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Neuromonitoring with Near-Infrared Spectroscopy (NIRS) in Aneurysmal Subarachnoid Hemorrhage: A Systematic Review Protocol

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Keywords: NIRS, DCI, aSAH.

ABSTRACT

Introduction: Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating disease associated with a mortality rate of up to 45% and leaving less than half of the patients independent with activities of daily living. The main threat to survivors of the initial bleed is delayed cerebral ischemia (DCI). Near-infrared spectroscopy (NIRS) is a recent technology allowing continuous, real-time, non-invasive cerebral oximetry that could permit timely detection of impending DCI and therefore appropriate intervention to improve outcomes. However, the ability of rSO2 to detect DCI, its association to the outcome, or benefits of any interventions based on NIRS data, are lacking.

Methods and analysis: MEDLINE, EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews will be searched from their inception and without language restriction. Our search strategy will cover the themes of subarachnoid hemorrhage and cerebral oximetry, without limitations regarding studied outcomes. We will identify all observational and interventional human studies of adult patients (≥ 18 years old) hospitalized after aSAH that were monitored using NIRS-based cerebral oximeter. The Cochrane Risk of Bias tool will be used for RCTs, the ROBINS-I tool to assess non-randomized studies of interventions and the Newcastle-Ottawa Scale for cohort or case-control studies. The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) will be applied to studies evaluating NIRS diagnostic accuracy for DCI. Suitability for meta-analysis will be determined by the degree of heterogeneity (clinical and statistical) observed between the studies. We will evaluate the quality of the evidence of the effect based on the GRADE methodology.

Ethics and dissemination: The acquired knowledge will inform clinicians on the appropriate use of NIRS technology in aSAH patients based on the available evidence and inform subsequent trials.

Registration: This protocol is registered in PROSPERO under CRD42020077522.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1- First systematic review on the use of NIRS in aSAH patients
2- Rigorous methodology, in accordance with current guidelines, without language restriction, with a registered and published protocol
3- Two independent reviewers in each phase using specific and well-recognized risk of bias assessment tools
4- Expected low-quality studies
5- Lack of consistency in outcome measures in aSAH patients and evolving definition of DCI in the literature

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating disease accounting for only 5% of all strokes[1], but associated with a mortality rate of up to 45% and leaving less than half of the survivors independent with activities of daily living[2]. The main threat to survivors of the initial bleed is a complex syndrome known as delayed cerebral ischemia (DCI)[3] occurring in a third of patients and leading to an increase in case fatality as well as poor functional outcomes. Although the underlying pathobiological processes of DCI are not well understood, they are thought to culminate in brain tissue ischemia, and hence the long-term poor functional outcome and even death affecting the majority of severe aSAH. It is assumed that early DCI intervention positively affects the outcome. Unfortunately, the lack of adequate neurological exam in high-grade SAH precludes timely detection of ischemia and therefore appropriate intervention. To circumvent this situation, most intensive care units rely on multiple monitoring modalities for early detection of cerebral changes. These usually are either invasive, unreliable or static[4].

Near-infrared spectroscopy (NIRS) is a recent technology purportedly allowing continuous, real-time, non-invasive cerebral oximetry, thereby allowing detection of brain ischemia. It provides regional cortical saturation (rSO_2), a reflection of the balance between oxygen delivery and utilization in a given region and has been shown to correlate well with jugular venous bulb saturation and brain tissue oxygen pressure[5]. Clinical studies suggest that it is reliable in detecting perioperative cerebral oxygen desaturation events, especially in cardiac surgery, although clinical benefits remain to be proven[6]. Albeit promising in the ICU environment and in the aSAH population, data is still limited[7][8]. Threshold rSO_2 values associated with poor outcomes or that should trigger intervention are poorly defined and findings associated with one specific device do not necessarily apply to other devices on the market.

Although DCI has been the focus of much work, the ultimate objective is to improve outcomes in aSAH patients. Nimodipine notwithstanding[9], trials have so far failed to identify specific therapies fulfilling this goal[4]. Furthermore, reducing incidence of vasospasm does not always equate outcome improvement[10]. Despite the lack of evidence, many critical care units around the world now routinely use NIRS technology to guide interventions in this population. However, the demonstration of an association of rSO2 parameters to the outcome, or benefits of any interventions based on NIRS data, is lacking. This gap in knowledge needs urgently to be addressed before widespread use of NIRS as a tool to improve outcome could be recommended.

