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Prolonged ventilation and postnatal growth of preterm infants

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ABSTRACT

Background: Extremely premature infants often need invasive respiratory support from birth, but have low nutritional reserves and high metabolic demands. Our aim was to determine if there was a relationship between prolonged ventilation and reduced postnatal growth in such infants.

Methods: A retrospective, observational study was undertaken. Data from infants born at less than 28 weeks of gestational age and ventilated for seven days or more were analysed including gestational age, gender, birth and discharge weight, birth and discharge head circumference, days of invasive mechanical ventilation and use of postnatal corticosteroids were collected. The duration of invasive mechanical ventilation and the differences in weight (ΔWz) and head circumference (ΔHz) z-score from birth to discharge were calculated.

Results: Fifty-five infants were studied with a median (IQR) gestational age at birth of 25.3 (24.3-26.7) weeks and birth weight of 0.73 (0.65-0.87) kg. The median duration of mechanical ventilation was 45(33-68) days. Both ΔWz and ΔHz were significantly negatively correlated to the number of invasive mechanical ventilation days (p=0.01 and p=0.03 respectively), but not to the use of postnatal corticosteroids.

Conclusions: Poor postnatal growth is significantly negatively associated with a longer duration of mechanical ventilation in extremely prematurely born infants.

Key words: Growth, preterm, mechanical ventilation, nutrition

LIST OF ABBREVIATIONS

ΔWz	Weight z-score
ΔHz	Head circumference z-score
BPD	Bronchopulmonary dysplasia
FiO_2	Fraction of inspired oxygen concentration
HFOV	High frequency oscillation
NEC	Necrotizing enterocolitis
PIP	Peak inflating pressure

INTRODUCTION

Extremely premature infants often need invasive respiratory support from birth, but have low nutritional reserves and high metabolic demands that can make optimising their nutritional status challenging. Under-malnutrition can detrimentally affect outcomes. A study of newborn rats demonstrated that body growth, lung growth and lung DNA levels were significantly reduced by both undernutrition and hyperoxia [1]. Malnutrition can delay the development of new alveoli and also have a detrimental effect on diaphragmatic and intercostal muscle strength, hence, in animal studies prolonging the need for mechanical ventilation [2]. Poor nutritional status is also implicated in bronchopulmonary dysplasia (BPD) development [3] and can lead to loss of neuronal cells [4] and suboptimal nutrition during the sensitive stages in early brain development may have long-term effects on cognitive function [5]. Poor head growth during neonatal admission in preterm infants has been strongly associated with adverse neurodevelopmental outcomes and correlated with subsequent poor cognition, particularly if the inadequate growth persists post discharge [6]. A higher rate of head circumference growth from birth to discharge has been associated with a lower incidence of cerebral palsy and neurodevelopmental impairment [7]. Furthermore, head circumference growth from birth to discharge has been shown to be a predictor of neurodevelopmental outcome and gross motor development at five years of age [8].

It is, therefore, important to determine which modifiable factors in extremely preterm infants affect body weight and head circumference growth. Very low birth weight infants with severe BPD have been demonstrated to have insufficient

weight gain. Infants with BPD are frequently tachypnoeic due to a reduced lung compliance [9], which would increase their energy expenditure [10]. The binary outcome of BPD, however, often fails to capture the whole spectrum of on-going respiratory morbidity. Indeed, preterm infants can suffer chronic respiratory morbidity independent of a diagnosis of BPD [11]. Although clinicians anecdotally appreciate that prolonged ventilation is associated with impaired growth, this relationship has rarely been studied. In one study, there was a significant correlation between the duration of mechanical ventilation, poor head growth and adverse neurodevelopmental outcomes that persisted at two years of age [6].

We hypothesised that quantified growth indices, defined as the difference in both weight and head circumference z-scores from birth to discharge, would be negatively associated with respiratory disease severity as assessed by the duration of invasive ventilation. The aim of this study was to test that hypothesis as such data would further encourage practitioners to develop efficacious management strategies to achieve successful early extubation.

