


BMJ Open Seizure prophylaxis following aneurysmal subarachnoid haemorrhage (SPSAH): study protocol for a multicentre randomised placebo-controlled trial of short-term sodium valproate prophylaxis in patients with acute subarachnoid haemorrhage

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ABSTRACT

Introduction Seizures are a common complication that leads to neurological deficits and affects outcomes after aneurysmal subarachnoid haemorrhage (aSAH). However, whether to use prophylactic anticonvulsants in patients with aSAH remains controversial. Our study aims to determine whether short-term (7 days) sodium valproate could prevent seizure occurrence and improve neurological function in patients with SAH caused by anterior circulation aneurysm rupture and treated with clipping.

Methods and analysis In this multicentre randomised evaluator-blind placebo-controlled trial, 182 eligible patients with good-grade aSAH planned for surgical clipping will be enrolled from four neurosurgical centres in China. In addition to standard care, patients will be randomly assigned to receive sodium valproate 20 mg/kg daily or matching placebo. After aneurysmal clipping, patients will be followed up at discharge, 90 days and 180 days. The primary outcomes are the incidence of early and late seizures. The secondary outcomes include aSAH-related complications, sodium valproate-related adverse effects, modified Rankin Scale (mRS) (on discharge, at 90 days, 180 days), rate of good outcome (defined as mRS 0–2), all-cause death (at 90 days, 180 days) and Montreal Cognitive Assessment score (at 180 days). All analyses are by intention-to-treat.

Ethics and dissemination This study will be conducted according to the principles of Declaration of Helsinki and good clinical practice guidelines. This trial involves human participants and has been approved by the ethics committee of West China Hospital. Informed consent will be achieved from each included patient and/or their legally authorised representative. Preliminary and final results from this study will be disseminated through manuscript publishing and international congresses presentations. Any protocol amendments will be approved by the ethics committee of West China Hospital and subsequently updated on ChiCTR.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Our study is a multicentre, randomised, evaluator-blind, placebo-controlled trial to assess the safety and effectiveness of short-term sodium valproate prophylaxis in patients with aneurysmal subarachnoid haemorrhage (SAH).
- ⇒ Only patients with good Hunt and Hess grade SAH (grades 1–3) who suffered from anterior circulation aneurysm rupture and plan to accept surgical clipping will be enrolled in our trial.
- ⇒ A possible limitation is that we only record clinical seizures, while subclinical seizures will not be recorded.

Trial registration number ChiCTR.org identifier: ChiCTR2100050161.

INTRODUCTION

Spontaneous subarachnoid haemorrhage (SAH), one of the most common types of haemorrhagic stroke, accounts for approximately 5% of all stroke cases.¹ SAH is characterised by acute onset, rapid progress and high disability and mortality, which cause a serious burden on individuals and society. Rupture of intracranial aneurysm is the most frequent cause of SAH, which accounts for nearly 85% of SAH.² With advancements in surgical treatment (clipping, endovascular therapy) and medical therapy (application of nimodipine), the prognosis of aneurysmal SAH (aSAH) has been substantially improved.^{3–5} On the other hand, complications after aSAH, which could

also affect clinical outcomes, have attracted increasing attention.⁴

Seizures are a common complication after aSAH with an incidence between 6% and 15.3%.^{6–9} Risk factors for seizure include rupture of anterior circulation aneurysm, surgical clipping treatment, thicker blood clots in aSAH, intracranial haematoma, rebleeding, infarction, etc.^{10–13} Two well-designed retrospective studies have shown that seizure after aSAH is a significant independent risk factor for death or worse functional and cognitive outcomes.^{14,15} However, it remains controversial whether prophylactic anticonvulsants should be administered in patients with aSAH. In 2005, Naidech *et al* summarised data from 527 patients with aSAH and found higher serum phenytoin level is associated with poor prognosis at 3 months.¹⁶ While the mechanisms for phenytoin use leads to functional and cognitive disability are not fully understood, possible reasons might include worsening neurological recovery, causing fever and compromising the protective effects of nimodipine.¹⁷ According to the consensus conference in 2011 and the aSAH management guideline in 2012, although routine use of anticonvulsant prophylaxis after SAH with phenytoin is not recommended, use of other anticonvulsants for prophylaxis may be considered.^{18,19} On the other hand, there is a lack of high-quality evidence in the fields of anticonvulsant prophylaxis other than phenytoin in patients with aSAH.²⁰ Until now, only two randomised controlled trials have been published, with neither directly compared the difference between the prophylaxis and non-prophylaxis groups.^{21,22} In spontaneous intracerebral haemorrhage, prophylactic sodium valproate was reported to improve neurological deficits with a tendency to reduce the occurrence of early seizures.²³

