Trends and Variations in the Use of Inhaled Nitric Oxide in Preterm Infants in Canadian Neonatal Intensive Care Units

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Abstract

Objective To determine the proportion of infants who receive inhaled nitric oxide (iNO), and to characterize the variations in its use by gestational age (GA) and center in infants <34 weeks’ gestation.

Design Retrospective analysis was performed in infants born at <34 weeks’ gestation and admitted to neonatal intensive care units participating in the Canadian Neonatal Network between January 2010 and December 2013.

Results Of 19,525 infants, 831 (4.2%) received iNO. A total of 369 infants (44%) received iNO during the first 2 days after birth. The proportion of neonates who received iNO in the 22 to 25, 26 to 29, and 30 to 33 weeks’ GA groups was 16.1, 6.0, and 1.3%, respectively. Infants in whom iNO was initiated in the first 2 days of age received it for a shorter duration (median, 3 days; interquartile range [IQR], 2–5) as compared with those who started after 2 days (median, 5 days; IQR, 2–11). The use of iNO varied by center, ranging from 0 to 15.5% (p < 0.001).

Conclusion Out of every 25 infants born at <34 weeks’ gestation in Canada received iNO, with the highest rate of use in infants born at lower gestation. Further research to identify reasoning, efficacy, and safety of iNO in preterm infants is warranted.
Inhaled nitric oxide (iNO) is used in term and late preterm infants with pulmonary hypertension and oxygenation failure but its use in preterm infants is controversial. The two main uses in the preterm population are acute hypoxic respiratory failure, which is similar to the indication in term infants, and prevention of bronchopulmonary dysplasia (BPD). However, both indications lack definitive evidence of benefit in preterm infants.1–6

The National Institute of Health (NIH) consensus conference report,6 American Academy of Pediatrics (AAP) guideline,7 Fetus and Newborn Committee of the Canadian Pediatric Society guideline,8 and regulatory approvals for iNO from the Food and Drug Administration in the United States and Health Canada discourage the use of iNO in preterm infants born at <34 weeks’ gestation outside of clinical trials except in individual cases with documented pulmonary hypertension. Recent studies point to wide variability in iNO use in the preterm population in the United States9–12 and unclear overall benefit.10,11,13

In the context of potential significantly different practices as compared with historical Canadian cohorts14 and possibly with U.S. data, we sought to determine the current rate of use of iNO among preterm infants born at younger than 34 weeks’ gestation in Canada. The objectives of this study were to (1) describe yearly trends in frequency, postnatal age at initiation, and duration of iNO use among preterm infants born at <34 weeks’ gestation; and (2) describe variations in the proportion of infants who received iNO according to gestational age categories and centers.

Methods

Study Population

This was a retrospective cohort study of preterm infants born at <34 weeks’ gestation and admitted to participating centers in the Canadian Neonatal Network (CNN) between January 1, 2010, and December 31, 2013. Infants with major congenital or chromosomal anomalies, those with a palliative care plan before delivery, infants who were moribund on admission, or those with missing birth date or missing data at last discharge were excluded from the analysis.

Data Collection

Trained data abstractors collected neonatal data from infants at the participating sites and submitted it to the central CNN database. Details of data collection and management for the CNN have been published previously.14 The CNN collects data on the receipt of iNO on any given day that documents the start date and duration of therapy. Data collection at each site was approved by the respective research ethics board or quality improvement and data management committee. The retrospective evaluation of de-identified data for this study was approved by the CNN Executive Committee and by the Conjoint Research Ethics Board of the University of Calgary.

Data Analysis

The characteristics of the study population in each of the four admission years (2010–2013) were summarized using descriptive statistical methods and compared using the chi-square test for categorical variables and the F-test by analysis of variance or Kruskal–Wallis test, as appropriate, for continuous variables. The proportion of infants who received iNO according to gestational age at birth in completed weeks was examined by LOESS regression and presented graphically. Infants were also divided into three groups according to their gestational age at birth: 22 to 25, 26 to 29, and 30 to 33 weeks, and the trend in the overall use of iNO in each of the groups was tested using the Cochran–Armitage trend test, as were the trends in annual iNO use in each of the three groups.

We examined the age at initiation and duration of iNO use in all infants and in gestational age groups of 22 to 29 and 30 to 33 weeks. We compared the duration of iNO use between those who received iNO before 2 days and after 2 days of age using the chi-square test. Due to a highly positive skew in the duration of iNO use, the association between the timing of iNO start and the duration of iNO use was tested using the Kruskal–Wallis test. The proportion of infants who received iNO across participating neonatal intensive care units (NICUs) was presented graphically and differences were examined using the chi-square test. Because iNO use was high among infants born at <29 weeks’ gestation, we classified NICUs into four categories based on the number of <29 weeks’ gestational age infants admitted per year—small: <30 infants/year; medium: 30 to 60 infants/year; large: 61 to 90 infants/year; and very large: >90 infants/year—and compared the iNO use among these centers. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC) and R 3.1.2 (cran.r-project.org).

Results

Study Population

A total of 20,737 infants born at <34 weeks’ gestation were admitted to the 30 NICUs participating in the CNN between 2010 and 2013. We excluded 1,212 infants because of major congenital anomalies (999), chromosomal anomaly (39), moribund status on admission (88), planned palliative care before delivery (29), missing last discharge date (46), or missing birth date (11). The remaining 19,525 infants formed the study population.

Extent of iNO Use

Of the 19,525 eligible infants, 831 (4.2%) infants received iNO during their hospital stay.

There were no significant differences in any of the characteristics of infants who received iNO during each of the 4 years of the study period (Table 1).

- Fig. 1 shows the proportion of infants born at <34 weeks’ gestation who received iNO according to gestational age in completed weeks. The proportion of infants who received iNO at 22 to 25, 26 to 29, and 30 to 33 weeks’ gestation was 16.1, 6.0, and 1.3%, respectively—a significant decrease with increasing gestational age (p < 0.001). - Fig. 2 illustrates the yearly trend in iNO use in each of the gestational age groups. Overall, there were no significant differences in the proportion of infants who received iNO when compared year by year during the study period.
Timing of Initiation and Duration of iNO Use

Of the 831 infants who received iNO, 369 infants (44%) received iNO during the first 2 days after birth and the remaining 462 (56%) received it after 2 days of age. The duration of iNO use was significantly shorter among those infants who received iNO in the first 2 days of age (median, 3 days; interquartile range [IQR], 2–5 days) as compared with those who started iNO after 2 days (median, 5 days; IQR, 2–11 days; \( p < 0.001 \)). The association between timing of iNO start and duration of use is shown in Table 2.

Associated Conditions

Rupture of membranes >7 days occurred in 9.3 and 7.5% among the 22 to 29 weeks’ and 30 to 33 weeks’ gestational age groups. When compared with those infants with rupture of membranes <7 days, the proportion of infants with rupture of membranes >7 days was significantly lower (\( p < 0.001 \)).

