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Medically induced hypertension, hypervolaemia and haemodilution for the treatment and prophylaxis of vasospasm following aneurysmal subarachnoid haemorrhage: systematic review

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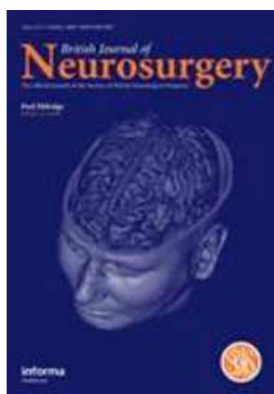
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Medically induced hypertension, hypervolaemia and haemodilution for the treatment and prophylaxis of vasospasm following aneurysmal subarachnoid haemorrhage: Systematic Review

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Table 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8,9,15



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-14, Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11-15
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	15-18
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	15-18
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	nil
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18-19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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3 **Medically induced hypertension, hypervolaemia and haemodilution**
4 **for the treatment and prophylaxis of vasospasm following**
5 **aneurysmal subarachnoid haemorrhage: Systematic Review**
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9 **Responses to reviewers comments**
10

11 James JM. Loan MRCS MSc¹, Anthony N. Wiggins MRCS², Paul M.
12 Brennan FRCS PhD³.
13
14

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3 Dear Sir/Madam,
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6 We thank the reviewers for their time and effort in reviewing our
7 manuscript. We have considered their criticisms and improved our
8 manuscript accordingly. The reviewers' comments, our responses,
9 and rationales for them are set out below. Should any further
10 changes/clarifications be thought to be necessary we would be
11 delighted for the opportunity to undertake them.
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13

14
15 Yours Sincerely,
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23 The authors

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25 James JM. Loan
26 Paul M. Brennan
27 Anthony N. Wiggins
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Reviewer: 1

Comments to the Author

Loan et al perform a systematic review of triple-H therapy for the prophylaxis and treatment of aneurysmal subarachnoid haemorrhage. My comments are included below:

Major issues

1. No large randomized trial of induced hypertension for subarachnoid haemorrhage has been undertaken. But the rapid improvement of most patients with this therapy and their worsening when it is stopped prematurely are convincing evidence of efficacy. While induced hypertension is now hardwired in clinical practice and in every guideline, its impact on outcome has not yet been submitted to the scrutiny of an adequately powered RCT. This was the aim of the HIMALAIA study (Hypertension Induction in the Management of Aneurysmal subArachnoid haemorrhage with secondary Ischaemia), a multicenter RCT that was terminated in 2015 due to slow recruitment. This termination confirms that it seems unlikely any such trial will ever be conducted given the lack of clinical equipoise. The authors should acknowledge the evidence base for hypertensive therapy as stated above, and the wide acceptance of its use.

Response: Whilst some clinicians feel strongly that induced hypertension is an effective intervention, surveys of practice (cited in our study) do not demonstrate tight adherence to guidelines recommending inducement of hypertension. Furthermore, our study has demonstrated - and guidelines acknowledge a lack of - satisfactory evidence of efficacy. The incidence of harm in use of vasopressors/inotropic drugs following SAH has been poorly quantified. It is our contention that anecdote and observational evidence described by reviewer one is not convincing of evidence of efficacy. Nonetheless we have added to our discussion this paragraph acknowledging the perceived lack of equipoise and difficulty in recruitment to RCT as described by reviewer 1: "Induced hypertension using vasopressor or inotropic support is at present recommended in favor of HHH by most guidelines and many units have adopted this approach^{3, 8, 9}. Indeed, a perceived lack of equipoise by treating clinicians may have been a factor in the HIMALAIA study's failure to match recruitment targets^{19, 20}. However, at present only insufficiently powered randomised studies, observational studies and anecdote exist on which to base this. As induction of hypertension may be associated with increased serious adverse events it is essential that an adequately powered RCT be conducted to provide clinical guideline writing groups and individual clinicians with the evidence base necessary to balance risks and benefits when recommending widespread adoption of high risk management strategies⁸."

2. The evidence for hypertensive therapy in SAH has been summarised in a published systematic review in the British Journal of Anaesthesia in 2016 (Veldman et al). Loan et al in this paper under review claim that their study adds a number of elements to the published literature. However, It is incorrect to state that the Lennihan 2000 and Egge 2001 papers were not identified by the 2015 BJA review. They are both referenced within the BJA paper as references 87 and

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3 89. They were not included in the analysis as only studies published in the
4 previous 5 years were analysed.

5 *Response: we have adjusted the wording of this statement to more accurately*
6 *reflect this: "Furthermore, we have identified an additional three cohort studies,*
7 *which, although identified, have not been included in previous systematic reviews^{24,}*
8 *25, 28, 37."*
9

10
11 In addition, the stated benefit of including the 3 cohort studies in providing
12 '...the most comprehensive contemporary review of the evidence' is very limited
13 given the low quality of the cohort studies, which the authors acknowledge in the
14 preceding paragraph.

15 *Response: updated to acknowledge this: "Our study therefore provides a*
16 *comprehensive contemporary review of the limited evidence base and unanswered*
17 *questions concerning the use of haemodynamic therapy for the treatment and*
18 *prophylaxis of vasospasm following SAH."*
19

20
21 Finally, the rationale for the exclusion of the 2 papers published in 'Neurocritical
22 Care' applies more rigorous criteria in a selective manner. Rondeau et al (2012)
23 examining dobutamine to increase CI versus noradrenaline to increase MAP; and
24 Ibrahim et al (2013) a propensity-score matched analysis examining colloid and
25 fluid balance of patients enrolled in the CONSCIOUS-1 study.

26
27 *Response: we have carefully and fully re-reviewed both of these papers. We believe*
28 *that our initial decision not to include these was correct. Ibrahim, et al. (2013)'s*
29 *paper did not meet our inclusion criteria as the treatment group included patients*
30 *with either induced hypervolaemia or maintained normovolaemia using colloids*
31 *and as a consequence any treatment effect could not be attributed to a particular*
32 *haemodynamic manipulation. This rationale has been clarified and we believe*
33 *applies the same standard for non-inclusion as we have for all other studies, in*
34 *particular Frontera (2010) and Kissoon (2015) – which were excluded for similar*
35 *reasons as documented in the text. Our clarification is: "One study was excluded as*
36 *the treatment group included both those with hypervolaemic fluid supplementation*
37 *and normovolaemic colloid administration and consequently effects of either of*
38 *these interventions and consequent physiological changes could not be reliably*
39 *attributed.³⁰"*
40

41 *The paper by Rondeau (2012) was excluded at the screening stage and*
42 *consequently the rationale for exclusion was not documented in our previously*
43 *submitted manuscript.. Nonetheless, we have subjected this study to full review and*
44 *have therefore updated our manuscript to reflect this, with rationale for exclusion*
45 *documented. This trial randomised patients to either dopamine (to increase*
46 *cardiac index) or - what presumably at the author's institution is - standard care*
47 *including use of noradrenaline to induce hypertension. Although the control arm*
48 *did achieve a statistically significantly higher MAP than the dopamine group, the*
49 *majority of both arms of the study received noradrenaline for blood pressure*
50 *augmentation. Furthermore the study report does not disclose whether these*
51 *interventions were undertaken prior to vasospasm onset. As this is their primary*
52 *outcome and as angiography was undertaken at enrollment this information is*
53 *crucial. Whilst this is an interesting study of augmentation of cardiac index, it is not*
54 *designed to assess the impact of noradrenaline as a prophylactic measure or*
55 *treatment for vasospasm and cannot inform on this matter. We have updated our*
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manuscript as follows: "One study was excluded as it was unclear what fraction of the treatment and control groups had the primary outcome of vasospasm at enrollment and both treatment arms received noradrenaline for induction of hypertension³⁰." This applies the same reasons for exclusion as Reynolds (2015) and Murphy (2017).

We have argued here that these studies were excluded on similar bases to other studies which were excluded to reviewer one's satisfaction, with reasons documented, following full text review. Were these two studies to be included in our study therefore, this would require modification of our inclusion criteria and consequently repetition of the abstract screening process.

3. If the protocol was not registered beforehand, the authors should submit the protocol with the paper for assessment.

Response: we have submitted the protocol for assessment and also expanded our methods to fully represent it, as per reviewer two.

4. The primary outcome is vague. Which outcomes do the authors refer to? Mortality? Neurologic deficit? The term 'clinical outcome' covers a multitude. The authors should be more specific.

Response: amended: "Our primary research question was: "does prophylactic HHH therapy using crystalloid volume expansion improve outcome as assessed using a standardised neurological clinical outcome score - such as modified Rankin Scale (mRS) or Glasgow Coma Scale (GCS) score - following aneurysmal SAH compared with no those managed with no haemodynamic augmentation?"^{17, 18}."

5. Where is the table of included studies? In a summary of the literature such as this, a table of included studies is essential to allow the reader to have a clear view of interventions, populations, outcomes etc.

Response: we have produced a table of included studies and referenced to it in the text.

Minor issues

1. Page 6, Line 50:

"...vary considerably: indicating uncertainty..." – incorrect usage of colon.

Response: corrected

2. Page 7, Line 16:

"...the incidence of is believed..." – has the word 'vasospasm' been omitted here?

Response: yes – corrected.

3. Page 7, Line 18:

"...it remains unclear if is a prophylactic..." – the word 'is' is extraneous here.

Response: corrected

4. Page 11, Line 14:

"...or attempt statistically quantify..." – attempt to

Response: corrected

5. Page 13, Line 3:

"Vasospasm detected..." – should this be 'Vasospasm was detected...'?

Response: corrected

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4 6. Page 17, Line 25:

5 “Vermeij et al showed reduced rates of DND at 28 days ($P > 0.001$)”. – should this
6 read $P < 0.001$? I was unable to find this figure for DND at 28 days in the Vermeij
7 paper – where was this found?

8 *Response: corrected and clarified. This can be found on page 928 of Vermeij’s*
9 *paper: “the occurrence of cerebral ischemia in group B was significantly lower than*
10 *that in group A2 ($P < 0.00005$ by log rank test)”. Our updated manuscript reads:*
11 *“Vermeij, et al.²⁶ Showed reduced rates of DND at 28 days ($P < 0.001$) and 3 months*
12 *($p = 0.006$) in the hypervolaemia group. However, these figures are associated with*
13 *significant risk of confounding as the hypervolaemia group was treated with*
14 *nimodipine whereas the normovolaemia group was not. For this analysis both*
15 *groups received tranexamic acid”*
16
17

18
19 7. Page 20, Line 5:

20 “One cohort study of moderate quality was included demonstrated...” – should
21 this be “One cohort study of moderate quality demonstrated...” or similar?

22 *Response: amended*
23

24 8. References

25 2, 6, 7, 10,

26 14, 18, 21, 24, 25, 26 are incomplete.

27 23 and 36 are identical.

