EFFECT OF EARLY HYDROCORTISONE ON RISK OF GASTROINTESTINAL PERFORATIONS IN EXTREMELY PRETERM INFANTS: A PROTOCOL FOR A RETROSPECTIVE COHORT STUDY USING ROUTINELY COLLECTED DATA

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ABSTRACT

Introduction

A large, randomised control trial, the PREMILOC trial, has established that giving low dose hydrocortisone prophylactically in the first ten days of life reduces the risk of bronchopulmonary dysplasia in babies born before 32 weeks' gestation. However, the PREMILOC trial was underpowered to investigate rarer side effects, such as gastrointestinal perforation. This study aims to establish whether the odds of gastrointestinal perforation increase when extremely preterm infants are given prophylactic hydrocortisone in the first ten days of life.

Methods and analysis

This retrospective cohort study will use routinely collected data from the U.K. National Neonatal Research Database. We will examine the records of all infants born before 28 weeks' gestation and cared for in English and Welsh neonatal units between 2016 and 2023. Infants will be considered exposed if they received hydrocortisone for at least eight consecutive days, beginning on postnatal day 1 or 2. The primary outcome will be gastrointestinal perforation, as recorded in the infant's neonatal unit record. This outcome will be validated with the original care teams for a sample of babies. Data will be analysed using a propensity score matched approach to reduce the impact of confounding.

Ethics and dissemination

Ethics approval for this study was granted as part of NeoWONDER: Neonatal Whole Population Data linkage approach to improving long-term health and wellbeing of preterm and sick babies (REC ref: 21/EM/0130). The results of this study will be disseminated via peer-reviewed academic journals, conferences and the social media channels of the study team.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Use of the National Neonatal Research Database provides data on the complete population of babies treated in English and Welsh neonatal units during the study period.
- The National Neonatal Research Database is a rich dataset, which includes data on the primary outcome and many potential confounders.
- Propensity matching is utilised to reduce the impact of confounding.
- The National Neonatal Research Database does not include information about dosages or indications, so it is possible that the exposure (prophylactic hydrocortisone to prevent bronchopulmonary dysplasia) may be miscategorised.
- It can be clinically difficult to distinguish gastrointestinal perforation from necrotising enterocolitis unless the diagnosis is confirmed at surgery. As the database records may not be

updated with surgical or histological findings, misclassification of outcome status is possible. The impact of this is estimated by the validation of a sample of the outcomes.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a serious, but common, complication of preterm birth. It is estimated that between 26% and 40% of babies born before 32 weeks' gestation will be diagnosed with BPD (1-3). Advances in neonatal care mean that the smallest and sickest babies, who are more likely to develop this complication, are also more likely to survive than previously. BPD is a leading cause of mortality in very preterm infants and is associated with long-term respiratory morbidity (4) and poor neurological and motor outcomes (5).

Corticosteroids, primarily dexamethasone, have been used to both prevent and treat BPD since the 1980s. However, concerns were raised as early as 1998 about the long term effects of dexamethasone on neurodevelopment (6). Subsequent meta-analyses have found high certainty evidence that early exposure to dexamethasone is associated with an increased risk of cerebral palsy (7, 8). The most common dexamethasone treatment regimen analysed by Doyle et al (7) consisted of a total dose of 2.76mg/kg, beginning with 0.5mg/kg for postnatal days 1-3 and tapering over the first 12 days of life. In response to the concerns about dexamethasone, clinicians have increasingly used hydrocortisone as an alternative to prevent BPD (9). Whilst exposure to hydrocortisone does not appear to be associated with increased risk of cerebral palsy (7, 10), there is evidence that early exposure to hydrocortisone may increase the risk of gastrointestinal perforation (7).

A l multicentre trial (n=521) published in 2016 (PREMILOC) treated preterm babies born before 28 weeks' gestation with either a placebo or 1mg/kg hydrocortisone daily for the first week of life from the day of birth, followed by 0.5mg/kg on postnatal days 8-10. The trial team concluded that prophylactic, early treatment with low dose hydrocortisone reduced the incidence of BPD (11). The authors investigated gastrointestinal perforations as one of several secondary outcomes and found no evidence of an association between early hydrocortisone treatment and gastrointestinal perforation. However, the trial was terminated early before reaching its target sample size and, even at the target sample size, the study would have been underpowered to investigate gastrointestinal perforations. The numbers of perforations in the trial were small, leading to an imprecise estimate of the association between hydrocortisone and gastrointestinal perforations.

