SYSTEMATIC REVIEW

The future of non-invasive cerebral oximetry in neurosurgical procedures: A systematic review [version 1; referees: 1 approved with reservations]

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Abstract

Background: Cerebral hypoxia is one of the most important causes of secondary brain injury during neurosurgical procedures and in neurointensive care. In patients with brain injury, cerebrovascular reactivity may be impaired and a decrease in mean arterial pressure or cerebral perfusion pressure may lead to inadequate cerebral blood flow and secondary ischemia. There are several techniques available to measure brain oxygenation. In particular, near infrared spectroscopy (NIRS) is a non-invasive neuromonitoring technique and there has been a rapid expansion of clinical evidence that NIRS reduces perioperative neurologic complications.

Methods: This systematic review synthesizes prospective and retrospective cohort studies that investigate the benefit of using NIRS in prevention of perioperative neurologic complications. The methodological quality of these studies is appraised.

Results: Seven studies were included in this systematic review. The methodological quality of each study was assessed. They had representative patient populations, clear selection criteria and clear descriptions of study designs. Reproducible study protocols with ethics board approval were present. Clinical results were described in sufficient detail and were applicable to patient undergoing neurosurgical procedures and in neurointensive care. Limitations included small sample sizes and lack of reference standard.

Conclusions: This systematic review synthesizes the most current evidence of non-invasive, inexpensive, and continuous measurement of cerebral oxygenation by NIRS. Results gained from these studies are clinically useful and shed light on how this neuromonitoring technique is beneficial in preventing perioperative neurological complications.

Keywords

Near infrared spectroscopy, cerebral oximetry, neurosurgery, neuroradiology, neurointensive care, systematic review
Introduction

The human brain constitutes approximately 2% of body weight. However, its energy consumption counts up to 25% of total body energy expenditure and 20% of total oxygen consumption. Therefore, it is needless to say that efficient energy and oxygen supply is crucial for the brain, and its significance is even greater during surgical procedures as well as in neurocritical care.

The brain is uniquely sensitive to injury compared to other organ systems, largely due to its poor regenerative capacity. Injury to the brain is also often not static, but rather progressive with potential secondary injury that is mediated by pathologies such as cerebral edema, hypoxia/ischemia and energy dysfunction. Neuromonitoring, therefore, plays a crucial role not only in identifying changes in neurological function in pre, peri and post-surgical procedures, but also in improving pathophysiological understanding of cerebral disease in critical illness, and most importantly providing with prognostication. With this, neuromonitoring offers physiological information for individualized therapy.

Cerebral hypoxia is one of the most important causes of secondary brain injury. In the normal brain, decline in systemic pressure activates a vasodilatory response to maintain cerebral blood flow (CBF) constant over changes of mean arterial pressure (MAP), thereby preventing cerebral hypoperfusion, the process of which is also called cerebral pressure autoregulation. In patients with brain injury, cerebrovascular reactivity may be impaired, and a decrease in MAP or cerebral perfusion pressure (CPP) may thus lead to inadequate CBF and secondary ischemia.

Cerebral oximetry

There are several techniques that can measure brain oxygenation, the most common being jugular venous bulb oximetry (SjvO₂) and direct brain tissue oxygenation (PbtO₂) measurement until recently. The former requires placement of a fiberoptic oximeter retrograde into the jugular bulb and measures the arterio-jugular difference of oxygen content (AJDO₂) that is proportional to CBF and inversely proportional to cerebral oxygen consumption, well indicating cerebral perfusion. Previous studies demonstrated its significance in the global measurement of cerebral oxygen saturation and the prognostication of low SjvO₂ in brain injury. However, continuous SjvO₂ monitoring carries many limitations. First, it is relatively insensitive in detecting focal hypoperfusion that may be at risk for secondary insult. There are also complications associated with central catheter placement and its invasiveness, and SjvO₂ has limited consistency from one measurement to another.

