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Cerebral near-infrared spectroscopy monitoring for prevention of brain injury in very preterm infants (Review)

Hyttel-Sorensen S, Greisen G, Als-Nielsen B, Gluud C

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[Intervention Review]

Cerebral near-infrared spectroscopy monitoring for prevention of brain injury in very preterm infants

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ABSTRACT

Background

Cerebral injury and long-term neurodevelopmental impairment is common in extremely preterm infants. Cerebral near-infrared spectroscopy (NIRS) enables continuous estimation of cerebral oxygenation. This diagnostic method coupled with appropriate interventions if NIRS is out of normal range (that is cerebral oxygenation within the 55% to 85% range) may offer benefits without causing more harms. Therefore, NIRS coupled with appropriate responses to abnormal findings on NIRS needs assessment in a systematic review of randomised clinical trials and quasi-randomised studies.

Objectives

To evaluate the benefits and harms of interventions that attempt to alter cerebral oxygenation guided by cerebral NIRS monitoring in order to prevent cerebral injury, improve neurological outcome, and increase survival in preterm infants born more than 8 weeks preterm.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group to search the Cochrane Central Register of Controlled Trials (CENTRAL 2016, Issue 8), MEDLINE via PubMed (1966 to 10 September 2016), Embase (1980 to 10 September 2016), and CINAHL (1982 to 10 September 2016). We also searched clinical trial databases, conference proceedings, and the reference lists of retrieved articles for randomised clinical trials and quasi-randomised studies.

Selection criteria

Randomised clinical trials and quasi-randomised clinical studies comparing continuous cerebral NIRS monitoring for at least 24 hours versus blinded NIRS or versus no NIRS monitoring.

Data collection and analysis

Two review authors independently selected, assessed the quality of, and extracted data from the included trials and studies. If necessary, we contacted authors for further information. We conducted assessments of risks of bias; risks of design errors; and controlled the risks of random errors with Trial Sequential Analysis. We assessed the quality of the evidence with GRADE.

Main results

One randomised clinical trial met inclusion criteria, including infants born more than 12 weeks preterm. The trial employed adequate methodologies and was assessed at low risk of bias. One hundred and sixty-six infants were randomised to start continuous cerebral NIRS monitoring less than 3 hours after birth until 72 hours after birth plus appropriate interventions if NIRS was out of normal range according to a guideline versus conventional monitoring with blinded NIRS. There was no effect of NIRS plus guideline of mortality until term-equivalent age (RR 0.50, 95% CI 0.29 to 1.00; one trial; 166 participants). There were no effects of NIRS plus guideline on intraventricular haemorrhages: all grades (RR 0.93, 95% CI 0.65 to 1.34; one trial; 166 participants); grade III/IV (RR 0.57, 95% CI 0.25 to 1.31; one trial; 166 participants); and cystic periventricular leukomalacia (which did not occur in either group). Likewise, there was no effect of NIRS plus guideline on the occurrence of a patent ductus arteriosus (RR 1.96, 95% CI 0.94 to 4.08; one trial; 166 participants); chronic lung disease (RR 1.27, 95% CI 0.94 to 1.50; one trial; 166 participants); necrotising enterocolitis (RR 0.83, 95% CI 0.33 to 1.94; one trial; 166 participants); and retinopathy of prematurity (RR 1.64, 95% CI 0.75 to 3.00; one trial; 166 participants). There were no serious adverse events in any of the intervention groups. NIRS plus guideline caused more skin marks from the NIRS sensor in the control group than in the experimental group (unadjusted RR 0.31, 95% CI 0.10 to 0.92; one trial; 166 participants). There are no data regarding neurodevelopmental outcome, renal impairment or air leaks.

The quality of evidence for all comparisons discussed above was assessed as very low apart from all-cause mortality and adverse events: these were assessed as low and moderate, respectively. The validity of all comparisons is hampered by a small sample of randomised infants, risk of bias due to lack of blinding, and indirectness of outcomes.

Authors' conclusions

The only eligible randomised clinical trial did not demonstrate any consistent effects of NIRS plus a guideline on the assessed clinical outcomes. The trial was, however, only powered to detect difference in cerebral oxygenation, not morbidities or mortality. Our systematic review did not reach sufficient power to prove or disprove effects on clinical outcomes. Further randomised clinical trials with low risks of bias and low risks of random errors are needed.

PLAIN LANGUAGE SUMMARY

Cerebral near-infrared spectroscopy monitoring for prevention of brain injury in very preterm infants

Review question
To determine the benefits and harms of continuous non-invasive estimation of the oxygen levels of the brain tissue by near-infrared spectroscopy (NIRS) on mortality and later development in infants born more than 8 weeks preterm.

Background
Babies born more than 8 weeks before term are at risk of brain injury and developmental impairment. NIRS enables the oxygen content of the brain tissue to be measured continuously by emitting different light waves in the near-infrared range into the tissue and measuring the reflected light intensity a few inches away from the light source. It has been proposed that avoiding very low or very high oxygen levels in the brain could be beneficial in these small infants.

Study characteristics

In evidence current to September 2016, we found one trial that primarily tested if brain oxygenation can be stabilised by combining NIRS measurements of the brain with a treatment guideline on how to intervene when the brain oxygenation is outside the normal range. The 166 infants included were born more than 12 weeks before term. They were monitored during the first three days of life. The study was funded by government agency, and we found that the methods used in trial were as good as possible.

Key results
The single trial we found showed a large and significant difference in brain oxygenation between the experimental group and the control group. Low oxygenation was far more common in the control group. It did not, however, find that monitoring with NIRS reduces mortality or the occurrence of the most common complications of very preterm birth, i.e. intracranial bleedings, chronic lung disease, damage of the intestines (necrotising enterocolitis), and blindness (retinopathy of prematurity).

The NIRS monitoring did not cause serious harm, but skin marks from the NIRS sensor were seen in about 1 in 10 patients.

