Nutritional management in newborn babies receiving therapeutic hypothermia: two retrospective observational studies using propensity score matching

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Scientific summary

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Background

Therapeutic hypothermia is standard of care for babies born at ≥ 36 gestational weeks with hypoxic–ischaemic encephalopathy in high-income settings. There is limited evidence to inform provision of nutrition during therapeutic hypothermia, and nutritional practice varies widely.

Nutritional management has two main components: (1) enteral nutrition in the form of milk feeds and (2) parenteral (intravenous) nutrition. We sought to identify optimal nutritional strategies for term and near-term infants receiving therapeutic hypothermia. We examined the enteral and parenteral components independently.

Objectives

The primary objective of the enteral feeding analysis was to assess the association between milk feeding during therapeutic hypothermia and the incidence of necrotising enterocolitis.

The primary objective of the parenteral nutrition analysis was to assess the association between administering parenteral nutrition during therapeutic hypothermia and the incidence of bloodstream infection after the first 3 days.

The following secondary outcomes were also evaluated: survival at discharge from the neonatal unit, length of neonatal stay, hypoglycaemia, time to first feed with maternal breast milk, onset of breastfeeding, breastfeeding at discharge, number of days with a central line in situ and weight at neonatal discharge. The number of days parenteral nutrition was administered was examined only for the enteral comparison.

Methods

This was a retrospective, population-based cohort study using data held in the National Neonatal Research Database and applying propensity score methodology to form matched groups for analysis.

Data source

The National Neonatal Research Database holds de-identified routinely recorded clinical data from all infants admitted to NHS neonatal units in England, Scotland and Wales. A defined data extract (i.e. the Neonatal Data Set) of approximately 450 data items is extracted quarterly from neonatal electronic health records that have been completed by health professionals during routine clinical care. A patient-level data set was extracted from the National Neonatal Research Database for this analysis. Data linkage with other databases was not performed for this study.

Participants

We included babies born and admitted to NHS neonatal units in England, Scotland or Wales between 1 January 2010 and 31 December 2017 with a gestational age of $\geq 36^{+0}$ weeks$^{+\text{days}}$ at birth and who received therapeutic hypothermia for at least 3 days or died during therapeutic hypothermia.

Comparator groups

We undertook two comparisons in matched groups:

1. enteral feeding analysis [babies who were enterally fed during therapeutic hypothermia (intervention) compared with babies who received no enteral feeds during therapeutic hypothermia (control)]
2. parenteral nutrition analysis [babies who were receiving parenteral nutrition during therapeutic hypothermia (intervention) compared with babies who received no parenteral nutrition during therapeutic hypothermia (control)].

Outcomes

The primary outcome for the enteral feeding analysis was severe necrotising enterocolitis confirmed at surgery or causing death and validated with neonatal units. The primary outcome for the parenteral nutrition analysis was late-onset bloodstream infection confirmed by pure growth of a known pathogen.

Secondary outcomes were necrotising enterocolitis using a pragmatic definition (i.e. a record of necrotising enterocolitis with 5 consecutive days of antibiotics while nil by mouth), late-onset infection using a pragmatic definition (i.e. 5 consecutive days of antibiotics commenced after day 3), survival at neonatal discharge, length of neonatal stay, breastfeeding at discharge, hypoglycaemia during neonatal unit stay, onset of breastfeeding, time to first maternal breast milk feed, number of days with a central line in situ, duration of parenteral nutrition, time taken to reach full enteral feeds and weight for gestation standard deviation score at neonatal discharge.

Background variables used for matching

The following background variables were used to form matched groups for the enteral feeding and parenteral nutrition comparisons: birth year, umbilical arterial pH, birthweight, gestational age, sex, resuscitation factors, mode of delivery, maternal factors (i.e. smoking, suspected chorioamnionitis, medical and obstetric conditions), Apgar score at 1 and 5 minutes, umbilical cord blood base excess, condition at first neonatal unit admission (i.e. oxygen saturation, blood glucose concentration and mean blood pressure), maximum support needed on day 1 (i.e. respiratory, inotropic and transfusion of blood products), maternal socioeconomic decile and postnatal transfer within 24 hours.

Statistical methods

Analyses applied the potential outcomes framework and propensity score methodology. We performed 1 : 1 matching of babies who had no enteral feeds to those who were enterally fed for the enteral nutrition analysis, and of babies who received no parenteral nutrition to those who received parenteral nutrition for the parenteral nutrition analysis. Background groups were first defined using birth year (four 2-year bands) and arterial umbilical cord pH (three categories), giving 12 groups in total. Matched pairs were then formed within propensity score deciles defined separately for each background group. The matched pairs were then reconstituted as an intervention group (i.e. babies who received enteral feeds or parenteral nutrition) and a control group (i.e. babies who did not receive enteral feeds or parenteral nutrition). Their outcomes were compared using methods appropriate if the two matched groups arose in a randomised controlled trial. We undertook prespecified sensitivity analyses limited to babies born in 2012–17, when the geographical coverage was more complete, and using alternative definitions of enteral feeds or parenteral nutrition. We undertook post hoc sensitivity analyses when

parenteral nutrition or enteral feeds on day 1 were included within the propensity model for the enteral feeding and parenteral nutrition analyses, respectively.

Parent and patient involvement

The study was planned and designed by a multiprofessional investigator group that included a parent of a baby who had received therapeutic hypothermia and a parent representative. Study outcomes were chosen to reflect those prioritised as important by parents, patients and professionals, and were informed by parents and parent representatives.

Results

Between 1 January 2010 and 31 December 2017, a total of 703,911 babies were admitted to NHS neonatal units in England, Scotland and Wales, and 6030 were at ≥ 36 weeks' gestational age and treated with therapeutic hypothermia for 3 days or died during treatment. Of these babies, 31.1% received enteral feeds and 24.5% received parenteral nutrition during therapeutic hypothermia. These proportions changed only slightly over time. When enteral feeds were given during therapeutic hypothermia these were most commonly maternal breast milk.

In the total study cohort and prior to matching, seven babies (0.1%) who received therapeutic hypothermia were diagnosed with severe necrotising enterocolitis and 68 babies (1.1%) were classified as having necrotising enterocolitis when using the more pragmatic definition. Thirty babies (0.5%) had a pure growth of a recognised pathogen in a blood culture after day 3. Pragmatically defined late-onset infection was more common, with 1559 cases (25.5%). Breastfeeding at discharge was recorded for 2784 babies (46.2%) and the proportion increased over the study period. Among babies who did suckle at the breast, the first breastfeed was at a median age of 7 days (interquartile range 6–9 days), and among babies who were fed maternal breast milk the median age at first receipt of maternal breast milk was 5 days (interquartile range 4–6 days). Survival to discharge rates were high ($n = 5444$, 90.3%). The median length of stay in the neonatal unit was 11 days (interquartile range 8–16 days). Most babies ($n = 5640$, 93.6%) had a central line placed in situ for a median duration of 5 days (interquartile range 3–6 days). A total of 1208 babies (20.0%) had an episode of hypoglycaemia recorded during their neonatal stay.

For the primary enteral feeding analysis, a matched cohort of 3236 babies (1618 pairs) was formed and good balance was achieved for all recorded background variables. The incidence of severe necrotising enterocolitis was so low that comparative analyses were not undertaken. Following matching, the incidence of pragmatically defined necrotising enterocolitis was lower among babies fed ($n = 9$, 0.5%) than among those not fed ($n = 18$, 1.1%) during therapeutic hypothermia (rate difference −0.5%, 95% confidence interval −1.0% to 0.1%; $p = 0.03$). The rate of culture-positive late-onset infection was similar for babies fed ($n < 5$, 0.3%) and those not fed ($n = 8$, 0.5%) (rate difference −0.2%, 95% confidence interval −0.5% to 0.1%; $p = 0.19$). However, pragmatically defined late-onset infection was less common in babies who were fed ($n = 271$, 16.8%) than in babies who were not fed ($n = 460$, 28.4%) (rate difference −11.6%, 95% confidence interval −14.0% to −9.3%; $p < 0.001$). Survival to discharge rates were higher in babies who were fed ($n = 1552$, 96.0%) than in babies who were not fed ($n = 1465$, 90.6%) (rate difference 5.2%, 95% confidence interval 3.9% to 6.6%; $p < 0.001$), as was rates of breastfeeding at discharge [babies who were fed ($n = 883$), 54.6%; babies who were not fed ($n = 752$), 46.5%; rate difference 8.0%, 95% confidence interval 5.1% to 10.8%; $p < 0.001$]. The incidence of recorded hypoglycaemia was similar in babies fed ($n = 269$, 16.6%) and babies not fed ($n = 293$, 18.1%) (rate difference −1.5%, 95% confidence interval −3.7% to 0.6%; $p = 0.17$). The weight for gestation standard deviation score at neonatal unit discharge was also similar (babies fed −0.7 vs. babies not fed −0.6, difference 0.06, 95% confidence interval −0.01 to 0.13).