28 *Response: All references reviewed and amended where appropriate.*
29
30

31 Reviewer: 2
32

33 Comments to the Author

34 In this manuscript, the authors perform a systematic literature review to
35 determine the efficacy of prophylactic “HHH” therapy (e.g., hypervolemia,
36 hypertension, and hemodilution) in the setting of patients with aneurysmal SAH
37 and vasospasm. From their conclusions, they deduce that there is insufficient
38 evidence to determine the efficacy, or non-efficacy, of HHH therapy for the
39 treatment or prophylaxis of vasospasm following SAH. This manuscript is a topic
40 of great interest to physicians involved in the treatment of aneurysmal SAH (e.g.,
41 neurosurgeons, vascular neurologists, neuro critical care specialists, and
42 interventional neuroradiologists alike). While the authors’ findings/conclusions
43 have been reported previously, this manuscript provides additional, important
44 information to the existing literature given that it (1) includes a more
45 comprehensive list of scientific articles than published previously, and (2)
46 proposes a new RCT by which that these important questions could be
47 adequately answered (including proposed number of patients and statistical
48 power calculations). As such, I believe that it is worth of publication in its current
49 form with minor modifications.
50

51 My suggestions are listed below:
52

53 1. In the Introduction and Methods section, the authors should more
54 carefully define their definition of “vasospasm” following SAH. Does this include
55 radiographic, clinical, and or NHND?, Do all forms of vasospasm require
56 treatment (e.g., asymptomatic, mild, radiographic spasm)?
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3 *Response: given the considerable uncertainty concerning the optimal definition of*
4 *vasospasm for clinical practice, including threshold for treatment, and wide degree*
5 *in variation in practice we elected to include studies reporting any definition of*
6 *vasospasm. The definitions used by each included study are documented in the text*
7 *and, as suggested we have updated our introduction and methods sections:*

8 *“Furthermore, a wide range of definitions for vasospasm exists – from the*
9 *development of new, clinically evident focal or global neurologic deficits not*
10 *attributable to another cause, to solely radiological diagnoses reliant on cerebral*
11 *angiography, transcranial doppler, CT evidence of new ischaemic change or*
12 *cerebral perfusion studies.” “To reflect the high degree of uncertainty concerning*
13 *the optimal mode of diagnosis of vasospasm following SAH as well as treatment*
14 *thresholds, we elected to include studies utilizing any means of diagnosis of*
15 *vasospasm.”*

16
17
18 2. To further underscore the importance of the authors’ clinical question,
19 they should include further data on the devastating natural history of untreated,
20 clinically-symptomatic, arterial vasospasm following SAH.

21 *Response: although little quality data exists to allow precise quantification of the*
22 *impact of untreated vasospasm we have expanded this section: “Undiagnosed and*
23 *insufficiently treated cerebral arterial vasospasm causing cerebral ischaemia has*
24 *historically been implicated as a major cause of death at autopsy following*
25 *subarachnoid haemorrhage, alongside re-bleeding from untreated aneurysms³.*
26 *Although with modern, active treatment including haemodynamic intervention the*
27 *association of vasospasm with mortality can be reduced, potentially disabling*
28 *neurological deficits attributable to vasospasm continue to affect 20% of those who*
29 *have not died prior to presentation to hospital⁴.”*

30
31 3. The review protocol should be included in the Methods section, as this is
32 the major crux of the manuscript

33 *Response: We have updated our methods section to include all relevant data from*
34 *our protocol. We did not include our strategy for meta-analysis as this was not*
35 *undertaken, but our rationale for not doing this has been described. Our protocol*
36 *has been submitted alongside this resubmission as per reviewer one.*

37
38 4. I would recommend that this article be reviewed by a member of the BJNS
39 editorial staff with an expansive knowledge and familiarity of systematic review
40 with specific attention to the methodologies of the manuscript

41 *Response: We agree*
42
43
44

45 Associate Editor's Comments to Author:

46
47 Associate Editor

48 Comments to the Author:

49 This is a well written paper but the authors need to address the concerns and
50 recommendations of the reviewers. I have only one additional comment: The
51 authors conclude with the suggestion of performing a randomised controlled
52 trial (RCT). Can you clarify exactly what would be the interventions in the 2 arms
53 of the trial? I think it would be very difficult to convince clinicians to randomise
54 patients into a trial where patients in one arm of the trial do not receive
55 hypertensive therapy.
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Response: This is a key issue and we have further developed our suggestion for future research: "Medically induced hypertension is an appropriate intervention for testing in an RCT as it can be more easily quantified and achieved than a positive fluid balance. Furthermore, concerns regarding the theoretically deleterious effects of haemodilution on oxygen carrying capacity of blood are not relevant to medically induced hypertension. As a radiological diagnosis of vasospasm does not always correlate with clinical outcome, primary outcome of such a study must be based on a validated, standardised clinical measure, such as the GOS or mRS.^{24, 36, 41} One RCT included in this study was terminated early because of slow patient recruitment²¹. We estimate to have 80% power to detect a 10% increase in patients with a favorable in 3-month GOS (4-5) an RCT would have to recruit 133 patients to each treatment and control arm⁴². Induced hypertension has become entrenched practice in some UK centers and consequently use of a normotensive control group might be considered to be unacceptable by these centers¹⁰. A pragmatic solution is to compare high and low hypertensive blood pressure thresholds achieved using a standardised protocol. Protocol development should be informed by a comprehensive national audit of practice. Audit data from centers not routinely employing vasopressor induced hypertension could feed into a before and after observational study with comparison against those enrolled in a subsequent RCT. Recent years have seen a proliferation in neurosurgical research collaboratives, such as the British Neurosurgical Trainees Research Collaborative, which have successfully pooled UK neurosurgical efforts to facilitate patient recruitment to large multicenter studies⁴³⁻⁴⁵. Use of a similar collaborative research model may allow for patient recruitment to be successfully completed"

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6 **Medically induced hypertension, hypervolaemia and haemodilution for**
7 **the treatment and prophylaxis of vasospasm following aneurysmal**
8 **subarachnoid haemorrhage: Systematic Review**
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13 Brennan FRCS PhD³.
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34
35 DISCLOSURE: The authors report no conflict of interest concerning the materials or methods
36 used in this study, or the findings specified in this paper.
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41 FUNDING: None
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46 AUTHOR CONTRIBUTIONS: JJML designed and conducted the study. ANW conducted
47 duplicate assessment of risk of bias of all included studies. PMB designed the study. All authors
48 were involved in manuscript preparation.
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53 BIOGRAPHICAL NOTE
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6 James JM. Loan: Neurosurgery Clinical Development Fellow and Honorary Research Fellow at
7 NHS Grampian and the University of Aberdeen. Academic interest in epidemiology and
8 systematic review methodology.
9

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11
12
13 Anthony N. Wiggins: Neurosurgery specialty trainee at NHS Grampian. Local trainee lead
14 investigator for the Dex-CSDH randomised clinical trial.
15

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17
18
19 Paul M. Brennan: Senior Clinical Lecturer and Honorary Consultant Neurosurgeon at the
20 University of Edinburgh and NHS Lothian. He combines his operative work with laboratory
21 research into the origin of gliomas. He also has an active involvement in clinical research and
22 was co-founder of the British Neurosurgical Trainee Research Collaborative that he helped
23 found as Chair of the British Neurosurgical Trainees Association in 2012.
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6 **Medically induced hypertension, hypervolaemia and haemodilution for the**
7 **treatment and prophylaxis of vasospasm following aneurysmal subarachnoid**
8 **haemorrhage: Systematic Review**
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11
12
13 ABSTRACT: Word count: 282

14 Purpose: Arterial vasospasm is a major cause of death and long-term disability
15 following subarachnoid haemorrhage (SAH). The use of medically induced
16 hypertension, hypervolaemia and/or haemodilution is widely practiced for
17 prophylaxis and treatment of vasospasm following SAH. We aimed to determine
18 if the quality of available research is adequate to inform use of haemodynamic
19 management strategies to prevent or treat vasospasm following SAH.
20

21 Methods: Individual searches of the following databases were conducted: The
22 Cochrane Database of Systematic Reviews, The Cochrane Central Register of
23 Controlled Trials, MEDLINE, EMBASE and OpenSIGLE. Pertinent randomised
24 clinical trials and cohort studies comparing any element or combination thereof:
25 medically induced hypertension, hypervolaemia, and haemodilution were
26 included. Data were extracted using standardised proformas and risk of bias
27 assessed using a domain-based risk of bias assessment tool.
28

29 Results: 348 study reports were identified by our literature search. Eight studies
30 were included, three of which examined both volume expansion and medically
31 induced hypertension. Three randomised clinical trials and two cohort studies
32 examining prophylactic volume expansion were included. Two trials of
33 prophylactic medically induced hypertension and two cohort studies were
34 included. One trial and one cohort study of medically induced hypertension for
35 treatment of established vasospasm was included. These trials demonstrated no
36 significant difference in any of the clinical outcome measures studied. No trials
37 of blood transfusion were included.
38

39 Conclusions: There is currently insufficient evidence to determine the efficacy or
40 non-efficacy of intravenous volume expansion, medically induced hypertension
41 or blood transfusion for the treatment or prophylaxis of vasospasm following
42 SAH. All of these approaches have been associated with adverse events, of
43 unclear incidence. The current evidence base therefore cannot be used to reliably
44 inform clinical practice. This is a priority for further research.
45

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therapy

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Introduction

Subarachnoid haemorrhage (SAH) accounts for around 5% of all cases of stroke and has a reported incidence of between 7-13 per 100,000 person years.¹ Death occurred by 6 months in 26% of cases in one large series, with angiographic presence of cerebral vasospasm being a major predictor of subsequent morbidity and mortality.²

Undiagnosed and insufficiently treated cerebral arterial vasospasm causing cerebral ischaemia has historically been implicated as a major cause of death at autopsy following subarachnoid haemorrhage, alongside rebleeding from untreated aneurysms³.
Although with modern, active treatment including haemodynamic intervention the association of vasospasm with mortality can be reduced, potentially disabling neurological deficits attributable to vasospasm continue to affect 20% of those who have not died prior to presentation to hospital⁴. Controversy exists regarding the optimal strategy for the diagnosis, the prevention and treatment of cerebral vasospasm.⁵ Options include use of systemic nimodipine, a calcium channel antagonist⁶; cerebral angiography with local application of intra-arterial antispasmodics,⁷ angioplasty and stenting⁸; and systemic haemodynamic manipulation.

Haemodynamic therapy, including medically induced hypertension, hypervolaemia and haemodilution – often referred to as HHH therapy – has been widely practiced for at least 20 years.⁹ American Stroke Association guidelines, based on a review of literature available in a single database prior to 2010, noted that evidence for all aspects of haemodynamic intervention was insufficient and consequently recommended maintenance of euvolaemia and induction of hypertension for management of suspected vasospasm¹⁰. Perhaps as a consequence of the limited strength of these recommendations, HHH therapy continues to be widely practiced - by

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6 100% of respondents to one survey¹¹. In one other recent survey of European practice,
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8 HHH was utilised more frequently than medically-induced hypertension alone⁵. Where
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10 haemodynamic augmentation is undertaken, the clinical targets, the timing and the
11
12 means of their achievement vary considerably¹¹, indicating uncertainty regarding the
13
14 relative merits and risks of each of the components of HHH.

15
16 Aggressive intravenous administration of crystalloid or colloid is associated with
17
18 hypertension and haemodilution.^{12, 13} This is proposed to optimize blood flow through
19
20 the vasospastic vessel by improving cerebral perfusion pressure and reducing blood
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22 viscosity.¹² However, excessive hypervolaemia risks precipitating acute heart failure.
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24 Significant haemodilution reduces the oxygen carrying capacity of blood and thus may
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26 impair cerebral oxygenation. To address these concerns, other approaches including
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28 normovolaemic fluid supplementation,¹⁴ vasopressor support,¹⁵ and blood transfusion¹⁶
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30 have been attempted.

