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Induced hypertension for preventing complications of delayed cerebral ischaemia in aneurysmal subarachnoid haemorrhage (Protocol)

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[Intervention Protocol]

Induced hypertension for preventing complications of delayed cerebral ischaemia in aneurysmal subarachnoid haemorrhage

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of induced hypertension in people with an aneurysmal subarachnoid haemorrhage, following treatment of the aneurysm (either surgical clipping, or intraluminal coiling), on favourable recovery, and recurrent haemorrhage.

BACKGROUND

Description of the condition

Aneurysmal subarachnoid haemorrhage (SAH), with an incidence of approximately eight people per 100,000 (ACROSS Group 2000), is one of the most devastating neurological diseases. Whilst it accounts for only 3% to 5% of all strokes, it is responsible for approximately a quarter of all cerebrovascular deaths. After aneurysmal SAH, delayed cerebral ischaemia (DCI) occurs in approximately 30% of patients and is associated with a 1.5 to 3-fold increase in case fatality (Vergouwen 2011). DCI is a clinical syndrome that occurs up to 14 days after the initial bleed, characterised by a decrease in the level of consciousness or a new focal deficit, or both. Symptoms of DCI are seen when the cerebral blood flow (CBF) does not meet the demand of the brain tissue. The most common cause of DCI is assumed to be vasospasm. In the first two weeks following aneurysm occlusion the prevalence of cerebral vasospasm, as measured by angiography, approaches 70% (Adamczyk 2013). Vasospasm causes symptomatic cerebral ischaemia and infarction in approximately 20% to 30% of patients, which may result in long-term morbidity and mortality.

Description of the intervention

Induced hypertension implies an active intervention to increase the blood pressure of people with SAH after the aneurysm has been treated by either surgery (clipping) or intraluminal therapy (coiling). This intervention usually involves the administration of vasoactive agents, such as noradrenaline, phenylephrine, metaraminol, or any other agent administered for that indication. Intravascular volume expansion is not considered to be an intervention to induce hypertension for the purpose of this review.

How the intervention might work

The underlying pathophysiological mechanism for the development of DCI is not clearly known. Clinically significant vasospasm of cerebral arteries is thought to be related to spasmogenic substances generated during the lysis of subarachnoid blood clots. In addition, novel pathological mechanisms have been suggested, including damage to cerebral tissue in the first 72 hours after aneurysmal rupture, cortical spreading depressions, and microthrombosis (Rowland 2012). Vasospasm may result in secondary ischaemia as a direct consequence of reduction in blood flow.

Possible factors responsible for clinical improvement can be as follows.

- Induced hypertension may reduce the incidence of vasospasm or the incidence of vasospasm-related complications by providing an increased perfusion pressure which may overcome the reduction in blood flow.
- SAH may be associated with increased intracranial pressure (ICP). Induced hypertension may improve the cerebral perfusion pressure (CPP), which is defined as the difference between mean arterial pressure (MAP) and ICP.
- Vasoactive agents - in particular noradrenaline - have been shown to have immunomodulating and anti-inflammatory properties resulting in additional physiological effects. Whether these effects could play a role in the prevention of DCI is currently unknown.

Why it is important to do this review

It is routine practice in neurosurgical intensive care units to prescribe supranormal blood pressure targets following surgical or intraluminal treatment of the aneurysm in people with SAH (Connolly 2012; Meyer 2011). Whilst improvements in CBF have been noted (Muench 2007; Treggiari 2011), it is not established whether targeting an increased blood pressure by means of administering vasoactive agents reduces the incidence of DCI and results in improved patient outcomes (Lee 2006; Treggiari 2003; Treggiari 2009).

In addition, the so-called Triple-H therapy, comprising of induced hypertension, hypervolaemia, and haemodilution, has been used for many years in an effort to increase CBF in people with DCI following SAH (Dabus 2013; Meyer 2011). Recent analysis, including a Cochrane Review, has shown that there is insufficient evidence that CBF improves as a result of these interventions (Diringer 2011; Rinkel 2004). From all components, induced hypertension appears most promising in increasing CBF (Dankbaar 2010).