Objectives

The present review therefore has two distinct objectives:

1) To evaluate NIRS technology as a therapeutic tool to improve outcomes in aSAH patients. To realize this first goal, we will
   a) examine the association between rSO_2 values and patient-centred outcomes in the aSAH patient population
   b) determine the most appropriate threshold value that should trigger further investigations or therapeutic intervention
   c) evaluate NIRS-based intervention protocols in this specific clinical setting.
2) To evaluate NIRS technology as a diagnostic tool for DCI. To realize this second goal, we will
   a) determine its validity, reliability and accuracy in detecting DCI
   b) examine data comparing NIRS to other monitoring modalities for DCI detection.

METHODS AND ANALYSIS

Design

The research question and study design were developed by a multidisciplinary team of intensivists, neurologists, health information specialists and epidemiologists. This review will be conducted in accordance with The Cochrane Collaboration principles for Systematic Reviews[11], the Cochrane Methods for Screening and Diagnostic tests[12] and reported following PRISMA guidelines[13]. This protocol has been registered in PROSPERO under registration number: CRD42020077522.

Information Sources and Search Strategy

MEDLINE, EMBASE, Web of Science, Google Scholar, OpenGrey, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews will be searched from their inception. EMBASE also includes the abstract publications from major international conferences including the International Stroke Conference, Neurocritical Care Society Meeting, Society of Critical Care Medicine, and the International Symposium on Intensive Care and Emergency Medicine, and we will add a manual search of the above conferences from the last two years. Google Scholar US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov), the controlled-trials.com registry, the Trials Central database, Stroke Trials Registry, ISRCTN Registry, DORIS (Database of Research in Stroke) and World Health Organisation International Clinical Trials Registry Platform will also be searched for ongoing or unpublished trials. The search will be updated before submission for publication.

Our search strategy will cover the themes of subarachnoid hemorrhage and cerebral oximetry, without limitations regarding studied outcomes. There will be no language restriction. It will use MeSH terms to capture each of the principal elements of the research question, along with appropriate keywords. The proposed MEDLINE search strategy is available (Appendix 1) and will be adapted for the other databases.

Study Selection

We aim to identify all observational and interventional human studies, including randomized controlled trials (RCT), non-randomized studies of intervention and

prospective and retrospective observational studies, of adult patients (≥ 18 years old) hospitalized after aSAH that were monitored using NIRS-based cerebral oximeter without restriction of outcome. We will use Covidence[14] as a citation manager and remove all duplicates. Two reviewers (MRB, CLF) will independently screen retrieved citations by title and abstract to exclude irrelevant studies. Remaining citations will undergo a full article review to assess eligibility for inclusion by the same independent reviewers. Discordance will be resolved by consensus and when necessary in consultation with a third independent senior reviewer (SWE).

Data Collection

The same reviewers will independently extract data from eligible studies using a standardized, pilot-tested data extraction form developed using RedCap[15], a web-based tool. Discordance will be resolved by consensus and if necessary in consultation with a third reviewer (SWE). The information collected will include:

1) Study characteristics: title, authors, journal/source, year and language of publication, country, type of study, total number of patients, inclusion/exclusion criteria, DCI definition and ascertainment, randomization, allocation concealment, blinding methods (where applicable) and financial support;
2) Population characteristics: age, gender distribution, clinical setting (ICU, OR, other) aSAH clinical grade (World Federation of Neurological Surgeons grading scale, Hunt and Hess grading system, Glasgow Coma Scale) and imaging severity

(Fisher scale, Claassen CT rating scale), aneurysm size and location, elevated intracranial pressure;

3) Exposure and/or Interventions of interest: number of patients monitored with NIRS or in an intervention arm, specific cerebral oximetry device used, location of NIRS sensors, timing and duration of monitoring, data quality (missing monitoring data, monitoring interruptions, inability to monitor), rSO2 threshold for intervention or investigation, rSO2 metrics (means, medians, dispersion), rSO2 threshold (s) with best predictive accuracy according to authors as well as a detailed description of all elements of NIRS-based intervention protocols if any (i.e., any investigation or any treatment triggered or based on NIRS parameters)
4) Co-interventions of interest: Hemodynamic support, invasive ventilatory support, nimodipine use, intracranial pressure monitoring and intracranial hypertension treatment, red blood cells transfusions, surgical or endovascular aneurysm treatment, endovascular treatment of vasospasm, medical DCI management
5) Outcomes: there is a lack of consistency in outcome measures reported in aSAH, and a core outcome set has yet to be developed[16][17]. We will focus on functional outcome measures as our primary outcome, evaluated with the modified Rankin Scale (mRS), the Glasgow Outcome Scale (GOS) and its extended version (GOSe) or the Barthel index, at 90 days or more. Secondary outcomes will also be collected and include any functional outcome at fewer than 90 days, cognitive outcomes as measured with neuropsychological tests such as the Mini-Mental State Exam (MMSE), the Montreal Cognitive Assessment (MoCA) or other validated metrics, quality of life outcomes as measured by

