The prevalence of non-contrast CT abnormalities in reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

TITLE PAGE

TITLE: The prevalence of non-contrast CT abnormalities in reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

CORRESPONDING AUTHOR:

Ryan Gotesman, rgote014@uottawa.ca, Phone #: 613-761-5073, Fax #: 613-761-5360

451 Smyth Rd

Ottawa ON K1H 8L1

Authorship: Ryan Gotesman[1], Naomi Niznick[2], Brian Dewar[3], Dean Fergusson[3], Risa Shorr[4], Michel Shamy[2,3], Dar Dowlatshahi[2,3]

   (1) Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
   (2) Division of Neurology, Department of Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada
   (3) Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada
   (4) Learning Services, The Ottawa Hospital, Ottawa, Ontario, Canada

E-MAIL ADDRESS:

Ryan Gotesman – rgote014@uottawa.ca

Naomi Niznick - naniznick@toh.ca

Brian Dewar – bdewar@ohri.ca

Dean Fergusson – dafergusson@ohri.ca

Risa Shorr – rshorr@toh.ca

Michel Shamy – mshamy@toh.ca

Dar Dowlatshahi - ddowlat@toh.ca

WORD COUNT: 1336

KEY WORDS: reversible cerebral vasoconstriction syndrome, ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage

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

TITLE: The prevalence of non-contrast CT abnormalities in reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

ABSTRACT:

Introduction: Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe, recurrent thunderclap headaches (TCHs) and vasoconstriction of cerebral arteries that resolve within 3 months. Abnormalities on non-contrast CT (NCCT) such as ischemic strokes, intracerebral hemorrhage (ICH) and subarachnoid hemorrhages (SAH) are frequently observed on brain imaging of RCVS patients though their prevalence varies considerably between studies. The aim of this systematic review and meta-analysis is to estimate the prevalence of NCCT abnormalities seen on neuroimaging of patients with RCVS.

Methods and analysis: We will search the Medline, Embase and the Cochrane Library databases for studies on the prevalence of NCCT abnormalities on neuroimaging of RCVS patients. Search results will be screened for eligibility by title and abstract. Suitable studies will be fully reviewed and relevant data extracted using a data abstraction form. The studies will be assessed for methodological quality, risk of bias and heterogeneity. Prevalence estimates across studies will be pooled using a random-effects model and subgroup analysis will be performed to assess the impact of age, sex, publication year and study design on prevalence of vascular lesions. Sensitivity analysis will be used to investigate the robustness of the findings. This protocol has been devised using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist. **Ethics and dissemination:** Formal ethics is not required as primary date will not be collected. The findings of this study will be disseminated through a peer-reviewed publication and conference presentations. **PROSPERO registration number:** Registration is complete but under review.

ARTICLE SUMMARY:

Strengths and limitations of this study:

- This study will be the first to provide an estimate of the prevalence of NCCT abnormalities on imaging in RCVS patients.
- Risk of bias will be minimized by having 2 reviewers independently screen studies and extract data.
- The results of this study will help differentiate RCVS from illnesses that may present with similar symptoms.
- As this study will include several studies designs, including case-series and observational studies, the results have a risk of heterogeneity.

INTRODUCTION:

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe headaches, most often recurrent thunderclap headaches (TCHs), and segmental vasoconstriction of cerebral arteries that resolves within 3 months.(1) Patients are predominantly female, between the age of 20-50 and may present with other focal neurological symptoms related to strokes, seizures or cerebral edema.(1) RCVS has been linked to several precipitating factors including hypertension, pre-eclampsia and eclampsia, illicit substance use such as cannabis and cocaine, and multiple medications including anti-depressants, sympathomimetic drugs, triptans, immunosuppressant medications, among many others.(2) Current

management for RCVS involves eliminating precipitating factors, analgesic therapy and use of a calcium channel block such as nimodipine or verapamil.(3)

RCVS is diagnosed based on characteristic clinical, imaging and angiographic features. Initial imaging modalities include non-invasive techniques such as non-contrast computed tomography (NCCT) to assess the brain parenchyma, and either computed tomography angiography (CTA) or magnetic resonance angiography (MRA) to assess the vasculature.(4) Digital subtraction angiography (DSA) is typically reserved for circumstances where there is a high clinical suspicion of RCVS and normal non-invasive imaging.(4) Angiography typically demonstrates segmental narrowing and dilatation of the cerebral arteries with a classic string-of-beads appearance, though imaging may be normal in a third of patients if completed early in the course of disease.(5)

Imaging abnormalities such as acute ischemic stroke, intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) can frequently occur in RCVS making it a challenge to distinguish from other vascular conditions, such as aneurysmal SAH and primary angiitis of the central nervous system (PACNS) on imaging.(2) Current RCVS literature includes primarily small case series and the exact proportion of RCVS patients presenting with these radiological lesions is therefore unclear. For instance, the prevalence of ischemic stroke is estimated to range from 8-39% and estimates of intracerebral hemorrhage range from 6-20%.(2, 6-9) We seek to better understand the imaging features of RCVS. The main objective of this systematic review is to estimate the prevalence of imaging findings consistent with ischemic stroke, ICH and SAH on NCCT in patients with RCVS. We hope that the results of this review will help describe the initial imaging features of RCVS in order increase diagnostic certainty at presentation, and to better define the population of interest for future clinical trials.

