Role of brain tissue oxygenation (PbtO₂) in the management of subarachnoid haemorrhage: a scoping review protocol

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ABSTRACT

Introduction In patients with subarachnoid haemorrhage (SAH), the initial brain oedema and increased blood volume can cause an increase in intracranial pressure (ICP) leading to impaired cerebral perfusion and tissue hypoxia. However, ICP monitoring may not be enough to detect tissue hypoxia, which can also occur in the absence of elevated ICP. Moreover, some patients will experience tissue hypoxia in a later phase after admission due to the occurrence of delayed cerebral ischaemia. Therefore, the measurement of brain oxygenation using invasive techniques has become of great interest. This scoping review seeks to examine the role of brain tissue oxygenation in the management of patients with SAH, mapping the existing literature to identify areas for future research.

Methods and analysis This scoping review has been planned following the Joanna Briggs Institute recommendations and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The literature search will be performed using several databases: Medline, EMBASE, the Cochrane Central Register of Controlled Trials and Grey literature. The database searches are planned from the inception to May 2020. Two reviewers will independently screen titles and abstracts, followed by full-text screening of potentially relevant articles with a standardised data extraction. Articles eligible for the inclusion will be discussed with a third reviewer.

Ethics and dissemination This paper does not require ethics approval. The results of our evaluation will be disseminated on author’s web sites. Additional dissemination will occur through presentations at conferences, such as courses and science education conferences, regionally and nationally, and through articles published in peer-reviewed journals.

Scoping review registration Open Science Framework Registration: https://doi.org/10.17605/OSF.IO/2YJ7R. Trial registration number ClinicalTrials.gov Identifier: NCT03754114.

BACKGROUND

Subarachnoid haemorrhage (SAH) is a devastating acute neurological disease that affects many people worldwide. An estimated 25% of patients with SAH admitted to the hospital will eventually die, while half of the survivors will experience long-term neurological disabilities. The most important cause of non-traumatic SAH is aneurysm rupture, representing 5% of all strokes and 85% of all non-traumatic SAH. The incidence of aneurysmatic SAH (aSAH) varies significantly depending on region, gender, age, time period, smoking habits and blood pressure levels. A recent meta-analysis has shown a decrease of 40% in the incidence of aSAH since 1980, estimating to be around 6% in 2010.

Immediately after blood is spilled in the subarachnoid space, there is an elevation in intracranial pressure (ICP), a decrease in cerebral perfusion and possibly ischaemia. This causes neuronal death and endothelial damage, resulting in cytotoxic oedema. Furthermore, there is brain blood barrier rupture, which aggravates the development of vasogenic oedema. This process is responsible for further ICP increase. Moreover, the activated inflammatory response increases brain injury and contributes to microcirculatory failure and microthrombi formation, which further deteriorates ischaemia. These events are responsible for the so-called ‘early
brain injury' after SAH. Without a specific and prompt intervention, these phenomena will lead to irreversible brain damage and neuronal death. However, monitoring of ICP/cerebral perfusion pressure may not be enough to prevent cerebral complications. Although therapies aimed at reducing elevated ICP may decrease the risk of early death, the effectiveness of ICP monitoring and ICP-driven therapies have not significantly increased the probability of good neurological recovery in this setting. Additionally, tissue hypoxia can occur in the absence of elevated ICP and can significantly impact patients’ outcome. Therefore, measurement of brain tissue oxygenation (PbtO₂) has become of great interest in the early phase of aSAH.

After the initial phase of SAH pathogenesis, patients become susceptible to secondary brain injury, such as hydrocephalus, cerebral vasospasm and delayed cerebral ischaemia (DCI). DCI occurs in 30% of patients with aSAH and is the most important preventable cause of death and poor neurologic recovery in this setting. DCI has a complex pathogenesis that includes vasospasm of large vessels leading to low perfusion as well as neuro-inflammatory injury leading to microthrombi formation and microcirculatory failure. Moreover, electric phenomena such as cortical spread depolarisation seem to play a role in the pathogenesis of DCI. Early recognition of DCI is essential for timely intervention to minimise brain damage. This can be challenging, especially in patients with poor clinical status because of the difficulty to perform clinical examination and detect neuro-worsening. In this setting, multimodal neuromonitoring can help identify patients suffering from DCI and optimise treatment. Indeed, PbtO₂ can be relevant in detecting episodes of brain tissue hypoxia.

In other acute brain injury disorders, such as traumatic brain injury (TBI), PbO₂/ICP combined therapies seem to improve long-term outcomes when compared with ICP-guided therapy. A phase 2 randomised controlled trial suggests that PbtO₂ monitoring reduces the duration of brain hypoxia. A phase 3 trial with a similar design is actually recruiting patients to demonstrate an effect of such approach on the neurological outcome of patients with TBI. The ongoing trials on the use of transcranial oxygen saturation measurement in TBI and SAH are summarised in Table 1.

