Discontinuation of Prophylactic Antiepileptic Drugs in Patients with Intracerebral Hemorrhage

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Abstract:

Background: The risk factors for seizures in patients with intracerebral hemorrhage (ICH) stroke and the effect of prophylactic anticonvulsant are not well understood. Limited studies investigated the risk of seizure after discontinuing prophylactic antiepileptic drugs in patients with ICH. This study aimed to investigate the role of valproic acid (VA) for seizure prevention and to access the risk of seizure after anticonvulsant withdrawal in patients with spontaneous ICH.

Methods:

Between 2013 and 2015, 177 patients with ICH were enrolled in this 3-year retrospective study. Seizure was classified as early seizure (first seizure within 1 week of ICH), delayed seizure (first seizure after 1 week), and late seizure (any seizure after 1 week). Binary logistic regression was used to evaluate the relationship between baseline clinical factors and late seizure between study periods. VA was prescribed or discontinued based on the decision of the physician in charge.

Results:

Seizures occurred in 24 patients, including early seizure in 6.78% (12/177) of the patients, delayed seizure in 7.27% (12/165) of the patients without early seizure, and late seizure in 9.60% (17/177) of the patients. Most seizures occurred within the first year. Binary logistic regression analysis showed ICH with cortex involvement as the independent risk factor for seizures. VA did not decrease the risk of seizure. Patients with ICH with cortical involvement using prophylactic anticonvulsant for longer than 3 months did not decrease risk of seizure (Odds ratio 1.86, 95% CI: 0.43-8.05).

Conclusion:

Spontaneous ICH with cortex involvement is the risk factor for seizure. Most seizures occurred within 1 year after stroke onset over a 3-year follow up. Discontinuation Prophylactic antiepileptic drug within 3 months in patients do not increase risk of seizure. VA cannot prevent seizure in patients with ICH.

Key Words: intracerebral hemorrhage, stroke, seizure, anticonvulsant, valproic acid, prophylaxis

Background:

Stroke is one of the most common causes of epilepsy. In old patients, more than 50% of the cases of seizure are related to stroke [1, 2]. The frequency of seizures after stroke was found to be approximately 4%–10% in patients with ischemic stroke and 4%–27% in patients with hemorrhagic stroke [3-6]. The seizures after stroke include acute symptomatic seizure (early) attack within 1 week after stroke onset and unprovoked (late) seizure onset lateral after 1 week of stroke [5, 7, 8]. In patients with early seizure, approximately 50% seizures were found to occur at the onset of intracerebral hemorrhage (ICH) [5]. A previous study reported that patients with stroke who have experienced early seizure have a higher risk of developing late seizure than those who have not [9]. A study by Biffi et al, including 872 patients, found that after 3.9 years of follow up, approximately 50% (42/86) of the patients with early seizure experienced recurrent seizure, and 4.24% (37/872) experienced late seizure [10].

The effect of early seizure is controversial. A study by Hert et al reported that in patients with ICH, early seizure does not influence the patient's 6-month outcome [5, 11, 12]. However, another study showed the association between early seizure and poor outcome in a patient with ICH [13]. The factors that may increase the risk of seizure in patients with ICH include cortical involvement,

intraparenchymal hemorrhage with midline shift, patients with non-neurologic infection, and hemorrhage volume [6, 14-16].

Although the guidelines for the management of ICH does not recommend the use of prophylactic anticonvulsant treatment for patients without seizures [17], prophylactic anticonvulsant treatment in patients with ICH is common. A previous study found that prophylactic anticonvulsant for seizure in patients with ICH can reduce early seizure and improve neurological outcome [18, 19]. However, some studies found that prophylactic antiepileptic agents do not reduce the occurrence of seizure. A study by Naidech et al found that prophylactic leveticacetam in patients with ICH does not affect seizure and functional outcome but has worse cognitive function and health-related quality of life [20].

The duration for which prophylactic anticonvulsants should be used after ICH is controversial. A study by Chumnanvej et al showed that 3 days of phenytoin prophylaxis is adequate to prevent seizure [21]. However, a study by Murphy-Human et al found that short-duration levetiracetam prophylaxis after subarachnoid hemorrhage (SAH) has a higher risk of seizures than an extended course of phenytoin [22].

At present, most of the existing studies have investigated the effect of

prophylactic anticonvulsant on patients with ICH, who use phenytoin or leveticacteam. Few studies have investigated the effect of VA. However, there are no studies investigating the duration of prophylactic anticonvulsant in patients with ICH have been reported. Hence, we performed a study investigating the prophylactic effect of valporic acid (VA) on seizure in patients with ICH.

The aim of the study was to investigate the incidence and associated factors of early and late seizure in patients with ICH. We also investigated whether the discontinuation of the prophylactic anticonvulsant increased the risk of late seizure in patients with ICH.

Methods:

Between 2013 and 2015, 287 patients with intracerebral hemorrhage stroke were admitted to Chia Yi Christian hospital. The hospital is a 1000-bed teaching hospital in central Taiwan. This study was a retrospective study; we reviewed the patients' medical records, including demographic data, vascular risk factors, and the process of care from stroke onset to 3 years after the stroke. Brain computed tomography (CT) was performed based on the electrical medical records.

All consecutive patients with acute neurological symptoms arrived at the emergency department and underwent brain CT, and patients with acute hemorrhagic stroke were included in the study. Patients with ICH due to trauma, tissue plasminogen activator-related hemorrhage, arteriovenous malformation rupture, SAH, cerebellar hemorrhage, and brain stem hemorrhage were excluded from the study. All patients were evaluated by a neurosurgeon, and seizures were classified according to the criteria of an international league for epilepsy [23]. The definition of seizure was according to that used in previous studies. Early seizure (ES) was defined as the first seizure occurring within 7 days after stroke. The first seizure occurring beyond 1 week after stroke was defined as delayed seizure (DS). Late seizure was defined as seizure that occurred after 1 week of stroke onset, including patients who had experienced ES and those who had not.10 The end point of the study was 3 years after stroke onset. If patients had no seizure till 3 years after stroke onset, they were considered to have had no seizure. In the emergency department and ward, the patients or their families were inquired about seizures and the onset of stroke.

Demographic characteristics and medical history

During hospitalization, the following information was collected: 1. Age and gender, 2. Consciousness level (Glasgow coma scale) at admission, 3. Risk factors of stroke, 4. Previous stroke history (infarct, hemorrhage, and undetermined), 5. Previous therapy before stroke. All of the patients were treated according the guidelines of American Heart Association for blood pressure control, fluid and nutrition supply, airway management, and surgery [24]. If seizure developed, 400-mgVA was administered twice per day. The decision of administering prophylactic anticonvulsant for the patients without seizure was made by the physician in charge. When prophylactic anticonvulsant was used for the patients without seizure, 200-mg or 400-mg VA was administered twice per day. The timing of discontinuation of the anticonvulsant was decided by the physician.

Radiology assessment

Brain CT was performed soon after the patients arrived at the emergency department. Follow-up brain CT was performed if necessary, including neurological deficit worsening, seizure attack, consciousness level worsening, or if the patient received surgery. Brain CT images were reviewed in digital

image by a neuroradiologist who was blinded to the patients. The hemorrhage volume for ICH was determined according to A × B × C/2 method. A represents the longitudinal diameter, B represents the diameter perpendicular to A, and C represents the number of 10-mm images containing hematoma [6, 25]. CT image showing a lobar hemorrhage and deep hemorrhage extending to the cortex indicated cortex involvement. The study protocol was approved by the Chia Yi Christian hospital's Institutional Review Committee on human research.

Statistical analysis

The risk factors for seizure including sex, risk of vascular disease and clinical manifestation were analyzed with the Chi-square or Fisher exact test. Patient age, AND coma scale were analyzed using independent t-test. Binary logistic regression was used to evaluate the relationship between baseline clinical factors and late seizure occurrence during study period. All statistical analyses were conducted using a commercially available software, version 21 of the SPSS system for windows (version 21.0. IBM Corporation. Somers, NY, USA). Two-sided P values of <0.05 were considered statistically significant.

Results

Between Jan 1, 2013, and Dec 31, 2015, a total 287 patients diagnosed with ICH were admitted to our hospital. After excluding the patients who died within 2 years, were lost to follow up, or had epilepsy and brain tumor, 177 patients were included in the analysis. The flow chart of patient enrollment and exclusion is shown in Figure 1. The characteristics of the patients with ICH are shown in Table 1. In the 177 patients, 24 patients had seizure attack within 3 years after stroke onset, 12had seizure within 1 week, 12 had the first seizure attack after 1 week of stroke onset, and 153 did not experience seizure. The timing of seizure attack is shown in Figure 2. In the 12 patients who had ES, 50% (6/12) of the seizures occurred within 24 hours after stroke onset. In the 12 patients who had DS, 66.7% (8/12) of the seizures occurred within 1 year after stroke onset. Late seizure was found in 17 patients, including 5 recurrent seizures and 12 delayed seizures.

Factors affecting seizure attack

Age, sex, Glasgow coma scale, diabetes mellitus, hypertension, atrial fibrillation, stroke history, hemorrhagic volume, and operation do not affect the risk of ES. Cortex involvement significantly increases the risk of ES (Table 1).

In the 12 patients with ES, no recurrent seizure occurred in the 3 patients who had hemorrhage with no cortex involvement. Five of the 9 (55.5%) patients who had hemorrhage with cortex involvement had recurrent seizures (Table 2).

Sex, age, Glasgow coma scale, diabetes mellitus, hypertension, atrial fibrillation, stroke history, and operation were not significantly different between the patients with DS and those without seizure. In the patients with hemorrhage with cortex involvement, there was a significant increase in the risk of DS ($p = 0.006$). Of the 123 patients without cortex involvement, 2.43% (3/123) patients had DS, and 16.7% (9/54) of the patients with hemorrhage with cortex involvement had DS (Table 1). Under univariate analysis, cortex involvement was found to significant increase the risk of DS with an odds ratio of 7.7 (95% CI 1.56-38.5). (Table 3).

The factors affecting late seizure are the same as those affecting early and delayed seizures; the binary logistic regression analysis showed that cortex involvement increases the risk of late seizure with and odds ratio 17.7 (95% CI: 3.15-99.2). The patients who used prophylactic anticonvulsant for >3 months after stroke did not show a decrease in the risk of late seizure (Table 4).

The effect of discontinuation of prophylactic anticonvulsant on late seizure

Among the 49 patients who received hematoma evacuation and used prophylactic anticonvulsant, 23.3% (6/26) using VA for >3 months had late seizure. Three of the 23 (13.0%) patients who discontinued VA within 3 months after stroke onset had late seizure. The risk of seizure was not significantly different between the patients who discontinued anticonvulsant within 3 months and those who used VA for >3 months ($p = 0.47$, 95% CI: 0.43–9.12). Among patients with hematoma volume >30 CC, 20% (3/15) using VA for >3 months had late seizure, and 25% (2/8) who discontinued VA within 3 months after stroke onset had late seizure. The risk of seizure was not significantly different between the patients who no used VA or discontinued VA within 3 months and those who used VA for >3 months ($p = 0.75$, 95% CI: 0.09–5.76). Among patients with cortical involvement, 50% (28/56) using VA for >3 months had late seizure, and 35.7% (10/28) who discontinued VA within 3 months after stroke onset had late seizure. The risk of late seizure was no significant difference in the patients who discontinued VA within 3 months and the patients who used VA for >3 months (OR = 3.05, 95% CI: 0.81–11.3) (Table 5). The results show that discontinuation of VA within 3 months in patients with cortical involvement do not increase the risk of late seizure.

Among 43 patients with cortical involvement and using prophylactic drug, 11.5% (3/26) of patient seizure occurred after they discontinued prophylactic anticonvulsants, 58.8% (10/17) of patient seizure occurred during they continue use prophylactic anticonvulsant.

Discussion:

In the study, seizure attack was found in 13.6% (24/177) of patients with ICH, ES in 6.7% (12/177),, and DS in 6.7% (12/177). ICH with cortical involvement is the only factor affecting early and late seizures. The incidence of seizure is close to that reported by a study by Qian et al; their study showed seizure attack in 13.9% (130/95) of patients with ICH [8], and another study in Korea showed a seizure rate of 8.4% (22/263) [14]. The ES rate was higher than that in a study by Zöllner et al in Germany, which showed a 4% incidence rate of ES in patients with ICH. This was followed by a lower value reported by a study by Herdt et al [5]. The difference is suspected to be attributed to most of the ES that occurred at stroke onset and within 24 hours after stroke onset [5]. In the present study, we systemically interviewed the patients and their families about the occurrence of seizure, including seizure attack at stroke onset and before they arrived at the hospital. The study by Herdt et al found that >50% of

ESs occur at stroke onset, whereas the study by Zöllner et al only included seizures during inpatient treatment, which may have underestimated the patient seizure attack before they were brought to the hospital [19].

In our study, 41.7% (5/12) of patients with early seizure had late seizure within 36 months follow up. The recurrent seizure rate is higher than that reported by Kilpatric et al; approximately 32% of their patients had late seizure [9]. The difference is suspected to be related to our study, which had a longer follow-up time.

Several studies have investigated early seizure and delay seizure after intracerebral hemorrhage [5, 8, 10, 14]. In the present study, cortical involvement was found to be an independent factor for early, delayed, and late seizures. Previous studies have reported that ICH with cortical involvement increases the risk of early and late seizures [5, 10, 26, 27]. ES after ICH is suspected to be related to hemorrhage with direct cortical irritation [5]. Delayed and late seizures after ICH are suspected to be related to progressive neuronal and white matter damage due to small vessel disease, which amplify the epileptogenic process at the site of hemorrhage [10].

A previous study found young age (≦60 years) to be a predictor of seizure after ICH [14]. Our study also found that the patients who had DS were younger

than those without DS, but it is not statistically significant.

Several studies have investigated the effect of prophylactic anticonvulsant on the outcome and late seizure in patients with ICH stroke. Some studies found that prophylactic anticonvulsant cannot reduce the risk of seizure [14, 28]. Some studies found that prophylactic anticonvulsant may worsen consciousness level or is associated with poor outcome [20, 29]. Recently, most of the studies investigating prophylactic anticonvulsant in patients with ICH used levetiracetam for seizure prevention [19, 28, 29]. Recently, some studies have compared the effect of phenytoin and levetiracetam, but the results are inconsistent. Jones et al found that levetiracetam is as effective as phenytoin in the prevention of post-traumatic ES, but an EEG analysis showed that levetiracetam is associated with an increased seizure tendency [19]. Naidech et al found that in comparison to levetiracetam, patients with ICH use phenytoin more frequently resulting in fever and poor outcome [30]. In our study, our patients used VA for seizure prevention. We did not find an association between anticonvulsant and poor outcome but found that in patients with ICH with cortical involvement, discontinuation of prophylactic anticonvulsant within 3 months did not

increase risk of late seizure.

Although the guidelines for the management of ICH do not recommend that patients without seizures receive prophylactic anticonvulsant treatment [17], antiepileptic drug prophylaxis after ICH is common [31]. Previous studies found that prophylactic antiepileptic agent use was associated with a worse 3-month functional outcome [30, 32]. At present, there is no data available on the duration of prophylactic anticonvulsant in patients with ICH. Chumnanvej et al found that 3 days are adequate to prevent seizure in patients with SAH [21]. However, Murphy-Human et al found that 3-day prophylaxis is associated with a higher risk of seizure than extended course of phenytoin prophylaxis [22]. In this study, our result showed that the patients with ICH receiving prophylactic drug for more than 3 months do not decrease the risk of seizure than the patients discontinue anticonvulsant within 3 months.

Our study has several limitations. First, the study is a retrospective study; we cannot measure VA serum level, which may affect the effect of VA. Second, the use of prophylactic anticonvulsant was based on the physician’s decision, which may have introduced a bias of a higher risk of the patients receiving prophylactic anticonvulsant and lower seizure risk of the patients not receiving

prophylactic anticonvulsant. However, we compared the risk of seizure in patients with high seizure risk, who used anticonvulsant and discontinued prophylactic anticonvulsant before and after 3 months of ICH. Third, the study is a single-center study, including a small number of patients.

Conclusion:

Spontaneous ICH with cortical involvement may be a risk factor of early and late seizures. For preventing delayed and late seizures in patients with ICH, most patient discontinued prophylactic anticonvulsant within 3 months was adequate. Valproic acid cannot prevent seizure in patients with ICH. Further prospective, randomized, double blind study to investigate the effect and timing of discontinuation of prophylactic anticonvulsant for seizure in patients with ICH may be necessary.

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Figure Legend

Figure 1. Flow chart of patient enrollment

Figure 2. Delay of occurrence of the first seizure (n = 24)

409. Abbreviations:

410. CI: confidence interval, CT: Computed Tomography, DS: delay seizure, ES: early

411. seizure, GCS: Glasgow Coma Scale, ICH: Intracerebral hemorrhage, OR: odds

412. ratio, SAH: Subarachnoid hemorrhage, VA: valproic acid

413.

414. Declaration

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418.

419. Authors contributions

420. Wong YS and Ong CT were responsible for the study design. Wu CS was

421. responsible for data collection, performed the analyses and interpreted the

422. results. Wong YS drafted the manuscript. Ong CT and Wu CS reviewed and

423. revised the manuscript. All authors have read and approved the manuscript

424. submitted.

425.

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428. Availability of data and materials

429. All data used and/or analyzed in the manuscript are available from the

430. corresponding author on reasonable request.

431.

432. Ethics approval and consent to participate

433. The study was approved by the ethical committee of the Chia-Yi Christian

434. Hospital

435.

436. Consent for publication

437. Not applicable.

438.