patient-reported outcome instruments such as the Short Form (SF-12 or SF-36) Health Survey, the EQ5D score or other validated metric, early and late mortality (before and after 90 days), incidence of DCI, incidence of vasospasm (detected by transcranial doppler, computed tomography or digital subtraction angiography), length of stay in hospital and of mechanical ventilation. DCI definitions and adjudication mechanisms will also be extracted.

For observational studies, both crude and adjusted estimates of outcomes will be extracted. The confounders adjusted for will be reported.

6) Diagnostic accuracy and comparators for DCI detection: description of reference standard for diagnosis of DCI, true and false positives and negatives, sensitivity, specificity, positive predictive value and negative predictive value for DCI as reported by authors, Receiver Operating Characteristics (ROC) curve, likelihood ratios for the respective test results, description of comparators with applied criteria if any, including transcranial dopplers, computed tomography or digital subtraction angiography, invasive brain oxygen monitoring, microdialysis, invasive or non-invasive cerebral blood flow monitoring, quantitative or raw EEG.

Study authors will be contacted for clarification or additional results as needed.

Assessment of methodological quality and Risk of bias assessment

The risk of bias assessment will be performed independently by the same reviewers (MRB and CLF), with disagreement resolved by consensus or a third reviewer if

necessary. The Cochrane Risk of Bias tool[18] will be used for RCTs, the ROBINS-I tool[19] to assess non-randomized studies of interventions and the Newcastle-Ottawa Scale for cohort or case-control studies[20]. The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2)[21] will be applied to studies evaluating NIRS diagnostic accuracy for DCI.

Data Synthesis and Analytical Plan

A description of all included studies will first be reported with the aid of tables and text. Both a narrative synthesis and, where possible, a quantitative meta-analysis of the data will be presented. Studies will be clustered according to design (intervention vs. observational, randomized versus non-randomized) and main objective (clinical outcome vs. DCI detection) and analyzed separately. Suitability for meta-analysis will be determined by the degree of heterogeneity (clinical and statistical) observed between the studies. The I^2 index will be used to evaluate the presence of statistical heterogeneity. For observational studies, analysis will be conducted with adjusted estimates, and confounding factors taken into account will be detailed. Pooled continuous effect measures will be expressed as mean differences (MD) and pooled dichotomous effect measures as risk ratios (RR), both with 95% confidence intervals (CI). We will perform pooled analyses using random effects models with the DerSimonian and Laird method when appropriate. Funnel plot analysis will be used to detect potential reporting bias. For diagnostic accuracy studies, summary estimates of sensitivity and specificity and hierarchical ROC curve summary will be presented.

Primary outcome will be converted to a standardized dichotomous variable with a mRS of 0-3, a GOS of 4-5, a GOSe of 4-8 and a Barthel index of 75[22] or more representing a favourable outcome. Results will be presented in tabular format.

We will use the author's definitions of DCI, and its incidence (excluding case-control and cross-sectional studies) will be defined as the number of patients suffering from DCI during hospitalization for aSAH divided by the total number of patients hospitalized for SAH (at risk population). Sensitivity analyses will be conducted by excluding studies where DCI definition relies exclusively on radiological vasospasm and also by including only studies where DCI diagnosis is made based on new infarcts on CT or MRI. We will perform subgroup analyses based on the severity of the injury (high clinical grade on admission constituting the majority of patients or not) and the risk of bias (low vs. other risks).

Quality of evidence

We will evaluate the quality of the evidence of the effect based on the GRADE methodology[23].