METHODS

The records of ventilated infants born at less than 28 weeks of gestation between 1/1/2012 and 1/12/2016 and solely cared for at a tertiary Neonatal Intensive Care Unit were reviewed. Infants who were ventilated for less than seven days and those who died before discharge home were excluded from the analysis. We excluded infants who were ventilated for less than seven days in order to assess postnatal growth in the most at risk group of infants, as a requirement for mechanical ventilation after one week of age has been shown to be a predictor of

the development and severity of BPD [12]. The study was registered as a service evaluation with the Clinical Governance Department. The Health Research Authority Toolkit of the National Health System, United Kingdom confirmed that the study would not be considered as research and would not need regulatory approval by a research ethics committee.

According to the unit's routine policies, preterm infants born at less than twenty-eight weeks of gestation with respiratory distress, who failed to stabilise with continuous positive airway pressure via facemask, were intubated and given surfactant in the delivery suite [13]. Further doses of surfactant were given on the neonatal unit according to clinical need i.e. a fraction of inspired oxygen concentration (FiO_2) >0.3 despite adequate ventilatory pressures. Infants in the delivery suite were started on a peak inflating pressure (PIP) of 20-25cm H_2O and an FiO_2 of 0.21-0.3 [14] which were altered according to chest wall rise and to keep oxygen saturation levels between 90% and 94%. Infants subsequently received volume-targeted or pressure-controlled time-cycled ventilation using either the SLE5000 or SLE6000 neonatal ventilators (SLE, Croydon, UK). High frequency oscillation (HFOV) was considered on the neonatal unit in infants with homogeneous lung disease and severe respiratory distress. Extubation on the neonatal unit was considered if the FiO_2 was less than 0.4 and the infant had acceptable blood gases (pH >7.25 and $PaCO_2$ <8.5kPa) (conversion factor to mmHg is 7.5) and an adequate respiratory drive with a breathing rate above the set ventilator rate. All infants received a loading dose and subsequent maintenance doses of caffeine citrate. As per Trust guidelines, infants born less than 34 weeks of gestation were prescribed a loading dose (20 mg/kg) of intravenous caffeine

citrate before day three after birth. Twenty-four hours after the loading dose, a daily maintenance dose (5 mg/kg) was administered until 34 weeks postmenstrual age.

Parenteral nutrition was prescribed within the first 24 hours post-delivery as per the unit's guidelines. Infants were initially prescribed bags of standard parenteral nutrition, which contained both aqueous parenteral nutrition and lipid with the addition of electrolytes and trace elements as determined by laboratory results. Individualised bags of parenteral nutrition were prescribed as needed. Nutritional decisions were made daily during consultant-led ward rounds and reviewed weekly during the nutrition ward round, (comprising of a consultant neonatologist with a specialist interest in nutrition, a gastroenterologist, a senior dietician and a senior pharmacist), with regular monitoring of the infant's biochemical and anthropometric status. Generally, an infant born at less than 28 weeks of gestation was commenced on parenteral nutrition on day one after birth and received an average daily energy intake of between 110-135kcal/kg as per the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines [15]. Infants were commenced on two hourly trophic feeds on day one at 10-20mls/kg/day with advancement if tolerated by 10mls/kg/day twice daily every 24 hours as one to two hourly feeds until a total of 180mls/kg/day enteral feeds were reached. Our practice was to achieve an intake of at least 130 kcal/kg/day with either fortified breast milk or preterm formula in keeping with current consensus guidelines for protein, carbohydrate and fat intake. The choice of milk feeds for preterm infants was maternal expressed breast milk if available or, if not available, donor expressed breast milk for infants at risk of necrotizing

enterocolitis (NEC). The decision to continue donor expressed breast milk beyond seven to ten days was made on a case-by-case basis. Infants at low risk of NEC were gradually changed on to a preterm formula. For very low birth weight infants solely fed on maternal expressed breast milk, once 180-200mls/kg/d had been reached the addition of breast milk fortifier was routinely added (if tolerated).