For patients with SAH, CT angiography (CTA) or digital subtraction angiography (DSA) can be used for identifying the source of bleeding. DSA is the gold standard for aneurysm detection, while CTA is faster, non-invasive and more efficient to be obtained. For cases with negative CTA, DSA or repeated CTA is necessary. Hunt and Hess grading system is one of the most widely used tools to evaluate the severity of SAH.²⁴ Modified Rankin Scale (mRS) is a simple 6-point assessment used to measure disability degree in patients who suffered a stroke.²⁵ All above examinations and evaluations would be used in our study to screen eligible patients and perform follow-up.

In this study, we designed a multicentre, randomised, evaluator-blind, placebo-controlled trial to assess the safety and effectiveness of short-term sodium valproate prophylaxis in high-risk patients with aSAH caused by anterior circulation aneurysm rupture and treated with clipping.

METHODS AND ANALYSIS

Patient and public involvement

There is no direct patient involvement in the design, recruitment or conduct of the study. When the study

is completed, the result of this trial will be notified to participants through direct consultation with their trial clinician.

Design

SPSAH trial is a prospective, multicentre, randomised, single-blind, placebo-controlled trial. **Figure 1** illustrated the flow chart of the SPSAH trial. This trial will be conducted at four neurosurgical centres, including departments of neurosurgery in West China Hospital, Sichuan University; The Second Affiliated Hospital, Zhejiang University School of Medicine; The First Affiliated Hospital, Harbin Medical University; and People's Hospital of Leshan. All participating institutions can perform skilled surgical treatment for neurovascular diseases, including clipping and endovascular therapy for ruptured aneurysms. The study starts recruitment in August 2021 and is anticipated to complete in December 2022.

Patient population: inclusion and exclusion criteria

Patients will be considered eligible if they meet all of the following inclusion criteria:

- ▶ Age ≥ 18 years old.
- ▶ mRS score 0–1 before ictus.
- ▶ CTA or DSA confirmed diagnosis of aSAH caused by rupture of anterior circulation aneurysm.
- ▶ Symptoms onset of aSAH occurred < 24 hours prior to presentation at the hospital.
- ▶ Hunt-Hess grade ≤ 3 on admission.
- ▶ Surgical clipping is planned for treatment.
- ▶ Patient is willing and able to accept long-term study follow-up.
- ▶ Patient or their legally authorised representative (LAR) has provided written informed consent.

The following patients will be excluded:

- ▶ Concurrent non-ruptured aneurysm on the same admission.
- ▶ SAH secondary to rupture of traumatic or infected aneurysm.
- ▶ Prior anticonvulsant therapy or epilepsy.
- ▶ Seizure before enrolment.
- ▶ Use of carbapenem antibiotics within 7 days before enrolment.
- ▶ History of coagulopathy.
- ▶ Concurrent significant intracranial pathology, including but not limited to Moyamoya disease, arteriovenous malformation, arteriovenous fistula or malignant brain tumour.
- ▶ Serious comorbidities, including but not limited to dementia, severe major depression, cancer (likely to cause death in 2 years), multisystem organ failure.
- ▶ History of previous ruptured cerebral aneurysm.
- ▶ Liver dysfunction (clinical laboratory markers for liver function three times greater than normal or cirrhosis), with acute or chronic hepatitis, history or family history of serious hepatitis (especially drug-induced hepatitis).