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32 Although the incidence of vasospasm is believed to peak between 6-10 days
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34 post-SAH,^{17, 18}, it remains unclear if ~~is~~ a prophylactic or a reactive approach to
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36 haemodynamic augmentation is best? It is also unclear which haemodynamic
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38 management strategy, if any, is preferable. Furthermore, a wide range of definitions for
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40 vasospasm exists – from the development of new, clinically evident focal or global
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42 neurologic deficits not attributable to another cause, to solely radiological diagnoses
43
44 reliant on cerebral angiography, transcranial doppler, CT evidence of new ischaemic
45
46 change or cerebral perfusion studies.¹⁹⁻²³

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48 Given the lack of existing literature to address these uncertainties in clinical
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50 practice, and inform guideline development we conducted a sensitive systematic review
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52 of published literature using multiple databases to determine if there is sufficient
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54 evidence to guide practice in use of medically induced hypertension, hypervolaemia and
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6 haemodilution for the treatment and prophylaxis of vasospasm following aneurysmal
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8 SAH.
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10 11 12 13 **Methods**

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16 Our review protocol was not registered a priori. It is available on request from the
17
18 corresponding author. This study was conducted as part of a series of systematic
19
20 reviews and the study protocol specified our inclusion criteria for population,
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22 interventions, comparisons, outcomes and study types. It also specified how data-
23
24 extraction and assessment of risk of bias would be conducted.
25

26 27 **Objectives**

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29 Our primary research question was: “does prophylactic HHH therapy using crystalloid
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31 volume expansion improve ~~clinical~~ outcome as assessed using a standardised
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33 neurological clinical outcome score - such as modified Rankin Scale (mRS) or Glasgow
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35 Coma Scale (GCS) score - following aneurysmal SAH compared with no those
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37 managed with no haemodynamic augmentation?”^{24, 25}. Secondary outcomes included
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39 comparisons of outcome, rates of clinically evident delayed neurological deficit (DND)
40
41 and of complications between patients managed with volume expansion, medically
42
43 induced hypertension and blood transfusion – either therapeutically or as a prophylactic
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45 measure.
46

47 48 **Inclusion criteria**

49 50 *Types of studies*

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53 We ~~sought to identify~~ included studies using a RCTs and/or all-cohort studies-study
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~~methodology. Prospective and retrospective studies were included, comparing HHH, or an element of HHH, with any alternative management strategy. Studies where both arms were treated with an element of HHH (e.g. induced hypervolaemia) but only one was managed with another element (e.g. induced hypertension) were included. Prospective and retrospective studies were included.~~

Types of participants

Studies of patients older than the age of 16 who had radiographic or biochemical evidence of SAH were identified. Only studies of patients with intracranial ruptured aneurysms secured using surgical clipping or endovascular coiling were included. Both studies reporting patients with vasospasm prior to intervention commencement and patients without vasospasm prior to intervention commencement were included but were analysed separately.

Types of intervention

~~Studies comparing HHH, or an element of HHH, with any alternative management strategy were included. Studies where both arms were treated with an element of HHH (e.g. induced hypervolaemia) but only one was managed with another element (e.g. induced hypertension) were included.~~

Types of comparator group

~~Studies using a valid comparison group receiving the same management strategy except for the intervention of interest were included.~~

Types of outcome measure

We included studies meeting the preceding criteria that used any reported outcome

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6 measure, including clinical outcome scores, incidence of vasospasm, and radiological
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8 evidence of ischaemic injury. To reflect the high degree of uncertainty concerning the
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10 optimal mode of diagnosis of vasospasm following SAH as well as treatment
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12 thresholds, we elected to include studies utilizing any means of diagnosis of vasospasm,
13
14 with different definitions of vasospasm considered separately.
15
16 ~~Vasospasm definitions permitted included clinical definitions of DND and radiological~~
17
18 ~~evidence of vasospasm, although these groups were considered separately.~~
19

20 21 Search strategy

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23
24 Scoping searches identified appropriate MeSH headings and keywords to allow for
25
26 sensitive systematic searches to be conducted. Keywords were mapped to appropriate
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28 MeSH headings and truncated terms mapped to the first 600 appropriate MeSH
29
30 headings. The following electronic databases were then searched for items published up
31
32 to 9 May 2017: The Cochrane Database of Systematic Reviews, The Cochrane Central
33
34 Register of Controlled Trials, MEDLINE (PubMed) and EMBASE (1947-2016). Grey
35
36 Literature searching was performed for the OpenSIGLE database. Table 1 shows the
37
38 abbreviated search strategy. Snowballing and Pearl search strategies were used as
39
40 appropriate. The abstracts of all studies identified by our electronic search were
41
42 screened and if inclusion criteria were met the full study report was accessed and
43
44 considered for inclusion. If it was unclear from the abstract if inclusion criteria would
45
46 be met then the whole study was accessed for review.
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48 49 ***Data collection and analysis***

50 51 *Data extraction and quality assessment*

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54 Each included study was reviewed by two authors (JL, AW) and the following data
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6 recorded: the study design, participants, details and timing of interventions,
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8 comparisons drawn and study results. Any reported outcome measure was collected.

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10 For RCTs, risk of bias in the following domains was assessed and judged as high, low
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12 or unknown risk, as per the validated Cochrane Risk of Bias Assessment Tool²⁶:

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14 Random sequence generation; allocation concealment; blinding of trial participants and
15
16 trial personnel; blinding of outcome assessment; completeness of data collection; and
17
18 completeness of data reporting.

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20 For cohort studies the following were assessed²⁶: selection bias; allocation
21
22 concealment; blinding of trial participants and trial personnel; blinding of outcome
23
24 assessment; completeness of data collection; and completeness of data reporting.

25
26 Differences in reviewer opinion were resolved by consensus discussion.

27 28 29 *Data analysis*

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31 Following quality assessment and data extraction, outputs of included studies were
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33 independently considered as applied to each of the following subgroups to determine
34
35 their adequacy to inform clinical practice.

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38 • Prophylactic (intervention introduced prior to vasospasm)
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40 ○ Crystalloid or colloid volume expansion
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42 ○ Blood transfusion
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44 ○ Medically induced hypertension
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46 • Therapeutic (intervention introduced following proven or suspected vasospasm)
 - 47
48 ○ Crystalloid or colloid volume expansion
 - 49
50 ○ Blood transfusion
 - 51
52 ○ Medically induced hypertension
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Meta-analysis and meta-biases

~~We~~ As significant methodological heterogeneity was found between studies it was not possible for us to attempt ~~to~~ meaningful meta-analysis or attempt to statistically quantify for meta-biases such as publication bias.

Results

Description of studies

Our literature search yielded 348 abstracts (Figure 1). Of these, ~~165~~ reports of ~~154~~ studies were considered for inclusion in our review.^{15, 16, 19-23, 27-34} One study was excluded as the treatment group included both those with hypervolaemic fluid supplementation and normovolaemic colloid administration and consequently effects of either of these interventions and consequent physiological changes could not be reliably attributed.³⁵ Two studies were excluded as the majority of patients in the treatment group had suspected vasospasm whilst those in the control did not.^{15, 34} One study was excluded as it was unclear what fraction of the treatment and control groups had the primary outcome of vasospasm at enrollment and both treatment arms received noradrenaline for induction of hypertension.²³ Another two were excluded because treatment with hypervolaemic and normovolaemic fluid administration was not dichotomized and fluid boluses were administered in all patients as a response to suspected vasospasm.^{31,32} One other study was excluded as two of the three studied populations contained both patients who were receiving the study intervention to treat vasospasm and also patients for whom it was prophylactic.¹⁶ Eight studies were included in this review (Table 2).^{19-22, 27-30, 33}

Four of the included studies were RCTs.^{19-22, 28} Four were cohort studies^{27, 29, 30, 33}; for one of these the study protocol was published prospectively.²⁷ Seven reported

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6 clinical outcomes.^{19, 20, 27-30, 33} One reported only on cerebral blood flow (CBF), as
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8 measured using CT perfusion scanning.^{21, 22} In six studies, the intervention was
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10 introduced as a prophylactic measure.^{19, 20, 27-30} In two studies the intervention was with
11
12 therapeutic intent.^{21, 22, 33}

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15 ***Included RCTs: risk of bias (figure 2)***

16
17
18 *Lennihan 2000*¹⁹

19
20 Patients in this RCT were randomly assigned to prophylactic hypervolaemic fluid
21
22 management (n=41) or normovolaemia (n=41). All patients had SAH secondary to
23
24 ruptured aneurysms, which underwent surgical clipping <6 days post-ictus. All patients
25
26 were managed with intravenous colloid, with those in the hypervolaemic group
27
28 receiving prophylactic supplementary 5% albumin solution targeting central venous
29
30 pressure (CVP) 8mmHg or pulmonary artery diastolic pressure 14mmHg. All patients
31
32 who developed vasospasm were managed according to the same protocol regardless of
33
34 their group assignment. The primary outcome measure was difference in mean global
35
36 CBF. Incidence of vasospasm and 3, 6 and 12 month Glasgow Outcome Scale (GOS)
37
38 score were also collected.³⁶ 12 month GOS was not reported. Patients and outcome
39
40 assessors were blinded but the treating team was not.

41
42
43 *Egge 2001*²⁰

44
45 In this trial, 32 patients with confirmed aneurysmal SAH were randomised to either
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47 HHH therapy (n=16) or normovolaemic fluid therapy (n=16). Ruptured aneurysms were
48
49 secured surgically within 72h of ictus onset. HHH was maintained using 5.0-5.5L daily
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51 intravenous fluid supplementation using colloid and crystalloid to target CVP 8-
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53 12mmHg and haematocrit 30-35%. Additional dobutamine infusion was used if
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6 required to maintain mean arterial pressure (MAP) >20mmHg above preoperative
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8 baseline. The primary outcome was not stated. GOS at 14 days and 1 year was
9
10 measured. Vasospasm was detected on transcranial Doppler and single-photon emission
11
12 computed tomography at day 12 ~~and 1 year~~. Batteries of neuropsychological tests were
13
14 also reported at 1 year. Patients and personnel were unblinded. Outcome assessors were
15
16 blinded for most outcomes except GOS measurement.

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19 *Togashi 2015*²⁸

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21 This trial used a 2x2 factorial design to randomise 20 patients to either 10 days
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23 normovolaemia (n=10) or hypervolaemia (n=10) and to either 10 days of conventional
24
25 blood pressure (CBP) or augmented blood pressure (ABP) control. All patients had
26
27 angiographically proven SAH, underwent clipping or coiling <72h post-ictus and were
28
29 randomised <72h post-ictus. Hypervolaemia was achieved with intravenous fluid
30
31 supplementation at 60ml/kg/24h targeting a positive fluid balance of 1-2L/24h and CVP
32
33 >8mmHg. The ABP group received noradrenaline or phenylephrine infusion to target
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35 systolic blood pressure (SBP) 140-160mmHg or SBP>160mmHg in the presence of
36
37 vasospasm. The primary outcome measure was the modified Rankin Scale (mRS) score
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39 at 6 months post-ictus.²⁴ Just 20 of 190 screened patients were randomised. This study
40
41 was single blinded, with adequate allocation concealment and loss of one patient to
42
43 follow up.

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46 *Gathier 2015*^{21, 22}

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48 This trial randomised 36 patients to induced hypertension (n=13) or no hypertension
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50 (n=12). 11 patients were excluded because of protocol violations. All patients had
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52 aneurysmal subarachnoid haemorrhage and DND, defined as a decrease ≥ 1 point on the
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54 Glasgow coma scale (GCS) or development of new focal neurological deficit not
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6 attributable to other cause.²⁵ Patients in the induced hypertension group received
7
8 noradrenaline infusion to raise MAP or SBP to a maximum of 130mmHg or 230mmHg,
9
10 respectively. The primary outcome as published a priori in the study protocol was “the
11 proportion of poor outcome three months after randomization, defined as a modified
12 Rankin scale of 4, 5, or death”. This however was not reported in the published report,
13 which provided ~~was~~ change in mean CBF at 36h post-randomisation, estimated using
14 CT perfusion scanning at development of DND and 24-36h post-randomisation as the
15 primary outcome measure. Baseline differences in mean World Federation of
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17 Neurosurgical Societies SAH grade between groups were noted and patients and
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19 personnel were unblinded. Outcome assessment was blinded.