ETHICS AND DISSEMINATION

Outcomes in SAH patients might intrinsically be associated to early detection of DCI and its proper management. High-grade patients are both at higher risk of DCI and without available clinical exam to detect it. Invasive monitoring is limited by its very local evaluation and most imaging modalities are static, implying deleterious lags in event detection. However, critical care in general, and neurocritical care more specifically, is

submerged with monitoring alternatives, most of which have yet to be submitted to meticulous evaluation before incorporating the information they provide to usual patient management. More important, sound evaluation dictates that technology impact on patient-centered outcomes be prioritized. Our systematic review will identify, analyze and summarize the evidence supporting the use of cerebral oximetry monitoring in aSAH patients. It will inform subsequent steps in the design and implementation of further research on the matter, with the ultimate objective of studying the role of cerebral oximetry both as a diagnostic tool and a potential aide to guide DCI therapy and subsequently improve outcomes in this population in dire need of evolution in their management.

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APPENDIX 1

Medline Search Strategy

#	Searches
1	exp Spectroscopy, Near-Infrared/
2	NIRS.mp.
3	exp Oximetry/
4	oximeter*.mp.
5	rSO2.mp.
6	rScO2.mp.
7	Oxygen Consumption/
8	oxygen/
9	(oxygen or oxygenation or O2).mp.
10	7 or 8 or 9
11	exp Monitoring, Physiologic/

12 monitor*.mp.

13 11 or 12

14 10 and 13

15 invos.mp.

16 fore-sight.mp.

17 equanox.mp.

18 niro.mp.

19 oxiplex.mp.

20 nonin.mp.

21 (near adj3 infrared).mp.

22 1 or 2 or 3 or 4 or 5 or 6

23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

24 22 or 23

25 exp Subarachnoid Hemorrhage/

26 exp Intracranial Hemorrhages/

27 exp Intracranial Aneurysm/

28 vasospasm, intracranial/

29 (sah or asah or delayed cerebral ischemi*).mp.

30 (cerebral or intracranial or cerebrovascular or brain or meninge* or arachnoid* or subarachnoid*).mp.

31 exp brain/ or exp meninges/

32 30 or 31

33 (vasospasm* or dci or spasm or spasms or aneurysm* or haemorrhag* or hemorrhag* or bleed or bleeding or blood or hypoxia).mp.

34 Hemorrhage/ or aneurysm/ or aneurysm, ruptured/ or exp hypoxia/

35 33 or 34

36 32 and 35

37 25 or 26 or 27 or 28 or 29 or 36

38 24 and 37

39 exp animals/ not exp humans/

40 (exp child/ or exp infant/) not exp adult/

41 38 not 39 not 40

AUTHORS CONTRIBUTIONS

Mohamed Reda Bensaidane: Conceptualization, Methodology, Writing -Original Draft

Alexis Turgeon: Resources, Supervision

Francois Lauzier Resources, Supervision

Shane W. English: Methodology, Writing – Review and Editing, Supervision

Guillaume Leblanc Supervision

Charles L Francoeur: Conceptualization, Methodology, Writing -Original Draft, Writing – Review and Editing, Supervision

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COMPETING INTERESTS STATEMENT

The authors have no conflict of interest to disclose.

Additional file 1: PRISMA-P CHECKLIST

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Completed
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Pg. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Pg. 4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Pg. 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Pg. 17
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
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Pg. 17
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
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	Pg. 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)	Pg. 3-4
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	Pg. 4-5
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	Pg. 4-5
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	Pg. 15-16
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Pg. 6-7-8

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)	Pg. 5
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	Pg. 6-8
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	Pg. 6-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Pg. 6-9
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	Pg. 8-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Pg. 8-10
	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 I^2, Kendall's τ)	Pg. 8-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Pg. 8-10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Pg. 8-10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Pg. 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Pg. 10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Neuromonitoring with Near-Infrared Spectroscopy (NIRS) in Aneurysmal Subarachnoid Hemorrhage: A Systematic Review Protocol

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Keywords: NIRS, DCI, aSAH.

ABSTRACT

Introduction: Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating disease associated with high mortality and morbidity. The main threat to patients is delayed cerebral ischemia (DCI). Near-infrared spectroscopy (NIRS) is a recent technology allowing continuous, non-invasive cerebral oximetry that could permit timely detection of impending DCI and appropriate intervention to improve outcomes. However, the ability of regional oxygen saturation (rSO_2) to detect DCI, its association to the outcome, or benefits of any interventions based on NIRS data, are lacking. Our aims are to evaluate NIRS technology both as a therapeutic tool to improve outcomes in aSAH patients and as a diagnostic tool for DCI.