Data on administration of antenatal corticosteroids, gender, gestational age at birth, birth weight, duration of invasive mechanical ventilation, days of non-invasive ventilation post extubation, development of BPD and weight and age at discharge, were collected. BPD was defined as the need for supplemental oxygen therapy for a least 28 days [16]. Data were also collected on postnatal corticosteroid administration. Dexamethasone was given if infants could not be weaned from mechanical ventilation [17]. A nine-day course was started at a dose of 0.25mg/kg twice daily for the first three days; the dose was then weaned to 0.15mg/kg twice daily for the next three days and then further weaned to 0.05mg/kg twice daily for the last three days. If there was no response to postnatal steroid treatment after the first three days the course was discontinued.

Analysis

The difference in weight z-score from birth to discharge (ΔWz) and the difference in head circumference z-score from birth to discharge (ΔHz) were calculated using the UK-WHO preterm reference chart [18] and the Microsoft Excel add-in LMSgrowth (version 2.77; www.healthforallchildren.co.uk). The Shapiro–Wilk test was used to assess if the data were normally distributed and found to be non-normally distributed. Univariate analysis was, therefore, performed to determine

if differences between groups were statistically significant, by use of Mann Whitney U test. To test the strength of any correlations, Spearman's rank correlation coefficients were calculated. Statistical analysis was performed using SPSS software (SPSS Inc., Chicago IL).

RESULTS

Two hundred and fourteen ventilated, preterm infants born at less than 28 weeks of gestation were cared for within the study period; 117 infants were transferred to another neonatal unit prior to discharge home, 17 infants were ventilated for less than seven days and 25 infants died on the neonatal unit, these 159 infants were excluded from analysis.

All 55 infants (28 male) who fulfilled the eligibility for the study were included in the analysis; they had a median gestational age at birth of 25.3 (range 24.3-26.7) weeks (Table 1). Twenty-nine infants (52.7%) received a full course of antenatal steroids; only six (10.9%) received no antenatal steroids. All infants included in the study developed BPD, with 31 (56.4%) being discharged on supplementary oxygen. Their median duration of mechanical ventilation was 45 (33-68) days and median duration of subsequent non-invasive ventilation was 39 (28-65) days. Twenty-eight infants (50.9%) received at least one course of postnatal steroids with ten receiving more than one course administered at a median postmenstrual age of 30.7 (IQR 29.7 to 33.3) weeks. Infants receiving postnatal steroids were ventilated for significantly longer than those infants who did not receive postnatal steroids ($p=0.017$). The median birth weight z-score of the 55 infants was -0.57 (-1.24 - -0.36) and head circumference z-score was -0.57 (-1.41 – 0.20). The median (IQR)

ΔWz was -1.21 (-1.79 - -0.39) and ΔHz was -0.72 (-1.42 – 0.61). Both ΔWz and ΔHz (Figure 1) were significantly negatively related to the number of ventilation days (r = -0.345, p = 0.01; r = - 0.508, p = 0.03 respectively). Univariate analysis showed that there were no statistically significant results between those who received postnatal steroids and those who did not in relation to both ΔWz and ΔHz (p=0.417, p=0.158). There were no significant correlations between days of non-invasive ventilation and either ΔWz (r = 0.156, p=0.256) or ΔHz (r = 0.069, p=0.708). Combining total days of invasive mechanical ventilation with total days of non-invasive ventilation there was still no significant correlation with ΔWz (r = -1.11, p=0.421) or ΔHz (r = -0.238, p=0.190).

DISCUSSION

We have demonstrated that the growth of extremely premature infants was significantly negatively associated with the number of days of invasive ventilation. Mechanical ventilation in preterm infants can be a stimulus for systemic inflammation and a duration of invasive mechanical ventilation greater than seven days in newborns has been positively associated with a larger postnatal systemic inflammatory response, which can subsequently lead to adverse pulmonary and neurodevelopmental outcomes [19]. Long periods of ventilation can increase circulating pro-inflammatory cytokines [19] and those cytokines have inhibitory effects on the growth hormone axis [20]. Prolonged mechanical ventilation in animal studies has resulted in a significant impairment upon diaphragmatic muscle function [21] which would increase energy requirements. Studies in adult patients exhibiting under-malnutrition have shown a reduction in neural respiratory drive and a decrease in diaphragmatic muscle mass [22]. In another study of ventilated

adults, the risk of remaining ventilated for at least three weeks was significantly greater in those patients who exhibited atrophy of the diaphragm on imaging done within the first few days following intubation [23].

