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# Terminal seizure frequency and its relation to SUDEP

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ABSTRACT

*Background:* Sudden unexpected death in epilepsy (SUDEP) is a major cause of death in patients with epilepsy. Several risk factors have been implicated, including early age of onset, tonic–clonic seizures and antiepileptic drugs. However, whether patients who die from SUDEP have a greater frequency of seizures in the few months before death is unclear. We investigated the terminal seizure frequency and its relation to SUDEP among a large group of patients with tonic-clonic seizures in rural West China.

*Methods:* We used the database from the Convulsive Epilepsy Control and Management Program in West China, which routinely provides phenobarbital (PB) as a treatment for convulsive epilepsy. Patients with probable SUDEP were included according to pre-set criteria. A verbal autopsy was undertaken for each case. By matching each patient's age, sex, date of joining the program, time in follow-up, and baseline seizure frequency, we set up a 1:5 ratio control group. SPSS 21.0 statistics were applied to compare the differences in seizure frequency 3 months prior to SUDEP between patients with probable SUDEP and controls. Furthermore, the dynamic changes of terminal seizure frequency 6–9 months, 3–6 months, and 3 months prior to SUDEP was also analyzed.

*Results:* A total of 41 patients who died from probable SUDEP were identified out of 7844 patients during 10 years of follow-up. The SUDEP group had a significantly higher tonic–clonic seizure frequency 3 months before their deaths than the control group ($p = 0.023$). At the same time, their seizure-free rate was lower than the control group ($p = 0.025$). Patients with probable SUDEP who were followed up over 12 months were further studied as a subgroup. They had more tonic–clonic seizures 3 months prior to death compared to the control group ($p = 0.010$). They also had an increase in seizure frequency in their terminal phase (3 months prior) compared to an earlier stage (3–6 months prior) ($p = 0.029$). Furthermore, the terminal PB dose in the SUDEP group was higher than the control group ($p = 0.002$).

*Conclusion:* Patients who died from SUDEP had more frequent tonic–clonic seizures 3 months before their deaths. Higher seizure frequency increases the exposure to peri-ictal pathophysiological events, which possibly relate to SUDEP. This phenomenon may be due to the drug resistance potential of these patients or the high dose of PB. Further research is required to ascertain the underlying mechanisms of SUDEP.

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## 1. Background

Sudden unexpected death in epilepsy (SUDEP) is one of the major causes of death in patients with epilepsy [1,2], and was first defined by Nashef [3]. In different studies, the incidence of SUDEP was reported to range from 0.35 to 9.3 per 1000 person-years [4,5]. The current understanding of SUDEP mostly comes from a series of cases or case control studies [6]. These studies managed to identify several risk factors for SUDEP [4], in which increased frequency of seizures was most commonly reported [4,5,7,8].

Seizure frequency was most often measured by actual seizure counts annually or monthly. In one large cohort study by Nilsson for SUDEP [9], patients having seizures over one observational year had a 23-times higher relative risk for SUDEP than patients without seizures. A more detailed analysis on seizure types revealed that tonic–clonic seizures significantly increased the risk [4]. These studies were inconsistent in the magnitude of the increased risks, but this could be explained by the different designs of the studies [5]. In general, high seizure frequency, especially tonic–clonic seizures, was regarded as the strongest risk factor [4,5,10].

However, the distribution of seizures according to time was not determined in these studies. The dynamic change in seizure frequency was not sufficiently reported. In 2014, a community-based study in Cornwall, UK [11] reported that 91% of patients with probable SUDEP had increased seizure frequency or seizure deterioration 3–6 months prior to their deaths. In an earlier study [12], we concluded that patients with ongoing seizures were at an increased risk for SUDEP, especially in the months leading up to their deaths. These results implied that patients

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who succumb to SUDEP may have more seizures before their deaths. We have now conducted a case control study in rural West China in order to clarify the relation between terminal seizure frequency and SUDEP.

## 2. Methods

This study was approved by the Sichuan University Ethical Standards Committee on Human Experimentation.

All patient data were obtained from the database of the Convulsive Epilepsy Control and Management Program in West China [13,14], which focused on monitoring epilepsy epidemiology and treating patients with phenobarbital (PB) under guidance. The program included 16 centers in rural West China from May 2005 to December 2015 and covered more than 10,000 patients with epilepsy. The inclusion criteria for this program were published in our prior report [13].

Patients were diagnosed by primary healthcare physicians and diagnoses were confirmed by referral neurologists according to the International League Against Epilepsy definition of generalized tonic–clonic epilepsy [15]. Patients were given PB as an initial treatment at a dose of 60 mg/d, which was adjusted according to their seizure control. Continuous monthly follow-ups were conducted by primary healthcare physicians. Data were collected annually by local Centres for Disease Control and Prevention (CDC) and further processed by this research team.

The criteria for probable SUDEP were:

(1) Witnessed or unwitnessed death of patients while they were in a reasonable state of health;
(2) Patients who were in relatively safe circumstances and performing normal activities;
(3) No evidence on the cause of death according to autopsy or verbal autopsy, including status epilepticus or death caused by a particular seizure directly;
(4) Sudden death with no obvious symptoms or signs of approaching death at the last follow-up.