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Included cohort studies: risk of bias

Yano 1993³⁰

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32 This prospective cohort study compared 15 patients receiving prophylactic intravenous
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34 dobutamine infusion and volume expansion using 25% albumin or plasma fractionates
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36 with 13 patients treated with a dobutamine infusion and thromboxane A₂ synthetase
37
38 inhibitor. Patients were admitted between 1989-1992. Treatment was instituted within
39
40 72h post-ictus in all patients immediately following surgical clipping of the ruptured
41
42 aneurysm and continued until day 14 post-subarachnoid haemorrhage. The primary
43
44 outcome was DND that the authors could not attribute to intraoperative complication,
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46 hydrocephalus, rebleed or metabolic disturbance. Study patients, personnel and outcome
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48 assessors were unblinded. Patient selection was not described and the protocol was not
49
50 published a priori.

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6 *Vermeij 1998*²⁹
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8 This retrospective cohort study compared 176 patients admitted consecutively between
9 1977-1982 with 172 admitted from 1989-1992 with SAH secondary to angiographically
10 proven aneurysm, or aneurysm suspected on the basis of distribution of blood. 176
11 patients admitted from 1977-1982 were empirically restricted to 1.5-2.0L daily fluid
12 intake and treated with intravenous tranexamic acid 6g/24h. Those admitted from 1989-
13 1992 prophylactically received >3L fluid intake daily, tranexamic acid 6g/24h and
14 nimodipine (6x60mg/24h oral or 2mg/h intravenous). Patients underwent surgical
15 clipping at day 12 post-ictus (intention to treat). This study was entirely unblinded with
16 no protocol published a priori. Follow up at 3 month was complete. The primary
17 outcome was not stated but DND and rebleeding rates were presented. Suspected
18 ischaemic DND vs. autopsy/ computed tomography (CT) proven data was collected but
19 not presented.
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33 *Tagami 2014*²⁷
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35 This multicenter prospective cohort study compared 62 patients treated with
36 prophylactic HHH therapy with 116 who were not. All patients had angiographically
37 proven aneurysmal SAH and underwent surgical clipping or endovascular coiling <4
38 days post-ictus. Entry into the treatment arm was selected by the treating physician, as
39 was the means of achieving physiological HHH: either with fluid supplementation or
40 drug induced hypertension. This study was registered with University Hospital Medical
41 Information Network (UMIN) Clinical Trials Registry as UMIN-CTR ID
42 UMIN000003794. The a priori stated primary outcomes were “patients' outcome,
43 incidence of symptomatic vasospasm”. However the study report states the primary
44 outcome as being changes in haemodynamic measures. Delayed cerebral ischaemia at
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6 14 days was defined as symptomatic vasospasm, infarction attributable to vasospasm, or
7 both.^{37, 38} Patient selection was not described and the study was unblinded. Follow-up
8 data for 30 patients was incomplete.
9

10 11 12 13 *Roy 2017*³³

14
15 This retrospective cohort study included all patients who were treated at a single US
16 center for DND secondary to SAH between January 2012 and October 2014 with either
17 phenylephrine or noradrenaline. All patients had secured aneurysms. 45 patients
18 received phenylephrine. 18 received norepinephrine. The choice of vasopressor was
19 made at the discretion of the treating physician and no attempt at stratification was
20 made. No blinding was described. Follow-up of all included patients at 3 months was
21 complete. It is unclear if cases where follow up was incomplete were excluded. The
22 primary outcome was not stated but requirement for change of vasopressor,
23 cardiorespiratory complications and neurological outcome, mortality and discharge
24 disposition were presented, with comparisons drawn between patients who received
25 phenylephrine and those who received noradrenaline. Analysis was by intention to treat.
26 Statistical analysis used univariate analyses only and although no significant differences
27 were detected between groups at baseline, more patients in the noradrenaline group had
28 a GCS<12, focal neurological deficits and radiologically proven vasospasm at baseline.
29 No multivariable analysis was undertaken to attempt to adjust for these differences.
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46 *Effects of interventions*

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48 Included RCTs were highly heterogeneous: they utilised different means of primary
49 outcome assessment and reported these at different time points post-ictus. Statistical
50 assessment of heterogeneity by calculation of the I^2 statistic would have been unreliable
51 and was therefore not undertaken. Meta-analysis was not attempted because of the high
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6 degree of methodological heterogeneity.
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10 *Vasospasm prophylaxis: hypervolaemia vs. normovolaemia*

11 Three RCTs compared prophylactic volume expansion using supplementary crystalloid
12 or colloid to normovolaemic management.^{19, 20, 28} Lennihan, et al.¹⁹ demonstrated no
13 statistically or clinically significant difference in their primary outcome of mean global
14 CBF or in 3 or 6 month GOS. Complications occurred similarly frequently between
15 groups.
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21 Egge, et al.²⁰ likewise demonstrated no significant differences in 14 day or 1
22 year GOS, radiological, or neuropsychological outcomes. They did however
23 demonstrate a significant ($p < 0.001$) increase in pooled complications occurring in the
24 volume expansion group, including haemorrhagic diathesis and congestive cardiac
25 failure.
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31 Togashi, et al.²⁸ also demonstrated no significant difference in 6-month mRS
32 between groups. A non-significant trend towards increased serious adverse events in the
33 hypervolaemic groups was demonstrated (risk ratio 4.0; 95% confidence interval 0.5-
34 29.8; $p = 0.12$).
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39 Two cohort studies compared prophylactic volume expansion to normovolaemic
40 treatment.^{27, 29} Vermeij, et al.²⁹ Showed reduced rates of DND at 28 days ($P \leq 0.001$)
41 and 3 months ($p = 0.006$) in the hypervolaemia group. However, these figures are
42 associated with significant risk of confounding as the hypervolaemia group was treated
43 with nimodipine whereas the normovolaemia group was not. For this analysis both
44 groups received tranexamic acid. Rebleeding occurred in 59% of hypervolaemic cases
45 vs. 31% of normovolaemic cases ($p = 0.011$). Although some patients included in
46 Tagami et al.'s²⁷ study population received fluid supplementation, the proportion that
47 did is not clear and outcome cannot be commented on.
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Vasospasm prophylaxis: blood transfusion vs. no transfusion

None of the included studies examined the impact of prophylactic blood transfusion following SAH on vasospasm rates or clinical outcome.

Vasospasm prophylaxis: medically induced hypertension

Two RCTs compared medically induced hypertension to normotensive management as prophylaxis for vasospasm.^{20, 28} Egge et al.²⁰ used dobutamine in addition to fluid supplementation to raise MAP to >20mmHg above baseline blood pressure and the results of this trial are discussed above.

Togashi et al.²⁸ used noradrenaline or phenylephrine to augment blood pressure and demonstrated no difference in 6 month mRS in the ABP group compared with CBP group. Neuropsychological outcomes were significantly worse in the ABP group compared with the CBP group (57 vs. 85; p=0.04). There were no differences in adverse events between groups.

Two cohort studies^{27, 30} compared medically induced hypertension to normovolaemic therapy. Tagami et al.'s²⁷ study has been discussed above. In Yano et al.'s³⁰ study the induced hypertension group was the control group for comparison with experimental use of a thromboxane A₂ synthetase inhibitor. This study demonstrated unexpectedly high rates of DND in the experimental group and does not provide a valid comparison group to inform normal clinical practice.

Vasospasm treatment: induced hypertension

One RCT by Gathier, et al.^{21, 22} examined the impact of noradrenaline infusion on change in CBF during active vasospasm. This study demonstrated a non-significant trend toward reduced drop in CBF during vasospasm with the treatment group having a

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6 median difference of 0.1 (range -31 to 43) and the control having -8.5 (-42 to 30;
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8 p=0.25). Five serious adverse events, including death, myocardial infarction and cardiac
9
10 arrhythmia, were recorded in the treatment group versus one in the control group.

11
12 One cohort study by Roy, et al.³³ compared outcomes between patients treated
13
14 for DND with noradrenaline with those treated with phenylephrine. This demonstrated
15
16 that significantly more patients in the noradrenaline group exhibited neurological
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18 improvement (94% vs. 71%; p=0.01) and were discharged to home or an acute
19
20 rehabilitation facility (94% vs 73%; p=0.02) than in the phenylephrine group. More
21
22 patients in the phenylephrine group crossed over to use of a different vasopressor (64%
23
24 vs. 33%; p=0.03). Similar numbers of complications were noted in both groups: 49%
25
26 vs. 50% cardiac arrhythmia, 16% vs. 11% troponin elevation, and 24% vs. 22%
27
28 pulmonary oedema for phenylephrine and noradrenaline, respectively.

31 *Vasospasm treatment: volume expansion and blood transfusion*

32
33 No studies were included that examined the use of volume expansion or blood
34
35 transfusion as treatments for vasospasm following SAH.

38 **Discussion**

41 *Summary of Evidence*

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43 This systematic review included three small RCTs^{19, 21, 22, 28}. These did not demonstrate
44
45 any significant difference in any clinical outcome score following induced
46
47 hypervolaemia and haemodilution using intravenous fluid administration for vasospasm
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49 prophylaxis.^{19, 20, 28} One trial demonstrated a significant increase in serious adverse
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51 events associated with intravenous fluid administration.²⁰
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Two small RCTs were included which did not demonstrate any significant difference in outcome following medically induced hypertension for vasospasm prophylaxis.^{20, 28} Induced hypertension, hypervolaemia, and haemodilution were associated with increased serious adverse events in one trial.²⁰ Isolated induced hypertension was associated with worsened neuropsychological performance in another trial.²⁸

One small RCT was included which did not demonstrate any significant difference in outcome following medically induced hypertension for the treatment of established vasospasm.^{21, 22} More patients in the hypertension group suffered serious adverse events than in the control group, although this was not statistically quantified.

One cohort study of moderate quality ~~was included~~which demonstrated significant improvements in clinical outcome associated with initial noradrenaline use for treatment of DND, compared with phenylephrine ~~was included~~³³.

Three low quality cohort studies were included, however, methodological and reporting limitations to these studies mean that they are unable to meaningfully inform on any of the studied interventions.^{27, 29, 30}

What our study adds

Our study identified two additional RCTs, not identified by the most recent previous systematic review of this subject, one of which is the largest RCT of any haemodynamic intervention in SAH conducted to date^{19, 20, 39}. Furthermore, we have identified an additional three cohort studies, which ~~although identified~~ have ~~been omitted from this~~ ~~prior~~not been included in previous systematic reviews^{29, 30, 33, 39}. Our study therefore provides ~~the most~~a comprehensive contemporary review of the limited evidence base ~~and unanswered questions available to guide concerning the use of~~ haemodynamic therapy for the treatment and prophylaxis of vasospasm following SAH. In spite of

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6 years of intense research and the publication of numerous studies, it is disappointing
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8 that because, of methodological limitations and a lack of statistical power, the efficacy
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10 or non-efficacy of haemodynamic interventions for SAH remains unproven. Induced
11 hypertension using vasopressor or inotropic support is at present recommended in favor
12 of HHH by most guidelines and many units have adopted this approach^{5, 10, 11}. Indeed, a
13 perceived lack of equipoise by treating clinicians may have been a factor in the
14 HIMALAIA study's failure to match recruitment targets^{21, 22}. However, at present only
15 insufficiently powered randomised studies, observational studies and anecdote exist on
16 which to base this. As induction of hypertension may be associated with increased
17 serious adverse events it is essential that an adequately powered~~As a consequence,~~
18 ~~recommendations from~~ RCT be conducted to provide clinical guideline writing ~~groups~~
19 ~~lack a strong~~ groups and individual clinicians with the evidence ~~evidence base~~
20 necessary to balance risks and benefits when recommending widespread adoption of
21 high risk management strategies¹⁰.

Recommendations for further study

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The studies included in this review do not provide a satisfactory evidence base on which
to guide clinical practice. Studies performed when the majority of aneurysms were
treated with surgical clipping may not be relevant in centers where endovascular coiling
predominates.¹³ It is therefore important that the efficacy of potentially harmful
haemodynamic manipulations for the treatment or prophylaxis of vasospasm following
SAH be investigated in an appropriately powered, blinded and randomised study.