In direct PbtO₂ measurement, a small flexible microcatheter is inserted directly into the white matter allowing a focal measurement of cerebral oxygenation. There are two widely used probes: Licox (Integra NeuroSciences, San Diego, California, USA) and Neurotrend (Codman, Raynham, Massachusetts, USA). The Licox probe uses a polarographic Clark electrode to measure the PbtO₂ whereas the Neurotrend microcatheter uses optical luminescence to measure PbtO₂ as well as PbtCO₂ and pH. Low PbtO₂ along with prolonged duration and high intensity of the decrease have repeatedly shown to be related to poor clinical outcomes. PbtO₂ monitoring can also be used in combination with other intra-parenchymal monitors such as ICP monitor.

Near infrared spectroscopy (NIRS) is an emerging technique for the same purpose while it offers non-invasive, in vivo and real-time monitoring of cerebral tissue oxygenation. NIRS uses essentially the same approach as pulse oximetry in measuring hemoglobin saturation and is based on the transmission and absorption of near infrared (NIR) ray (ranging between 700 and 850 nm) as it travels through tissue. In adults, NIR light cannot pass across the whole head, thus the light source and detecting optode(s) are placed on the same side of the head only a few centimeters apart, which allows the measurement of the superficial cortex (called reflectance spectroscopy).

Oxygenated and deoxygenated hemoglobin have distinct absorption spectra in the NIR and their relative concentrations in tissue can thus be determined by their relative absorption of light in wavelength. Unlike pulse oximeter that measures oxygen saturation of hemoglobin in arterial blood, cerebral oximeter measures oxygen saturation of hemoglobin in the entire tissue bed including brain parenchyma, arterial and venous blood although it is mainly venous blood.

In the last decade, NIRS has proven its potential as a non-invasive neuromonitoring technique across a spectrum of disorders: carotid endarterectomy, cardiac surgery, beachchair surgery, and neurosurgery. There has been a rapid expansion of clinical experience using NIRS to monitor cerebral oxygenation, and many evidences showed that NIRS-guided brain protection protocol leads to a reduction in perioperative neurologic complications of surgical procedures.

Objectives

The purpose of this systematic review was to synthesize prospective and retrospective cohort studies that investigate the benefit of using NIRS in prevention of perioperative and neurointensive care neurologic complications. This systematic review also critically appraises the methodological quality of these studies.

Methods

Study eligibility criteria

Studies that were eligible for this systematic review included:

Studies of adult patients with neurosurgical conditions requiring neurointensive care.

The patients received neuromonitoring system to investigate the cerebral oxygenation status using NIRS with or without reference standard testing to appraise the effectiveness of NIRS.
Prospective and retrospective cohort studies investigating the effectiveness of NIRS on cerebral oxygenation monitoring technique.

The following studies were excluded:

Studies based on expert opinions,

Studies that do not characterize the use of NIRS for the cerebral ischemic outcome,

Eligible studies were limited to those published from January 1, 2005 to December 31, 2016. We truncated eligible studies to this time period because of:

Advancement and availability of non-invasive monitoring system, such as NIRS, in major academic institutions,

Advancement of neurosurgical and neuroradiologic procedures as well as neurocritical care establishment in major academic institutions.

Literature search
Two reviewers (WooJin Kim [WJK] and Benjamin Lo [BL]) independently searched two electronic databases: PubMed and Web of Science. Relevant studies were identified from these databases first without language restrictions. For example, the following search terms were used on PubMed: Cerebral Oximetry AND Neurosurgery.

Study selection and data collection process
Both investigators (WJK and BL) reviewed all titles and abstracts and full reports of all potentially relevant studies. The initial literature search yielded 210 citations (Figure 1). First screening by the limited date of publication (January 1, 2005 – December 31, 2016) and removal of duplicates from the multiple sources yielded 88 citations, which were identified as potentially relevant. These articles were then assessed by screening their titles and abstracts with the following exclusion criteria and, from which, 68 articles were excluded:

- Inappropriate study design (n=37)
- Inappropriate study method (n=18)
- Inappropriate study subject (n=1)
- Language other than English (n=9)
- Full text unavailable online (n=3)

Full-text article excluded (n=13)
- Inappropriate patient inclusion/exclusion (n=4)
- Inappropriate/insufficient outcome report (n=9)

Studies included in systematic review (n=7)

Figure 1. Flow diagram of study selection.
Inappropriate study design, method, subject
Language other than English
Full text unavailable online

The investigators (WJK and BL) then independently applied the inclusion criteria to the full 20 articles. The final selection of seven articles were based on the following exclusion criteria:

- Inappropriate patient inclusion/exclusion
- Inappropriate/inadequate outcome report

Each report was then carefully examined for its methodological quality as outlined in the section Methodological quality assessment, and relevant data were extracted for this study in agreement by both investigators.