It must be considered that earlier use of non-invasive ventilation might have resulted in better postnatal growth. We, however, used a standardised protocol with regard when to intubate and use invasive mechanical ventilation and when to extubate infants, which are in line with current protocols [13]. The severity of respiratory illness and hence a longer duration of mechanical ventilation, may cause difficulties in establishing oral feeding regimes which may contribute to the postnatal decline in growth velocity [24]. Nevertheless, we optimised nutritional management for preterm infants according to current consensus guidance [15, 25].

Postnatal steroids are frequently administered to infants with respiratory morbidity to enhance successful extubation from invasive mechanical ventilation. Dexamethasone is known to alter weight gain composition by decreasing the accretion of protein and increasing the laying down of fat [26]. A previous study found a short-term negative effect between postnatal steroid administration and poor growth (both weight and head circumference), but with no statistically significant long-term effects [27]. Inhaled steroids, such as budesonide, have been shown to have less short-term effects on the growth of very low birth weight infants [28]. In our study, all the infants received corticosteroids systematically, but we did not see any statistically significant difference in postnatal growth between those who did and did not receive corticosteroids. This lack of difference

may be explained by the nature of our study population, that is we only included very immature, ventilated infants.

Our study has strengths and some limitations. It is the first to describe the association between duration of invasive ventilation and postnatal growth in extremely preterm infants routinely exposed to antenatal steroids and postnatal surfactant. We used standardised weight and head circumferences [29]. It is a retrospective review, but we present data on all eligible infants and only included infants who had their entire “neonatal” admission in our institution thus ensuring reliable data.

In conclusion, we have demonstrated that there is a significantly negative association between prolonged ventilation and postnatal growth in extremely prematurely born infants. This may be explained by the increased respiratory load of affected patients and emphasises the need for further research to optimise nutrition in such infants.

REFERENCES

1. Frank L, Groseclose E. Oxygen toxicity in newborn rats: the adverse effects of undernutrition. J Appl Physiol Respir Environ Exerc Physiol. 1982;53:1248-55.

2. Bhatia J, Parish A. Nutrition and the lung. Neonatology. 2009;95:362-7.

3. Frank L, Sosenko IR. Undernutrition as a major contributing factor in the pathogenesis of bronchopulmonary dysplasia. Am Rev Respir Dis. 1988;138:725-9.

4. Prado EL, Dewey KG. Nutrition and brain development in early life. Nutr Rev. 2014;72:267-84.

5. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. BMJ. 1998;317:1481-7.

6. Raghuram K, Yang J, Church PT, Cieslak Z, Synnes A, Mukerji A, et al. Head growth trajectory and neurodevelopmental outcomes in preterm neonates. Pediatrics. 2017;140:e20170216.

7. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics. 2006;117:1253-61.

8. Franz AR, Pohlandt F, Bode H, Mihatsch WA, Sander S, Kron M, et al. Intrauterine, early neonatal, and postdischarge growth and neurodevelopmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. Pediatrics. 2009;123:e101-9.

9. Kurzner SI, Garg M, Bautista DB, Sargent CW, Bowman CM, Keens TG. Growth failure in bronchopulmonary dysplasia: elevated metabolic rates and pulmonary mechanics. J Pediatr. 1988;112:73-80.

10. de Meer K, Westerterp KR, Houwen RH, Brouwers HA, Berger R, Okken A. Total energy expenditure in infants with bronchopulmonary dysplasia is associated with respiratory status. Eur J Pediatr. 1997;156:299-304.

11. Ciuffini F, Robertson CF, Tingay DG. How best to capture the respiratory consequences of prematurity? Eur Respir Rev. 2018;27:170178.

12. Hunt KA, Dassios T, Ali K, Greenough A. Prediction of bronchopulmonary dysplasia development. Arch Dis Child Fetal Neonatal Ed. 2018;103:F598-9.

13. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, et al. European consensus guidelines on the management of respiratory distress syndrome - 2019 Update. Neonatology. 2019;115:432-51.