Medically induced hypertension is an appropriate intervention for testing in an
RCT as it can be more easily quantified and achieved than a positive fluid balance.
Furthermore, concerns regarding the theoretically deleterious effects of haemodilution
on oxygen carrying capacity of blood are not relevant to medically induced

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6 hypertension. As a radiological diagnosis of vasospasm does not always correlate with
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8 clinical outcome, primary outcome of such a study must be based on a validated,
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10 standardised clinical measure, such as the GOS or mRS.^{24, 36, 40} One RCT included in
11
12 this study was terminated early because of slow patient recruitment²¹. We estimate to
13
14 have 80% power to detect a 10% increase in patients with a favorable in 3-month GOS
15
16 (4-5) an RCT would have to recruit 133 patients to each treatment and control arm⁴¹.

17
18 Induced hypertension has become entrenched practice in some UK centers and
19
20 consequently use of a normotensive control group might be considered to be
21
22 unacceptable by these centers¹⁰. A pragmatic solution is to compare high and low
23
24 hypertensive blood pressure thresholds achieved using a standardised protocol. Protocol
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26 development should be informed by a comprehensive national audit of practice. Audit
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28 data from centers not routinely employing vasopressor induced hypertension could feed
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30 into a before and after observational study with comparison against those enrolled in a
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32 subsequent RCT. Recent years have seen a proliferation in neurosurgical research
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34 collaboratives, such as the British Neurosurgical Trainees Research Collaborative,
35
36 which have successfully pooled UK neurosurgical efforts to facilitate patient
37
38 recruitment to large multicenter studies⁴²⁻⁴⁴. Use of a similar collaborative research
39
40 model may allow for patient recruitment to be successfully completed.¹⁰

41 42 ***Limitations***

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44
45 The trials included in this study were all small and not powered to reliably detect
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47 differences in clinical outcomes. As a consequence it is not possible to determine
48
49 efficacy or non-efficacy of any of the studied interventions on the basis of this
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51 systematic review. As the included trials were heterogeneous, meta-analysis would
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53 have been misleading and was therefore not conducted.
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Our study only surveyed the published literature and it is therefore possible that our conclusions are distorted by publication bias. However, publication bias tends to distort towards type 1 error, whereas our study has not demonstrated any statistically significant findings in favor of intervention.⁴⁵

Conclusions

There is currently insufficient evidence to determine the efficacy or non-efficacy of intravenous volume expansion for prophylaxis or treatment of vasospasm following SAH. The use of intravenous pharmacological agents to induce systemic hypertension also lacks evidence of efficacy or non-efficacy for the treatment or prophylaxis of vasospasm following SAH. Both approaches are associated with serious adverse effects, the incidence of which is poorly quantified.

Table Caption

Table 1: Search terms

Table 2: Characteristics of included studies. NICU specialist neurointensive care unit; ICU general or not specified intensive care unit; MCU medium care unit; A Treatment was prophylactic (P) if commenced prior to suspicion of vasospasm and reactive (R) if introduced as a consequence of this. HV induced hypervolaemia; NV normovolaemia; NT normotension; HTN hypertension; B % lost to follow-up; C comparison group; I intervention group; NS primary outcome not stated – a representative outcome reported instead; CBF Cerebral blood flow; TXA₂ Thromboxane A₂; FR fluid restriction; D means of achieving HHH varied from patient to patient and HHH was defined by treating clinician; MAP Mean arterial pressure; CI Cardiac index; GEDI Global end diastolic volume index; PE phenylephrine; NA Noradrenaline

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Figure captions

Figure 1: Flow diagram of study selection: see text for details of excluded and included studies

Figure 2: Risk of bias in included RCTs. (Green – low risk; Red high risk)

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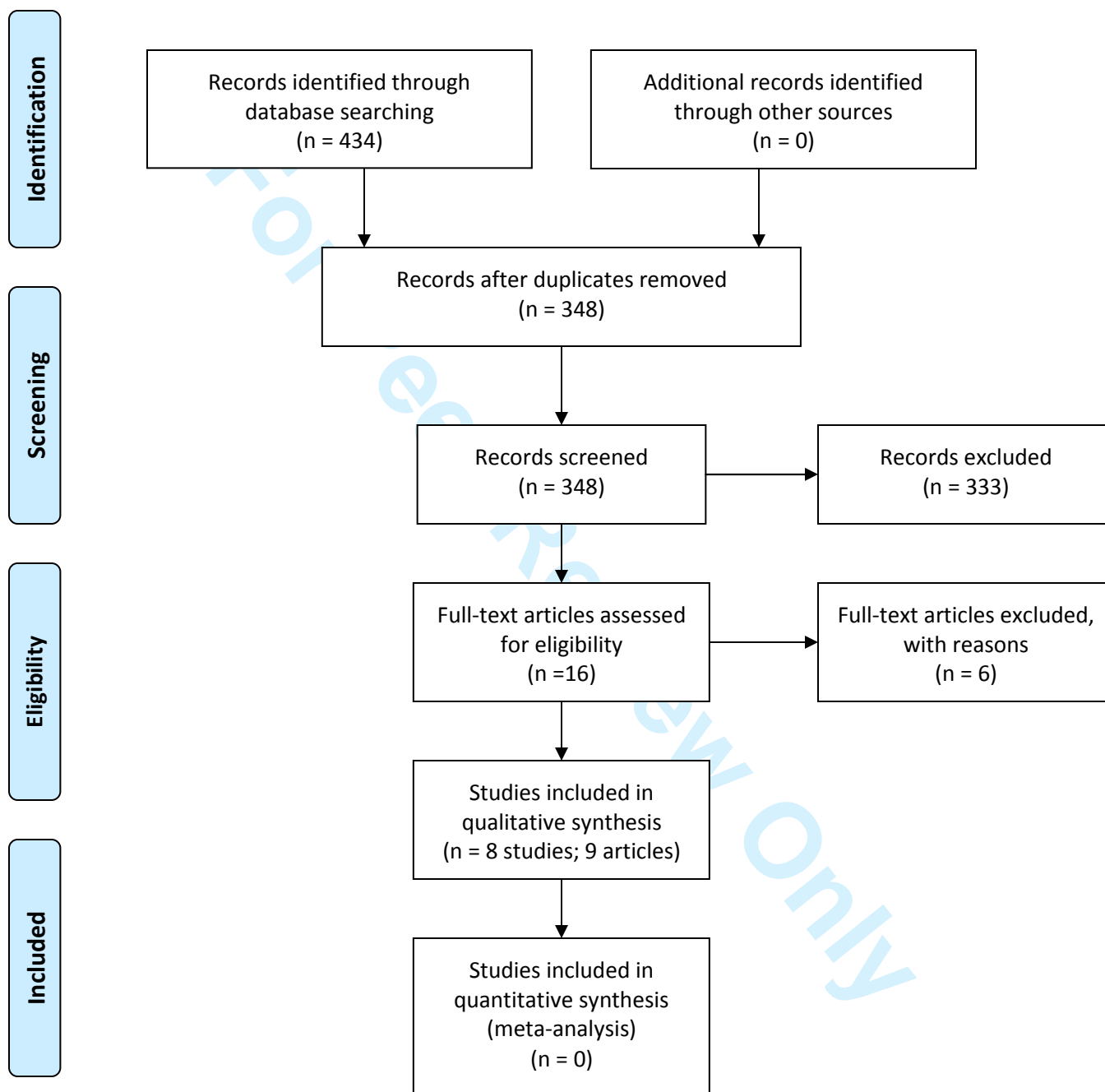
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PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

URL: <http://mc.manuscriptcentral.com/cbjn>

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	+	-	-	-	+	+	-
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Figure 2: Risk of bias in included RCTs. (Green – low risk; Red high risk)

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Search terms	
1	Treat
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4	HHH
5	Triple H
6	Hypertens*
7	Haemodilut*
8	Hemodilut*
9	Hypervolaemi*
10	Hypervolemi*
11	4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10
12	3 AND 11
13	Subarachnoid haemorrhage
14	Subarachnoid hemorrhage
15	SAH
16	13 OR 14 OR 15
17	Cerebral vasospasm
18	Delayed cerebral ischaemia
19	Delayed cerebral ischemia
20	17 OR 18 OR 19
21	16 AND 20
22	12 AND 21

	Lennihan 2000	Egge 2001	Togashi 2015	Gathier 2015	Yano 1993	Vermeij 1998	Tagami 2014	Roy 2017
Design	RCT	RCT	RCT	RCT	Prospective cohort	Retrospective cohort	Prospective cohort	Retrospective cohort
Setting	NICU	ICU	NICU	ICU/MCU	Municipal Hospital	ICU	ICU	Hospital
Country	USA	Norway	USA	Netherlands	Japan	Netherlands	Japan	USA
Number of patients	82	32	20	36	28	348	178	63
Mean age (years)	C: 46.8 I: 50.1	C: 48.6 I: 47.4	HV 56 NV 53 NT 53 HTN 56	C: 59 I: 54	HV: 57.5 NV: 57.5	C: 52.1 I: 51.5	C: 62.3 I: 63.7	PE: 54.9 NA: 52.8
Intervention	HV	HHH	HV/HTN	HTN	NV & TXA ₂ synthetase inhibitor	HHH & nimodipine	HHH ^D	PE
Prophylactic vs. reactive ^A	P	P	P	R	P	P	P	R
Comparison	NV	NV	NV/NT	NT	HV	FR	Not HHH ^D	NA
Primary outcome	Change in mean global CBF	NS GOS	mRS	mRS/CBF	New neurologic deficit	New neurologic deficit	MAP, CI, GEDI	mRS
Time of primary outcome assessment	14 days	1 year	6 months	3 months/36h	14 days	3 months	14 days	3 months
Attrition at primary outcome assessment ^B	C 9.8% I 17.1%	C 0% I 0%	HV 0% NV 0% NT 0% HTN 0%	CBF: 30.5%	Unclear	0%	Unclear	0%

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For Peer Review Only

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3 **Medically induced hypertension, hypervolaemia and haemodilution**
4 **for the treatment and prophylaxis of vasospasm following aneurysmal**
5 **subarachnoid haemorrhage: Systematic Review Study Protocol**
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10 James JM. Loan MRCS MSc¹, Anthony N. Wiggins MRCS², Paul M.
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PROTOCOL

Methods

Questions

- 1) Do medically induced prophylactic hypertension, haemodilution and hypervolaemia (HHH), or any combination thereof, improve clinical outcome following subarachnoid haemorrhage (SAH) compared with any other haemodynamic management strategy?
- 2) Do medically induced therapeutic hypertension, haemodilution and hypervolaemia (HHH), or any combination thereof, improve clinical outcome following subarachnoid haemorrhage (SAH) with delayed neurological deficit or vasospasm compared with any other haemodynamic management strategy?

Searches

We will search the following electronic databases: The Cochrane Database of Systematic Reviews, The Cochrane Central Register of Controlled Trials, MEDLINE (PubMed) and EMBASE (1947-2016). Grey Literature searching will be conducted on the OpenSIGLE database.

The search strategy has been designed using MeSH headings and Keywords identified by scoping searches.

Where references are identified from pearl or snowballing search strategies, these will be reported.

Search terms

Our search strategy has been developed on PubMed and includes the following terms (using standard abbreviations):

((((subarachnoid haemorrhage) OR subarachnoid hemorrhage) OR SAH)) AND (((Cerebral vasospasm) OR delayed cerebral ischaemia) OR delayed cerebral ischemia))) AND (((treat) OR Therap*)) AND ((((((HHH) OR Triple H) OR Hypertens*) OR Haemodilut*) OR Hemodilut*) OR Hypervolaemi*) OR Hypervolemi*))*

This will be adapted for all other electronic databases.

Inclusion criteria

Condition being studied

We will include studies of all patients with spontaneous aneurysmal SAH where clipping or endovascular coiling has secured the aneurysm.

Participants

We will include studies of patients aged greater than 16 years. These may be drawn from any population with the condition of interest.

