Use of parenteral nutrition in the first postnatal week in England and Wales: an observational study using real-world data

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ABSTRACT
Background Parenteral nutrition (PN) is used to provide supplemental support to neonates while enteral feeding is being established. PN is a high-cost intervention with beneficial and harmful effects. Internationally, there is substantial variation in how PN is used, and there are limited contemporary data describing use across Great Britain.

Objective To describe PN use in the first postnatal week in infants born and admitted to neonatal care in England, Scotland and Wales.

Method Data describing neonates admitted to National Health Service neonatal units between 1 January 2012 and 31 December 2017, extracted from routinely recorded data held the National Neonatal Research Database (NNRD); the denominator was live births, from Office for National Statistics.

Results Over the study period 62,145 neonates were given PN in the first postnatal week (1.4% of all live births); use was higher in more preterm neonates (76% of livebirths at <28 weeks, 0.2% of term livebirths) and in neonates with lower birth weight. 15% (9181/62145) of neonates given PN in the first postnatal week were born at term. There was geographic variation in PN administration: the proportion of live births given PN within neonatal networks ranged from 1.0% (95% CIs 1.0 to 1.0) to 2.8% (95% CI 2.7 to 2.9).

Conclusions and relevance Significant variation exists in neonatal PN use; it is unlikely this reflects optimal use of an expensive intervention. Research is needed to identify which babies will benefit most and which are at risk of harm from early PN.

Trial registration number ClinicalTrials.gov: NCT03767634; registration date: 6 December 2018.

INTRODUCTION
In 1968, parenteral nutrition (PN) was used to support the metabolic needs of a term neonate with small bowel atresia.1 Following this, PN has been increasingly used to supplement the nutrition of sick or preterm neonates. The widespread use of PN has been encouraged on the basis that optimising nutrition will improve short and long-term outcomes.2 It is considered most beneficial for neonates born preterm or with lower birth weight who have fewer reserves and may accrue large nutritional deficits before enteral feeds are established.3 Despite widespread use, the impact of PN on key neonatal outcomes has not been evaluated in randomised controlled neonatal trials powered for clinically meaningful and functional end-points.

Therefore, while effects on short-term biochemical markers such as nitrogen balance are well described,4 evidence to support beneficial effects on survival and neurodevelopment are lacking.4 Conversely, PN carries well-described risks, of which the most serious and common is bloodstream infection.5 Recent evidence from large randomised controlled trials in critically unwell adults6 and children7 showed that use of PN during...
the first 7 days of admission to an intensive care unit led to worse outcomes, when compared with delayed PN administration, indicating that the harms of early PN outweigh benefits in these populations. Although there has not been a similar trial in neonatal care, subgroup analysis in the PePaNIC trial of term neonates looked after on paediatric intensive care units also showed increased rates of nosocomial infection with early PN use, suggesting that early PN use should be targeted at neonates with most potential for benefit.

Given the uncertain balance of risk and benefit for neonatal PN use, it is unsurprising that international practice is variable: some neonatal units in high-income countries provide PN to up to 70% of neonatal admissions, while others report not using PN. In the Great Britain, a 2011 report from the National Confidential Enquiry into Patient Outcome and Death found considerable variation in neonatal management in 2008 with only 24% of patients receiving PN that was considered best practice.

Following this, a national framework and National Institute for Health and Care Excellence (NICE) guidance have been developed. The most recent NICE guidance makes recommendations about prescription, administration, monitoring and recipients of PN in neonatal units; recommending all neonates born before 30+0 weeks gestation or weighing under 1250 g at birth, and any who are unable (or not expected) to establish milk feeds of ≥100 mL/kg/day by postnatal day 5, receive early PN.

We aimed to describe how PN is used in the first postnatal week, to explore how use is influenced by gestational age, birth weight, geographical region and to compare how use has changed over time in the period prior to the publication of 2020 NICE guidance.

**OBJECTIVE**

To describe the pattern of PN use in neonatal units in England, Scotland and Wales in the first 7 postnatal days.

**METHODS**

**Study design**

This study was an epidemiological description of practice: we preregistered it (Clinicaltrials.gov) and published the study protocol. We report it in line with REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines.

**Data source**

We used deidentified data held in the National Neonatal Research Database (NNRD). The NNRD holds data extracted from electronic health records completed by health professionals during routine clinical care. The Neonatal Data Set, a defined national data standard comprising approximately 450 items, is extracted and transmitted to the Neonatal Data Analysis Unit at Imperial College London. The NNRD holds data from all neonates admitted to National Health Service (NHS) neonatal units and is currently held at Imperial College London.

