Effect of interventions related to blood pressure on cerebral oxygenation in preterm infants

a systematic review (protocol).

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Abbreviations: BP, blood pressure; CBF, cerebral blood flow; GA, gestational age; IVH, intraventricular haemorrhage; NIRS, near-infrared spectroscopy; PDA, patent ductus arteriosus; PNA, postnatal age; PVL, periventricular leukomalacia.
Title
Effect of interventions related to blood pressure on cerebral oxygenation in preterm infants: a systematic review.

Objectives
The purpose of this systematic review is to assess the effect of interventions related to blood pressure on cerebral oxygenation in preterm infants.

We will evaluate the effect of following interventions:

a. treatment with dopamine,
b. treatment with dobutamine,
c. treatment with epinephrine,
d. treatment with normal saline bolus, and
e. pharmacological treatment of PDA.

The effect will be considered in comparison to:

- treatment with any other vasopressor or inotropic drug;
- treatment with fluid infusion, with exception of d.;
- any other pharmacological treatment of PDA;
- placebo; and
- no treatment.

Background
Preterm birth rates have generally increased worldwide throughout the last decade (Blencowe et al., 2012). While survival rate and viability for premature infants have improved due to advances in neonatal care, a substantial risk of health-related complications and sequelae remains (Murray et al., 2012; Saigal & Doyle, 2008).

An estimated seven per cent (Blencowe et al., 2013) of survivors of preterm birth suffer from long-term neurodevelopmental disabilities in form of motor-, cognitive- and sensory impairments, with both prevalence and severity inversely related to gestational age (Blencowe et al., 2013; Saigal & Doyle, 2008).

Periventricular leukomalacia, a type of white matter injury, and intraventricular haemorrhage, are the principal preterm birth-related brain lesions associated with subsequent high risk of neurodevelopmental morbidity (Al Rifai & Al
Tawil, 2015; Bolisetty et al., 2014; Imamura et al., 2013; Luu et al., 2009). Cerebral hypoxia-ischemia and hemodynamic instability have been implicated in the underlying pathogenesis of PVL (Volpe, Kinney, Jensen, & Rosenberg, 2011) and IVH (Ballabh, 2014). Moreover, early hypotension has been linked to poor neurodevelopmental outcome in itself (Batton et al., 2009; Martens et al., 2003).

Hypotension occurs relatively frequently in premature neonates during the transition to postnatal life (Noori, Stavroudis, & Seri, 2009). Although a standardized, evidence-based definition of a hypotensive threshold is still lacking (Engle, 2012), anti-hypotensive therapy is often commenced in presumed hypotensive preterm infants in order to restore and maintain sufficient vital organ perfusion and ultimately ensure an adequate oxygen supply, especially to the immature and particularly vulnerable brain. However, the effect of different interventions on the cerebral oxygenation in this specific group of patients is yet unclear; hence, we find undertaking a review of the existing evidence highly relevant. Currently, the only existing review on this topic is a narrative review exploring the impact of blood pressure management in animals primarily, including just a single study examining the effect on cerebral oxygenation in preterm infants (Azhan & Wong, 2012).

While blood pressure management varies widely, treatment strategies commonly involve volume expansion and/or administration of vasoactive drugs or treatment of a hemodynamically significant patent ductus arteriosus. In this systematic review, we have chosen to focus on treatment with dopamine-, dobutamine-, adrenaline-, normal saline bolus and pharmacological treatment of PDAs based on the SafeBoosC II trial’s treatment guidelines for interventions related to cardiovascular status affecting oxygen delivery to the brain (Pellicer et al., 2013).

Methods

Criteria for selection of studies:

Types of studies:

In order to provide a review as informative as possible all studies examining the effect of treatment with either dopamine, dobutamine, epinephrine, fluid bolus or pharmacological PDA treatment on cerebral oxygenation or observing the association between treatment and cerebral oxygenation will be included irrespective of study design and publication status and regardless of whether cerebral oxygenation is assessed as a primary or secondary outcome.
Consequently, both randomised controlled trials and non-randomised studies will be included.

Types of participants:
Studies on preterm infants of GA <37 weeks and PNA <1 month with hypotension and/or PDA will be included with no birth weight limits and no gender restriction. Studies on neonates with major congenital malformations, circulatory arrest or while undergoing surgery will be excluded.

Types of intervention:
We will include studies with intervention groups consisting of premature neonates treated with dopamine, dobutamine, epinephrine, normal saline bolus or pharmacotherapy for PDA in any dose. The control group will include participants receiving treatment with any other vasopressor or inotropic drug, fluid infusion, another non-surgical treatment for PDA, placebo or no treatment.

Outcome measures
1. Primary:
   Cerebral oxygenation measured via NIRS.