Intervention

We will include studies comparing patients with medically induced hypertension, hypervolaemia and/or haemodilution, or any combination thereof, with any other systemic haemodynamic management strategy for treatment/prophylaxis of vasospasm.

Comparator

Studies using valid comparison group receiving the same management strategy except for the intervention of interest will be included.

Types of study to be included

We will include studies using Randomised Clinical Trial (RCT) or Cohort study methodology.

Setting

We will include studies of patients managed in any hospital environment including critical care.

Outcome

We will include studies reporting any clinical outcome measure, including clinical outcome scores, vasospasm, and radiological evidence of ischaemic injury. Different definitions of vasospasm reported in the included literature will be described and analysed separately. Our primary outcomes are clinical outcome score using the Glasgow Outcome Score or modified Rankin score. Secondary outcomes include mortality and incidences of hyponatraemia, pulmonary oedema and cardiac events. Where other outcomes are reported these will be described.

Data handling and analysis*Data extraction*

For each included study, the following data will be recorded: study design, participants, details and timing of interventions, comparisons drawn and study results. Any reported outcome measure will be collected.

Risk of bias assessment

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3 For each included study risk of bias will be assessed by two authors (JJML, ANW).
4 Any discrepancies between outcomes of risk of bias assessment will be resolved with
5 consensus discussion between the whole review team. Risk of bias for RCTs will be
6 assessed using the Cochrane Risk of Bias Assessment Tool. This assesses risk of bias
7 in the following domains: Random sequence generation; allocation concealment;
8 blinding of trial participants and trial personnel; blinding of outcome assessment;
9 completeness of data collection; and completeness of data reporting. Risk of bias for
10 Cohort studies will be assessed in the following domains: selection bias; allocation
11 concealment; blinding of trial participants and trial personnel; blinding of outcome
12 assessment; completeness of data collection; and completeness of data reporting.

13 *Strategy for data synthesis*

14 All included studies will be reviewed for heterogeneity in methodology or differences
15 in study populations, interventions and outcome assessment. Where low heterogeneity
16 between multiple studies is detected on narrative review and effect size is reported, the
17 I-squared statistic (%) will be calculated, with greater than 50% suggesting substantial
18 heterogeneity. If substantial heterogeneity is detected, meta-analysis will not be
19 attempted and we will present a narrative review only. If low heterogeneity is detected
20 meta-analysis will be conducted according to the Cochrane Handbook For Systematic
21 Reviews of Interventions.

22 *Analysis of subgroups*

23 We will analyse patients who receive haemodynamic interventions as a prophylactic or
24 therapeutic measure separately. Different means of achieving the same physiological
25 goal will be analysed separately.
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6 **Medically induced hypertension, hypervolaemia and haemodilution for the**
7 **treatment and prophylaxis of vasospasm following aneurysmal subarachnoid**
8 **haemorrhage: Systematic Review**
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13 ABSTRACT: Word count: 282

14 Purpose: Arterial vasospasm is a major cause of death and long-term disability
15 following subarachnoid haemorrhage (SAH). The use of medically induced
16 hypertension, hypervolaemia and/or haemodilution is widely practiced for
17 prophylaxis and treatment of vasospasm following SAH. We aimed to determine
18 if the quality of available research is adequate to inform use of haemodynamic
19 management strategies to prevent or treat vasospasm following SAH.
20

21 Methods: Individual searches of the following databases were conducted: The
22 Cochrane Database of Systematic Reviews, The Cochrane Central Register of
23 Controlled Trials, MEDLINE, EMBASE and OpenSIGLE. Pertinent randomised
24 clinical trials and cohort studies comparing any element or combination thereof:
25 medically induced hypertension, hypervolaemia, and haemodilution were
26 included. Data were extracted using standardised proformas and risk of bias
27 assessed using a domain-based risk of bias assessment tool.
28

29 Results: 348 study reports were identified by our literature search. Eight studies
30 were included, three of which examined both volume expansion and medically
31 induced hypertension. Three randomised clinical trials and two cohort studies
32 examining prophylactic volume expansion were included. Two trials of
33 prophylactic medically induced hypertension and two cohort studies were
34 included. One trial and one cohort study of medically induced hypertension for
35 treatment of established vasospasm was included. These trials demonstrated no
36 significant difference in any of the clinical outcome measures studied. No trials
37 of blood transfusion were included.
38

39 Conclusions: There is currently insufficient evidence to determine the efficacy or
40 non-efficacy of intravenous volume expansion, medically induced hypertension
41 or blood transfusion for the treatment or prophylaxis of vasospasm following
42 SAH. All of these approaches have been associated with adverse events, of
43 unclear incidence. The current evidence base therefore cannot be used to reliably
44 inform clinical practice. This is a priority for further research.
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Keywords: subarachnoid haemorrhage, vasospasm, HHH, haemodynamic
therapy

MANUSCRIPT Word count: **38154343**

Introduction

Subarachnoid haemorrhage (SAH) accounts for around 5% of all cases of stroke and has a reported incidence of between 7-13 per 100,000 person years.¹ Death occurred by 6 months in 26% of cases in one large series, with angiographic presence of cerebral vasospasm being a major predictor of subsequent morbidity and mortality.²

Undiagnosed and insufficiently treated cerebral arterial vasospasm causing cerebral ischaemia has historically been implicated as a major cause of death at autopsy following subarachnoid haemorrhage, alongside rebleeding from untreated aneurysms³. Although with modern, active treatment including haemodynamic intervention the association of vasospasm with mortality can be reduced, potentially disabling neurological deficits attributable to vasospasm continue to affect 20% of those who have not died prior to presentation to hospital⁴. Controversy exists regarding the optimal strategy for the diagnosis, the prevention and treatment of cerebral vasospasm.⁵ Options include use of systemic nimodipine, a calcium channel antagonist⁶; cerebral angiography with local application of intra-arterial antispasmodics,⁷ angioplasty and stenting⁸; and systemic haemodynamic manipulation.

Haemodynamic therapy, including medically induced hypertension, hypervolaemia and haemodilution – often referred to as HHH therapy – has been widely practiced for at least 20 years.⁹ American Stroke Association guidelines, based on a review of literature available in a single database prior to 2010, noted that evidence for all aspects of haemodynamic intervention was insufficient and consequently recommended maintenance of euvolaemia and induction of hypertension for management of suspected vasospasm¹⁰. Perhaps as a consequence of the limited strength of these recommendations, HHH therapy continues to be widely practiced - by

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6 100% of respondents to one survey¹¹. In one other recent survey of European practice,
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8 HHH was utilised more frequently than medically-induced hypertension alone⁵. Where
9
10 haemodynamic augmentation is undertaken, the clinical targets, the timing and the
11
12 means of their achievement vary considerably¹¹, indicating uncertainty regarding the
13
14 relative merits and risks of each of the components of HHH.

15
16 Aggressive intravenous administration of crystalloid or colloid is associated with
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18 hypertension and haemodilution.^{12, 13} This is proposed to optimize blood flow through
19
20 the vasospastic vessel by improving cerebral perfusion pressure and reducing blood
21
22 viscosity.¹² However, excessive hypervolaemia risks precipitating acute heart failure.
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24 Significant haemodilution reduces the oxygen carrying capacity of blood and thus may
25
26 impair cerebral oxygenation. To address these concerns, other approaches including
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28 normovolaemic fluid supplementation,¹⁴ vasopressor support,¹⁵ and blood transfusion¹⁶
29
30 have been attempted.

31
32 Although the incidence of vasospasm is believed to peak between 6-10 days
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34 post-SAH,^{17, 18}, it remains unclear if ~~is~~ a prophylactic or a reactive approach to
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36 haemodynamic augmentation is best? It is also unclear which haemodynamic
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38 management strategy, if any, is preferable. Furthermore, a wide range of definitions for
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40 vasospasm exists – from the development of new, clinically evident focal or global
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42 neurologic deficits not attributable to another cause, to solely radiological diagnoses
43
44 reliant on cerebral angiography, transcranial doppler, CT evidence of new ischaemic
45
46 change or cerebral perfusion studies.¹⁹⁻²³

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48 Given the lack of existing literature to address these uncertainties in clinical
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50 practice, and inform guideline development we conducted a sensitive systematic review
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52 of published literature using multiple databases to determine if there is sufficient
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54 evidence to guide practice in use of medically induced hypertension, hypervolaemia and

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6 haemodilution for the treatment and prophylaxis of vasospasm following aneurysmal
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8 SAH.
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10 11 12 13 **Methods**

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16 Our review protocol was not registered a priori. It is available on request from the
17
18 corresponding author. This study was conducted as part of a series of systematic
19
20 reviews and the study protocol specified our inclusion criteria for population,
21
22 interventions, comparisons, outcomes and study types. It also specified how data-
23
24 extraction and assessment of risk of bias would be conducted.
25

26 27 **Objectives**

28
29 Our primary research question was: “does prophylactic HHH therapy using crystalloid
30
31 volume expansion improve ~~clinical~~ outcome as assessed using a standardised
32
33 neurological clinical outcome score - such as modified Rankin Scale (mRS) or Glasgow
34
35 Coma Scale (GCS) score - following aneurysmal SAH compared with no those
36
37 managed with no haemodynamic augmentation?”^{24, 25}. Secondary outcomes included
38
39 comparisons of outcome, rates of clinically evident delayed neurological deficit (DND)
40
41 and of complications between patients managed with volume expansion, medically
42
43 induced hypertension and blood transfusion – either therapeutically or as a prophylactic
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45 measure.
46

47 48 **Inclusion criteria**

49 50 *Types of studies*

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52
53 We ~~sought to identify~~ included studies using a RCTs and/or all-cohort studies study
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methodology. Prospective and retrospective studies were included, comparing HHHH, or an element of HHHH, with any alternative management strategy. Studies where both arms were treated with an element of HHHH (e.g. induced hypervolaemia) but only one was managed with another element (e.g. induced hypertension) were included. Prospective and retrospective studies were included.

Types of participants

Studies of patients older than the age of 16 who had radiographic or biochemical evidence of SAH were identified. Only studies of patients with intracranial ruptured aneurysms secured using surgical clipping or endovascular coiling were included. Both studies reporting patients with vasospasm prior to intervention commencement and patients without vasospasm prior to intervention commencement were included but were analysed separately.

Types of intervention

Studies comparing HHHH, or an element of HHHH, with any alternative management strategy were included. Studies where both arms were treated with an element of HHHH (e.g. induced hypervolaemia) but only one was managed with another element (e.g. induced hypertension) were included.

Types of comparator group

Studies using a valid comparison group receiving the same management strategy except for the intervention of interest were included.

Types of outcome measure

We included studies meeting the preceding criteria that used any reported outcome

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6 measure, including clinical outcome scores, incidence of vasospasm, and radiological
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8 evidence of ischaemic injury. To reflect the high degree of uncertainty concerning the
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10 optimal mode of diagnosis of vasospasm following SAH as well as treatment
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12 thresholds, we elected to include studies utilizing any means of diagnosis of vasospasm,
13
14 with different definitions of vasospasm considered separately.
15
16 ~~Vasospasm definitions permitted included clinical definitions of DND and radiological~~
17
18 ~~evidence of vasospasm, although these groups were considered separately.~~
19

20 21 Search strategy

22
23
24 Scoping searches identified appropriate MeSH headings and keywords to allow for
25
26 sensitive systematic searches to be conducted. Keywords were mapped to appropriate
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28 MeSH headings and truncated terms mapped to the first 600 appropriate MeSH
29
30 headings. The following electronic databases were then searched for items published up
31
32 to 9 May 2017: The Cochrane Database of Systematic Reviews, The Cochrane Central
33
34 Register of Controlled Trials, MEDLINE (PubMed) and EMBASE (1947-2016). Grey
35
36 Literature searching was performed for the OpenSIGLE database. Table 1 shows the
37
38 abbreviated search strategy. Snowballing and Pearl search strategies were used as
39
40 appropriate. The abstracts of all studies identified by our electronic search were
41
42 screened and if inclusion criteria were met the full study report was accessed and
43
44 considered for inclusion. If it was unclear from the abstract if inclusion criteria would
45
46 be met then the whole study was accessed for review.
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48 49 ***Data collection and analysis***

50 51 52 *Data extraction and quality assessment*

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54 Each included study was reviewed by two authors (JL, AW) and the following data
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6 recorded: the study design, participants, details and timing of interventions,
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8 comparisons drawn and study results. Any reported outcome measure was collected.

