

Protocol

Title: Outcomes of early versus late commencement of parenteral nutrition in very preterm infants.

Principal Investigator: Sabita Uthaya

Co-investigators: Nicholas Longford, Cheryl Battersby, Neena Modi

Background: Recent evidence from high quality randomised controlled trials in critically ill adults and children, including term babies, showed that commencing parenteral nutrition (PN) on day 1 compared to a delayed start resulted in increased late-onset sepsis, length of mechanical ventilation and hospital stay (1-3). There was also evidence of poorer neurodevelopmental outcome at age 2 years in the early group (4). A study (5) by our own group using data from the National Neonatal Research Database (NNRD) comparing outcomes in moderately preterm infants who received PN versus no PN in the first postnatal week, shows higher rates of sepsis, BPD and NEC (submitted). Very preterm babies are among the heaviest users of PN of all NHS patient groups. Although early commencement of PN is a standard of care, the impact of this practice on outcomes has not been investigated.

Aim: To explore the impact on outcomes of the timing of commencement after birth of PN in very preterm babies (born < 31 weeks of gestational age).

Research question: In babies born < 31 weeks of gestation (Population), does commencing PN after the second postnatal day (Intervention) compared to in the first two days after birth (Comparator) result in increased survival to discharge from neonatal care (Primary Outcome).

Inclusion criteria: Babies born < 31 weeks of gestation (up to 30⁺⁶ weeks) who were admitted to and received all their neonatal care in neonatal units in England and Wales between 1 Jan 2008 and 31 December 2019.

Exclusion criteria: Babies receiving care in units who choose to opt out of this study. Babies with life-threatening conditions, congenital gastro-intestinal malformations or those requiring surgery in the neonatal period. Babies with missing key information including demographic variables such as gestational age, birth weight or data for the intervention or primary outcome will be excluded.

Primary outcome: Survival to discharge from neonatal care.

Secondary outcomes: Late onset-sepsis, bronchopulmonary dysplasia, necrotising enterocolitis, retinopathy of prematurity, brain injury, growth and survival to neonatal unit discharge without major morbidity; 2-year neurodevelopment

Design: Observational study using propensity matched comparison of outcomes in babies who commenced PN in the first two postnatal days and those who commenced PN after the second postnatal day. Infants will be matched on gestational age at birth (in bands, 22-24 weeks, 25-26 weeks, 27-28 weeks and 29-30 weeks), weight standard deviation score bands and propensity score. The propensity model will include maternal factors, infant factors at birth, infant factors occurring on the first day of birth (preceding the decision to administer PN) and organisational factors.

Sample size: Around 6000 babies are born < 31 weeks each year in the England and Wales. Since 2012, all units in England and Wales have contributed data. Assuming a 30% contribution between 2008 and 2012 we estimate there are records of 50,000 babies in the NNRD that fit the inclusion criteria. Pilot data from the NNRD suggests that 50%, 30%, 20% and 15% of infants born at 30, 29, 27-28, 22- 26 weeks gestation respectively, receive PN after the first two postnatal days. Assuming a conservative value of 30% in the late group we anticipate n=15,000 in the late and n=35,000 in the early group. Hence, assuming 15,000 matched pairs, this will allow detection of a difference in mortality of 1.5% between the groups with 96% power and a two-sided significance of 5%.

References

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