Inhaled Nitric Oxide Use in Neonates With Congenital Diaphragmatic Hernia

WHAT’S KNOWN ON THIS SUBJECT: The role of inhaled nitric oxide (INO) in the treatment of newborns with congenital diaphragmatic hernia (CDH) is poorly defined and not rigorously proven. Contemporary rates of INO use for CDH have not been reported.

WHAT THIS STUDY ADDS: INO use in neonates with CDH is widespread, and has increased in many US tertiary pediatric hospitals without associated decrease in extracorporeal membrane oxygenation use or mortality.

abstract

OBJECTIVE: To describe the use of inhaled nitric oxide (INO) in newborns with congenital diaphragmatic hernia (CDH).

METHODS: Pediatric Health Information System data were queried for newborns with CDH admitted at <8 days of age at tertiary care US pediatric hospitals between 2003 and 2011. INO treatment status and timing in relation to CDH repair were determined for each infant. Hospital-specific rates of INO use, extracorporeal membrane oxygenation (ECMO) use, and mortality were determined.

RESULTS: Data were analyzed for 1713 neonates with CDH admitted to 33 hospitals. More than half (57%) received INO during their inpatient stay, and utilization varied dramatically between hospitals (34% to 92%). Neonates treated with INO accumulated >$81 million in pharmacy charges. The proportion of infants receiving INO as well as their duration of therapy increased significantly during the study period. The rate of ECMO utilization and mortality did not change significantly during the study period. Hospital-specific mortality rates did not correlate with INO therapy, ECMO utilization, or case volume.

CONCLUSIONS: INO use in neonates with CDH is widespread, and has increased at many US tertiary pediatric hospitals without contemporaneous change in ECMO utilization or mortality. The improvement of evidence-based guidelines for the use of INO in newborns with CDH could lead to a reduction in health care costs for these patients. Pediatrics 2014;134:e420–e426

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KEY WORDS congenital diaphragmatic hernia, nitric oxide, pulmonary hypertension, health expenditures

ABBREVIATIONS

CDH—congenital diaphragmatic hernia
CI—confidence interval
ECMO—extracorporeal membrane oxygenation
INO—inhaled nitric oxide
IQR—interquartile range
OR—odds ratio
PHIS—Pediatric Health Information System

Drs Campbell and Ruscher conceptualized and designed the study; Ms Herbst conceptualized and designed the study, and performed data collection and analysis; Dr Briden conceptualized and designed the study, and drafted the initial manuscript; Mr Neff conceptualized and designed the study, and performed data collection; Dr Hagadorn conceptualized and designed the study, and performed data analysis; and all authors reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Congenital diaphragmatic hernia (CDH) occurs in 1 of every 2200 to 4200 births.1 Neonates with CDH frequently develop hypoxic respiratory failure requiring aggressive support to maintain gas exchange in hypoplasic lungs that are subject to severe pulmonary hypertension. Initial treatment of hypoxic respiratory failure in newborns with CDH is generally consistent with management of persistent pulmonary hypertension of the newborn, and includes sedation, permissive hypercapnia, high-frequency oscillatory ventilation, and the avoidance of acidosis and barotrauma.2,3 When these modalities fail, neonates with CDH may be supported with extracorporeal membrane oxygenation (ECMO), which has been shown to improve survival.4,5 Nitric oxide, an important endogenous mediator of vascular tone, causes vascular smooth muscle relaxation and subsequent vasodilatation.6,7 Inhaled nitric oxide (INO) has a prominent role in the treatment of severe hypoxic respiratory failure from a variety of causes because of its proven efficacy in decreasing ventilation-perfusion mismatch and improving oxygenation.8,9 In both primary and secondary persistent pulmonary hypertension of the newborn, INO improves oxygenation, reduces the need for ECMO, or improves neurodevelopmental outcomes when other therapies fail.10–12 Clinicians have hoped that pulmonary hypertension in patients with CDH would respond similarly; however, no randomized trial has demonstrated that INO improves outcomes in these patients. Two well-designed, methodologically sound trials found that early INO treatment fails to improve survival or reduce need for ECMO in newborns with CDH.13,14 In fact, INO therapy may actually increase the need for ECMO in this population. A Cochrane review concluded that early INO does not improve outcomes in neonates with CDH, may in fact worsen outcomes, and recommends against using INO to manage early hypoxic respiratory failure in these patients.11 The purpose of this study was to describe the current utilization, trends, interhospital variability, and costs associated with INO use in a nationally representative cohort of newborns with CDH treated at pediatric referral centers in the United States.