14. Wylie JP AS, Tinnion R. Preterm babies. Newborn Life Support. London: Resuscitation Council UK. 2016.

15. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2010;50:85-91.

16. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med. 2001;163:1723-9.

17. Doyle LW, Ehrenkranz RA, Halliday HL. Late (> 7 days) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane Database Syst Rev. 2014;5:CD001145.

18. Wright CM, Williams AF, Elliman D, Bedford H, Birks E, Butler G, et al. Using the new UK-WHO growth charts. BMJ. 2010;340:c1140.

19. Bose CL, Laughon MM, Allred EN, O'Shea TM, Van Marter LJ, Ehrenkranz RA, et al. Systemic inflammation associated with mechanical ventilation among extremely preterm infants. Cytokine. 2013;61:315-22.

20. Cuestas E, Aguilera B, Cerutti M, Rizzotti A. Sustained neonatal inflammation is associated with poor growth in infants born very preterm during the first year of life. J Pediatr. 2019;205:91-7.

21. Anzueto A, Peters JI, Seidner SR, Cox WJ, Schroeder W, Coalson JJ. Effects of continuous bed rotation and prolonged mechanical ventilation on healthy, adult baboons. Crit Care Med. 1997;25:1560-4.

22. Rochester DF, Esau SA. Malnutrition and the respiratory system. Chest. 1984;85:411-5.

23. Goligher EC, Dres M, Fan E, Rubenfeld GD, Scales DC, Herridge MS, et al. Mechanical ventilation-induced diaphragm atrophy strongly impacts clinical outcomes. Am J Respir Crit Care Med. 2018;197:204-13.

24. Natarajan G, Johnson YR, Brozanski B, Farrow KN, Zaniletti I, Padula MA, et al. Postnatal weight gain in preterm infants with severe bronchopulmonary dysplasia. Am J Perinatol. 2014;31:223-30.

25. Kumar RK, Singhal A, Vaidya U, Banerjee S, Anwar F, Rao S. Optimizing nutrition in preterm low birth weight infants-consensus summary. Front Nutr. 2017;4:20.

26. Leitch CA, Ahlrichs J, Karn C, Denne SC. Energy expenditure and energy intake during dexamethasone therapy for chronic lung disease. Pediatr Res. 1999;46:109-13.

27. Papile LA, Tyson JE, Stoll BJ, Wright LL, Donovan EF, Bauer CR, et al. A multicenter trial of two dexamethasone regimens in ventilator-dependent premature infants. N Engl J Med. 1998;338:1112-8.

28. Nicholl RM, Greenough A, King M, Cheeseman P, Gamsu HR. Growth effects of systemic versus inhaled steroids in chronic lung disease. Arch Dis Child Fetal Neonatal Ed. 2002;87:F59-61.

29. Villar J, Giuliani F, Fenton TR, Ohuma EO, Ismail LC, Kennedy SH. INTERGROWTH-21st very preterm size at birth reference charts. Lancet. 2016;387:844-5.