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10 For RCTs, risk of bias in the following domains was assessed and judged as high, low
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12 or unknown risk, as per the validated Cochrane Risk of Bias Assessment Tool²⁶:

13
14 Random sequence generation; allocation concealment; blinding of trial participants and
15
16 trial personnel; blinding of outcome assessment; completeness of data collection; and
17
18 completeness of data reporting.

19
20 For cohort studies the following were assessed²⁶: selection bias; allocation
21
22 concealment; blinding of trial participants and trial personnel; blinding of outcome
23
24 assessment; completeness of data collection; and completeness of data reporting.

25
26 Differences in reviewer opinion were resolved by consensus discussion.

27 28 29 *Data analysis*

30
31 Following quality assessment and data extraction, outputs of included studies were
32
33 independently considered as applied to each of the following subgroups to determine
34
35 their adequacy to inform clinical practice.

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38 • Prophylactic (intervention introduced prior to vasospasm)
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40 ○ Crystalloid or colloid volume expansion
 - 41
42 ○ Blood transfusion
 - 43
44 ○ Medically induced hypertension
 - 45
46 • Therapeutic (intervention introduced following proven or suspected vasospasm)
 - 47
48 ○ Crystalloid or colloid volume expansion
 - 49
50 ○ Blood transfusion
 - 51
52 ○ Medically induced hypertension
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Meta-analysis and meta-biases

We As significant methodological heterogeneity was found between studies it was not possible for us to attempt meaningful meta-analysis or attempt to statistically quantify for meta-biases such as publication bias.

Results

Description of studies

Our literature search yielded 348 abstracts (Figure 1). Of these, ~~165~~ reports of ~~154~~ studies were considered for inclusion in our review.^{15, 16, 19-23, 27-34} One study was excluded as the treatment group included both those with hypervolaemic fluid supplementation and normovolaemic colloid administration and consequently effects of either of these interventions and consequent physiological changes could not be reliably attributed.³⁵ Two studies were excluded as the majority of patients in the treatment group had suspected vasospasm whilst those in the control did not.^{15, 34} One study was excluded as it was unclear what fraction of the treatment and control groups had the primary outcome of vasospasm at enrollment and both treatment arms received noradrenaline for induction of hypertension²³. Another two were excluded because treatment with hypervolaemic and normovolaemic fluid administration was not dichotomized and fluid boluses were administered in all patients as a response to suspected vasospasm.^{31,32} One other study was excluded as two of the three studied populations contained both patients who were receiving the study intervention to treat vasospasm and also patients for whom it was prophylactic.¹⁶ Eight studies were included in this review (Table 2).^{19-22, 27-30, 33}

Four of the included studies were RCTs.^{19-22, 28} Four were cohort studies^{27, 29, 30, 33}; for one of these the study protocol was published prospectively.²⁷ Seven reported

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6 clinical outcomes.^{19, 20, 27-30, 33} One reported only on cerebral blood flow (CBF), as
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8 measured using CT perfusion scanning.^{21, 22} In six studies, the intervention was
9
10 introduced as a prophylactic measure.^{19, 20, 27-30} In two studies the intervention was with
11
12 therapeutic intent.^{21, 22, 33}

13 14 15 **Included RCTs: risk of bias (figure 2)**

16 17 18 *Lennihan 2000*¹⁹

19
20 Patients in this RCT were randomly assigned to prophylactic hypervolaemic fluid
21
22 management (n=41) or normovolaemia (n=41). All patients had SAH secondary to
23
24 ruptured aneurysms, which underwent surgical clipping <6 days post-ictus. All patients
25
26 were managed with intravenous colloid, with those in the hypervolaemic group
27
28 receiving prophylactic supplementary 5% albumin solution targeting central venous
29
30 pressure (CVP) 8mmHg or pulmonary artery diastolic pressure 14mmHg. All patients
31
32 who developed vasospasm were managed according to the same protocol regardless of
33
34 their group assignment. The primary outcome measure was difference in mean global
35
36 CBF. Incidence of vasospasm and 3, 6 and 12 month Glasgow Outcome Scale (GOS)
37
38 score were also collected.³⁶ 12 month GOS was not reported. Patients and outcome
39
40 assessors were blinded but the treating team was not.

41 42 43 *Egge 2001*²⁰

44
45 In this trial, 32 patients with confirmed aneurysmal SAH were randomised to either
46
47 HHH therapy (n=16) or normovolaemic fluid therapy (n=16). Ruptured aneurysms were
48
49 secured surgically within 72h of ictus onset. HHH was maintained using 5.0-5.5L daily
50
51 intravenous fluid supplementation using colloid and crystalloid to target CVP 8-
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53 12mmHg and haematocrit 30-35%. Additional dobutamine infusion was used if
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6 required to maintain mean arterial pressure (MAP) >20mmHg above preoperative
7
8 baseline. The primary outcome was not stated. GOS at 14 days and 1 year was
9
10 measured. Vasospasm was detected on transcranial Doppler and single-photon emission
11
12 computed tomography at day 12 ~~and 1 year~~. Batteries of neuropsychological tests were
13
14 also reported at 1 year. Patients and personnel were unblinded. Outcome assessors were
15
16 blinded for most outcomes except GOS measurement.

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19 *Togashi 2015*²⁸

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21 This trial used a 2x2 factorial design to randomise 20 patients to either 10 days
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23 normovolaemia (n=10) or hypervolaemia (n=10) and to either 10 days of conventional
24
25 blood pressure (CBP) or augmented blood pressure (ABP) control. All patients had
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27 angiographically proven SAH, underwent clipping or coiling <72h post-ictus and were
28
29 randomised <72h post-ictus. Hypervolaemia was achieved with intravenous fluid
30
31 supplementation at 60ml/kg/24h targeting a positive fluid balance of 1-2L/24h and CVP
32
33 >8mmHg. The ABP group received noradrenaline or phenylephrine infusion to target
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35 systolic blood pressure (SBP) 140-160mmHg or SBP>160mmHg in the presence of
36
37 vasospasm. The primary outcome measure was the ~~modified Rankin Scale (mRS)~~ score
38
39 at 6 months post-ictus.²⁴ Just 20 of 190 screened patients were randomised. This study
40
41 was single blinded, with adequate allocation concealment and loss of one patient to
42
43 follow up.

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45
46 *Gathier 2015*^{21, 22}

47
48 This trial randomised 36 patients to induced hypertension (n=13) or no hypertension
49
50 (n=12). 11 patients were excluded because of protocol violations. All patients had
51
52 aneurysmal subarachnoid haemorrhage and DND, defined as a decrease ≥ 1 point on the
53
54 ~~Glasgow coma scale (GCS)~~ or development of new focal neurological deficit not
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6 attributable to other cause.²⁵ Patients in the induced hypertension group received
7
8 noradrenaline infusion to raise MAP or SBP to a maximum of 130mmHg or 230mmHg,
9
10 respectively. The primary outcome as published a priori in the study protocol was “the
11 proportion of poor outcome three months after randomization, defined as a modified
12 Rankin scale of 4, 5, or death”. This however was not reported in the published report,
13 which provided ~~was~~ change in mean CBF at 36h post-randomisation, estimated using
14 CT perfusion scanning at development of DND and 24-36h post-randomisation as the
15 primary outcome measure. Baseline differences in mean World Federation of
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17 Neurosurgical Societies SAH grade between groups were noted and patients and
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19 personnel were unblinded. Outcome assessment was blinded.

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Included cohort studies: risk of bias

Yano 1993³⁰

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32 This prospective cohort study compared 15 patients receiving prophylactic intravenous
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34 dobutamine infusion and volume expansion using 25% albumin or plasma fractionates
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36 with 13 patients treated with a dobutamine infusion and thromboxane A₂ synthetase
37
38 inhibitor. Patients were admitted between 1989-1992. Treatment was instituted within
39
40 72h post-ictus in all patients immediately following surgical clipping of the ruptured
41
42 aneurysm and continued until day 14 post-subarachnoid haemorrhage. The primary
43
44 outcome was DND that the authors could not attribute to intraoperative complication,
45
46 hydrocephalus, rebleed or metabolic disturbance. Study patients, personnel and outcome
47
48 assessors were unblinded. Patient selection was not described and the protocol was not
49
50 published a priori.

*Vermeij 1998*²⁹

This retrospective cohort study compared 176 patients admitted consecutively between 1977-1982 with 172 admitted from 1989-1992 with SAH secondary to angiographically proven aneurysm, or aneurysm suspected on the basis of distribution of blood. 176 patients admitted from 1977-1982 were empirically restricted to 1.5-2.0L daily fluid intake and treated with intravenous tranexamic acid 6g/24h. Those admitted from 1989-1992 prophylactically received >3L fluid intake daily, tranexamic acid 6g/24h and nimodipine (6x60mg/24h oral or 2mg/h intravenous). Patients underwent surgical clipping at day 12 post-ictus (intention to treat). This study was entirely unblinded with no protocol published a priori. Follow up at 3 month was complete. The primary outcome was not stated but DND and rebleeding rates were presented. Suspected ischaemic DND vs. autopsy/ computed tomography (CT) proven data was collected but not presented.

*Tagami 2014*²⁷

This multicenter prospective cohort study compared 62 patients treated with prophylactic HHH therapy with 116 who were not. All patients had angiographically proven aneurysmal SAH and underwent surgical clipping or endovascular coiling <4 days post-ictus. Entry into the treatment arm was selected by the treating physician, as was the means of achieving physiological HHH: either with fluid supplementation or drug induced hypertension. This study was registered with University Hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN-CTR ID UMIN000003794. The a priori stated primary outcomes were “patients' outcome, incidence of symptomatic vasospasm”. However the study report states the primary outcome as being changes in haemodynamic measures. Delayed cerebral ischaemia at

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6 14 days was defined as symptomatic vasospasm, infarction attributable to vasospasm, or
7 both.^{37, 38} Patient selection was not described and the study was unblinded. Follow-up
8 data for 30 patients was incomplete.
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11 12 13 *Roy 2017*³³

14
15 This retrospective cohort study included all patients who were treated at a single US
16 center for DND secondary to SAH between January 2012 and October 2014 with either
17 phenylephrine or noradrenaline. All patients had secured aneurysms. 45 patients
18 received phenylephrine. 18 received norepinephrine. The choice of vasopressor was
19 made at the discretion of the treating physician and no attempt at stratification was
20 made. No blinding was described. Follow-up of all included patients at 3 months was
21 complete. It is unclear if cases where follow up was incomplete were excluded. The
22 primary outcome was not stated but requirement for change of vasopressor,
23 cardiorespiratory complications and neurological outcome, mortality and discharge
24 disposition were presented, with comparisons drawn between patients who received
25 phenylephrine and those who received noradrenaline. Analysis was by intention to treat.
26 Statistical analysis used univariate analyses only and although no significant differences
27 were detected between groups at baseline, more patients in the noradrenaline group had
28 a GCS<12, focal neurological deficits and radiologically proven vasospasm at baseline.
29 No multivariable analysis was undertaken to attempt to adjust for these differences.
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46 *Effects of interventions*