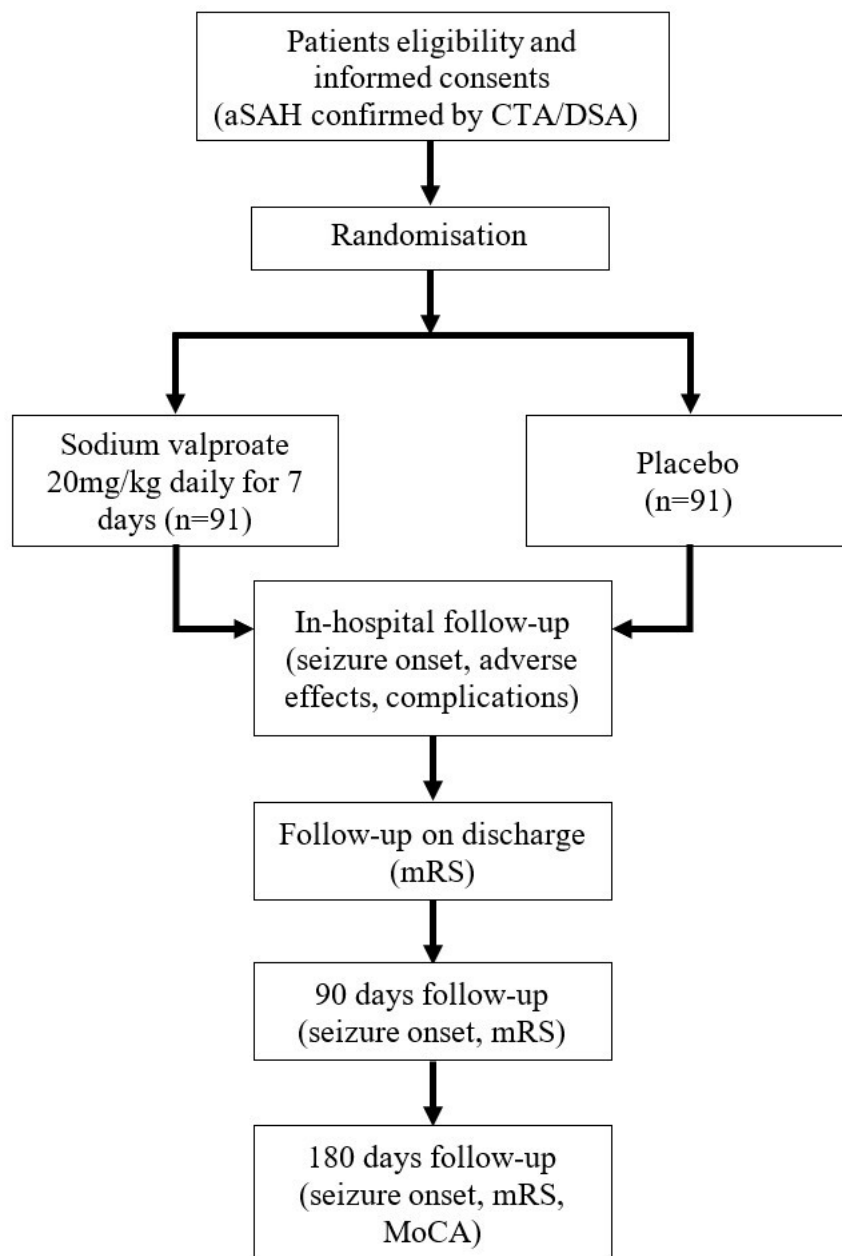


Figure 1 SPSAH trial flow chart. aSAH, aneurysmal subarachnoid haemorrhage; CTA, CT angiography; DSA, digital subtraction angiography; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin Scale; SPSAH, seizure prophylaxis following aneurysmal subarachnoid haemorrhage.

- ▶ Known allergy to sodium valproate.
- ▶ Pregnant woman.
- ▶ Patients and/or LAR refuse treatment.
- ▶ Enrolment in another research study that would conflict with this study.
- ▶ Any other reason that the investigator considers the patient is inappropriate for enrolment.