Methods and analysis: MEDLINE, EMBASE, Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews will be searched from their inception and without language restriction. Our search strategy will cover the themes of subarachnoid hemorrhage and cerebral oximetry, without limitations regarding studied outcomes. We will identify all observational and interventional human studies of adult patients hospitalized after aSAH that were monitored using NIRS. Functional outcome measures, including the modified Rankin Scale (mRS), the Glasgow Outcome Scale (GOS) and the Barthel index, will constitute the primary outcome. The Cochrane Risk of Bias tool will be used for RCTs, the ROBINS-I tool to assess non-randomized studies of interventions and the Newcastle-Ottawa Scale for cohort or case-control studies. The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) will be applied to studies evaluating NIRS diagnostic accuracy for DCI. We will evaluate the quality of the evidence of the effect based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Ethics and dissemination: Dissemination will proceed through submission for journal publication, trial registry completion and abstract presentation. Ethics approval is not required.

Registration: This protocol is registered in PROSPERO under CRD42020077522.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1- First systematic review on the use of NIRS in aSAH patients
2- Rigorous methodology, in accordance with current guidelines, without language restriction, with a registered and published protocol
3- Two independent reviewers in each phase using specific and well-recognized risk of bias assessment tools
4- Expected low-quality studies
5- Lack of consistency in outcome measures in aSAH patients and evolving definition of DCI in the literature

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a devastating disease accounting for only 5% of all strokes[1], but associated with a mortality rate of up to 45% and leaving less than half of the survivors independent with activities of daily living[2]. The main threat to survivors of the initial bleed is a complex syndrome known as delayed cerebral ischemia (DCI)[3] occurring in a third of patients and leading to an increase in case fatality as well as poor functional outcomes. Although the underlying pathobiological processes of DCI are not well understood, they are thought to culminate in brain tissue ischemia, and hence the long-term poor functional outcome and even death affecting the majority of severe aSAH. It is assumed that early DCI intervention positively affects the outcome. Unfortunately, the lack of adequate neurological exam in high-grade SAH precludes timely detection of ischemia and therefore appropriate intervention. To circumvent this situation, most intensive care units rely on multiple monitoring modalities for early detection of cerebral changes. These are usually either invasive, unreliable or static[4].

Near-infrared spectroscopy (NIRS) is a recent technology purportedly allowing continuous, real-time, non-invasive cerebral oximetry, thereby allowing detection of brain ischemia. It provides regional cortical saturation (rSO_2), a reflection of the balance between oxygen delivery and utilization in a given region and has been shown to correlate well with jugular venous bulb saturation and brain tissue oxygen pressure[5]. Clinical studies suggest that it is reliable in detecting perioperative cerebral oxygen desaturation events, especially in cardiac surgery, although clinical benefits remain to be proven[6]. Albeit promising in the ICU environment and in the aSAH population, data is still limited[7][8]. Threshold rSO_2 values associated with poor outcomes or that should trigger intervention are poorly defined and findings associated with one specific device do not necessarily apply to other devices on the market.

Although DCI has been the focus of much work, the ultimate objective is to improve outcomes in aSAH patients. Nimodipine notwithstanding[9], trials have so far failed to identify specific therapies fulfilling this goal[4]. Despite the lack of evidence, many critical care units around the world now routinely use NIRS technology to guide interventions in this population. However, the demonstration of an association of rSO_2 parameters to the outcome, or benefits of any interventions based on NIRS data, is lacking. This gap in knowledge needs urgently to be addressed before widespread use of NIRS as a tool to improve outcomes could be recommended.

Objectives

The present review therefore has two distinct objectives:

1) To evaluate NIRS technology as a therapeutic tool to improve outcomes in aSAH patients. To realize this first goal, we will
   a) examine the association between rSO_2 values and patient-centred outcomes in the aSAH patient population
   b) defining the most appropriate threshold that should trigger further investigations or therapeutic intervention, including absolute rSO_2 values, changes from the baseline or discrepancy with the contralateral side.
   c) evaluate NIRS-based intervention protocols in this specific clinical setting.
2) To evaluate NIRS technology as a diagnostic tool for DCI. To realize this second goal, we will
   a) determine its validity, reliability and accuracy in detecting DCI
   b) examine data comparing NIRS to other monitoring modalities for DCI detection.

METHODS AND ANALYSIS

Design

The research question and study design were developed by a multidisciplinary team of intensivists, neurologists, health information specialists and epidemiologists. This review will be conducted in accordance with The Cochrane Collaboration principles for Systematic Reviews[10], the Cochrane Methods for Screening and Diagnostic tests[11] and reported following PRISMA guidelines[12]. This protocol has been registered in PROSPERO under registration number: CRD42020077522.

