Impact of Stewardship on Inhaled Nitric Oxide Utilization in a Neonatal ICU

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ABSTRACT

OBJECTIVES: Inhaled nitric oxide (iNO) remains the “gold standard” therapy for hypoxemic respiratory failure in newborns. Despite good quality evidence to guide iNO use in this population, we observed considerable practice variation, particularly in timing and rate of weaning. To promote evidence-based practice, we launched an iNO stewardship program in April 2013. Our objective was to determine whether iNO stewardship led to changes in iNO utilization and weaning.

METHODS: We conducted a quality improvement project in an outborn quaternary NICU, targeting improved iNO guideline compliance. We compared patterns of iNO utilization between 2 cohorts: prestewardship (April 2011–March 2013; retrospective data collection) and poststewardship (April 2013–March 2015; prospective data collection).

RESULTS: Eighty-seven neonates received 88 courses of iNO in the 2 years prestewardship, and 64 neonates received 64 courses of iNO in the 2 years poststewardship. There were no significant differences (P > .05) in patient demographics, in the proportion of patients receiving iNO “off-label,” in proportion initiated at the referring hospital, or in outcomes (death or extracorporeal membrane oxygenation). There were significant (P < .05) reductions in median total hours on iNO per patient (47 vs 20; P < .001), in iNO hours per patient from maximum dose to initial wean (28 vs 9; P < .01), and in hours from initial wean to discontinuation (14 vs 8; P < .05).

CONCLUSIONS: The introduction of iNO stewardship was associated with improved adherence to evidence-based guidelines and an overall reduction in total and per-patient iNO use.
Persistent pulmonary hypertension of the newborn (PPHN) arises either as a primary condition or secondary to respiratory distress syndrome, meconium aspiration, sepsis, or birth asphyxia. PPHN is characterized by persistently raised pulmonary vascular resistance and arterial pressure, generally associated with extrapulmonary right-to-left shunting leading to hypoxemic respiratory failure (HRF). Before the availability of inhaled nitric oxide (iNO), therapy was largely supportive with extracorporeal membrane oxygenation (ECMO) employed as a final resort. Improved oxygenation with iNO treatment in cases of PPHN was first reported in 1992 with subsequent large randomized trials demonstrating a significant reduction in the need for ECMO. Despite there being no evidence to suggest that iNO decreases mortality, length of hospital stay or the incidence of adverse neurodevelopmental outcomes after PPHN, iNO has greatly simplified the management of PPHN, with no evidence of adverse effects, either in the short- or long-term.

When inhaled, nitric oxide rapidly reaches pulmonary vascular smooth muscle where it binds to soluble guanylate cyclase, stimulating relaxation. Relative pulmonary selectivity of this effect is conferred by the rapid reaction of NO with oxyhemoglobin to produce methemoglobin. Toxicity of NO may result from direct inhibitory effects on platelet function, or via its products and reactive metabolites, including methemoglobin, nitrogen dioxide, and peroxynitrite. At the dose range applied clinically (≤ 20 ppm), iNO rarely causes clinically significant bleeding, or leads to potentially toxic levels of either methemoglobin or nitrogen dioxide. Nor has iNO been demonstrated to increase peroxynitrite formation in the lungs or other tissues of human newborns. However, the potential for such effects and the fact that iNO is an exceptionally resource-intensive therapy, argues for administering iNO judiciously, at the lowest effective dose and for the shortest time possible. Despite approval being restricted to term and near-term infants with PPHN, use in preterm neonates with HRF and in neonates with conditions other than HRF has been steadily increasing, despite authoritative recommendations to the contrary. At best, such practices have major economic consequences; at worst, have the potential to cause harm. Lack of adherence to guidelines relating to commencement and weaning of iNO therapy represents another practice with major economic and patient safety implications; however, compliance with guidelines relating to iNO use has not been previously examined in the NICU setting.