Quality of evidence
The accrued information size with one small randomised trial is too small to conclude anything about the benefits and harms of cerebral near-infrared spectroscopy in preterm infants. Thus further studies are needed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Cerebral NIRS oximetry compared to no cerebral NIRS oximetry in very preterm infants

Cerebral NIRS oximetry compared to no cerebral NIRS oximetry in very preterm infants

Patient or population: prevention of morbidities in very preterm infants
Setting:
Intervention: cerebral NIRS oximetry
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with Cerebral NIRS oximetry				
All-cause mortality	Study population		RR 0.50 (0.29 to 1.00)	166 (1 RCT)	⊕⊕⊖⊖ LOW [1 2]	
	250 per 1000	125 per 1000 (73 to 250)				
Intraventricular haemorrhage grade III or IV	Study population		RR 0.57 (0.25 to 1.31)	166 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2 3]	
	163 per 1000	93 per 1000 (41 to 213)				
Cystic periventricular leukomalacia (diagnosed by cranial ultrasound)	Study population		not estimable	166 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2 3]	
	0 per 1000	0 per 1000 (0 to 0)				
Patent ductus arteriosus	Study population		RR 1.96 (0.94 to 4.08)	166 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2 4]	
	113 per 1000	221 per 1000 (106 to 459)				
Chronic lung disease (oxygen supplementation at 36 weeks' postmenstrual age)	Study population		RR 1.27 (0.94 to 1.50)	132 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2 3]	
	467 per 1000	593 per 1000 (439 to 700)				
Proven necrotising enterocolitis (Bell's stage II or III)	Study population		RR 0.83 (0.33 to 1.94)	166 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2 3]	
	125 per 1000	104 per 1000				

		(41 to 243)			
Retinopathy of prematurity, any or severe (stage ≥ III)	Study population		RR 1.64 (0.75 to 3.00)	166 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2 3]
	100 per 1000	164 per 1000 (75 to 300)			
Other adverse effects	Study population		not estimable	166 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2 4]
	0 per 1000	0 per 1000 (0 to 0)			

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Optimal information size not met.
[2] Treatment group allocation not blinded.
[3] Surrogate outcome close in the causal pathway to patient-important outcomes.
[4] Surrogate outcome far removed in the causal pathway from patient-important outcomes.

BACKGROUND

Description of the condition

Preterm birth carries a high risk of cerebral impairment and death. Twenty-five per cent of infants born more than 12 weeks before term die before being discharged from the hospital, and about 25% of survivors will suffer from cerebral palsy or other neurodevelopmental delays (Volpe 2009).

The aetiology behind the long-term complications of preterm birth is multifactorial. It is believed that cerebral hypoxia-ischaemia is important (Whitelaw 2001). Hypoxia-ischaemia represents a mismatch between cerebral oxygen supply and demand that may be caused by, for example, hypotension (Munro 2004), low systemic blood flow (Takami 2010), increased cerebral oxygen demand, or low arterial blood oxygen content. Conversely, it has been suggested that too much oxygen to the immature brain is deleterious (Deulofeut 2006).

Specific brain lesions thought to be associated with hypoxia-ischaemia include germinal matrix haemorrhage, interventricular haemorrhage (Verhagen 2010), and periventricular leukomalacia (Khwaja 2008; Kuint 2009).

To prevent or minimise permanent neurological damage from hypoxia-ischaemia or hyper-oxygenation, immediate and appropriate interventions are essential. This remains a challenge as cerebral hypoxia-ischaemia often passes silently without many clinical signs or symptoms (Highton 2010).

Description of the intervention

Near-infrared spectroscopy (NIRS) enables a measurement of an absolute value of regional tissue haemoglobin oxygen saturation ($rStO_2$) (Wolf 2009). $rStO_2$ represents a weighted average of arterial and venous oxygen saturation. The weight is commonly assumed to be 25% arterial and 75% venous, but may vary within and among patients (Watzman 2000). A reference standard remains to be established. Several studies have found a significant correlation between $rStO_2$ measured by cerebral NIRS and venous jugular bulb blood oxygen saturation, but the agreement is generally poor with about plus or minus 17 percentage points limits of agreement (Buunk 1998; Nagdyman 2005), possibly reflecting the fact that NIRS is a volume-weighted measurement, whereas jugular bulb oxygen saturation is a flow-weighted one.

The relationship between cerebral $rStO_2$ and brain damage has been assessed in several piglet studies. It seems that both the magnitude of cerebral $rStO_2$ deviation from baseline and the duration of deviation matter (Hou 2007; Kurth 2002; Kurth 2009). It is thus reasonable to assume that the $rStO_2$ must be kept within a safe range and that brief or minor deviations from that range are harmless.

Data on the clinical significance of cerebral $rStO_2$ are still rather scant. In adults, Heringlake and colleagues found that a pre-cardiac surgery cerebral $rStO_2$ less than 50% was an independent risk factor for 30-day and 1-year mortality (Heringlake 2010). Furthermore, intraoperative desaturation during cardiac surgery has been shown to be associated with post-operative cognitive dysfunction (de Tournay-Jetté 2011; Slater 2009).

In infants, Toet and colleagues found that $rStO_2$ was a predictor of neurodevelopmental outcome in term newborns suffering from hypoxic-ischaemic encephalopathy (Toet 2006). Children with adverse outcomes had a significantly elevated cerebral $rStO_2$ at 24 hours postpartum compared to infants with normal outcome. In preterm infants, Sorensen and colleagues saw a correlation between the degree of cerebral hypoxia estimated by NIRS and the severity of brain damage (Sorensen 2006). The association between low $rStO_2$ and cerebral injury was also found by two other studies in preterm infants (Balegar 2014; Verhagen 2010). In accordance with these findings, Alderlisten and colleagues found that having a $rStO_2$ below 50% for more than 10% of the time during the first 3 days of life was associated with a 5 point lower developmental quotient (Alderliesten 2014).

The precise safe range of cerebral $rStO_2$ is not established, and both inter- and intravariance is likely. In adults undergoing surgery, thresholds for intervention are dependent on the pre-surgery baseline $rStO_2$, for example to intervene when $rStO_2$ has dropped 20 percentage points (Denault 2007). For preterm infants, who can be haemodynamically unstable from birth, the usefulness of such a baseline measurement is less evident. Thresholds for intervention must rely on the absolute values of $rStO_2$, like pulse oximetry-guided adjustment of the fraction of inspired oxygen (Finer 2010). It is then a problem that the repeated measures within subject standard deviation is about 5% to 6% (Hyttel-Sorensen 2011; Sorensen 2006), while there is a systematic bias between sensors from INVOS 5100 and NIRO 300 (Dullenkopf 2003). In addition, Hessel and colleagues found that INVOS 5100 and FORE-SIGHT show increasing difference in $rStO_2$ estimate with decreasing oxygenation in infants (Hessel 2014).

There is now accumulating evidence that it is possible to minimise cerebral desaturation in adults undergoing cardiac surgery (Deschamps 2016; Murkin 2007), and non-cardiac surgery (Casati 2005). It remains to be established if this improves patient-relevant outcomes.

The focus of the current review is the cerebral NIRS in neonatal intensive care units. The optimal timing of monitoring in preterm infants has not been determined, but it should follow the notion that cerebral NIRS monitoring has to be continuous if it is to have the greatest possible impact on clinical outcomes. Moreover, as the first week of life is the most vulnerable in respect to low cerebral blood flow and brain damage (Meek 1999; Perlman 2000; Volpe 2009), early NIRS monitoring within hours or a few days of birth is likely to be most efficient (Greisen 2011). Most NIRS devices estimate the $rStO_2$ every 5 seconds, but the clinical interpretation is based not only on the current absolute cerebral $rStO_2$ value, but perhaps even more so on the trend in $rStO_2$ over minutes and hours.

