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# Efficacy and safety of low-dose versus high-dose hydrocortisone to treat hypotension in neonates: a protocol for a systematic review and meta-analysis

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## ABSTRACT

**Background** Impaired adrenal function is a well-described entity in critically ill term and preterm neonates with systemic hypotension. The standard treatment for neonatal hypotension includes volume expanders and vasopressors. Recent evidence supports the use of glucocorticoids for the primary or rescue treatment of neonatal hypotension associated with impaired adrenal function. However, inconsistency regarding the prescribed dosing regimen to provide the best balance between efficacy and safety in this vulnerable population remains an area of concern.

**Methods** We will conduct a systematic review and meta-analysis to evaluate low-dosing compared with high-dosing regimens of hydrocortisone for the treatment of hypotension in critically ill term, preterm and very low birth weight neonates. Ovid MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and Web of Science will be searched from inception to November 2021. Study screening and selection will be completed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline. Our primary outcomes will be (1) an improvement in end-organ perfusion, defined as an increase in blood pressure along with an increase in urine output or a reduction in serum lactate and (2) mortality prior to discharge. Our secondary outcomes will be the development of (1) major neurosensory abnormality, (2) bronchopulmonary dysplasia and (3) the occurrence of adverse events.

**Discussion** Hydrocortisone may be beneficial in the treatment of hypotension associated with impaired adrenal function among critically ill neonates. However, its optimal dosing to balance desired efficacy with the risk of adverse events is yet to be determined. Our systematic review and meta-analysis aims to address this evidence gap, providing valuable knowledge for a large audience, including guideline developers, policy-makers and clinicians.

**PROSPERO registration number** This protocol is submitted for registration to the international database of prospectively registered systematic reviews (PROSPERO, awaiting registration number).

## INTRODUCTION

The use of corticosteroids for the treatment of hypotension associated with impaired adrenal

## What is already known on this topic?

- Critically ill and very low birth weight neonates are at risk of developing hypotension associated with impaired adrenal function.
- Animal and human models support the use of glucocorticoids, such as hydrocortisone, for the treatment of hypotension unresponsive to standard treatment.
- Optimal dosing of hydrocortisone, to best balance efficacy and safety, for the treatment of neonatal hypotension associated with impaired adrenal function is unknown.

## What this study hopes to add?

- Knowledge on the efficacy of low-dosing compared with high-dosing regimens of hydrocortisone in the treatment of neonatal hypotension associated with impaired adrenal function.
- Knowledge on the safety of low-dosing compared with high-dosing regimens of hydrocortisone in the treatment of neonatal hypotension associated with impaired adrenal function.
- Knowledge on the information gaps and areas in need of future research regarding the use of hydrocortisone in the treatment of neonatal hypotension associated with impaired adrenal function.

function in neonates hospitalised in the intensive care unit has been described for more than 25 years.<sup>1</sup> Existing evidence suggests that critically ill neonates are at risk of developing relative adrenal insufficiency, defined as the absence of an appropriate cortisol response for the degree of illness.<sup>2</sup> This condition is thought to be associated with the downregulation of adrenergic receptors, cardiovascular dysfunction and a deranged inflammatory response.<sup>3</sup>

In addition to the relative adrenal insufficiency observed in critically ill term and



preterm neonates, very low birth weight (VLBW) neonates may also experience a suboptimal stress response and limited cortisol production in the immediate postnatal period.<sup>4</sup> Possible explanations for this transient adrenal insufficiency among VLBW neonates include their developmental immaturity and the increased demands of early birth. Furthermore, the preterm neonate's adrenal cortex has a limited capacity for de novo cortisol synthesis until 30 weeks' gestation, despite having an established hypothalamic–pituitary–adrenal axis by 20 weeks' gestation.<sup>5 6</sup> Thus, relatively low basal cortisol concentrations and a reduced ability for adequate cortisol production position the VLBW neonate for a failed stress response.<sup>7</sup> The possible link between inadequate cortisol production and poor haemodynamic adaptation of VLBW infants in the immediate postnatal period has prompted some to question whether glucocorticoids rather than vasopressors should be the first-line pharmacotherapy for haemodynamic support in this population.<sup>3</sup>