METHODS AND ANALYSIS

This *a priori* protocol for a systematic review and meta-analysis was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.(10)

Eligibility Criteria

In order to be eligible for inclusion in this systematic review, the study must meet the following:

Population**:** The study population will be all adult patients (>=18 years old) with CT-angiography or equivalent (conventional angiogram or MR-angiogram) confirmed RCVS. Studies that report on other illnesses apart from RCVS will be included if they also independently report on imaging findings in RCVS.

Outcome**:** The primary outcomes will be prevalence of imaging findings consistent with ischemic strokes, ICH and SAH on NCCT. Prevalence will be reported as the proportion of cases to the number of evaluated participants.

Study Design**:** All case-series, observational studies and clinical trials that report on prevalence of imaging findings in patients with RCVS will be included.

Publication type**:** All case reports, abstracts conference proceedings, letters and duplicate publications will be excluded, as will literature not published in the English language.

Information sources

Electronic searches will be conducted in Medline, Embase, and the Cochrane Register of Clinical Trials from inception to May 1, 2020. Referenced of identified studies will be manually reviewed to identify relevant papers missed in the database searches. Full search strategies for all databases are included in the appendix.

Search strategy

The search will be performed by combining terms related to RCVS, neuroimaging and vascular imaging abnormalities. The full search strategy can be found in Appendix 1.

Study selection

Covidence will be used to screen articles for inclusion. Two trained reviewers will independently screen titles and abstracts for inclusion based of predefined criteria. The reviewers will meet after 10% of the sample has been screened to identify, resolve and codify area of ambiguity when screening the rest of the sample. Conflicts will be resolved by consensus or a third independent reviewer. Full-texts will then be reviewed by two independent reviewers and final inclusion will be based on the criteria mentioned above. Reasons for exclusion of eligible studies will be documented and a Preferred Reporting Items or Systematic Reviews and Meta-Analyses (PRISMA) flow diagram will be used to describe the study screening and selection process.

Data extraction

Two reviewers will independently extract information from the selected studies using a data extraction form. The form will be pilot tested on a small sample of included studies and modified if it fails to capture all pertinent information. Areas of disagreement between extractors will be identified and clarified. Any remaining disagreements of extracted data will be resolved through consensus or an independent third reviewer.

Study characteristics that will be collected include:

- General study information: title, name of the journal and authors, year of publication, number of sites and location of the central site
- Study design: study duration, study design (case-series, observational or randomized trial), number of patients with RCVS, mean age of patients with RCVS and male-female distribution of RCVS patients.
- Primary outcomes of interest: prevalence of imaging findings diagnostic with acute ischemic stroke on NCCT in patients with RCVS, prevalence of imaging findings diagnostic of ICH on NCCT in patients with RCVS, and prevalence of imaging findings diagnostic of SAH on NCCT in patients with RCVS. We will also extract and report the criteria used by each study to diagnose ischemic stroke, ICH and SAH on NCCT.

Risk of Bias Assessment

The methodological quality of case series and observational studies shall be assessed using Newcastle-Ottawa based scales that account for selection, ascertainment, causality and reporting.(11, 12) The Cochrane Risk of Bias Tool for Randomized Controlled Trials will be used to assess included randomised trials.(13)

Data Synthesis

Key study characteristics and clinical findings will be synthesized and presented in tables.

Pooled prevalence of imaging features will be calculated using the inverse variance-weighted method. Random-effects meta-analysis models will be used over fixed effect models to take into account variability both within and between studies. The Q- and I^2 statistic will be used as measures of heterogeneity among studies.

Subgroup analysis will be done to assess the impact of specific variables on prevalence of vascular lesions. When enough data is available, we will consider age, sex, publication year and study design as grouping variables.

Sensitivity analysis will be performed to assess the robustness of the findings. We will perform sensitivity analysis by removing studies with an outlying prevalence, excluding high bias studies as well as removing by study design.

Meta-bias(es)

We will attempt to minimize publication bias by generating and examining funnel plots. Duplicate publication bias will be minimized during the study screening phase by carefully screening publications to ensure duplications do not enter the analysis.

Patient and Public Involvement

There will be no involvement of patients or the public in this review.

ETHICS AND DISSEMINATION: Formal ethics is not required as primary date will not be collected. The findings of this study will be disseminated through a peer-reviewed publication and conference presentations.

REFERENCES:

1.   Calabrese LH, Dodick DW, Schwedt TJ, et al. Narrative review: reversible cerebral vasoconstriction syndromes. *Annals of internal medicine*. 2007;146(1):34-44.
2.   de Boysson H, Parienti JJ, Mawet J, et al. Primary angiitis of the CNS and reversible cerebral vasoconstriction syndrome: A comparative study. *Neurology*. 2018;91(16):e1468-e78.
3.   Cappelen-Smith C, Calic Z, Cordato D. Reversible Cerebral Vasoconstriction Syndrome: Recognition and Treatment. *Current treatment options in neurology*. 2017;19(6):21.
4.   Burton TM, Bushnell CD. Reversible Cerebral Vasoconstriction Syndrome. *Stroke*. 2019;50(8):2253-8.
5.   Ducros A, Boukobza M, Porcher R, et al. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain : a journal of neurology*. 2007;130(Pt 12):3091-101.
6.   Caria F, Zedde M, Gamba M, et al. The clinical spectrum of reversible cerebral vasoconstriction syndrome: The Italian Project on Stroke at Young Age (IPSYS). *Cephalalgia*. 2019;39(10):1267-76.
7.   Singhal AB, Hajj-Ali RA, Topcuoglu MA, et al. Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. *Archives of neurology*. 2011;68(8):1005-12.
8.   Chen SP, Fuh JL, Wang SJ, et al. Magnetic resonance angiography in reversible cerebral vasoconstriction syndromes. *Annals of neurology*. 2010;67(5):648-56.