NIRS-guided intensive care is a complex intervention as it consists of monitoring a physiological quantity (similar to a diagnostic test) coupled with a number of possible specific interventions either given alone or in concert. In other words, NIRS monitoring will have no impact on clinical outcomes if it does not lead to changes in clinical management. In a trial setting, a pre-specified treatment guideline will most likely increase the likelihood that out-of-range cerebral $rStO_2$ values are dealt with in a consistent manner. The appropriateness of the treatment guideline also depends on whether it defines cerebral $rStO_2$ thresholds for intervention, if these thresholds are appropriate, and if there is a clear guidance on how to react when outside these thresholds.

For comparison, with pulse oximetry, a target range of 85% to 89% saturation has been shown to be associated with a lower survival rate compared to a target range of 91% to 95% in the extremely preterm population (Stenson 2011). Cerebral $rStO_2$ is a more complex physiological quantity than oxygen saturation (SpO_2), and its safe ranges are likely to be broader. Furthermore, as described above, the appropriate $rStO_2$ thresholds could well be device-dependent. The quality of the overall intervention depends on the NIRS monitoring and the treatment guideline describing how to normalise the $rStO_2$ as well as adherence to the guideline; differences in compliance could be a sources of heterogeneity. Although quality of interventions should be incorporated in a meta-analysis of complex interventions (Herbert 2005), there is no generally accepted framework for such an analysis. Moreover, few trial reports provide sufficient detail on how to assess the quality of the intervention (Boutron 2008). We suggest subgroup analyses based on duration of NIRS monitoring, assessment of trial treatment guideline, and adherence to these guidelines to assess the quality of the intervention.

Adverse effects directly relating to the NIRS device are similar to those of the widely applied pulse oximetry, that is primarily local skin damages such as burns, pressure sores, and skin irritation (Hyttel-Sorensen 2013a). Another concern is that NIRS-driven interventions could be deleterious. The SpO_2 level is related to the $rStO_2$, and it is likely not appropriate to aim for SpO_2 higher than the normal target range in order to increase a low $rStO_2$. It could lead to a higher incidence of retinopathy.

How the intervention might work

Cerebral NIRS monitoring could benefit the clinical outcomes of preterm infants because NIRS has the potential to alert healthcare workers when cerebral hypoxia or hyperoxia occurs. Cerebral $rStO_2$ is dependent on three variables: oxygen delivery to the brain, cerebral oxygen consumption, and the arterial–venous volume ratio. The second variable is not easily controlled in preterm infants and the third variable is not relevant for oxygen sufficiency of the brain, so interventions guided by cerebral oxygenation in preterm infants focus on oxygen delivery to the brain, that is the oxygen content of arterial blood, cerebral blood flow, or the combination of both. Interventions that alter the oxygen content include changing the fractional inspiratory oxygen or elevating the haematocrit by blood transfusion, while cerebral blood flow can be affected by changing mean airway pressure and ventilatory rate during mechanical ventilation or by increasing blood pressure and cardiac output by fluid or vasopressors or inotropes. Observation of abnormal values could thus motivate reactive interventions such as changes in ventilator settings and initiation of haemodynamic support. The possible relevant interventions depend on the situation at hand (Pellicer 2013). The main goal is to respond to the NIRS measurement of cerebral $rStO_2$ in order to initiate treatments that are known to normalise cerebral blood flow or blood oxygen content (Denault 2007).

Why it is important to do this review

Despite the lack of firm evidence and the potential limitations of NIRS, the monitoring technique is increasingly implemented in clinical routine care of preterm infants. A review on the use of NIRS in congenital heart disease found four randomised clinical trials, but none of them reported on important patient-relevant clinical outcomes (Hirsch 2009). A systematic review of the evidence of benefits and harms in preterm infants is needed to establish the available support behind this new tool.

This review is based on our published protocol (Hyttel-Sorensen 2015b).

OBJECTIVES

To evaluate the benefits and harms of interventions that attempt to alter cerebral oxygenation guided by cerebral NIRS monitoring in order to prevent cerebral injury, improve neurological outcome, and increase survival in preterm infants born more than 8 weeks preterm.

In subgroup analyses, we plan to examine the effectiveness and safety of NIRS-guided treatments in relation to the following criteria: gestational age (GA), quality of intervention, i.e. duration of NIRS monitoring, assessment of trial treatment guideline, and adherence to these guidelines, and level of support during the first seven days of life.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised clinical trials and quasi-randomised clinical studies irrespective of language and publication status.

Types of participants

Infants born before 32 weeks of gestational age (GA). We included both singletons and infants from multiple births (see Unit of analysis issues section). We chose the cut-off at 32 weeks because the risk associated with preterm birth including brain injury increases with decreasing GA (MacKay 2010; Mohangoo 2011).

Types of interventions

Continuous cerebral NIRS monitoring versus blinded NIRS monitoring or versus conventional monitoring with no NIRS during intensive care. The monitoring should start within one week from birth, be continuous, and last for at least 24 hours.

We included trials where detection of $rStO_2$ values lead to changes in treatment in the experimental group.

The only prerequisite for the NIRS equipment was that it had to show a value for tissue oxygenation in percentage similar to arterial haemoglobin oxygen saturation. If several different brands of NIRS devices were used in a specific trial, this had to be addressed in the randomisation process to ensure equal distribution of the device intervention among groups.

The control group could use conventional monitoring such as invasive or non-invasive blood pressure monitoring, pulse oximetry, electrocardiographic monitoring, and/or transcutaneous oxygen partial pressure (pO_2) and carbon dioxide partial pressure (pCO_2) monitoring without the use of NIRS or with NIRS monitoring where the $rStO_2$ values were concealed to the treating healthcare workers.

Concomitant interventions or treatments were allowed provided that the intervention groups were offered these treatments equally.

We planned to exclude studies where NIRS monitoring is part of multi-monitoring, that is trials where other monitoring modalities than NIRS differ between groups.

Types of outcome measures

Primary outcomes

1. All-cause mortality: neonatal mortality (death during the first 28 days of life) and during the first year of life.
2. Major neurodevelopmental disability.
   a. Cerebral palsy.
   b. Severe neurodevelopmental impairment as evaluated by validated developmental assessment tool, e.g. more than 2 standard deviations (SD) below the mean in Bayley Scales of Infant Development.
   c. Blindness (vision < 6/60 in both eyes).

We planned to report these components of long-term outcome for all studies that have evaluated children after 18 months' chronological age, and to perform separate analyses for children aged 18 to 24 months and 3 to 5 years.