Hydrocortisone is the glucocorticoid of choice for the treatment of hypotension associated with impaired adrenal function in neonates.<sup>8</sup> Despite the lack of convincing evidence for long-term benefit, the short-term efficacy of this drug has driven its continued and widespread use.<sup>9</sup> The significant lack of data on the pharmacokinetics and pharmacodynamics of hydrocortisone in neonates has, however, resulted in a wide range of dosing recommendations, with daily cumulative dosing that may vary up to 10 times depending on the centre and guideline. This is while available evidence has shown that daily doses of as little as 2 mg/kg could be sufficient in elevating the levels of steroids to stress levels and improve end-organ perfusion.<sup>10 11</sup> The lack of consistent dosing is a major concern, considering the current data indicating that exposure to hydrocortisone, especially in unnecessarily high doses and particularly in preterm neonates, can cause serious adverse events.<sup>3</sup> Thus, the dilemma remains around the optimal dosing of hydrocortisone to achieve the desired efficacy with minimal risk of short-term and long-term adverse events.<sup>3 9</sup>

### Objective

In this systematic review and meta-analysis, we aim to determine the comparative effectiveness and safety of low-dose versus high-dose regimens of hydrocortisone, administered to neonates as primary or rescue therapy for hypotension (box 1).

### Hypothesis

Low-dose hydrocortisone (initial dose of  $\leq 1$  mg/kg, followed by  $\leq 2$  mg/kg/day or cumulative daily dose of  $\leq 3$  mg/kg on the first day of treatment) is as effective as high-dose hydrocortisone (initial dose of  $> 1$  mg/kg, followed by  $> 2$  mg/kg/day or cumulative daily dose of  $> 3$  mg/kg on the first day of treatment) at improving end-organ perfusion in critically ill neonates with hypotension.

### Box 1 PICO framework

**Population:** Preterm or term neonates with postmenstrual age  $\leq 44$  weeks with hypotension (defined as mean blood pressure less than gestational age or hypotension requiring fluid or vasoactive therapy).

**Intervention:** Intravenous hydrocortisone initiated at any time, in any dose and for any duration as a primary or rescue treatment for hypotension.

**Comparator:** (1) Hydrocortisone compared with standard treatment, placebo or any other vasoactive agent. (2) Low-dose (initial dose of  $\leq 1$  mg/kg, followed by  $\leq 2$  mg/kg/day) compared with high-dose (initial dose of  $> 1$  mg/kg, followed by  $> 2$  mg/kg/day) hydrocortisone.

**Outcomes:** Primary—(i) Improvement in end-organ perfusion defined as an increase in mean, diastolic or systolic blood pressure within 1 hour of the start of treatment with one of the additional following criteria: an increase in urine output or a reduction in serum lactate within 12 hours of treatment initiation, as defined by the authors in the primary studies and (2) mortality prior to discharge.

Our secondary outcomes are (1) development of bronchopulmonary dysplasia, (2) development of major neurosensory disability defined as moderate to severe motor or cognitive impairment or severe visual or hearing impairment as identified in the primary study and (3) occurrence of adverse events defined as hypertension, hyperglycemia, gastrointestinal events (occurrence of gastrointestinal perforation, necrotising enterocolitis or gastrointestinal bleed), or hospital-acquired infection within 2 weeks of hydrocortisone administration

**Study designs:** Randomised and non-randomised controlled trials, cohort studies.

## MATERIALS AND METHODS

### Protocol registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P)<sup>12</sup> statement was used to guide the reporting of this protocol. The Meta-analyses Of Observational Studies in Epidemiology Checklist<sup>12</sup> and the PRISMA statement<sup>13</sup> will be used to guide the reporting of the final review and meta-analysis.