Randomisation

The central random method will be adopted in this research, and West China Hospital will undertake the central randomisation. All eligible patients will be randomly allocated to either intervention or placebo using a computer-generated random number. We apply

the evaluator-blinded design. Clinicians in charge of patients' treatment will know the allocation of patients. The follow-up evaluator will not know each patient's grouping. After the final statistical analyses have been finished, the randomisation sequence will be non-blinded.

Intervention

All participants will be delivered standard treatment according to the latest guidelines and expert consensus.¹⁸¹⁹ The standard treatment mainly includes blood pressure control, euvolaemia maintenance, nimodipine, neurological monitoring, deep venous thrombosis prophylaxis and general care. Patients allocated into the intervention group will receive sodium valproate 20 mg/kg daily

intravenously in 0.9% normal saline (divided to two times per day, once every 12 hours). Patients allocated into the control group will receive matching placebo. Sodium valproate will be supplied by the local hospital.

Primary outcomes

The incidence of total seizures is the primary outcome of this study. We only record clinical seizures, while subclinical seizures will not be recorded. Diagnosis of seizure is mainly based on the description from medical staff, patients themselves or the caregiver.

Secondary outcomes

The secondary outcome includes the incidence of early seizures (≤ 7 days from SAH ictus), the incidence of late seizures (≥ 7 days from ictus), aSAH-related complications (mainly include rebleeding, fever, pulmonary and urinary infection, cerebral vasospasm, cerebral infarction), sodium valproate-related adverse effects, mRS (on discharge, at 90 days, 180 days), rate of good outcomes (mRS 0–2 will be defined as ‘good outcome’), all-cause death (at 90 days, 180 days) and MoCA score (at 180 days). The mRS will be assessed by a neurologist using structured interviews.²⁶ All neuropsychiatric evaluations (MoCA, Chinese version) will be performed by a qualified specialist in psychiatry.

Data monitoring body

This study will be conducted according to the principles of Declaration of Helsinki and good clinical practice guidelines. An independent data safety and monitoring board (DSMB) composed of physicians, neurosurgeons and intensivists will independently perform non-blinded reviews of all patients’ efficacy and safety data, including adverse events (AEs) and dropout rates, reported from informed consent to 180 days postrandomisation. The DSMB will meet at least every 6 months and hold an interim analysis meeting when half cases have finished 180 days of follow-up. The data generated in our study will be handled while parametric maintaining the anonymity and confidentiality of the participants.

Any untoward medical occurrence of the enrolled patients during this trial will be defined as AE, which does not necessarily have a causal relationship with the intervention. AEs possibly happened during this study mainly include: (1) gastroenterological abnormalities (nausea, vomit, gingival hyperplasia, upper abdominal pain, diarrhoea); (2) abnormal liver function; (3) blood and lymphatic system disorders (anaemia, thrombocytopenia and bone marrow failure); (4) neurological abnormalities (tremor, drowsiness, confusion); (5) skin and subcutaneous tissue disorders (alopecia, angio-neurotic oedema, rash, toxic epidermal necrolysis and Steven-Johnson syndrome). All death due to the progression of AEs will be defined as severe adverse event (SAE). The details of all AEs and SAEs should be reported to DSMB in the corresponding case report form. For SAEs, the report must be submitted within 24 hours.

Sample size estimates

Previous studies reported that patients with aSAH have a 15.3% risk of seizures,⁹ and anticonvulsant (levetiracetam) treatments reduce in-hospital seizure rate to 9% in the short duration (3 days) group compared with 2% in the extended duration (until discharge) arm.²¹ We assume that sodium valproate prophylaxis could reduce the seizure incidence from 15.3% to 3%. The sample size was calculated based on an alpha of 0.05, statistical power of 90% and 10% loss to follow-up, which yielded 182 patients (91 in each arm).