Secondary outcomes

1. Use of interventions with possible impact on cerebral oxygenation. Interventions to normalise $rStO_2$ that may act as effect modifiers on the outcomes at 7 and 28 days of life.
   a. Number of changes in mean airway pressure per time-unit (i.e. to increase or decrease continuous positive airway pressure or positive end-expiratory pressure).
   b. Number of changes per time-unit in inspiratory oxygen fraction FiO_2.
   c. Number of changes per time-unit in blood pCO_2 (i.e. to change ventilation by changing respiratory rate on mechanically ventilated infants).
   d. Number of changes per time-unit in vasopressor or inotrope dosage, or both (i.e. to initiate, stop, increase, or decrease the use of vasopressors/inotropic agents).
   e. Number of fluid bolus treatments (i.e. to give a bolus of fluid at 5 to 20 ml/kg body weight) to increase systemic blood circulation per time-unit.
   f. Number of blood transfusions administered.
   g. Number of patent ductus arteriosus treatments (i.e. attempt to close the duct medically or surgically) received.
2. Morbidities.
   a. Intraventricular haemorrhage (all grades) (Papile 1978).
   b. Intraventricular haemorrhage grade III or IV (Papile 1978).
   c. Cystic periventricular leukomalacia (diagnosed by cranial ultrasound).
   d. Patent ductus arteriosus diagnosed by echocardiography.
   e. Renal impairment (creatinine ≥ 120 µmol/L, oliguria ≤ 0.5 ml/kg/hour at 1 week of age).
   f. Air leak (any and gross including pneumothorax or pneumomediastinum).
   g. Chronic lung disease (oxygen supplementation at 36 weeks' postmenstrual age).
   h. Proven necrotising enterocolitis (Bell's stage II or III) (Bell 1978).
   i. Retinopathy of prematurity, any or severe (stage ≥ III) (International Committee 2005).
3. Adverse events.
   a. Skin marks at term considered to be caused by the NIRS monitoring.
   b. Adverse effects not listed as an outcome above but reported by the authors as an adverse event.

Search methods for identification of studies

Electronic searches

We used the criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group (see the Cochrane Neonatal Group search strategy for specialized register).

We conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 8) in The Cochrane Library; MEDLINE via PubMed (1996 to 10 September 2016); Embase (1980 to 10 September 2016); and CINAHL (1982 to 10 September 2016) using the following search terms: (NIRS OR near-infrared spectroscope OR near infrared spectroscopy), plus database-specific limiters for randomised controlled trials (RCTs) and neonates (see Appendix 1 for the full search strategies for each database). We did not apply any language restrictions.

We searched clinical trial registries for ongoing or recently completed trials (ClinicalTrials.gov; the World Health Organization's International Clinical Trials Registry Platform www.who.int/ictrp/search/en, and the ISRCTN Registry).

Searching other resources

We asked experts in the NIRS field about their knowledge of unpublished randomised clinical trials.

Data collection and analysis

Selection of studies

Two review authors (SHS and GG) independently assessed the trials for eligibility. Excluded trials and reasons for exclusion are in the 'Characteristics of excluded studies' table. SHS and GG would have involved a third review author in the event of disagreements.

Data extraction and management

Two review authors (SHS and GG, independently validated by BAN) independently extracted information on each trial including data

concerning trial design, participants, interventions, and outcomes as detailed in the selection criteria described above.

Assessment of risk of bias in included studies

We assessed bias according to each domain of bias described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We regarded trials at low risk of bias if all of the following criteria were fulfilled: adequate generation of allocation sequence, adequate allocation concealment, adequate blinding, adequate outcome measure reporting, and analysis performed by intention to treat, no vested interest, no recruitment bias, and no other sources of bias. We considered blinding adequate if the outcome assessors were blinded to the type of intervention (allocation group).

Two review authors (SHS and GG) independently assessed the risk of bias in each trial.

We assessed risk of bias according to the following domains (Higgins 2011; Lundh 2017; Savović 2012a; Savović 2012b; Wood 2008).

Sequence generation

Low risk: the investigators described a random component in the sequence generation process such as coin toss, card draw, etc.

High risk: the investigators describe a nonrandom component in the sequence generation process. This would typically involve a systematic, nonrandom approach like sequence generated by date of birth. We planned to exclude such studies for assessment of benefits and safety.

Unclear: insufficient information about the sequence generation process to permit judgement of 'low' or 'high' risk.

Allocation concealment

Low risk: participants and investigators enrolling participants could not foresee assignment due to central allocation (telephone or web-based).

High risk: participants or investigators enrolling participants could possibly foresee assignments. We planned to exclude such studies for assessment of benefits.

Unclear: insufficient information to permit judgement of 'low' or 'high' risk.

Blinding of participants, personnel, and outcome assessors

Preterm infants are de-facto blinded, but due to the nature of the intervention blinding of the participants and personnel is impossible.

Low risk: participants, personnel and outcome assessors were blinded. Method of blinding is described.

High risk: no or incomplete blinding of one or more of 'participants', 'personnel', and 'outcome assessors'.

Unclear: insufficient information to permit judgement of 'low' or 'high' risk.

Incomplete outcome data

Low risk: no missing outcome data, or reasons for missing outcome data unlikely to be related to true outcome. Missing outcome data balanced across intervention groups.

High risk: number of or reasons for dropouts and withdrawals were not described.

Unclear: insufficient reporting of attrition/exclusions to permit judgement of 'low' or 'high' risk.

Selective outcome reporting

Low risk: the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.

High risk: not all of the trial's pre-specified outcomes have been reported. One or more primary outcomes are reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not pre-specified. One or more reported primary outcomes were not pre-specified.

Unclear: insufficient information to permit judgement of 'low' or 'high' risk.

Vested interest bias

Low risk: the trial's funding was not from parties that might have conflicting interest.

High risk: trial funded by a medical device manufacturer.

Unclear: source of funding not described.

Recruitment bias

Assessment was only applicable for studies including twins.

Low risk: individuals in a cluster were randomised and allocated together.

High risk: second twin was included after the first has been randomised.

Unclear: insufficient information to permit judgement of 'low' or 'high' risk.

Other sources of bias

Low risk: the study appears to be free of other sources of bias.

High risk: there was at least one important risk of bias. For example, the study had a potential source of bias related to the specific study design used, or has been claimed to have been fraudulent, or had some other problem.

Unclear: there may be a risk of bias, but insufficient information to permit judgement of 'low' or 'high' risk.

Overall risks of bias

We considered trials to be at low risk of bias if all of the above domains were deemed low risk. Per-protocol, all other studies were to be regarded at high risk of bias.

We restricted the meta-analysis to trials at low risk of bias (Higgins 2011); however, we also included trials that had high risk of performance bias, but where outcome assessors were blinded adequately.

