Cerebral near-infrared spectroscopy monitoring to predict periventricular-intraventricular haemorrhage and neurodevelopmental outcomes in preterm infants: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Periventricular-intraventricular haemorrhage (PV-IVH) is one of the major cause of mortality and long-term neurodevelopmental sequelae in preterm infants born at less than 32 weeks of gestation. Near-infrared spectroscopy (NIRS) monitoring can detect brain tissue oxygen saturation changes before the occurrence of PV-IVH in the early postnatal period. However, the time window for NIRS monitoring, the absolute value or change value of brain tissue oxygen saturation, and the accuracy of NIRS in predicting PV-IVH and its neurodevelopmental outcomes has not been systematically reviewed. In this review, we will investigate the diagnostic accuracy (sensitivity, specificity and accuracy) of NIRS in predicting PV-IVH, its severity and outcomes.

Methods and analysis Literature will be searched in the PubMed, EMBASE, Web of Science and Cochrane Library databases without limitation of region or time of publication. All published literature without language restrictions, including randomised/quasi-controlled trials and observational studies, will be considered. Studies providing index test values (the absolute value or change value of oxygen saturation using NIRS) will be included. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies (DTA) process will be followed for writing. The risk of bias will be assessed according to the Quality Assessment of Diagnostic Accuracy Studies-2 tool. The outcomes will be the diagnostic accuracy (sensitivity, specificity and accuracy) of NIRS in predicting PV-IVH, long-term neurodevelopmental outcomes and infant mortality. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool will be used to evaluate the quality of the evidence.

Ethics and dissemination In this systematic review, data will be collected from published articles for collation and analysis, without a separate ethical review.

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INTRODUCTION

Premature birth and complications were one of the main causes of death in children under 5 years of age from 2000 to 2015.1 With therapeutic advances in neonatology, the survival rates for extremely preterm infants (born at less than 28 weeks gestational age (GA)) and very preterm infants (born at 2810–3116 weeks GA) are constantly improving. However, the risk of neurological damage and associated sequelae remains an important issue in these infants. Periventricular-intraventricular haemorrhage (PV-IVH), the most common neurological complication for preterm infants in early postnatal days, occurs in approximately 30% of extremely preterm infants.2 PV-IVH is often associated with mortality and long-term neurodevelopmental sequelae.3 With the deterioration of PV-IVH,
mortality rates vary from 4% (grade I) to 40% (grade IV) during initial hospitalisation.

Severe PV-IVH (grades III and IV) can lead to ventricle enlargement, hydrocephalus and white matter injury after haemorrhage. About 30% of post haemorrhagic hydrocephalus require multiple surgical treatments. Infants with severe PV-IVH and associated PV leukomalacia are at high risk of death and severe neurodevelopmental disorders. Increased cerebroventricular size after PV-IVH is closely associated with long-term impaired neurocognitive functions. Furthermore, PV-IVH also has a significant correlation with blindness and deafness, which affects exercise and behavioural abilities in childhood. Thus, PV–IVH, especially severe PV-IVH, significantly increases the rate of hospitalisation in childhood.

To avoid the occurrence of serious sequelae, early monitoring and prediction of PV-IVH could promote appropriate intervention and improve the long-term prognosis. It will make a significant contribution to reducing the family and social burden due to neurological sequelae. Currently, the prediction of preterm infants with a high risk of PV-IVH is a hot topic in PV-IVH research. In the neonatal intensive care unit (NICU), neuromonitoring is mainly based on neuroimaging monitoring, such as ultrasound and MRI, neuroelectrophysiological monitoring (amplitude integrated electroencephalogram, aEEG), cerebral blood flow monitoring and cerebral oxygenation monitoring (near-infrared spectroscopy, NIRS) techniques. Each neuromonitoring method has its own shortcomings. For neuroimaging monitoring, it is difficult to perform continuous dynamic monitoring, and most newborns undergoing MRI need to be sedated for evaluation; aEEG provides information only from electrophysiological aspects, as the means of neuronal cell electrical activity changes may just be the outcome of neural damage. NIRS involves the use of noninvasive monitoring equipment, which is economical, and the results are easy to interpret. It has been widely used for the prediction of possible neurological dysfunction, surgery monitoring and pain assessment in newborn infants. NIRS is used to monitor the oxygen saturation of local tissue by using the different absorption rates of oxygen, haemoglobin and deoxyhaemoglobin. The oxygen consumption of local tissue can be calculated in combination with the whole-body oxygen saturation in the same period.

NIRS could provide a reference value for the clinical prediction of subsequent nerve haemorrhage injury events. NIRS may be useful in evaluating children with intracranial haemorrhage. The trends in brain oxygen saturation changes during the first 72 hours of life in newborns with PV-IVH were different from those of healthy controls. A study using continuous NIRS monitoring for 4 weeks found that preterm infants with any grade of PV-IVH had lower cerebral oxygen saturation than non-PV-IVH infants. The difference between the two groups disappeared at 36 weeks of corrected GA.

Surviving premature infants with PV-IVH are at high risk for adverse neurodevelopmental outcomes. Predicting the prognosis of these infants will enable clinicians to recognise potential adverse neurodevelopmental outcomes early. This could facilitate intervention at the early stages of disease and improve the prognosis. Early NIRS monitoring has been applied for premature infants with PV-IVH in clinical practice with contradictory conclusions. However, the diagnostic accuracy of NIRS monitoring for the diagnosis of PV-IVH and its outcomes have not been systematically reviewed. The systematic review will include the published literature regarding NIRS monitoring of premature infants for predicting PV-IVH and its prognosis. The specificity, accuracy and sensitivity of NIRS monitoring will be assessed for PV-IVH and prognosis prediction (including all grades, mild or severe PV-IVH, mortality, and neurodevelopmental outcomes).

To analyse the predictive accuracy of NIRS (index tests) in the prediction of PV-IVH, long-term neurodevelopmental outcomes, and infant mortality. We will also determine the threshold of cerebral oxygenation saturation by NIRS technology in the prediction of PV-IVH.

We will explore heterogeneity among studies evaluating NIRS by analysing the following subgroups: test threshold, postnatal age/corrected GA at testing and GA at birth. We will follow the method recommended by the Cochrane Diagnostic Test Accuracy Working Group (http://srdta.cochrane.org/).

Literature will be searched in the PubMed, EMBASE, Web of Science and Cochrane Library databases without limitations of region or time of publication. The search strategy will be established using free words and subject word of PV-IVH, NIRS and preterm infants. The detailed search strategy is shown in online supplemental table 1.

Types of studies to be included

Population
Preterm infants born at less than 32 weeks gestation.

Comparison
Preterm infants with PV-IVH will be compared with those without PV-IVH. Infants with different grades of PV-IVH will be compared.

Index tests
Absolute and change value of regional cerebral tissue oxygen saturation (rSO2), measured with NIRS and fractional tissue oxygen extraction (FTOE) will be calculated to obtain an indication of cerebral perfusion in infants with PV-IVH.

Target conditions
Generally, serial ultrasound was performed routinely for PV-IVH screenings in NICUs. PV-IVH is defined according
to the Papile grading system by as follows: grade I: haemorrhage restricted to the periventricular germinal matrix or germinal matrix regions; grade II: intraventricular haemorrhage without ventricular dilatation; grade III: extended haemorrhage into dilated ventricles and grade IV: haemorrhage within the ventricular system and parenchyma. In addition, PV-IVH could be detected by MRI or CT.

**Study design**

Randomised/quasicontrolled trials and observational studies (cross-sectional studies, cohort studies and case-control studies) on the diagnostic accuracy of NIRS in the prediction of PV-IVH, long-term neurodevelopmental outcomes, and infant mortality in preterm neonates. If there is study for other index (such as ultrasound) plus NIRS for predicting prognosis, we will include the study.

**Selection of studies**

We will include references in all languages without language restrictions. However, if the reference could not be translated, and then it will be excluded. The referred Reporting Item (PRISMA-DTA) statement will be followed (online supplemental figure 1).29–31 We will perform the review according to Cochrane Diagnostic Test Accuracy Working Group guidelines (https://methods.cochrane.org/sdt/). Outcome measure definitions are shown in online supplemental table 2. We will manage citations retrieved through the search by using EndNote software. Two researchers (YZ and YM) will independently screen the titles and abstracts and perform a full text review if needed. Then, both researchers will independently review the full-text articles for eligibility. A manual search of the references of relevant articles will also be performed. We will resolve disagreements through discussion. If agreement cannot be achieved, we will consult a third member of the review team (QG or TX). This paper is written according to PRISMA-Protocols (PRISMA-P).32

**Data extraction and management**

The standard data extraction form is shown in online supplemental table 3.

