Study Protocol

Title: Nutrition and respiratory morbidity in extremely premature infants: a retrospective five-year whole population study of neonatal networks in England

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Rationale and Background

Extremely premature infants (born before 28 weeks of gestation) face numerous and multisystemic challenges and a number of distinct pathological entities that explain their increased morbidity and mortality (1). Among them, historically, respiratory morbidity in the form of respiratory distress syndrome (RDS) initially and bronchopulmonary dysplasia (BPD) later constitutes the biggest burden that will influence survival and fitness for discharge (2). A significant number of these infants suffer from profound respiratory impairment, are discharged home on supplemental oxygen and are at increased risk of sudden infant death syndrome (3). Concurrently, postnatally these infants suffer from growth failure (commonly dropping more than two standard deviations below birth weight) and in the absence of targeted aggressive nutritional support, end up falling far short of their target growth trajectory (4).

A number of smaller experimental, non-neonatal studies have linked malnutrition to respiratory morbidity: initially, infants with respiratory disorders have increased energy needs because of an increased work of breathing, while later factors such as the inability to advance enteral nutrition, restrictive fluid regimens of parenteral nutrition, oral aversion related to prolonged mechanical ventilation and episodes of infection or necrotising enterocolitis (NEC) preclude the provision of adequate nutritional support (5). Studies of newborn animals have linked malnutrition to respiratory morbidity via several potential intermediaries including the inadequate provision of specific antioxidant nutrients such as vitamin A and glutathione that renders premature ventilated infants susceptible to oxidation damage in the face of hyperoxic treatment (6, 7, 8). Furthermore, mechanical ventilation per se and the ensuing triggering of the inflammatory process, could be a way via which these infants are susceptible to oxidative damage which is not adequately repaired in the face of inadequate nutrition (9).

Despite the plausibility of the relation of inadequate nutrition to respiratory morbidity, this link has not been established in population-wide studies. Some authors have highlighted a relationship on the basis of poorer growth in infants diagnosed with BPD (10), however there is growing acceptance that the definition of BPD is a binary outcome that fails to capture the whole spectrum of respiratory morbidity or the associated implications for healthcare strategies (11, 12). Another way to quantify respiratory morbidity would be using the duration of invasive mechanical ventilation (13) and the duration of oxygen therapy as proxies for the severity of respiratory disease as well as additional clinically relevant respiratory outcomes such as the need for home-oxygen at discharge. Growth can be quantified with the difference in weight from birth to discharge using national validated z-scores (14), with growth failure being defined as falling greater than two standard deviations below birth weight in this preterm infant population (15) .

The neonatal unit at King's College Hospital has a long tradition of research in respiratory physiology and a dedicated multidisciplinary team of nutritional support lead jointly by both medical and dietetic professionals. In this regard, we believe that as a unit it is ideally positioned to examine this relationship.

Our hypothesis is that respiratory morbidity (prolonged ventilation and supplementary oxygen) in extremely premature infants is significantly negatively related to weight accretion and that neonatal mortality is significantly and independently higher in extremely premature infants with respiratory disease and lower adjusted weight accretion. We aim to test this hypothesis in a population-wide basis using data from the national neonatal database.

Study goals and objectives

The primary objective of this study is to explore the relation of respiratory morbidity (prolonged ventilation and supplementary oxygen) with nutritional deficits in extremely premature infants. A secondary objective is to compare nutrition in infants that survived discharge from the neonatal unit compared to infants that did not and ascertain whether impaired nutrition is independently associated to neonatal mortality in infants with respiratory disease.

Study design

This will be a retrospective, whole-population study of infants born before 28 completed weeks of gestation. We will use data from the national neonatal database in England for five years from 1st January 2013- 31st December 2017. This period was selected for consistent quality of data input and with a view to describe current clinical practice.

Variables that will be used can be grouped in nutritional outcomes, respiratory outcomes and possible confounders. The main nutritional outcome will be the change in z-score weight from birth to discharge. For this, we will collect gestational age at birth (weeks), weight at birth (kg), corrected gestational age at discharge (weeks), weight at discharge (kg). We will also collect the weight at 36 weeks corrected gestational age as an interim time endpoint. Secondary nutrition outcomes will be the change in z-score in head circumference (HC). For this we will collect head circumference at birth and at discharge (cm). Weight and HC will be transformed to z-score according to national data (14). The main respiratory outcome will be the duration of mechanical ventilation (days). Secondary respiratory outcomes will be duration of oxygen therapy (days), duration of non-invasive respiratory support (days), BPD at 28 days of age (yes/no), BPD at 36 weeks of corrected age (yes/no), home oxygen

(yes/no), death before discharge from neonatal care (yes/no), age at death (days). Variables that will be collected as possible confounders include: antenatal steroids (yes/no), postnatal steroids (yes/no) (Hydrocortisone or Dexamethasone for at least five consecutive days), corrected gestational age on day 1 of the first course of postnatal steroids (weeks), number of courses of postnatal steroids, administration of Frusemide or Spironolactone or Potassium Canreonate or Chlorthiazide for at least 7 consecutive days (yes/no), maternal age (years), surgical NEC (yes/no), milk at discharge (none/breast/term formula/preterm formula/other), duration of parenteral nutrition (days), Apgar score at 5 minutes, level of admitting unit at birth (1, 2 or 3), discharged home from the tertiary unit of care (yes/no), intraventricular haemorrhage grade 3 and above (yes/no), treatment for retinopathy of prematurity (yes/no), PDA ligation (yes/no), and Network of care at birth.

Data management and statistical analysis

The variables will be tested for normality using histogram inspection and Kolmogorov-Smirnoff tests. The relation of normally distributed variables will be tested with the Pearson correlation coefficient and of non-normally distributed variables with the non-parametric correlation analysis. The difference in the difference in z-scores between birth and discharge between infants that survived to discharge and infants that did not will be assessed with the Student's t-test if normally distributed or the Mann-Whitney test if non-normally distributed. Confounders will be compared between infants that survived to discharge and infants that did not. If the confounding variables are different between the two groups a binary regression analysis will be undertaken with survival to discharge as the outcome variable and the variables that have been identified to differ between the two groups as potential predictor variables. Non-normally distributed variables will be logarithmically transformed for the purposes of the binary regression analysis.

Statistical analyses will be performed using SPSS software (SPSS Inc, Chicago, Illinois, USA).

Quality assurances

The database will be held in a password protected computers and on encrypted devices.

Expected outcomes of the study

We anticipate proving at a population level the relation of impaired nutrition to respiratory morbidity. This will raise the awareness of appropriate and adequate nutritional support in extremely premature infants with respiratory disease. We could further identify subpopulations of infants in whom the interrelation of malnutrition and respiratory morbidity has augmented detrimental effects such as infants that are born small or growth retarded.

Dissemination of Results and Publication Policy

We intend to report and disseminate the results of our study via internal report, conference presentation and publication in peer reviewed scientific journals.

Duration of the project

The project will last for 12 months and during this time the data will be reviewed and analysed.

Ethics

We anticipate that ethical concerns will not arise in the context of this study as there is no active intervention and we will only be recording retrospective information which forms part of standard clinical care.

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