Assessment
For this systematic review, the following items were reviewed in order to clarify the effectiveness of using non-invasive NIRS in neurosurgical and neurocritical settings:

- Study design – including description of study protocol, study setting, and recruitment,
- Patient population – including representative of cohort, inclusion and exclusion criteria, and sample size,
- Investigations – including diagnostic and reference neuromonitoring modality to document cerebral oxygenation and cerebral ischemia,
- Outcome – including discussions on cerebral ischemia secondary to impaired brain oxygenation, and
- Ethical conduct of study – including institutional ethics board approval and funding declarations.

Methodological quality assessment
For this systematic review, we sampled the QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy Studies Tool–Revised Version). The following nine areas were used in methodological quality assessment, as they would apply to effectiveness of non-invasive NIRS in neurosurgical and neurocritical settings:

- Whether subjects included are representative of those treated in clinical practice,
- Clear study designs and descriptions of study protocols, inclusion and exclusion criteria, study settings, and recruitment,
- Inclusion of study findings with adequate discussions,
- Clear descriptions of reference standards to document cerebral oxygenation,
- Whether diagnostic tests to investigate cerebral ischemia,
- Whether clinical data for study subjects are reproducible for those treated in clinical practice,
- Reporting of non-interpretable test results,
- Explanation of study withdrawals, and
- Whether the measure is clinically useful.

We also followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement 2009 and flow diagram to ensure adequate reporting items.

Results
Study selection
Seven studies were included in this systematic review after careful selection from 88 citations and articles (Figure 1).

A meta-analysis was not feasible in this review to statistically pool outcomes obtained from the included studies. Marked between-study differences was noted with:

- Differing neurosurgical and neurocritical conditions that patients presented with,
- Differing diagnostic tests and reference standard testing, and
- Differing clinical outcome endpoint measures.

In addition, there is no standardization of diagnostic tests and no reference value of these tests between investigating centres.

Study result and synthesis of results
This systematic review identified four prospective and two retrospective cohort studies. Of the seven methodologically rigorous studies identified in this systematic review, the following neurosurgical and neurocritical conditions were presented:

- Article 1: Neurovascular procedures including aneurysm clipping, arteriovenous malformation (AVM) resection, carotid endarterectomy (CEA), superficial temporal artery (STA)-middle cerebral artery (MCA) bypass surgery, external carotid artery (ECA)-MCA bypass surgery, encephaloduroarteriosynangiosis (EDMS), and balloon occlusion testing (BOT)
- Article 2: Cerebral ischemia secondary to internal carotid artery (ICA)/MCA stenosis
- Article 3: Endovascular embolization following subarachnoid hemorrhage (SAH)
- Article 4: SAH and traumatic brain injury (TBI)
- Article 5: Endovascular embolization following cerebral aneurysm, AVM, dural arteriovenous fistula (AVF), and meningioma
- Article 6: SAH, ischemic stroke, and intracerebral hemorrhage (ICH)
- Article 7: Cerebral hyperperfusion syndrome (CHS) following carotid artery stenting