9.   Ducros A, Fiedler U, Porcher R, et al. Hemorrhagic manifestations of reversible cerebral vasoconstriction syndrome: frequency, features, and risk factors. *Stroke*. 2010;41(11):2505-11.

10.   Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews*. 2015;4(1):1.

11.   Murad MH, Sultan S, Haffar S, et al. Methodological quality and synthesis of case series and case reports. *BMJ evidence-based medicine*. 2018;23(2):60-3.

12.   Wells GA, Tugwell P, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2015.

13.   Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed)*. 2011;343:d5928.

AUTHOR CONTRIBUTIONS: RG conceived the manuscript. RG, NN, BW, DF, MS and DD wrote and reviewed the manuscript. RS devised the search strategy. All authors approved the final version of the manuscript.

COMPETING INTERESTS STATEMENT: There are no competing interests to report.

WORD COUNT: 1336

APPENDIX:

Search strategy:

The Medline, Embase and Cochrane Central Register of Controlled Trials databases were searched on May 1, 2020 using the following search strategy:

1   Vasospasm, Intracranial/ or Headache Disorders, Primary/ (10841)
2   Vasoconstriction/ and exp Cerebrovascular Disorders/ (3047)
3   ((intracranial or intracereb* or intercereb* or cerebrum or cerebral or brain) and (vasoconstrict* or vasospasm*)).tw,kf. (27084)
4   or/1-3 (33053)
5   reversible.tw,kw. (331842)
6   4 and 5 (2251)
7   rcvs.tw,kw. (1936)
8   (Call-Fleming or benign angiopathy of the central nervous system or acute benign cerebral angiopathy or postpartum angiopathy or thunderclap headache with reversible vasospasm or migrainous vasospasm or migraine angiitis or drug-induced cerebral arteritis or drug-induced arteritis or drug-unded cerebral angiopathy or drug-induced angiopathy or CNS pseudovasculitis).tw,kw. (211)
9   or/6-8 (3479)
10   tomography, x-ray computed/ or computed tomography angiography/ (458137)
11   (ct or computed tomograph*).tw,kw. (1290654)
12   angiography/ or angiography, digital subtraction/ or cerebral angiography/ (251469)
13   (angiograph* or angiogram*).tw,kw. (516573)
14   magnetic resonance imaging/ or magnetic resonance angiography/ (966147)
15   (mri or magnetic resonance imag*).tw,kw. (1000047)
16   Ultrasonography, Doppler, Transcranial/ (9652)

17 transcran* doppler*.tw,kw. or (transcran* ultrasonograph* or transcran* sonograph* or transcran* ultrasound*).kw. (23105)

18 (transcran* adj2 (ultrasonograph* or sonograph* or ultrasound*)).tw. (12072)

19 (neuroimag* or neuro imag*).tw,kw. (131450)

20 or/10-19 (3168483)

21 9 and 20 (1694)

22 exp brain ischemia/ or exp stroke/ (549189)

23 stroke*.tw,kw. (702880)

24 ((brain or cerebral) adj3 isch?em*).tw. (115810)

25 ((brain or cerebral) and isch?em*).kf. (6322)

26 Brain Edema/ or Edema/ (207804)

27 ed?ema*.tw,kw. (310397)

28 intracranial hemorrhages/ or exp subarachnoid hemorrhage/ (123665)

29 h?emorrhag*.tw,kw. (674036)

30 sah.tw,kw. (26870)

31 (isch?em* adj2 infarct*).tw. (20021)

32 isch?em* infarct*.kw. (181)

33 or/22-32 (1923029)

34 21 and 33 (1386)

35 exp animals/ not humans/ (17829136)

36 34 not 35 (864)

37 limit 36 to english language (794)

38 37 use medall (338) Medline

39 reversible cerebral vasoconstriction syndrome/ (976)

40 ((intracranial or intracereb* or intercereb* or cerebrum or cerebral or brain) and (vasoconstrict* or vasospasm*) and reversible).tw. (2142)

41 rcvs.tw. (1917)

42 (Call-Fleming or benign angiopathy of the central nervous system or acute benign cerebral angiopathy or postpartum angiopathy or thunderclap headache with reversible vasospasm or migrainous vasospasm or migraine angiitis or drug-induced cerebral arteritis or drug-induced arteritis or drug-unded cerebral angiopathy or drug-induced angiopathy or CNS pseudovasculitis).tw. (188)

43 or/39-42 (3549)

44 *computer assisted tomography/ or computed tomographic angiography/ (175821)

45 (ct or computed tomograph*).tw. (1268996)

46 *angiography/ or exp brain angiography/ or *digital subtraction angiography/ (85232)

47 (angiograph* or angiogram*).tw. (502770)

48 magnetic resonance angiography/ or *nuclear magnetic resonance imaging/ (229626)

49 (mri or magnetic resonance imag*).tw. (956815)