The first breastfeed was earlier, on average, for babies who were fed during therapeutic hypothermia (mean 7.3 days) than for those babies not fed (mean 8.7 days) (difference −1.4 days, 95% confidence interval −1.9 to −0.9 days; $p < 0.001$), and the first breast milk feed was earlier in babies fed (mean 3.3 days) than in those babies not fed (mean 5.4 days) (difference −2.1 days, 95% confidence interval −2.2 to −2.0 days; $p < 0.001$). The length of neonatal unit stay was shorter for babies who were fed (mean 12.7 days) than for those babies who were not fed (mean 14.8 days) (difference −2.2 days, 95% confidence interval −3.0 to −1.2 days; $p < 0.001$), as was duration of parenteral nutrition (babies fed mean 3.0 days vs. babies not fed mean 3.7 days, difference −0.7 days, 95% confidence interval −1.1 to −0.2 days; $p = 0.02$) and number of days with a central line in situ (babies fed mean 4.3 days vs. babies not fed 5.5 days, difference −1.2 days, 95% confidence interval −1.5 to −0.9 days). These findings were robust to sensitivity analyses.

For the parenteral nutrition analysis, matched cohorts consisting of 2480 babies (i.e. 1240 pairs) were formed. The two matched groups were well balanced on all of the observed background variables. Following matching, the rate of culture-positive late-onset infection was higher for babies who received parenteral nutrition ($n = 11$, 0.9%) than for those who did not ($n < 5$) (rate difference 0.6%, 95% confidence interval 0.1% to 1.2%; $p = 0.03$); however, pragmatically defined late-onset infection was seen at similar rates among those babies who received parenteral nutrition ($n = 323$, 26.1%) and those babies who received no parenteral nutrition ($n = 313$, 25.3%) (rate difference 0.8%, 95% confidence interval −2.1% to 3.6%; $p = 0.61$). The incidence of severe necrotising enterocolitis was low and comparative analyses were not undertaken for this outcome. The incidence of pragmatically defined necrotising enterocolitis was similar for babies who received parenteral nutrition (11 babies, 1.1%) and for those who did not (17 babies, 1.4%) (rate difference −0.3%, 95% confidence interval −1.0% to 0.4%; $p = 0.39$). Survival to discharge rates were higher for babies who received parenteral nutrition ($n = 1154$, 93.1%) than for those babies who did not ($n = 1116$, 90.0%) (rate difference 3.1%, 95% confidence interval 1.5% to 4.7%; $p < 0.001$). The rates of breastfeeding at discharge [parenteral nutrition, $n = 575$ (46.4%), vs. no parenteral nutrition, $n = 582$ (47.0%); rate difference −0.6%, 95% confidence interval −3.8% to 2.6%; $p = 0.71$] and recorded hypoglycaemia [parenteral nutrition, $n = 212$ (17.1%), vs. no parenteral nutrition, $n = 235$ (18.9%), rate difference −2.1%, 95% confidence interval −4.5% to 0.4%; $p = 0.10$] were similar in the two groups, as was weight for gestation standard deviation score at neonatal unit discharge (parenteral nutrition −0.6 vs. no parenteral nutrition −0.7, difference 0.02, 95% confidence interval −0.07 to 0.10; $p = 0.68$). The first breastfeed was at a similar age in babies who received parenteral nutrition (mean 8.6 days) and in those babies who did not (mean 8.4 days) (difference 0.2 days, 95% confidence interval −0.5 to 0.8 days; $p = 0.56$). In addition, age at first milk feed was similar in babies who received parenteral nutrition (mean 4.6 days) and in those babies who did not (mean 4.9 days) (difference −0.2 days, 95% confidence interval −0.4 to −0.1; $p = 0.01$). The length of neonatal unit stay was also similar for babies who received parenteral nutrition (mean 15.0 days) and for those babies who did not (mean 14.1 days) (difference 0.8 days, 95% confidence interval −0.2 to 1.8 days; $p = 0.12$). The duration of time that a baby had a central line in situ was higher in babies who received parenteral nutrition (6.0 days) than in those babies who did not (5.1 days) (difference 0.9 days, 95% confidence interval 0.5 to 1.2 days; $p < 0.001$). These findings were robust to sensitivity analyses.

