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Antiepileptic drugs for the primary and secondary prevention of seizures after subarachnoid haemorrhage (Review)

Marigold R, Günther A, Tiwari D, Kwan J

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[Intervention Review]

Antiepileptic drugs for the primary and secondary prevention of seizures after subarachnoid haemorrhage

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ABSTRACT

Background

Subarachnoid haemorrhage may result in seizures both acutely and in the longer term. The use of antiepileptic drugs (AEDs) in the primary and secondary prevention of seizures after subarachnoid haemorrhage is uncertain, and there is currently no consensus on treatment.

Objectives

To assess the effects of AEDs for the primary and secondary prevention of seizures after subarachnoid haemorrhage.

Search methods

We searched the Cochrane Epilepsy Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 1) in *The Cochrane Library*, and MEDLINE (1946 to 12th March 2013). We checked the reference lists of articles retrieved from these searches.

Selection criteria

We considered all randomised and quasi-randomised controlled trials in which patients were assigned to a treatment (one or more AEDs) or placebo.

Data collection and analysis

Two review authors (RM and JK) independently screened and assessed the methodological quality of the studies. If studies were included, one author extracted the data and the other checked it.

Main results

No relevant studies were found.

Authors' conclusions

There was no evidence to support or refute the use of antiepileptic drugs for the primary or secondary prevention of seizures related to subarachnoid haemorrhage. Well-designed randomised controlled trials are urgently needed to guide clinical practice.

PLAIN LANGUAGE SUMMARY

Antiepileptic drugs for the primary and secondary prevention of seizures after subarachnoid haemorrhage

The purpose of this review was to examine whether the routine use of antiepileptic medication in preventing epileptic seizures following subarachnoid haemorrhage can be justified. This includes patients who have not yet had a seizure (primary prevention) and those who have already had one (secondary prevention).

Epileptic seizures are caused by abnormal, rhythmic discharges of nerve cells within the brain leading to involuntary changes in body movement or function, sensation, awareness, or behaviour. Following a subarachnoid haemorrhage seizures can occur in up to 25% of patients, triggered by nerve cell damage caused by the blood itself, the formation of scar tissue, and swelling around the site of bleeding. Recurrent uncontrolled seizures can cause considerable morbidity and mortality, preventing neurological recovery and reducing quality of life. Conversely, side effects of antiepileptic medication include diarrhoea, nausea and vomiting, drowsiness, dizziness, agitation, tremor, confusion and skin rash. These need to be considered when prescribing antiepileptic medication, as the medication itself may hinder neurological recovery and rehabilitation.

To date there have been no randomised controlled trials comparing antiepileptic drugs with placebo following subarachnoid haemorrhage. Some retrospective studies have suggested worse outcomes in patients on higher doses and a longer duration of antiepileptic treatment, as explained in the review, but they do not provide the strength of evidence required for their use as a routine recommendation.

Currently, there is insufficient evidence to justify the routine use of antiepileptic medication for the primary and secondary prevention of seizures after subarachnoid haemorrhage, and a double blind randomised controlled trial comparing antiepileptic medication with placebo would help to clarify this important question.

BACKGROUND

Description of the condition

Subarachnoid haemorrhage (SAH) occurs when blood is released into the subarachnoid space that surrounds the brain and spinal cord (Van Gijn 2001). Although SAH accounts for only 3% of all strokes, it is associated with 5% of all stroke deaths, and for more than 25% of potential life years lost through stroke (Van Gijn 2001). Significant developments have taken place in the management of SAH in the past three decades, including the use of early angiography, endovascular coil embolisation and more sophisticated intensive care support (Butzkueven 2000). Consequently, the outcome of patients with SAH has improved substantially. In the 1970s, the early mortality rate after SAH was as high as 65% (Fogelholm 1981), but in recent years it has fallen to between 20% and 30% (Qureshi 2005). However, 50% of long-term survivors are still permanently disabled (Claassen 2003).

Seizures and epilepsy are well recognised complications after SAH. Seizures can occur at different time points after SAH:
a. 'onset' seizures occur around the time of the initial haemorrhage;
b. 'early' seizures occur during the first two weeks of recovery after SAH or surgery;
c. 'late' seizures occur after the first two weeks of recovery post-SAH or following surgery (Bederson 1997; Buczacki 2004).

However, the definitions of early and late seizures differ between authors, and there is conflicting evidence on whether onset seizures predict late seizures or post-SAH epilepsy (Butzkueven 2000; Byrne 2003). Post-SAH epilepsy refers to the condition where at least two spontaneous seizures occur (some have specified that they should be separated by at least 24 hours) after the first few months following the initial SAH or operation (Buczacki 2004; Lin 2003). One study found that post-SAH epilepsy was more frequent in patients with severe residual neurological impairment (the risk of developing epilepsy was 28% at one year and 47% at four years) compared with patients who had mild or no impairment (the risk was 12% at one year and 15% at four years) (Olafsson 2000). The majority of post-SAH seizure types are secondary generalised tonic-clonic seizures or simple partial seizures (Claassen 2003; Lin 2003). Pinto 1996 reported that although early post-SAH seizures did not predict longer-term prognosis, they were related to a higher risk of re-bleeding, death or dependency by the time of hospital discharge. However, other studies have not found such an association (Sundaram 1986).

The incidence of post-SAH seizures varies widely between observational studies mainly as a result of differences in the patient selection methods, the definitions used to describe the timing of post-SAH seizures, and the administration of prophylactic antiepileptic drugs (AEDs) after admission. In a previous literature review (Lin 2003), 4% to 26% of patients with SAH had onset seizures, 1% to 28% had early seizures (within the first two weeks) and 1% to 35% had late seizures (after two weeks) (Byrne 2003; Lin 2003). Modern techniques, such as continuous electroencephalogram (EEG) monitoring, have assisted with the less common diagnosis of non-convulsive seizures and non-convulsive status epilepticus (Vespa 2005). In one study, 18% of the patients admitted to neurological intensive care units with SAH had non-convulsive seizures (Claassen 2004). Another study reported that 3% of such patients were in non-convulsive status epilepticus (Dennis 2002), and this should be considered in patients with poor neurological status or deterioration (Lanzino 2011).

Risk factors associated with the occurrence of post-SAH seizures include increasing age, a history of hypertension, poor neurological grade (for example Hunt and Hess grade > 3), the presence of an anterior circulation aneurysm (especially middle cerebral artery aneurysms), the volume of subarachnoid blood and occurrence of aneurysmal re-bleeding, vasospasm, cerebral infarction, subdural haematoma, hyponatraemia and hydrocephalus (Claassen 2003; Lin 2003; Ohman 1990). Intracranial aneurysm treatment, either by neurosurgical clipping or endovascular coiling, has a seizure rate of about 2% (Lanzino 2011). Unruptured aneurysms treated with surgical clipping have reported seizure rates of 9.2% to 13%, whereas with coiling this ranges between 6.2% and 8.3% (Hart 2011; Hoh 2011). Endovascular intervention had lower seizure rates (1.3% to 3.3%) compared with surgery (2.2% to 5.2%) in the first year (Hart 2011; Molyneux 2005).

Description of the intervention

There is substantial variability among physicians in the use of AEDs for patients after SAH (Rhoney 2000). Some physicians recommend using prophylactic AEDs for all patients with SAH, especially those undergoing open aneurysmal surgery (King 1994; Ohkuma 1990; Olafsson 2000). Others recommend using AEDs for the in-hospital stay, but not beyond discharge (Varelas 2004). A third approach recommends targeting AEDs to patients with risk factors that predict future seizure (Butzkueven 2000). Some clinicians do not recommend the routine use of AEDs following SAH (Buczacki 2004; Byrne 2003; Claassen 2003), suggesting that further randomised controlled trials are required (Lin 2003; Rapaport 2012; Rhoney 2000). This lack of consensus stems from uncertainty regarding the need for AEDs, the best AED to use, which patients should receive prophylactic AEDs, and the optimal dosage and duration of treatment (Rapaport 2012; Rhoney 2000; Riordan 2010).

How the intervention might work

The intervention might work if, in offering routine prophylaxis to patients with SAH, the risk of seizures exceeded the risk of AED-related adverse effects. Why is seizure prevention important? There is conflicting evidence about whether or not in-hospital post-SAH seizures are associated with a poor functional outcome. Some studies have suggested seizures correlate with poorer outcomes (Butzkueven 2000; Claassen 2003). In 247 patients admitted to a neurological intensive care unit with SAH, the occurrence of in-hospital seizures was an independent predictor of one-year mortality (65% with seizures versus 23% without seizures) (Claassen 2003). This may reflect the severity of the SAH itself, as one retrospective study showed that the higher the grade of SAH, the greater the likelihood of seizure, but there was little association with a poorer prognosis at one year (Lin 2008). Why are AED-related adverse effects significant? Some authors have suggested that poor patient recovery might actually be caused by AED treatment itself, particularly with phenytoin, rather than seizure activity (Claassen 2003; Naidech 2005; Rosengart 2007). A number of studies have assessed neurological outcomes following short and long-term phenytoin treatment (Chumnanvej 2007; Naidech 2005). Poorer outcomes were associated with higher doses and longer duration of phenytoin treatment. In comparing levetiracetam with phenytoin, levetiracetam use resulted in a higher short-term seizure recurrence (Murphy-Human 2011), but

better long-term neurological outcomes and fewer adverse effects (Lewis 2009; Szaflarski 2010). There is also evidence from animal and human studies that the administration of certain AEDs after brain injury (including stroke and SAH) might lower the chance of a good functional recovery (Brailowsky 1986; Claassen 2003; Naidech 2005).

Why it is important to do this review

It is important to do this review to establish whether the use of AEDs in seizure prevention post-SAH can be justified, given the morbidity and mortality associated with untreated epileptic seizures and the potential adverse effects of AED treatment.

OBJECTIVES

The main aim was to assess the effects of AEDs for the primary and secondary prevention of seizures after SAH. For primary prevention, we examined whether AEDs reduced the likelihood of seizures in patients who had had an SAH, but not had a seizure. For secondary prevention, we examined whether AEDs reduced the likelihood of further seizures in patients who had had an SAH and at least one post-SAH seizure.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised and quasi-randomised controlled trials in which patients were assigned to a treatment group (that is receiving at least one AED) or a control group (that is receiving placebo or no treatment).

Types of participants

For a detailed description of the internationally accepted definitions for seizures and epilepsy, please refer to Fisher 2005; for the different types of epileptic seizures, please refer to Engel 2001 and Engel 2006 (by the International League Against Epilepsy). In this review, we considered all studies that recruited patients with a diagnosis of SAH, regardless of whether they had or had not had post-SAH seizures. The diagnosis of SAH was confirmed by neuroimaging using computed tomography (CT) or magnetic resonance (MR) imaging, with or without lumbar puncture (Van Gijn 2001). Studies that exclusively recruited patients with cerebral infarction, primary intracranial haemorrhage, intracranial venous thrombosis or non-stroke conditions (including subdural haemorrhage, extradural haemorrhage, infection- or tumour-related infarction or haemorrhage) were excluded. Patients with a history of epilepsy were excluded. In cases where studies recruited a mixture of patients with and without a history of epilepsy, attempts were made to extract only the results related to those patients without a history of epilepsy.

Children or adults with clinically overt generalised or focal seizures were included, regardless of whether EEG monitoring was used to confirm the diagnosis. For studies that included patients with non-convulsive seizures diagnosed only by EEG (Bearden 2008), the results for these patients were extracted and analysed separately. In cases where studies recruited patients who had prior neurosurgical procedures (for example aneurysmal clipping or coil embolisation) for SAH, the results for these patients were extracted and analysed separately from those of patients who had not received neurosurgery.