50 transcranial doppler ultrasonography/ (9223)

51 (transcran* adj2 (ultrasonograph* or sonograph* or ultrasound* or doppler)).tw. (24783)

52 *neuroimaging/ or *functional neuroimaging/ (30347)

53 (neuroimag* or neuro imag*).tw. (121906)

54 or/44-53 (2625546)

55 43 and 54 (1606)

56 cerebrovascular accident/ (305682)

57 exp brain ischemia/ (296962)

58 stroke*.tw. (687694)

59 ((brain or cerebral) adj3 isch?em*).tw. (115810)

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

60   brain edema/ (49139)

61   ed?ema*.tw. (301725)

62   subarachnoid hemorrhage/ (66623)

63   brain hemorrhage/ (112308)

64   h?emorrhag*.tw. (651322)

65   sah.tw. (26518)

66   (isch?em* adj2 infarct*).tw. (20021)

67   or/56-66 (1812092)

68   55 and 67 (1343)

69   (exp animals/ or animal experiment/) not exp humans/ (10414540)

70   68 not 69 (1326)

71   limit 70 to english language (1234)

72   conference abstract.pt. (3784455)

73   71 not 72 (883)

74   73 use emczd (588) Embase

75   Vasospasm, Intracranial/ or Headache Disorders, Primary/ (10841)

76   Vasoconstriction/ and exp Cerebrovascular Disorders/ (3047)

77   ((intracranial or intracereb* or intercereb* or cerebrum or cerebral or brain) and (vasoconstrict* or vasospasm*)).tw,kw. (27730)

78   or/75-77 (33585)

79   reversible.tw,kw. (331842)

80   78 and 79 (2273)

81   rcvs.tw,kw. (1936)

82   (Call-Fleming or benign angiopathy of the central nervous system or acute benign cerebral angiopathy or postpartum angiopathy or thunderclap headache with reversible vasospasm or migrainous vasospasm or migraine angiitis or drug-induced cerebral arteritis or drug-induced arteritis or drug-unded cerebral angiopathy or drug-induced angiopathy or CNS pseudovasculitis).tw,kw. (211)

83   or/80-82 (3494)

84   tomography, x-ray computed/ or computed tomography angiography/ (458137)

85   (ct or computed tomograph*).tw,kw. (1290654)

86   angiography/ or angiography, digital subtraction/ or cerebral angiography/ (251469)

87   (angiograph* or angiogram*).tw,kw. (516573)

88   magnetic resonance imaging/ or magnetic resonance angiography/ (966147)

89   (mri or magnetic resonance imag*).tw,kw. (1000047)

90   Ultrasonography, Doppler, Transcranial/ (9652)

91   transcran* doppler*.tw,kw. or (transcran* ultrasonograph* or transcran* sonograph* or transcran* ultrasound*).kw. (23105)

92   (transcran* adj2 (ultrasonograph* or sonograph* or ultrasound*)).tw. (12072)

93   (neuroimag* or neuro imag*).tw,kw. (131450)

94   or/84-93 (3168483)

95   83 and 94 (1708)

96   exp brain ischemia/ or exp stroke/ (549189)

97   stroke*.tw,kw. (702880)

98   ((brain or cerebral) adj3 isch?em*).tw. (115810)

99   (brain isch?em* or cerebral isch?em*).kw. (22194)

100   Brain Edema/ or Edema/ (207804)

101   ed?ema*.tw,kw. (310397)

102   intracranial hemorrhages/ or exp subarachnoid hemorrhage/ (123665)

103   h?emorrhag*.tw,kw. (674036)
104   sah.tw,kw. (26870)
105   (isch?em* adj2 infarct*).tw. (20021)
106   isch?em* infarct*.kw. (181)
107   or/96-106 (1923351)
108   95 and 107 (1398)
109   limit 108 to english language (1297)
110   109 use cctr (5) Cochrane
111   38 or 74 or 110 (931)
112   remove duplicates from 111 (644)
113   112 use medall (337)
114   112 use emczd (303)
115   112 use cctr (4)

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

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a - This is not an update

Registration

| | #2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 2 - Registration is complete on PROSPERO but under review so don't have a registration number yet |

Authors

| Contact | #3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contribution | #3b | Describe contributions of protocol authors and identify the guarantor of the review | 6 |

Amendments

| | #4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | N/A - no amendments |

Support

| Sources | #5a | Indicate sources of financial or other support for the review | 6 |

| Sponsor | #5b | Provide name for the review funder and / or sponsor | N/A - no sponsor |
| Role of sponsor or funder | #5c | Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol | N/A |

Introduction

| Rationale | #6 | Describe the rationale for the review in the context of what is already known | 2-3 |
| Objectives | #7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 3 |

Methods

| Eligibility criteria | #8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 3 |
| Information sources | #9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 3-4 |

Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4, 6-9
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	4
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	4
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4

Risk of bias in individual studies	[#14](#14)	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	4
Data synthesis	[#15a](#15a)	Describe criteria under which study data will be quantitatively synthesised	5
Data synthesis	[#15b](#15b)	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's т)	5
Data synthesis	[#15c](#15c)	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
Data synthesis	[#15d](#15d)	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	[#16](#16)	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5

| Confidence in cumulative evidence | #17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | N/A - This is an exploratory review |

Notes:

- 1b: n/a - This is not an update

- 2: 2 - Registration is complete on PROSPERO but under review so don't have a registration number yet