Information Sources and Search Strategy

MEDLINE, EMBASE, Web of Science, Google Scholar, OpenGrey, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews will be searched from their inception.

Conference proceedings from the last two years for the following meetings will be reviewed manually: American Association of Neurological Surgeons' Annual scientific meeting, Congress of Neurosurgical Surgeons, Critical Care Canada Forum, the International Symposium on Intensive Care and Emergency Medicine, the International Stroke Conference, Neurocritical Care Society Meeting, the Society of Critical Care Medicine Congress, and World Congress of Neurosurgery. Google Scholar US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov), the controlled-trials.com registry, the Trials Central database, Stroke Trials Registry, ISRCTN Registry, DORIS (Database of Research in Stroke) and World Health Organisation International Clinical Trials Registry Platform will also be searched for ongoing or unpublished trials. The search will be updated before submission for publication.

Our search strategy will cover the themes of subarachnoid hemorrhage and cerebral oximetry, without limitations regarding studied outcomes. There will be no language restriction. It will use MeSH terms to capture each of the principal elements of the research question, along with appropriate keywords. The proposed MEDLINE search strategy is available (Appendix 1) and will be adapted for the other databases.

Study Selection

Population

We will include all original observational and interventional human studies, including randomized controlled trials (RCT), non-randomized studies of intervention and prospective and retrospective observational studies, of adult patients (≥ 18 years old) hospitalized after aSAH. In the case of studies on mixed populations, we will exclude studies were aSAH patients constitute less than 80% of the studied population and will apply the same approach for the age criteria.

Intervention and Control

We will include studies using NIRS monitoring during the index hospitalization, either as a diagnostic, prognostic, or therapeutic tool or in a blinded fashion. We will exclude studies where NIRS monitoring is limited to the time of aneurysm surgery. A control group is not required for inclusion.

Outcome

Inclusion in our systematic review will not be limited based on reported outcome, although our analyses will focus on functional outcome and measures of test utility as described in the methodology section.

We will use Covidence[13] as a citation manager and remove all duplicates. Two reviewers (MRB, CLF) will independently screen retrieved citations by title and abstract to exclude irrelevant studies. Remaining citations will undergo a full article review to assess eligibility for inclusion by the same independent reviewers. Discordance will be resolved by consensus and when necessary in consultation with a third independent senior reviewer (SWE).

Data Collection

The same reviewers will independently extract data from eligible studies using a standardized, pilot-tested data extraction form developed using RedCap[14], a web-based tool. Discordance will be resolved by consensus and if necessary in consultation with a third reviewer (SWE). The information collected will include:

1) Study characteristics: title, authors, journal/source, year and language of publication, country, type of study, total number of patients, inclusion/exclusion criteria, DCI definition and ascertainment, randomization, allocation concealment, blinding methods (where applicable) and financial support;
2) Population characteristics: age, gender distribution, clinical setting (ICU, OR, other) aSAH clinical grade (World Federation of Neurological Surgeons grading scale, Hunt and Hess grading system, Glasgow Coma Scale) and imaging severity (Fisher scale, Claassen CT rating scale), aneurysm size and location, elevated intracranial pressure;
3) Exposure and/or Interventions of interest: number of patients monitored with NIRS or in an intervention arm, specific cerebral oximetry device used, location of NIRS sensors, timing and duration of monitoring, data quality (missing monitoring data, monitoring interruptions, inability to monitor), rSO_2 threshold for intervention or investigation, rSO_2 metrics (means, medians, dispersion), rSO_2 threshold (s) with best predictive accuracy according to authors as well as a detailed description of all elements of NIRS-based intervention protocols if any (i.e., any investigation or any treatment triggered or based on NIRS parameters)

4) Co-interventions of interest: Hemodynamic support, invasive ventilatory support, nimodipine use, intracranial pressure monitoring and intracranial hypertension treatment, red blood cells transfusions, surgical or endovascular aneurysm treatment, endovascular treatment of vasospasm, medical DCI management

5) Outcomes: there is a lack of consistency in outcome measures reported in aSAH, and a core outcome set has yet to be developed[15][16]. We will focus on functional outcome measures as our primary outcome, evaluated with the modified Rankin Scale (mRS), the Glasgow Outcome Scale (GOS) and its extended version (GOSe) or the Barthel index, at 90 days or more. Secondary outcomes will also be collected and include any functional outcome at fewer than 90 days, cognitive outcomes as measured with neuropsychological tests such as the Mini-Mental State Exam (MMSE), the Montreal Cognitive Assessment (MoCA) or other validated metrics, quality of life outcomes as measured by patient-reported outcome instruments such as the Short Form (SF-12 or SF-36) Health Survey, the EQ5D score or other validated metric, early and late mortality (before and after 90 days), incidence of DCI, incidence of vasospasm (detected by transcranial doppler, computed tomography or digital subtraction angiography), length of stay in hospital and of mechanical ventilation. DCI definitions and adjudication mechanisms will also be extracted.