Measures of treatment effect

We present dichotomous outcomes as risk ratio (RR) with naive 95% confidence intervals (CI) and planned to calculate Trial Sequential Analysis-adjusted CI (Thorlund 2011; Wetterslev 2017). Values less than 1.00 favour NIRS-guided treatment. We planned to report continuous neurological outcomes data as weighted mean difference with naive 95% CI and Trial Sequential Analysis-adjusted CI in case different scales were used. We planned to calculate the risk difference (RD) and 95% CI and convert the RD into the number needed to treat for an additional beneficial outcome or the number needed to treat for an additional harmful outcome if statistically significant intervention effects were found. We planned to analyse continuous data using mean difference (MD).

Unit of analysis issues

Trials including twins in the same intervention group are cluster trials unless data from only one of the twins are used in the analysis in a randomised fashion. Data from twins cannot be assumed to be independent from one another. Appropriate statistical analysis will take this into account. In a meta-analysis, trials where the analysis does not account for the twin correlation will receive more weight than appropriate. In cluster-randomised trials, the following biases must be considered: i) recruitment bias; ii) baseline imbalance; iii) loss of clusters; iv) incorrect analysis; and v) comparability with individually randomised trials.

We describe assessment of risk of recruitment bias above. The risk of baseline imbalance and loss of clusters is negligible as studies including twins are characterised by many small clusters. We assessed included trials for appropriate analyses. If clusters were not accounted for, inflation of the standard errors would be done according to Section 16.3.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We planned to contact the original investigators and authors for any missing data then use a 'complete-participant analysis' by excluding all participants with the outcome missing from the analysis, and lastly perform a sensitivity analysis (see Sensitivity analysis section).

Assessment of heterogeneity

We planned to test for statistical heterogeneity using the Chi^2 test with significance set at $P < 0.1$; and quantify inconsistency by I^2, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). The degree of heterogeneity was defined as: no heterogeneity – less than 25%; low heterogeneity – 25% to 49%; moderate heterogeneity – 50% to 74%; high heterogeneity – 75% and above. We intended to explore the possible causes of statistical heterogeneity, using planned and post hoc subgroup analyses.

Assessment of reporting biases

We planned to assess reporting biases using funnel plots of the effect estimates using Review Manager 5 (RevMan 2014) software if 10 or more studies were included.

Data synthesis

We planned to do a fixed-effect model meta-analysis in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions*, and summarise data statistically if available, sufficiently similar, and of sufficient quality.

If the estimated heterogeneity using the Chi^2 test was I^2 greater than 25%, we would carry out a random-effects model meta-analysis to compare to the fixed-effects estimates of the intervention effect. This is in accordance with Section 10.4.4.1 of the *Cochrane Handbook for Systematic Reviews of Interventions*.

In assessing the treatment effects for dichotomous outcomes, we planned to use the RR and RD, with naive 95% CI and RR Trial Sequential Analysis-adjusted CI; and for outcomes measured on a continuous scale, we planned to use the MD, with naive 95% CI and Trial sequential Analysis-adjusted CI.

For binary and continuous outcome measures, we intended to conduct Trial Sequential Analysis (TSA) in order to calculate the desired quantity of information and the cumulative Z-curve's breach of relevant trial sequential monitoring boundaries (Wetterslev 2008). For binary outcomes, we planned to estimate the required information size based on the proportion of participants with an outcome in the control group, a RR suggested by the trials with low risk of bias; or if not possible a relative risk reduction (RRR) of 20%, an alpha of 5%, a beta of 10%, and diversity of 30% and 60%. For continuous outcomes, we estimated the required information size based on the SD observed in the control group of trials with low risk of bias and a minimal relevant difference of 25% of this SD, an alpha of 5%, a beta of 10%, and diversity of 30% and 60%.

Subgroup analysis and investigation of heterogeneity

In subgroup analyses we planned to examine the effectiveness and safety of NIRS-guided treatment in relation to the following criteria: gestational age, duration of NIRS monitoring, and quality of intervention.

- Gestational age (GA): possibly extracted from subgroups within each trial; GA ≤ 28 weeks compared to GA > 28 weeks.
- Duration of NIRS monitoring: the trials were to be ranked from shortest to longest NIRS duration and the subgroups defined as below the median or equal to and above the median.
- Quality of intervention: high-quality intervention trials compared to low-quality intervention trials.

For the third bullet point above, high-quality intervention trials would have been defined as follows: the treatment guideline gives device-specific, pre-specified ranges of $rStO_2$ with guidance on when to intervene and a pre-specified treatment algorithm incorporating guidance on respiratory and cardiovascular care including target ranges of SpO_2, blood pressure, and pCO_2; the final publication reports on the duration of NIRS monitoring, methods to standardise the intervention across centres or practitioners, adherence-improving strategies, and description of treatment in the comparator group.

For the third bullet point above, low-quality intervention trials would have been defined as follows: unclear or no defined ranges of $rStO_2$ or no specified treatment algorithm, or the algorithm does not incorporate guidance on respiratory and cardiovascular care; proper procedures to standardise the intervention or to insure adherence to protocol are lacking or not described; no report on duration of NIRS monitoring; no description of treatment in comparator group.

We planned to conduct a test of interaction of fixed-effect model meta-analyses of the subgroups according to Altman and Bland (Altman 2003).

Sensitivity analysis

We planned to perform a sensitivity analysis to determine the influence of the bias quality criteria.

For missing data, we planned to conduct sensitivity analyses for our primary outcomes by applying best- and worst-case scenarios. The best-case scenario: all participants lost to follow-up in the experimental group had a beneficial outcome, and all participants lost to follow-up in the control group had the opposite. The worst-case scenario: all participants lost to follow-up in the experimental group had a detrimental outcome, and all participants lost to follow-up in the control group had a beneficial outcome.

Quality of evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: all-cause mortality; major neurodevelopmental disability; intraventricular haemorrhage (all grades); intraventricular haemorrhage grade III or IV; cystic periventricular leukomalacia; patent ductus arteriosus; renal impairment; air leak; chronic lung disease; necrotising enterocolitis; retinopathy of prematurity, any or severe (stage ≥ III); skin marks at term considered to be caused by the NIRS monitoring; adverse effects not listed as an outcome above but reported by the authors as an adverse event (see Types of outcome measures for diagnostic criteria).