Stewardship programs are systematic interventions aimed at improving adherence to protocols, promoting better practices, and/or reducing costs. Stewardship programs to reduce antimicrobial use are now common and programs targeting blood products, pain, and adverse drug interactions are also reported. Such programs have been successful at reducing variations in medical care that stem from human- and system-related causes. Motivated by a 65% increase in utilization of iNO in our institution from the beginning to the end of fiscal years 2009–2011, we audited our iNO use across the hospital and observed significant variation in weaning practices leading to a longer duration of iNO therapy than recommended by institutional guidelines. After consultation with key stakeholders (physicians and respiratory therapists), we instituted a hospital-wide iNO stewardship program in an effort to reduce unintended variations in practice. The objective of this study was to determine whether the introduction of stewardship influenced iNO utilization and weaning practices in the NICU. Specifically, we sought to determine whether stewardship led to improved compliance with our unit-specific weaning guideline, thus leading to reduced hours of iNO per course of treatment.

METHODS

Study Design

We performed a combined retrospective and prospective cohort study using a deidentified data set. The Quality and Risk Management Department at The Hospital for Sick Children approved this study as a quality improvement project.

Population and Setting

The Hospital for Sick Children is a major pediatric referral center serving south-central Ontario, Canada, with 3 intensive care units (neonatal, pediatric, and cardiac). The NICU is a 34-bed (average daily census = 36) quaternary newborn unit with 700 to 750 admissions annually within a regionalized tertiary and quaternary neonatal complex serving ~80,000 deliveries annually. All neonates requiring, or potentially requiring, tertiary-level neonatal care are retrieved by a dedicated transport team consisting primarily of nurses and respiratory therapists, but also physicians. Throughout the period of study, iNO was instituted only on attending physician order and commencement and weaning of iNO were conducted by respiratory therapists under the auspices of a unit-specific guideline. Patients potentially requiring ECMO were transferred to the PICU. The current study included all neonates admitted to our NICU from April 1, 2011, to March 31, 2015, who received iNO initiated on transport or after admission to the NICU. Infants with major congenital heart disease were excluded. The study period was divided into 2 epochs: a prestewardship epoch (April 1, 2011–March 31, 2013) and a post-stewardship epoch (April 1, 2013–March 31, 2015).

Data Extraction and Analysis

In the prestewardship epoch, we retrospectively identified all patients who received iNO by searching the medications and respiratory support tables recorded in our electronic charting software (CIMS, Allscripts Sunrise Clinical Care, Richmond, British Columbia, Canada) for the term “nitric oxide.” Chart data collected for each patient included sex, gestational age, and weight at initiation of iNO, underlying clinical problem leading to initiation of iNO, place of initiation of iNO and outcomes, including the need for ECMO or death. Deidentified data were entered into tables that were subsequently queried for quality improvement purposes. The total duration of iNO therapy was determined by subtracting the age (to the nearest hour) at which iNO was initiated from the age (to the nearest hour) at which iNO was...
discontinued. The age (to the nearest hour) at which the patient reached 5 ppm was used to calculate hours for initial wean (from maximum dose – 5 ppm) and hours for final wean (from 5 ppm – discontinuation). Use of iNO was considered off-label if gestational age at initiation was <35 completed weeks, postnatal age was >14 days, or if iNO was used for conditions other than HRF. Patients transferred from the NICU to the PICU for consideration of ECMO or who died in the NICU while on iNO were excluded from analyses of iNO weaning times. In the poststewardship epoch, patients commenced on iNO were identified and data (as above) were recorded prospectively on a dedicated data form that was subsequently transcribed into a deidentified table. Comparisons between epochs were conducted by Student’s t test, Mann-Whitney U test or χ², as appropriate, using Sigma Plot (version 12.5, SyStat Software, San Jose, CA). A P value of <.05 was considered statistically significant.

To demonstrate changes in the outcomes measure (iNO use) and in process measures (compliance rate), process control charts were used. An X (individual) chart revealing monthly iNO use as continuous measured data. For protocol compliance, a P chart was used for proportion of conformities in a changing sample size. Analysis of statistical process control charts was based on the Institute for Healthcare Improvement rules defining special cause variations.