Conclusions

Approximately one in three babies who receive therapeutic hypothermia in NHS neonatal units have enteral feeds introduced during hypothermia, predominantly with maternal breast milk. Necrotising enterocolitis is rare in these babies. After matching for an extensive list of background characteristics, pragmatically defined necrotising enterocolitis was diagnosed at a lower rate among babies for whom feeds were introduced during therapeutic hypothermia. Introduction of milk feeding during therapeutic hypothermia was also associated with beneficial outcomes, including shorter lengths of stay, higher rates of breastfeeding and a lower incidence of suspected infection, after matching for multiple

potential confounding factors. This was an observational study in which matched groups were formed using propensity score methodology. The study was able to address confounding related to measured factors only. Survival to discharge rates were higher for babies who were fed than for babies who were not fed during therapeutic hypothermia. This difference is unlikely to be explained by enteral feeding and, therefore, suggests residual confounding by indication, favouring babies who received milk feeds. Despite this limitation we conclude that initiating milk feeds, preferably maternal breast milk, during therapeutic hypothermia appears safe and may be beneficial.

One in four babies who received therapeutic hypothermia in NHS neonatal units received parenteral nutrition during hypothermia. Culture-positive infection was rare in this group, but after matching for multiple background characteristics it was more common in babies who received parenteral nutrition. This accords with data from a randomised controlled trial in neonates on paediatric intensive care units, in which early provision of parenteral nutrition led to a higher incidence of infection. In contrast, we found that survival until neonatal unit discharge was higher in babies who received parenteral nutrition than in those babies who did not. This may reflect residual confounding by indication, favouring babies who received parenteral nutrition. Optimal parenteral nutritional support for babies receiving therapeutic hypothermia is unknown and could not be established in this large observational study using population-level routinely recorded neonatal clinical data.

Despite the importance of longer-term developmental outcomes in this population we were unable to examine such end points in this study because population-level neurodevelopmental follow-up data in these babies were highly incomplete.

Implications for health care

- The incremental introduction of enteral feeds in term and near-term babies during therapeutic hypothermia appears safe and may be associated with benefits including higher rates of breastfeeding at discharge and shorter lengths of stay.
- Necrotising enterocolitis is rare in term and near-term babies receiving therapeutic hypothermia and may be less common in babies who were fed during therapeutic hypothermia.

Recommendations for research (listed in priority order)

- Optimal use of parenteral nutrition for term and near-term babies receiving therapeutic hypothermia is unknown. This should be examined in a randomised controlled trial comparing early with delayed provision of parenteral nutrition, which should examine both short-term outcomes, such as late-onset infection and neonatal survival, and longer-term outcomes, such as neurodevelopment.
- Given our study findings and the rarity of important outcomes such as necrotising enterocolitis, in this cohort, future randomised controlled trials to examine enteral feeding during therapeutic hypothermia are unlikely to be warranted or feasible. The optimal speed of introduction of enteral feeds or optimal choice of milk when the mother's milk is not available are not known and may benefit from further research.
- Mechanisms to obtain population-level long-term outcome data for babies who receive neonatal care, such as data linkage and national reporting, should be prioritised.

Trial registration

This trial is registered as ISRCTN474042962.

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