Two authors independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from randomised clinical trials as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades:

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

RESULTS

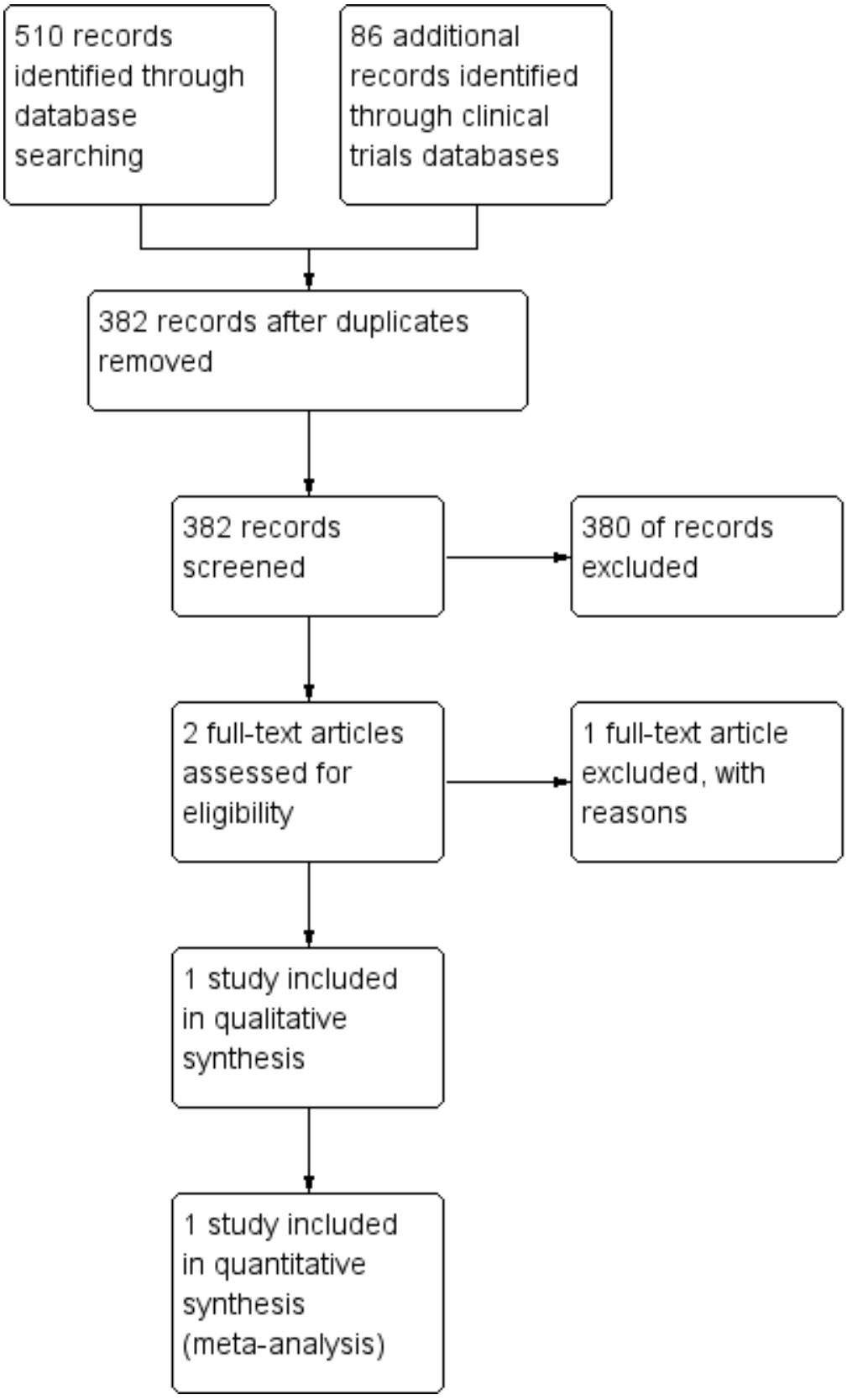
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Only one randomised clinical trial was identified that compared continuous cerebral NIRS monitoring plus a guideline versus conventional NICU monitoring plus blinded NIRS in preterm infants (Hyttel-Sorensen 2015a) Figure 1.

Figure 1. Study flow diagram.



Included studies

One randomised clinical trial met inclusion criteria (Hyttel-Sorensen 2015a). See Characteristics of included studies table.

Hyttel-Sorensen 2015a was a multi-centre trial enrolling infants of less than 28 weeks' gestation with no major congenital malformations and a decision to provide full life support. One hundred and sixty-six infants were randomised to start continuous cerebral NIRS monitoring less than 3 hours after birth until 72 hours after birth versus conventional monitoring plus blinded NIRS. In the experimental group, the treatment was adjusted according to a specific guideline recommending interventions to keep the cerebral oxygenation $rStO_2$ within the 55% to 85% range. The control were NIRS-monitored, but the $rStO_2$ results were blinded to the clinical staff. Two different NIRS instruments were used: INVOS 5100 with an adult sensor (Covidien, Boulder, CO, USA); and NIRO 200NX (Hamamatsu Phototonics, Hamamatsu City, Japan).

The treatment guideline of the study has been described in detail elsewhere (Pellicer 2013). In short, it constitutes a non-prioritised list of possible interventions to normalise an out-of-normal range $rStO_2$. Basically it suggests that the clinician assess the respiratory, cardiovascular, haemoglobin and blood glucose status, when hypoxia or hyperoxia occurs. The guideline emphasises that all parameters, such as blood pressure and SpO_2, should be kept within normal ranges; but if for example the pCO_2 is low in the normal range, measures to increase the pCO_2 could be a means to increase a $rStO_2$ in the hypoxic range.

The primary outcome was the duration and extent of $rStO_2$ outside the target range. This 'burden of hypo- and hyperoxia' in %hours was lower in the experimental group (36.1 %hours vs 81.3 %hours, $P < 0.0001$).

Secondary outcomes included all-cause mortality at term-equivalent age, electrical activity of the brain estimated by electroencephalography (EEG), and a brain injury score determined by ultrasonography at ages 1, 4, 7, 14, and 35 days and at term equivalent age. This brain injury score was based on the occurrence and severity of intracranial haemorrhages, white matter abnormalities, ventricular dilation, and cerebral atrophy.

A two-year follow-up is planned (Hyttel-Sorensen 2013b).

Excluded studies

See: Characteristics of excluded studies.

Risk of bias in included studies

Due to the nature of the intervention it is not possible to blind the clinical staff to the group allocation. It is in that respect important that all other potential sources of bias are handled in a rational manner, reducing the risk of systematic errors to a minimum.

Allocation

Hyttel-Sorensen 2015a reported adequate randomisation and allocation concealment.

Blinding

Hyttel-Sorensen 2015a had a high risk of performance bias as the group allocation was evident to the personnel and parents. There was, however, a low risk of detection bias as all outcomes were assessed without knowledge of the allocated interventions.

Incomplete outcome data

Hyttel-Sorensen 2015a reported that two infants in the control group did not have NIRS data recorded; one due to withdrawal of consent and the other due to technical problems. All other data were recorded per protocol and the risk of attrition bias is thus estimated to be low.

Selective reporting

Hyttel-Sorensen 2015a refers to publication of the protocol: Hyttel-Sorensen 2013b. All outcomes are per-protocol, albeit the blood biomarkers and electroencephalography are published elsewhere (Plomgaard 2016).