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48 Included RCTs were highly heterogeneous: they utilised different means of primary
49 outcome assessment and reported these at different time points post-ictus. Statistical
50 assessment of heterogeneity by calculation of the I^2 statistic would have been unreliable
51 and was therefore not undertaken. Meta-analysis was not attempted because of the high
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6 degree of methodological heterogeneity.
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10 *Vasospasm prophylaxis: hypervolaemia vs. normovolaemia*

11 Three RCTs compared prophylactic volume expansion using supplementary crystalloid
12 or colloid to normovolaemic management.^{19, 20, 28} Lennihan, et al.¹⁹ demonstrated no
13 statistically or clinically significant difference in their primary outcome of mean global
14 CBF or in 3 or 6 month GOS. Complications occurred similarly frequently between
15 groups.
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21 Egge, et al.²⁰ likewise demonstrated no significant differences in 14 day or 1
22 year GOS, radiological, or neuropsychological outcomes. They did however
23 demonstrate a significant ($p < 0.001$) increase in pooled complications occurring in the
24 volume expansion group, including haemorrhagic diathesis and congestive cardiac
25 failure.
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31 Togashi, et al.²⁸ also demonstrated no significant difference in 6-month mRS
32 between groups. A non-significant trend towards increased serious adverse events in the
33 hypervolaemic groups was demonstrated (risk ratio 4.0; 95% confidence interval 0.5-
34 29.8; $p = 0.12$).
35
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39 Two cohort studies compared prophylactic volume expansion to normovolaemic
40 treatment.^{27, 29} Vermeij, et al.²⁹ Showed reduced rates of DND at 28 days ($P \leq 0.001$)
41 and 3 months ($p = 0.006$) in the hypervolaemia group. However, these figures are
42 associated with significant risk of confounding as the hypervolaemia group was treated
43 with nimodipine whereas the normovolaemia group was not. For this analysis both
44 groups received tranexamic acid. Rebleeding occurred in 59% of hypervolaemic cases
45 vs. 31% of normovolaemic cases ($p = 0.011$). Although some patients included in
46 Tagami et al.'s²⁷ study population received fluid supplementation, the proportion that
47 did is not clear and outcome cannot be commented on.
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Vasospasm prophylaxis: blood transfusion vs. no transfusion

None of the included studies examined the impact of prophylactic blood transfusion following SAH on vasospasm rates or clinical outcome.

Vasospasm prophylaxis: medically induced hypertension

Two RCTs compared medically induced hypertension to normotensive management as prophylaxis for vasospasm.^{20, 28} Egge et al.²⁰ used dobutamine in addition to fluid supplementation to raise MAP to >20mmHg above baseline blood pressure and the results of this trial are discussed above.

Togashi et al.²⁸ used noradrenaline or phenylephrine to augment blood pressure and demonstrated no difference in 6 month mRS in the ABP group compared with CBP group. Neuropsychological outcomes were significantly worse in the ABP group compared with the CBP group (57 vs. 85; p=0.04). There were no differences in adverse events between groups.

Two cohort studies^{27, 30} compared medically induced hypertension to normovolaemic therapy. Tagami et al.'s²⁷ study has been discussed above. In Yano et al.'s³⁰ study the induced hypertension group was the control group for comparison with experimental use of a thromboxane A₂ synthetase inhibitor. This study demonstrated unexpectedly high rates of DND in the experimental group and does not provide a valid comparison group to inform normal clinical practice.

Vasospasm treatment: induced hypertension

One RCT by Gathier, et al.^{21, 22} examined the impact of noradrenaline infusion on change in CBF during active vasospasm. This study demonstrated a non-significant trend toward reduced drop in CBF during vasospasm with the treatment group having a

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6 median difference of 0.1 (range -31 to 43) and the control having -8.5 (-42 to 30;
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8 p=0.25). Five serious adverse events, including death, myocardial infarction and cardiac
9
10 arrhythmia, were recorded in the treatment group versus one in the control group.

11
12 One cohort study by Roy, et al.³³ compared outcomes between patients treated
13
14 for DND with noradrenaline with those treated with phenylephrine. This demonstrated
15
16 that significantly more patients in the noradrenaline group exhibited neurological
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18 improvement (94% vs. 71%; p=0.01) and were discharged to home or an acute
19
20 rehabilitation facility (94% vs 73%; p=0.02) than in the phenylephrine group. More
21
22 patients in the phenylephrine group crossed over to use of a different vasopressor (64%
23
24 vs. 33%; p=0.03). Similar numbers of complications were noted in both groups: 49%
25
26 vs. 50% cardiac arrhythmia, 16% vs. 11% troponin elevation, and 24% vs. 22%
27
28 pulmonary oedema for phenylephrine and noradrenaline, respectively.

31 *Vasospasm treatment: volume expansion and blood transfusion*

32
33 No studies were included that examined the use of volume expansion or blood
34
35 transfusion as treatments for vasospasm following SAH.
36

38 **Discussion**

41 *Summary of Evidence*

42
43 This systematic review included three small RCTs^{19, 21, 22, 28}. These did not demonstrate
44
45 any significant difference in any clinical outcome score following induced
46
47 hypervolaemia and haemodilution using intravenous fluid administration for vasospasm
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49 prophylaxis.^{19, 20, 28} One trial demonstrated a significant increase in serious adverse
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51 events associated with intravenous fluid administration.²⁰
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Two small RCTs were included which did not demonstrate any significant difference in outcome following medically induced hypertension for vasospasm prophylaxis.^{20, 28} Induced hypertension, hypervolaemia, and haemodilution were associated with increased serious adverse events in one trial.²⁰ Isolated induced hypertension was associated with worsened neuropsychological performance in another trial.²⁸

One small RCT was included which did not demonstrate any significant difference in outcome following medically induced hypertension for the treatment of established vasospasm.^{21, 22} More patients in the hypertension group suffered serious adverse events than in the control group, although this was not statistically quantified.

One cohort study of moderate quality ~~was included~~which demonstrated significant improvements in clinical outcome associated with initial noradrenaline use for treatment of DND, compared with phenylephrine ~~was included~~³³.

Three low quality cohort studies were included, however, methodological and reporting limitations to these studies mean that they are unable to meaningfully inform on any of the studied interventions.^{27, 29, 30}

What our study adds

Our study identified two additional RCTs, not identified by the most recent previous systematic review of this subject, one of which is the largest RCT of any haemodynamic intervention in SAH conducted to date^{19, 20, 39}. Furthermore, we have identified an additional three cohort studies, which ~~although identified~~ have ~~been omitted from this~~ ~~prior~~not been included in previous systematic reviews^{29, 30, 33, 39}. Our study therefore provides ~~the most~~a comprehensive contemporary review of the limited evidence base ~~and unanswered questions available to guide concerning the use of~~ haemodynamic therapy for the treatment and prophylaxis of vasospasm following SAH. In spite of

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6 years of intense research and the publication of numerous studies, it is disappointing
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8 that because, of methodological limitations and a lack of statistical power, the efficacy
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10 or non-efficacy of haemodynamic interventions for SAH remains unproven. Induced
11 hypertension using vasopressor or inotropic support is at present recommended in favor
12 of HHH by most guidelines and many units have adopted this approach^{5, 10, 11}. Indeed, a
13 perceived lack of equipoise by treating clinicians may have been a factor in the
14 HIMALAIA study's failure to match recruitment targets^{21, 22}. However, at present only
15 insufficiently powered randomised studies, observational studies and anecdote exist on
16 which to base this. As induction of hypertension may be associated with increased
17 serious adverse events it is essential that an adequately powered~~As a consequence,~~
18 ~~recommendations from~~ RCT be conducted to provide clinical guideline writing ~~groups~~
19 ~~lack a strong~~ groups and individual clinicians with the evidence ~~evidence base~~
20 necessary to balance risks and benefits when recommending widespread adoption of
21 high risk management strategies¹⁰.
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Recommendations for further study

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37 The studies included in this review do not provide a satisfactory evidence base on which
38
39 to guide clinical practice. Studies performed when the majority of aneurysms were
40
41 treated with surgical clipping may not be relevant in centers where endovascular coiling
42
43 predominates.¹³ It is therefore important that the efficacy of potentially harmful
44
45 haemodynamic manipulations for the treatment or prophylaxis of vasospasm following
46
47 SAH be investigated in an appropriately powered, blinded and randomised study.
48

49 Medically induced hypertension is an appropriate intervention for testing in an
50
51 RCT as it can be more easily quantified and achieved than a positive fluid balance.
52
53 Furthermore, concerns regarding the theoretically deleterious effects of haemodilution
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55 on oxygen carrying capacity of blood are not relevant to medically induced
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6 hypertension. As a radiological diagnosis of vasospasm does not always correlate with
7
8 clinical outcome, primary outcome of such a study must be based on a validated,
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10 standardised clinical measure, such as the GOS or mRS.^{24, 36, 40} One RCT included in
11
12 this study was terminated early because of slow patient recruitment²¹. We estimate to
13
14 have 80% power to detect a 10% increase in patients with a favorable in 3-month GOS
15
16 (4-5) an RCT would have to recruit 133 patients to each treatment and control arm⁴¹.

17
18 Induced hypertension has become entrenched practice in some UK centers and
19
20 consequently use of a normotensive control group might be considered to be
21
22 unacceptable by these centers¹⁰. A pragmatic solution is to compare high and low
23
24 hypertensive blood pressure thresholds achieved using a standardised protocol. Protocol
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26 development should be informed by a comprehensive national audit of practice. Audit
27
28 data from centers not routinely employing vasopressor induced hypertension could feed
29
30 into a before and after observational study with comparison against those enrolled in a
31
32 subsequent RCT. Recent years have seen a proliferation in neurosurgical research
33
34 collaboratives, such as the British Neurosurgical Trainees Research Collaborative,
35
36 which have successfully pooled UK neurosurgical efforts to facilitate patient
37
38 recruitment to large multicenter studies⁴²⁻⁴⁴. Use of a similar collaborative research
39
40 model may allow for patient recruitment to be successfully completed.¹⁰

41 42 **Limitations**

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44
45 The trials included in this study were all small and not powered to reliably detect
46
47 differences in clinical outcomes. As a consequence it is not possible to determine
48
49 efficacy or non-efficacy of any of the studied interventions on the basis of this
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51 systematic review. As the included trials were heterogeneous, meta-analysis would
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53 have been misleading and was therefore not conducted.
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Our study only surveyed the published literature and it is therefore possible that our conclusions are distorted by publication bias. However, publication bias tends to distort towards type 1 error, whereas our study has not demonstrated any statistically significant findings in favor of intervention.⁴⁵

Conclusions

There is currently insufficient evidence to determine the efficacy or non-efficacy of intravenous volume expansion for prophylaxis or treatment of vasospasm following SAH. The use of intravenous pharmacological agents to induce systemic hypertension also lacks evidence of efficacy or non-efficacy for the treatment or prophylaxis of vasospasm following SAH. Both approaches are associated with serious adverse effects, the incidence of which is poorly quantified.

Table Caption

Table 1: Search terms

Table 2: Characteristics of included studies. NICU specialist neurointensive care unit; ICU general or not specified intensive care unit; MCU medium care unit; A Treatment was prophylactic (P) if commenced prior to suspicion of vasospasm and reactive (R) if introduced as a consequence of this. HV induced hypervolaemia; NV normovolaemia; NT normotension; HTN hypertension; B % lost to follow-up; C comparison group; I intervention group; NS primary outcome not stated – a representative outcome reported instead; CBF Cerebral blood flow; TXA₂ Thromboxane A₂; FR fluid restriction; D means of achieving HHH varied from patient to patient and HHH was defined by treating clinician; MAP Mean arterial pressure; CI Cardiac index; GEDI Global end diastolic volume index; PE phenylephrine; NA Noradrenaline

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Figure captions

Figure 1: Flow diagram of study selection: see text for details of excluded and included studies

Figure 2: Risk of bias in included RCTs. (Green – low risk; Red high risk)

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