Assessment of the studies
Article 1: Detection of cerebral ischemia in neurovascular surgery using quantitative frequency-domain near-infrared spectroscopy. In this prospective cohort study, Calderon-Arnulphi et al. directly assessed the use of NIRS (Oxiplex TS, ISS) in monitoring cerebral ischemia during open neurovascular procedures. The authors monitored 25 neurovascular procedures including aneurysm clipping, AVM resection, CEA, STA-MCA bypass, ECA-MCA bypass, EDMS and BOT performed between May 2004 and February 2006 at the University of...
Illinois at Chicago for cerebral oxygenation. Diagnostic testing using quantitative NIRS (Q-NIRS) measured tissue oxyhemoglobin, deoxyhemoglobin, and total hemoglobin, and brain tissue oxygen saturation as evidence of intraoperative cerebral ischemia. Reference standard testing was absent in this study although the authors compared the measurements to the unaffected contralateral hemisphere for comparison. In addition due to the quantitative nature of Q-NIRS measurements, recordings could only be compared over time as well as with recordings obtained in other patients. In five cases that exhibited clinical evidence of ischemic events during the procedure, Q-NIRS monitoring showed a decrease in oxyhemoglobin, total hemoglobin and PtO₂, and an increase in deoxyhemoglobin in the affected region, validating NIRS as a continuous and non-invasive intraoperative cerebral oxygenation monitoring technique29.

**Article 2: Evaluation of cerebral ischemia using near-infrared spectroscopy with oxygen inhalation.** In this prospective cohort study, Ebihara et al.29 employed 30 normal volunteers without a history or risk factors of cerebral disease to evaluate cerebral hemodynamics in comparison with 33 patients with cerebral ischemia by NIRS (TEG-4000, Hitachi Medical Cooperation) upon oxygen inhalation at Jichi Medical University, Tokyo29. The patients with ischemia were determined by the prediagnosed conditions of stenosis or occlusion of the ICA or MCA visualized by MR angiography. In these patients, change in CBF in the arc of the MCA was evaluated with N-isopropl-p-[125I] Iodoamphetamine single-photon-emission computed tomography ([125I]-IMP SPECT) as reference standard testing with NIRS as diagnostic testing. In all patients with ischemia, NIRS found lower tissue oxygenation in ischemic regions than in normal regions, 85% of which (28 of 33 cases) agreed with those measured by SPECT confirming its efficacy in replacing some of the conventional methods to evaluate cerebral oxygenation29.

**Article 3: The application of near-infrared oximetry to cerebral monitoring during aneurysm embolization: a comparison with intraprocedural angiography.** In this prospective cohort study, Bhatia et al. also compared the values of NIRS (INVOS-4100, Somanetics Corp) acquired during coil embolization with incidence of vasospasm as detected from angiography29. Thirty-two SAH patients who underwent embolization at the Kings College Hospital, London, UK between February and November 2005 were included. While bilateral NIRS were placed on the forehead at constant anatomic positions, ipsilateral angiography was performed every 10 to 15 minutes. An independent neuroradiologist classified any vasospasm in the parent vessel as mild (25% baseline), moderate (50%), severe (75%) or total (100%). There also was no significant association between the side of aneurysm and baseline regional cerebral oxygenation signal measured by NIRS (p = 0.243). However, the authors found a significant association between vasospasm (and its degree) and reduction in ipsilateral NIRS data on regional cerebral oxygen saturation (p < 0.001)24.

**Article 4: Correlation between cerebral blood flow and oxygen saturation in patients with subarachnoid hemorrhage and traumatic brain injury.** In this prospective cohort study, Shafer et al. evaluated NIRS (INVOS-5100, Somanetics Corp) in relation with portable xenon enhanced CT (Xe/CT), which is considered to be gold standard for assessing cerebral perfusion in patients in the neurointensive care unit (ICU) of numerous established medical centres30. The authors performed cross sectional analysis of imaging studies conducted in 22 patients with SAH and TBI at the University of New Mexico Hospital from June 2008 to December 2009. No statistically significant relationship was found between two diagnostic testing methods as evaluated by using the Spearman correlation coefficients: 0.05 and -0.05, right and left side respectively. The authors, however, report few limitations of this study such as the small sample size, the different etiology and location of brain injury, and the different patient specific physiologic factors.