Other potential sources of bias

Hyttel-Sorensen 2015a had no other apparent sources of bias, including no interim analyses.

Effects of interventions

See: **Summary of findings for the main comparison** Cerebral NIRS oximetry compared to no cerebral NIRS oximetry in very preterm infants

We identified only one RCT, thus the data synthesis including TSA described above was not feasible due to too small information sizes. It is important to stress that TSA-adjusted confidence intervals would be much wider than the intervals presented below. We downgraded the quality of the evidence on all outcomes due to impression (few participants), lack of blinding, and surrogate outcomes (outcomes not directly related to long-term patient-important outcomes). All outcomes were rated low or very low quality of evidence according to the GRADE system.

Primary outcomes

Hyttel-Sorensen 2015a reported no significant difference in mortality until term equivalent age (RR 0.50, 95% CI 0.29 to 1.00; one trial; 166 participants; low quality of the evidence). There are no data available on first-year mortality, major neurodevelopmental disability, or blindness.

Secondary outcomes

Use of interventions

Hyttel-Sorensen 2015a reported selected interventions and physiological variables during the intervention period of first 72 hours of life. They did not test these differences between the groups statistically. The following RRs are unadjusted estimates. Number of fluid boluses during the intervention period was similar in the two groups (MD −0.30, 95% CI −0.79 to 0.19; one trial; 166 participants; very low quality of evidence), as was number of infants receiving any blood transfusion (RR 0.83, 95% CI 0.52 to 1.31; one trial; 166 participants; very low quality of evidence), and the use of vasopressors/inotropes (RR 0.98, 95% CI 0.57 to 1.70; one trial; 166 participants; very low quality of evidence). Treatment of a patent ductus arteriosus was more common in the experimental group (RR 2.98, 95% CI 1.14 to 7.75; one trial; 166 participants; very low quality of evidence). Changes in mean airway pressure, inspiratory oxygen fraction, and ventilation were not reported.

Morbidities

Hyttel-Sorensen 2015a did not report specifically on intraventricular haemorrhage and patent ductus arteriosus. The numbers presented here are retrieved post-hoc and the RRs on these outcomes are unadjusted. There were no differences in intraventricular haemorrhages: all grades (RR 0.93, 95% CI 0.65 to 1.34; one trial; 166 participants; very low quality of evidence); grade III/IV (RR 0.57, 95% CI 0.25 to 1.31; one trial; 166 participants; very low quality of evidence), whereas cystic periventricular leukomalacia did not occur in either group. Likewise, the SafeBoosC investigators found no significant differences in the occurrence of a patent ductus arteriosus (RR 1.96, 95% CI 0.94 to 4.08; one trial; 166 participants; very low quality of evidence), chronic lung disease (RR 1.27, 95% CI 0.94 to 1.50; one trial; 166 participants; very low quality of evidence), necrotising enterocolitis (RR 0.83, 95% CI 0.33 to 1.94; one trial; 166 participants; very low quality of evidence), and retinopathy of prematurity (RR 1.64, 95% CI 0.75 to 3.00; one trial; 166 participants; very low quality of evidence). They did not collect data on renal impairment or air leaks.

The post hoc data retrieval was performed by the SafeBoosC group, including three of the authors of this review (SHS, CG, GG).

Adverse events

Hyttel-Sorensen 2015a reported no serious adverse events. They found significantly more skin marks from the NIRS sensor in the control group (RR 0.31, 95% CI 0.10 to 0.92 (unadjusted RR); one trial; 166 participants; very low quality of evidence).

DISCUSSION

Summary of main results

The single randomised clinical trial on cerebral NIRS together with a treatment guideline included in this review, enrolling 166 infants born before 28 weeks of gestation, was designed and powered to explore differences in cerebral oxygenation rather than clinical outcomes. Although a significant reduction in cerebral oxygenation out of normal range was seen in the experimental group, no consistent differences were reported in neonatal morbidities or mortality at term equivalent age. The accrued information size, 166 participants, is too small to do Trial Sequential Analysis. The results of the two-year neurodevelopmental follow-up is still pending.

Overall completeness and applicability of evidence

The findings of this review show that the current evidence is inadequate to either support or refute the use of NIRS monitoring in preterm infants.

A single trial not powered to detect clinical differences did suggest that it is possible to stabilise the oxygenation of the brain tissue (Hyttel-Sorensen 2015a). How this translates into patient-relevant outcomes is uncertain and the trends toward reduced mortality and less severe brain injury in the trial should be interpreted with great caution. The differences could be by chance; and over-enthusiasm after early trials have on numerous occasions later proved to be unfounded (Ioannidis 2005). Perhaps the most prominent example was the trial by Rivers and colleagues showing a significant reduction in mortality by early goal-directed therapy in severe sepsis and septic shock, a result that could not be reproduced in three subsequent major RCTs (Rivers 2001).

The combination of NIRS monitoring and a treatment guideline is complex intervention. However, the only documented difference in treatment between the two groups was medical or surgical closure of patent ductus arteriosus. The data regarding the association between a patent ductus and cerebral $rStO_2$ are conflicting (Lemmers 2008; Petrova 2011), and it remains to be determined whether treatment of a patent ductus is beneficial (Benitz 2012). It seems unlikely that the difference in treatment of a patent ductus alone could drive the difference in cerebral oxygenation between the two groups. One could suspect that more readily available interventions in the treatment guideline, such as adjusting the FiO_2 or the respiratory rate on the ventilator, were less meticulously documented. Lastly, the result was achieved with two commercial NIRS instruments, INVOS 5100 and NIRO 200NX, with similar device-specific $rStO_2$ normal ranges of 55% to 85%: we do not know how this extrapolates to different instrumentation. It is thus important to stress that larger trials are needed as the available evidence cannot stand alone.

The only other randomised clinical trial addressing cerebral NIRS oximetry in preterm infants is Pichler 2016, that examines the feasibility of reducing the burden of cerebral hypoxia and hyperoxia outside the target range during the immediate transition in preterm infants. The intervention period was restricted to the first 15 minutes of life and the cerebral NIRS oximetry was used to guide supplemental oxygen therapy when the pulse oximeter reading was within normal range, but $rStO_2$ was not. They found that the burden of hypoxia was reduced by providing extra oxygen, but saw no clinically relevant differences in outcomes.

Pichler 2016 is not eligible for this review as we only included trials with more than 24 hours of NIRS monitoring.

There were no serious adverse effects of the NIRS monitoring, but 16 infants had skin marks after the 72 hours of monitoring. This is not surprising as it is well known from pulse oximetry that local skin damage can occur from the sensor and the heat generated. What remains to be determined is if NIRS together with the treatment guideline may result in deleterious interventions. To identify such adverse effects will take a larger trial adequately powered to detect differences in morbidities and mortality.