1. **Study characteristics:** year of publication, year(s) of study, study design, country, sample size.
2. **Neonatal characteristics:** GA, birth weight (BW), twins, c-section, sex, small for GA, antenatal steroids, complete course, mechanical ventilation, the need for surfactant replacement, Apgar score, maternal infection, early-onset sepsis and other neonatal complications.
3. **Reference standard and performance of the reference standard, index tests (NIRS cut-off value, such as the threshold of the rcSO2 and FTOE), performance of the index tests, information about quality assessment items based on Quality Assessment of Diagnostic-Accuracy Studies (QUADAS-2),33 and data for 2×2 tables (online supplemental table 4). If needed, any other useful information to clarify the study design and data will be sought from original authors via email. All the data will be independently extracted and entered in Microsoft Excel spreadsheets (YZ and DL) to compare potential differences, and disagreements will be resolved by discussion.

**Assessment of methodological quality**

**Risk of bias (quality) assessment**

The methodological quality of each included study will be assessed by the QUADAS-2 tool (online supplemental table 5) as recommended by the Cochrane Diagnostic Test Accuracy Working Group33 or the risk of bias tool (Cochrane.org). The four domains for risk of bias include participant selection, index test, reference test and flow and timing. For three domains (participant selection, index test, reference test), applicability concerns will be determined. In each domain, ‘yes’, ‘no’ or ‘unclear’ will be the answer options for the questions, and ‘low’, ‘high’ or ‘unclear’ risk will be selected for the risk of bias. Two researchers (YZ and YM) will independently assess the risk of bias of each study. If agreement cannot be achieved, we will consult a third member of the review team (QG or TX).

**GRADE assessment**

The quality of evidence will be assessed using GRADE methodology recommended for diagnostic tests (online supplemental table 6).34 The quality of evidence will be graded as high, moderate, low or very low according to available data.

**Strategy for data synthesis**

In our included studies, the index tests (NIRS) will be continuous outcomes. The selected NIRS cut-off thresholds in the original studies will be used to construct two-by-two tables (for a positive or a negative test). We will enumerate true positives, false-positives, false-negatives and true negatives. For the studies that report sensitivity and specificity at defined thresholds, reverse calculation will be performed in RevMan to generate 2×2 tables. Data will be entered in RevMan, and forest plots with 95% CIs for sensitivity and specificity will be generated.

If the amount of search results data is sufficient (three studies), the heterogeneity test results will be used to select the effect model. Both the Q-statistics and $I^2$ values will be used to assess heterogeneity. A $p<0.1$ indicated that Q was statistically significant, while $I^2$ value >50% represented significant heterogeneity. If $p>0.1$ and the $I^2$ value <50%, the fixed effects model will be performed for meta-analysis; otherwise, we will select the random effects model. If the number of retrieved results is insufficient or significant heterogeneity exists, only the retrieved results will be systematically evaluated.

The results will also be plotted in the receiver operating characteristic space with 95% confidence estimates, summary points and summary curves. The meta-analyses will be performed by a bivariate random effects model.
through metandi module in the statistical software Stata\textsuperscript{15} (StataCorp).

Analysis of subgroups or subsets
We will investigate heterogeneity through subgroup analyses if more than four studies are available for the subgroup:
1. GA of infants: <28 weeks vs 28–32 weeks.
2. The severity of PV-IVH: mild or severe PV-IVH.
3. BW (<1000 g, 1000–1500 g, 1500–2500 g, >2500 g).
5. The design of the study (cross-sectional studies, cohort studies and case–control studies).
We will assess the robustness of the results by excluding low-quality studies.

Patient and public involvement
This systematic review will collect data from published articles for collation and analysis without involvement of patients.

DISCUSSION
As a non-invasive technology, NIRS has been used more and more widely in neonatal wards. However, the meanings of absolute value of NIRS monitoring and the relationship between monitoring values with specific diseases still need to be further explored. This manuscript attempts to summarise the relevant researches exploring the monitoring value of PV-IVH by NIRS. We will explore the relationship between the monitoring value and the development of PV-IVH and subsequent neurodevelopmental outcomes. The different monitoring instruments used by each centre, the inconsistent monitoring time points of each centre and other factors may affect the combination of the outcomes and may affect our final conclusions in this study. Further studies need to explore the influence of above factors.

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Acknowledgements
QG and TX contributed equally to the correspondence work. YM will independently screen the titles and abstracts, QG and TX will assess the robustness of the results by excluding low-quality studies. We will use metandi module in the statistical software Stata\textsuperscript{15} (StataCorp). The design of the study (cross-sectional studies, cohort studies and case–control studies) will be resolved by discussion. The meta-analysis will be performed by a bivariate random effects model using the statistical software Stata (StataCorp). QG and TX will arbitrate in cases of any disagreement and ensure no errors occur during the study.

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Competing interests
None declared.

Patient and public involvement
Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

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Supplemental material
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