### Search strategy and data sources

A comprehensive search strategy will be developed in consultation with a professional librarian for the following electronic databases: Ovid EMBASE (1974 to November 2021), Ovid MEDLINE (1964 to November 2021), Web of Science (1900 to November 2021) and the Cochrane Central Register of Controlled Trials (online supplemental figure 1). The search strategy will first be developed in MEDLINE (Ovid interface) and will contain database-specific subject headings and text word terms for concepts. The search strategy will be translated as appropriate for the other databases. A peer review of our search strategy using the Peer Review for Electronic Search Strategies guideline<sup>14</sup> will be completed by a professional librarian (online supplemental appendix). We will also search the bibliographies of included studies and relevant reviews for additional references and seek out relevant studies that are not commercially published, such as ongoing or unpublished clinical trials (WHO International Clinical Trials Registry Platform, European Clinical Trials Database and Clinicaltrials.gov),

conference proceedings and abstracts (Conference Proceeding Citation Index, Web of Science), dissertations and thesis (OpenGrey and ProQuest) and book chapters. We will also contact study authors to clarify information when necessary. Animal studies and duplicate studies will be excluded. We will not apply any language or study design limitations.

### Eligibility criteria

Randomised and non-randomised controlled trials and prospective and retrospective cohort studies describing the use of intravenous hydrocortisone as primary or rescue treatment for hypotension in preterm and term neonates with post menstrual age of  $\leq 44$  weeks that describe mortality prior to discharge or improvement in end-organ perfusion as defined by our primary outcomes will be eligible for inclusion, irrespective of the dose and frequency of administration and duration of treatment (box 1). We will include both studies comparing low-dose versus high-dose hydrocortisone and studies comparing low dose or high dose with placebo, or no control or any other vasoactive agent.

### Study selection and data extraction

Covidence<sup>15</sup> will be used as the primary screening and data extraction tool. Following deduplication, two independent reviewers (NA-R and KS) will screen the resulting articles at the title and abstract level for eligibility. Eligible articles will then be independently reviewed at the full-text level by the same two reviewers. A PRISMA flow diagram will be created to illustrate the study selection process. Data will then be extracted by the same reviewers in duplicate related to the population, intervention, control and outcome for each study (table 1). Any identified discrepancies throughout the study selection and data extraction process will be resolved by discussion between three reviewers (NA-R, KS and SS-Z). The authors of the included studies will be contacted in the case of unclear or missing information.

### Assessment of risk of bias and certainty of evidence

Two reviewers (NA-R and KS) will independently evaluate the methodological quality of the included studies using standardised risk of bias assessment tools, including V.2 of the Cochrane risk-of-bias tool (RoB V.2) for randomised trials,<sup>16</sup> risk of bias in non-randomised studies of interventions<sup>17</sup> and the Newcastle-Ottawa Quality Assessment Scale for cohort studies.<sup>18</sup> We determined a priori that Newcastle-Ottawa Quality Assessment Scale scores of 0–3, 4–6 and 7–9 will be considered high, moderate and low risk of bias, respectively.<sup>19</sup> Using the Grading of Recommendations Assessment, Development, and Evaluation approach,<sup>20</sup> two reviewers (NA-R and KS) will independently judge the certainty of the evidence. Any disagreement will be solved through discussion with a third reviewer (SS-Z).

### Outcomes and variable

Our primary outcomes are (1) improvement in end-organ perfusion, defined as an increase in mean, diastolic or

**Table 1** Data extraction form for studies included in the review and meta-analysis

#### General information

Data form completed (dd/mm/yyyy)

Name/ID of data extractor

Study ID

Author last name\_study year

Study citation

Year of study conduct

Country of study conduct

Funding source

Conflict of interest

#### Characteristics of included studies

##### Methods

Aim of study

Study design

Method of randomisation

Start date

End date

##### Participant characteristics

Population description

Setting

Inclusion criteria

Exclusion criteria

Number of participants

Baseline imbalances\*

Birth weight (grams)

Gestational age (weeks)

Postnatal age (hours, days or weeks)

Underlying condition/cause of hypotension

Comorbidities

Concurrent medications

##### Intervention/exposure characteristics

##### Hydrocortisone details

Timing of administration

Primary or rescue therapy or other

Dosing details

Initial dose (mg/kg)