Quality of the evidence

Considering it is impossible to blind the clinical staff and parents to the intervention, the study included in this review was of adequate methodology and reported outcomes prespecified in the protocol. However, the overall quality of the evidence provided by the meta-analyses using the GRADE approach for each outcome was assessed as low to very low. As mentioned, the lack of blinding creates an inherent risk of bias; moreover the small sample size causes possible imprecision of effect estimates, and the surrogate outcomes are indirectly linked to the patient-relevant long-term outcomes.

We decided post hoc not to conduct the Trial Sequential Analyses, as we were quite far from the required information sizes for the different comparisons. This makes both the Trial Sequential Analysis figures hard to understand and hampers the calculation of Trial Sequential Analysis-adjusted CI. Therefore, our presented naive 95% CI should be regarded as too optimistic and likely misleading. In future updates, we shall take multiplicity issues into

consideration as stipulated in our protocol according to Jakobsen 2014 and Jakobsen 2016.

Potential biases in the review process

The review has been performed by part of the research team who conducted the only eligible study.

We selected to focus on randomised clinical trials and quasi-randomised studies. These selections are bound to make us focus most on benefits, as randomised trials and quasi-randomised studies are known to report harms less well (Ioannidis 2009). If we eventually find significant and clinically relevant benefits of NIRS on patient-centred outcomes, then we will need to conduct a systematic review on harms based on all observational studies.

Agreements and disagreements with other studies or reviews

We have found no other reviews considering the potential benefits and harms of cerebral NIRS oximetry in preterm infants.

AUTHORS' CONCLUSIONS

Implications for practice

The benefits and harms of cerebral NIRS oximetry in preterm infants cannot be established based on the limited available evidence and its use should be restricted within the context of randomised clinical trials.

Implications for research

Randomised clinical trials are needed to support or refute the use of cerebral NIRS oximetry in preterm infants. Although Hyttel-Sorensen 2015a showed that it is possible to affect the $rStO_2$, it is clear that the evidence behind the treatment used in that trial is weak (Pellicer 2013). Research into the construction of an evidence-based treatment guideline could further the likelihood that cerebral NIRS oximetry could benefit the care of preterm infants. Such research could be a combination of pre-clinical and smaller clinical studies focusing on single elements of potential treatment guideline. This ambition should, however, not slow down the efforts to establish a sufficiently powered trial on clinical outcomes. These research goals must be achieved in parallel. A larger trial could in that respect strive to utilise electronic health records and new ways of analysing 'big data' loads (Angus 2015). It also important that further work is done into the issue of normal ranges of cerebral oxygenation in the preterm population. Moreover a more complete description of the available commercial NIRS equipment is needed.

Future trials ought to be designed according to the SPIRIT guideline (www.spirit-statement.org) and reported according to the CONSORT guideline (www.consort-statement.org).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Hyttel-Sorensen 2015a

Methods	Randomised clinical trial.
Participants	166 participants (86 intervention, 80 control) who were born more than 12 weeks before term (GA less than 28 weeks) with no major congenital malformations, a decision to provide full life support, and the possibility to begin NIRS monitoring within 3 hours from birth.
Interventions	Intervention: monitoring of cerebral oxygenation using NIRS in combination with a dedicated treatment guideline during the first 72 hours of life. Control: blinded cerebral NIRS oxygenation monitoring with standard care.
Outcomes	Burden of hypoxia and hyperoxia (time spent outside the target range of 55% to 85% for cerebral oxygenation multiplied by the mean absolute deviation, expressed in %hours). All-cause mortality at term equivalent age. Brain injury score (none/mild-moderate/severe - assessed by cerebral ultrasonography). Necrotising enterocolitis (modified Bell's stage II or III). Bronchopulmonary dysplasia (extra oxygen requirement at 36 weeks of gestation). Retinopathy of prematurity (Stage ≥ 3 on international classification).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The web based randomisation was set up and handled by the Copenhagen Trial Unit according to a computer generated allocation sequence of 1:1 with block sizes 4 and 6 in random order concealed for the investigators".
Allocation concealment (selection bias)	Low risk	Quote: "The web based randomisation was set up and handled by the Copenhagen Trial Unit according to a computer generated allocation sequence of 1:1 with block sizes 4 and 6 in random order concealed for the investigators".
Blinding of participants and personnel (performance bias) All outcomes	High risk	Due to the nature of the intervention blinding of the participants and personnel is impossible.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All analyses were based on the intention to treat principle and conducted blinded."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Two infants in the control group did not have any NIRS data recorded; one had consent withdrawn and there were technical problems for the other. All other data were collected per protocol for both."

Hyttel-Sorensen 2015a *(Continued)*

Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
Vested interest bias	Low risk	Quote: "This work was supported by an unconditional and unrestricted grant from the Danish Council for Strategic Research (DKK 11,100,105). The funder had no role in the design, conduct, or analysis of the trial".
Recruitment bias	Low risk	Quote: "Twins were allocated to the same treatment group. If both twins could not be included owing to lack of equipment, we included the infant born last".
Other bias	Low risk	The trial appears to be free of other sources of bias.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Pichler 2016	The infants were only NIRS-monitored the first 15 minutes of life.

APPENDICES

Appendix 1. Standard search methodology

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW)

WHAT'S NEW

Date	Event	Description
3 October 2017	Amended	Minor edits have been made for clarity in the Plain Language Summary.

CONTRIBUTIONS OF AUTHORS

Simon Hyttel-Sorensen coordinated and did data collection for the review, screened search results, organised retrieval of papers, screened retrieved papers against eligibility criteria, appraised quality of papers, extracted data from papers, managed data for the review, entered data into Review Manager 5, analysed data, interpreted data, and wrote the review.

Gorm Greisen screened retrieved papers against eligibility criteria and appraised quality of papers. He provided clinical research perspectives, and contributed to the development of the protocol.

Bodil Als-Nielsen contributed to the assessment of the data extraction and the quality of the evidence. She contributed to the writing of the protocol and reviewed the analyses and manuscript critically.

Christian Gluud conceived the idea for the systematic review; provided methodological perspective; and participated in the writing of the protocol and the review.

DECLARATIONS OF INTEREST

Gorm Greisen has done research using near-infrared spectroscopy for 20 years and therefore could be perceived to be biased by academic interests.

Simon Hyttel-Sørensen, Gorm Greisen, and Christian Gluud participated in the SafeBoosC trial (Hyttel-Sorensen 2015a) which could bias their views.

Bodil Als-Nielsen has none known bias risks.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added the methodology and plan for 'Summary of findings' tables and GRADE recommendations, which were not included in the original protocol. We changed the plan for the Trial Sequential Analysis from a beta of 20% to 10%.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Extremely Premature; *Oxygen Consumption; *Spectroscopy, Near-Infrared; Brain [*metabolism]; Brain Injuries [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn