotherapy at adequate dosage [3].

Patients fitting the following criteria were excluded: (i) exposure to combination therapy;(ii) poor compliances (discontinuation of AEDs exceeding two weeks, the cumulative total discontinuation time exceeding 20% of the total observation period, AED being not taken in accordance with the prescribed dosage, or the dosage being always below the initial target dose); (iii) less than two follow-up visits after medication; (iv) idiopathic focal epilepsy patients with childhood or adolescent onset; (v) patients with idiopathic or genetic epilepsy; (vi) progressive epileptogenic condition; (vii) regular use of benzodiazepine drugs; or (viii) severe liver or kidney diseases.

2.3. Outcome measures

The major point was seizure remission rate. Seizure remission is defined as patient being free from seizures at least three times for the longest pre-intervention interseizure interval (based on seizures occurring within the past 12 months) or 12 months, whichever is longer [17]. We calculated the time from the initial target doses (ITDs) to the start point of seizure remission in a 3-year follow-up period. The daily doses that specialists planned to titrate to and maintain for at least for one visit (4 weeks) were defined as ITDs. The secondary points were retention rate and incidence of adverse effects. Retention rate was calculated from the time of ITDs to treatment failure. Discontinuation of the original monotherapy, addition or replacement by another AED, receiving surgery, and death caused by seizures were regarded as treatment failure. Incidence of adverse effects and intolerable adverse effects were both analyzed.

2.4. Statistical analysis

Descriptive statistics were used to demonstrate baseline characteristics of the patients receiving the two different treatments. To calculate the seizure remission rates and retention rates, Kaplan-Meier survival analysis was used. The Cox proportional hazard regression model was used to adjust confounding factors. Chi-square test was used to compare the incidences of adverse effects. To exclude the influence of confounding factors, the study used significance level of 0.1, and the others used level of 0.05. Data was analyzed by SPSS 22.0 for Windows.

3. Results

3.1. Effectiveness comparison between the substitution and add-on therapy in patients after their first monotherapy failed

3.1.1. Characteristics and demographics of 596 patients at baseline

The study flow chart is shown in Fig. 1. A total of 596 patients were enrolled in this study. After failure of the first AED, 209 of these patients received substitution therapy, but the another 387 received add-on therapy. The second strategies were selected according to reasons for failure of first treatment (Fig. 1). Table 1 showed the baseline demographic and clinical characteristics of patients. Age (range 9–82), sex, disease duration, age of initial drug use, history of taking AED irregularly, seizures with the past 1 year, the longest preintervention interseizure interval, epilepsy syndrome, imagining (CT or MRI result), VEEG or EEG finding, and, prescribed daily dose (PDD)/defined daily dose (DDD) ratios were all considered as confounding factors. There were significant differences in demographics between the substitution and add-on groups.

3.1.2. Seizure remission rate and retention rate of 596 patients

Seizure remission rate of the 596 patients was analyzed. As shown in Fig. 2A, seizure remission rates of 3 years were 56.5% and 39.0%, respectively, for substitution and add-on ($p < 0.001$). The Cox proportional hazard model showed that the confounding biases generated in comparing seizure remission rates were given as follows: disease

Table 1
Baseline demographic and clinical characteristics of the patients.

Variables	Substitution	Add-on	P value
Patients	209	387	
Sex			0.445
Male (%)	99 (47.4)	196 (50.6)	
Female (%)	110 (52.6)	191 (49.4)	
Age (years), Mean	37.5	37.2	0.821
Age of seizure onset (year) (%)			0.111
< 10	13 (6.2)	46 (11.9)	
10-15	38 (18.2)	79 (20.4)	
16-39	130 (62.2)	213 (55.0)	
≥40	28 (13.4)	49 (12.7)	
Duration (months)	67.0	87.8	0.025
Age of initial drug use (years) (%)			0.000
< 10	13 (6.2)	6 (1.6)	
10-15	38 (18.2)	28 (7.2)	
16-39	130 (62.2)	267 (69.0)	
≥40	28 (13.4)	86 (22.2)	
History of taking AED irregularly	156 (74.6)	245 (63.3)	0.005
Seizures within the past 1 year			0.000
≤20	131 (62.7)	178 (46.0)	
>20	78 (37.3)	209 (54.0)	
The longest preintervention interseizure interval (months) (%)			0.000
≤4	153 (73.2)	335 (86.6)	
>4	56 (26.8)	52 (13.4)	
Antecedents[a]	78 (37.3)	140 (36.2)	0.782
Seizure types			0.095
SPS or CPS only	22 (10.5)	60 (15.5)	
sGTCS	187 (89.5)	328 (84.5)	
Epilepsy syndromes			0.196
Symptomatic	110 (52.6)	225 (58.1)	
Cryptogenic	99 (47.4)	162 (41.9)	
Imagining (CT or MRI result)[a] (%)			0.108
Abnormal	79 (37.8)	175 (45.2)	
Normal	104 (49.8)	158 (40.8)	
Loss or not done	26 (12.4)	54 (14.0)	
VEEG or EEG findings (%)			0.317
Abnormal	174 (83.3)	314 (81.1)	
Normal	22 (10.5)	42 (10.6)	
Loss or not done	13 (6.2)	13 (8.3)	
PDD/DDD ratio[b]			0.000
< 0.5	33 (15.8)	2 (0.5)	
0.5-1.5	169 (80.9)	256 (66.1)	
> 1.5	9 (4.3)	128 (33.4)	