2. Secondary:
   - CBF measured via NIRS;
   - BP;
   - adverse effects;
   - short term brain injury in form of:
     - IVH, any grade;
     - PVL.

Search methods
For identification of studies, the following databases will be searched using controlled vocabulary and key words: MEDLINE/PubMed, Embase, Cochrane Central Register.
of Controlled Trials (CENTRAL) and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

Our preliminary search strategy includes following search terms:

- brain, cerebral OR cerebr*

AND

- near-infrared spectroscopy, near-infrared spectrometry, NIRS, oximetry, oxymetry, oximet*, oxygen, oxygen*, oxygenation OR saturation

AND

- dopamine, adrenaline, epinephrine, dobutamine, vasoconstrictor, vasoconstrict*, vasopressor, vasopress*, blood pressure, hypotension, PDA, patent ductus arteriosus, indomethacin, ibuprofen, NSAID*, infusion, fluid, bolus, saline, inotropic, inotrop*, cardiotonic OR cardioton*

AND

- infant*, baby, babies, neonate, neonat*, premat*, preterm*, newborn OR newborns

Language will be limited to English, Danish, Swedish, Norwegian, German, French, Serbian, Turkish, Urdu, Chinese and Arabic. No publication period restrictions will be applied.

Grey literature will be identified and reviewed using OpenGrey.eu, Google Scholar and Web of Science.

Unpublished studies will be identified through ClinicalTrials.gov and the ICTRP database (WHO’s International Clinical Trials Registry Platform) and relevant data sought out.

Reference lists of obtained articles will be hand-searched to identify additional studies of relevance.

Data collection and extraction
SEM will undertake the initial title and abstract screening of all citations yielded by the search using the online software Covidence (Covidence). Full-text assessment of eligibility will be performed by SEM in accordance with the pre-specified criteria, and reasons for exclusion will be recorded.

SEM and BA will perform an independent double data extraction. Any case of disagreement will be resolved through discussion and, if necessary, with involvement of GG.

Information screening and study selection will be outlined using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Moher, Liberati, Tetzlaff, Altman, & Group, 2009).

Data to be extracted include:

- Study characteristics: study design; setting; authors; noteworthy conflicts of interest.
- Information about population: population characteristics; criteria for inclusion and exclusion; number of participants; GA; PNA; birth weight; PDA status and significance; baseline measures of cerebral oxygenation, CBF and BP.
- Information about intervention: type of intervention; timing, dosage and duration of treatment; additional treatments.
- Information about comparison groups.
- Information about outcomes: cerebral oxygenation, NIRS monitor and sensor used; time of measurements; CBF; BP; brain injury and method of assessment.
- Information needed to assess risk of bias.

Assessment of risk of bias

For RCTs, risk of bias will be evaluated with use of the Cochrane Collaboration tool for assessment of risk of bias (Higgins, Green, & Cochrane, 2011). Following domains will be evaluated:

- selection bias,
- performance bias,
- attrition bias,
• detection bias,
• reporting bias, and
• other sources of bias.

The overall risk of bias will then be categorised as “low”, “high” or “unclear”.

For NRS, risk of bias will be assessed using the “Risk Of Bias In Non-randomised Studies of Interventions” (ROBINS-I) assessment tool (Sterne et al., 2016), evaluating seven domains in which there is a risk of bias being introduced:

• bias in confounding,
• bias in selection of participants,
• bias in classification of intervention,
• bias in deviations from intended interventions,
• bias in missing data,
• bias in measurement of outcomes, and
• bias in selection of the reported outcomes.

Subsequently, the overall risk of bias in each NRS will be categorised as “low”, “moderate”, “serious”, “critical” or “no information”.

**Synthesis and analyses**

SEM will provide a narrative synthesis, reporting findings from included RCTs and NRS separately and in subsections based on study intervention.

Our qualitative synthesis will include an evaluation of direction of effects in addition to an assessment of whether the effects are consistent across studies.

We anticipate limited opportunity for meta-analysis within the scope of this systematic review as the included studies likely have different outcome measures.

If possible, and provided there is a fair clinical comparability between studies with same type of intervention, comparator and outcome measures, a meta-analysis will be undertaken by SEM including randomised controlled trials with low risk of bias only.

If necessary data is available, subgroup analyses will be undertaken based on GA in following groups: extremely preterm, <28 weeks; very preterm, 28 to <32 weeks; moderate preterm, 32 to <34 weeks; late preterm, 34 to <37 weeks.
**Dissemination plan**

Upon completion, the review will be submitted for peer-review publication.

**Review team**

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**Declaration of interests**

None.

**Sources of support:**

The Novo Nordic Foundation is funding Sahla El Mahdaoui (research year student).
References