Types of interventions

The AEDs included were: carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, gabapentin, lamotrigine, levetiracetam, lorazepam, oxcarbazepine, phenytoin, phenobarbitone, primidone, sodium valproate, tiagabine, topiramate, vigabatrin and zonisamide. We considered all trials in which the intervention was compared with a placebo or no treatment. Studies comparing different AEDs were excluded.

Types of outcome measures

Primary outcomes

1. Proportion of patients who experienced clinical seizures in the scheduled follow-up period. In cases where seizures occurred, we noted their nature (generalised or focal), timing and whether an EEG was performed to aid the diagnosis and seizure classification.
2. Proportion of patients with a previous seizure who achieved remission for a predefined period of time (e.g. 12 or 24 months).
3. Proportion of patients who withdrew from the allocated treatment within the scheduled follow-up period. This was a composite outcome that took into account several factors, including adverse events, compliance and effectiveness of treatment. We were particularly interested in the occurrence of side effects for the different AEDs, which might be physical or neurobehavioural (e.g. problems with memory, attention and performance skills).
4. Proportion of patients who had either died or were dependent at the end of the scheduled follow-up period. 'Independent' individuals were defined as those who did not require regular physical assistance from another person for activities of daily living such as mobility, dressing, transfers and feeding. 'Dependent' individuals were those who failed to meet one or more of these criteria.

Other outcomes of interest

1. Quality of life (e.g. using a recognised scoring system such as the Short Form-36 (SF-36) or EuroQol).
2. Duration of stay for the acute phase of stroke recovery.
3. 'Optimal' duration of treatment (i.e. the length of time that the intervention should be administered).

Search methods for identification of studies

This review drew on the search strategies developed for the Cochrane Epilepsy Group and identified relevant studies in the Cochrane Epilepsy Group Specialized Register.

We searched the following databases:

1. Cochrane Epilepsy Group Specialized Register (15 March 2013) using the search strategy outlined in Appendix 1;
2. the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 1) in *The Cochrane Library* using the search strategy outlined in Appendix 2; and
3. MEDLINE (Ovid) (1946 to 12 March 2013) using the search strategy outlined in Appendix 3.

We also checked the reference lists of articles retrieved from the above searches.

Data collection and analysis

Selection of studies

One review author (RM) screened the titles, abstracts and keywords of publications identified by the searches to assess their eligibility. Publications that did not meet the inclusion criteria were excluded at this stage. A paper copy of the full publication of each study that was relevant was obtained. Two review authors (RM and JK) assessed these studies according to pre-specified selection criteria.

Data extraction and management

One review author (RM) recorded the data on an extraction form. Another review author (JK) independently checked the extracted data. Data reported by the published sources were used for analyses in this review. We extracted demographic data (for example total number of participants randomly assigned, number of participants per group, and age and sex of participants) and possible confounding factors (for example timing of randomisation, method of SAH diagnosis, level of sedation after surgery, location of aneurysm, severity of neurological deficit, presence of vasospasm or secondary cerebral infarction, history of epilepsy, other comorbid disorders, number of patients who were lost to follow-up, duration of follow-up, and method of treatment, such as aneurysmal clipping or coil embolisation).

Assessment of risk of bias in included studies

Two review authors (RM and JK) independently assessed the methodological quality of all the included studies and recorded the findings. We noted the important aspects of methodology: study design, type of control, method of allocation concealment, completeness of follow-up, and the presence of blinding for assessments of non-fatal outcomes.

