Off-Label Use of Inhaled Nitric Oxide After Release of NIH Consensus Statement

Marc A. Ellsworth, MDa, Malinda N. Harris, MDa, William A. Carey, MDa, Alan R. Spitzer, MDb, Reese H. Clark, MDb

BACKGROUND: Inhaled nitric oxide (iNO) therapy is an off-label medication in infants <34 weeks gestational age. In 2011, the National Institutes of Health released a statement discouraging routine iNO use in premature infants. The objective of this study was to describe utilization patterns of iNO in American NICUs in the years surrounding the release of the National Institutes of Health statement. We hypothesized that iNO prescription rates in premature infants have remained unchanged since 2011.

METHODS: The Pediatrix Medical Group Clinical Data Warehouse was queried for the years 2009–2013 to describe first exposure iNO use among all admitted neonates stratified by gestational age.

RESULTS: Between 2009 and 2013, the rate of iNO utilization in 23- to 29-week neonates increased from 5.03% to 6.19%, a relative increase of 23% (confidence interval: 8%–40%; \( P = .003 \)). Of all neonates who received iNO therapy in 2013, nearly half were <34 weeks’ gestation, with these infants accounting for more than half of all first exposure iNO days each year of the study period.

CONCLUSIONS: The rates of off-label iNO use in preterm infants continue to rise despite evidence revealing no clear benefit in this population. This pattern of iNO prescription is not benign and comes with economic consequences.

WHAT'S KNOWN ON THIS SUBJECT: Off-label prescription of inhaled nitric oxide (iNO) to neonates <34 weeks' gestation has increased during the past decade. In early 2011, the National Institutes of Health determined that the available evidence did not support iNO use in this population.

WHAT THIS STUDY ADDS: Use of iNO among neonates <34 weeks' gestation has increased since 2011, entirely from greater use in extremely preterm neonates. Off-label prescription of this drug now accounts for nearly half of all iNO use in American NICUs.
In 1999, inhaled nitric oxide (iNO) was approved for treatment of hypoxic respiratory failure in term and near-term neonates. Given its efficacy and safety in this population,\textsuperscript{1–4} iNO utilization increased during the following decade, most notably among neonates  34 weeks’ gestational age.\textsuperscript{5} This marked rise in off-label use occurred at the same time that multiple randomized clinical trials failed to demonstrate clear benefit in this high-risk preterm population,\textsuperscript{6–16} a collective result that has been borne out in subsequent systematic reviews.\textsuperscript{17–19} Beyond the absence of evidence of benefit, an additional concern is that off-label prescription of iNO to preterm neonates contributes substantially to the cost of health care delivery in the NICU.\textsuperscript{10,20}

As iNO use in the preterm population continued to rise,\textsuperscript{5,21} the National Institutes of Health (NIH) and the American Academy of Pediatrics assembled content experts to develop consensus-based guidance for practicing neonatologists. The resulting NIH statement\textsuperscript{22} and American Academy of Pediatrics clinical report\textsuperscript{23} indicated that available evidence did not support the routine use of iNO in preterm infants, though rare clinical situations and new management strategies did merit further study. After issuance of the NIH statement in early 2011, the Neonatal Research Network (NRN) reported decreased use of iNO among neonates <29 weeks’ gestation.\textsuperscript{24}

Despite this overall decline, the iNO utilization rates of some NRN centers were much higher than previously published national averages.\textsuperscript{5,21}

We conducted the current study to test our hypothesis that the rate at which iNO is prescribed off-label to preterm neonates has not changed significantly in the years after the NIH consensus statement.

**METHODS**

**Study Design**

We performed a retrospective cohort study by using a deidentified data set that is approved by the Western Institutional Review Board (IRB). The study was also approved by the Greenville Memorial Hospital IRB (Greenville, SC) and considered exempt by the Mayo Clinic IRB (Rochester, MN).

**Study Population**

Neonates were included in our study sample if they required admission to a Pediatric Medical Group (PMG) NICU and were discharged between January 1, 2009, and December 31, 2013. Neonates who died in the delivery room or those who were not admitted for neonatal intensive care (eg, comfort care) were not included in the analysis.

**Data Set**

PMG provides intensive care services in 310 hospitals throughout the United States and Puerto Rico. The physicians and nurse practitioners who provide care to neonates in PMG NICUs use a proprietary software system to generate clinical admission, progress, and discharge notes. These local data are consolidated within the PMG Clinical Data Warehouse (CDW), deidentified, and made compliant with Health Insurance Portability and Accountability Act of 1996 regulations. Data are also configured into tables that can be joined and queried for quality improvement and research.\textsuperscript{25–27}

**Data Analysis**

We queried specific CDW tables to perform our analysis, namely patients, admissions, diagnoses, medications, and respiratory support. Data on estimated gestational age (EGA) represented the best estimates from both obstetrical data and neonatal examination findings. We identified all patients who received iNO by searching the medications and respiratory support tables for the term “nitric oxide.” For each patient, we estimated the duration of the first course of iNO therapy by subtracting the age at which iNO was first initiated from the age at which it was discontinued (excluding subsequent courses of iNO therapy). The total number of iNO days was calculated by summing these values for each year.

Patients were categorized by EGA (23–29 weeks, 30–33 weeks, and ≥34 weeks) and differences in their demographic characteristics were analyzed by year (Table 1). Continuous variables (eg, EGA and birth weight) were evaluated with analysis of variance and post hoc analysis to identify specific subgroup differences. Categorical variables (eg, race and gender) were evaluated with 2-tailed χ\textsuperscript{2} tests. Nonparametric data were assessed with Kruskal-Wallis analysis of variance. We used the linear trend test and the Cochran-Armitage trend test to evaluate time-related changes. All statistical analyses were performed by using JMP 11 (SAS Institute, Inc, Cary, NC).

**RESULTS**

There were a total of 420 571 infants admitted to PMG NICUs from 2009 to 2013. Of these, 5676 (1.3%) were exposed to iNO during their hospitalization. Aside from an increase in the median birth weight of infants treated in 2011 (P = .01), demographic characteristics did not vary from year to year among those receiving iNO therapy (Table 1).

Between 2009 and 2013, the rate of iNO utilization in 23- to 29-week neonates increased 23% (confidence interval: 8%–40%), from 5.03% to 6.19% (P = .003, Fig 1). Although iNO use in this cohort declined in 2011, this change was transient and not statistically different than 2010 utilization rates. Utilization of iNO in the other 2 gestational age cohorts did not change during the study period. Raw data for 1997–2008 are included for illustration purposes and were not included in any statistical or descriptive analyses. The data on this subgroup of patients have been previously described.\textsuperscript{5}
Among all neonates <34 weeks admitted to level III or IV PMG NICUs in 2013, iNO utilization rates were inversely proportional to gestational age (Fig 2). For example, 13.9% of all 23- to 24-week infants were treated with iNO, compared with 0.6% of 33-week neonates. Of all neonates who received iNO therapy in 2013, nearly half (46%; Fig 3) were 34 weeks' gestation and thus received this drug off-label. Because only 1.3% of iNO-exposed patients were treated at level II NICUs, data for these patients were not included in the above analyses.

Specifics regarding the age at initiation for all neonates and duration of use (first course) for those with complete data are displayed in Tables 2 and 3, respectively. There were no significant differences in either pattern of use within gestational age cohorts from 2009 to 2013. Infants <34 weeks' gestation accounted for more than half of all iNO days each year of the study period.

**DISCUSSION**

We demonstrate that off-label prescription of iNO to preterm neonates has not declined in the years after the NIH statement discouraging routine use in this population. Similar to NRN-affiliated clinicians, we detected a small decrement in iNO use in 2011 among premature infants, though this change was not statistically significant. By extending our analysis through 2013, we were able to determine that the overall rate of off-label iNO use among all gestational age subgroups persisted at its baseline level and the rate increased among neonates <30 weeks’ gestation. Between 2009 and 2013, for the 79 434 infants 23 to 29 weeks cared for at the 703 hospitals in the United States participating in the

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**TABLE 1 Distribution of iNO Use in PMG NICUs**

<table>
<thead>
<tr>
<th>Discharge Year</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients in CDW, n</td>
<td>79,883</td>
<td>82,778</td>
<td>85,149</td>
<td>85,994</td>
<td>86,767</td>
</tr>
<tr>
<td>iNO-treated patients, n (%)</td>
<td>1049 (1.3)</td>
<td>1120 (1.4)</td>
<td>1085 (1.3)</td>
<td>1159 (1.3)</td>
<td>1263 (1.5)</td>
</tr>
<tr>
<td>EGA group, n (%), wk a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23–29</td>
<td>392 (37)</td>
<td>397 (35)</td>
<td>386 (34)</td>
<td>441 (38)</td>
<td>476 (38)</td>
</tr>
<tr>
<td>30–33</td>
<td>98 (9)</td>
<td>97 (9)</td>
<td>91 (8)</td>
<td>107 (9)</td>
<td>106 (8)</td>
</tr>
<tr>
<td>≥34</td>
<td>556 (53)</td>
<td>621 (55)</td>
<td>630 (58)</td>
<td>602 (52)</td>
<td>674 (53)</td>
</tr>
<tr>
<td>Birth weight, median (10th–90th)</td>
<td>2.27 (0.62–3.71)</td>
<td>2.42 (0.60–3.80)</td>
<td>2.59 (0.62–3.75)</td>
<td>2.20 (0.59–3.79)</td>
<td>2.27 (0.60–3.78)</td>
</tr>
<tr>
<td>Boy, n (%)</td>
<td>614 (59)</td>
<td>686 (59)</td>
<td>639 (59)</td>
<td>684 (59)</td>
<td>721 (57)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%) a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>504 (48)</td>
<td>548 (49)</td>
<td>498 (46)</td>
<td>580 (48)</td>
<td>631 (50)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>223 (21)</td>
<td>251 (22)</td>
<td>261 (24)</td>
<td>227 (20)</td>
<td>224 (18)</td>
</tr>
<tr>
<td>African American</td>
<td>211 (20)</td>
<td>221 (20)</td>
<td>222 (20)</td>
<td>263 (23)</td>
<td>258 (20)</td>
</tr>
<tr>
<td>Asian</td>
<td>64 (6)</td>
<td>50 (4)</td>
<td>56 (5)</td>
<td>63 (5)</td>
<td>88 (7)</td>
</tr>
<tr>
<td>American/Alaska Native</td>
<td>15 (1)</td>
<td>16 (1)</td>
<td>10 (1)</td>
<td>10 (1)</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Pacific Islander</td>
<td>3 (0)</td>
<td>3 (0)</td>
<td>5 (0)</td>
<td>6 (1)</td>
<td>11 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>64 (6)</td>
<td>50 (4)</td>
<td>56 (5)</td>
<td>63 (5)</td>
<td>88 (7)</td>
</tr>
<tr>
<td>Cesarean delivery, n (%)</td>
<td>704 (67)</td>
<td>772 (69)</td>
<td>731 (67)</td>
<td>768 (68)</td>
<td>858 (68)</td>
</tr>
<tr>
<td>Outborn, n (%)</td>
<td>419 (40)</td>
<td>445 (40)</td>
<td>404 (37)</td>
<td>416 (36)</td>
<td>456 (35)</td>
</tr>
<tr>
<td>Disposition, n (%) b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>586 (56)</td>
<td>604 (54)</td>
<td>604 (56)</td>
<td>634 (55)</td>
<td>713 (58)</td>
</tr>
<tr>
<td>Died</td>
<td>231 (22)</td>
<td>246 (22)</td>
<td>213 (20)</td>
<td>264 (23)</td>
<td>261 (21)</td>
</tr>
<tr>
<td>Transfer</td>
<td>232 (22)</td>
<td>270 (24)</td>
<td>269 (25)</td>
<td>261 (23)</td>
<td>269 (23)</td>
</tr>
</tbody>
</table>

a Based on 2-tailed x2 testing evaluating the group.

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**FIGURE 1**

Change in percentage of infants treated with iNO at PMG NICUs within 3 gestational age groupings from 1997 to 2013.
Vermont Oxford Network, the rate of iNO utilization increased from 6.7% to 6.9% (unpublished data provided by the Vermont Oxford Network). iNO use within PMG has accelerated most rapidly among extremely preterm neonates, a subgroup that now accounts for nearly half of all iNO use in the NICU despite the potential for morbidities in this population.\textsuperscript{11,28} Given increased iNO utilization in higher-acuity units,\textsuperscript{24} it may be that iNO is directed at more critically ill neonates for which evidence of benefit and safety of use is most limited.\textsuperscript{6–16} The observation that neonatologists would increasingly prescribe iNO in a manner contrary to clinical evidence and expert opinion\textsuperscript{22,23} is fascinating and provocative.

We suspect that off-label iNO utilization is driven by the idea that iNO promotes increased survival. Despite no clear evidence that there is improved survival in iNO-exposed premature infants, the immediate physiologic effect of iNO is well described, with an increase in oxygen saturation being readily apparent in many infants who are exposed to iNO.\textsuperscript{6,29,30} We speculate that this physiologic effect likely leads many neonatologists to attribute the survival of iNO-exposed neonates to iNO therapy, when in fact a number of other factors could have led to that infant’s outcome. We acknowledge that it is possible that iNO may be therapeutic in the premature neonate, but clearly its role has not been delineated. For example, there may be a role for use in infants with premature rupture of membranes, oligohydramnios, and pulmonary hypoplasia, but currently there are no prospective studies in this population.\textsuperscript{31} Perhaps the history of iNO eventually will resemble that of another 1-time controversial therapy, extracorporeal membrane oxygenation. Once regarded as unsafe and founded on suboptimal clinical evidence,\textsuperscript{32,33} extracorporeal membrane oxygenation is now regarded as lifesaving therapy with a clear role for utilization in select groups of neonates.\textsuperscript{34}

Until that time, we must consider the increased costs that the use of iNO therapy contributes to caring for critically ill neonates. Among the 456

Vermont Oxford Network, the rate of iNO utilization increased from 6.7% to 6.9% (unpublished data provided by the Vermont Oxford Network).
neonates <34 weeks gestation with complete first exposure duration of use data in PMG NICUs in 2013, iNO was used for a total of 3409 patient days. Given the estimated median per day cost of iNO therapy ($5753), this off-label prescription of iNO may have generated a cost to payers of $153 million for off-label use. The most recent vital statistics report indicates that ∼135 000 infants were born at <34 weeks’ gestation in 2012.36 If these infants were treated at the same rate and average duration as the above PMG cohort (2.63%, 7.48 days per treated patient), the estimated total cost to US health care would be ∼$153 million for off-label use. The accuracy of this estimate is uncertain, however, given that some hospitals pay for hourly usage of iNO, whereas others pay an up-front cost for anticipated use over a given period of time.

The strength of this study relates to the quality of the data housed within the CDW. This database includes demographic and clinical information about more than 420 000 subjects hospitalized in PMG NICUs during the study period. Thus, our cohort represents a large sample of the total population of neonates admitted to NICUs throughout the country. Currently our data collection techniques do not permit us to understand why iNO therapy was used. Specifically, we cannot know the primary reasons clinicians initiated treatment with iNO (eg, bronchopulmonary dysplasia prevention, “rescue” therapy in respiratory failure, pulmonary hypertension, and pulmonary hypoplasia). However, it may be possible to infer different therapeutic groupings based on the timing of initiation of therapy. We chose not to address safety and efficacy concerns in this study, because it would have been challenging to draw meaningful inferences from retrospective analyses of a highly selected population of ventilated infants whose mortality rate suggested that they were critically ill. Only carefully designed prospective studies will answer which subset of premature infants might benefit from treatment with iNO.

CONCLUSIONS

The rates of off-label iNO use in PMG NICUs continue to rise despite clinical evidence and expert opinion suggesting no clear benefit in preterm neonates. This pattern of iNO prescription is not benign and comes with economic consequences. Despite evidence suggesting that iNO is a safe therapy in premature neonates, there is insufficient efficacy data to recommend continued use.

ACKNOWLEDGMENT

We thank the Vermont Oxford Network for providing unpublished data for inclusion in the article.

TABLE 3 Duration of iNO Use Per Patient

<table>
<thead>
<tr>
<th>EGA Group</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>23–29 wk</td>
<td>n</td>
<td>Mean, d</td>
<td>% of total iNO days</td>
<td>n</td>
<td>Mean, d</td>
</tr>
<tr>
<td>30–33 wk</td>
<td>n</td>
<td>Mean, d</td>
<td>% of total iNO days</td>
<td>n</td>
<td>Mean, d</td>
</tr>
<tr>
<td>≥34 wk</td>
<td>n</td>
<td>Mean, d</td>
<td>% of total iNO days</td>
<td>n</td>
<td>Mean, d</td>
</tr>
</tbody>
</table>

Only infants with complete duration of use data were included.

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5. Clark RH, Ursprung RL, Walker MW, Ellsbury DL, Spitzer AR. The changing


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