The aim of this review is to systematically analyze all controlled trials of induced hypertension in people with SAH for preventing or treating DCI to provide the best available evidence for clinical practice and to guide further research in this field.

OBJECTIVES

To assess the effects of induced hypertension in people with an aneurysmal subarachnoid haemorrhage, following treatment of the aneurysm (either surgical clipping, or intraluminal coiling), on favourable recovery, and recurrent haemorrhage.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs) and cluster-RCTs if available. If these are unavailable, we will consider including controlled trials based on consecutive groups of patients quasi-randomly allocated to treatment or control.

Types of participants

People of any age and gender with an aneurysmal SAH documented by computed tomography (CT) scan, who underwent treatment of the aneurysm (either surgical clipping, or intraluminal coiling) and who entered the trial within two weeks after the SAH.

Types of interventions

We will include trials that compare treatment with any blood-pressure-increasing intervention (induced hypertension), such as vasoconstricting agents (including noradrenaline, metaraminol, phenylephrine) versus placebo or no treatment.

Types of outcome measures

Primary outcomes

- Unfavourable outcome (death, persistent vegetative state, or severe disability (modified Rankin Scale (mRS) score 4 to 6, Extended Glasgow Outcome Scale (GOSE) 4 to 6 or equivalent) at 90 days after SAH.

Secondary outcomes

- Death (any cause) after 90 days, death (any cause) in the intensive care unit, death (any cause) in hospital.
- Unfavourable outcome (death, persistent vegetative state, or severe disability (mRS score 4 to 6, GOSE 4 to 6 or equivalent) at six months after SAH.

- Established cerebral infarction at any time within 90 days after SAH, confirmed radiologically by CT or magnetic resonance imaging (MRI).
- Incidence of DCI and vasospasm-related complications within three weeks of the SAH based on clinical examination. DCI is defined as a neurological deterioration, seen at least three to four days after the haemorrhagic ictus, not explained by other causes, including re-bleeding, seizures, hydrocephalus, or other as determined by brain imaging.
- Re-bleeding: recurrent haemorrhage during the intervention or within 24 hours after the intervention. This may be considered probable (where a sudden deterioration leading to death, without confirmation of rebleeding by CT, MRI or post-mortem examination), or definite (where a sudden clinical deterioration with rebleeding is confirmed by CT, MRI, or post-mortem examination).
- Complications of the treatment. We will define a complication as a clinical deterioration observed during the intervention or within 24 hours after the intervention. These complications include arrhythmias, cardiac ischaemia, mesenteric ischaemia, digital ischaemia, and haemorrhagic stroke unrelated to the primary disease.
- Physiological outcome measures during the intervention or within 24 hours after the intervention. These include CBF, cerebral perfusion pressure, cerebral tissue oxygenation, cerebral microdialysis, cardiac output, and MAP.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We will search for trials in all languages and arrange for the translation of relevant articles where necessary.

Electronic searches

We will search the Cochrane Stroke Group Trials Register and the following electronic databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library, latest issue).
- MEDLINE Ovid (from 1948) (Appendix 1).
- Embase Ovid (from 1980).

We developed the MEDLINE search strategy (Appendix 1) with the help of the Cochrane Stroke Group Information Specialist and will adapt it for the other databases.

We will also search the following ongoing trials registers.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/).
- Stroke Trials Registry (www.strokecenter.org/trials/).
- ISRCTN Registry (www.isrctn.com).
- DORIS (Database Of Research In Stroke: askdoris.org).
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

Searching other resources

We will screen the reference lists of relevant studies to identify further studies for potential inclusion in the review. We will also use Science Citation Index Cited Reference Search to find references that cite a particular author or journal article (implicit citations). We will also contact trialists of the identified trials for any published or unpublished studies they might be aware of. We may contact study authors for clarification and further data if trial reports are unclear.