Since gastrointestinal perforations occur in around 5% of very preterm infants, very large numbers of participants would be required to adequately power a clinical trial investigating the effect of early hydrocortisone on this outcome. We propose using routinely collected data from all neonatal units in England and Wales to examine whether early hydrocortisone exposure is associated with an increased risk of gastrointestinal perforation. We anticipate that our study will include three times as many babies treated with early hydrocortisone as the PREMILOC trial and therefore we will be better powered to examine the association between early treatment with hydrocortisone and gastrointestinal perforations.

This study aims to:

1. determine the prevalence and patterns of use of early hydrocortisone for BPD prevention in English and Welsh neonatal units;
2. examine the extent of any association between early exposure to hydrocortisone and gastrointestinal perforations in the first 14 days of life

METHODS AND ANALYSIS

Study design

This study is an analysis of an existing national electronic population cohort using anonymised, routinely recorded clinical data from the National Neonatal Research Database (NNRD).

Data source

The NNRD is an approved research database constituting real-world prospective clinical data extracted from point-of-care neonatal electronic health records with complete coverage of infants admitted for neonatal care to National Health Service (NHS) neonatal units in England and Wales since 2012. A defined data extract of approximately 450 items (the Neonatal Data Set) is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London for data linkage and cleaning prior to entry into the NNRD. To date, the NNRD contains data for over a million babies (approximately 80,000 babies annually). High completeness and accuracy (>95%) of a selection of the variables held in the NNRD has been confirmed by formal comparison with a multi-centre, randomised placebo-controlled trial (12).

Extracted data items will include baby and maternal demographic characteristics (such as birthweight, gestational age at delivery, gender), antenatal and labour/delivery variables (such as medical complications in current pregnancy, provision of antenatal steroids and magnesium sulphate and antibiotics), care procedures in the neonatal unit (such as provision of hydrocortisone, other corticosteroids and inotropic support) and neonatal outcome data (such as survival to discharge, proportion of days on mechanical ventilation and diagnoses e.g. gastrointestinal perforation, sepsis, BPD, brain injury, necrotising enterocolitis (NEC)). Please see Appendix for the full data extraction schema.

Validation study of gastrointestinal perforation data to distinguish between gastrointestinal perforations and necrotising enterocolitis

Diagnosis data is collected in the NNRD to identify which babies have experienced a gastrointestinal perforation or necrotising enterocolitis. However, the two conditions have some similarities at clinical presentation and a definitive differential diagnosis may only be possible during surgery. The NNRD record may therefore contain multiple or preliminary diagnoses that are not updated when the diagnosis is confirmed at surgery. To resolve this

issue, we will conduct a validation study to differentiate between babies who had gastrointestinal perforations and those who had necrotising enterocolitis.

All babies whose NNRD records show diagnoses of both gastrointestinal perforation and necrotising enterocolitis, but no record of surgery for necrotising enterocolitis in the first 14 days of life, will be included in the validation study. Although the NNRD includes an internal NHS baby ID, the study team are unable to access any identifiable data using this ID. Only the clinical care team who cared for the baby can review the complete care notes using this ID. Therefore using secure NHS email, the NHS baby ID of the sample babies will be sent by a clinician to the neonatal units who cared for them. The units will be asked to review the baby's clinical notes and confirm by email the diagnosis of gastrointestinal perforation or necrotising enterocolitis and the corrected gestational age when any gastrointestinal perforation occurred. All staff involved in accessing and reviewing clinical data have received and comply with institutional confidentiality and data protection policies and research conduct.

All neonatal units that contribute data to the NNRD will be informed about the study beforehand and will have the possibility to opt out from the validation study if they wish to.