Data synthesis

Data analysis was designed according to the guidelines set out by The Cochrane Collaboration regarding statistical methods. Primary analyses were by intention to treat. For dichotomous data, we expressed the relative treatment effects as an odds ratio with 95% confidence interval. For continuous data, we calculated the weighted mean difference with 95% confidence interval. A P value of less than 0.05 was considered statistically significant. Clinical heterogeneity was assessed by the distribution of demographic and prognostic variables across the treatment and control groups. Statistical heterogeneity among the studies was tested using the I^2 statistic. In cases where the results could be sensibly combined and there was no significant clinical or statistical heterogeneity, a meta-analysis was undertaken using a fixed-effect or random-effects model, or both. Sensitivity analyses were undertaken to test the robustness of the meta-analysis as described above. The influence of the following factors on the overall results was assessed: methodological quality, excluding the study with the smallest or largest sample size, and removing the study with the smallest or largest treatment effects.

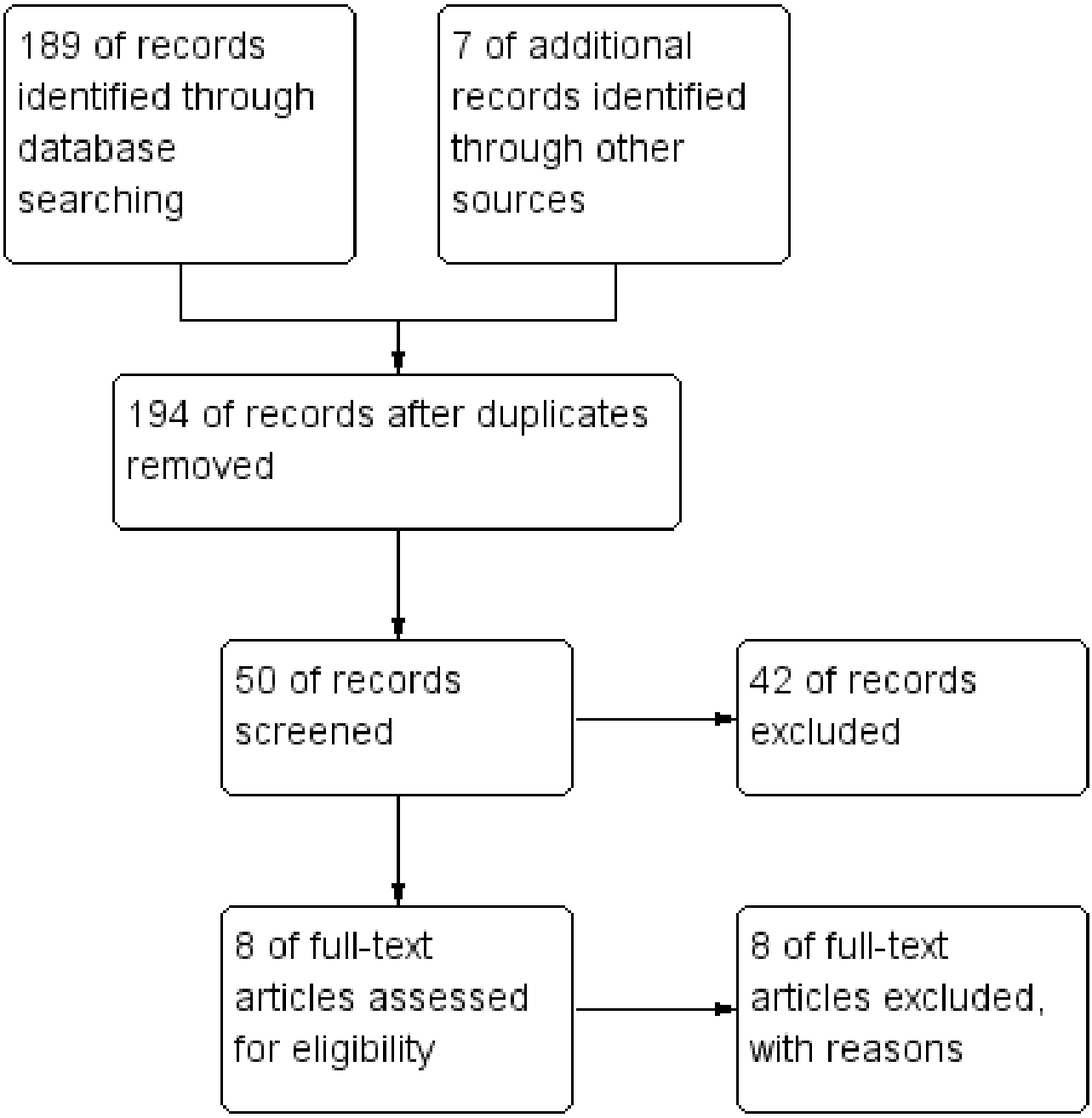
RESULTS

Description of studies

Results of the search

A total of 194 studies were identified by the search: 50 records were screened, 42 were initially excluded, and the remaining eight were excluded with reasons following analysis of the full texts. The eight studies were excluded due to lack of randomisation of the AED versus placebo, and most of these studies were retrospective analyses. Consequently, no studies met the inclusion criteria, see Figure 1.

Figure 1. Study flow diagram.



Excluded studies

No studies provided a randomised controlled trial of an AED versus placebo, but there were a number of retrospective analyses which provided useful information upon which future randomised studies could be based. See Characteristics of excluded studies.

Risk of bias in included studies

No studies were included in the review.

Effects of interventions

No studies met the inclusion criteria.

DISCUSSION

The purpose of this review was to assess the effects of AEDs for the primary and secondary prevention of seizures after SAH. None of the studies selected in the review could be used for further analysis as there were no randomised or quasi-randomised controlled trials comparing antiepileptic drugs (AEDs) with placebo or no drug. As demonstrated by the table of excluded studies, the data that are currently available were mainly limited to retrospective analyses following a change in AED protocol, rather than randomised, placebo controlled trials (Chumnanvej 2007; Murphy-Human 2011; Naidech 2005; Szaflarski 2010). These have limited applicability both due to their retrospective nature and the small number of patients studied.