[a] Antecedents included family history, cerebral trauma or infection, cerebrovascular disease, metabolic poisoning encephalopathy infantile febrile convulsion, premature birth.

[b] AED loads were calculated as the sum of prescribed daily dose (PDD)/defined daily dose (DDD) ratios for each coprescribed AED [17,18].

duration (HR 0.997 [95%CI: 0.996–0.999], p = 0.001), seizure frequency one year before medication (HR 0.587 [0.458–0.752], p = 0.000), and the maximal dose (PDD/DDD ratio) (HR1 0.831 [1.074–3.120], p = 0.026). Unbalanced factors, including age of initial drug use, history of taking AED irregularly, and the longest preintervention interseizure interval, were adjusted. After adjusting, the results showed that substitution resulted in better remission rate than add-on therapy (p = 0.025) (Fig. 2B).

Retention rate of the 596 patients was analyzed. As shown in Fig. 2C, retention rate of 3 years for substitution was 49.3%, but 36.2% for add-on (p = 0.001). The confounding biases were described as following: sex (HR 1.377 [1.116–1.699], p = 0.003), disease duration (HR 1.002, [1.001–1.003], p = 0.001), history of taking AED irregularly (HR 1.294 [1.1044–1.605], p = 0.019), seizure frequency (HR 1.796 [1.454–2.220], p = 0.000), and seizure types (HR 0.736 [0.562–0.964], p = 0.026). The results after adjusting confounding bias using Cox regression model showed that substitution therapy led to better retention rate than add-on (p = 0.031) (Fig. 2D). As to the rates of total adverse effects, the percentages were 43.1% (with 90 adverse effects) for substitution therapy and 32.8% (with 127 adverse effects) for add-on therapy (p = 0.013). The percentages of intolerable adverse events were 4.8% (10) for substitution therapy and 7.2% (28) for add-on therapy (p = 0.243).

3.2. Baseline features, seizure remission rate, and retention rate for substitution and add-on among 457 patients, whose first monotherapy failed due to lack of efficacy

There were 457 patients whose first monotherapy failed due to lack of efficacy. Baseline demographic and clinical characteristics were compared among the 457 patients. It was found that the confounding factors include disease duration, age of initial drug use, history of taking AED irregularly, seizures with the past 1 year, the longest preintervention interseizure interval, and PDD/DDD ratio.

Among the 457 patients, it was investigated that seizure remission rate is 51.0% for those receiving substitution and 38.1% for those receiving add-on therapy. The retention rate was 48.1% for those receiving substitution and 36.0% for those receiving add-on therapy among the 457 patients. For seizure remission rate and retention rate, no significant differences (p = 0.171 and 0.136) were found between patients who received substitution and those who received add-on therapy (Fig. 3).Incidences of the total adverse events and intolerable adverse events in the 457 patients were 42.3% (44) and 32.9% (116) (p = 0.076) for those receiving substitution therapy, and, 2.9% (3) and 6.8% (24) (p = 0.137) for those receiving add-on therapy.

3.3. Other adverse effects

The percentage of failure due to adverse effects of the first drug was 16.9%, and that of the second drug was 6.4%. Patients whose treatment failed due to intolerable adverse effects had both higher incidences of the total adverse events and intolerable adverse events than those whose treatment failed not due to intolerable adverse effects. The number was 47.5% (48) for substitution and 33.9% (168) for add-on therapy, p = 0.010, and 11.7% (10) for substitution and 5.9% (29) for add-on therapy, p = 0.035, respectively.

In addition, this study summarized the incidences of adverse effects in different treatment periods. The incidences of adverse effects were 29.5%, 39.6%, and 30.9%, respectively, in early stage (0–1 month), mid-stage (2–6 months), and end-stage (7–36 months) of treatment. Adverse effects on the neuropsychiatric system were the most common one occurring in every stage. The common symptoms included dizziness, drowsiness, and hypomnesis. Equivalently, 113 patients had neuropsychiatric system adverse effects, accounting for 52.1% of the total 217. Some other symptoms, such as rash, gastrointestinal reaction, and hepatic function damage, were also observed.

4. Discussion

Our study showed that for focal epilepsy patients, substitution therapy has better seizure remission rate and retention rate than add-on therapy after their first AED fails. This conclusion may be kind of different from previous studies. For example, Beghi et al [6] carried out a randomized controlled trial (RCT) in 2003, in which 157 patients were enrolled, including 76 receiving substitution and 81 receiving add-on therapy. The retention rates of one year were 55% and 65% for the two therapies, respectively, with insignificant differences. Similarly, the seizure-free rates were 14% and 16% for the two therapies, respectively, no significant differences as well. Semah et al [13] reached the same conclusion in a RCT of 264 patients with six months observation period. Some other researches [19,20] showed no statistical significances between alternative monotherapy and early add-on therapy.

RCT has limitations as followings. Firstly, the observation time is short and the sample size is usually insufficient. Secondly, the reduction percentage of seizure frequency is used rather than seizure freedom. Thirdly, the drug dosage, efficacy, and safety profiles of enrolled

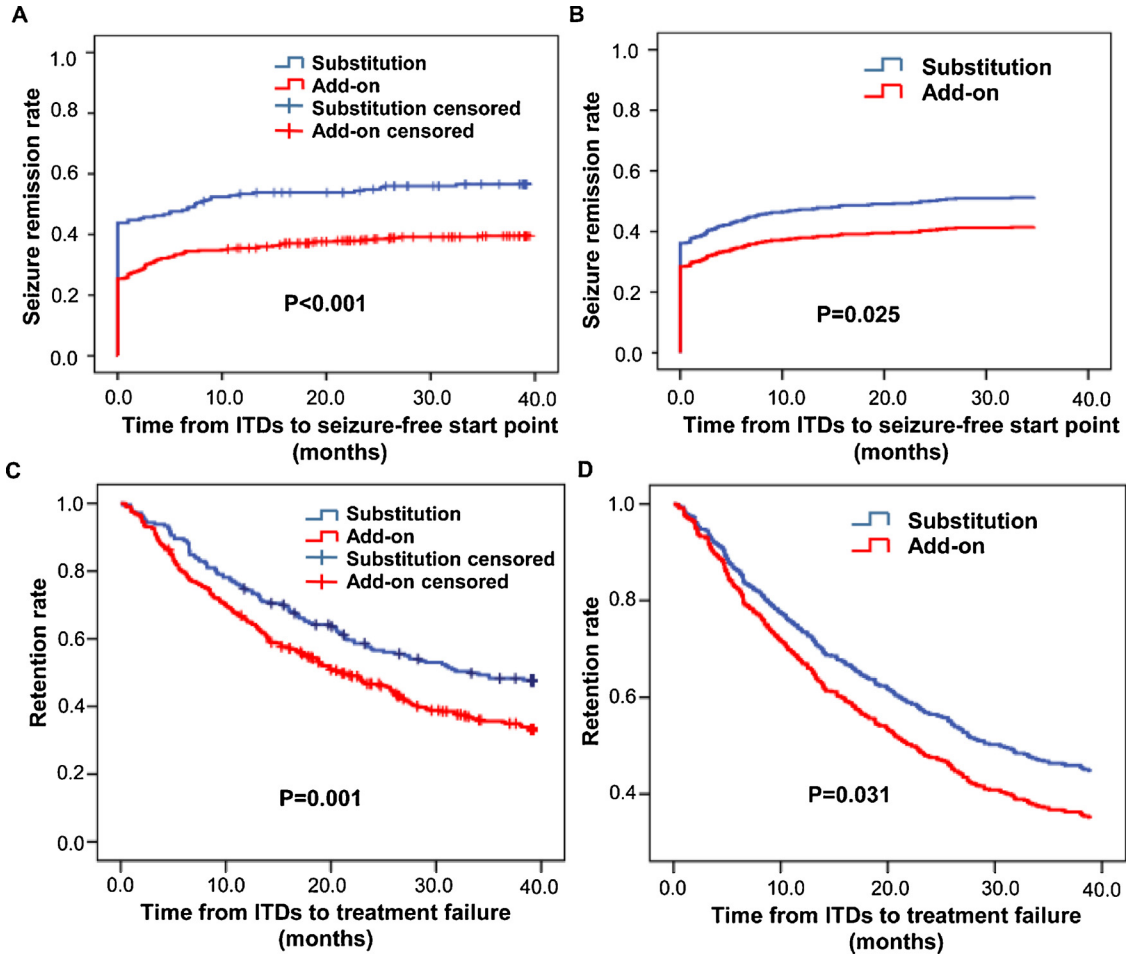

Fig. 2. Seizure remission rate and retention rate of 596 patients. (A) Seizure remission rate of 3 years for substitution and add-on therapy calculated by Kaplan-Meier. (B) Seizure remission rate of 3 years for substitution and add-on therapy adjusted by Cox regression model. (C) Retention rate of 3 years for substitution and add-on calculated by Kaplan-Meier. (D) Retention rate of 3 years for substitution and add-on adjusted by Cox regression model.

patients are different from those of clinical practice. RCT has good internal consistency, but lacks external application suitability. Epilepsy is a chronic disease, and needs long-term observation. Real-world evidence can supplement the content of RCT and has the most promising effectiveness among different treatment strategies [21]. More and more researchers propose that well-designed long-term clinical trials with head-to-head comparisons are required [22–25]. The American Academy of Neurology and International League Against Epilepsy Commission has recommended more meaningful long-term comparative trials representative of real-world clinical practices [26,27]. The United State Congress announced the final version of 21 st Century Cures Act on December 25, 2016, which approved the use of the "real world evidence" to replace traditional clinical trials to expand indications. Our epilepsy registry study mirrored “real world” clinical practice, compensating for the deficiency of RCT and indicating direction of clinical decision.

In our study, a total of 596 patients were included and the results showed that substitution therapy was better than add-on therapy. These patients were further divided into those with their treatments failed due to lack of efficacy (n = 457), failed due to adverse effects (n = 101), and failed due to other reasons (n = 38), respectively. Failure due to lack of efficacy is the most common reason in clinical practice and this was also in the case in our study. Therefore, we performed subgroup analysis on patients whose treatments failed due to lack of efficacy. The results showed that there was no significant difference between substitution and add-on therapy in this group of patients, which is consistent with the result reported by Brodie et al [28] in 2000. However, due to the small sample size, especially the small number of patients receiving add-on therapy due to adverse effect (n = 18) or due to other reasons (n = 16), subgroup analysis was not performed in the 101 patients whose treatments failed due to adverse effect or in the 38 patients whose treatments failed due to other reasons. Importantly, because the proportions of patients with different failure reasons for the first monotherapy in the total study population were quite different, the results may have a certain statistical bias. Thus, further studies with similar proportion of patients with different failure reasons for the first monotherapy are needed to further confirm our results.

Treatment-related adverse effects strongly correlate with life quality of patients [29]. Thus, we also paid attention to adverse effects. The proportion of patients whose treatments failed due to lack of efficacy to those their treatments failed due to adverse effect was 4.5:1. This is consistent with a multi-center long-term retrospective study in China [23]. Along with the increase of treatment methods, the incidence of intolerant adverse effect had a downturn trend. Adverse effects, including both the total adverse events and intolerable adverse effects, more easily occurred in patients whose treatments failed due to adverse effect than in patients whose treatments failed not due to adverse effect. Neuropsychiatric system adverse effect is the most common adverse effect as reported in other studies [30,31]. PDD is generally lower than DDD in clinical practice in China [32,33]. In our center, most of the patients had PDD/DDD ratio between 0.5 and 1.5, while there were still some patients with PDD/DDD ratio lower than 0.5 or high than 2.0. For those lower than 0.5, seizure was easily controlled with small dose and so we didn’t continue adding dose. For those lower than 2.0, we strictly

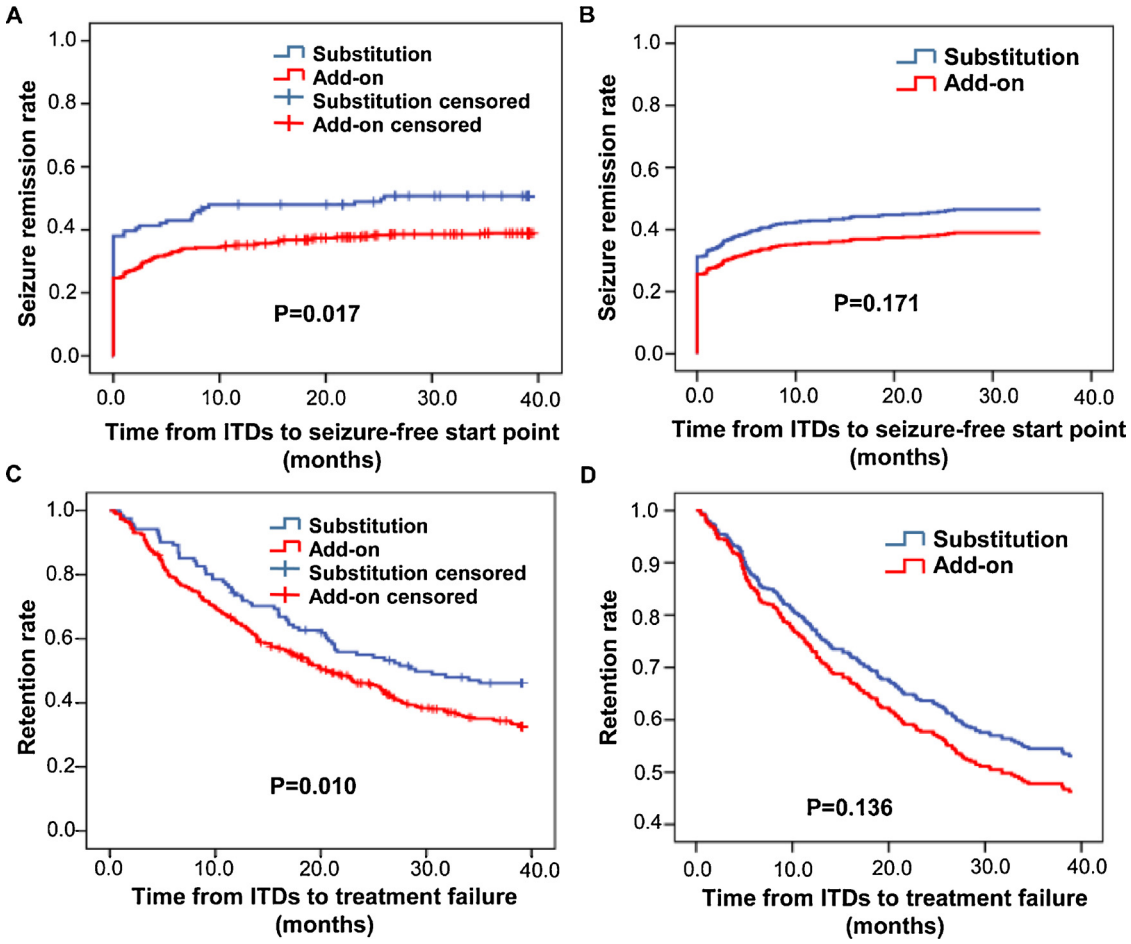

Fig. 3. Seizure remission rate and retention rate of patients, whose treatments failed due to lack of efficacy. Seizure remission rate for substitution and add-on among patients failed due to lack of efficacy calculated by Kaplan Meier (A) and adjusted by Cox regression model (B). Retention rate for substitution and add-on among patients failed due to lack of efficacy calculated by Kaplan Meier (C) and adjusted by Cox regression model (D).

monitored OSL/AToxL to avoid toxic reaction.

This study is a prospective observational study with long-term follow-up. It is a real-world evidence study based on clinical practice and individualized treatments. Therefore, confounding factors, such as the course of disease and the history of irregular medication, are inevitable. To adjust the confounding factors and minimize the sample bias, multi-factor analysis was used to analyze the comparative data. The results are reasonable and solid.

There are some limitations in this study, since our study involved only the first center of WEFURD. Thus, lack of data diversification, including region, race, custom, and the therapy strategies our specialists made, may result in some bias in the study. We expect to cooperate with more epilepsy treatment centers. Besides, some patients were lost to follow up and the overall loss of follow-up rate was 16.6%. Moreover, this study started from 2003, when the new ILAE classifications of seizures and epilepsies were not widely applied. Thus, the new ILAE classifications of seizures and epilepsies were not used in this study. Further studies are warranted.

5. Conclusions

Our findings reveal that substitution therapy has better seizure remission rate and retention rate than add-on therapy for focal epilepsy patients whose first antiepileptic drug treatment failed regardless of failure reasons. However, no significant difference is found between substitution and add-on therapy in seizure remission rate, retention rate, as well as adverse effect rates among patients whose first antiepileptic drug treatment failed due to lack of efficacy. Our results may provide evidence for clinical decision-making after failure of the first monotherapy for newly diagnosed patients with focal epilepsy in daily clinical practice.

Conflict of interest

The authors declare that they have no competing interests.

Funding

This study is supported by the Epilepsy Research Fund of China Association Against Epilepsy [Grant No. 2017004] and Zhejiang Provincial Natural Science Foundation of China [Grant No. LY15H090015].

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