Stewardship and Guideline Development Process

An iNO stewardship program was launched at The Hospital for Sick Children as a hospital-wide initiative on April 1, 2013, which coincided with the release of a revised institutional guideline for iNO use in the NICU. The NICU guideline was revised as part of a process engaging key stakeholders (attending medical staff and respiratory therapists) that included presentation of audit data highlighting practice variation in duration on maximum dose of iNO and weaning intervals, consultation to ensure universal buy-in to the revised guideline and a description of monitoring and prospective data collection as part of the stewardship process. Substantive changes to the revised guideline were few, but included the following: (1) consideration of iNO in patients with an oxygenation index of 15 to 20 (the previous guideline recommended ≥20), (2) recommendations to optimize pH and lung recruitment before commencing iNO (not stated in the previous guideline), (3) a recommendation to avoid any changes in therapy while response to iNO was being evaluated (not stated in the previous guideline), (4) inclusion of an explicit statement that iNO should be discontinued if no response is observed within 1 hour (the previous guideline simply stated that it is possible to abruptly discontinue iNO within 1 hour of commencement), and (5) the provision of supplemental flow charts as a visual aid in guiding the initial and subsequent weans (not present in the previous guideline; see Figs 1 and 2). The stewardship process began when initiation of iNO therapy, documented in the computerized chart, alerted the primary and supervising researchers, who with the respiratory therapist/s, followed each case until iNO therapy was discontinued. The responsible respiratory therapist managed the initiation and weaning of iNO according to the guideline, in communication with the medical team, and recorded the data. All iNO-treated patients were captured and followed during the poststewardship period.

The stewardship committee was led by respiratory therapists and included physician leads and clinical fellows from the NICU and the PICU/Cardiac critical care unit. Over the 2-year period of study, the committee met monthly to review iNO usage data over the preceding month. Respiratory therapists collected data for each patient on iNO at the bedside and total weekly hours was crosschecked against downloaded usage data from the iNO delivery devices. All instances of iNO use over the preceding month were reviewed by the committee chair, with a particular focus on the indications for use of iNO and the duration of iNO therapy in each case. Compliant uses of iNO were defined as dose and duration of iNO therapy given in accordance with the guideline, regardless of indication. Treatment courses where initial dose iNO was continued beyond 1 hour, despite a lack of response, or where weaning did not occur within the recommended time frame, despite meeting oxygenation criteria, were considered noncompliant. In cases where the indication for use of iNO was ambiguous, or where therapy was noncompliant with the guideline for reasons that were not clear at the time of the meeting, a chart review was undertaken, which was followed if necessary by a discussion between the stewardship physician and the attending physician. New information derived from the chart review and discussion was recorded in the patient data sheet. All members of the committee regularly interacted with medical staff, trainees, and respiratory therapists from their respective intensive care units to ensure ongoing awareness of the guideline and to review the criteria for commencement and weaning of iNO. General data on trends in iNO use were presented to the attending staff every 6 months at a minimum, which included discussions on common reasons for noncompliance with the guideline. The committee also followed total hours of usage, targeting a yearly hospital-wide reduction from an average of 11 938 hours annually in the 2 years prestewardship, to 7600 hours annually. Target hours were agreed upon with all stakeholders at the beginning of the process.

Flow charts summarizing the revised guidelines are shown in Fig 1 (institution of iNO) and Fig 2 (weaning and cessation of iNO). Throughout the period of study (April 1, 2011–March 31, 2015), the guidelines had not changed regarding indications for iNO therapy (no gestational age or postnatal age restriction was specified), maximum dose, criteria for weaning, or weaning intervals. As shown in Figs 1 and 2, the range for the duration of iNO therapy in a patient responding to iNO and persistently meeting criteria for weaning is 6 hours for the initial wean (20–5 ppm) and 5 to 10 hours for weaning from 5 ppm to discontinuation (total time from commencement is 11–16 hours).