International guidelines suggest that prophylactic AEDs should not be routinely prescribed, but considered in selected cases. The American Stroke Association (Bederson 2009) states that for aneurysmal SAH, AED prophylaxis may be considered in the post-haemorrhagic period and longer term for those with risk factors for seizure recurrence. This includes prior seizure, parenchymal infarct or haematoma and a middle cerebral artery aneurysm. European Stroke Initiative (ESI) Guidance on intracerebral haemorrhage (Steiner 2006) recommends consideration of prophylactic AEDs for seven days in patients with lobar haemorrhage, after which AED treatment should be stopped. Should seizures recur, the ESI recommends AEDs be restarted and continued for 30 days then stopped following a gradual reduction in dose.

Given the lack of robust evidence to determine best practice, we recommend that a large randomised, double blind, placebo controlled trial is conducted to assess the effectiveness, adverse event profile and optimum duration of AEDs to prevent seizures following SAH. Examples would be double blind randomised trials comparing phenytoin with placebo and levetiracetam with placebo. The results of such studies will then inform decision making in weighing up the benefits of AEDs in both primary and secondary seizure prophylaxis against the risk of long-term adverse neurological, cognitive and functional outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Currently, there is insufficient evidence to support the routine use of antiepileptic drugs for the primary or secondary prevention of seizures after subarachnoid haemorrhage.

Implications for research

More research is needed to assess the efficacy and tolerability of antiepileptic drugs for the primary and secondary prevention of seizures after subarachnoid haemorrhage. Future studies should be randomised double-blind trials comparing one or more AEDs to placebo. These should aim to recruit large numbers of patients and generate answers to the optimal dosing, timing and duration of AED treatment as well as defining side effects and longer-term cognitive and functional outcomes.

ACKNOWLEDGEMENTS

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hemorrhage: "to detect and protect". *Journal of Clinical Neurophysiology* 2005;**22**(2):99-106.