For observational studies, both crude and adjusted estimates of outcomes will be extracted. The confounders adjusted for will be reported.

6) Diagnostic accuracy and comparators for DCI detection: description of reference standard for diagnosis of DCI, true and false positives and negatives, sensitivity,

specificity, positive predictive value and negative predictive value for DCI as reported by authors, Receiver Operating Characteristics (ROC) curve, likelihood ratios for the respective test results, description of comparators with applied criteria if any, including transcranial dopplers, computed tomography or digital subtraction angiography, invasive brain oxygen monitoring, microdialysis, invasive or non-invasive cerebral blood flow monitoring, quantitative or raw EEG.

Study authors will be contacted for clarification or additional results as needed.

Assessment of methodological quality and Risk of bias assessment

The risk of bias assessment will be performed independently by the same reviewers (MRB and CLF), with disagreement resolved by consensus or a third reviewer if necessary. The Cochrane Risk of Bias tool[17] will be used for RCTs, the ROBINS-I tool[18] to assess non-randomized studies of interventions and the Newcastle-Ottawa Scale for cohort or case-control studies[19]. The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2)[20] will be applied to studies evaluating NIRS diagnostic accuracy for DCI.

Data Synthesis and Analytical Plan

A description of all included studies will first be reported with the aid of tables and text. Both a narrative synthesis and, where possible, a quantitative meta-analysis of the data will be presented. Studies will be clustered according to design (intervention vs.

observational, randomized versus non-randomized) and main objective (clinical outcome vs. DCI detection) and analyzed separately. Suitability for meta-analysis will be determined by the degree of heterogeneity (clinical and statistical) observed between the studies. The I^2 index will be used to evaluate the presence of statistical heterogeneity. For observational studies, analysis will be conducted with adjusted estimates, and confounding factors taken into account will be detailed. We will perform pooled analyses using random effects models with the DerSimonian and Laird method when appropriate. Funnel plot analysis will be used to detect potential reporting bias and the trim-and-fill method[21] will be applied to allow estimation of the number of missing studies that might exist and adjustment of the overall effect estimate. For diagnostic accuracy studies, summary estimates of sensitivity and specificity and hierarchical ROC curve summary will be presented.

Primary outcome will be converted to a standardized dichotomous variable with a mRS of 0-3, a GOS of 4-5, a GOSe of 4-8 and a Barthel index of 75[22] or more representing a favourable outcome. Results will be presented in tabular format. Secondary outcomes will be analyzed according to the data type. Pooled dichotomous outcomes such as mortality will be expressed as risk ratios and presented in tabular format, whereas pooled continuous effect measures will be expressed as mean differences, both with 95% confidence intervals. Heterogeneity of cognitive and quality of life outcome measures will not allow pooling or conversion to a standardized dichotomous outcome across different metrics.

We will use the author's definitions of DCI, and its incidence (excluding case-control and cross-sectional studies) will be defined as the number of patients suffering from DCI

during hospitalization for aSAH divided by the total number of patients hospitalized for SAH (at risk population). Sensitivity analyses will be conducted by excluding studies where DCI definition relies exclusively on radiological vasospasm and also by including only studies where DCI diagnosis is made based on new infarcts on CT or MRI. We will perform subgroup analyses based on the severity of the injury (high clinical grade on admission constituting the majority of patients or not) and the risk of bias (low vs. other risks).

Missing Data

Studies will not be excluded based on missing data. Original investigators will be contacted for any missing information regarding outcomes, summary data, individual or study-level characteristics. Analysis will be performed on available data when data can be assumed to be missing at random. Other missing values will be imputed with replacement values as appropriate and the underlying assumptions reported. Sensitivity analyses will be performed to assess the latter. The potential impact of missing data will be discussed.

Quality of evidence

We will evaluate the quality of the evidence of the effect based on the GRADE methodology[23].