RESULTS

Hospital-wide iNO use decreased from 23 876 hours (n = 212 courses of therapy)
in the 2 years prestewardship (April 2011–March 2013) to 13,663 hours (n = 209 courses of therapy) in the 2 years poststewardship (April 2013–March 2015). In the NICU, 89 infants received 90 courses of iNO in the prestewardship epoch and 65 infants received 65 courses of iNO in the poststewardship epoch. Three patients were excluded due to a diagnosis of major congenital heart disease: 2 in the pre- and 1 in the poststewardship epoch. Among the 88 and 64 courses of treatment, respectively, total hours of iNO use were 5368 hours (23% of hospital-wide hours) prestewardship and 2540 hours (19% of hospital-wide hours) poststewardship. There were no significant differences in patient characteristics between epochs (sex, gestational age, weight, and age at initiation; Table 1) or in outcomes (need for ECMO or death; Table 1). The percentage of patients in whom iNO was initiated on transport or received off-label was also similar between epochs (Table 1). Off-label iNO use was, in the majority of cases, related to prematurity (50% and 61% in pre- and postepochs, respectively), postnatal age (13% and 17%, respectively), both prematurity and postnatal age (27% and 17%, respectively), and indications other than HRF (10% and 5%, respectively). The most common reason for commencing iNO other than HRF was severe pulmonary hypertension associated with right ventricular dysfunction, diagnosed by echocardiography. The mean and median completed weeks’ gestational age among

FIGURE 1 Flowchart summarizing recommendations on initiation of iNO, determination of response, safety monitoring, and initiation of weaning.

ABG, arterial blood gas; CXR, chest x-ray; FiO2, fraction of inspired oxygen; Hgb, hemoglobin; MRP, most-responsible physician; OI, oxygenation index; SpO2, pulse oxygen saturation.
premature infants receiving off-label iNO was 30 weeks (range 24–34 weeks) in both epochs. No patients were treated with alternative pulmonary vasodilators before iNO, none were exposed to iNO at concentrations higher than 20 ppm, and none required sildenafil or other pulmonary vasodilators to facilitate weaning off iNO. There was no significant change in mortality or ECMO usage between the groups.

Analyses of total iNO hours per patient, time to initial wean, and time from initial wean to discontinuation between epochs are shown in Table 2. Analyses of weaning times included 75 (85%) patients from the prestewardship epoch and 49 (77%) patients from the poststewardship epoch. Of the 13 patients excluded prestewardship, 3 were transferred to the PICU for consideration of ECMO (2 received ECMO) and 10 died in the NICU while on iNO. Of the 15 patients excluded poststewardship, 8 were transferred to the PICU for consideration of ECMO (5 received ECMO) and 7 died in the NICU while on iNO. The most common reason for noncompliance with the weaning guideline was persistent echocardiographic evidence of severe pulmonary hypertension with or without right ventricular dysfunction. Comparing weaning times between epochs, we observed a significant reduction in total hours on iNO per course of treatment poststewardship, whether patients were excluded from analyses. We also observed a significant decrease in iNO hours per patient from maximum dose to initial wean (to 5 ppm) and in hours from 5 ppm to discontinuation of iNO in the poststewardship epoch (Table 2). As shown in Fig 3A, there was a persistent reduction of iNO usage from 224 hours/month to

FIGURE 2 Flowchart summarizing weaning recommendations for iNO. FIO2, fraction of inspired oxygen; SpO2, pulse oxygen saturation.

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TABLE 1 Patient Demographics and Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Prestewardship</th>
<th>Poststewardship</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>87</td>
<td>64</td>
<td>NA</td>
</tr>
<tr>
<td>Sex</td>
<td>F/M: 37/50</td>
<td>F/M: 31/53</td>
<td>.55</td>
</tr>
<tr>
<td>Gestational age in completed weeks at initiation of iNO$^a$</td>
<td>38 (33–40)</td>
<td>38 (34–40)</td>
<td>.88</td>
</tr>
<tr>
<td>Day of life at initiation of iNO$^a$</td>
<td>2 (1–5)</td>
<td>2 (2–9)</td>
<td>.083</td>
</tr>
<tr>
<td>Grams body weight at initiation of iNO$^a$</td>
<td>3080 (1753–3675)</td>
<td>3020 (1931–3500)</td>
<td>.75</td>
</tr>
<tr>
<td>Off-label use (%)</td>
<td>30 (54)</td>
<td>23 (36)</td>
<td>.95</td>
</tr>
<tr>
<td>iNO initiated before admission (%)</td>
<td>32 (58)</td>
<td>29 (45)</td>
<td>.55</td>
</tr>
<tr>
<td>ECMO (%)</td>
<td>2 (2)</td>
<td>5 (8)</td>
<td>.11</td>
</tr>
<tr>
<td>Died (%)</td>
<td>23 (26)</td>
<td>14 (22)</td>
<td>.52</td>
</tr>
</tbody>
</table>

NA, not applicable.

$^a$ Data are presented as median (interquartile range).

106 hours/month between the pre- and poststewardship eras. As shown in Fig 3B, monthly percentage compliance with the guideline increased from a mean of 3.2% of iNO courses prestewardship to 25.8% poststewardship.

DISCUSSION

Despite there being high quality evidence to inform use of iNO in neonates, our guideline was being frequently ignored. Concerns surrounding the costly, and perhaps unnecessary, use of iNO led us to re-examine our guideline and to develop strategies to improve adherence. Our findings demonstrated that implementation of an iNO stewardship program improved adherence to guidelines, leading to meaningful reductions in total and per-patient hours of iNO use. To our knowledge, the current study is the first to examine adherence to evidence-based guidelines in the context of iNO therapy in the NICU and the first to describe the impact of a stewardship program on utilization patterns of iNO. Major drivers of change in iNO utilization likely included an enhanced awareness of the guideline by front line staff, increased vigilance by respiratory therapists regarding opportunities for weaning, the observer (Hawthorne) effect and unmeasured cointerventions (eg, arrival of new staff or discussion of rational use of iNO at conferences, etc), which modified physician behavior. Clinical practice guidelines are widely regarded as key to reducing practice variation and improving the quality of care.$^{29,32}$ However, to be effective, guidelines must be updated regularly to reflect current evidence or expert opinion, must be minimally controversial to ensure maximum buy-in, and must be implemented in an environment characterized by sustained communication and vigilance. The stewardship model has been used successfully in the pediatric setting to promote safe and evidence-based use of antimicrobial agents.$^{34}$ Key elements of our iNO stewardship program included an identified staff physician and trainee, widespread dissemination of evidence-based practice guidelines that were approved by all members of the medical and respiratory therapy team, detailed prospective data collection, setting targets for total yearly utilization, regular reviews of iNO use by an interprofessional stewardship committee, discussion of specific cases with the attending physician, and feedback on general trends in iNO use to NICU staff.

Our guidelines did not set limits on gestational age for treatment with iNO. Despite this, our rate of off-label use for prematurity was less than recently published rates, which were as high as 50%.$^{21}$ This disparity likely reflected inherent differences in our outborn population, which is made up predominantly of complex term and near-term infants, rather than attitudes discouraging use of iNO in the very preterm. Indeed, the pathophysiology of HRF in the preterm may be identical to the term infant with PPHN, making the use of iNO a logical and potentially useful extension of therapy, though responsiveness may diminish with decreasing gestational age.$^{35}$ Similar to term infants with PPHN, clinical trials examining effects of iNO for HRF in premature infants have confirmed short-term improvements in oxygenation, but no reduction in mortality.$^{36-42}$ In the absence of specific evidence to guide iNO therapy in this population, our guidelines for starting dose and weaning of iNO were the same, regardless of gestational age.

A significant minority of our iNO-treated infants in both epochs did not have HRF. In most cases, iNO was instituted based on echocardiographic evidence of chronic pulmonary hypertension with associated right ventricular dysfunction. Most such cases were considered noncompliant in the current study, due to avoidance of weaning until repeat evaluation by echocardiogram, which greatly prolonged iNO therapy. In patients with poorly responsive pulmonary hypertension and/or right ventricular dysfunction, prolonged treatment with iNO may be justified; however, use of iNO for such indications is difficult to incorporate into weaning guidelines, particularly in a

### TABLE 2 iNO Utilization

<table>
<thead>
<tr>
<th></th>
<th>Prestewardship</th>
<th>Poststewardship</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Courses of iNO treatment given</td>
<td>88</td>
<td>64</td>
<td>NA</td>
</tr>
<tr>
<td>Total iNO hours</td>
<td>5368</td>
<td>2540</td>
<td>NA</td>
</tr>
<tr>
<td>Hours/course$^a,b$ all patients</td>
<td>47 (23–66)</td>
<td>20 (13–46)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hours/course$^a,b$ with exclusions$^b$</td>
<td>49 (25–66)</td>
<td>22 (14–46)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hours from maximum dose to 5 ppm$^a,b$</td>
<td>28 (12–51)</td>
<td>9 (5–26)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Hours from 5 ppm to discontinuation$^a,b$</td>
<td>14 (7–24)</td>
<td>8 (6–15)</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

NA, not applicable.

$^a$ Data are presented as median (interquartile range).

$^b$ Patients who died on iNO or were transferred to the PICU for consideration of ECMO were excluded.
population in which iNO is used predominantly for oxygenation failure. Our current approach to such cases is to use iNO as a bridge to other therapies, if required, at the lowest dose at which a response is observed (generally 5 or 10 ppm), while consulting with experts in the management of pulmonary hypertension.

**Improving Quality**

This study evaluated a process that improved cost-effectiveness by reducing unnecessary exposure to a medication, without evidence of harm, thus enhancing quality of health care.

**Limitations of the Study**

Data from the prestewardship epoch was collected retrospectively, which has many...
inherent limitations. In particular, it was frequently challenging or impossible to determine the reasons behind patterns of iNO utilization that deviated greatly from our guideline. We observed no significant change in proportion of infants dying or receiving ECMO between the pre- and post-stewardship eras, suggesting a lack of harm related to decreased iNO use. However, we did not prospectively collect data on other possible consequences of decreased iNO utilization, including changes in patterns of muscle relaxant, narcotic and sedative use, or on duration of invasive mechanical ventilation or length of hospital stay. This work was conducted in a single quaternary outborn NICU populated by infants across the gestational age spectrum, among which there was significant complexity and heterogeneity; this has potential implications for interpretation of outcomes reflecting safety (use of ECMO or death), at least in the short-term. Due to the observational design of this study, we cannot be certain that the changes in iNO utilization over time were primarily due to the introduction of stewardship, rather than a secular trend. A major factor in favor of an important impact of stewardship on iNO utilization patterns was that our guideline, and the method by which iNO was prescribed and monitored, did not change substantively throughout the period of study.

**Generalizability and Spread**

Our experience suggests that the stewardship model can be implemented in any NICU. Toward this goal, national Canadian guidelines guiding practice in neonates were collaboratively developed and promulgated under the auspices of the Canadian Association of Pediatric Health Centres. A Canadian Association of Pediatric Health Centres-sponsored national iNO stewardship network is currently in the planning phase.

**CONCLUSIONS**

Variation in the use of iNO leading to unnecessary prolongation of therapy carries a significant economic burden and has potential to cause harm. Implementation of a stewardship program improved adherence to evidence-based guidelines, leading to significant and important decreases in total and per-patient iNO use in our NICU. We conclude that the stewardship model has utility in reducing practice variation in iNO use in the NICU setting and has the potential to generate new knowledge that will inform future practice.

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