Participant entry criteria

Inclusion criteria

The cohort will be extracted from the NNRD and will include babies who fulfil all the following criteria:

- were admitted to a neonatal unit between the 1st January 2016 and 31st March 2023 and
- received any of their care in a NHS neonatal unit in England and Wales (part of UK Neonatal Collaborative and therefore contributing data to the NNRD) and
- born before 28 weeks' gestation.

Exclusion criteria

Infants will be excluded if:

- They have missing data for principal background variables (gestational age at birth, birth weight, year of birth and date of death for those that died).
- Their NNRD birthweight absolute value z score exceeds 4 or is missing.
- They died on postnatal day 1 or 2.

Definition of exposure to prophylactic hydrocortisone

A baby will be considered to be exposed if:

1. They receive early hydrocortisone started on postnatal day 1 or 2 and given for more than seven consecutive days OR

2. They receive early hydrocortisone started on postnatal day 1 or 2 and are being cared for in a PROHYDRO unit but die on or before postnatal day 8.

PROHYDRO units are defined as units who, at the time the baby was born, had implemented a protocol for use of prophylactic hydrocortisone as part of routine care for babies born less than 28 weeks' gestation. A unit may change from being a non-PROHYDRO unit to a PROHYDRO unit if a new early hydrocortisone protocol is introduced during the study period (2016-2023). We will use data from NNRD to identify potential PROHYDRO units i.e. units that have high proportions of cohort babies that receive early hydrocortisone started on postnatal day 1 or 2 and given for >7 consecutive days. We will then check the status of any PROHYDRO units with the neonatal unit NNRD coordinator and determine the date a new early hydrocortisone protocol was introduced.

Outcomes

Principal outcome

A baby will be considered to have had a gastrointestinal perforation if their NNRD record includes a record of a GI perforation in the diagnoses field. The primary outcome data will be validated prior to data analysis (see the previous "Data Source" section).

Secondary outcomes

- Survival without gastrointestinal perforation
- Mortality before discharge to home
- Total length of stay
- Proportion of days in neonatal unit on mechanical ventilation
- BPD (defined as any respiratory or ventilatory support or supplemental oxygen at 36 weeks' postmenstrual age (PMA)
- BPD (defined using an adapted Jensen criteria (13) based on the highest level of respiratory support at 36 weeks PMA)

Other outcomes of interest

We will also report on other outcomes that have been identified by Webbe et al (14) as of importance to key stakeholders, such as patients, parents, clinical staff and researchers. These include:

- NEC is defined as:

- UK National Neonatal Audit Programme (NNAP) definition i.e. at least one clinical feature (bilious gastric aspirate or emesis, abdominal distension, occult, gross blood in stool) and at least one radiographic feature (pneumatosis, hepato-biliary gas, pneumoperitoneum) (15)
- Severe NEC as per Battersby et al (16) i.e. necrotising enterocolitis confirmed at surgery or post-mortem or stated as cause of death
- Pragmatically defined NEC i.e. babies who had a recorded diagnosis of necrotising enterocolitis and received at least 5 consecutive days of antibiotics whilst also nil by mouth

- Late onset sepsis (defined as one or more episodes of a positive blood or cerebrospinal fluid culture with either a pure or mixed growth of a known pathogenic organism after the first three days following birth)
- Brain injury occurring at or soon after birth including intracranial haemorrhage, perinatal stroke, central nervous system infection, kernicterus (bilirubin encephalopathy), periventricular leukomalacia or any recorded seizure
- Treated retinopathy of prematurity (defined as cryotherapy, laser therapy or injection of anti-vascular endothelial growth factor therapy for ROP in either or both eyes)

Data analysis plan

Determining the prevalence and patterns of use of early hydrocortisone within the cohort

The number of babies who received early hydrocortisone, in line with our definition of exposure, will be presented by birth year as a proportion of the total number of babies included in the study and born in the same year. This analysis will therefore describe any changes in patterns of steroid use over time.
The number of babies who received early hydrocortisone treatment will be presented by gestational age as a proportion of the total number of babies included.

The number of units providing early hydrocortisone treatment will be recorded and presented by birth year.

Examine the extent of any association between early exposure to hydrocortisone and gastrointestinal perforations

The background maternal and neonatal characteristics, birth and neonatal admission details, clinical course and outcomes of the cohort will be described. Results will be presented as means (with standard deviation), medians (with interquartile ranges) or count and proportions as appropriate.