Data collection and analysis

Selection of studies

Two review authors (PV and PM) will independently screen titles and abstracts of the references obtained as a result of our searching activities and will exclude obviously irrelevant reports. We will retrieve the full-text articles of the remaining potentially relevant references. Two review authors (PV and PM) will independently screen the full-text articles and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies in the 'Characteristics of excluded studies' table. We will resolve any disagreements through discussion or, if required, we will consult a third review author (FvH). We will collate multiple reports of the same study so that each study, not each reference, is the unit of interest in the review. We will record the study selection process and complete a PRISMA flow diagram.

Data extraction and management

Two review authors (PV and SC) will independently extract data from the included studies using a data collection form. We will resolve any disagreements through discussion or, if required, we will consult a third review author (FvH).

Assessment of risk of bias in included studies

Two review authors (CL and SC) will independently assess the risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving a third review author (FvH). We will assess the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We will assess the risk of bias for each domain as either high, low, or unclear and will provide information from the study report together with a justification for our judgment in the 'Risk of bias' tables.

Measures of treatment effect

We will undertake the following analysis: we will base the primary analysis on the intention-to-treat results (if available) of the individual trials, for case fatality, 'unfavourable outcome' (death, vegetative state, or severe disability), and for the occurrence of specific events (DCI, cerebral infarction, rebleeding, complications of treatment, and effect on physiological parameters).

Unit of analysis issues

If included studies utilised different blood pressure targets, we will combine them into comparison groups 'induced hypertension' versus 'normotension' (control). For 'unfavourable outcome' (primary outcome), we will examine results at 90 days following SAH. For 'death: any cause' (secondary outcome), we will examine intensive care unit, hospital, and 90-day mortality separately.
If we identify cluster-RCTs, we will conduct the analysis at the same level as the allocation, using a summary measurement from each cluster, so the sample size is the number of clusters and we will do the analysis as if the trial was individually randomized (though the clusters become the individuals).

Dealing with missing data

lf primary analyses suggest a beneficial effect but follow-up was not complete, we will perform a worst-case scenario analysis. If the effects of primary and worst-case meta-analyses are in the same direction and magnitude, a definitive conclusion about the treatment effectiveness can be made; otherwise no definitive conclusion can be made. Where possible, we will contact study authors for incomplete or missing data.

Assessment of heterogeneity

We will calculate an estimate of the treatment effect across trials (relative risk (RR) with a 95% confidence interval (CI)) using standard methods. To quantify inconsistency across studies, we will use the I^2 statistic to describe the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). We will use the following I^2 thresholds: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity; while acknowledging that thresholds for the interpretation of I^2 can be misleading, since the importance of inconsistency depends on several factors.

Assessment of reporting biases

We aim to reduce reporting bias through a comprehensive search strategy with the inclusion of multiple search engines. We will use funnel plots to make a visual assessment of whether small-study effects - as often caused by publication bias - may be present in the meta-analysis. If there are more than 10 studies included in the meta-analysis, we will use statistical tests for funnel plot asymmetry.

Data synthesis

Where we consider studies to be sufficiently similar, we will conduct a meta-analysis by pooling the appropriate data using Review Manager 5 (RevMan 5) (RevMan 2014).

'Summary of findings' table

We will summarise included studies in a 'Summary of findings' table, listing the following information grouped by outcomes: absolute risk, comparative risks, relative effect, number of participants (studies), and the quality of the evidence (Table 1). We will assess the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (GRADE 2013).

Subgroup analysis and investigation of heterogeneity

Induced hypertension may have different effects and outcomes when applied as a preventative strategy in all people with SAH following aneurysmal occlusion, compared with applying the intervention as treatment for people who have developed DCI. We plan to do the following subgroup analyses.

- Induced hypertension to prevent DCI (prophylaxis).
- Induced hypertension to treat DCI (treatment).

Sensitivity analysis

We aim to perform a sensitivity analysis to test the robustness of our results by investigating the impact of methodological study quality on the results: high risk of bias versus unclear risk. We aim to examine the resulting forest plot for direction of treatment effect, for the effect sizes in studies with high risk of bias versus studies at unclear risk of bias.

ACKNOWLEDGEMENTS

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versus delayed cerebral ischemia as an outcome event in clinical trials and observational studies. *Neurocritical Care* 2011;**15**(2):308–11.

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. 'Summary of findings' table template

Induced hypertension versus no induced hypertension in people with aneurysmal subarachnoid haemorrhage (SAH)						
Participants: people with aneurysmal subarachnoid haemorrhage documented by CT scan, who underwent treatment of the aneurysm (either surgical clipping or intraluminal coiling) and entered the trial within 2 weeks after the SAH **Setting:** hospital **Intervention:** induced hypertension **Comparison:** without induced hypertension						
Outcomes	**Absolute risk**	**Comparative risk (95% CI)**	**Relative effect (95% CI)**	**Number of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Unfavourable outcome[1] (90 days)						
Death (any cause) at 90 days; in the intensive care unit; in hospital						
Unfavourable outcome[1] (6 months)						
Incidence of DCI and vasospasm-related complications within 3 weeks of the SAH						
Cerebral infarction[2]						
Re-bleeding[3]						
Complications of intervention[4]						

Table 1. 'Summary of findings' table template (*Continued*)

Physiological outcome measures[5]						

Abbreviations: CT scan: computed tomography scan; MRI scan: magnetic resonance imaging scan; SAH: subarachnoid haemorrhage; DCI: delayed cerebral ischaemia; CI: confidence interval; RR: risk ratio; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MAP: mean arterial blood pressure.

[1]Unfavourable outcome: death, persistent vegetative state, or severe disability (modified Rankin Scale (mRS) score 4 to 6, Extended Glasgow Outcome Scale (GOSE) 4 to 6 or equivalent) at 90 days after SAH.

[2]Established cerebral infarction at any time within 90 days after SAH, confirmed radiologically by CT or MRI scan.

[3]Recurrent haemorrhage during the intervention or within 24 hours after the intervention.

[4]Complications of intervention, defined as a clinical deterioration observed during the intervention or within 24 hours after the intervention. These complications include arrhythmias, cardiac ischaemia, mesenteric ischaemia, digital ischaemia, and haemorrhagic stroke unrelated to the primary disease.

[5]Physiological outcome measures during the intervention or within 24 hours after the intervention. These include cerebral blood flow (CBF), cerebral perfusion pressure, cerebral tissue oxygenation, cerebral microdialysis, cardiac output and mean arterial blood pressure (MAP).

APPENDICES

Appendix 1. MEDLINE search strategy

1. Subarachnoid Hemorrhage/
2. intracranial hemorrhages/ or cerebral hemorrhage/
3. Intracranial Aneurysm/
4. Rupture, Spontaneous/
5. 3 and 4
6. Aneurysm, Ruptured/
7. exp brain/ or exp meninges/
8. 6 and 7
9. ((subarachnoid or arachnoid) adj6 (haemorrhage$ or hemorrhage$ or bleed$ or blood$)).tw.
10. SAH.tw.
11. 1 or 2 or 5 or 8 or 9 or 10
12. Vasospasm, Intracranial/
13. ((cerebral or brain or intracranial or cerebrovascular) adj6 (vasospasm or spasm)).tw.
14. Ischemic Attack, Transient/ or brain ischemia/
15. (delay$ adj5 neurol$ adj5 deficit$).tw.
16. (DND or DIND).tw.
17. (delay$ adj5 (ischemi$ or ischaemi$)).tw.
18. or/12-17
19. 11 or 18
20. hypertension/ci or intracranial hypertension/ or blood pressure/ or arterial pressure/
21. (triple H or triple-H or HHH or hyperdynamic).tw.
22. ((increase$ or raise$) adj5 (blood or plasma or fluid) adj5 volume).tw.

23. ((increase$ or raise$ or maintain$) adj5 blood pressure).tw.
24. ((reduce$ or decreas$ or lower$) adj5 blood viscosity).tw.
25. (hypervolemi$ or hypervolaemi$ or (induc$ adj5 hypertension) or hypertensive or hemodilut$ or haemodilut$).tw.
26. blood volume/ or plasma volume/ or blood viscosity/
27. hemodilution/ or fluid therapy/
28. blood substitutes/ or plasma exchange/ or exp plasma substitutes/
29. hetastarch/ or dextrans/ or poly geline/ or povidone/ or exp albumins/ or sodium chloride/ or saline solution, hypertonic/ or expcolloids/
30. (hemodilut$ or haemodilut$).tw.
31. (plasma adj3 (expand$ or expansion or exchange$ or substitut$ or replace$)).tw.
32. (blood adj3 (expand$ or expansion or exchange$ or substitute$ or replace$ or remov$ or dilut$)).tw.
33. (hetastarch or pentastarch or hydroxyethy lstarch or hydroxyethyl-starch or dextran$ or polygeline or povidone or albumin or salineor colloid$).tw.
34. VIH.tw.
35. or/20-34
36. exp vasoconstrictor agents/ or calcium channel agonists/
37. vasopressins/ or arginine vasopressin/
38. ((vasoconstrict$ adj3 (agent$ or agonist$)) or vasopress$).tw.
39. (calcium channel adj3 (agonist$ or activat$)).tw.
40. exp angiotensins/
41. (angiotensin or arginine vasopressin or dihydroergotamine or ephedrine or epinephrine or ergotamine or etilefrine or felypressin or lypressin or mephentermine or metaraminol or methoxamine or methysergide or midodrine or nordefrin or norepinephrine or octopamine or ornipressin or phenylephrine or racepinephrine or sumatriptan or synephrine or vasopressins or vasotocin).tw.
42. exp Dopamine Agents/
43. (dopamin$ adj3 agonist$).tw.
44. (alnespirone or apomorphine or brexpiprazole or bromocriptine or cabergoline or cy 208-243 or dihydrexidine or dihydroergocornine or dihydroergocryptine or dihydroergotamine or dihydroergotoxine or dironyl or docarpamine or dopexamine or ergocryptine or fananserin or fenoldopam or ibopamine or lisuride or mesulergine or metergoline or "n 0437" or naxagolide or ncq 298 or pd 158771 or pergolide or piribedil or pramipexole or preclamol or quinagolide or quinelorane or quinpirole or ropinirole or stepholidine or talipexole).tw.
45. exp Adrenergic Agonists/
46. exp Sympathomimetics/
47. sympathomimet$.tw.
48. (adrenerg$ adj3 agonist$).tw.
49. (albuterol or clenbuterol or clonidine or dexmedetomidine or dobutamine or epinephrine or ergotamine or etilefrine or fenoterol or formoterol fumarate or guanabenz or guanfacine or hexoprenaline or isoetharine or isoproterenol or isoxsuprine or medetomidine or mephentermine or metaproterenol or metaraminol or methoxamine or methyldopa or midodrine or naphazoline or nebivolol or norepinephrine or nylidrin or octopamine or oxyfedrine or oxymetazoline or phenylephrine or phenylpropanolamine or prenalterol or procaterol or racepinephrine or ritodrine or salmeterol xinafoate or synephrine or terbutaline or tretoquinol or xamoterol or xylazine).tw.
50. or/36-49
51. 35 or 50
52. Randomized Controlled Trials as Topic/
53. Random Allocation/
54. Controlled Clinical Trials as Topic/
55. control groups/
56. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
57. double-blind method/
58. single-blind method/
59. Placebos/
60. placebo effect/
61. cross-over studies/
62. randomized controlled trial.pt.

63. controlled clinical trial.pt.
64. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
65. (random$ or RCT or RCTs).tw.
66. (controlled adj5 (trial$ or stud$)).tw.
67. (clinical$ adj5 trial$).tw.
68. ((control or treatment or experiment$ or intervention) adj5 (group$ or subject$ or patient$)).tw.
69. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
70. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
71. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.
72. (cross-over or cross over or crossover).tw.
73. (placebo$ or sham).tw.
74. trial.ti.
75. (assign$ or allocat$).tw.
76. controls.tw.
77. or/52-76
78. 19 and 51 and 77

CONTRIBUTIONS OF AUTHORS

FvH wrote the protocol, which was reviewed by PV, SC, PM, and CJL.

DECLARATIONS OF INTEREST

Frank Van Haren: none known.

Peter Velloza: none known.

Sean Chan: none known.

Peter Mews: none known.

Christian J Lueck: none known.