Maintenance dose (mg/kg/day)

Treatment interval (hours)

Treatment length (hours)

Cumulative dose (mg/kg)

##### Control/comparator details

Pharmacotherapy

Dopamine

Dobutamine

Epinephrine

Norepinephrine

Milrinone

Vasopressin

Placebo

Other

##### Outcomes details†

Continued

**Table 1** Continued

<b>Primary outcomes</b>		
	Improvement Yes or No	If Yes, Timing‡
SBP		
DBP		
MBP		
Urine output		
Inotropic support		
Serum lactate		
Mortality	Death in the ICU Yes or No	
<b>Secondary outcomes§</b>		
<b>Major neurosensory disability</b>		
Moderate to severe motor impairment		
Moderate to severe cognitive impairment		
Cerebral palsy		
Visual impairment		
Hearing impairment		
BPD		
<b>Occurrence of adverse events</b>		
Gastrointestinal events		
Hyperglycemia		
Hypertension		
Hospital acquired infection		

\*Statistically significant ( $p < 0.05$ ) differences in baseline characteristics between intervention and control or exposed and unexposed participant groups, as reported by the study authors.

‡The primary and secondary outcome variables are defined as per the primary studies.

‡Within first 12 hours of treatment initiation.

§For all secondary outcome variables, the number or % in exposed vs unexposed groups; attributed to hydrocortisone will be applied for the analysis.

BPD, bronchopulmonary dysplasia; DBP, diastolic blood pressure; ICU, intensive care unit; MBP, mean blood pressure; SBP, systolic blood pressure.

systolic blood pressure within 12 hours of the start of treatment, with one of the additional following criteria: an increase in urine output or a reduction in serum lactate within 12 hours of treatment initiation, as defined by the authors in the primary studies and (2) mortality prior to discharge.

Our secondary outcomes are (1) development of bronchopulmonary dysplasia, (2) major neurosensory disability, defined as moderate to severe motor or cognitive impairment, cerebral palsy, or severe visual or hearing impairment as defined in the primary study and (3) occurrence of adverse events defined as hypertension, hyperglycemia, gastrointestinal events (occurrence of gastrointestinal perforation, necrotising enterocolitis or gastrointestinal bleed), or hospital-acquired infections within 2 weeks of hydrocortisone administration (table 2).

**Table 2** Primary and secondary outcome variables\*

<b>Primary outcomes</b>	<b>Primary outcome variables</b>
Improvement in end-organ perfusion	<ul style="list-style-type: none"> <li>▶ SBP</li> <li>▶ DBP</li> <li>▶ MBP</li> <li>▶ Urine output</li> <li>▶ Inotropic support</li> <li>▶ Serum lactate</li> </ul>
Mortality	▶ Death before discharge
<b>Secondary outcomes</b>	<b>Secondary outcome variables†</b>
Major neurosensory disability	<ul style="list-style-type: none"> <li>▶ Moderate to severe motor impairment</li> <li>▶ Moderate to severe cognitive impairment</li> <li>▶ Cerebral palsy</li> <li>▶ Visual impairment</li> <li>▶ Hearing impairment</li> </ul>
BPD Occurrence of adverse events	<b>Adverse events</b> <ul style="list-style-type: none"> <li>▶ Hyperglycemia</li> <li>▶ Gastrointestinal events</li> <li>▶ Hospital-acquired infection</li> <li>▶ Hypertension</li> </ul>

\*The primary and secondary outcome variables are defined as per the primary studies.

†For all secondary outcome variables, the number or % in exposed versus unexposed groups; attributed to hydrocortisone will be applied for the analysis.

BPD, bronchopulmonary dysplasia; DBP, diastolic blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure.