Levels of missingness will be described for each potential confounder or mediator. Variables for consideration are shown in Appendix 1 NNRD Data Extraction Schema (potential risk factors). These demographic and clinical characteristics will be described for those babies

with complete and incomplete records. If levels of missingness are less than 5%, then a complete case analysis will be conducted. If levels of missingness are between 5% and 40% then multiple imputation will be used to create a minimum of ten complete datasets. Any variables with more than 40% missing will be excluded from the analysis.

We will use propensity score matching to improve balance in covariate distributions between groups. The methods described by Imbens and Rubins will be used to select the demographic and clinical variables that are used in the propensity score model (17). The potential variables for inclusion in the propensity score model are shown in supplementary materials appendix 1, "NNRD data extraction schema potential risk factors". Gestational age and birthweight z score will be included *a priori* in the propensity score model. A propensity score will be calculated for every baby in the cohort. Each baby receiving early hydrocortisone treatment will be matched with at least two other babies who have similar propensity scores and who did not receive hydrocortisone treatment consistent with our exposure definition.

Logistic regression will be used to calculate a measure of association between early hydrocortisone and odds of gastrointestinal perforation in the matched sample. Any variables included in the propensity score model will be included as covariates in the logistic regression to reduce any residual confounding that remains in the matched sample. An identical regression analysis will be performed for each of the imputed datasets. Effect estimates will be combined to create a pooled effect estimate. General estimating equations will be used in the logistic regression to take account of correlation within a neonatal unit.

Sensitivity analyses

In addition to the main analyses we will conduct a number of pre-planned sensitivity analyses. The sensitivity analyses will include analyses that address the definition of exposure. The main exposure of interest is the use of prophylactic hydrocortisone for BPD prevention. Whilst the NNRD does contain data describing daily drugs, there are no data describing dosages or indication for use. It is therefore not possible to easily distinguish the use of hydrocortisone for BPD from treatment of low blood pressure (another common indication in extremely preterm infants).

It is biologically plausible that early hydrocortisone treatment for either indication may increase the risk of gastrointestinal perforation, hence we will conduct a sensitivity analysis where we define hydrocortisone exposure broadly. We will conduct an analysis contrasting all babies who received hydrocortisone on postnatal day 1 or 2 with babies who did not receive any hydrocortisone in the first ten postnatal days.

Treatment for low blood pressure is of a higher dose and will usually be for a shorter duration compared with hydrocortisone prophylaxis to prevent BPD. Hence our main definition of exposure requires that babies receive hydrocortisone for at least eight consecutive days in the first 10 days of life. This length of exposure makes it more likely

hydrocortisone is being used to prevent BPD, rather than as a treatment for low blood pressure. To address any remaining potential concerns about the indication for receipt of hydrocortisone, we will conduct two analyses with a narrower definition of hydrocortisone exposure. These sensitivity analyses attempt to further isolate those babies receiving prophylactic hydrocortisone in contrast to receipt for other indications:

1. An analysis contrasting babies who received hydrocortisone treatment consistent with our hydrocortisone exposure definition AND were treated in a PROHYDRO unit, vs babies who did not receive hydrocortisone in line with our main definition of exposure.

2. An analysis that excludes from the exposed group babies who received inotropes, paracetamol or ibuprofen during the period when they also received hydrocortisone.

Sample size

We expect to extract anonymised data on approximately 15,000 admissions to neonatal units in England and Wales between 2016 and 2023 for babies born before 28 weeks' gestation. A small pilot study has suggested approximately 5.3% of neonatal unit admissions in the NNRD receive early hydrocortisone treatment consistent with the exposure definition. We have therefore projected that approximately 800 babies are exposed to early hydrocortisone.

Based on the PREMILOC trial, we anticipate rates of gastrointestinal perforation of approximately 4.5%. Using this data, we have calculated sample sizes using the R package pwr (18). We anticipate being able to detect a difference in the risk of gastrointestinal perforation between the early hydrocortisone and not early hydrocortisone groups of approximately 2.8% i.e. rates of gastrointestinal perforation of 4.5% in the control group and 7.3% in the early hydrocortisone group. This calculation assumes power of 80% and a two-sided alpha of 5% and 2:1 matching.