**METHODS**

Data for this study were obtained from the Pediatric Health Information System (PHIS), an administrative database that contains inpatient, emergency department, ambulatory surgery, and observation data from 43 not-for-profit, tertiary care pediatric hospitals in the United States. These hospitals are affiliated with the Children’s Hospital Association. The data warehouse function for the PHIS database is managed by Truven Health Analytics. Data are de-identified at the time of data submission and are subjected to reliability and validity checks before inclusion in the database. Hospitals were excluded from the study if they did not submit billing data, or did not have an ECMO program during the study period.

This research used unlinked de-identified data and was not considered human subjects research in accordance with the Common Rule (45CFR §46.102[f]) and the policy of the Connecticut Children’s Medical Center Institutional Review Board.

**Subjects**

Included in this study were neonates born between January 1, 2003, and December 31, 2011, whose records reported an initial PHIS hospital admission during their first week of life, an *International Classification of Diseases, Ninth Revision* diagnosis code for CDH (552.3, 553.3) or anomalies of the diaphragm (756.6), and either died or had an *International Classification of Diseases, Ninth Revision* procedure code for diaphragmatic hernia repair (53.7–53.84) by 60 days of life. Our study excluded readmittance inpatient stays, neonates with a diagnosis code for any significant congenital cardiac anomaly (745.0–745.7, 746.0–746.9, and 747.1–747.49), and neonates with CDH who were alive at 60 days and did not undergo CDH repair. Patients with missing billing data or $0 total billed from all sources during their inpatient stay were excluded, as presence or absence of INO treatment was determined by using billing data.

Patient data obtained from the PHIS database included date of birth, dates of therapy with INO or ECMO, date of CDH repair, charges for INO, and disposition data. Length of stay and age at time of specific events were determined by subtraction. Patients were counted as receiving INO if their billing record reflected INO charges during their inpatient stay. INO treatment status and timing in relation to CDH repair were determined for each infant. Annual and overall rates of INO use, ECMO use, and mortality were determined for each hospital.

All charges in the data set are hospital charges billed, and may be an overestimation of actual cost. INO charge per inpatient day for each infant was calculated by dividing total INO charges for the hospital stay by INO days. Because hospitals were inconsistent in the services they included when reporting INO charges (ie, some hospitals included charges for respiratory therapist, equipment, and so forth, as well as the cost of INO), we used the median INO charge per day to standardize estimated INO charges across PHIS hospitals.

**Statistics**

Analyses of independent data were performed by using SPSS 17.0 (IBM...
RESULTS

A total of 1713 neonates with CDH were identified from 33 PHIS hospitals from 2003 to 2011. We excluded records for patients who were readmitted \((n = 6)\), had congenital cardiac anomalies \((n = 2008)\), were alive and did not undergo CDH repair during the first 60 days of life \((n = 220)\), or had missing or incomplete billing data \((n = 108)\). Most subjects were white boys with a median gestational age of 38 weeks and a median birth weight of 3000 g (Table 1). More than three-quarters were admitted to the PHIS hospital on their first day of life. Median inpatient stay was 25 days (interquartile range [IQR] 14–47), overall, including 32 days (IQR 20–59) for survivors and 15 days (IQR 2–29) for nonsurvivors. Median age for CDH repair was 5 days (IQR 3–10). Overall mortality rate was 54% \((n = 578)\) for the study cohort, ranging from 14% to 65% between hospitals. Mortality rate was 100% among infants not undergoing CDH repair. One-third of nonsurvivors (33%) died during the first 3 days of life.

More than half (57%) of neonates with CDH received INO, with a median course of therapy of 8 days (IQR 2–18). Eleven percent of neonates receiving INO had a course of therapy of 30 days or longer, and 3% received >60 days of treatment. Peak INO use was on the second day of life, with 38% of patients being treated (Fig 1). Treated infants received a total of 14 205 days of INO therapy, including 1264 days among infants who died without undergoing surgical repair. Of the 1374 infants undergoing CDH repair, nearly half (48%) received INO before surgery (Table 2), for a total of 4186 days of INO treatment. Forty percent of patients received INO after surgical repair, accounting for 8358 treatment days and most (59%) of INO use.

Wide variation in INO use was seen between PHIS hospitals, ranging from 34% to 92%. Hospital case volume, defined as total CDH cases treated by a hospital during the study period, ranged from 15 to 120 and did not correlate with repair rate \(\left(r_s = 0.14\right)\), INO use \(\left(r_s = -0.17\right)\), ECMO therapy \(\left(r_s = -0.07\right)\), or mortality \(\left(r_s = -0.03\right)\).

TABLE 1

Population and In-Patient Stay Characteristics \((n = 1713)\)

<table>
<thead>
<tr>
<th>Demographic and Characteristics</th>
<th>n (% or median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys</td>
<td>1039 (61)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1108 (65)</td>
</tr>
<tr>
<td>African American</td>
<td>147 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>458 (26)</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>38 (37–39)</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3000 (2585–3400)</td>
</tr>
<tr>
<td>Age at admission</td>
<td></td>
</tr>
<tr>
<td>Day of birth</td>
<td>1361 (79)</td>
</tr>
<tr>
<td>Birth +1 d</td>
<td>280 (16)</td>
</tr>
<tr>
<td>≥2 d after birth</td>
<td>72 (5)</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>25 (14–47)</td>
</tr>
<tr>
<td>CDH repaired</td>
<td>1374 (80)</td>
</tr>
<tr>
<td>Age at CDH repair, d</td>
<td>5 (3–10)</td>
</tr>
</tbody>
</table>

Nearly one-quarter (23%) of patients with CDH were treated with ECMO for a total of 4814 days. This included 2414 days of ECMO before surgical repair, and 939 days in infants who died before repair. Peak ECMO use occurred on the seventh and eighth days of life, and 40% of patients were repaired on ECMO. ECMO runs had a median of 11 days (IQR 7–17). Most (80%) infants were treated with INO on the day of ECMO cannulation.

The proportion of patients treated with INO and their duration of treatment increased significantly during the study period (Fig 2). In multivariate regression analysis, the adjusted baseline percentage of infants receiving INO at studied hospitals was 51.1%, and increased by an average of 1.4% per year during the study period (95% confidence interval [CI] 0.2%–2.7%, \(P < .05\)). Odds of receiving INO increased by 6.1% per year for infants at PHIS hospitals during the study period (odds ratio [OR] 1.06, 95% CI 1.01–1.12, \(P < .05\)). This included significant increases in use of INO on the day of CDH repair (OR 1.09, 95% CI 1.03–1.15, \(P < .05\)) and after repair (OR 1.07, 95% CI 1.01–1.14, \(P < .05\)). Infants receiving INO had an adjusted baseline of 5.7 days of therapy, increasing by a little more than 1 day of therapy per treated infant each year during the study period (coefficient 1.04, 95% CI 1.01–1.07, \(P < .01\)). Rate of ECMO use (23% overall, hospital range 0%–52%), days of ECMO therapy per treated infant, and rate of CDH repair did not change significantly over the study period.

Mortality rates ranged from 14% to 65% between PHIS hospitals during the study period. Hospital-specific mortality rates for infants with CDH for the 9-year study period had a strong negative correlation with hospital-specific rates of CDH repair \(\left(r_s = -0.79\right)\) (Fig 3). However, hospital-specific rates...
of INO use did not correlate with mortality rates ($r_s = 0.26$) or ECMO use ($r_s = 0.11$). Similar results were found when this portion of the analysis was repeated to include only infants who underwent surgical repair. In multivariate analysis, hospital-specific mortality rates for repaired infants was not associated with hospital-specific rates of ECMO use, INO use before repair, INO use after repair, or case volume.