DISCUSSION

Outcomes in SAH patients might intrinsically be associated to early detection of DCI and its proper management. High-grade patients are both at higher risk of DCI and without available clinical exam to detect it. Invasive monitoring is limited by its very local

evaluation and most imaging modalities are static, implying deleterious lags in event detection. However, critical care in general, and neurocritical care more specifically, is submerged with monitoring alternatives, most of which have yet to be submitted to meticulous evaluation before incorporating the information they provide to usual patient management. More important, sound evaluation dictates that technology impact on patient-centered outcomes be prioritized. Our systematic review will identify, analyze and summarize the evidence supporting the use of cerebral oximetry monitoring in aSAH patients. It will inform subsequent steps in the design and implementation of further research on the matter, with the ultimate objective of studying the role of cerebral oximetry both as a diagnostic tool and a potential aide to guide DCI therapy and subsequently improve outcomes in this population in dire need of evolution in their management. Potential limitations to our study include expected low-quality studies, a lack of consistency in outcome measures in our population, an evolving definition of DCI in the literature and the absence of a gold standard for DCI diagnosis in high-grade aSAH patients.

ETHICS AND DISSEMINATION

The study results will be released to the general medical community through submission for publication in a peer-reviewed journal within three months of completion, regardless of the magnitude or direction of the reported findings. Trial registry will also be updated with the study results. Finally, the results will be submitted for presentation as an abstract at a national or international conference targeting an appropriate audience (neurology, neurosurgery and/or critical care). Ethics approval is not required.

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PATIENTS AND PUBLIC INVOLVEMENT

The present study focuses on patient-centered outcomes, including survival, functional outcomes, and quality of life. No patient was involved in the design of the study protocol.

AUTHORS CONTRIBUTIONS

Mohamed Reda Bensaidane: Conceptualization, Methodology, Writing -Original Draft

Alexis Turgeon: Resources, Supervision

Francois Lauzier Resources, Supervision

Shane W. English: Methodology, Writing – Review and Editing, Supervision

Guillaume Leblanc Supervision

Charles L Francoeur: Conceptualization, Methodology, Writing -Original Draft, Writing – Review and Editing, Supervision

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This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

COMPETING INTERESTS STATEMENT

The authors have no conflict of interest to disclose.

APPENDIX 1

Medline Search Strategy

#	Searches
1	exp Spectroscopy, Near-Infrared/
2	NIRS.mp.
3	exp Oximetry/
4	oximeter*.mp.
5	rSO2.mp.
6	rScO2.mp.
7	Oxygen Consumption/
8	oxygen/
9	(oxygen or oxygenation or O2).mp.
10	7 or 8 or 9
11	exp Monitoring, Physiologic/
12	monitor*.mp.
13	11 or 12
14	10 and 13
15	invos.mp.
16	fore-sight.mp.
17	equanox.mp.
18	niro.mp.
19	oxiplex.mp.
20	nonin.mp.

21 (near adj3 infrared).mp.

22 1 or 2 or 3 or 4 or 5 or 6

23 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

24 22 or 23

25 exp Subarachnoid Hemorrhage/

26 exp Intracranial Hemorrhages/

27 exp Intracranial Aneurysm/

28 vasospasm, intracranial/

29 (sah or asah or delayed cerebral ischemi*).mp.

30 (cerebral or intracranial or cerebrovascular or brain or meninge* or arachnoid* or subarachnoid*).mp.

31 exp brain/ or exp meninges/

32 30 or 31

33 (vasospasm* or dci or spasm or spasms or aneurysm* or haemorrhag* or hemorrhag* or bleed or bleeding or blood or hypoxia).mp.

34 Hemorrhage/ or aneurysm/ or aneurysm, ruptured/ or exp hypoxia/

35 33 or 34

36 32 and 35

37 25 or 26 or 27 or 28 or 29 or 36

38 24 and 37

39 exp animals/ not exp humans/

40 (exp child/ or exp infant/) not exp adult/

41 38 not 39 not 40

Additional file 1: PRISMA-P CHECKLIST

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Completed
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Pg. 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Pg. 4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Pg. 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Pg. 17
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
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Pg. 17
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
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	Pg. 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)	Pg. 3-4
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	Pg. 4-5
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	Pg. 4-5
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	Pg. 15-16
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Pg. 6-7-8

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)	Pg. 5
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	Pg. 6-8
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	Pg. 6-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Pg. 6-9
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	Pg. 8-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Pg. 8-10
	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 I^2, Kendall's τ)	Pg. 8-10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Pg. 8-10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Pg. 8-10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Pg. 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Pg. 10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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