A verbal autopsy [16] was performed for each eligible case by directly contacting the first witness and gathering information from the local CDC and hospital. One unified autopsy form was applied for quality control as our previous paper reported [13].

For each probable SUDEP case included, we assigned five controls from the database by matching age (±5 years), sex, date of joining the program (same year), time in follow-up, and baseline seizure frequency (it is done by selecting the 5 closest cases in seizure frequency according to the baseline data collected when they joined the program). The follow-up records of each case and its controls were extracted from the database of the program and merged into two groups: the probable SUDEP group and the control group.

SPSS 21.0 was applied for statistical analysis. Qualitative data were compared with a chi-square test. For independent measurement samples, data with a normal distribution were compared on the Student's t-test, and other forms of distributions were examined by the Mann–Whitney U test. Pairing samples were also analyzed by either the matched-pair t-test or the Wilcoxon matched-pairs signed-rank test, according to their distributions. In addition, data in normal distributions were expressed with mean and variance; other forms of data were presented by quartile. We assigned $\alpha = 0.05$ as a degree of inspection, with $p < 0.05$ considered as statistically significant.

We focused on comparing seizure frequency at different times in both groups. A subgroup patients with follow-up lasting for more than 12 months was utilized to analyze the dynamic changes in each patient's seizure frequency.

## 3. Results

Since 2005, a total of 7844 patients with convulsive epilepsy have been enrolled in the project with a total follow-up person-years of 23,739.58, from which 41 probable SUDEP cases were reported, making the incidence of SUDEP 1.72‰ every person-year. Each probable SUDEP was assigned with five control cases, as described above. The baseline characteristics of the two cohorts are listed in Table 1.

**Table 1**
Baseline characteristics.

| | Probable SUDEP | Control | P value |
|---|---|---|---|
| Sex | 19 male (46.34%) | 95 male (46.34%) | P = 1.00[a] |
| Age | 40.61 ± 15.39 y | 40.08 ± 15.47 y | P = 0.84[b] |
| Height | 157.39 ± 8.28 cm | 158.70 ± 8.76 cm | P = 0.38[b] |
| Weight | 54.24 ± 9.21 kg | 52.98 ± 11.46 kg | P = 0.55[b] |
| Baseline tonic–clonic seizure frequency | 8.10 ± 10.83/y | 6.07 ± 9.43/y | P = 0.32[b] |
| Baseline dosage of PB | 84.88 ± 34.14 mg | 76.52 ± 28.60 mg | P = 0.13[b] |
| Mean duration of epilepsy | 20.64 ± 15.28 y | 20.20 ± 12.69 y | P = 0.82[b] |
| Age of onset | 20.43 ± 14.57 y | 22.67 ± 16.68 y | P = 0.44[b] |
| Combined medication | 6 (14.63%) | 27 (13.17%) | P = 0.88[a] |

[a] Chi-square test.
[b] Student's t test.

The program was successful in controlling tonic–clonic seizures. In both groups, the seizure counts were lower than baseline after treatments (Mann–Whitney U test, SUDEP group: $p < 0.001$; control group: $p < 0.001$).

The annual seizure frequency was designed to measure the severity of the epilepsy. A Kolmogorov–Smirnov test was applied to the data of both cohorts, but no normal distribution fitted either one. Thus, the Mann–Whitney U test was applied for this calculation. The average annual seizure frequency of the SUDEP group was 6.53/y, which was higher than the control group (3.96/y), but was statistically insignificant ($p = 0.59$).

To be seizure-free for 3 months before death was counted as an index for seizure remission. In this study, 19 out of 41 patients with probable SUDEP were reported as seizure-free for 3 months before they died; in the control group, 155 patients were seizure-free over the same time span. A chi-square test indicated that the SUDEP group had significantly higher non-seizure-free incidences than the control group ($p < 0.001$). Another comparison on actual seizure counts for the 3 months before death between the two groups showed that the SUDEP group had more seizures before they died than the control group (Mann–Whitney U test, $p = 0.023$).

Another interesting finding was the shift of dosage on PB. While having comparable initial doses of PB, the SUDEP group had a significant increase in PB dosage from baseline until their deaths (Mann–Whitney U test, $p = 0.020$). However, at the same time, the control group also had an increase in dosage but clearly not enough to make a difference (Mann–Whitney U test, $p = 0.13$). The PB doses in the end were also higher in the probable SUDEP group ($p = 0.0020$). The key findings are summarized in Table 2.

**Table 2**
Key findings in this research.

| | Probable SUDEP | Control | P value |
|---|---|---|---|
| Average annual seizure frequency | 4.138 (0.356, 7.900)/y | 1.5 (0, 5.547)/y | P = 0.59[a] |
| Seizure frequency 3 months prior to death | 0 (0, 10)/y | 0 (0, 0)/y | P = 0.023[a] |
| Seizure free 3 months prior to death | 19 | 155 | P < 0.001[b] |
| PB dosage prior to death | 90 mg (90 mg, 165 mg) | 90 mg (60 mg, 120 mg) | P = 0.002[a] |
| Poor compliance | 7 | 19 | P = 0.16[b] |
| Combined medication | 4 | 17 | P = 0.77[b] |

[a] Mann–Whitney U test.
[b] Chi-square test.

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