- 4: N/A - no amendments

- 5b: N/A - no sponsor

- 17: N/A - This is an exploratory review The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License CC-BY 4.0. This checklist was completed on 13. June 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

The prevalence of non-contrast CT abnormalities in adults with reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

SCHOLARONE™
Manuscripts

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

BMJ

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

TITLE PAGE

TITLE: The prevalence of non-contrast CT abnormalities in adults with reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

CORRESPONDING AUTHOR:

Ryan Gotesman, rgote014@uottawa.ca, Phone #: 613-761-5073, Fax #: 613-761-5360

451 Smyth Rd

Ottawa ON K1H 8L1

Authorship: Ryan Gotesman[1], Naomi Niznick[2], Brian Dewar[3], Dean Fergusson[3], Risa Shorr[4], Michel Shamy[2,3], Dar Dowlatshahi[2,3]

(1) Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
(2) Division of Neurology, Department of Medicine, The Ottawa Hospital, Ottawa, Ontario, Canada
(3) Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, Canada
(4) Learning Services, The Ottawa Hospital, Ottawa, Ontario, Canada

E-MAIL ADDRESS:

Ryan Gotesman – rgote014@uottawa.ca

Naomi Niznick - naniznick@toh.ca

Brian Dewar – bdewar@ohri.ca

Dean Fergusson – dafergusson@ohri.ca

Risa Shorr – rshorr@toh.ca

Michel Shamy – mshamy@toh.ca

Dar Dowlatshahi - ddowlat@toh.ca

WORD COUNT: 1348

KEY WORDS: reversible cerebral vasoconstriction syndrome, ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage

TITLE: The prevalence of non-contrast CT abnormalities in adults with reversible cerebral vasoconstriction syndrome: protocol for a systematic review and meta-analysis

ABSTRACT:

Introduction: Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe, recurrent thunderclap headaches (TCHs) and vasoconstriction of cerebral arteries that resolve within 3 months. Abnormalities on non-contrast CT (NCCT) such as ischemic strokes, intracerebral hemorrhage (ICH) and subarachnoid hemorrhages (SAH) are frequently observed on brain imaging of RCVS patients though their prevalence varies considerably between studies. The aim of this systematic review and meta-analysis is to estimate the prevalence of NCCT abnormalities seen on neuroimaging of adult patients with RCVS.

Methods and analysis: We will search the Medline, Embase and the Cochrane Library databases for studies on the prevalence of NCCT abnormalities on neuroimaging of RCVS patients. Search results will be screened for eligibility by title and abstract. Suitable studies will be fully reviewed and relevant data extracted using a data abstraction form. The studies will be assessed for methodological quality, risk of bias and heterogeneity. Prevalence estimates across studies will be pooled using a random-effects model and subgroup analysis will be performed to assess the impact of age, sex, publication year and study design on prevalence of vascular lesions. Sensitivity analysis will be used to investigate the robustness of the findings. This protocol has been devised using the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist. **Ethics and dissemination:** Formal ethics is not required as primary data will not be collected. The findings of this study will be disseminated through a peer-reviewed publication and conference presentations. **PROSPERO registration number:** CRD42020190637.

ARTICLE SUMMARY:

Strengths and limitations of this study:

- This study will be the first to provide an estimate of the prevalence of NCCT abnormalities on imaging in RCVS patients.
- Risk of bias will be minimized by having 2 reviewers independently screen studies and extract data.
- The results of this study will help differentiate RCVS from illnesses that may present with similar symptoms.
- As this study will include several study designs, including case-series and observational studies, the results have a risk of heterogeneity.

INTRODUCTION:

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by severe headaches, most often recurrent thunderclap headaches (TCHs), and segmental vasoconstriction of cerebral arteries that resolves within 3 months.(1) Patients are predominantly middle-aged females and may present with other focal neurological symptoms related to strokes, seizures or cerebral edema.(1) RCVS has been linked to several precipitating factors including hypertension, pre-eclampsia and eclampsia, illicit substance use such as cannabis and cocaine, and multiple medications including anti-depressants, sympathomimetic drugs, triptans, immunosuppressant medications, among many others.(2) Current

management for RCVS involves eliminating precipitating factors, analgesic therapy and use of a calcium channel blocker such as nimodipine or verapamil.(3)

RCVS is diagnosed based on characteristic clinical, imaging and angiographic features. Initial imaging modalities include non-invasive techniques such as non-contrast computed tomography (NCCT) to assess the brain parenchyma, and either computed tomography angiography (CTA) or magnetic resonance angiography (MRA) to assess the vasculature.(4) Digital subtraction angiography (DSA) is typically reserved for circumstances where there is a high clinical suspicion of RCVS and normal non-invasive imaging.(4) Angiography typically demonstrates segmental narrowing and dilatation of the cerebral arteries with a classic string-of-beads appearance, though imaging may be normal in a third of patients if completed early in the course of disease.(5)

Imaging abnormalities such as acute ischemic stroke, intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) can frequently occur in RCVS making it a challenge to distinguish from other vascular conditions, such as aneurysmal SAH and primary angiitis of the central nervous system (PACNS) on imaging.(2) Current RCVS literature includes primarily small case series and the exact proportion of RCVS patients presenting with these radiological lesions is therefore unclear. For instance, the prevalence of ischemic stroke is estimated to range from 8-39% and estimates of intracerebral hemorrhage range from 6-20%.(2, 6-9) We seek to better understand the imaging features of RCVS. The main objective of this systematic review is to estimate the prevalence of imaging findings consistent with ischemic stroke, ICH and SAH on NCCT in adult patients with RCVS. We hope that the results of this review will help describe the initial imaging features of RCVS in order to increase diagnostic certainty at presentation, and to better define the population of interest for future clinical trials.