**Article 5: Usefulness and limits of near infrared spectroscopy monitoring during endovascular neuroradiologic procedures.** In this retrospective cohort study, Mazzeo et al. well demonstrated the continuous measurement of regional cerebral oxygenation using NIRS (INVOS-5100, Somanetics Corp) in 25 patients undergoing elective endovascular procedures following cerebral aneurysm, AVM, dural AVF and meningioma over a period of 12 months starting January 200731 at the University of Messina, Italy. Regional cerebral oxygenation was significantly affected by the different phases of the neuroendovascular procedure: induction of anesthesia, interventional procedure, and recovery from anesthesia, with the interventional procedure having the most reduction of cerebral oxygenation (p < 0.001). An effect of the different underlying pathology on cerebral oxygenation was also evident during the interventional procedure, the more invasive the procedure the greater the impact on cerebral oxygenation. Overall, this study showed an effect of the underlying cerebral pathology and also in relation to the advancing stages of the interventional procedure on regional cerebral oxygenation. NIRS monitoring was also able to early detect intraoperative harmful events resulting in cerebral hypoxic episodes. However, this study also lacks comparison to other reference standard monitoring modalities. The author also reports the possible artifacts related to contrast agent used31.

**Article 6: Validation of frontal near-infrared spectroscopy as noninvasive bedside monitoring for regional cerebral blood flow in brain-injured patients.** In this retrospective study, Tausky et al., similarly to the study by Shafer et al., assessed the statistical correlation of NIRS (CASMED FORE-SIGHT, Branford) and CT perfusion with respect to regional CBF measurements in their retrospective study over a period of 3 years from February 2008 to June 201132. This study involved 8 patients (6 suffered SAH, 1 ischemic stroke and 1 ICH) who were admitted to the neurointensive care unit at the Mayo Clinic in Jacksonville, Florida. Regions of interest was obtained 2.5 cm below the NIRS bifrontal scalp probe on CT perfusion with an average volume between 2 and 4 ml to accurately compare the physiologically identical location. The authors found a statistically significant linear correlation between frontal NIRS cerebral oxygenation measurement with regional
CBF on CT perfusion imaging\textsuperscript{32}. The authors also describe different methods of CBF measurements such as Kety-Schmidt model, Xe/CT, PET, and MRI with perfusion-weighted imaging in this article\textsuperscript{33,34}.

**Article 7: Near-infrared spectroscopy in carotid artery stenting predicts cerebral hyperperfusion syndrome.** In this final retrospective study, Matsumoto et al. conducted an evaluation study in 64 patients with internal carotid artery stenosis who underwent carotid artery stenting at the Kokura Memorial Hospital, Fukuoka, between June 2006 and June 2007, where NIRS (INVOS-5100, Somanetics Corp) was used as a perioperative monitor for regional cerebral oxygen saturation\textsuperscript{35}. Split-dose \textsuperscript{131}I iodoamphetamine single photon emission computed tomography (SPECT) and Technetium-99m hexamethylpropyleneamine oxime SPECT were performed before and after the procedure, respectively, as reference modalities to evaluate cerebral perfusion. In the patients who had neurological deterioration post-procedure and the subsequent diagnose of CHS by SPECT had the recorded increase of post-perfusion regional cerebral oxygen saturation (>24% vs. <10%) using NIRS perioperatively\textsuperscript{35}. This study shows that NIRS can be an excellent non-invasive predictor of CHS after carotid artery stenting.

**Methodological quality of included studies**
In summary, all seven studies have strong methodological quality (Table 1). They had representative patient populations, clear selection criteria and clear study design. Clear study protocols for reducibility with ethics board approval were included. Clinical results were described in sufficient detail and were applicable to appropriate clinical practice. The main methodological weakness in few studies included small sample size and lack of appropriate reference standard testing modality, which were stated by the authors.

The results gained from these studies are clinically useful and shed light on how the use of non-invasive and inexpensive continuous measurement of cerebral oxygenation by NIRS is effective in neurosurgical and neurocritical settings.

**Discussion**
Considering NIRS is a relatively new modality to be used in neuromonitoring, large scale multi-centre studies as well as randomized controlled trials comparing NIRS to traditional monitoring techniques are lacking at the present time. In the past decade (2005–2016), studies of NIRS in neurosurgical procedures have been mostly cohort observational.