The median daily charge for INO therapy was $5753$ (IQR $3514–8151$). When applied to the total number of INO therapy days (14 205) reported during the study period, estimated charges for INO therapy amounted to $>$81 million. More than $7$ million of these charges was associated with neonates who died before repair, and $>$24 million was associated with neonates receiving INO before CDH repair. Among neonates with INO courses of $\geq 30$ days, estimated charges for their course ranged from $172 590$ to $>$1 million.

**DISCUSSION**

Published protocols and case series recommend the use of INO to treat pulmonary hypertension in newborns with CDH even though evidence from prospective randomized studies does not support this practice. A detailed physiologic explanation for this failure to respond has been offered, and several literature reviews have concluded that routine early use of INO for CDH should be avoided.

Outcomes in addition to ECMO use and survival might be pertinent in considering whether INO treatment in newborns with CDH is indicated. There is evidence that early INO for CDH may provide short-term improvements before ECMO cannulation. The largest randomized controlled trial of early INO for CDH found that nearly half of infants treated with INO improved PaO2 by $\geq 10$ Torr, a significantly better response rate than controls. This improvement was not sufficient to reduce mortality or need for ECMO, and appears to be transient. These studies suggest that early treatment with INO might provide short-term improvement in oxygenation in patients with CDH and severe pulmonary hypertension, and buy neonatologists and pediatric surgeons valuable time in the “bridge” period immediately before ECMO cannulation. However, the safety and efficacy of prolonged INO therapy in patients with CDH has not been thoroughly investigated in studies published to date.

**FIGURE 1**


**TABLE 2 INO Use in Subgroups of 1713 Neonates With CDH at 33 PHIS Hospitals**

<table>
<thead>
<tr>
<th></th>
<th>$n$</th>
<th>Treated With INO, $n$ (%)</th>
<th>Days of INO Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median</td>
</tr>
<tr>
<td>Died before repair</td>
<td>339</td>
<td>252 (74)</td>
<td>2</td>
</tr>
<tr>
<td>Repaired</td>
<td>1374</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before day of repair</td>
<td></td>
<td>668 (48)</td>
<td>4</td>
</tr>
<tr>
<td>Day of repair</td>
<td></td>
<td>397 (29)</td>
<td></td>
</tr>
<tr>
<td>After day of repair</td>
<td></td>
<td>557 (40)</td>
<td>8</td>
</tr>
<tr>
<td>Not treated with ECMO</td>
<td>1322</td>
<td>622 (47)</td>
<td>7</td>
</tr>
<tr>
<td>Treated with ECMO</td>
<td>391</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before first day of ECMO</td>
<td></td>
<td>163 (42)</td>
<td>1</td>
</tr>
<tr>
<td>Concurrent with ECMO*</td>
<td></td>
<td>352 (90)</td>
<td>4</td>
</tr>
<tr>
<td>After last day of ECMO</td>
<td></td>
<td>228 (58)</td>
<td>9</td>
</tr>
</tbody>
</table>

---, not applicable.

* Includes INO on day of ECMO cannulation, if applicable.
Small, open-label studies suggest that there may be a role for a safe, efficacious, and cost-effective pulmonary vasodilators for the treatment of significant postrepair pulmonary hypertension. INO significantly improved PaO₂ in cases of postrepair pulmonary hypertension, including in some infants who were nonresponders before repair, in an open-label crossover study. Kinsella et al described a case series (n = 40) in which ~30% of infants with CDH developed postrepair pulmonary hypertension. Ten infants were treated with low-dose open-label INO via nasal cannula for median duration of 17 days (range, 5–60 days). INO was discontinued when echocardiography demonstrated resolution of suprasystemic pulmonary artery pressures. These promising preliminary reports warrant more detailed evaluation of the utility of INO therapy in CDH status post repair. Currently available evidence provides no demonstration of improvement in mortality or long-term outcomes associated with postrepair INO therapy, and no blinded assessment of changes in oxygenation or echocardiographic findings. The significant increase in use of INO post repair that we report suggests that further research regarding chronic postrepair vasodilator therapy is needed. Such research should include promising candidate therapies such as sildenafil and bosentan. A randomized controlled trial of sildenafil for severe CDH is currently under way.

Congenital diaphragmatic hernia ranks among the most costly of correctable neonatal conditions with a mean hospital charge of $162 000 and an overall estimated annual cost of $179 470 456 in the United States. INO therapy is a significant contributor to this cost. Patients with CDH with unrestricted access to INO had increased direct costs and length of stay but no change in mortality or ECMO use compared with pre-INO historical controls in a single-center study. Data from the Kids’ Inpatient Database from 1997 and 2006 documented a decrease in ECMO use, and identified INO as an important predictor of higher cost in patients with CDH. Our results demonstrate that INO charges represent 12% of total hospital charges for patients with CDH, and shows that INO charges are greater than the combined charges for all the other drugs used to treat these patients.

Given the difficulty and cost of organizing randomized controlled trials for

FIGURE 2

FIGURE 3
Relationship between mortality and rate of CDH repair (A), mortality and nitric oxide use (B), and ECMO use and nitric oxide use (C) among infants with CDH at 33 PHIS hospitals, 2003 to 2011.
CDH, multicenter quality improvement collaboration may be a feasible alternative approach for improving CDH outcomes and reducing INO use.26–30 This type of study would require active collaboration between participating centers committed to a common quality improvement protocol, and would need to be data driven with the objective of identifying effective therapies and emphasizing the clinical application of evidence-based interventions.29–30 The infrastructure for such an effort already exists in the Congenital Diaphragmatic Hernia Study Group, a voluntary collaboration of international tertiary referral centers that provide data regarding patients with CDH to a central registry.31 The Congenital Diaphragmatic Hernia Study Group data have yielded numerous high-quality observational studies addressing a variety of important issues in CDH management.32–35

Overall survival (66%), repair (80%), and ECMO utilization (23%) rates in this study are consistent with other contemporary, multi-institutional data regarding patients with CDH.36 Our findings confirm and extend a previous report describing a trend of decreased use of ECMO and increased use of INO from 1995 to 2004 in 218 patients with diaphragmatic agenesis.37 Because they reflect actual clinical practice, administrative data such as those in this study are often used to target opportunities for quality improvement. However, such data can have significant limitations. Hospital discharge coding data are created primarily for the purpose of reimbursement and their utility depends on the accurate coding of diagnoses, procedures, and medications. Administrative databases, such as PHIS, have the potential to contain miscoded or inaccurate information. The Children's Health Corporation of America reduces these data problems by using validity and reliability checks.

The PHIS database does not contain several clinically important data points, such as side or size of hernia defect, inborn versus outborn status, clinical or echocardiographic response to INO treatment, or long-term pulmonary and neurodevelopmental outcomes. Moreover, because allocation of treatment in this observational study was not randomized, it is likely that infants in the PHIS database who were treated aggressively were sicker than those receiving less-aggressive therapy, resulting in confounding by indication.38,39 Such limitations make it impractical to use these data to examine relationships between INO therapy and subsequent mortality or need for ECMO for individual infants. However, cumulative hospital mortality rates are less subject to such confounding, as severity of CDH is likely to have varied less dramatically among pediatric referral hospitals with ECMO programs over the 9-year study period. We attempted to correct for any residual confounding due to illness severity by repeating analyses on only those infants who underwent surgical repair, and by adjusting for rates of repair and ECMO use in regression analyses examining the relationship between hospital-specific INO use and mortality rates.

**CONCLUSIONS**

INO is one of the most expensive drugs available in pediatric medicine. This study provides important new information regarding INO utilization and the costs associated with its use in neonates with CDH. Limiting the use of INO for newborns with CDH to clinical studies could lead to reduced costs without adversely affecting outcomes, and help determine which subpopulations with CDH, if any, benefit from INO treatment.

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