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chumnanvej 2007	Not a randomised controlled trial. Patients allocated to short (3 days) or longer-term (until hospital discharge) phenytoin treatment with no comparison with placebo
Lewis 2009	Retrospective analysis examining levetiracetam and phenytoin in seizure prophylaxis
Murphy-Human 2011	Not a randomised controlled study, retrospective analysis of seizure recurrence based on extended phenytoin use versus 3 days of levetiracetam
Naidech 2005	Not a randomised controlled trial. Calculation of phenytoin "burden" based on average serum levels and functional and cognitive outcomes then assessed
Rapaport 2012	Retrospective analysis of the outcome of antiepileptics used in non-traumatic intracranial haemorrhage, not a randomised controlled trial
Rhoney 2000	Retrospective analysis of patient charts, not a randomised controlled trial
Rosengart 2007	Retrospective analysis of AED prescribing patterns in patients randomised to tirilizad assessing neurological outcome and in-hospital complications. Not a randomised controlled trial of AED medication
Szaflarski 2010	Randomised single blind trial, but compared levetiracetam with phenytoin rather than placebo; 89% of patients with traumatic brain injury rather than subarachnoid haemorrhage

APPENDICES

Appendix 1. Cochrane Epilepsy Group Specialized Register search strategy

#1 MeSH DESCRIPTOR Subarachnoid Hemorrhage Explode All WITH BL CF CI CL CO CN DI DH DT EC EM EN EP EH ET GE HI IM ME MI MO NU PS PA PP PC PX RA RI RT RH SU TH US UR VE VI [REFERENCE] [STANDARD]

#2 MeSH DESCRIPTOR Intracranial Hemorrhages Explode All WITH BL CF CI CL CO CN DI DH DT EC EM EN EP EH ET GE HI IM ME MI MO NU PS PA PP PC PX RA RI RT RH SU TH US UR VE VI [REFERENCE] [STANDARD]

#3 MeSH DESCRIPTOR Intracranial Aneurysm WITH BL CF CI CL CO CN DI DH DT EC EM EN EP EH ET GE HI IM ME MI MO NU PS PA PP PC PX RA RI RT RH SU TH US UR VE VI [REFERENCE] [STANDARD]

#4 MeSH DESCRIPTOR Rupture, Spontaneous WITH BL CF CI CL CO CN DI DH DT EC EM EN EP EH ET GE HI IM ME MI MO NU PS PA PP PC PX RA RI RT RH SU TH US UR VE VI [REFERENCE] [STANDARD]

#5 #3 AND #4 [REFERENCE] [STANDARD]

#6 MeSH DESCRIPTOR Aneurysm WITH BL CF CI CL CO CN DI DH DT EC EM EN EP EH ET GE HI IM ME MI MO NU PS PA PP PC PX RA RI RT RH SU TH US UR VE VI [REFERENCE] [STANDARD]

#7 MeSH DESCRIPTOR Brain Explode All WITH AB AH BS CY DE EM EN GD IM ME MI PS PA PH PP RE RA RI SE SU UL VI [REFERENCE] [STANDARD]

#8 #6 AND #7 [REFERENCE] [STANDARD]

#9 (subarachnoid OR arachnoid) NEAR (haemorrhage* OR hemorrhage* OR bleed* or blood*) [REFERENCE] [STANDARD]

#10 MeSH DESCRIPTOR Vasospasm, Intracranial WITH BL CF CI CL CO CN DI DH DT EC EM EN EP EH ET GE HI IM ME MI MO NU PS PA PP PC PX RA RI RT RH SU TH US UR VE VI [REFERENCE] [STANDARD]

#11 (cerebral OR intracranial OR cerebrovascular) NEAR (vasospasm OR spasm) [REFERENCE] [STANDARD]

#12 sah [REFERENCE] [STANDARD]

#13 #1 OR #2 OR #5 OR #8 OR #9 OR #10 OR #11 OR #12 [REFERENCE] [STANDARD]

#14 2012 TO 2013:YR [REFERENCE] [STANDARD]

#15 #13 AND #14 [REFERENCE] [STANDARD]

Appendix 2. CENTRAL search strategy

1. MeSH descriptor Subarachnoid Hemorrhage explode all trees

2. MeSH descriptor Intracranial Hemorrhages explode all trees

3. MeSH descriptor Intracranial Aneurysm, this term only

4. MeSH descriptor Rupture, Spontaneous, this term only

5. (3 AND 4)

6. MeSH descriptor Aneurysm, Ruptured, this term only

7. MeSH descriptor Brain explode all trees

8. (6 AND 7)

9. (subarachnoid OR arachnoid):ti,ab,kw NEAR/6 (haemorrhage* OR hemorrhage* OR bleed* or blood*):ti,ab,kw

10. MeSH descriptor Vasospasm, Intracranial, this term only

11. (cerebral OR intracranial OR cerebrovascular):ti,ab,kw NEAR/6 (vasospasm OR spasm):ti,ab,kw

12. (sah):ti,ab,kw

13. (1 OR 2 OR 5 OR 8 OR 9 OR 10 OR 11 OR 12)

14. (epilep*):ti,ab,kw

15. MeSH descriptor Epilepsy explode all trees

16. (seizure*):ti,ab,kw

17. MeSH descriptor Seizures explode all trees

18. (convulsion*):ti,ab,kw

19. (anticonvulsant*):ti,ab,kw

20. MeSH descriptor Anticonvulsants explode all trees

21. (antiepilep*):ti,ab,kw

22. phenytoin:ti,ab,kw

23. valpro*:ti,ab,kw

24. carbamazepine;ti,ab,kw

25. ethosuximide:ti,ab,kw

26. primidone:ti,ab,kw

27. phenobarbit*:ti,ab,kw

28. MeSH descriptor Phenobarbital explode all trees

29. (14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28)

30. (13 AND 29)

Appendix 3. MEDLINE search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomised controlled trials (Lefebvre 2009).

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. clinical trials as topic.sh.

6. randomly.ab.

7. trial.ti.

8. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7

9. exp animals/ NOT humans.sh.

10. 8 NOT 9

11. exp Subarachnoid Hemorrhage/

12. exp Intracranial Hemorrhages/

13. Intracranial Aneurysm/

14. Rupture, Spontaneous/

15. 13 AND 14

16. Aneurysm, Ruptured/

17. exp Brain/

18. 16 AND 17

19. ((subarachnoid OR arachnoid) adj6 (haemorrhage$ OR hemorrhage$ OR bleed$ OR blood$)).tw.

20. Vasospasm, Intracranial/

21. ((cerebral OR intracranial OR cerebrovascular) adj6 (vasospasm OR spasm)).tw.

22. sah.tw.

23. 11 OR 12 OR 15 OR 18 OR 19 OR 20 OR 21 OR 22

24. epilep$.tw.

25. exp Epilepsy/

26. seizure$.tw.

27. exp Seizures/

28. convulsion$.tw.

29. anticonvulsant$.tw.

30. exp Anticonvulsants/

31. antiepilep$.tw.

32. phenytoin.tw.

33. valpro$.tw.

34. carbamazepine.tw.

35. ethosuximide.tw.

36. phenobarbit$.tw.

37. exp Phenobarbital/

38. primidone.tw.

39. OR/24-38

40. 10 AND 23 AND 39

CONTRIBUTIONS OF AUTHORS

Richard Marigold and Joseph Kwan undertook the literature search, Divya Tiwari and Albrecht Gunther provided expert opinion and editorial support. All authors contributed to the final manuscript.

DECLARATIONS OF INTEREST

None known

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INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Secondary Prevention [*methods]; Seizures [etiology] [*prevention & control]; Subarachnoid Hemorrhage [*complications]

MeSH check words

Humans