There are a number of notable narrative reviews on NIRS and its current applications\textsuperscript{36–46}. Many of these report a great deal of evidence that NIRS is an effective monitoring method for cerebral oxygenation in patients with neurocritical condition as well as evidence that NIRS may reduce perioperative neurologic complications. However, the latter was mostly demonstrated in cardiac surgery and the same evidence in neurosurgery is lacking\textsuperscript{44}. There are no reports on whether or not NIRS is well adapted as a routine neuromonitoring modality in established medical centres globally. However, Skoglund et al. in their systematic survey throughout 16 centres in Scandinavia reports that cerebral oxygenation monitoring, even by conventional jugular bulb oximetry, is infrequently used although it is on the rise from 1999 to 2009; while monitoring of ICP and CPP were widely used\textsuperscript{47}.

**Table 1. Methodological assessment of articles on effectiveness of non-invasive NIRS in neurosurgical and neurocritical care.**

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<td>Normal volunteers</td>
<td>Baseline, contralateral hemisphere</td>
<td>Between two modalities</td>
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<td>Between two modalities</td>
<td>Baseline vs post reperfusion</td>
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<td>Yes (NIRS)</td>
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<td>Yes (no correlation)</td>
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Limitation and neurosurgical considerations

One major limitation of NIRS in neuromonitoring is the lack of a universal standard threshold for normal cerebral oxygenation, unlike pulse oximetry. Each patient had different baseline values and the thresholds, which correlate with symptomatic cerebral ischemia is variable. It is therefore more useful in elective neurological and endovascular procedures (such as carotid artery stenting or angioplasty for vasospasm) where patients can be monitored before intervention to establish a reliable baseline.

The NIRS value would depend on the absorption of infrared signal between the sensor and the brain, i.e. the scalp, the skull bone, the dura, and any interposed tissue or implant. This physical limitation renders the application in common neurological condition problematic. For example, in head injury patients with scalp swelling or skull fracture, and those with recent craniotomy or cranioplasty. Finally, the NIRS sensor detects a relatively small area of brain parenchyma and may not reflect loco-regional ischemia that is distant from the sensor.

Conclusions and future perspectives

NIRS is an emerging non-invasive cerebral oximetry, and provides quantifiable and continuous real-time data on cerebral oxygenation in user-friendly manner that is accessible in any circumstances. This intraoperative oxygenation monitoring is a promising technique not only for detecting cerebral ischemia/hypoxia but also for characterizing the hemodynamics and metabolic responses to changes in cerebral function.

Conventional methods such as jugular bulb oximetry and direct PbtO₂ measurement that are widely used to evaluate cerebral hemodynamics are invasive and they require equipment that is not easily manageable, which makes it difficult to continue measurement at the patient’s bedside.

Although efficacy of NIRS as a routine neuromonitoring method has been repeatedly demonstrated in the literature, its complete story is still lacking due to insufficient large-scale studies or randomized control trials. There is also not enough evidence to support its use in neurosurgery where it is expected to have the most important role. Continuous investigations and technological advances of NIRS are necessary before it can be introduced more widely into clinical practice in the neuro-ICU and during neurosurgical procedures.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

Supplementary material

Supplementary File 1: PRISMA checklist.

Click here to access the data.

References

   Reference Source
12. Dearden NM, Midgley S: Technical considerations in continuous jugular venous


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Open Peer Review

Current Referee Status: ?

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In this manuscript, authors performed a systematic review to evaluate the clinical usefulness of near infrared spectroscopy (NIRS). The methods and modalities used for the selection of the clinical trials for the systematic review in this paper seem quite convincing. However, I have some questions.

The biggest concern for this article is that it lacks the information of the clinical implication and recommendation for NIRS obtained from the systemic review. Methodological assessment and the short summary for each article is described, however it would be better the authors make a table for the clinical characteristics of each trial including information such as what kind of diseases were included, number of patients, etc. Moreover authors are recommended to mention in more detailed summary the clinical usefulness of the NIRS and clinical recommendation obtained by this systematic review. Especially in the abstract, there is only methodological assessment of the articles in the “Results”. It would be better that more clinical information were included in the abstract.

For a minor point, abbreviation of encephaloduroarteriosynangiosis is “EDAS”. EDMS stands for encephaloduromyosynangiosis.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Not applicable

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.