METHODS AND ANALYSIS

This *a priori* protocol for a systematic review and meta-analysis was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.(10)

Eligibility Criteria

In order to be eligible for inclusion in this systematic review, the study must meet the following criteria:

   Population**:** The study population will be all adult patients (>=18 years old) with CT-angiography or equivalent (conventional angiogram or MR-angiogram) confirmed RCVS. Studies that report on other illnesses apart from RCVS will be included if they also independently report on imaging findings in RCVS.

   Outcome**:** The primary outcomes will be prevalence of imaging findings consistent with ischemic strokes, ICH and SAH on NCCT. Prevalence will be reported as the proportion of cases to the number of evaluated participants.

   Study Design**:** All case-series, observational studies and clinical trials that report on prevalence of imaging findings in patients with RCVS will be included.

   Publication type**:** All case reports, abstracts, conference proceedings, letters and duplicate publications will be excluded, as will literature not published in the English language.

Information sources

Electronic searches will be conducted in Medline, Embase, and the Cochrane Register of Clinical Trials from inception to May 1, 2020. References of identified studies will be manually reviewed to identify relevant papers missed in the database searches. Full search strategies for all databases are included in the supplementary file.

Search strategy

The search will be performed by combining terms related to RCVS, neuroimaging and vascular imaging abnormalities. The full search strategy can be found in the supplementary file.

Study selection

Covidence will be used to screen articles for inclusion. Two trained reviewers will independently screen titles and abstracts for inclusion based on predefined criteria. The reviewers will meet after 10% of the sample has been screened to identify, resolve and codify areas of ambiguity when screening the rest of the sample. Conflicts will be resolved by consensus of a third independent reviewer. Full-texts will then be reviewed by two independent reviewers and final inclusion will be based on the criteria mentioned above. Reasons for exclusion of eligible studies will be documented and a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram will be used to describe the study screening and selection process.

Data extraction

Two reviewers will independently extract information from the selected studies using a data extraction form. The form will be pilot tested on a small sample of included studies and modified if it fails to capture all pertinent information. Areas of disagreement between extractors will be identified and clarified. Any remaining disagreements of extracted data will be resolved through consensus or an independent third reviewer.

Study characteristics that will be collected include:

- General study information: title, name of the journal and authors, year of publication, number of sites and location of the central site
- Study design: study duration, study design (case-series, observational or randomized trial), number of patients with RCVS, mean age of patients with RCVS and male-female distribution of RCVS patients.
- Primary outcomes of interest: prevalence of imaging findings diagnostic of acute ischemic stroke on NCCT in patients with RCVS, prevalence of imaging findings diagnostic of ICH on NCCT in patients with RCVS, and prevalence of imaging findings diagnostic of SAH on NCCT in patients with RCVS. We will also extract and report the criteria used by each study to diagnose RCVS, ischemic stroke, ICH and SAH on NCCT as well as the timing of imaging with respect to symptom onset.

Risk of Bias Assessment

The methodological quality of case series and observational studies shall be assessed using Newcastle-Ottawa based scales that account for selection, ascertainment, causality and reporting.(11, 12) The Cochrane Risk of Bias Tool for Randomized Controlled Trials will be used to assess included randomised trials.(13)

Data Synthesis

Key study characteristics and clinical findings will be synthesized and presented in tables.

Pooled prevalence of imaging features will be calculated using the inverse variance-weighted method. Random-effects meta-analysis models will be used over fixed effect models to take into account variability both within and between studies. The Q- and I^2 statistic will be used as measures of heterogeneity among studies.

Subgroup analysis will be done to assess the impact of specific variables on prevalence of vascular lesions. When enough data is available, we will consider age, sex, publication year and study design as grouping variables.

Sensitivity analysis will be performed to assess the robustness of the findings. We will perform sensitivity analysis by removing studies with an outlying prevalence, excluding high bias studies as well as removing by study design.

Meta-bias(es)

We will attempt to minimize publication bias by generating and examining funnel plots. Duplicate publication bias will be minimized during the study screening phase by carefully screening publications to ensure duplications do not enter the analysis.

Patient and Public Involvement

There will be no involvement of patients or the public in this review.

ETHICS AND DISSEMINATION: Formal ethics is not required as primary data will not be collected. The findings of this study will be disseminated through a peer-reviewed publication and conference presentations.

