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Title:

Increasing use of inhaled nitric oxide in neonatal intensive care units in England: a retrospective population study

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Abstract

Objective

To describe temporal changes in inhaled Nitric Oxide (iNO) use in English neonatal units between 2010 to 2015

Design

Retrospective analysis using data extracted from the National Neonatal Research Database (NNRD)

Setting

All National Health Service neonatal units in England

Patients

Infants of all gestational ages born 2010- 2015 admitted to a neonatal unit and received intensive care

Main outcome measures

Proportion of infants who received iNO; age at initiation and duration of iNO use

Results

4.9% (6,346/129,883) of infants received iNO; 31% (1,959/6,346) were born <29 weeks, 18% (1,152/6,346) 29-33 weeks and 51% (3,235/6,346) ≥34 weeks gestation. Between epoch 1 (2010-2011) and epoch 3 (2014-2015), there was i) an increase in the proportion of infants receiving iNO: < 29 weeks (4.9 *vs* 15.9%); 29-33 weeks (1.1 *vs* 4.8%); ≥ 34 weeks (4.5 *vs* 5.0%) ii) increase in postnatal age at iNO initiation: <29 weeks 10 *vs* 18 days; 29-33 weeks 2 *vs* 10 days iii) reduction in iNO duration: <29 weeks (3 *vs* 2 days); 29-33 weeks (2 *vs* 1 day). There were no statistically significant differences in patient characteristics.

Conclusions

Between 2010 and 2015 there was an increase in the use of iNO among infants admitted to English neonatal units. This was most notable among the most premature infants with an almost four-fold increase. Given the paucity of evidence for iNO use in preterm infants, further research is needed to better understand the long-term impact and identify infants most likely to benefit.

Introduction

Inhaled nitric oxide (iNO) is widely used in the treatment of hypoxaemic respiratory failure and persistent pulmonary hypertension of the newborn. Although a well-established therapy in term and near-term infants with these conditions, the off-label use of iNO in preterm infants <34 weeks gestation remains controversial. Population-based data indicate that there is wide variation in administration rates amongst US hospitals, but there are no equivalent data from the UK or mainland Europe (1-4). Data from individual centres and multicentre studies suggest that the use of iNO is increasing (2-5), especially in preterm infants, despite the lack of evidence of benefit in this population.

We aimed to describe temporal changes in the use of iNO in neonates admitted to neonatal units in England using national data routinely recorded during clinical care and held in the National Neonatal Research database (NNRD). Our objectives were to i) describe the proportion and characteristics of preterm and term infants who receive iNO between 2010 and 2015; ii) determine whether there is variation in iNO use across tertiary level neonatal units, and over time between 2010 and 2015.

Methods

Setting, study design, data source and ethics approval

This retrospective cohort study used routinely recorded, de-identified data held in the NNRD. The NNRD has complete coverage of infants admitted for neonatal care at a National Health Service (NHS) neonatal unit in England, Scotland and Wales. The NNRD is formed from data extracted from neonatal electronic health record systems used by health professionals during routine clinical care. A defined data extract comprising approximately 450 items (6), the Neonatal Data Set, is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London where data are cleaned and entered into the NNRD. High completeness and accuracy (>95%) of data held in the NNRD has been confirmed by a formal comparison with those recorded in Case Record Forms of a multicentre, randomised placebo-controlled trial (7). Neonatal units in England contributing data to the NNRD consented for their unit data to be included in the study. The study was approved by West of Scotland Research Ethics Committee 5; reference number 16/WS/0228.

Study population and data extraction

We included data from infants who required any neonatal intensive care (defined using British Association of Perinatal Medicine categories of care 2011 (8), primarily as needing mechanical ventilation or non-invasive ventilation plus parenteral nutrition) over a 6-year period, 01/01/2010 to 31/12/2015 in England. Infants who did not receive intensive care on a neonatal unit or who were not cared for completely in units in Wales and Scotland, were excluded from the analysis.

We extracted daily variables (receipt of iNO, surfactant), demographic variables (birthweight, sex, gestational age), maternal factors (prolonged rupture of membranes >24 hours), diagnoses and survival to neonatal unit discharge. See supplementary file 1 for diagnostic codes.

Outcomes

The primary outcome was rate of iNO use as a proportion of infants that received neonatal intensive care, and unit level.

The following secondary outcomes were analysed for infants that received iNO:
- Timing of iNO initiation (postnatal age in days)
- Duration of iNO
- Diagnoses including respiratory distress syndrome (RDS), persistent pulmonary hypertension of the newborn (PPHN), pulmonary hypoplasia, congenital pneumonia, congenital diaphragmatic hernia, congenital heart disease, meconium aspiration syndrome (among infants ≥ 34 weeks gestation)
- Survival to neonatal unit discharge

Statistical analyses

We conducted analyses for the primary outcome at two levels: 1) at the level of the population of infants that received at least 1 day of neonatal intensive care; and 2) at the level of the neonatal unit. For all outcomes separate analyses were conducted by *a-priori* defined gestational age bands: (a) extremely preterm (< 29 weeks gestation); (b) moderately preterm (29-33 weeks gestation); and (c) late preterm/term (≥ 34 weeks gestation).

Results are presented using medians (interquartile ranges) and percentages for continuous and categorical variables, respectively. We tested whether iNO use and duration changed significantly between the first epoch (2010-2011) and the third epoch (2014-2015) using either chi-squared tests or Wilcoxon rank sum test.

For the neonatal unit-level analysis, we limited this to the 47 tertiary neonatal units in England who have treated 5 or more infants with nitric oxide. For this analysis we attributed iNO use to the first unit providing iNO therapy regardless of whether an infant was treated with iNO in more than one neonatal unit. The total number of neonatal units in England during this period decreased from 169 (in 2010-11) to 161 (in 2014-15); this

reflects the merger or closure of units. Rates of iNO use across tertiary units are presented graphically without comparative testing.

Patient and Public Involvement

Results will be disseminated to parents, ex-patients and members of the public through the Imperial College Neonatal Data Analysis Unit website, social media, and strong links between the authors and parent/patient groups.

Results

During the 6-year study period 129,883 infants received at least 1 day of intensive care in England; 4.9% (6,346) of these received iNO. Use of iNO increased significantly over time from 3.4% (1,293/37,885) in 2010-2011 to 6.4% (3,112/48,838) in 2014-2015. There were no significant differences in gestational age, birth weight or sex between birth year epochs (Table 1).

When analysed by gestational age band over the entire study period, 9.9% (1,959/19,727) of infants born <29 weeks received iNO; corresponding percentages are 2.8% (1,152/41,133) for 29-33 weeks and 4.7% (3,235/69,022) for ≥ 34 weeks (Tables 1-3). Mortality among iNO treated infants decreased over time in all gestational age groups.

By gestational age bands

<29 weeks

31% (1,959/6,346) of infants that received iNO were born < 29 weeks gestation (Table 1). Among infants born in the later epoch, a lower proportion had diagnoses of prolonged rupture of membranes or pulmonary hypoplasia recorded and a higher proportion had RDS recorded and received surfactant. (Table 1). 282 had congenital heart disease; the most common were atrial or ventricular septal defects (67%) (Supplementary Table 2).

29-33 weeks

18% (1,152/6,346) of infants that received iNO were born at 29-33 weeks gestation. A lower proportion of infants born in the later epoch had PPHN recorded and a higher proportion had RDS recorded, although surfactant use was lower in the later epoch. In the 2014-2015 epoch iNO was initiated later and administered for a shorter duration (Table 2). 264 infants had congenital heart disease; 52% were atrial or ventricular septal defects (Supplementary Table 2).

≥34 weeks

51% (3,235/6,346) of infants that received iNO had a gestational age of ≥ 34 weeks at birth. The proportion of these infants who received iNO increased marginally but significantly between 2010-2011 and 2014-2015. A lower proportion of these infants born in the later epoch had prolonged rupture of membranes, PPHN or meconium aspiration syndrome, and a higher proportion had RDS recorded and received surfactant. iNO was initiated later and administered for a shorter duration (Table 3). 616 of these infants that received iNO had congenital heart disease and 41.6% (256/616) were atrial or ventricular septal defects (Supplementary Table 2).

Comparison between tertiary units

There was wide variation in the proportion of infants receiving intensive care who also received iNO between the 47 tertiary neonatal intensive care units in England across all gestation groups (figure 1A). This was especially marked among infants < 29 weeks gestation where iNO use varied between 0.7% and 36.5% (Figure 1B).
When considering unit level trends over time, iNO use in >29 week gestation infants increased between 2010-2011 and 2014-2015 in almost all units (figure 1C), however a more mixed picture was seen in less preterm infants (figure 1D).

Table 1

Patient demographics and outcomes for infants born less than 29 weeks gestation admitted to neonatal units in England

	2010-11	2012-13	2014-15	p
Neonatal admissions requiring ≥ 1 day of intensive care	6730	6587	6410	
Infants treated with iNO	329 (4.9%)	611 (9.3%)	1019 (15.9%)	p<0.01
Birth weight (g)	790 (650,950)	795 (670,985)	790 (660,985)	0.31
Gestational age (weeks)	26 (24, 27)	26 (24, 27)	26 (24, 27)	0.25
Male sex	180(55%)	364 (60%)	553 (54%)	0.89
Prolonged rupture of membranes >24 hr∞	113 (34.4%)	190 (31.1%)	173 (17.0%)	P<0.001
Surfactant therapy in labour ward or neonatal unit	324 (98.5%)	589 (96.4%)	935(91.8%)	P<0.001
Initiation of iNO therapy (day)	10 (2,33)	13 (2,46)	18 (3,48)	P<0.001
Duration of iNO therapy (days)	3 (2,5)	2 (1,4)	2 (1,4)	P<0.001
Diagnosis (not mutually exclusive)^				
Respiratory distress syndrome (RDS)*	255 (77.5%)	505 (82.7%)	920 (90.3%)	P<0.001
Pulmonary hypoplasia	30 (9.1%)	40 (6.6%)	49 (4.8%)	P<0.01
Pulmonary hypertension	100 (30.4%)	164 (26.8%)	260 (25.5%)	0.08
Congenital pneumonia	2 (0.6%)	2 (0.3%)	10 (1.0%)	0.53

Congenital diaphragmatic hernia	0	0	1 (0.1%)	0.57
Death	143 (43.5%)	224 (36.7%)	242 (23.8%)	P<0.001

The denominator for all proportions is the number of babies treated with iNO

All values given as n, % or median (25^{th},75^{th} centiles), as appropriate.

*This includes the diagnosis *Respiratory distress syndrome* and *signs of respiratory distress of newborn (see supplementary file 1)*

^Extracted codes available in supplementary file

∞ Prolonged rupture of membranes >24 hrs uses a combination of discharge diagnoses and recorded duration of rupture of membranes

Table 2
Patient demographics and outcomes for infants born 29-33 weeks' admitted to neonatal units in England

	2010-11	2012-13	2014-15	p
Neonatal admissions requiring ≥ 1 day of intensive care	12781	13796	14556	
Infants treated with iNO	144 (1.1%)	315 (2.3%)	693 (4.8%)	p<0.001
Birth weight (g)	1603 (1311,1972)	1500 (1290,1800)	1500† (1256,1800)	0.01
Gestational age (weeks)	30 (29,32)	31 (29,32)	31 (30,32)	0.76
Male sex	91 (63.2%)	187 (59.4%)	406 (58.6%)	0.31
Prolonged rupture of membranes >24 hr∞	34 (23.6%)	86 (27.3%)	124 (17.9%)	0.11
Surfactant therapy in labour ward or neonatal unit	131 (91.0%)	229 (72.7%)	418 (60.3%)	p<0.001
Initiation of iNO therapy (days)	2 (1,3)	3 (1,20)	10 (2,24)	p<0.001
Duration of iNO therapy (days)	2 (2,4)	1 (1,3)	1 (1,2)	p<0.001
Diagnosis (not mutually exclusive)^				
Respiratory distress syndrome*	92 (63.9%)	240 (76.2%)	604(87.2%)	p<0.001
Pulmonary hypoplasia	23 (16.0%)	46 (14.6%)	72 (10.4%)	0.05
Pulmonary hypertension	76 (52.8%)	108 (34.3%)	163 (23.5%)	p<0.001

Congenital pneumonia	1 (0.7%)	3 (1.0%)	2 (0.3%)	0.46
Congenital diaphragmatic hernia	7 (4.9%)	11 (3.5%)	15 (2.2%)	0.07
Death	59 (41.0%)	68 (21.6%)	76 (11.0%)	p<0.001

The denominator for all proportions is the number of babies treated with iNO

All values given as n, % or median (25^{th},75^{th} centiles) as appropriate.

*This includes the diagnosis *Respiratory distress syndrome* and *signs of respiratory distress of newborn (see supplementary file 1)*

^Extracted codes available in supplementary file

∞ Prolonged rupture of membranes >24 hrs uses a combination of discharge diagnoses and recorded duration of rupture of membranes

† 1 baby with a birthweight less than 300 grams was removed from this calculation (n=692)

Table 3

Patient demographics and outcomes for infants born ≥34 weeks' gestation admitted to neonatal units in England

	2010-11	2012-13	2014-15	p
Neonatal admissions requiring ≥ 1 day of intensive care	18374	22777	27872	
Infants treated with iNO	820 (4.5%)	1015 (4.5%)	1400 (5.0%)	p<0.01
Birth weight (g)	3273 (2840,3665)	3240 (2760,3690)	3220† (2680,3630)	0.02
Gestational age (weeks)	40 (38,41)	39 (37,40)	39 (37,40)	p<0.001
Male sex	450 (54.9%)	577 (56.9%)	756 (54.0%)	0.69
Prolonged rupture of membranes >24 hr∞	82 (10.0%)	92 (9.1%)	68(4.9%)	p<0.001
Surfactant therapy in labour ward or neonatal unit	532 (64.9%)	613 (60.4%)	713(50.9%)	p<0.001
Initiation of iNO therapy (days)	2 (1,2)	2 (1,2)	2 (1,2)	0.02
Duration of iNO therapy (days)	3 (2,5)	3 (2,5)	2 (1,5)	p<0.001
Diagnosis (not mutually exclusive)^				
*Respiratory distress syndrome**	259 (31.6%)	378 (37.2%)	778 (55.6%)	p<0.001
Pulmonary hypoplasia	61 (7.4%)	67 (6.6%)	101 (7.2%)	0.84
Meconium aspiration syndrome	314 (38.3%)	378 (37.2%)	440 (31.4%)	p<0.01
Pulmonary hypertension	598 (72.9%)	703 (69.3%)	885 (63.2%)	p<0.001
Congenital pneumonia	42 (5.1%)	52 (5.1%)	74 (5.3%)	0.87

Congenital diaphragmatic hernia	55(6.7%)	57(5.6%)	83 (5.9%)	0.46
Death	165 (20.1%)	160 (15.8%)	212 (15.1%)	p<0.01

The denominator for all proportions is the number of babies treated with iNO

All values given as n, % or median (25^{th},75^{th} centiles) as appropriate.

*This includes the diagnosis *Respiratory distress syndrome* and *signs of respiratory distress of newborn (see supplementary file 1)*

^Extracted codes available in supplementary file

∞ Prolonged rupture of membranes >24 hrs uses a combination of discharge diagnoses and recorded duration of rupture of membranes

† 1 baby with a birthweight less than 300 grams was removed from this calculation (n=1399)

Discussion

In this large population-level study we found that almost 1 in 20 infants that received any period of intensive care at an English neonatal unit were treated with iNO, that this rate almost doubled between 2010-2011 and 2014-2015 and that the temporal increase in iNO use was seen across all gestational ages. The temporal increase was most evident among more preterm infants < 34 weeks, in whom the use of iNO increased three-fold from 2.4% to 8.2% and where evidence for iNO is most lacking. In the most preterm group an additional 690 infants born <29 gestational weeks were treated with iNO in 2014-15 compared with 2010-11.

It is difficult to compare these data with internationally reported iNO usage rates because other studies commonly report rates as a proportion of all neonatal admissions, whereas we report rates as a proportion of infants receiving neonatal intensive care. We used this denominator because of differences in the organisation of neonatal care, specifically the use of a networked model of care in the United Kingdom which results in numerous transfers between neonatal units as part of routine care, and to minimise the impact of variations in practice around admissions of term infants for short periods. Rates of iNO usage in US studies are reported between 0.9% and 1.3% (2, 3) of all neonatal admissions. To our knowledge, this is one of the largest studies of iNO use in neonatal practice and the only to report data at national level; other studies have reported iNO use in a various US healthcare organisations (including children's hospitals) and in all admissions including infants receiving lower acuity categories of neonatal care (1, 4, 9, 10).

Approximately half of all infants that received iNO in this study were born at < 34 weeks gestation. This is relevant because the licensed indication for iNO limits treatment to newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension (11). This finding is, however, broadly consistent with other studies from the US and Europe which showed that 40-46% of all treated infants were <34 weeks gestation (3, 12). Treatment rates for preterm infants in this study (5.1% of preterm infants < 34 weeks gestation) were

comparable to other studies from the US reporting rates of 2.6% to 7.2% in the same gestation groups (1, 4, 9, 10), and in this comparison the different denominator in US studies is less likely to influence results as the majority of more preterm infants will receive intensive care.

We find that not only is off-label treatment with iNO of preterm infants < 34 weeks gestation widespread, it is increasing – particularly in the most preterm infants. The evidence base supporting routine use in these most preterm infants, both in respect of safety and efficacy, is weakest (2-4). The reason for increasing use of iNO off-label in preterm infants is not known but is likely to be multifaceted and reflect the absence of other proven 'rescue' cardiorespiratory interventions for infants with severe hypoxaemic respiratory failure (such as ECMO) in this population, growing experience in the use of iNO, the absence of evidence of short-term harm, and that off-label use of iNO is fully reimbursed in England. Furthermore there is some limited evidence for the use of iNO in specific groups of preterm infants including those born following preterm prolonged rupture of membranes and those with echocardiographic criteria of PPHN physiology, supported by expert opinion and consensus statements (13-15). Treatment with iNO was started later and duration of treatment was shorter in later epochs, suggesting that preterm infants were more commonly treated outside the acute respiratory phase. Although there is little evidence of efficacy of iNO as rescue therapy in acute respiratory failure or later ventilator-dependent chronic lung disease (16, 17), we speculate that clinicians might be increasingly willing to use off-label iNO in such circumstances.

This study also demonstrates large variation between English neonatal units in rates of iNO use, in keeping with that reported in recent US studies (1, 10) where a similar degree of variation from 0.4% to 21.9% was seen in iNO use in preterm infants between 13 NICHD neonatal research network centres. The variation between neonatal units in the US decreased following publication of national guidance (18). Such national guidance is not available for the UK but might help to standardise practice in this area if it were to be developed.

Overall mortality decreased in iNO-treated infants during the study period. This trend mirrors national data reporting improved survival in extremely preterm infants in England (19) over a similar timeframe. The lower mortality seen in later epochs may also reflect a change in case-mix as iNO therapy is offered more readily to infants with less severe cardiorespiratory failure. This type of 'therapeutic creep' has been described with other neonatal interventions (20). This study was not designed to analyse changes in outcomes beyond simple descriptive data.

The strengths of this study include the use of a large national dataset derived from electronic patient data routinely entered by health professionals at the point of care, which has been shown to be accurate and complete. This contrasts with previous similar reports such as those from the National Institute of Child Health and Development Neonatal Research Network and the Pediatrix Medical Group that have focused on admissions to tertiary neonatal units or to a large network of neonatal care providers respectively (3, 9). Limitations of this study include that data held in the NNRD are recorded as part of routine clinical care and we cannot exclude the possibility of incomplete or inaccurate data. Also, we did not set out to capture information about neonatal iNO use in other critical care settings, such as paediatric or cardiac intensive care units and these data would have been excluded from this study. Our study was also not designed to describe specific aspects of iNO therapy such as indication for use and dosage regimens.

Our study describes the increasing use of iNO, especially in more preterm infants, but was not designed to address the issue of potential benefits and risks of this practice. While iNO might be effective in certain subgroups of preterm infants, such as those with pulmonary hypoplasia and/or PPHN physiology, its short- and long-term safety has not yet been established. Potential concerns include an association between neonatal iNO therapy and pulmonary toxicity, brain injury and an increased risk of childhood cancer (21, 22). Inhaled nitric oxide is also one of the most expensive treatments available in neonatal care and there are likely to be resource implications of increasing use.

Although there are limited data on costs of iNO therapy in the UK (23), estimates from the USA suggest a cost of approximately $125/hour or $3000/day (24).

In summary, the use of iNO in English neonatal units has almost doubled between 2010 and 2015, with the most notable increase seen in the most premature infants. There was substantial variation in iNO use between units. Approximately half of treated infants were preterm < 34 weeks gestation in whom iNO was used off-label and without high quality evidence of efficacy or safety. Development of consensus guidelines may help standardise practice. In light of the substantial cost of iNO therapy and uncertainty over the later life effects of this treatment, further research is needed to better understand the long-term impacts and to identify populations of infants most likely to benefit from iNO therapy.

What is already known on this topic

maximum of 3 brief statements (no more than 25 words per statement)

- Inhaled nitric oxide (iNO) is a well-established and licensed therapy in term and near-term infants with hypoxaemic respiratory failure and pulmonary hypertension
- Evidence for the safety and efficacy of iNO in preterm infants is lacking
- iNO use is highly variable internationally; data describing iNO use across neonatal units in the United Kingdom is lacking

What this study adds

maximum of 3 brief statements (no more than 25 words per statement).

- 4.9% of infants admitted for neonatal intensive care in England received treatment with iNO between 2010 and 2015
- The increase in use of iNO is most notable in the most preterm infants born <29 weeks for which there is a paucity of evidence of benefit
- There is wide variation in iNO usage between neonatal intensive care units in England

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Author contributions

Study concept and design: NS, CG

Development of source code: KO, SJ, CB

Analysis and interpretation of data: NS, SJ, CG, CB

Writing and revision of the manuscript: NS, SJ, KO, CG, CB

Competing interests

CG reports grants from Medical Research Council, the National Institute for Health Research, the Mason Medical Research Foundation, Rosetrees Foundation and Canadian Institute for Health Research outside the submitted work; and grants and personal fees to attend an educational conference from Chiesi Pharmaceuticals outside the submitted work; he is a voluntary, unremunerated member of the Neonatal Data Analysis Unit Steering Board, which oversees the National Neonatal Research Database (NNRD), and is vice-chair of the NIHR Research for Patient Benefit London Regional Assessment Panel.

CB reports grants from the National Institute for Health Research outside the submitted work; and grants and personal fees to attend educational conferences from Chiesi and Abbvie Pharmaceuticals outside the submitted work; and is a member of the NIHR HTA prioritisation committee.

Data and materials availability:

The NNRD is not immediately available to the public. However, requests can be made by researchers to acquire access through: https://www.imperial.ac.uk/neonatal-data-analysis-unit/neonatal-data/utilising-the-nnrd/

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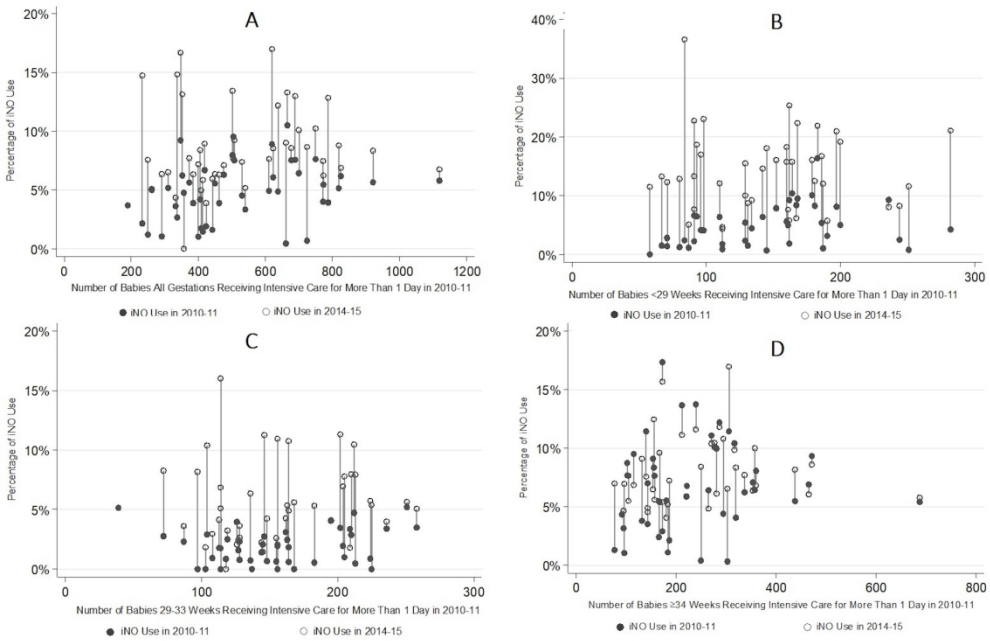

265x172mm (300 x 300 DPI)

Supplementary file 1

Diagnostic codes† extracted from the National Neonatal Research Database (NNRD):

Respiratory distress syndrome if any of the following:

'15574'- signs of respiratory distress of newborn
'15572'- Respiratory distress syndrome
'11010179'- respiratory distress-signs of
'15571' Respiratory Distress (ARDS)

Pulmonary hypoplasia if any of the following:

'16143'- Hypoplastic lungs
'16154'- Hypoplasia and dysplasia of lung
'10892'- Pulmonary hypoplasia
'16151'- Agenesis of lung

Persistent pulmonary hypertension of the newborn if any of the following:

'15241'- Primary pulmonary hypertension (not PPHN)
'15242'- Secondary pulmonary hypertension (not PPHN)
'10010891'- Pulmonary hypertension (secondary)
'10891'-Pulmonary hypertension (secondary)
'10890'- Pulmonary hypertension (primary)
'10010890'- Pulmonary hypertension (primary)
'15621'- Pulmonary hypertension (PPHN)
'10829'- Persistent Pulmonary Hypertension of the Newborn (PPHN)
'15630'- Persistent Pulmonary Hypertension (PPHN secondary to other condition)
'15629'- Persistent Pulmonary Hypertension (PPHN: idiopathic)

Meconium Aspiration Syndrome:

'15588'- Meconium aspiration syndrome

Congenital pneumonia if any of the following:

'15577'- Congenital pneumonia due to viral agent
'15581'- Congenital pneumonia due to Streptococcus, group B
'15580'- Congenital pneumonia due to Staphylococcus
'15583'- Congenital pneumonia due to Pseudomonas
'15585'- Congenital pneumonia due to other organisms
'15584'- Congenital pneumonia due to other bacterial agents
'15582'- Congenital pneumonia due to Escherichia coli
'15578'- Congenital pneumonia due to Chlamydia
'15586'- Congenital pneumonia (unknown or unspecified cause)
'15587'- Congenital pneumonia

Congenital diaphragmatic hernia if any of the following:

'16495'- Congenital diaphragic hernia
'16497'- Eventration of diaphragic hernia
'1001925'- Unspecified repair of diaphragmatic hernia
'1006671'- Repair of congenital diaphragmatic hernia
'10905'- Recurrent congenital diaphragmatic hernia
'11660'- Prosthetic repair of congenital diaphragmatic hernia (specify)
'11657'- Primary repair of congenital diaphragmatic hernia
'1001924'- Other specified repair of diaphragmatic hernia
'11597'- Other repair of diaphragmatic hernia (specify)
'10694'- Morgagni diaphragmatic hernia
'1015977'- Diaphragmatic hernia - right
'1015978'- Diaphragmatic hernia - left
'1010217'- Diaphragmatic hernia - left
'10010246'- Diaphragmatic hernia - congenital

Prolonged rupture of membranes >24 hr if any of the following:

'15406'- Prolonged preterm rupture membranes >24hr
'15459'- Prolonged rupture membranes (PROM: Term)
'15407'- Prolonged rupture membranes >24hr
'15462'- Preterm pre-labour rupture of membranes (PROM >24hrs)

† These diagnostic codes are specific to the Badger Net EPR system developed by Clevermed Ltd and from which the NNRD pulls neonatal data.

Supplementary file 2

Congenital heart disease diagnoses in order of frequency

	Gestation (Weeks)			
Diagnoses	**<29**	**29 to 33**	**≥34**	N (column percentage)
Ventricular Septal Defect (VSD)	79	85	160	324 (27.9%)
Atrial Septal Defect (ASD)	111	52	96	259 (22.2%)
Pulmonary stenosis	31	23	15	69 (5.9%)
Transposition of the great arteries	4	11	52	67 (5.8%)
Ventricular hypertrophy	11	13	26	50 (4.3%)
Atrioventricular Septal Defect (AVSD)	1	8	25	34 (2.9%)
Coarctation of aorta	4	7	19	30 (2.6%)
Congenital malformations of cardiac chambers and connections	2	4	23	29 (2.5%)
Tetralogy of Fallot	5	6	14	25 (2.2%)
Other congenital heart diagnoses	34	55	186	275 (23.7%)
Total	**282**	**264**	**616**	**1162**

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Title:

Increasing use of inhaled nitric oxide in neonatal intensive care units in England: a retrospective population study

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Abstract

Objective

To describe temporal changes in inhaled Nitric Oxide (iNO) use in English neonatal units between 2010 to 2015

Design

Retrospective analysis using data extracted from the National Neonatal Research Database (NNRD)

Setting

All National Health Service neonatal units in England

Patients

Infants of all gestational ages born 2010- 2015 admitted to a neonatal unit and received intensive care

Main outcome measures

Proportion of infants who received iNO; age at initiation and duration of iNO use

Results

4.9% (6,346/129,883) of infants received iNO; 31% (1,959/6,346) were born <29 weeks, 18% (1,152/6,346) 29-33 weeks and 51% (3,235/6,346) >34 weeks gestation. Between epoch 1 (2010-2011) and epoch 3 (2014-2015), there was i) an increase in the proportion of infants receiving iNO: < 29 weeks (4.9 *vs* 15.9%); 29-33 weeks (1.1 *vs* 4.8%); > 34 weeks (4.5 *vs* 5.0%) ii) increase in postnatal age at iNO initiation: <29 weeks 10 *vs* 18 days; 29-33 weeks 2 *vs* 10 days iii) reduction in iNO duration: <29 weeks (3 *vs* 2 days); 29-33 weeks (2 *vs* 1 day). There were no statistically significant differences in patient characteristics.

Conclusions

Between 2010 and 2015 there was an increase in the use of iNO among infants admitted to English neonatal units. This was most notable among the most premature infants with an almost four-fold increase. Given the cost of iNO therapy, limited evidence of efficacy in preterm infants, and potential for harm, we suggest that exposure to iNO should be limited, ideally to infants included in research studies (either observational or RCT) or within a protocolised pathway. Development of consensus guidelines may also help to standardise practice.

Introduction

Inhaled nitric oxide (iNO) is widely used in the treatment of hypoxaemic respiratory failure and persistent pulmonary hypertension of the newborn. Although a well-established therapy in term and near-term infants with these conditions, the off-label use of iNO in preterm infants <34 weeks gestation remains controversial. Population-based data indicate that there is wide variation in administration rates amongst US hospitals, but there are no equivalent data from the UK or mainland Europe (1-4). Data from individual centres and multicentre studies suggest that the use of iNO is increasing (2-5), especially in preterm infants, despite the lack of evidence of benefit in this population.

We aimed to describe temporal changes in the use of iNO in neonates admitted to neonatal units in England using national data routinely recorded during clinical care and held in the National Neonatal Research database (NNRD). Our objectives were to i) describe the proportion and characteristics of preterm and term infants who receive iNO between 2010 and 2015; ii) determine whether there is variation in iNO use across tertiary level neonatal units, and over time between 2010 and 2015.

Methods

Setting, study design, data source and ethics approval

This retrospective cohort study used routinely recorded, de-identified data held in the NNRD. The NNRD has complete coverage of infants admitted for neonatal care at a National Health Service (NHS) neonatal unit in England, Scotland and Wales. The NNRD is formed from data extracted from neonatal electronic health record systems used by health professionals during routine clinical care. A defined data extract comprising approximately 450 items (6), the Neonatal Data Set, is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London where data are cleaned and entered into the NNRD. High completeness and accuracy (>95%) of data held in the NNRD has been confirmed by a formal comparison with those recorded in Case Record Forms of a multicentre, randomised placebo-controlled trial (RCT) (7). Neonatal units in England contributing data to the NNRD consented for their unit data to be included in the study. This study using anonymised data was approved by the West of Scotland Research Ethics Committee 5; reference number 16/WS/0228.

Study population and data extraction

We included data from infants who required any neonatal intensive care (defined using British Association of Perinatal Medicine categories of care 2011 (8), primarily as needing mechanical ventilation or non-invasive ventilation plus parenteral nutrition) over a 6-year period, 01/01/2010 to 31/12/2015 in England. Infants who did not receive intensive care on a neonatal unit or who were not cared for completely in units in Wales and Scotland, were excluded from the analysis.

We extracted daily variables (receipt of iNO, surfactant), demographic variables (birthweight, sex, gestational age), maternal factors (prolonged rupture of membranes >24 hours), diagnoses and survival to neonatal unit discharge. See supplementary file 1 for diagnostic codes.

Outcomes

The primary outcome was rate of iNO use as a proportion of infants that received neonatal intensive care, and unit level.

The following secondary outcomes were analysed for infants that received iNO:

- Timing of iNO initiation (postnatal age in days)

- Duration of iNO

- Diagnoses including respiratory distress syndrome (RDS), persistent pulmonary hypertension of the newborn (PPHN), pulmonary hypoplasia, congenital pneumonia, congenital diaphragmatic hernia, congenital heart disease, meconium aspiration syndrome (among infants ≥ 34 weeks gestation)

- Survival to neonatal unit discharge

Statistical analyses

We describe the cohort at two levels: 1) at the level of the population of infants that received at least 1 day of neonatal intensive care; and 2) at the level of the neonatal unit. For all outcomes separate analyses were conducted by *a-priori* defined gestational age bands: (a) extremely preterm (< 29 weeks gestation); (b) moderately preterm (29-33 weeks gestation); and (c) late preterm/term (> 34 weeks gestation).

Results are presented using medians (interquartile ranges) and percentages for continuous and categorical variables, respectively. We tested whether iNO use and duration changed significantly between the first epoch (2010-2011) and the third epoch (2014-2015) using either chi-squared tests or Wilcoxon rank sum test.

For the neonatal unit-level analysis, we limited this to the 47 tertiary neonatal units in England who have treated 5 or more infants with nitric oxide. For this analysis we attributed iNO use to the first unit providing iNO therapy regardless of whether an infant was treated with iNO in more than one neonatal unit. The total number of neonatal units in England during this period decreased from 169 (in 2010-11) to 161 (in 2014-15); this

reflects the merger or closure of units. Rates of iNO use across tertiary units are presented graphically without comparative testing.

Patient and Public Involvement

Results will be disseminated to parents, ex-patients and members of the public through the Imperial College Neonatal Data Analysis Unit website, social media, and strong links between the authors and parent/patient groups.

Results

During the 6-year study period 129,883 infants received at least 1 day of intensive care in England; 4.9% (6,346) of these received iNO. Use of iNO increased significantly over time from 3.4% (1,293/37,885) in 2010-2011 to 6.4% (3,112/48,838) in 2014-2015. There were no significant differences in gestational age, birth weight or sex between birth year epochs (Table 1).

When analysed by gestational age band over the entire study period, 9.9% (1,959/19,727) of infants born <29 weeks received iNO; corresponding percentages are 2.8% (1,152/41,133) for 29-33 weeks and 4.7% (3,235/69,022) for ≥ 34 weeks (Tables 1-3). Mortality among iNO treated infants decreased over time in all gestational age groups.

By gestational age bands

<29 weeks

31% (1,959/6,346) of infants that received iNO were born < 29 weeks gestation (Table 1). Among infants born in the later epoch, a lower proportion had diagnoses of prolonged rupture of membranes or pulmonary hypoplasia recorded and a higher proportion had RDS recorded and received surfactant. (Table 1). 282 had congenital heart disease; the most common were atrial or ventricular septal defects (67%) (Supplementary Table 2).

29-33 weeks

18% (1,152/6,346) of infants that received iNO were born at 29-33 weeks gestation. A lower proportion of infants born in the later epoch had PPHN recorded and a higher proportion had RDS recorded, although surfactant use was lower in the later epoch. In the 2014-2015 epoch iNO was initiated later and administered for a shorter duration (Table 2). 264 infants had congenital heart disease; 52% were atrial or ventricular septal defects (Supplementary Table 2).

≥34 weeks

51% (3,235/6,346) of infants that received iNO had a gestational age of ≥ 34 weeks at birth. The proportion of these infants who received iNO increased marginally but significantly between 2010-2011 and 2014-2015. A lower proportion of these infants born in the later epoch had prolonged rupture of membranes, PPHN or meconium aspiration syndrome, and a higher proportion had RDS recorded and received surfactant. iNO was initiated later and administered for a shorter duration (Table 3). 616 of these infants that received iNO had congenital heart disease and 41.6% (256/616) were atrial or ventricular septal defects (Supplementary Table 2).

Comparison between tertiary units

There was wide variation in the proportion of infants receiving intensive care who also received iNO between the 47 tertiary neonatal intensive care units in England across all gestation groups (figure 1A). This was especially marked among infants < 29 weeks gestation where iNO use varied between 0.7% and 36.5% (Figure 1B).

When considering unit level trends over time, iNO use in >29 week gestation infants increased between 2010-2011 and 2014-2015 in almost all units (figure 1C), however a more mixed picture was seen in less preterm infants (figure 1D).

Table 1

Patient demographics and outcomes for infants born less than 29 weeks gestation admitted to neonatal units in England and treated with iNO

	2010-11	**2012-13**	**2014-15**	**p**
Neonatal admissions requiring ≥ 1 day of intensive care (with and without iNO)	6730	6587	6410	
Infants treated with iNO	329 (4.9%†)	611 (9.3%†)	1019 (15.9%†)	p<0.01
Birth weight (g)	790 (650,950)	795 (670,985)	790 (660,985)	0.31
Gestational age (weeks)	26 (24, 27)	26 (24, 27)	26 (24, 27)	0.25
Male sex	180(55%)	364 (60%)	553 (54%)	0.89
Prolonged rupture of membranes >24 hr∞	113 (34.4%)	190 (31.1%)	173 (17.0%)	P<0.001
Surfactant therapy in labour ward or neonatal unit	324 (98.5%)	589 (96.4%)	935(91.8%)	P<0.001
Initiation of iNO therapy (day)	10 (2,33)	13 (2,46)	18 (3,48)	P<0.001
Duration of iNO therapy (days)	3 (2,5)	2 (1,4)	2 (1,4)	P<0.001
Diagnosis (not mutually exclusive)^				

Respiratory distress syndrome (RDS)*	255 (77.5%)	505 (82.7%)	920 (90.3%)	P<0.001
Pulmonary hypoplasia	30 (9.1%)	40 (6.6%)	49 (4.8%)	P<0.01
Pulmonary hypertension	100 (30.4%)	164 (26.8%)	260 (25.5%)	0.08
Congenital pneumonia	2 (0.6%)	2 (0.3%)	10 (1.0%)	0.53
Congenital diaphragmatic hernia	0	0	1 (0.1%)	0.57
Death among infants who received iNO	143 (43.5%)	224 (36.7%)	242 (23.8%)	P<0.001

The denominator for all proportions is the number of babies treated with iNO unless indicated otherwise

† Denominator is all admissions to neonatal unit admissions requiring ≥ 1 day of intensive care

All values given as n, % or median (25^{th},75^{th} centiles), as appropriate.

*This includes the diagnosis *Respiratory distress syndrome* and *signs of respiratory distress of newborn (see supplementary file 1)*

^Extracted codes available in supplementary file

∞ Prolonged rupture of membranes >24 hrs uses a combination of discharge diagnoses and recorded duration of rupture of membranes

Table 2

Patient demographics and outcomes for infants born 29-33 weeks' admitted to neonatal units in England and treated with iNO

	2010-11	**2012-13**	**2014-15**	**p**
Neonatal admissions requiring ≥ 1 day of intensive care (with and without iNO)	12781	13796	14556	
Infants treated with iNO	144 (1.1%†)	315 (2.3%†)	693 (4.8%†)	p<0.001
Birth weight (g)	1603 (1311,1972)	1500 (1290,1800)	1500† (1256,1800)	0.01
Gestational age (weeks)	30 (29,32)	31 (29,32)	31 (30,32)	0.76
Male sex	91 (63.2%)	187 (59.4%)	406 (58.6%)	0.31
Prolonged rupture of membranes >24 hr∞	34 (23.6%)	86 (27.3%)	124 (17.9%)	0.11
Surfactant therapy in labour ward or neonatal unit	131 (91.0%)	229 (72.7%)	418 (60.3%)	p<0.001
Initiation of iNO therapy (days)	2 (1,3)	3 (1,20)	10 (2,24)	p<0.001
Duration of iNO therapy (days)	2 (2,4)	1 (1,3)	1 (1,2)	p<0.001
Diagnosis (not mutually exclusive)^				

Respiratory distress syndrome*	92 (63.9%)	240 (76.2%)	604(87.2%)	p<0.001
Pulmonary hypoplasia	23 (16.0%)	46 (14.6%)	72 (10.4%)	0.05
Pulmonary hypertension	76 (52.8%)	108 (34.3%)	163 (23.5%)	p<0.001
Congenital pneumonia	1 (0.7%)	3 (1.0%)	2 (0.3%)	0.46
Congenital diaphragmatic hernia	7 (4.9%)	11 (3.5%)	15 (2.2%)	0.07
Death among infants who received iNO	59 (41.0%)	68 (21.6%)	76 (11.0%)	p<0.001

The denominator for all proportions is the number of babies treated with iNO unless indicated otherwise

† Denominator is all admissions to neonatal unit admissions requiring ≥ 1 day of intensive care

All values given as n, % or median (25^{th},75^{th} centiles) as appropriate.

*This includes the diagnosis *Respiratory distress syndrome* and *signs of respiratory distress of newborn (see supplementary file 1)*

^Extracted codes available in supplementary file

∞ Prolonged rupture of membranes >24 hrs uses a combination of discharge diagnoses and recorded duration of rupture of membranes

† 1 baby with a birthweight less than 300 grams was removed from this calculation (n=692)

Table 3

Patient demographics and outcomes for infants born >34 weeks' gestation admitted to neonatal units in England and treated with iNO

	2010-11	**2012-13**	**2014-15**	**p**
Neonatal admissions requiring ≥ 1 day of intensive care (with and	18374	22777	27872	
Infants treated with iNO	820 (4.5%†)	1015 (4.5%†)	1400 (5.0%†)	p<0.01
Birth weight (g)	3273 (2840,3665)	3240 (2760,3690)	3220† (2680,3630)	0.02
Gestational age (weeks)	40 (38,41)	39 (37,40)	39 (37,40)	p<0.001
Male sex	450 (54.9%)	577 (56.9%)	756 (54.0%)	0.69
Prolonged rupture of membranes >24 hr∞	82 (10.0%)	92 (9.1%)	68(4.9%)	p<0.001
Surfactant therapy in labour ward or neonatal unit	532 (64.9%)	613 (60.4%)	713(50.9%)	p<0.001
Initiation of iNO therapy (days)	2 (1,2)	2 (1,2)	2 (1,2)	0.02
Duration of iNO therapy (days)	3 (2,5)	3 (2,5)	2 (1,5)	p<0.001
Diagnosis (not mutually exclusive)^				
*Respiratory distress syndrome**	259 (31.6%)	378 (37.2%)	778 (55.6%)	p<0.001
Pulmonary hypoplasia	61 (7.4%)	67 (6.6%)	101 (7.2%)	0.84
Meconium aspiration syndrome	314 (38.3%)	378 (37.2%)	440 (31.4%)	p<0.01
Pulmonary hypertension	598 (72.9%)	703 (69.3%)	885 (63.2%)	p<0.001

Congenital pneumonia	42 (5.1%)	52 (5.1%)	74 (5.3%)	0.87
Congenital diaphragmatic hernia	55(6.7%)	57(5.6%)	83 (5.9%)	0.46
Death among infants who received iNO	165 (20.1%)	160 (15.8%)	212 (15.1%)	p<0.01

The denominator for all proportions is the number of babies treated with iNO unless indicated otherwise

† Denominator is all admissions to neonatal unit admissions requiring ≥ 1 day of intensive care

All values given as n, % or median (25^{th},75^{th} centiles) as appropriate.

*This includes the diagnosis *Respiratory distress syndrome* and *signs of respiratory distress of newborn (see supplementary file 1)*

^Extracted codes available in supplementary file

∞ Prolonged rupture of membranes >24 hrs uses a combination of discharge diagnoses and recorded duration of rupture of membranes

† 1 baby with a birthweight less than 300 grams was removed from this calculation (n=1399)

Discussion

In this large population-level study we found that almost 1 in 20 infants that received any period of intensive care at an English neonatal unit were treated with iNO, that this rate almost doubled between 2010-2011 and 2014-2015 and that the temporal increase in iNO use was seen across all gestational ages. The temporal increase was most evident among more preterm infants < 34 weeks, in whom the use of iNO increased three-fold from 2.4% to 8.2% and where evidence for iNO is most lacking. There was a similar 3-4 fold increase in rates of iNO use for infants born <29 weeks and 29-33 weeks, from 4.9 to 15.9% and 1.1 to 4.8% for infants, respectively. In the most preterm group an additional 690 infants born <29 gestational weeks were treated with iNO in 2014-15 compared with 2010-11.

It is difficult to compare these data with internationally reported iNO usage rates because other studies commonly report rates as a proportion of all neonatal admissions, whereas we report rates as a proportion of infants receiving neonatal intensive care. We used this denominator because of differences in the organisation of neonatal care, specifically the use of a networked model of care in the United Kingdom which results in numerous transfers between neonatal units as part of routine care, and to minimise the impact of variations in practice around admissions of term infants for short periods. Rates of iNO usage in US studies are reported between 0.9% and 1.3% (2, 3) of all neonatal admissions. To our knowledge, this is one of the largest studies of iNO use in neonatal practice and the only to report data at national level; other studies have reported iNO use in a various US healthcare organisations (including children's hospitals) and in all admissions including infants receiving lower acuity categories of neonatal care (1, 4, 9, 10).

The Canadian Neonatal network (CNN) found similar rates (1 in 25; 4.2%) of iNO use among infants born <34 weeks between 2010 and 2013. As different gestational age categories were used, direct comparisons cannot be made, but the use of iNO was broadly similar to the recent UK figures. However, in contrast to the increasing use in the UK, iNO use was stable across the 4 years in the CNN (11).

Approximately half of all infants that received iNO in this study were born at < 34 weeks gestation. This is relevant because the licensed indication for iNO limits treatment to newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension (12). This finding is, however, broadly consistent with other studies from the US and Europe which showed that 40-46% of all treated infants were <34 weeks gestation (3, 13). Treatment rates for preterm infants in this study (5.1% of preterm infants < 34 weeks gestation) were comparable to other studies from the US reporting rates of 2.6% to 7.2% in the same gestation groups (1, 4, 9, 10), and in this comparison the different denominator in US studies is less likely to influence results as the majority of more preterm infants will receive intensive care.

We find that not only is off-label treatment with iNO of preterm infants < 34 weeks gestation widespread, it is increasing – particularly in the most preterm infants. The evidence base supporting routine use in these most preterm infants, both in respect of safety and efficacy, is weakest (2-4). Post-hoc analyses from a study which randomised 420 neonates born <34 weeks gestation to placebo or iNO found an apparent increase in mortality and higher rate of intraventricular haemorrhage in infants with a birth weight ≤1000g (14).

The reason for increasing use of iNO off-label in particularly in the most preterm infants is not known but is likely to be multifaceted and reflect the absence of other proven 'rescue' cardiorespiratory interventions for these smaller infants with severe hypoxaemic respiratory failure (such as extracorporeal membrane oxygenation) and full reimbursement of off-label iNO use in England. Furthermore there is some limited evidence for the use of iNO in specific groups of preterm infants including those born following preterm prolonged rupture of membranes and those with echocardiographic criteria of PPHN physiology, supported by expert opinion and consensus statements (15-18). There is growing experience in the use of iNO and the immediate short-term oxygenation response can be gratifying for clinicians, and may encourage further use. However, whether the short-term benefit in oxygenation is translated into longer-term benefit in preterm infants is unknown and needs further investigation. Moreover, the

perception of absence of harm should not be extrapolated from term infants simply because there is a lack of convincing evidence of harm in preterm infants.

Treatment with iNO was started later and duration of treatment was shorter in later epochs, suggesting that preterm infants were more commonly treated outside the acute respiratory phase. Although there is little evidence of efficacy of iNO as rescue therapy in acute respiratory failure or later ventilator-dependent chronic lung disease (19, 20), we speculate that clinicians might be increasingly willing to use off-label iNO in such circumstances.

This study also demonstrates large variation between English neonatal units in rates of iNO use, in keeping with that reported in recent US studies (1, 10) where a similar degree of variation from 0.4% to 21.9% was seen in iNO use in preterm infants between 13 NICHD neonatal research network centres. The variation between neonatal units in the US decreased following publication of national guidance (21). Such national guidance is not available for the UK but might help to standardise practice in this area if it were to be developed.

Overall mortality decreased in iNO-treated infants during the study period. This trend mirrors national data reporting improved survival in extremely preterm infants in England (22) over a similar timeframe. The lower mortality seen in later epochs may also reflect a change in case-mix as iNO therapy is offered more readily to infants with less severe cardiorespiratory failure. This type of 'therapeutic creep' has been described with other neonatal interventions (23). This study was not designed to analyse changes in outcomes beyond simple descriptive data.

The strengths of this study include the use of a large national dataset derived from electronic patient data routinely entered by health professionals at the point of care, which has been shown to be accurate and complete. This contrasts with previous similar reports such as those from the National Institute of Child Health and Development Neonatal Research Network and the Pediatrix Medical Group that have focused on admissions to tertiary neonatal units or to a large network of neonatal care providers respectively (3, 9). Limitations of this study include that data held in the NNRD are recorded as part of routine clinical care and we cannot exclude the possibility

of incomplete or inaccurate data. Also, we did not set out to capture information about neonatal iNO use in other critical care settings, such as paediatric or cardiac intensive care units and these data would have been excluded from this study. Our study was also not designed to describe specific aspects of iNO therapy such as indication for use and dosage regimens.

Our study describes the increasing use of iNO, especially in more preterm infants, but was not designed to address the issue of potential benefits and risks of this practice. While iNO might be effective in certain subgroups of preterm infants, such as those with pulmonary hypoplasia and/or PPHN physiology, its short- and long-term safety has not yet been established. Potential concerns include an association between neonatal iNO therapy and pulmonary toxicity, brain injury and an increased risk of childhood cancer (24, 25). Inhaled nitric oxide is also one of the most expensive treatments available in neonatal care and there are likely to be resource implications of increasing use. Although there are limited data on costs of iNO therapy in the UK (26), estimates from the USA suggest a cost of approximately $125/hour or $3000/day (27).

In summary, the use of iNO in English neonatal units has almost doubled between 2010 and 2015, with the most notable increase seen in the most premature infants. There was substantial variation in iNO use between units. Approximately half of treated infants were preterm < 34 weeks gestation in whom iNO was used off-label and without high quality evidence of efficacy or safety. Development of consensus guidelines may help standardise practice. Given the cost of iNO therapy, limited evidence of efficacy in preterm infants, and potential for harm, we suggest that exposure to iNO should be limited, ideally to infants included in research studies (either observational or RCT) or within a protocolised pathway that permits a short trial of iNO to assess acute oxygenation response. Development of consensus guidelines might also help to standardise practice.

What is already known on this topic

maximum of 3 brief statements (no more than 25 words per statement)

- Inhaled nitric oxide (iNO) is a well-established and licensed therapy in term and near-term infants with hypoxaemic respiratory failure and pulmonary hypertension
- Evidence for the safety and efficacy of iNO in preterm infants is lacking
- iNO use is highly variable internationally; data describing iNO use across neonatal units in the United Kingdom is lacking

What this study adds

maximum of 3 brief statements (no more than 25 words per statement).

- Use of iNO increased significantly over time from 3.4% (1,293/37,885) in 2010-2011 to 6.4% (3,112/48,838) in 2014-2015
- The increase in use of iNO is most notable in the most preterm infants born <29 weeks for which there is a paucity of evidence of benefit
- There is wide variation in iNO usage between neonatal intensive care units in England

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Author contributions

Study concept and design: NS, CG

Development of source code: KO, SJ, CB

Analysis and interpretation of data: NS, SJ, CG, CB

Writing and revision of the manuscript: NS, SJ, KO, CG, CB

Competing interests

CG reports grants from Medical Research Council, the National Institute for Health Research, the Mason Medical Research Foundation, Rosetrees Foundation and Canadian Institute for Health Research outside the submitted work; and grants and personal fees to attend an educational conference from Chiesi Pharmaceuticals outside the submitted work; he is a voluntary, unremunerated member of the Neonatal Data Analysis Unit Steering Board, which oversees the National Neonatal Research Database (NNRD), and is vice-chair of the NIHR Research for Patient Benefit London Regional Assessment Panel.

CB reports grants from the National Institute for Health Research outside the submitted work; and grants and personal fees to attend educational conferences from Chiesi and Abbvie Pharmaceuticals outside the submitted work; and is a member of the NIHR HTA prioritisation committee.

Data and materials availability:

The NNRD is not immediately available to the public. However, requests can be made by researchers to acquire access through: https://www.imperial.ac.uk/neonatal-data-analysis-unit/neonatal-data/utilising-the-nnrd/

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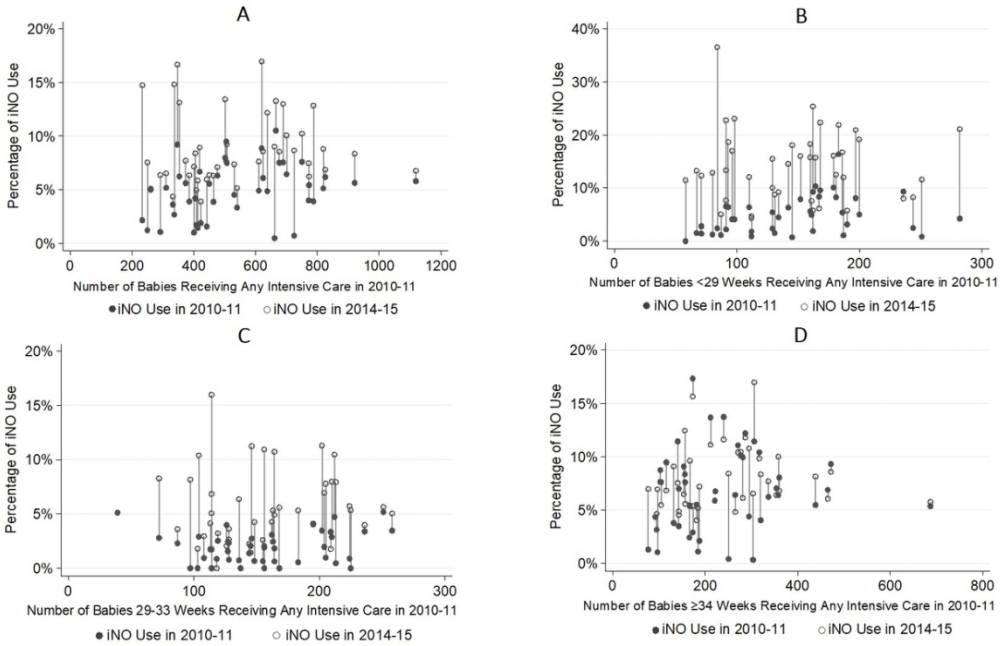

103x70mm (300 x 300 DPI)

Supplementary file 1

Diagnostic codes† extracted from the National Neonatal Research Database (NNRD):

Respiratory distress syndrome if any of the following:

'15574'- signs of respiratory distress of newborn
'15572'- Respiratory distress syndrome
'11010179'- respiratory distress-signs of
'15571' Respiratory Distress (ARDS)

Pulmonary hypoplasia if any of the following:

'16143'- Hypoplastic lungs
'16154'- Hypoplasia and dysplasia of lung
'10892'- Pulmonary hypoplasia
'16151'- Agenesis of lung

Persistent pulmonary hypertension of the newborn if any of the following:

'15241'- Primary pulmonary hypertension (not PPHN)
'15242'- Secondary pulmonary hypertension (not PPHN)
'10010891'- Pulmonary hypertension (secondary)
'10891'-Pulmonary hypertension (secondary)
'10890'- Pulmonary hypertension (primary)
'10010890'- Pulmonary hypertension (primary)
'15621'- Pulmonary hypertension (PPHN)
'10829'- Persistent Pulmonary Hypertension of the Newborn (PPHN)
'15630'- Persistent Pulmonary Hypertension (PPHN secondary to other condition)
'15629'- Persistent Pulmonary Hypertension (PPHN: idiopathic)

Meconium Aspiration Syndrome:

'15588'- Meconium aspiration syndrome

Congenital pneumonia if any of the following:

'15577'- Congenital pneumonia due to viral agent
'15581'- Congenital pneumonia due to Streptococcus, group B
'15580'- Congenital pneumonia due to Staphylococcus
'15583'- Congenital pneumonia due to Pseudomonas
'15585'- Congenital pneumonia due to other organisms
'15584'- Congenital pneumonia due to other bacterial agents
'15582'- Congenital pneumonia due to Escherichia coli
'15578'- Congenital pneumonia due to Chlamydia
'15586'- Congenital pneumonia (unknown or unspecified cause)
'15587'- Congenital pneumonia

Congenital diaphragmatic hernia if any of the following:

'16495'- Congenital diaphragic hernia
'16497'- Eventration of diaphragic hernia
'1001925'- Unspecified repair of diaphragmatic hernia
'1006671'- Repair of congenital diaphragmatic hernia
'10905'- Recurrent congenital diaphragmatic hernia
'11660'- Prosthetic repair of congenital diaphragmatic hernia (specify)
'11657'- Primary repair of congenital diaphragmatic hernia
'1001924'- Other specified repair of diaphragmatic hernia
'11597'- Other repair of diaphragmatic hernia (specify)
'10694'- Morgagni diaphragmatic hernia
'1015977'- Diaphragmatic hernia - right
'1015978'- Diaphragmatic hernia - left
'1010217'- Diaphragmatic hernia - left
'10010246'- Diaphragmatic hernia - congenital

Prolonged rupture of membranes >24 hr if any of the following:

'15406'- Prolonged preterm rupture membranes >24hr
'15459'- Prolonged rupture membranes (PROM: Term)
'15407'- Prolonged rupture membranes >24hr
'15462'- Preterm pre-labour rupture of membranes (PROM >24hrs)

† These diagnostic codes are specific to the Badger Net EPR system developed by Clevermed Ltd and from which the NNRD pulls neonatal data.

Supplementary file 2

Congenital heart disease diagnoses in order of frequency

	Gestation (Weeks)			
Diagnoses	**<29**	**29 to 33**	**≥34**	N (column percentage)
Ventricular Septal Defect (VSD)	79	85	160	324 (27.9%)
Atrial Septal Defect (ASD)	111	52	96	259 (22.2%)
Pulmonary stenosis	31	23	15	69 (5.9%)
Transposition of the great arteries	4	11	52	67 (5.8%)
Ventricular hypertrophy	11	13	26	50 (4.3%)
Atrioventricular Septal Defect (AVSD)	1	8	25	34 (2.9%)
Coarctation of aorta	4	7	19	30 (2.6%)
Congenital malformations of cardiac chambers and connections	2	4	23	29 (2.5%)
Tetralogy of Fallot	5	6	14	25 (2.2%)
Other congenital heart diagnoses	34	55	186	275 (23.7%)
Total	**282**	**264**	**616**	**1162**

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Title:

Increasing use of inhaled nitric oxide in neonatal intensive care units in England: a retrospective population study

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Abstract

Objective

To describe temporal changes in inhaled Nitric Oxide (iNO) use in English neonatal units between 2010 to 2015

Design

Retrospective analysis using data extracted from the National Neonatal Research Database (NNRD)

Setting

All National Health Service neonatal units in England

Patients

Infants of all gestational ages born 2010- 2015 admitted to a neonatal unit and received intensive care

Main outcome measures

Proportion of infants who received iNO; age at initiation and duration of iNO use

Results

4.9% (6,346/129,883) of infants received iNO; 31% (1,959/6,346) were born <29 weeks, 18% (1,152/6,346) 29-33 weeks and 51% (3,235/6,346) >34 weeks gestation. Between epoch 1 (2010-2011) and epoch 3 (2014-2015), there was i) an increase in the proportion of infants receiving iNO: < 29 weeks (4.9 *vs* 15.9%); 29-33 weeks (1.1 *vs* 4.8%); > 34 weeks (4.5 *vs* 5.0%) ii) increase in postnatal age at iNO initiation: <29 weeks 10 *vs* 18 days; 29-33 weeks 2 *vs* 10 days iii) reduction in iNO duration: <29 weeks (3 *vs* 2 days); 29-33 weeks (2 *vs* 1 day).

Conclusions

Between 2010 and 2015 there was an increase in the use of iNO among infants admitted to English neonatal units. This was most notable among the most premature infants with an almost four-fold increase. Given the cost of iNO therapy, limited evidence of efficacy in preterm infants, and potential for harm, we suggest that exposure to iNO should be limited, ideally to infants included in research studies (either observational or RCT) or within a protocolised pathway. Development of consensus guidelines may also help to standardise practice.

Introduction

Inhaled nitric oxide (iNO) is widely used in the treatment of hypoxaemic respiratory failure and persistent pulmonary hypertension of the newborn. Although a well-established therapy in term and near-term infants with these conditions, the off-label use of iNO in preterm infants <34 weeks gestation remains controversial. Population-based data indicate that there is wide variation in administration rates amongst US hospitals, but there are no equivalent data from the UK or mainland Europe (1-4). Data from individual centres and multicentre studies suggest that the use of iNO is increasing (2-5), especially in preterm infants, despite the lack of evidence of benefit in this population.

We aimed to describe temporal changes in the use of iNO in neonates admitted to neonatal units in England using national data routinely recorded during clinical care and held in the National Neonatal Research database (NNRD). Our objectives were to i) describe the proportion and characteristics of preterm and term infants who receive iNO between 2010 and 2015; ii) determine whether there is variation in iNO use across tertiary level neonatal units, and over time between 2010 and 2015.

Methods

Setting, study design, data source and ethics approval

This retrospective cohort study used routinely recorded, de-identified data held in the NNRD. The NNRD has complete coverage of infants admitted for neonatal care at a National Health Service (NHS) neonatal unit in England, Scotland and Wales. The NNRD is formed from data extracted from neonatal electronic health record systems used by health professionals during routine clinical care. A defined data extract comprising approximately 450 items (6), the Neonatal Data Set, is transmitted quarterly to the Neonatal Data Analysis Unit at Imperial College London where data are cleaned and entered into the NNRD. High completeness and accuracy (>95%) of data held in the NNRD has been confirmed by a formal comparison with those recorded in Case Record Forms of a multicentre, randomised placebo-controlled trial (RCT) (7). Neonatal units in England contributing data to the NNRD consented for their unit data to be included in the study. This study using anonymised data was approved by the West of Scotland Research Ethics Committee 5; reference number 16/WS/0228.

Study population and data extraction

We included data from infants who required any neonatal intensive care (defined using British Association of Perinatal Medicine categories of care 2011 (8), primarily as needing mechanical ventilation or non-invasive ventilation plus parenteral nutrition) over a 6-year period, 01/01/2010 to 31/12/2015 in England. Infants who did not receive intensive care on a neonatal unit or who were not cared for completely in units in Wales and Scotland, were excluded from the analysis.

We extracted daily variables (receipt of iNO, surfactant), demographic variables (birthweight, sex, gestational age), maternal factors (prolonged rupture of membranes >24 hours), diagnoses and survival to neonatal unit discharge. See supplementary file 1 for diagnostic codes.

Outcomes

The primary outcome was rate of iNO use as a proportion of infants that received neonatal intensive care, and unit level.

The following secondary outcomes were analysed for infants that received iNO:

- Timing of iNO initiation (postnatal age in days)

- Duration of iNO

- Diagnoses including respiratory distress syndrome (RDS), persistent pulmonary hypertension of the newborn (PPHN), pulmonary hypoplasia, congenital pneumonia, congenital diaphragmatic hernia, congenital heart disease, meconium aspiration syndrome (among infants ≥ 34 weeks gestation)

- Survival to neonatal unit discharge

Statistical analyses

We describe the cohort at two levels: 1) at the level of the population of infants that received at least 1 day of neonatal intensive care; and 2) at the level of the neonatal unit. For all outcomes separate analyses were conducted by *a-priori* defined gestational age bands: (a) extremely preterm (< 29 weeks gestation); (b) moderately preterm (29-33 weeks gestation); and (c) late preterm/term (> 34 weeks gestation).

Results are presented using medians (interquartile ranges) and percentages for continuous and categorical variables, respectively.

For the neonatal unit-level analysis, we limited this to the 47 tertiary neonatal units in England who have treated 5 or more infants with nitric oxide. For this analysis we attributed iNO use to the first unit providing iNO therapy regardless of whether an infant was treated with iNO in more than one neonatal unit. The total number of neonatal units in England during this period decreased from 169 (in 2010-11) to 161 (in 2014-15); this reflects the merger or closure of units. Rates of iNO use across tertiary units are presented graphically without comparative testing.

Patient and Public Involvement

Results will be disseminated to parents, ex-patients and members of the public through the Imperial College Neonatal Data Analysis Unit website, social media, and strong links between the authors and parent/patient groups.

Results

During the 6-year study period 129,883 infants received at least 1 day of intensive care in England; 4.9% (6,346) of these received iNO. Use of iNO increased over time from 3.4% (1,293/37,885) in 2010-2011 to 6.4% (3,112/48,838) in 2014-2015.

When analysed by gestational age band over the entire study period, 9.9% (1,959/19,727) of infants born <29 weeks received iNO; corresponding percentages are 2.8% (1,152/41,133) for 29-33 weeks and 4.7% (3,235/69,022) for ≥ 34 weeks (Tables 1-3). Mortality among iNO treated infants decreased over time in all gestational age groups.

By gestational age bands

<29 weeks

31% (1,959/6,346) of infants that received iNO were born < 29 weeks gestation (Table 1). Among infants born in the later epoch, a lower proportion had diagnoses of prolonged rupture of membranes or pulmonary hypoplasia recorded and a higher proportion had RDS recorded and received surfactant. (Table 1). 282 had congenital heart disease; the most common were atrial or ventricular septal defects (67%) (Supplementary Table 2).

29-33 weeks

18% (1,152/6,346) of infants that received iNO were born at 29-33 weeks gestation. A lower proportion of infants born in the later epoch had PPHN recorded and a higher proportion had RDS recorded, although surfactant use was lower in the later epoch. In

the 2014-2015 epoch iNO was initiated later and administered for a shorter duration (Table 2). 264 infants had congenital heart disease; 52% were atrial or ventricular septal defects (Supplementary Table 2).

≥34 weeks

51% (3,235/6,346) of infants that received iNO had a gestational age of ≥ 34 weeks at birth. The proportion of these infants who received iNO increased marginally between 2010-2011 and 2014-2015. A lower proportion of these infants born in the later epoch had prolonged rupture of membranes, PPHN or meconium aspiration syndrome, and a higher proportion had RDS recorded and received surfactant. iNO was initiated later and administered for a shorter duration (Table 3). 616 of these infants that received iNO had congenital heart disease and 41.6% (256/616) were atrial or ventricular septal defects (Supplementary Table 2).

Comparison between tertiary units

There was wide variation in the proportion of infants receiving intensive care who also received iNO between the 47 tertiary neonatal intensive care units in England across all gestation groups (figure 1A). This was especially marked among infants < 29 weeks gestation where iNO use varied between 0.7% and 36.5% (Figure 1B).

When considering unit level trends over time, iNO use in >29 week gestation infants increased between 2010-2011 and 2014-2015 in almost all units (figure 1C), however a more mixed picture was seen in less preterm infants (figure 1D).

Table 1

Patient demographics and outcomes for infants born less than 29 weeks gestation admitted to neonatal units in England and treated with iNO

	2010-11	2012-13	2014-15

Neonatal admissions requiring ≥ 1 day of intensive care (with and without iNO)	6730	6587	6410
Infants treated with iNO	329 (4.9%†)	611 (9.3%†)	1019 (15.9%†)
Birth weight (g)	790 (650,950)	795 (670,985)	790 (660,985)
Gestational age (weeks)	26 (24, 27)	26 (24, 27)	26 (24, 27)
Male sex	180(55%)	364 (60%)	553 (54%)
Prolonged rupture of membranes >24 hr∞	113 (34.4%)	190 (31.1%)	173 (17.0%)
Surfactant therapy in labour ward or neonatal unit	324 (98.5%)	589 (96.4%)	935(91.8%)
Initiation of iNO therapy (day)	10 (2,33)	13 (2,46)	18 (3,48)
Duration of iNO therapy (days)	3 (2,5)	2 (1,4)	2 (1,4)
Diagnosis (not mutually exclusive)^			
Respiratory distress syndrome (RDS)*	255 (77.5%)	505 (82.7%)	920 (90.3%)
Pulmonary hypoplasia	30 (9.1%)	40 (6.6%)	49 (4.8%)
Pulmonary hypertension	100 (30.4%)	164 (26.8%)	260 (25.5%)
Congenital pneumonia	2 (0.6%)	2 (0.3%)	10 (1.0%)

Congenital diaphragmatic hernia	0	0	1 (0.1%)
Death among infants who received iNO	143 (43.5%)	224 (36.7%)	242 (23.8%)

The denominator for all proportions is the number of babies treated with iNO unless indicated otherwise

† Denominator is all admissions to neonatal unit admissions requiring ≥ 1 day of intensive care

All values given as n, % or median (25^{th},75^{th} centiles), as appropriate.

*This includes the diagnosis *Respiratory distress syndrome* and *signs of respiratory distress of newborn (see supplementary file 1)*

^Extracted codes available in supplementary file

∞ Prolonged rupture of membranes >24 hrs uses a combination of discharge diagnoses and recorded duration of rupture of membranes

Table 2

Patient demographics and outcomes for infants born 29-33 weeks' admitted to neonatal units in England and treated with iNO

	2010-11	**2012-13**	**2014-15**
Neonatal admissions requiring ≥ 1 day of intensive care (with and without iNO)	12781	13796	14556
Infants treated with iNO	144 (1.1%†)	315 (2.3%†)	693 (4.8%†)
Birth weight (g)	1603 (1311,1972)	1500 (1290,1800)	1500† (1256,1800)
Gestational age (weeks)	30 (29,32)	31 (29,32)	31 (30,32)
Male sex	91 (63.2%)	187 (59.4%)	406 (58.6%)
Prolonged rupture of membranes >24 hr∞	34 (23.6%)	86 (27.3%)	124 (17.9%)
Surfactant therapy in labour ward or neonatal unit	131 (91.0%)	229 (72.7%)	418 (60.3%)
Initiation of iNO therapy (days)	2 (1,3)	3 (1,20)	10 (2,24)
Duration of iNO therapy (days)	2 (2,4)	1 (1,3)	1 (1,2)
Diagnosis (not mutually exclusive)^			

Respiratory distress syndrome*	92 (63.9%)	240 (76.2%)	604(87.2%)
Pulmonary hypoplasia	23 (16.0%)	46 (14.6%)	72 (10.4%)
Pulmonary hypertension	76 (52.8%)	108 (34.3%)	163 (23.5%)
Congenital pneumonia	1 (0.7%)	3 (1.0%)	2 (0.3%)
Congenital diaphragmatic hernia	7 (4.9%)	11 (3.5%)	15 (2.2%)
Death among infants who received iNO	59 (41.0%)	68 (21.6%)	76 (11.0%)

The denominator for all proportions is the number of babies treated with iNO unless indicated otherwise

† Denominator is all admissions to neonatal unit admissions requiring ≥ 1 day of intensive care

All values given as n, % or median (25^{th},75^{th} centiles) as appropriate.

*This includes the diagnosis *Respiratory distress syndrome* and *signs of respiratory distress of newborn (see supplementary file 1)*

^Extracted codes available in supplementary file

∞ Prolonged rupture of membranes >24 hrs uses a combination of discharge diagnoses and recorded duration of rupture of membranes

† 1 baby with a birthweight less than 300 grams was removed from this calculation (n=692)

Table 3

Patient demographics and outcomes for infants born >34 weeks' gestation admitted to neonatal units in England and treated with iNO

	2010-11	**2012-13**	**2014-15**
Neonatal admissions requiring ≥ 1 day of intensive care (with and	18374	22777	27872
Infants treated with iNO	820 (4.5%†)	1015 (4.5%†)	1400 (5.0%†)
Birth weight (g)	3273 (2840,3665)	3240 (2760,3690)	3220† (2680,3630)
Gestational age (weeks)	40 (38,41)	39 (37,40)	39 (37,40)
Male sex	450 (54.9%)	577 (56.9%)	756 (54.0%)
Prolonged rupture of membranes >24 hr∞	82 (10.0%)	92 (9.1%)	68(4.9%)
Surfactant therapy in labour ward or neonatal unit	532 (64.9%)	613 (60.4%)	713(50.9%)
Initiation of iNO therapy (days)	2 (1,2)	2 (1,2)	2 (1,2)
Duration of iNO therapy (days)	3 (2,5)	3 (2,5)	2 (1,5)
Diagnosis (not mutually exclusive)^			
*Respiratory distress syndrome**	259 (31.6%)	378 (37.2%)	778 (55.6%)
Pulmonary hypoplasia	61 (7.4%)	67 (6.6%)	101 (7.2%)
Meconium aspiration syndrome	314 (38.3%)	378 (37.2%)	440 (31.4%)
Pulmonary hypertension	598 (72.9%)	703 (69.3%)	885 (63.2%)

Congenital pneumonia	42 (5.1%)	52 (5.1%)	74 (5.3%)
Congenital diaphragmatic hernia	55(6.7%)	57(5.6%)	83 (5.9%)
Death among infants who received iNO	165 (20.1%)	160 (15.8%)	212 (15.1%)

The denominator for all proportions is the number of babies treated with iNO unless indicated otherwise

† Denominator is all admissions to neonatal unit admissions requiring ≥ 1 day of intensive care

All values given as n, % or median (25^{th},75^{th} centiles) as appropriate.

*This includes the diagnosis *Respiratory distress syndrome* and *signs of respiratory distress of newborn (see supplementary file 1)*

^Extracted codes available in supplementary file

∞ Prolonged rupture of membranes >24 hrs uses a combination of discharge diagnoses and recorded duration of rupture of membranes

† 1 baby with a birthweight less than 300 grams was removed from this calculation (n=1399)

Discussion

In this large population-level study we found that almost 1 in 20 infants that received any period of intensive care at an English neonatal unit were treated with iNO, that this rate almost doubled between 2010-2011 and 2014-2015 and that the temporal increase in iNO use was seen across all gestational ages. The temporal increase was most evident among more preterm infants < 34 weeks, in whom the use of iNO increased three-fold from 2.4% to 8.2% and where evidence for iNO is most lacking. There was a similar 3-4 fold increase in rates of iNO use for infants born <29 weeks and 29-33 weeks, from 4.9 to 15.9% and 1.1 to 4.8% for infants, respectively. In the most preterm group an additional 690 infants born <29 gestational weeks were treated with iNO in 2014-15 compared with 2010-11.

It is difficult to compare these data with internationally reported iNO usage rates because other studies commonly report rates as a proportion of all neonatal admissions, whereas we report rates as a proportion of infants receiving neonatal intensive care. We used this denominator because of differences in the organisation of neonatal care, specifically the use of a networked model of care in the United Kingdom which results in numerous transfers between neonatal units as part of routine care, and to minimise the impact of variations in practice around admissions of term infants for short periods. Rates of iNO usage in US studies are reported between 0.9% and 1.3% (2, 3) of all neonatal admissions. To our knowledge, this is one of the largest studies of iNO use in neonatal practice; other studies have reported iNO use in a various US healthcare organisations (including children's hospitals) and in all admissions including infants receiving lower acuity categories of neonatal care (1, 4, 9, 10).

The Canadian Neonatal network (CNN) found similar rates (1 in 25; 4.2%) of iNO use among infants born <34 weeks between 2010 and 2013. As different gestational age categories were used, direct comparisons cannot be made, but the use of iNO was broadly similar to the recent UK figures. However, in contrast to the increasing use in the UK, iNO use was stable across the 4 years in the CNN (11).

Approximately half of all infants that received iNO in this study were born at < 34 weeks gestation. This is relevant because the licensed indication for iNO limits treatment to

newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension (12). This finding is, however, broadly consistent with other studies from the US and Europe which showed that 40-46% of all treated infants were <34 weeks gestation (3, 13). Treatment rates for preterm infants in this study (5.1% of preterm infants < 34 weeks gestation) were comparable to other studies from the US reporting rates of 2.6% to 7.2% in the same gestation groups (1, 4, 9, 10), and in this comparison the different denominator in US studies is less likely to influence results as the majority of more preterm infants will receive intensive care.

We find that not only is off-label treatment with iNO of preterm infants < 34 weeks gestation widespread, it is increasing – particularly in the most preterm infants. The evidence base supporting routine use in these most preterm infants, both in respect of safety and efficacy, is weakest (2-4). Post-hoc analyses from a study which randomised 420 neonates born <34 weeks gestation to placebo or iNO found an apparent increase in mortality and higher rate of intraventricular haemorrhage in infants with a birth weight ≤1000g (14).

The reason for increasing use of iNO off-label in particularly in the most preterm infants is not known but is likely to be multifaceted and reflect the absence of other proven 'rescue' cardiorespiratory interventions for these smaller infants with severe hypoxaemic respiratory failure (such as extracorporeal membrane oxygenation) and full reimbursement of off-label iNO use in England. Furthermore there is some limited evidence for the use of iNO in specific groups of preterm infants including those born following preterm prolonged rupture of membranes and those with echocardiographic criteria of PPHN physiology, supported by expert opinion and consensus statements (15-18). There is growing experience in the use of iNO and the immediate short-term oxygenation response can be gratifying for clinicians, and may encourage further use. However, whether the short-term benefit in oxygenation is translated into longer-term benefit in preterm infants is unknown and needs further investigation. Moreover, the perception of absence of harm should not be extrapolated from term infants simply because there is a lack of convincing evidence of harm in preterm infants.

Treatment with iNO was started later and duration of treatment was shorter in later epochs, suggesting that preterm infants were more commonly treated outside the acute respiratory phase. Although there is little evidence of efficacy of iNO as rescue therapy in acute respiratory failure or later ventilator-dependent chronic lung disease (19, 20), we speculate that clinicians might be increasingly willing to use off-label iNO in such circumstances.

This study also demonstrates large variation between English neonatal units in rates of iNO use, in keeping with that reported in recent US studies (1, 10) where a similar degree of variation from 0.4% to 21.9% was seen in iNO use in preterm infants between 13 NICHD neonatal research network centres. The variation between neonatal units in the US decreased following publication of national guidance (21). Such national guidance is not available for the UK but might help to standardise practice in this area if it were to be developed.

Overall mortality decreased in iNO-treated infants during the study period. This trend mirrors national data reporting improved survival in extremely preterm infants in England (22) over a similar timeframe. The lower mortality seen in later epochs may also reflect a change in case-mix as iNO therapy is offered more readily to infants with less severe cardiorespiratory failure. This type of 'therapeutic creep' has been described with other neonatal interventions (23). This study was not designed to analyse changes in outcomes beyond simple descriptive data.

The strengths of this study include the use of a large national dataset derived from electronic patient data routinely entered by health professionals at the point of care, which has been shown to be accurate and complete. This contrasts with previous similar reports such as those from the National Institute of Child Health and Development Neonatal Research Network and the Pediatrix Medical Group that have focused on admissions to tertiary neonatal units or to a large network of neonatal care providers respectively (3, 9). Limitations of this study include that data held in the NNRD are recorded as part of routine clinical care and we cannot exclude the possibility of incomplete or inaccurate data. Also, we did not set out to capture information about neonatal iNO use in other critical care settings, such as paediatric or cardiac intensive

care units and these data would have been excluded from this study. Our study was also not designed to describe specific aspects of iNO therapy such as indication for use and dosage regimens.

Our study describes the increasing use of iNO, especially in more preterm infants, but was not designed to address the issue of potential benefits and risks of this practice. While iNO might be effective in certain subgroups of preterm infants, such as those with pulmonary hypoplasia and/or PPHN physiology, its short- and long-term safety has not yet been established. Potential concerns include an association between neonatal iNO therapy and pulmonary toxicity, brain injury and an increased risk of childhood cancer (24, 25). Inhaled nitric oxide is also one of the most expensive treatments available in neonatal care and there are likely to be resource implications of increasing use. Although there are limited data on costs of iNO therapy in the UK (26), estimates from the USA suggest a cost of approximately $125/hour or $3000/day (27).

In summary, the use of iNO in English neonatal units has almost doubled between 2010 and 2015, with the most notable increase seen in the most premature infants. There was substantial variation in iNO use between units. Approximately half of treated infants were preterm < 34 weeks gestation in whom iNO was used off-label and without high quality evidence of efficacy or safety. Given the cost of iNO therapy, limited evidence of efficacy in preterm infants, and potential for harm, we suggest that exposure to iNO should be limited, ideally to infants included in research studies (either observational or RCT) or within a protocolised pathway that permits a short trial of iNO to assess acute oxygenation response. Development of consensus guidelines might also help to standardise practice.

What is already known on this topic

maximum of 3 brief statements (no more than 25 words per statement)

- Inhaled nitric oxide (iNO) is a well-established and licensed therapy in term and near-term infants with hypoxaemic respiratory failure and pulmonary hypertension
- Evidence for the safety and efficacy of iNO in preterm infants is lacking
- iNO use is highly variable internationally; data describing iNO use across neonatal units in the United Kingdom is lacking

What this study adds

maximum of 3 brief statements (no more than 25 words per statement).

- Use of iNO increased over time from 3.4% (1,293/37,885) in 2010-2011 to 6.4% (3,112/48,838) in 2014-2015
- The increase in use of iNO is most notable in the most preterm infants born <29 weeks for which there is a paucity of evidence of benefit
- There is wide variation in iNO usage between neonatal intensive care units in England

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Author contributions

Study concept and design: NS, CG

Development of source code: KO, SJ, CB

Analysis and interpretation of data: NS, SJ, CG, CB

Writing and revision of the manuscript: NS, SJ, KO, CG, CB

Competing interests

CG reports grants from Medical Research Council, the National Institute for Health Research, the Mason Medical Research Foundation, Rosetrees Foundation and Canadian Institute for Health Research outside the submitted work; and grants and personal fees to attend an educational conference from Chiesi Pharmaceuticals outside the submitted work; he is a voluntary, unremunerated member of the Neonatal Data Analysis Unit Steering Board, which oversees the National Neonatal Research Database (NNRD), and is vice-chair of the NIHR Research for Patient Benefit London Regional Assessment Panel.

CB reports grants from the National Institute for Health Research outside the submitted work; and grants and personal fees to attend educational conferences from Chiesi and Abbvie Pharmaceuticals outside the submitted work; and is a member of the NIHR HTA prioritisation committee.

Data and materials availability:

The NNRD is not immediately available to the public. However, requests can be made by researchers to acquire access through: https://www.imperial.ac.uk/neonatal-data-analysis-unit/neonatal-data/utilising-the-nnrd/

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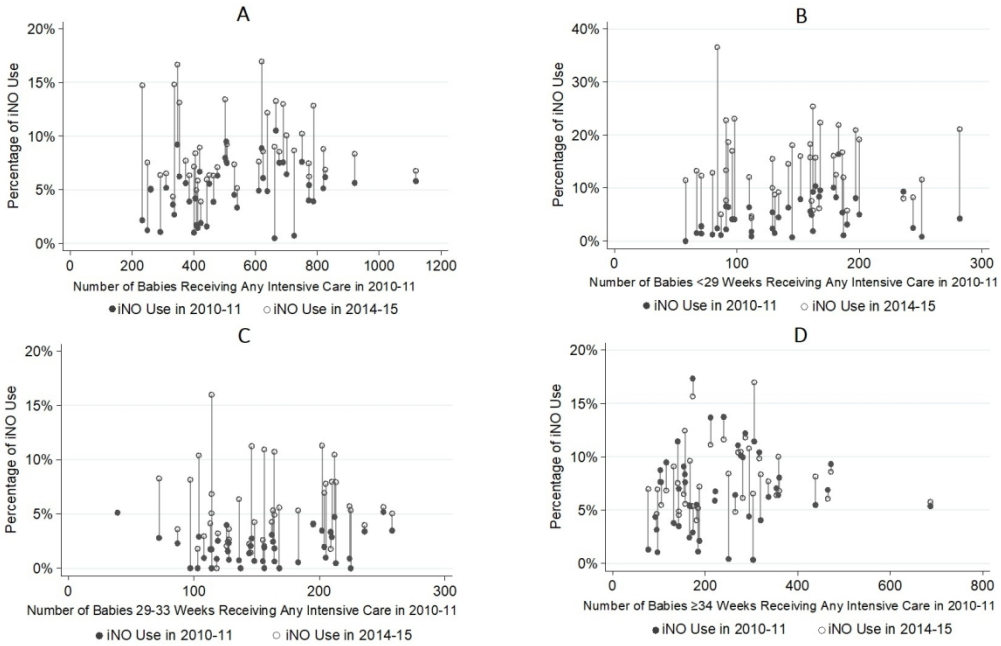

103x70mm (400 x 400 DPI)

Supplementary file 1

Diagnostic codes† extracted from the National Neonatal Research Database (NNRD):

Respiratory distress syndrome if any of the following:

'15574'- signs of respiratory distress of newborn
'15572'- Respiratory distress syndrome
'11010179'- respiratory distress-signs of
'15571' Respiratory Distress (ARDS)

Pulmonary hypoplasia if any of the following:

'16143'- Hypoplastic lungs
'16154'- Hypoplasia and dysplasia of lung
'10892'- Pulmonary hypoplasia
'16151'- Agenesis of lung

Persistent pulmonary hypertension of the newborn if any of the following:

'15241'- Primary pulmonary hypertension (not PPHN)
'15242'- Secondary pulmonary hypertension (not PPHN)
'10010891'- Pulmonary hypertension (secondary)
'10891'-Pulmonary hypertension (secondary)
'10890'- Pulmonary hypertension (primary)
'10010890'- Pulmonary hypertension (primary)
'15621'- Pulmonary hypertension (PPHN)
'10829'- Persistent Pulmonary Hypertension of the Newborn (PPHN)
'15630'- Persistent Pulmonary Hypertension (PPHN secondary to other condition)
'15629'- Persistent Pulmonary Hypertension (PPHN: idiopathic)

Meconium Aspiration Syndrome:

'15588'- Meconium aspiration syndrome

Congenital pneumonia if any of the following:

'15577'- Congenital pneumonia due to viral agent
'15581'- Congenital pneumonia due to Streptococcus, group B
'15580'- Congenital pneumonia due to Staphylococcus
'15583'- Congenital pneumonia due to Pseudomonas
'15585'- Congenital pneumonia due to other organisms
'15584'- Congenital pneumonia due to other bacterial agents
'15582'- Congenital pneumonia due to Escherichia coli
'15578'- Congenital pneumonia due to Chlamydia
'15586'- Congenital pneumonia (unknown or unspecified cause)
'15587'- Congenital pneumonia

Congenital diaphragmatic hernia if any of the following:

'16495'- Congenital diaphragic hernia
'16497'- Eventration of diaphragic hernia
'1001925'- Unspecified repair of diaphragmatic hernia
'1006671'- Repair of congenital diaphragmatic hernia
'10905'- Recurrent congenital diaphragmatic hernia
'11660'- Prosthetic repair of congenital diaphragmatic hernia (specify)
'11657'- Primary repair of congenital diaphragmatic hernia
'1001924'- Other specified repair of diaphragmatic hernia
'11597'- Other repair of diaphragmatic hernia (specify)
'10694'- Morgagni diaphragmatic hernia
'1015977'- Diaphragmatic hernia - right
'1015978'- Diaphragmatic hernia - left
'1010217'- Diaphragmatic hernia - left
'10010246'- Diaphragmatic hernia - congenital

Prolonged rupture of membranes >24 hr if any of the following:

'15406'- Prolonged preterm rupture membranes >24hr
'15459'- Prolonged rupture membranes (PROM: Term)
'15407'- Prolonged rupture membranes >24hr
'15462'- Preterm pre-labour rupture of membranes (PROM >24hrs)

† These diagnostic codes are specific to the Badger Net EPR system developed by Clevermed Ltd and from which the NNRD pulls neonatal data.

Supplementary file 2

Congenital heart disease diagnoses in order of frequency

	Gestation (Weeks)			
Diagnoses	**<29**	**29 to 33**	**≥34**	N (column percentage)
Ventricular Septal Defect (VSD)	79	85	160	324 (27.9%)
Atrial Septal Defect (ASD)	111	52	96	259 (22.2%)
Pulmonary stenosis	31	23	15	69 (5.9%)
Transposition of the great arteries	4	11	52	67 (5.8%)
Ventricular hypertrophy	11	13	26	50 (4.3%)
Atrioventricular Septal Defect (AVSD)	1	8	25	34 (2.9%)
Coarctation of aorta	4	7	19	30 (2.6%)
Congenital malformations of cardiac chambers and connections	2	4	23	29 (2.5%)
Tetralogy of Fallot	5	6	14	25 (2.2%)
Other congenital heart diagnoses	34	55	186	275 (23.7%)
Total	**282**	**264**	**616**	**1162**