**Table 1** Gestational age of neonates receiving PN in the first postnatal week as a proportion of total live births

| Gestational age category | Neonates receiving PN in the first postnatal week by year of birth | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 |
|--------------------------|---------------------------------------------------------------|------|------|------|------|------|------|
| Extremely preterm        |                                                               | 2317 (72) | 2309 (75) | 2267 (77) | 2348 (78) | 2421 (76) | 2325 (75) |
| Very preterm             |                                                               | 3493 (61) | 3900 (71) | 3896 (71) | 4059 (73) | 4135 (73) | 4110 (74) |
| Moderate and late preterm|                                                               | 2343 (5.3) | 2640 (6.1) | 2796 (6.4) | 2683 (6.0) | 2547 (5.6) | 2375 (5.2) |
| Term                     |                                                               | 1370 (0.2) | 1688 (0.3) | 1618 (0.3) | 1528 (0.2) | 1484 (0.2) | 1493 (0.2) |
| Total                    |                                                               | 9523 (1.3) | 10 537 (1.5) | 10 577 (1.5) | 10 618 (1.5) | 10 587 (1.5) | 10 303 (1.5) |

Extremely preterm: <28+0 weeks, very preterm: 28+0–31+6 weeks, moderate and late preterm; 32+0–36+6 weeks, term >36+6 weeks.

Number in brackets indicates the percentage of all live births given PN in each category (Denominator data from ONS birth characteristics in England and Wales).

Neonates with missing data for gestational age=3.

*Gestational age at birth categorised using WHO definitions.

ONS, Office for National Statistics; PN, parenteral nutrition.

**Figure 1** Proportion of live births receiving PN during the first postnatal week of life from 2012 to 2017. All births included from 2012-2017. Total number of births = 4,196,314 Neonates with missing data for gestational age = 3.
units in England, Scotland and Wales; in total, the NNRD contains data from about one million neonates from 2008 to the present. Accuracy and completeness of NNRD data have been confirmed by comparison with Case Record Forms from a prospective clinical trial, which showed high data completeness and accuracy (>95%). Data for this study were extracted by author KO, operating within the guidelines established by these approvals; no other investigators had accessed the wider NNRD for this study. No data cleaning methods were required for this study, and no data linkage was required. We obtained population-level data for total live births by gestational age and birth weight from the Office for National Statistics (ONS) and for live births by neonatal network from Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK (MBRRACE-UK) reports, for denominator data. Population-level data for total neonatal unit admissions by gestational age and birth weight were obtained from the NNRD for denominator data.

**Participants**

The study population was all neonates born between 1 January 2012 and 31 December 2017 and admitted to a neonatal unit in England and Wales. There were no exclusion criteria: this was intended to maximise the sample size and ensure complete, population-level data.

**Variables**

The primary outcome was any use of PN in the first 7 postnatal days. To describe the background characteristics of neonates given PN, we extracted data relating to gestational age at birth, birth weight, year of birth and neonatal network of birth. We compared changes in PN prescribing over time by grouping neonates according to the year of birth.

**Statistical methods**

We described the characteristics of neonates that received PN in the first 7 postnatal days and compared use between different groups. For gestational age and birth weight, we grouped neonates according to well-established and widely accepted WHO categories and for denominator data. Population-level data for total neonatal unit admissions by gestational age and birth weight were obtained from the NNRD for denominator data.

**RESULTS**

The only deviation from the protocol is related to the use of data from neonatal units in Scotland. We were unable to use data on babies from Scottish neonatal units due to difficulties obtaining the institutional approvals required for Public Benefit and Privacy Panel for Health and Social Care approval. The project was completed using data from neonatal units in England and Wales only.

Over the 6-year study period, 4 196 314 neonates were born in England and Wales. Of these, 347 959 neonates were admitted to NHS neonatal units and had data...
The use of PN differed across networks, with a range from 1.0% to 2.8% of all live births given PN in the first postnatal week (table 2) (figure 2) (table 3). Rates of PN administration within neonatal networks varied less over time than the differences seen between networks.

**DISCUSSION**

In this work, we described the characteristics of neonates born in England and Wales who receive PN in the first postnatal week. PN is a common intervention on neonatal units and is given to 17% of all admissions. While PN use is higher in neonates born prematurely and with lower birth weight, a considerable proportion is born at term. We also show that use varies between different neonatal networks.

That higher rates of PN use are seen in neonates born more preterm is unsurprising, as these populations are considered most likely to benefit. The lower rates seen in the most preterm neonates (those born at <26 gestational weeks) are likely because many of these babies die before admission to a neonatal unit and before PN is commenced. However, because of the much larger proportion of babies born at more mature gestations, it is noteworthy that around 15% of all babies given PN are born at term (although this still means that only 0.2% of term births receive PN). The energy requirements,

indications for use and metabolic stability of these groups differ, thus the risks and benefits of PN may also differ substantially across gestational ages: guidelines and practice appropriate in one group may not be optimal in differing populations.

