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Effect of surfactant dose on outcomes in preterm infants with respiratory distress syndrome: the OPTI-SURF study protocol

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ABSTRACT

Introduction Respiratory distress syndrome is a condition seen in preterm infants primarily due to surfactant insufficiency. European guidelines recommend the dose and method of surfactant administration. However, in routine practice, clinicians often use a 'whole vial' approach to surfactant dosing. The aim of this study is to assess whether in preterm infants of gestational age 36^{+6} weeks^{+days} or less, a low first dose of surfactant (100–130 mg/kg) compared with a high first dose (170–200 mg/kg) affects survival with no mechanical ventilation on either on postnatal days 3 and 4, and other outcomes.

Methods and analysis In this prospective, observational study, we will use the National Neonatal Research Database as the main data source. We will obtain additional information describing the dose and method of surfactant administration through the neonatal EPR system. We will use propensity scores to form matched groups with low first dose and high first dose for comparison.

Ethics and dissemination This study was approved by the West Midlands—Black Country Research Ethics Committee (REC reference: 18/WM/0132; IRAS project ID: 237111). The results of the research will be made publicly available through presentations at local, national or international conferences and will be submitted for publication in a peer-reviewed journal.

Trial registration number NCT03808402; Pre-results.

Strengths and limitations of this study

- We will use routinely recorded data held in the National Neonatal Research Database (NNRD); these have been shown to be complete and of high quality.
- The NNRD covers the entire neonatal population of England, Scotland and Wales and thus provides power to explore associations between surfactant use and outcomes.
- This study has prospectively added six further data items to the NNRD that will reflect the real-world scenario for dosing of surfactant.
- The NNRD contains a large number of variables that will assist in propensity score matching to form well-balanced groups, diminishing potential confounding.
- This study is not a randomised controlled trial; propensity score methodology can only address imbalances in observed confounders, and residual confounding by unmeasured or poorly recorded variables cannot be ruled out.

INTRODUCTION

Respiratory distress syndrome (RDS) is a condition that develops shortly after birth and increases in severity during the first 12–24 hours.[1] RDS is mainly seen in preterm infants, due, at least in part, to the insufficiency of pulmonary surfactant.[1–3] The aim of RDS management is to minimise lung damage using the least invasive treatment and avoid unnecessary intubation and mechanical ventilation.

The European Consensus Guidelines for the management of RDS recommend stabilisation of the infant using non-invasive respiratory support such as high-flow or continuous positive airway pressure (CPAP).[4] The infant's oxygen requirements are monitored, and should the fraction of inspired oxygen (FiO_2) required increase above 0.3, surfactant administration is recommended. Between 21% and 68% of infants initially managed on CPAP will require mechanical ventilation, termed CPAP failure and defined as intubation within the first 48–72 hours of starting CPAP.[5–11] Infants who fail on CPAP have similar outcomes to those who are mechanically ventilated in terms of rates of bronchopulmonary dysplasia, mortality, pneumothorax, periventricular haemorrhage and discharge on oxygen.[8 9 11]

The licensed dose of surfactant for preterm infants with RDS is 100–200 mg/kg.[12] A dose of 200 mg/kg reduces FiO_2 requirements and the need for redosing,[13 14] as well as indicating possibility of reduced mortality and oxygen requirement at 36 weeks after menstrual age.[15] A pharmacokinetic study

has also demonstrated that a dose of 200 mg/kg results in a higher half-life of surfactant compared with a dose of 100 mg/kg.[15]

In a research environment, the dose of surfactant is rigorously controlled and usually administered at a dose of exactly 100 mg/kg or 200 mg/kg. In clinical practice, clinicians more frequently follow the 'whole vial dosing' approach, where a full vial is given aiming to get as close as possible to the desired dose. Reasons for whole vial dosing approach include reduction of waste and administration of surfactant shortly after birth when an infant's weight is unknown. It is unclear whether whole vial dosing leads to underdosing or overdosing and whether either deviation affects outcomes. The dose of surfactant delivered and the method of administration are not currently routinely recorded in the UK.

The aim of the OPTI-SURF (Optimal surfactant delivery for preterm babies with respiratory distress) study is to assess whether the dose and method of administration of surfactant given to preterm infants with RDS in the immediate postnatal period affect neonatal outcomes.

Here, we describe the design of the OPTI-SURF study.

METHODS

Study design

Prospective, observational study using propensity scores to form matched groups for analysis.

Study population, and inclusion and exclusion criteria

Preterm infants born in neonatal units in England, Scotland or Wales will be included if they meet the following criteria: gestational age of 36^{+6} weeks^{+days} or less at birth, diagnosis of RDS made by the attending clinician according to local guidelines, treatment with surfactant, record of birth weight available and born after study initiation.

Primary objective

The primary objective was to determine whether the first dose of surfactant (low dose of 100–130 mg/kg compared with high dose of 170–200 mg/kg) has an effect on survival with no mechanical ventilation on either on postnatal days 3 and 4 (regardless of the mechanical ventilation on days 1 and 2).

Secondary objectives

The secondary objective was to measure the association between the size of the first dose of surfactant and the following: survival, total number of doses of surfactant, total cumulative dose of surfactant (including first dose), survival to postnatal day 28 with no respiratory support on that day (for infants born ≤32 weeks), survival to 36^{+0} weeks of gestation with no respiratory support on that day (for infants born ≤32 weeks), survival to discharge with no oxygen requirement, duration of mechanical ventilation (days), duration of respiratory support (days) and respiratory support at 2 years. Respiratory support is defined as any respiratory support, including supplemental oxygen.

Exploratory objectives

The exploratory objective was to study the effect of first dose of surfactant, method of surfactant administration, FiO_2 (at the point of decision to administer surfactant) and use of sedation/analgesia (at the time of surfactant administration, including dose of sedative/analgesic) on the following factors: mechanical ventilation on days 3 and 4 of life, survival, survival to postnatal day 28 with no respiratory support on that day (for infants born ≤32 weeks), survival to 36^{+0} weeks of gestation with no respiratory support on that day (for infants born ≤32 weeks), survival to discharge with no oxygen requirement, duration of mechanical ventilation (days), duration of respiratory support (days), incidence of complications such as retinopathy of prematurity and periventricular haemorrhage, respiratory support at 2 years, development at 2 years and Bayley-III score at 2 years.

Data source

OPTI-SURF is a prospective study using deidentified data from the National Neonatal Research Database (NNRD) that contains information on all admissions to a National Health Service (NHS) neonatal unit in England, Scotland or Wales.

There are approximately 450 data items held in the NNRD, which are extracted quarterly from routinely recorded clinical data entered by health professionals at the point of clinical care through existing neonatal electronic patient record (EPR) systems. The most commonly used neonatal EPR system in NHS neonatal units is provided by the commercial supplier Clevermed.

The NNRD currently holds data describing surfactant administration at birth (yes/no/unknown) and the number of doses administered during an infant's neonatal stay. For the OPTI-SURF study, six additional data items on dose and method of surfactant administration, and surfactant dosing frequency were added by Clevermed to their existing supplied EPR systems (BadgerEPR and BadgerNet) under a separate 'OPTI-SURF' page (see table 1). Where more than one dose of surfactant was administered, the additional data items were completed for each dose.

Planned follow-up

The study will continue recruiting until 300 matched pairs of infants have been enrolled and will remain open until 2-year follow-up data have been obtained for those infants born at <30 weeks of gestation.

Study centres

Thirty centres in the UK will participate in the study. Potential study centres were identified by retrospectively analysing the NNRD records for the previous 12 months for the number of infants in each hospital who would have met eligibility criteria for this study. The hospitals with

Table 1 Additional data items under 'OPTI-SURF' page

	Question	Available responses
1	Time administered: date and time the surfactant was administered	Date and time
2	Surfactant used	► Curosurf (poractant alpha) ► Survanta (beractant)
3	Method of administration	► Endotracheal tube ► Intubate-surfactant-extubate (endotracheal tube in place for 15 min or less) ► Thin catheter for minimally invasive/less invasive surfactant administration ► Other (free text)
4	Dose administered (mg)	(free text)
5	Analgesics and/or sedatives used	(free text)
6	FiO_2 at the point of decision to administer surfactant	► <30% ► 30%–39% ► 40%–49% ► 50%–59% ► ≥60%

FiO_2, fraction of inspired oxygen.

the highest number of infants identified were invited to participate until 30 centres joined the study. Only hospitals in England are participating in the study.

Consent

The study was designed and received ethical approval to use opt-out consent for all eligible infants born in the participating units. The parents of eligible infants were offered the opportunity to opt out of their infant's data being included in the study.

Patient and public involvement

Patient groups were not formally involved in the development of the study design.

Statistical considerations and analyses

Sample size calculation

The study was powered based on assumed proportions of preterm infants requiring mechanical ventilation within 72 hours of birth of 60% and 45% in the dosing groups 100–130 mg/kg and 170–200 mg/kg, respectively. This is the assumption underpinning the choice of doses, rather than the assumption underpinning the expected efficacy of the doses. The required power was 80%, with the treatment comparison being undertaken at the two-sided 5% level of significance. To ensure that the assumed proportions were reflected in clinical practice, there is a planned review of the anonymised observational first dosing data by the study group, and these first dosing data will be reviewed periodically until 300 matched pairs are recruited. These reviews will only consider the number of patients in each group, and no study data will be evaluated.

Primary and secondary analyses

The primary and secondary outcomes will be analysed by propensity score matching to deal with the non-randomised (ie, observational) nature of the study. Infants with a first surfactant dose lower than 100 mg/kg, higher than 200 mg/kg or in the intermediate range of 131–169 mg/kg will be discarded from the primary and secondary analyses.

Matching

Matching will be based on gestational age category and propensity score using a calliper (width of 0.10 on the logit scale). Gestational age categories are based on WHO,[16] with extremely preterm being up to 27^{+6} weeks; very preterm, 28^{+0}–31^{+6} weeks; and preterm, 32^{+0}–36^{+6} weeks.

Propensity score

The propensity score will be derived by logistic regression on the background variables, with variables dropped and interactions added, using a model selection algorithm.[17] Propensity score variables include birth weight Z score, gestational age, sex, singleton/multiple, Apgar score at 1 min, Apgar score at 5 min, FiO_2 at the time of the first surfactant dose, transfer within 48 hours, birth outside hospital, any antenatal steroids, age at first surfactant administration, location of administration, method of surfactant administration, mother's socioeconomic background (Index of Multiple Deprivation), mode of delivery, parity, maternal age, maternal smoking, maternal diabetes, maternal hypertension, maternal antepartum haemorrhage, maternal infection, prolonged rupture of membranes and sedation/analgesia before surfactant administration.

Comparison of primary and secondary outcomes

The matched subgroups will be compared using the t test, applied to the within-subgroup means for continuous outcomes and to the within-subgroup rates (proportions or percentages) for dichotomous outcomes. The rate of a dichotomous outcome is defined as 100× Y/P, where Y is the number of infants with a positive outcome (survival without requiring mechanical ventilation on days 3 and 4) and P is the number of matched pairs.

Exploratory analyses

All infants in the study, without any restrictions on the size of the first dose, will be included in the exploratory analyses.

Regression analyses

Four exploratory regression analyses will be conducted at a 1% significance level and 99% confidence limits, with no correction for multiple testing: (1) first dose of surfactant, (2) method of surfactant administration, (3) FiO_2

(at the point of decision to administer surfactant) and (4) use of sedation/analgesia (at the time of surfactant administration).

The effect of the size of the first dose of surfactant on the primary outcome will be presented as a receiver operating characteristic curve.

Sensitivity analyses

The sensitivity analysis involves the following steps: (1) removing forced-gestational age matching on the propensity score primary analysis; (2) using the alternative calliper widths of 0.05, 0.15 and 0.20; and (3) recoding the length of stay and duration of mechanical ventilation for infants who died.

DISCUSSION

This study is the first for neonatal real-world clinical practice research. In this study, we will minimise data collection requirements using the existing NNRD, where data are extracted from the EPRs on all admissions to an NHS neonatal unit in England, Wales and Scotland. These clinical data are entered by healthcare professionals as part of the routine clinical practice. In addition to the routine data held in the NNRD, a small number of additional fields specific to this study will be incorporated into the EPR, which will only be completed for infants enrolled in the study. This type of study has not yet been performed in neonatal care and will be an exemplar for use in future research. The study opened for recruitment in August 2018. The study was paused for recruitment in all centres for several weeks from March 2020 due to local and national prioritisation for COVID-19 research.

Ethics and dissemination

The study was approved by the ethics committee at West Midlands—Black Country Research Ethics Committee (REC reference: 18/WM/0132; IRAS project ID: 237111).

The results of the research either will be made publicly available at presentations at local, national or international conferences or will be submitted as a publication in a peer-reviewed journal.

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Contributors The study concept and design was conceived by NM, CG, RM and KCWG. KCWG is the chief investigator for the study. KR prepared the first draft of this manuscript. All authors (KCWG, CG, RM, NL, KR and NM) provided edits and critiqued the manuscript for intellectual content.

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Competing interests KCWG is chief investigator for the OPTI-SURF study. He reports receiving personal fees from Chiesi Pharmaceuticals outside of the submitted work to support attendance at an educational meeting. CG reports grants from Medical Research Council and the National Institute for Health Research, Mason Medical Research Foundation, Rosetrees Foundation and Canadian Institute for Health Research outside this work. He reports receiving personal fees from Chiesi Pharmaceuticals outside of the submitted work to support attendance at educational meetings. NM is the director of the Neonatal Data Analysis Unit and the chief investigator for the National Neonatal Research Database. She is a trustee of the David Harvey Trust, Medical Women's Federation and Action Cerebral Palsy and Their World, and is a member of the Nestle Scientific Advisory Board. She reports research grants in the last 5 years from the British Heart Foundation, Medical Research Council, National Institute of Health Research, Westminster Research Fund, Collaboration for Leadership in Applied Health and Care Northwest London, Healthcare Quality Improvement Partnership, Bliss, Nestle, Prolacta Life Sciences, Chiesi, Shire and HCA International; travel and accommodation expenses from Prolacta, Nestle and Chiesi; and a lecture honorarium from Chiesi. NL is senior statistician at the Neonatal Data Analysis Unit. He reports no competing interests. RM and KR are full-time employees of Chiesi.

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

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