Our scoping review will assess most of the existing literature on this topic (ie, PbtO₂ and SAH); this scoping review will ask the following question based on the PCC (population, concept and context) elements of the

| Study title | ClinicalTrials.gov identifier | Status | Condition(s) | Intervention(s) |
|-------------|------------------------------|--------|--------------|-----------------|
| Cerebral autoregulation in patients with aneurysmal subarachnoid haemorrhage | NCT03987139 | Recruiting | aSAH | O: Hypertension O: Hyper- and hypoxia O: Hyper- and hypocapnia |
| Study of PtO₂ variation by body temperature and capnia in severe head trauma patients with intracranial refractory hypertension treated with targeted temperature control (TODAY) | NCT04109430 | Recruiting | Severe brain injury | NS |
| Brain oxygen optimisation in severe TBI (BOOST3): a comparative effectiveness study to test the efficacy of a prescribed treatment protocol based on monitoring the partial pressure of brain tissue oxygen | NCT03754114 | Recruiting | TBI | O: ICP +PbtO₂ guided management strategy O: ICP guided management strategy |
| Impact of early optimisation of brain oxygenation on neurological outcome after severe traumatic brain injury | NCT02754063 | Recruiting | TBI | D: PbtO₂ probes O: No PbtO₂ probes |
| NSI pulsed electromagnetic field (PEMF) biomarker study | NCT03654014 | Recruiting | TBI | D: SofPulse |
| Lactate therapy after traumatic brain injury | NCT01573507 | Recruiting | SAH TBI | O: sodium lactate infusion |
| Non-invasive near-infrared spectroscopy (NIRS) vs invasive licox intracranial pressure | NCT04247321 | Not yet recruiting | Brain injuries | D: Licox brain tissue oxygen monitoring system D: NIRS |

Search strings: “PbtO2” OR “Brain Tissue Oxygenation”. Recruitment status limited to a,Not yet recruiting b,Recruiting c,Enrolling by invitation d,Active, not recruiting. Eligibility criteria: adult (18–64) and older adult (65+) (accessed on February 19, 2020). aSAH, aneurysmatic subarachnoid haemorrhage; D, device; NIRS, near-infrared spectroscopy; NS, not specified; O, other; TBI, traumatic brain injury.
inclusion: ‘What is the role of PbtO₂ in SAH management of adult patients?’.

We will explore the existing and emerging evidence in the literature, with different levels of quality, from several databases. We will summarise the main results and discuss the limitations of the studies retrieved in order to map ‘the state of the art’ on the subject and identify knowledge gaps. These findings could be helpful to understand the actual knowledge for brain oxygen monitoring in patients with SAH and to guide the development of future, more specific, therapeutic protocols integrating this monitoring tool into dedicated algorithms. Since a scoping review aims to identify the nature of a broad field of evidence, this approach may help our research group to develop more specific questions to which a subsequent systematic review and meta-analysis will try to answer.

METHODS
Protocol design
The scoping review has been planned according to the five stages framework proposed by Arksey and O’Malley and Guidance of Peters et al, which has been further developed by Levac et al and the Joanna Briggs Institute: (1) identifying the review question, (2) identifying relevant studies, (3) study selection, (4) charting the data and (5) collating, summarising and reporting the results. Furthermore, it will be conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was registered prospectively with the Open Science Framework on 4 November 2019.

Patient and public involvement
Patients and public were not involved in the preparation of this protocol.

Stage 1: identifying the research question
The aim of this review is to map the available literature on PbtO₂ regarding the management of patients with SAH. To achieve this objective, the following research questions will be addressed:

1. Which patient with SAH benefit the most from PbtO₂ monitoring (ie, clinical and imaging severity, ICP levels)?
2. What is the rationale behind this technique (eg, PbtO₂ physiology, etc)?
3. Where is this technique performed (eg, mixed intensive care unit, neurological intensive care unit, etc)?
4. When is the technique implemented and when should it be stopped (eg, at hospital admission, at worsening of neurological conditions, etc)?
5. Why is the technique performed (diagnostic, predictive, prognostic)? Which are the major indications? Can PbtO₂ monitoring help detect brain injury (both early brain injury and DCI)? Can PbtO₂ monitoring help prevent brain injury? Can PbtO₂ monitoring guide therapy and improve mortality or neurologic outcome?
6. How is PbtO₂ monitoring performed (device insertion, device site, calibration, etc)?
7. How to apply this technique in the clinical practice? Is there a specific therapeutic protocol driven by PbtO₂? How to quantify the burden of hypoxia and what thresholds for brain hypoxia were applied in different studies?

Stage 2: identifying relevant studies
Eligibility criteria
This scoping review will consider all the studies focusing on PbtO₂ in the management of adult patients with SAH (≥18 years old).

In order to maximise the gathering of data, we will include both full peer-reviewed articles and grey literature (conference publications, abstracts, dissertations, etc). There will be no limitations regarding the year of publication. We will include all publications that have English title/abstract. There will be no language limitation.

Search strategy
We plan to follow a three-step search strategy to find and analyse fully published studies. First, we will conduct a limited search on Medline and CINAHL. This preliminary search will be followed by the analysis of the text words contained in the title and abstract and of the index terms used to describe articles. This information will allow us to develop a complete search strategy and tailored to each information source. A proposed search strategy for Medline is detailed in table 2. A subsequent search using keywords and index terms will then be started using the following databases: Medline, EMBASE and the Cochrane Central Register of Controlled Trials.

Regarding the analysis of grey literature, we will consult the following sources: Google Scholar, Conference Proceedings Citation Index via Web of Science, Dissertation Abstracts via ProQuest, Networked Digital Library of Theses and Dissertations, Open DOAR and Open Grey. Finally, we will use the reference list of all identified reports and articles to identify additional eligible studies.

Stage 3: study selection
The screening will be performed in two phases, namely ‘initial screening’ based on title and abstract, followed by a ‘full-text screening’ of the eligible articles for final inclusion. Duplicates will be excluded. Two authors (EB and MF) will independently evaluate the titles and abstracts of potentially eligible studies. The authors of the screened studies will be contacted in the case of missing data.

Stage 4: data charting
We will identify and retrieve the following data:

1. Study population description: age, gender, comorbidities, Glasgow Coma Scale at admission, Fisher scale or modified Fisher scale, world federation of neurological surgeons scale, aetiology
of SAH (aneurysmal, arteriovenous malformation, sinue materiae, etc).

2. Intervention: indication for PbtO2 catheter insertion; timing of testing of the catheter’s function; which devices were included in multimodal monitoring strategy (ICP monitoring, continuous EEG monitoring, microdialysis); comparison between PbtO2 and other techniques in the detection of brain hypoxia (ICP, near-infrared spectroscopy, jugular bulbous venous saturation); thresholds commonly used in the clinical practice to define brain hypoxia; when to start treatment based on PbtO2 values. What targets of PbtO2 should be sought to guide intervention.

3. Complications: bleeding due to catheter insertion, ischemia due to catheter insertion, malfunctioning or incorrectly inserted catheter, infections.

4. Outcomes: burden of hypoxia (how low was PbtO2, and for how long), neurologic outcome, mortality (intensive care mortality, hospital mortality, 30-day mortality)

Data will be extracted independently using the Joanna Briggs Institute’s System for the Unified Management, Assessment and Review of Information (SUMARI). The search strategies for the other databases will be similar in structure with similar search terms and synonyms.

### Table 2: Scoping review search strategy. Ovid medline search strategy (24 May 2020)

| Searches                                                                 | Results |
|-------------------------------------------------------------------------|---------|
| 1. (pbtO2 or licox or NeuroTrend). mp.                                   | 279     |
| 2. Oxygen/                                                               | 163532  |
| 3. (oxygen or oxygenation or O2). mp.                                    | 697827  |
| 4. 2 or 3                                                                | 697827  |
| 5. exp Monitoring, Physiologic/                                          | 173039  |
| 6. monitor*.mp.                                                         | 957907  |
| 7. 5 or 6                                                                | 991601  |
| 8. exp brain/ or exp meninges/                                           | 1217704 |
| 9. (cerebral or cerebrovascular or brain or meninge* or arachnoid* or subarachnoid*).mp. | 1744487 |
| 10. Cerebrovascular Circulation/                                          | 54723   |
| 11. 8 or 9 or 10                                                         | 2106957 |
| 12. Hemorrhage/ or aneurysm/ or aneurysm, ruptured/ or exp hypoxia/     | 166271  |
| 13. exp Subarachnoid Hemorrhage/                                         | 21143   |
| 14. 4 and 7 and 11                                                       | 7128    |
| 15. 1 or 14                                                             | 7239    |
| 16. 11 and 12                                                           | 22575   |
| 17. 13 or 16                                                             | 40694   |
| 18. 15 and 17                                                            | 653     |

The search strategies for the other databases will be similar in structure with similar search terms and synonyms.

### Discussion

To our knowledge, this is the first attempt to map all existing literature on the topic. PbtO2 monitoring is an invasive technique that is not easily available worldwide. In order to use PbtO2 correctly, it is mandatory to know why, when and how to implement it in patients with SAH. Furthermore, it is essential to understand how to use the information available to detect neuro-worsening and to potentially guide therapy. This review will aim to clarify these topics and hopefully guide potential randomised clinical trials on the use of PbtO2-guided therapy in patients with SAH.

### Ethics and dissemination

This paper does not require ethics approval as data will be obtained through review of primary studies already published.
published. This project will serve as a pilot for other reviews from our research group. The results of our evaluation will be disseminated on the author’s web sites. Additional dissemination will occur through presentations at conferences and through articles published in peer-reviewed journals. Finally, the investigators will use their networks to encourage broad dissemination of results.

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