REFERENCES:
1. Calabrese LH, Dodick DW, Schwedt TJ, et al. Narrative review: reversible cerebral vasoconstriction syndromes. *Annals of internal medicine*. 2007;146(1):34-44.
2. de Boysson H, Parienti JJ, Mawet J, et al. Primary angiitis of the CNS and reversible cerebral vasoconstriction syndrome: A comparative study. *Neurology*. 2018;91(16):e1468-e78.
3. Cappelen-Smith C, Calic Z, Cordato D. Reversible Cerebral Vasoconstriction Syndrome: Recognition and Treatment. *Current treatment options in neurology*. 2017;19(6):21.
4. Burton TM, Bushnell CD. Reversible Cerebral Vasoconstriction Syndrome. *Stroke*. 2019;50(8):2253-8.
5. Ducros A, Boukobza M, Porcher R, et al. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain : a journal of neurology*. 2007;130(Pt 12):3091-101.
6. Caria F, Zedde M, Gamba M, et al. The clinical spectrum of reversible cerebral vasoconstriction syndrome: The Italian Project on Stroke at Young Age (IPSYS). *Cephalalgia*. 2019;39(10):1267-76.
7. Singhal AB, Hajj-Ali RA, Topcuoglu MA, et al. Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. *Archives of neurology*. 2011;68(8):1005-12.
8. Chen SP, Fuh JL, Wang SJ, et al. Magnetic resonance angiography in reversible cerebral vasoconstriction syndromes. *Annals of neurology*. 2010;67(5):648-56.

9.   Ducros A, Fiedler U, Porcher R, et al. Hemorrhagic manifestations of reversible cerebral vasoconstriction syndrome: frequency, features, and risk factors. *Stroke*. 2010;41(11):2505-11.

10.   Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews*. 2015;4(1):1.

11.   Murad MH, Sultan S, Haffar S, et al. Methodological quality and synthesis of case series and case reports. *BMJ evidence-based medicine*. 2018;23(2):60-3.

12.   Wells GA, Tugwell P, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2015.

13.   Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical research ed)*. 2011;343:d5928.

AUTHOR CONTRIBUTIONS: RG conceived the manuscript. RG, NN, BW, DF, MS and DD wrote and reviewed the manuscript. RS devised the search strategy. All authors approved the final version of the manuscript.

COMPETING INTERESTS STATEMENT: There are no competing interests to report.

WORD COUNT: 1348

Search strategy:

The Medline, Embase and Cochrane Central Register of Controlled Trials databases were searched on May 1, 2020 using the following search strategy:

1   Vasospasm, Intracranial/ or Headache Disorders, Primary/ (10841)
2   Vasoconstriction/ and exp Cerebrovascular Disorders/ (3047)
3   ((intracranial or intracereb* or intercereb* or cerebrum or cerebral or brain) and (vasoconstrict* or vasospasm*)).tw,kf. (27084)
4   or/1-3 (33053)
5   reversible.tw,kw. (331842)
6   4 and 5 (2251)
7   rcvs.tw,kw. (1936)
8   (Call-Fleming or benign angiopathy of the central nervous system or acute benign cerebral angiopathy or postpartum angiopathy or thunderclap headache with reversible vasospasm or migrainous vasospasm or migraine angiitis or drug-induced cerebral arteritis or drug-induced arteritis or drug-unded cerebral angiopathy or drug-induced angiopathy or CNS pseudovasculitis).tw,kw. (211)
9   or/6-8 (3479)
10   tomography, x-ray computed/ or computed tomography angiography/ (458137)
11   (ct or computed tomograph*).tw,kw. (1290654)
12   angiography/ or angiography, digital subtraction/ or cerebral angiography/ (251469)
13   (angiograph* or angiogram*).tw,kw. (516573)
14   magnetic resonance imaging/ or magnetic resonance angiography/ (966147)
15   (mri or magnetic resonance imag*).tw,kw. (1000047)
16   Ultrasonography, Doppler, Transcranial/ (9652)
17   transcran* doppler*.tw,kw. or (transcran* ultrasonograph* or transcran* sonograph* or transcran* ultrasound*).kw. (23105)
18   (transcran* adj2 (ultrasonograph* or sonograph* or ultrasound*)).tw. (12072)
19   (neuroimag* or neuro imag*).tw,kw. (131450)
20   or/10-19 (3168483)
21   9 and 20 (1694)
22   exp brain ischemia/ or exp stroke/ (549189)
23   stroke*.tw,kw. (702880)
24   ((brain or cerebral) adj3 isch?em*).tw. (115810)
25   ((brain or cerebral) and isch?em*).kf. (6322)
26   Brain Edema/ or Edema/ (207804)
27   ed?ema*.tw,kw. (310397)
28   intracranial hemorrhages/ or exp subarachnoid hemorrhage/ (123665)
29   h?emorrhag*.tw,kw. (674036)
30   sah.tw,kw. (26870)
31   (isch?em* adj2 infarct*).tw. (20021)
32   isch?em* infarct*.kw. (181)
33   or/22-32 (1923029)
34   21 and 33 (1386)
35   exp animals/ not humans/ (17829136)
36   34 not 35 (864)
37   limit 36 to english language (794)
38   37 use medall (338) Medline

39   reversible cerebral vasoconstriction syndrome/ (976)
40   ((intracranial or intracereb* or intercereb* or cerebrum or cerebral or brain) and (vasoconstrict* or vasospasm*) and reversible).tw. (2142)
41   rcvs.tw. (1917)
42   (Call-Fleming or benign angiopathy of the central nervous system or acute benign cerebral angiopathy or postpartum angiopathy or thunderclap headache with reversible vasospasm or migrainous vasospasm or migraine angiitis or drug-induced cerebral arteritis or drug-induced arteritis or drug-unded cerebral angiopathy or drug-induced angiopathy or CNS pseudovasculitis).tw. (188)
43   or/39-42 (3549)
44   *computer assisted tomography/ or computed tomographic angiography/ (175821)
45   (ct or computed tomograph*).tw. (1268996)
46   *angiography/ or exp brain angiography/ or *digital subtraction angiography/ (85232)
47   (angiograph* or angiogram*).tw. (502770)
48   magnetic resonance angiography/ or *nuclear magnetic resonance imaging/ (229626)
49   (mri or magnetic resonance imag*).tw. (956815)
50   transcranial doppler ultrasonography/ (9223)
51   (transcran* adj2 (ultrasonograph* or sonograph* or ultrasound* or doppler)).tw. (24783)
52   *neuroimaging/ or *functional neuroimaging/ (30347)
53   (neuroimag* or neuro imag*).tw. (121906)
54   or/44-53 (2625546)
55   43 and 54 (1606)
56   cerebrovascular accident/ (305682)
57   exp brain ischemia/ (296962)
58   stroke*.tw. (687694)
59   ((brain or cerebral) adj3 isch?em*).tw. (115810)
60   brain edema/ (49139)
61   ed?ema*.tw. (301725)
62   subarachnoid hemorrhage/ (66623)
63   brain hemorrhage/ (112308)
64   h?emorrhag*.tw. (651322)
65   sah.tw. (26518)
66   (isch?em* adj2 infarct*).tw. (20021)
67   or/56-66 (1812092)
68   55 and 67 (1343)
69   (exp animals/ or animal experiment/) not exp humans/ (10414540)
70   68 not 69 (1326)
71   limit 70 to english language (1234)
72   conference abstract.pt. (3784455)
73   71 not 72 (883)
74   73 use emczd (588) Embase
75   Vasospasm, Intracranial/ or Headache Disorders, Primary/ (10841)
76   Vasoconstriction/ and exp Cerebrovascular Disorders/ (3047)
77   ((intracranial or intracereb* or intercereb* or cerebrum or cerebral or brain) and (vasoconstrict* or vasospasm*)).tw,kw. (27730)
78   or/75-77 (33585)
79   reversible.tw,kw. (331842)
80   78 and 79 (2273)
81   rcvs.tw,kw. (1936)

82   (Call-Fleming or benign angiopathy of the central nervous system or acute benign cerebral angiopathy or postpartum angiopathy or thunderclap headache with reversible vasospasm or migrainous vasospasm or migraine angiitis or drug-induced cerebral arteritis or drug-induced arteritis or drug-unded cerebral angiopathy or drug-induced angiopathy or CNS pseudovasculitis).tw,kw. (211)

83   or/80-82 (3494)

84   tomography, x-ray computed/ or computed tomography angiography/ (458137)

85   (ct or computed tomograph*).tw,kw. (1290654)

86   angiography/ or angiography, digital subtraction/ or cerebral angiography/ (251469)

87   (angiograph* or angiogram*).tw,kw. (516573)

88   magnetic resonance imaging/ or magnetic resonance angiography/ (966147)

89   (mri or magnetic resonance imag*).tw,kw. (1000047)

90   Ultrasonography, Doppler, Transcranial/ (9652)

91   transcran* doppler*.tw,kw. or (transcran* ultrasonograph* or transcran* sonograph* or transcran* ultrasound*).kw. (23105)

92   (transcran* adj2 (ultrasonograph* or sonograph* or ultrasound*)).tw. (12072)

93   (neuroimag* or neuro imag*).tw,kw. (131450)

94   or/84-93 (3168483)

95   83 and 94 (1708)

96   exp brain ischemia/ or exp stroke/ (549189)

97   stroke*.tw,kw. (702880)

98   ((brain or cerebral) adj3 isch?em*).tw. (115810)

99   (brain isch?em* or cerebral isch?em*).kw. (22194)

100   Brain Edema/ or Edema/ (207804)

101   ed?ema*.tw,kw. (310397)

102   intracranial hemorrhages/ or exp subarachnoid hemorrhage/ (123665)

103   h?emorrhag*.tw,kw. (674036)

104   sah.tw,kw. (26870)

105   (isch?em* adj2 infarct*).tw. (20021)

106   isch?em* infarct*.kw. (181)

107   or/96-106 (1923351)

108   95 and 107 (1398)

109   limit 108 to english language (1297)

110   109 use cctr (5) Cochrane

111   38 or 74 or 110 (931)

112   remove duplicates from 111 (644)

113   112 use medall (337)

114   112 use emczd (303)

115   112 use cctr (4)

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

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a - This is not an update

Registration

| | #2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 2 |

Authors

| Contact | #3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contribution | #3b | Describe contributions of protocol authors and identify the guarantor of the review | 6 |

Amendments

| | #4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | N/A - no amendments |

Support

Sources	#5a	Indicate sources of financial or other support for the review	6
Sponsor	#5b	Provide name for the review funder and / or sponsor	N/A - no sponsor
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	N/A

Introduction

Rationale	#6	Describe the rationale for the review in the context of what is already known	2-3
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	3

Methods

Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	3
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	3-4
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4, 6-9
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through	4

		each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	4
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	4
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	4
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	5
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	5

Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	5
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	5
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	5
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A - This is an exploratory review

Notes:

- 1b: n/a - This is not an update

- 4: N/A - no amendments

- 5b: N/A - no sponsor

- 17: N/A - This is an exploratory review The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution License CC-BY 4.0. This checklist was completed on 13. June 2020 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai