Hospital Variation in Nitric Oxide Use for Premature Infants

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KEY WORDS

nitric oxide, practice variation, prematurity

ABBREVIATIONS

AAP—American Academy of Pediatrics

AHRQ—Agency for Healthcare Research and Quality

BPD—bronchopulmonary dysplasia

CI—confidence interval

iNO—inhaled nitric oxide

IVH—intraventricular hemorrhage

NIH—National Institutes of Health

OR—odds ratio

PHIS—Pediatric Health Information System

All named authors meet the criteria for authorship as defined in the instructions for authorship. Specific contributions were as follows: Drs Stenger, Kelleher, and Gardner developed the idea for the study; Drs Stenger, Gardner, and Slaughter were responsible for the original draft of the manuscript; Drs Stenger, Shepherd, Slaughter, and Nelin categorized *International Classification of Diseases, Ninth Revision codes*; Drs Gardner, Kelleher, Reagan, and Nelin provided statistical analysis and interpretation of data; and Drs Stenger, Slaughter, Kelleher, Shepherd, Nelin, Reagan, Gardner, and Klebanoff revised the manuscript for important intellectual content and provided final approval of the draft for submission.

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WHAT'S KNOWN ON THIS SUBJECT: Inhaled nitric oxide for premature infants has been evaluated in multiple studies; however, these trials differed in treatment initiation, duration of therapy, and inclusion criteria. Furthermore, these trials reached differing conclusions regarding the benefit of inhaled nitric oxide.

WHAT THIS STUDY ADDS: We used a large sample of infants from children's hospitals and found that the use of inhaled nitric oxide in premature infants was variable even when controlling for demographic characteristics and disease.

abstract

OBJECTIVE: To describe inter-center hospital variation in inhaled nitric oxide (iNO) administration to infants born prior to 34 weeks' gestation at US children's hospitals.

METHODS: This was a retrospective cohort study using the Pediatric Health Information System to determine the frequency, age at first administration, and length of iNO use among 22 699 consecutive first admissions of unique <34 weeks' gestation infants admitted to 37 children's hospitals from January 1, 2007, through December 31, 2010.

RESULTS: A total of 1644 (7.2%) infants received iNO during their hospitalization, with substantial variation in iNO use between hospitals (range across hospitals: 0.5%–26.2%; $P < .001$). The age at which iNO was started varied by hospital (mean: 20.0 days; range: 6.0–65.1 days, $P < .001$), as did the duration of therapy (mean: 13.1 days; range: 1.0–31.1 days; $P < .001$). Preterm infants who received iNO were less likely to survive (36.3% mortality vs 8.3%; odds ratio: 6.27; $P < .001$). The association between the use of iNO and mortality persists in propensity score–adjusted analyses controlling for demographic factors and diagnoses associated with the use of iNO (odds ratio: 3.79; $P < .001$).

CONCLUSIONS: iNO practice patterns in preterm infants varied widely among institutions. Infants who received iNO were less likely to survive, suggesting that iNO is used in infants already at high risk of death. Adherence to National Institutes of Health consensus guidelines may decrease variation in iNO use. *Pediatrics* 2012;129:e945–e951

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator approved for use in term and near-term infants with hypoxic respiratory failure. iNO has since been studied in infants <34 weeks' gestation to determine if it can prevent the complications of prematurity.^{1–7} These studies varied greatly in inclusion criteria, length of therapy, and duration of therapy. Unfortunately, the results of these studies have been equivocal, and a recent meta-analysis,⁸ a National Institutes of Health (NIH) Consensus Development Conference,⁹ and an evidence report from the Agency for Healthcare Research and Quality (AHRQ)¹⁰ have all concluded that there is no evidence to support the routine use of iNO in preterm infants who require respiratory support except in rigorously conducted randomized controlled trials. Despite these data, iNO use remains relatively common in preterm infants in NICUs of children's hospitals in the United States.^{8–10}

We hypothesized that iNO use is variable among NICUs with little measurable effect on outcomes. We describe care that was delivered immediately before the NIH and AHRQ statements. Our goal was to characterize variation in recent practice, which can help determine whether efforts to implement evidence-based standardization are needed. Specifically, we evaluated the following: (1) the variability across hospitals of iNO use, (2) the age when iNO was started and the duration of its use, and (3) the association of iNO with mortality.

METHODS

Study Design and Data

This study was approved by the institutional review board of Nationwide Children's Hospital (Columbus, OH). This trial was a retrospective cohort study of premature infants <34 weeks' gestation admitted to NICUs in children's hospitals participating in the Pediatric Health Information System (PHIS) database of the

Child Health Corporation of America, a database of administrative, billing, and record review data from 44 US children's hospitals. Three of the hospitals either do not have an NICU or do not contribute NICU data to PHIS, and 4 were excluded because they had missing or problematic data on either gestational age or on the date of admission; thus, 37 hospitals were included in the study. We used PHIS because it enabled us to obtain a large sample of unique-patient hospital visits. The PHIS database includes patient demographic characteristics, diagnoses, medications, and procedures. Data are accepted into PHIS only when classified errors occur in <2% of a hospital's quarterly data. PHIS data have been used in many recent analyses of pediatric care.^{11–20} Kaplan et al examined the validity of birth weight, vitamin A use, and discharge year and found that agreement was 91%, 97%, and 100%, respectively.¹⁵

The cohort included 22 699 unique infants admitted to participating NICUs from January 1, 2007, until June 30, 2010, with a gestational age of 22 to 33 weeks and a birth weight of 400 to 3999 g. We excluded infants born at <22 weeks' gestation and birth weight <400 g. We excluded infants with birth weight ≥4000 g because this finding was most likely a clerical error given our <34-week gestation population. Infants were also excluded if data were missing for age at admission or if that age was >30 days.

Statistical Analysis

Comparisons of infants receiving iNO with infants who did not receive iNO will be problematic in these data, because use of iNO was not randomly assigned and the comparisons are therefore subject to confounding by indication. Although this problem cannot be eliminated, we reduced it by estimating a propensity score for the probability of

receiving iNO.^{21,22} The propensity score was used in several of the analyses to adjust for patient factors that were associated with the receipt of iNO.

The propensity scores were estimated by using a logistic regression that included the patient's gender, race, age at admission, birth weight, and gestational age at birth, as well as a selection of the *International Classification of Diseases, Ninth Revision* diagnostic codes associated with the admission. These codes were selected as follows. First, we eliminated all codes that were recorded for <5 patients. Second, we selected conditions that were most likely to have started before the infant's NICU admission (eg, codes for congenital problems, complications of birth). A panel of 4 neonatologists, working by consensus, identified 409 such codes. We did include health problems that could potentially have developed after admission to the hospital. Because these problems could have developed after the initiation of iNO treatment, it would be an error to include such variables in a regression predicting iNO use. This decision was determined in part by a limitation of the PHIS data set, which does not include dates for when patients received diagnoses. Third, from among the 409 codes, we used an algorithm for developing "high-dimensional" propensity scores proposed by Schneeweiss et al²² to select codes to be used in the regression to estimate the propensity scores. High-dimensional refers to the use of a large number of covariates to estimate the propensity score, to maximize the similarity of patients within strata defined according to the propensity score. We estimated propensity scores with equations that used 100 diagnostic codes picked by using the criteria of Schneeweiss et al.

Mixed-effects logistic, Poisson, and linear regressions were performed to identify patient and hospital factors associated with the rate of iNO use, the

counts of days of iNO use, and the age at which iNO treatment was initiated. Hospital factors included geographical region, status as an American Academy of Pediatrics (AAP)-accredited training program, and NICU volume (ie, the patients meeting inclusion criteria treated per year). These mixed-effects regressions included random intercepts for hospitals, representing variation in iNO use that was not accounted for by the covariates.

We looked for evidence of benefit from iNO use by calculating a mixed model logistic regression, with patient death as the dependent variable and iNO use as a covariate. We then estimated a logistic regression, with death as the dependent variable, iNO as the treatment variable, and dummy variables representing the deciles of the propensity score to adjust for differences among infants in the likelihood of receiving iNO. Finally, we estimated a logistic regression with death as the dependent variable, iNO, dummy variables for the propensity score deciles, and covariates for bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC) stage II or III, and intraventricular hemorrhage (IVH) to determine whether including diagnoses that occur during NICU stays changed our estimate of the association between iNO and mortality.

All analyses were performed by using Stata version 10. (Stata Corp, College Station, TX).

RESULTS

Hospital Variation in Patterns of iNO Use

A total of 1644 patients from the original 22 699 (7.2%) were treated with iNO. Figure 1A presents the >50-fold variation among hospitals in the proportions of patients who received iNO. iNO was initiated, on average, at 20.0 days of age (median: 9). Figure 1B presents a >15-fold variation across hospitals in the average age at which iNO was

FIGURE 1

Study data are from 37 children's hospitals. A, Histogram of the proportions of patients receiving iNO at each hospital. Rates of iNO use varied from 0.4% to 26.2% across NICUs ($P < .0001$). B, Histogram of the average ages at which patients first received iNO at each hospital. The hospital-specific means of the age of initiation ranged from 5.5 to 83.4 days ($P < .001$). C, Histogram of the average number of days of iNO received by a patient at each hospital. The hospital-specific means of the number of days of iNO received ranged from 1.0 to 32.0 ($P < .001$). D, Scatter plot of the association between hospitals' rates of iNO use and the average number of days of iNO use, with regression line ($r = 0.65$; $P < .001$).

started. The mean length of iNO administration was 13.1 days (median: 6). Figure 1C presents a 32-fold variation across hospitals in the average number of days the patient received iNO (range: 1.0–32.0 days; $P < .001$). Figure 1D presents the strong correlation between the percentage of patients receiving iNO at a hospital and the average number of days they spent receiving iNO ($r = 0.65$; $P < .001$). There were no significant associations between the average age when iNO was started and either the rate of use of iNO ($r = -0.16$; $P = .33$) or the average number of days of iNO use per patient ($r = 0.16$; $P = .33$).

Factors Associated With NICU Variation in iNO Use

Table 1 reports odds ratios (ORs) describing the associations between patient demographic characteristics and the rate of iNO use. It also reports ORs adjusted for all covariates in the table. The use of iNO was more likely in infants

born at younger gestational ages, with lower birth weights, and admitted after the first day of life. There were no racial differences in rates of iNO use in the adjusted analyses. Finally, the rate of use of iNO increased from 2007 to 2009, and declined in 2010.

Looking at factors that differentiated the NICUs, NICUs with higher volume were substantially less likely to use iNO (Table 1, Fig 2). NICUs in the northeast region used less iNO, whereas having an AAP-accredited training program was not associated with iNO use. The adjusted estimates were calculated in a logistic regression that included a random effect for the hospital in which the patient was treated. There was statistically significant variation in the residual differences among hospitals in iNO usage, after accounting for the covariates in the regression ($\chi^2(1) = 316.8$; $P < .001$).

A mixed model Poisson regression analysis was used to examine factors

TABLE 1 Patient Demographic and Hospital Factors Associated with Use of iNO

Variable	N (%) ^a	% NO ^b	Bivariate Analyses ^c		Multiple Logistic Regression ^e	
			OR (95% CI)	P ^d	Adjusted OR (95% CI)	P
Patient demographic characteristics						
Female infant	10 185 (44.9)	6.6	0.85 (0.77–0.94)	.002	0.84 (0.76–0.94)	.002
Gestational age, wk						
22–24	2282 (10.1)	17.5	—	—		
25–27	4824 (21.3)	11.3	0.60 (0.52–0.69)	<.001	0.62 (0.53–0.72)	<.001
28–30	5913 (26.0)	5.9	0.29 (0.25–0.34)	<.001	0.41 (0.34–0.51)	<.001
31–33	9680 (42.6)	3.7	0.18 (0.15–0.21)	<.001	0.28 (0.22–0.37)	<.001
Birth weight, g						
400–1000	7115 (31.3)	13.3	—	—		
1001–1500	6568 (28.9)	5.3	0.37 (0.32–0.42)	<.001	0.60 (0.50–0.71)	<.001
1501–2000	5879 (25.9)	3.7	0.25 (0.21–0.29)	<.001	0.56 (0.44–0.71)	<.001
2001–2500	2566 (11.3)	3.5	0.23 (0.19–0.29)	<.001	0.58 (0.43–0.79)	.001
>2500	571 (2.5)	7.5	0.53 (0.38–0.72)	<.001	1.21 (0.82–1.77)	.338
Race/ethnicity						
White	10 246 (45.1)	6.9	—	—		
Black	4242 (18.7)	9.0	1.35 (1.18–1.54)	<.001	1.00 (0.87–1.16)	.947
Hispanic	3355 (14.8)	8.3	1.23 (1.06–1.42)	.006	1.12 (0.94–1.32)	.197
Asian	592 (2.6)	4.1	0.58 (0.37–0.86)	.005	0.55 (0.36–0.86)	.008
Other	4264 (18.8)	6.0	0.87 (0.75–1.01)	.067	1.01 (0.86–1.20)	.878
Admitted age 1 d						
No	6392 (28.2)	10.3	—	—		
Yes	16 307 (71.8)	6.0	0.56 (0.50–0.62)	<.001	0.91 (0.80–1.03)	.128
Admission year						
2007	6075 (26.8)	6.1	—	—		
2008	5579 (24.6)	7.5	1.24 (1.07–1.43)	.003	1.32 (1.13–1.54)	<.001
2009	5114 (22.5)	8.1	1.35 (1.17–1.57)	<.001	1.33 (1.13–1.55)	<.001
2010	5931 (26.1)	7.4	1.21 (1.05–1.40)	.008	1.32 (1.12–1.54)	.001
Hospital characteristics						
NICU volume						
1–250/y	12 619 (55.6)	9.3	—	—		
>250/y	10 080 (44.4)	4.7	0.48 (0.43–0.53)	<.001	0.48 (0.28–0.83)	.008
Region						
Northeast	1165 (5.1)	3.6	—	—		
North Central	8631 (38.0)	6.8	1.93 (1.42–2.70)	<.001	3.19 (1.36–7.46)	.007
South	6689 (29.5)	9.2	2.71 (2.00–3.79)	<.001	3.26 (1.44–7.37)	.005
West	6214 (27.4)	6.4	1.83 (1.34–2.57)	<.001	3.37 (1.43–7.94)	.006
AAP-accredited program	11 192 (49.3)	7.0	0.94 (0.85–1.04)	.269	0.85 (0.54–1.36)	.505

^a Frequency and percentage of the patients with the characteristic.^b Number and percentage of patients who received iNO.^c OR (95% CI) describing the simple association between the factor and the use of iNO.^d Statistical significance value associated with the OR describing the simple association between the factor and the use of iNO. Where a covariate has ≥ 3 levels, the ORs always compare the level against the first level.^e Multiple Logistic Regression/Adjusted OR (95% CI) and Multiple Logistic Regression/P are the same association measures, but the association measure was adjusted for all the other covariates in a multiple logistic regression that also included a random hospital-specific effect.

associated with the number of days of iNO treatment received by patients ($N = 1644$). Being born at a lower birth weight or at a younger gestational age was associated with more days of iNO use. Neither NICU volume nor the region of the hospital was associated with the number of days of iNO received. The variation in residual hospital effects on the duration of iNO treatment was statistically significant ($\chi^2(1) = 3230$; $P < .001$).

Similarly, a mixed model linear regression analysis was used to examine factors associated with the day of life when iNO was started. Being born at a lower birth weight was associated with starting iNO older ($P < .0001$). NICUs with an annual patient volume >250 started iNO when patients were 9.4 days older (95% confidence interval [CI]: 1.2–17.5; $P < .0001$). The variation in residual hospital effects on the age of initiation of iNO treatment was again

statistically significant ($\chi^2(1) = 17.8$; $P < 0.001$).

Use of iNO and Mortality

Of the 22 699 patients, 2332 (10.3%) died before discharge. The mortality rate among patients receiving iNO was 35.6% compared with 8.3% among the infants not receiving iNO (OR: 6.13 [95% CI: 5.48–6.85]; $P < <0.001$). Figure 3 presents mortality rates according to propensity score decile and iNO treatment

FIGURE 2

Study data are from 37 children's hospitals. The horizontal axis is the number of patients meeting inclusion and exclusion criteria in this study for each hospital, divided by 3.5 years. The vertical axis is the rate of iNO use (% of patients) for each hospital. The red line is the linear regression of iNO use on volume.

FIGURE 3

The horizontal axis represents deciles of the sample, grouped according to increasing probability that the patients would receive iNO (ie, the estimated propensity score). Within each decile, the mortality rates (with 95% CIs) were plotted for patients who did (blue points, line, and error bars) or did not receive iNO (in red).

status. In a logistic regression with death as the dependent variable, iNO status as the treatment variable, and dummy variables for propensity score deciles, the OR for death given use of iNO, adjusted for the propensity of receiving iNO, was 3.30 (95% CI: 2.93–3.72; $P < .0001$).

We re-estimated this logistic regression with additional covariates representing 3 major illnesses that occur during NICU care: BPD, NEC stage II or III, and IVH. BPD was associated with an adjusted OR of 0.13 (95% CI: 0.11–0.15; $P < .001$); the adjusted OR for IVH was 2.10 (95% CI:

1.85–2.38; $P < .001$); and the adjusted OR for NEC was 2.07 (95% CI: 1.69–2.55; $P < .001$). Inclusion of these diagnoses did not reduce the adjusted OR for death associated with iNO use (3.79 [95% CI: 3.32–4.32]; $P < .001$).

DISCUSSION

The off-label administration of iNO to infants born before 34 weeks' gestation involved $>7\%$ of our cohort and was significantly greater than the 1.6% to 1.8% rate reported by Clark et al²³ in 2007 and 2008. This finding may reflect differences in patient populations; for example, patients in this study may have had a higher acuity. Alternatively, children's hospitals may have a lower threshold for initiating iNO therapy. The mortality rate of 36.3% for premature infants who received iNO is similar to the 36.8% combined mortality rate reported by Clark et al. The rate of use of iNO in the hospitals in the PHIS database increased each year from 2007 through the first half of 2010.

Intercenter practice variation in iNO administration was substantial, with >17 -fold difference in utilization among hospitals. There was also substantial variation in the age of initiation of iNO treatment (an almost 10-fold difference) and the average number of days of use (an almost 20-fold difference). Hospitals that used iNO in more patients also used iNO for a longer duration. After accounting for many demographic and diagnostic variables that characterized the infants on admission and that are markers for acuity, large residual hospital effects were found for each parameter of iNO administration. Higher volume NICUs used less iNO and had lower mortality rates, a finding similar to recent reports regarding volume and mortality.^{24,25} We found regional differences in use of iNO, with northeastern hospitals reporting less use of iNO. In summary, the data revealed a pervasive lack of standardization in iNO use across

NICUs. It is likely that there were unmeasured patient severity factors that could explain some of these differences. Nevertheless, there are substantial differences in care patterns across NICUs, similar to variability in care that has been described for other treatments.^{12–15,20} The variation in care points to the importance of comparative effectiveness research to develop evidence-based treatment algorithms.

Did iNO use benefit patients? Because these data are observational, we cannot be certain. However, iNO use was associated with a high mortality rate even among groups of patients who, on the basis of their demographic and diagnostic profiles, would have had a reduced chance of either dying or receiving iNO. Although it is intuitively attractive to use iNO in this extremely high-risk population, and it is possible that randomized trials could identify a subgroup of these infants who can benefit from iNO, our findings are consistent with the Van Meurs trial,⁷ suggesting that the use of iNO in extremely low birth weight infants with the most severe forms of respiratory failure did not improve rates of mortality.

Our study was limited by the data available in the PHIS database, which includes only children's hospitals. Because these

hospitals are usually not birth hospitals, the patients in our cohort were presumably referred for specialized care, so these patients may not be representative of all patients <34 weeks' gestation. Information about care received at outside hospitals is not available in PHIS, and infants may have received iNO before admission at the children's hospital, including the possibility that iNO use might have been initiated at a previous hospital. Nor did we have information about the reasons why patients were referred. This factor limits our ability to explain variation across hospitals in the use of iNO. Because our clinical information is primarily the *International Classification of Diseases, Ninth Revision* diagnostic and procedure codes, nonbillable data are more likely to be omitted or unmeasured. Although PHIS has extensive quality-control procedures, we cannot verify that the diagnoses were made and coded in a similar way across hospitals. More importantly, lacking access to other clinical data, we had a limited ability to measure severity of illness. Finally, although we knew the duration of iNO therapy, we did not know the dose.

These limitations were balanced by important strengths, including a large

sample size. Second, the data included many NICUs. This factor is critical because attempts to identify factors that explain variation between NICUs require a large and diverse sample of NICUs.

CONCLUSIONS

The use of iNO among premature infants admitted to NICUs was variable across children's hospitals. Variation in practice remained even when we controlled for patient demographic characteristics and for diagnostic factors that were likely to characterize the patient on admission to the hospital; hence, it is evident that iNO has been used in a nonstandard way across NICUs. Carefully designed experimental trials to identify possible subgroups that might benefit from iNO are still warranted. However, given our findings, in combination with the findings of the recent Cochrane Review, the 2010 NIH Consensus Statement, and the AHRQ evidence report that insufficient evidence exists to recommend use of iNO in infants at <34 weeks' gestation,^{8–10} there is a need for adherence to and further development of evidence-based protocols to standardize care to avoid unnecessary and costly treatment.

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