### Data synthesis and statistical analysis

A meta-analysis will be performed for randomised and non-randomised studies, separately using the following comparisons:

1. Comparison 1: We will perform a meta-analysis of studies comparing low-dose (initial dose of  $\leq 1$  mg/kg, followed by  $\leq 2$  mg/kg/day or cumulative daily dose of  $\leq 3$  mg/kg on the first day of treatment) with high-dose (initial dose of  $> 1$  mg/kg, followed by  $> 2$  mg/kg/day or cumulative daily dose of  $> 3$  mg/kg on the first day of treatment) hydrocortisone. In this meta-analysis, the studies will be grouped based on the indication of treatment, such as, transient adrenal insufficiency in preterm infants and hypotension in critically ill term neonates.
2. Comparison 2: We will perform a meta-analysis of studies comparing hydrocortisone (any dose, low or high) with placebo or no medication or any other vasoactive agent. In this meta-analysis, the studies will be grouped based on the dose of hydrocortisone (low dose or high dose) to test for subgroup differences between low-dosing and high-dosing regimens.

For dichotomous outcomes, we will obtain the raw data from each study to calculate relative risk (RR) and 95% CI. We will use a random effects model to perform



the meta-analyses using Review Manager V.5.4 (Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark) to yield pooled RR and its 95% CI for each outcome. As risk data for observational studies are usually provided as odds ratios (OR), we plan to convert the ORs to RRs prior to meta-analysis. Individual studies that provide multiple ORs or RRs stratified by gestational age will be pooled using a fixed-effect model method to obtain a combined risk for the whole population included in the individual study. Publication bias will be visually assessed using a funnel plot<sup>21</sup> and Egger's regression test<sup>22</sup> if more than 10 studies are included for any individual meta-analysis.

### Assessment of heterogeneity

The pooled forest plots will be visually evaluated to assess for heterogeneity. Furthermore, we will determine the statistical heterogeneity using the  $p$  for  $\chi^2$  and  $I^2$  values (derived from the  $\chi^2$  Q-statistic) in the meta-analysis.<sup>23</sup> Statistical heterogeneity will be considered significant if the  $p$  value for  $\chi^2$  is  $<0.10$ . On identifying significant statistical heterogeneity, the data will be checked for mistakes and inconsistencies during the data extraction and data entry processes. We will perform subgroup analysis based on gestational age ( $\leq 28$  weeks and  $>28$  weeks), if data are available, to explore the heterogeneity.

### Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

## DISCUSSION

This review will include a comparative analysis of commonly prescribed dosing regimens of hydrocortisone in neonates. It will also investigate whether the efficacy and safety profile of high-dosing versus low-dosing regimens justifies the use of one universal recommendation. Evidence from the review will assist in the development of guidelines and clinical recommendations for critically ill neonates with hypotension as well as identify knowledge gaps and areas in need of further research related to glucocorticoids in the treatment of neonatal hypotension. The results of this review will be of interest to a broad audience, including policy-makers and guideline developers, neonatologists and paediatric intensivists. The strengths of our study include the use of explicit and reproducible methods to produce a rigorous and high-quality evidence synthesis.

## DEFINITIONS

We will define two dosing regimens of high-dose (initial dose of  $>1$  mg/kg, followed by  $>2$  mg/kg/day or cumulative daily dose of  $>3$  mg/kg on the first day of treatment) and low-dose (initial dose of  $\leq 1$  mg/kg, followed by  $\leq 2$  mg/kg/day or cumulative daily dose of  $\leq 3$  mg/kg

on the first day of treatment) hydrocortisone therapy<sup>3 24</sup> to assess their comparative effectiveness and safety.

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**Contributors** NA-R, KS and SS-Z contributed to the conception and design of the protocol. KS, NA-R and SS-Z contributed to planning the search strategy. NA-R, KW, JVDA, CL, JL, AR and SS-Z contributed to the critical review of the protocol and review of its scientific content.

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**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** We will not obtain ethical approval for this review, as it will be based on the analysis of publicly available evidence. The results of this review will be presented at conferences and symposia and submitted to a peer-reviewed journal focusing on paediatrics or neonatology for publication.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data sharing not applicable as no datasets generated and/or analysed for this study. Data sharing not applicable as no datasets generated and/or analysed for this protocol.

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