Statistical analyses

All analyses are by intention-to-treat. Categorical endpoints (eg, seizure rate, AEs, mortality, complications) will be compared using χ^2 tests. Continuous and scale variables will be analysed by non-parametric (Wilcoxon rank sum test) or parametric (Student’s t-test) test according to the distribution of different data. Time-to-event outcomes (time to seizure) will be analysed using the log-rank test, with Kaplan-Meier survival curves. Cox regression will also be performed. Subgroup analysis based on age (≥ 70), size of aneurysm, location of aneurysm, rebleeding will also be performed.

DISCUSSION

Although seizure prophylaxis after aSAH is controversial with little clinical evidence available, it is a common practice in SAH management. In a survey among 25 major American neurosurgical centres with high-volume aSAH cases (>100 annually), most administer prophylaxis, and the majority believe a randomised trial on this topic is both timely and ethical.²⁷ It needs to mention that levetiracetam was the first-line medication for the majority (94%) centres in this survey. Sodium valproate, which has been introduced into clinical practice for more than 50 years, is a mainstay of anticonvulsant therapy because of its effectiveness for a wide range of seizures as well as epileptic syndromes.²⁸ In China, sodium valproate is commonly used as prophylactic drug for patients with aSAH due to the low price and better accessibility. Therefore, we choose sodium valproate as the anticonvulsant drug in our study. Previous studies suggested that neurosurgical clipping, as well as the anterior circulation location, were independent risk factors for seizure after aSAH.^{12 29} In our study, only patients who suffered anterior circulation aneurysm rupture and planned to accept surgical clipping would be enrolled, with the aim to narrow into high-risk patients for seizure after aSAH. Our trial still has some limitations. First, although subclinical seizure might also have impact on the functional outcome, we do not apply continuous electroencephalography in our trial with only clinical seizure recorded. Second, we focus on patients with good-grade aSAH planned for clipping. These

strict inclusion criteria would bring barriers for the generalisation of our findings. Third, the sample size is calculated based on an optimistic effect size. Therefore, our trial might be underpowered to detect the effect of the sodium valproate on seizure occurrence after aSAH. Nonetheless, we believe well-designed secondary outcomes could also help us better understand the value of seizure prophylaxis. The results of our trial would have important implications for clinical practice.

ETHICS AND DISSEMINATION

This trial has been approved by the ethics committee of West China Hospital, and has been registered at <http://www.chictr.org/cn/> (ChiCTR2100050161). Informed consent will be achieved from each included patient and/or their legally authorised representative. Preliminary and final results from this study will be disseminated through manuscript publishing and international congresses presentations. Any protocol amendments will be approved by the ethics committee of West China Hospital, and subsequently updated on ChiCTR.

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Competing interests None declared.