We found that PN use in the first postnatal week varied significantly between neonatal networks. This is in keeping with variations between neonatal units in PN use in other settings. However, we were unable to find another comprehensive population-based study of national PN use. From our descriptive analysis, it is not possible to determine whether the variation we identified is explained by regional differences in rates of prematurity, neonatal sickness or other case-mix factors...
Parenteral nutrition is commonly used in the first postnatal week across the Great Britain, with higher use in neonates born more preterm. Across all gestational age categories, no change in PN use in the first postnatal week over time was found, but there is persisting variation in use between regional neonatal networks. Research is needed to ensure that PN use in this group is well targeted.

CONCLUSION

Limitations of this study include the population-level coverage involving a cohort of over 4 million neonates. The population-level data meant that recruitment bias was reduced, but not fully eliminated. The NNRD covers all neonatal units in England and Wales but does not include Paediatric Intensive Care Units and surgical units that admit neonates. Some term cardiac and surgical babies will be cared for on these units and, thus, we may have underestimated the amount of PN used in these groups. We followed a prespecified protocol and data analysis plan and limited the risk of false discovery associated with multiple comparisons by using the Holm-Bonferroni method. In keeping with previous studies that have used the NNRD, we had very little missing data. Limitations of this study include that we were not able to obtain permission to use data for neonates born in Scotland, reducing the study population. As the NNRD only holds data for neonates admitted to an NHS neonatal unit for denominator data, we used data from the ONS and MBRRACE-UK to provide total numbers of live births. As MBRRACE-UK did not produce a report in 2012, this limited the number of years for which we could undertake network-level comparisons. As has been found in previous studies, due to the lack of additional information about PN in the data extracted, we are unable to describe changes in how PN was used (eg, when PN was commenced or types of PN used).

Our findings show that PN use in the first postnatal week is common in England and Wales, with regional variation. In light of the potential harm found with early PN in critically unwell children, and the lack of evidence of benefit for clinically important endpoints in infants research is needed to ensure that PN use in neonates is underpinned by a robust evidence base. Our data will help in the planning of future trials to identify which neonates will benefit from early PN and ensure that clinical practice is based on strong evidence. Approximately, 28 neonates are started on PN each day in England and Wales; if all of these diverse patients are to receive optimal treatment, urgent research is needed to ensure that they are the neonates who will benefit most from this intervention and to avoid harm in others.
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REFERENCES
1. Wilmore DW, Dudrick SJ. Growth and development of an infant receiving all nutrients exclusively by vein. JAMA 1968;203:860–4.
2. Ziegler EE, Thureen PJ, Carlson SJ. Aggressive nutrition of the very low birthweight infant: a systematic review and meta-analysis. Am J Clin Nutr 2013;97:816–26.
3. Zingg W, Tomaske M, Martin M. Risk of parenteral nutrition in neonates—an overview. Nutrients 2012;4:1490–503.
4. Casey MP, Mesotten D, Hernmans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506–17.
5. Fizve T, Kerklaan D, Mesotten D, et al. Early versus late parenteral nutrition in critically ill children. N Engl J Med Overseas Ed 2016;374:111–22.
6. van Puffelen E, Vanoorebeek I, Joosten KFM, et al. Early versus late parenteral nutrition in critically ill children: a randomized controlled trial. Lancet Child Adolesc Health 2018;2:505–15.
7. Christiansen RD, Henry E, Wiedmeier SE, et al. Identifying patients, on the first day of life, at high-risk of developing parenteral nutrition-associated liver disease. Journal of Perinatology 2007;27:284–90.
8. Series J, Siewielski J, Brozek J, et al. [Parenteral nutrition in neonatal units—a survey of current practices in Poland]. Med Wiedu Rozwoju 2008;12:899–904.
9. Mason DG, Puntis JWL, McCormick K, et al. Parenteral nutrition for neonates and children: a mixed bag. Arch Dis Child 2011;96:209–10.
10. British Association of Perinatal Medicine. The Provision of Parenteral Nutrition within Neonatal Services - A Framework for Practice [Guideline], 2016. Available: http://www.bapm.org.uk/publications/documents/guidelines/Parenteral%20Nutrition%20April%202016.pdf
11. Excellence; NIfHaC. Neonatal parenteral nutrition: NICE guideline NG164, 2017.
12. Webbe J, Longford N, Uthaya S, et al. Outcomes following early parenteral nutrition use in preterm neonates: protocol for an observational study. BMJ Open 2019;9:e029065.
13. Benachori EI, Sheem L, Guttman A, et al. The reporting of studies conducted using observational Routinely-collected health data (record) statement. PLoS Med 2015;12:e1001885.
14. Gale C, Morris I. The UK national neonatal research database: using neonatal data for research, quality improvement and more. Arch Dis Child Educ Pract Ed 2016;101:216–8.
15. Spencer A, Modé N. National neonatal data to support specialist care and improve infant outcomes. Arch Dis Child Fetal Neonatal Ed 2013;98:F175–80.
16. NHS Digital. National neonatal data set, 2017. Available: http://www.datadictionary.nhs.uk/data_dictionary/messages/clinical_data_sets/data_sets/national_neonatal_data_set/national_neonatal_data_set_-_episodic_and_daily care_trasp?shownaa=1
17. Battersby C, Statnikov Y, Santhakumaran S, et al. The United Kingdom national neonatal research database: a validation study. PLoS One 2018;13:e0201815.
18. Office for National Statistics. Characteristics of birth 1, England and Wales: 2012. Fareham: Vital Statistics Outputs Branch, Office for National Statistics, 2013.
19. Office for National Statistics. Characteristics of birth 1, England and Wales: 2013. Fareham: Vital Statistics Outputs Branch, Office for National Statistics, 2014.
20. Office for National Statistics. Birth characteristics in England and Wales: 2014. Fareham: Vital Statistics Outputs Branch, Office for National Statistics, 2015.
21. Office for National Statistics. Birth characteristics in England and Wales: 2015. Fareham: Vital Statistics Outputs Branch, Office for National Statistics, 2016.
22. Office for National Statistics. Birth characteristics in England and Wales: 2016. Fareham: Vital Statistics Outputs Branch, Office for National Statistics, 2017.
23. Office for National Statistics. Birth characteristics in England and Wales: 2017. Fareham: Vital Statistics Outputs Branch, Office for National Statistics, 2018.
24. Draper ES, Gallimore ID, Kurinczuk JJ. MBRRACE-UK perinatal mortality surveillance report, UK perinatal deaths for births from January to December 2016. Leicester: The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester, 2018.
25. Manktelow BN, Smith LK, Prunet C. MBRRACE-UK perinatal mortality surveillance report: UK perinatal deaths for births from January to December 2015. Leicester: The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester, 2017.
26. Manktelow BN, Smith LK, Seaton SE. MBRRACE-UK perinatal mortality surveillance report, UK perinatal deaths for births from January to December 2014. Leicester: The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester, 2016.
27. Manktelow BN, Smith LK, Evans TA. Perinatal mortality surveillance report UK perinatal deaths for births from January to December 2013. Leicester: The Infant Mortality and Morbidity Group, Department of Health Sciences, University of Leicester, 2015.
28. Gale C, Santhakumaran S, Nagarajan S, et al. Impact of managed clinical networks on NHS specialist neonatal services in England: population based study. BMJ 2012;344:e6105.
29. Morris G, Gray A, Scott J. NHS Scotland public benefit and privacy panel (PBPP) – much ado about governance 3 years on. International Population Data Linkage Conference, Banff, Canada, 2018.
30. Schanler RJ, Garza C, Nichols BL. Fortified mothers’ milk for very low birth weight infants: results of growth and nutrient balance studies. J Pediatr 1985;107:43–45.
31. Soll RF, McGuire W. Evidence-Based practice: improving the quality of perinatal care. Neonatology 2019;116:193–8.
32. Walter E, Liu FX, Maton P, et al. Cost analysis of neonatal and pediatric parental nutrition in Europe: a multi-country study. Eur J Clin Nutr 2012;66:639–44.
33. Young SS, Karr A, Deming KA. Deming, data and observational studies. Signif 2011;8:116–20.
34. Battersby C, Longford N, Mandalia S, et al. Incidence and enteral feed antecedents of severe neonatal necrotising enterocolitis across neonatal networks in England, 2012–13: a whole-population surveillance study. Lancet Gastroenterol Hepatol 2017;2:43–51.
35. Gale C, Jeyakumaran D, Longford N, et al. Administration of parenteral nutrition during therapeutic hypothermia: a population level observational study using routinely collected data held in the National neonatal research database. Arch Dis Child Fetal Neonatal Ed 2021;106:608–13.
36. Uthaya S, Longford N, Battersby C, et al. Early versus later initiation of parenteral nutrition for very preterm infants: a propensity score-matched observational study. Arch Dis Child Fetal Neonatal Ed 2022;107:137–42.
37. Webbe JW, Longford N, Battersby C, et al. Outcomes in relation to early parenteral nutrition use in preterm neonates born between 30 and 33 weeks' gestation: a propensity score matched observational study. Arch Dis Child Fetal Neonatal Ed 2022;107:131–6.
38. Simmer K, Rao SC. Early introduction of lipids to parenterally-fed preterm infants. Cochrane Database Syst Rev 2005;2:CD005256.
39. Blencowe H, Cous ens S, Chou D, et al. Born too soon: the global epidemiology of 15 million preterm births. Reprod Health 2013;10 Suppl 1;S2.
40. World Health Organization. International statistical classification of diseases and related health problems 10th revision, 2016.