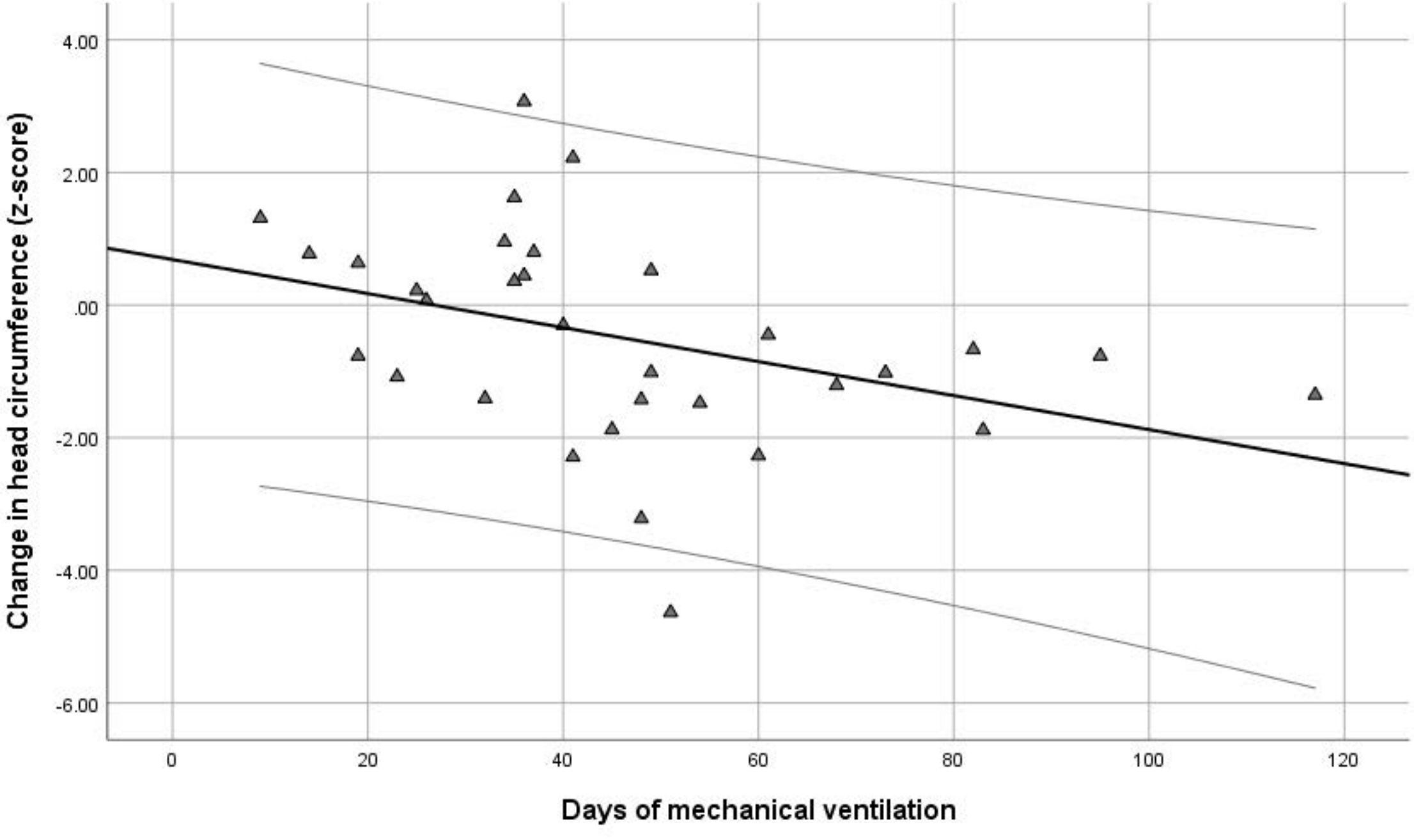
Table 1: Antenatal and postnatal demographics

Data are shown as median (IQR) or n (%)

Gestational age (weeks)	25.3 (24.3 – 26.7)
At least one dose of antenatal steroids	49 (89.1)
Male gender	28 (50.9)
Birth weight (kg)	0.73 (0.65 – 0.88)
Birth weight z-score	-0.57 (-1.24 - -0.36)
Small for gestational age	13 (23.6)
Birth head circumference (cm)	23.5 (22.5 – 24.5)
Birth head circumference z-score	-0.57 (-1.41 – 0.20)
Postnatal surfactant	54 (98.2)
Postnatal steroids	28 (50.9)
Total days of mechanical ventilation	45 (33 – 68)
Total days of non-invasive ventilation	39 (28 – 65)
Total days of parenteral nutrition	35 (22 – 48)
Discharge weight (kg)	3.17 (2.62 – 4.04)
Discharge head circumference (cm)	35.1 (33.5 – 37.2)
Discharge head circumference z-score	-0.91 (-1.88 – 0.12)

FIGURE LEGEND

Figure 1. The relationship between head circumference z-score from birth to discharge and days of invasive mechanical ventilation [y=0.69-0.03x (p=0.03)].


Change in head circumference (z-score)
4.00
2.00
.00
-2.00
-4.00
-6.00
0
20
40
60
80
100
120
Days of mechanical ventilation