439. Competing interests

440. All authors declare no competing interests.

Figures

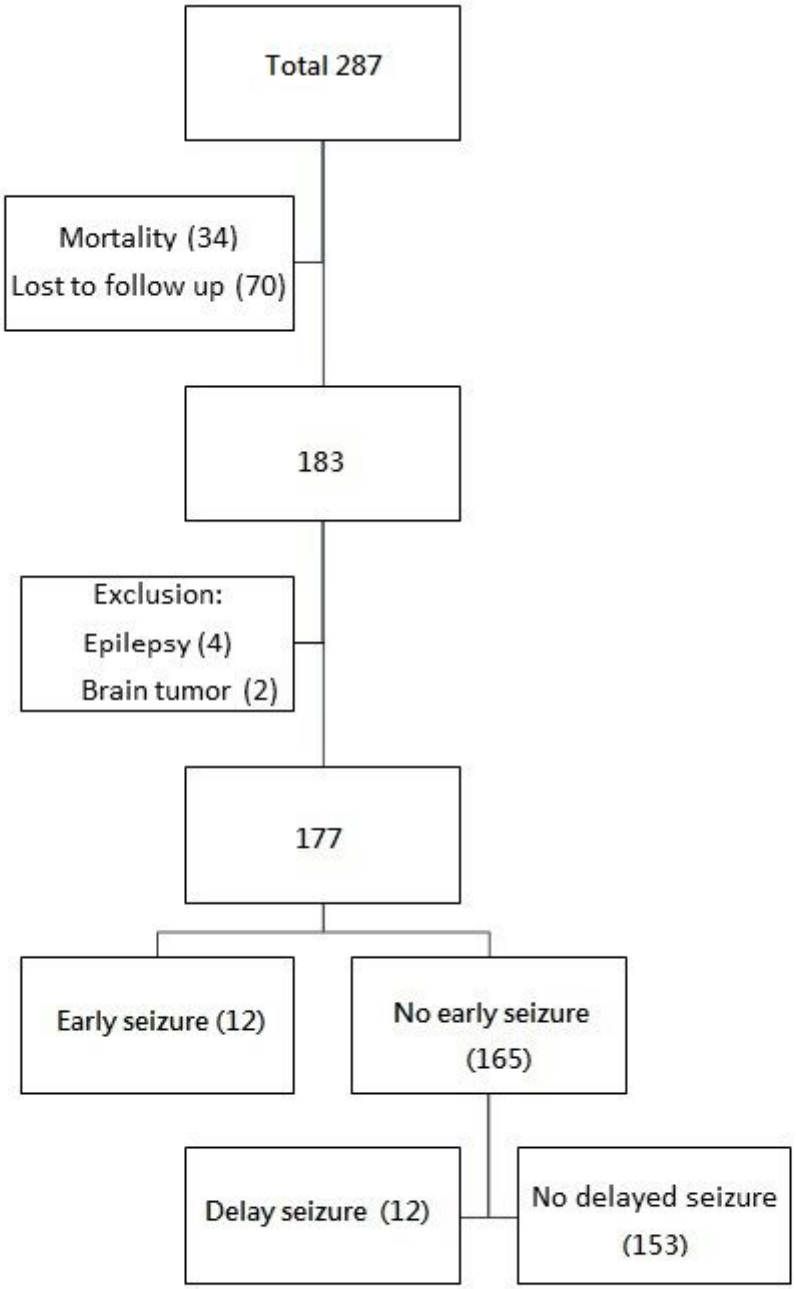

Figure 1

Flow chart of patient enrollment

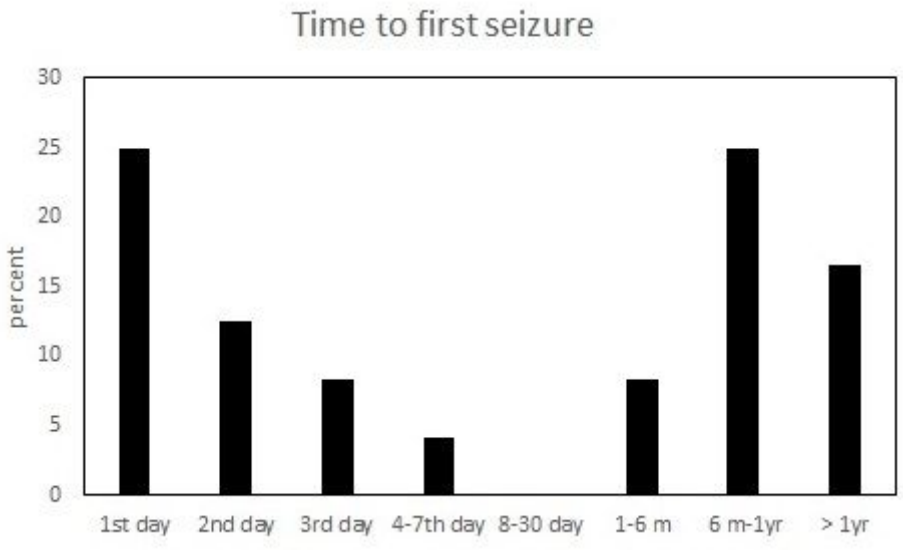

Figure 2

Delay of occurrence of the first seizure (n = 24)

Supplementary Files

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