### Table 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Admission year</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>( p )-Value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>( p )-Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of infants admitted</td>
<td></td>
<td>4,817</td>
<td>4,732</td>
<td>5,049</td>
<td>4,927</td>
<td>0.49</td>
<td>0.18</td>
</tr>
<tr>
<td>No. of iNO-treated infants, n (%)</td>
<td></td>
<td>221 (4.6)</td>
<td>205 (4.3)</td>
<td>202 (4.0)</td>
<td>203 (4.1)</td>
<td>0.49</td>
<td>0.18</td>
</tr>
<tr>
<td>Birth weight, mean (SD) (g)</td>
<td></td>
<td>1,002 (427)</td>
<td>957 (461)</td>
<td>1,019 (470)</td>
<td>1,021 (454)</td>
<td>0.44</td>
<td>0.41</td>
</tr>
<tr>
<td>GA group</td>
<td></td>
<td>0.48</td>
<td>0.57</td>
<td>0.48</td>
<td>0.57</td>
<td>0.48</td>
<td>0.57</td>
</tr>
<tr>
<td>22–29 wk</td>
<td></td>
<td>180 (81.4)</td>
<td>176 (85.8)</td>
<td>166 (82.2)</td>
<td>163 (80.3)</td>
<td>( -^c )</td>
<td>( -^c )</td>
</tr>
<tr>
<td>30–33 wk</td>
<td></td>
<td>41 (18.5)</td>
<td>29 (14.1)</td>
<td>166 (82.2)</td>
<td>40 (19.7)</td>
<td>( -^c )</td>
<td>( -^c )</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td></td>
<td>124 (56.3)</td>
<td>113 (55.1)</td>
<td>115 (56.9)</td>
<td>124 (61)</td>
<td>0.64</td>
<td>0.30</td>
</tr>
<tr>
<td>Cesarean, n (%)</td>
<td></td>
<td>127 (57.7)</td>
<td>118 (57.8)</td>
<td>125 (61.8)</td>
<td>126 (62)</td>
<td>0.68</td>
<td>0.26</td>
</tr>
<tr>
<td>Antenatal steroid, n (%)</td>
<td></td>
<td>187 (86.5)</td>
<td>169 (84.9)</td>
<td>168 (86.6)</td>
<td>172 (86)</td>
<td>0.95</td>
<td>0.98</td>
</tr>
<tr>
<td>Singleton, n (%)</td>
<td></td>
<td>156 (70.6)</td>
<td>160 (78)</td>
<td>161 (79.7)</td>
<td>152 (74.8)</td>
<td>0.13</td>
<td>0.25</td>
</tr>
<tr>
<td>SNAP-II score &gt; 20, n (%)</td>
<td></td>
<td>123 (58.3)</td>
<td>114 (57.3)</td>
<td>125 (63.4)</td>
<td>108 (54)</td>
<td>0.29</td>
<td>0.67</td>
</tr>
<tr>
<td>Outborn, n (%)</td>
<td></td>
<td>33 (14.9)</td>
<td>26 (12.7)</td>
<td>37 (18.3)</td>
<td>22 (10.8)</td>
<td>0.16</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Abbreviations: GA, gestational age; IQR, interquartile range; SD, standard deviation; SNAP-II, Score for Neonatal Acute Physiology-version II.

<sup>a</sup> \( p \)-Values based on chi-square test for categorical variables and \( F \)-test or Wilcoxon rank sum test for continuous variables.

<sup>b</sup> \( p \)-Values were based on Cochran–Armitage trend test for binary data or \( t \)-test for the slope in linear regression for continuous variables.

<sup>c</sup>No test.
rupture of membranes >7 days who received iNO was significantly increased to 18.1 and 7.5% in the 22 to 29 weeks’ and 30 to 33 weeks’ gestational age groups, respectively.

**Variation in Patterns of iNO Use among Centers**

There was a significant variation in iNO use among the 30 centers, ranging from 0 to 15.5% (Fig. 3). The median rate of iNO use was 3.4% (IQR, 1.4–5.1%). We examined whether there was an association between numbers of infants admitted per unit and use of iNO. The proportion of neonates who received iNO in small, medium, large, and very large units was 11, 15, 6, and 11%, respectively. The difference was significant, with medium-sized unit having the highest use.

**Discussion**

In this population-based cohort study, 1 in every 25 preterm infants born at <34 weeks’ gestation admitted to a Canadian NICU between 2010 and 2013 received iNO during their hospital stay, with the highest use of iNO in infants born at <26 weeks’ gestation. There was a significant variation in iNO use among NICUs, with the highest use of iNO reported in medium-sized units.

The first well-documented use of iNO in newborns was published in 1992. The 1996 to 1997 CNN cohort data were the first to quantitate the use of iNO in preterm and term newborns. At that time, ~1% of preterm infants received iNO and its use was largely restricted to late-preterm infants.

Outside Canada, data concerning use of iNO in preterm infants are available from U.S. as well as the Australian and New Zealand Neonatal Network. The Pediatrrix Medical Group in the United States reported a sixfold increase in the number of infants who received iNO among preterm infants born at <34 weeks’ gestation between 2000 and 2008, reaching 1.8%. For infants born at 23 to 26 weeks’ gestation, the iNO use was 6.6% in 2008. A recent study from the same group for the period 2009 to 2013 reported the continued rise of iNO use at the lowest gestational ages with no obvious impact of the 2011 NIH consensus statement.

The National Institute of Child Health and Development Neonatal Research Network (NICHD-NRN) was the only source to report a reduction in iNO use in preterm infants following the NIH consensus development conference and from a lower baseline than the current report. On the other hand, Stenger et al reported an even higher rate (7.2%) of iNO use among infants born at <34 weeks’ gestation admitted to 37 U.S. children’s hospitals participating in the Pediatric Health Information System during the period 2007 to 2010; however, the population characteristics of infants in these hospitals may be different. In Australia and New Zealand, ~3.4% of infants born at <34 weeks’ gestation received iNO in 2012 and distribution by gestational age was similar but slightly lower than in Canada. There was no significant decrease in iNO use after the NIH consensus statement.

Our findings that 4.2% of preterm infants born at <34 weeks’ gestation in Canada received iNO is a lot higher than our previous report and higher than the rates reported from the other countries. The commonalities are highest use in smallest infants and no obvious impact of the NIH consensus statement. In our cohort, there was an increase in iNO use in 2011 from 2010 especially in infants born at 22 to 25 weeks’ gestation but since then the rate of iNO use has slightly declined.

**Table 2** Association between the age of initiation and duration of inhaled nitric oxide therapy

<table>
<thead>
<tr>
<th>GA group</th>
<th>Age at first course of iNO</th>
<th>p-Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 2 d</td>
<td>2–4 d</td>
</tr>
<tr>
<td>22–29 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of infants</td>
<td>264</td>
<td>61</td>
</tr>
<tr>
<td>Duration of iNO&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (1.5–5)</td>
<td>3 (1–9)</td>
</tr>
<tr>
<td>30–33 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of infants</td>
<td>105</td>
<td>14</td>
</tr>
<tr>
<td>Duration of iNO&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2 (2–4)</td>
<td>3.5 (1–5)</td>
</tr>
<tr>
<td>Total 22–33 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of infants</td>
<td>369</td>
<td>75</td>
</tr>
<tr>
<td>Duration of iNO&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (2–4)</td>
<td>3 (1–7)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Median (IQ range).

<sup>b</sup>p-Value was based on the comparison of iNO duration across iNO timing groups using Mood median test.

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use has come back down to the 2010 level or lower. This change may be due to annual variation rather than any particular cause.

The causes for the high iNO use in the very preterm remain speculative based on our dataset. It is possible that the more frequent use of echocardiography including the advent and spread of targeted neonatal echocardiography in Canada has allowed for more neonates to be diagnosed with pulmonary hypertension. This may have given renewed impetus to the use of iNO in preterm neonates despite the lack of supporting outcome data. In a recent survey performed after the publication of the NIH consensus conference report, 87% of neonatologists in Canada, Australia, and New Zealand acknowledged their use of iNO in preterm infants born at <34 weeks’ gestation. This practice does not find support in the level of current evidence, which was recently underscored in the reaffirmed statement from the AAP. The use of iNO in preterm infants also represents a significant cost to the health care system. It is estimated that the total cost to U.S. health care is approximately $153 million for off-label use of iNO in the United States.

There are as yet no data showing a clear positive impact of iNO on any outcomes in preterm infants and concerns have been raised about a possible deleterious effect.

In as much as differences in iNO use are concerned, both the NICHD-NRN and Stenger et al. reported dramatic variation in iNO use in preterm infants among participating clinical sites. Stenger et al. also observed twice the amount of iNO use in smaller NICUs (<250 admissions/year) as compared with larger units. We similarly observed a wide variability in iNO use among the 30 NICUs participating in the CNN. The difference between individual centers in the CNN dataset is very large and persists when only units above the median number of preterm admissions are considered (data not shown). This degree of variation is very unlikely to be justified by any baseline variance in population characteristics. Medium-sized NICUs used iNO in a far larger proportion of infants than large and very large NICUs. This may reflect a systemic effect of unit size on specific disease management, training, staffing, and neonatologist presence, or a combination of these and other factors.

We observed that duration of iNO treatment was more than double when it was started after 2 days of age. Almost a third of infants had iNO started between days 3 and 14 and they had a similar duration of use with the ones for whom the iNO was started after 14 days. This may be due to less clear-cut indications later in the clinical course and/or difficulties to define response and thus criteria for weaning. About one in seven very preterm infants, evenly distributed from the end of first week of life onwards, received iNO for more than 2 weeks, possibly reflecting use of iNO to prevent BPD or, later on, as treatment of pulmonary hypertension associated with BPD.

A special case for iNO use in infants with prolonged premature rupture of membranes (PPROM) is being built as nitric oxide may be beneficial for a small number of critically ill infants in defined clinical situations, such as respiratory failure associated with oligohydramnios. The proportion of infants with PPROM who received iNO in Canada is in keeping with recent Finnish data on the prevalence of hypoxic respiratory failure with findings of pulmonary hypertension in this subgroup. Very preterm infants born after prolonged rupture of membranes may be the most suitable population for a future randomized control trial of iNO administration.

The strengths of this study are that this is a population-based multicenter cohort that included all level III NICUs in a country with perinatal programs that encourage transfer of the mother to an appropriate facility. The data were collected using uniform definitions. The limitations of this study include the retrospective nature of the study and a lack of information regarding the indications for starting iNO, initial or subsequent dosing, and reasons for stopping therapy, which are not collected in the current dataset.

**Conclusion**

In summary, this is a detailed report concerning current off-label use of iNO in the Canadian preterm population. The use of iNO is high as well as highly variable across participating Canadian NICUs, with the highest use in the 22 to 25 weeks’ gestational age group. To understand the rates, reasons, dose, duration, weaning strategy, and need for other pulmonary vasodilators and the consequent impact on outcomes, a nationwide detailed registry or at least a multicenter cross-sectional study is warranted as soon as possible. In addition, to evaluate the efficacy and safety of iNO in preterm neonates, well-designed randomized controlled trials with clear indications that incorporate standardized and systematic echocardiographic parameters and long-term outcomes are very much needed.
Contributors Statement
Amuchou S. Soraisham and Andrei Harabor designed the study, interpreted the data, drafted and revised the article, and approved the final article as submitted.

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Contributors Statement
Amuchou S. Soraisham and Andrei Harabor designed the study, interpreted the data, drafted and revised the article, and approved the final article as submitted.

Sandesh Shivananda and Ruben Alvaro evaluated the statistical analyses, reviewed and revised the article, and approved the final article as submitted.

Xiang Y. Ye critically did statistical analyses, reviewed and revised the article, and approved the final article as submitted.

Shoo K. Lee critically reviewed the data analysis, revised the article, and approved the final article as submitted.

Prakesh S. Shah conceptualized the study, designed and supervised the data collection, critically reviewed the article and the analyses, and approved the final article as submitted.

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References
7 Kumar P; Committee on Fetus and Newborn; American Academy of Pediatrics. Use of inhaled nitric oxide in preterm infants. Pediatrics 2014;133(1):164–170
8 Peliowski A; Canadian Paediatric Society, Fetus and Newborn Committee. Inhaled nitric oxide use in newborns. Paediatr Child Health 2012;17:95–100
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