ETHICS AND DISSEMINATION

Existing anonymised data will be extracted from the NNRD for use in this study and patient consent was not required. Approval was granted for use of the NNRD data via the NeoWONDER: Neonatal Whole Population Data linkage approach to improving long-term health and wellbeing of preterm and sick babies (IRAS 293603; REC ref: 21/EM/0130). An amendment to the original approval was agreed to allow the study team to contact the original care teams as part of the validation study.

The results of this study will be published in peer-reviewed academic journals, presented at conferences and local meetings and promoted on the social media channels of the Imperial College Neonatal Medicine Research Group. A summary of the study will also be publicised on the NNRD website.

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AUTHOR CONTRIBUTIONS

CB had the original idea for the study and submitted for approvals. CB and AA undertook the DAG. AA, CB, SU, AB and CG planned statistical analysis. AA, CB, SU, AM, AB, MT and CG all contributed to overall study design, protocol development and the writing and review of this paper. SM distributed the data validation requests and collated responses.

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COMPETING INTERESTS STATEMENT

None declared

SUPPLEMENTARY MATERIALS APPENDIX 1: NNRD DATA EXTRACTION SCHEMA

Purpose: Potential risk factors	NNRD data items to extract
Baby demographic	- Year and month of birth - Phenotypic sex - Gestational age at birth - Birthweight and birthweight z score
Maternal demographic	- Deprivation decile for maternal address - Maternal ethnicity - Maternal age
Antenatal variables	- Maternal pre-eclampsia - Maternal chorioamnionitis - Maternal hypertension - Maternal diabetes - Maternal smoker at booking
Labour and delivery	- Prelabour rupture of membranes - Placental abruption - Number of steroid courses given antenatally and completion status - Maternal magnesium sulphate - Maternal nifedipine - Multiple fetuses - Mode of delivery - Umbilical cord base excess - Apgar score at 5 and 10 minutes - Cardiac massage at birth - Resuscitation drugs administered - Intubated at resuscitation - Surfactant administered at birth
Baby condition on postnatal day 1 & 2	- Constituent items of CRIB-II score - Surfactant given on postnatal day 1 - Invasive ventilation on postnatal day 1 & 2 - Day 1 & 2 Inotropes - Day 1 & 2 Nitric oxide - Day 1 &2 Ibuprofen - Day 1& 2 Paracetamol - Day 1 Indomethacin - Early onset infection
Other risk factors	- Any congenital gastrointestinal abnormalities - Any congenital cardiac abnormalities - Transfer in first 24 hours

	- Transfer in first 48 hours - Postnatal age (in days) when enteral feeds are initiated
Purpose: Postnatal drugs excluding hydrocortisone	**NNRD data items to extract**
Other drug exposures in first 14 days (Duration in days, first day administered and daily data for days 1-14)	- Inotropes - Ibuprofen - Paracetamol
Purpose: Exposure	**NNRD data items to extract**
Hydrocortisone exposure	- Duration in days (for first 14 days and in total), first day administered and daily data for days 1-14. - Hydrocortisone given consistent with the Yao et al definition (i.e. started on postnatal day 1 or 2 and given for >7 consecutive days).
Place of birth and subsequent place of care	- Unit of first admission and level of unit of first admission - Unit and level of unit of second admission if baby is transferred in postnatal days 1-10
Purpose: Outcomes	**NNRD data items to extract**
Primary outcomes	- Death before discharge - Gastrointestinal perforation - Major surgery in the first 14 days of life and Severe NEC used in definition of gastrointestinal perforation
Secondary outcomes	- Total length of stay - Number of days of invasive respiratory support (to calculate proportion of stay on invasive respiratory support) - Bronchopulmonary dysplasia
Other outcomes	- NEC diagnosis consistent with the NNAP definition - Severe NEC as per Battersby et al (16) - Pragmatically defined NEC i.e. babies who had a recorded diagnosis of necrotising

	enterocolitis and received at least 5 consecutive days of antibiotics whilst also nil by mouth - Late onset sepsis - Brain injury - Retinopathy of prematurity