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REFERENCES

- Feigin VL, Lawes CMM, Bennett DA, *et al.* Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. *Lancet Neurol* 2009;8:355–69.
- Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. *Lancet* 2017;389:655–66.
- Milinin K, Thapar A, O'Neill K, *et al.* History of aneurysmal spontaneous subarachnoid hemorrhage. *Stroke* 2017;48:e280–3.
- Maher M, Schweizer TA, Macdonald RL. Treatment of spontaneous subarachnoid hemorrhage: guidelines and gaps. *Stroke* 2020;51:1326–32.
- Neifert SN, Chapman EK, Martini ML, *et al.* Aneurysmal subarachnoid hemorrhage: the last decade. *Transl Stroke Res* 2021;12:428–46.
- Butzkueven H, Evans AH, Pitman A, *et al.* Onset seizures independently predict poor outcome after subarachnoid hemorrhage. *Neurology* 2000;55:1315–20.
- Rhoney DH, Tipps LB, Murry KR, *et al.* Anticonvulsant prophylaxis and timing of seizures after aneurysmal subarachnoid hemorrhage. *Neurology* 2000;55:258–65.
- Lin C-L, Dumont AS, Lieu A-S, *et al.* Characterization of perioperative seizures and epilepsy following aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2003;99:978–85.
- Huttunen J, Kurki MI, von und zu Fraunberg M, *et al.* Epilepsy after aneurysmal subarachnoid hemorrhage: a population-based, long-term follow-up study. *Neurology* 2015;84:2229–37.
- Cabral NL, Gonçalves ARR, Longo AL, *et al.* Incidence of stroke subtypes, prognosis and prevalence of risk factors in Joinville, Brazil: a 2 year community based study. *J Neurol Neurosurg Psychiatry* 2009;80:755–61.
- Choi K-S, Chun H-J, Yi H-J, *et al.* Seizures and Epilepsy following Aneurysmal Subarachnoid Hemorrhage: Incidence and Risk Factors. *J Korean Neurosurg Soc* 2009;46:93–8.
- Jaja BNR, Schweizer TA, Claassen J, *et al.* The safari score to assess the risk of convulsive seizure during admission for aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2018;82:887–93.
- Hart Y, Sneade M, Birks J, *et al.* Epilepsy after subarachnoid hemorrhage: the frequency of seizures after clip occlusion or coil embolization of a ruptured cerebral aneurysm: results from the International subarachnoid aneurysm trial. *J Neurosurg* 2011;115:1159–68.
- Little AS, Kerrigan JF, McDougall CG, *et al.* Nonconvulsive status epilepticus in patients suffering spontaneous subarachnoid hemorrhage. *J Neurosurg* 2007;106:805–11.
- De Marchis GM, Pugin D, Meyers E, *et al.* Seizure burden in subarachnoid hemorrhage associated with functional and cognitive outcome. *Neurology* 2016;86:253–60.
- Naidech AM, Kreiter KT, Janjua N, *et al.* Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. *Stroke* 2005;36:583–7.
- Koch S, Gidal BE. Phenytoin and cognitive decline. *Stroke* 2005;36:2070–1.
- Diringer MN, Bleck TP, Claude Hemphill J, *et al.* Critical care management of patients following aneurysmal subarachnoid hemorrhage: recommendations from the neurocritical care Society's multidisciplinary consensus conference. *Neurocrit Care* 2011;15:211–40.
- Connolly ES, Rabinstein AA, Carhuapoma JR, *et al.* Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American heart Association/American stroke association. *Stroke* 2012;43:1711–37.
- Chen Y, Xia F, Cai C, *et al.* Duration and choices of prophylactic anticonvulsants in subarachnoid hemorrhage: a systematic review and meta-analysis. *Neurosurg Rev* 2021;44:2459–67.
- Human T, Diringer MN, Allen M, *et al.* A randomized trial of brief versus extended seizure prophylaxis after aneurysmal subarachnoid hemorrhage. *Neurocrit Care* 2018;28:169–74.
- Steinbaugh LA, Lindsell CJ, Shutter LA, *et al.* Initial EEG predicts outcomes in a trial of levetiracetam vs. fosphenytoin for seizure prevention. *Epilepsy Behav* 2012;23:280–4.
- Gilad R, Boaz M, Dabby R, *et al.* Are post intracerebral hemorrhage seizures prevented by anti-epileptic treatment? *Epilepsy Res* 2011;95:227–31.
- van Gijn J, Bromberg JE, Lindsay KW, *et al.* Definition of initial grading, specific events, and overall outcome in patients with aneurysmal subarachnoid hemorrhage. A survey. *Stroke* 1994;25:1623–7.
- Wilson JTL, Hareendran A, Grant M, *et al.* Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin scale. *Stroke* 2002;33:2243–6.
- Newcommon NJ, Green TL, Haley E, *et al.* Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the modified Rankin scale. *Stroke* 2003;34:377–8.
- Dewan MC, Mocco J. Current practice regarding seizure prophylaxis in aneurysmal subarachnoid hemorrhage across academic centers. *J Neurointerv Surg* 2015;7:146–9.



- 28 Romoli M, Mazzocchetti P, D'Alonzo R, *et al.* Valproic acid and epilepsy: from molecular mechanisms to clinical evidences. *Curr Neuropharmacol* 2019;17:926–46.
- 29 Molyneux AJ, Kerr RSC, Yu L-M, *et al.* International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* 2005;366:809–17.