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Review

Weaning of inhaled nitric oxide: is there a best strategy?

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Abstract

Background: Inhaled nitric oxide (iNO) has been used in the treatment of pulmonary hypertension in neonates for many years. iNO was approved by the FDA in 1999 for hypoxic respiratory failure (HRF) in term and near term infants, defined as > 34 weeks gestational age (GA). iNO is used for persistent pulmonary hypertension of the newborn (PPHN), secondary pulmonary hypertension caused by congenital heart disease (CHD), congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS), pneumonia, respiratory distress syndrome (RDS), and other pathologies. iNO has its effect locally on the pulmonary vasculature and has been studied extensively regarding its effect on morbidities such as: need for extracorporeal membrane oxygenation (ECMO), oxygen requirements, and mechanical ventilatory support. However, protocols for weaning iNO and for the duration of iNO weaning have not been studied extensively. It has been shown that an abrupt discontinuation leads to rebound pulmonary hypertension.

Methods: Electronic literature search and review of published articles on the use of iNO in the neonate.

Results: Electronic databases including Medline and PubMed were searched from the years 1995-2015, using the keywords "iNO", "nitric oxide", "neonate", and "weaning nitric oxide." This search revealed 2,124 articles. Articles were determined to be eligible for review if they included a specific protocol for weaning iNO, and were published in English. 16 articles with specific protocols for iNO weaning have been identified and reviewed. The studies had enrolled a total of 1,735 neonates either at term either preterm and with a mean birth weight of 3.3 kg (± 2 kg). Main diagnoses included MAS, CHD (total anomalous pulmonary venous return [TAPVR], d-transposition of the great vessels [DTGV], atrial septal defect [ASD], pulmonary atresia [PA], hypoplastic left heart syndrome [HLH]), pneumonia, RDS, hyaline membrane disease (HMD), PPHN, CDH, sepsis, pulmonary hypoplasia, pulmonary hemorrhage, hydrops fetalis, and other congenital anomalies. The average dose of iNO was 20 ppm (range = 2-80 ppm). The duration of exposure to iNO was on average 2 ± 2 days

(range = 15 min - 7 days). Weaning protocols were highly varied from duration of treatment, duration of time in between iNO decreases, initial dose, adjunctive medications used to wean, and increasing FiO_2 used to wean iNO. The weaning parameters were based on multiple variables including FiO_2, PaO_2, O_2 sats, and pulmonary arterial pressure.

Conclusion: There is a limited amount of data specific to weaning protocols for nitric oxide. There is no consensus on an appropriate method for weaning of iNO either on its own, or with adjunct medication. Further research to elucidate a strategy for weaning of iNO needs to be done. We propose that weaning iNO in a stepwise approach from 20 ppm in increments of 5 ppm per decrease until 5 ppm; and stepwise by 1 ppm from 5 ppm to off, while monitoring O_2 saturations and blood gases parameters and allowing transient increases in FiO_2 during adjustment to the transition is a safe approach (both for invansive and non-invasive modes of ventilation). This is not a protocol that is appropriate for every patient pathology, but is a safe starting point with allowance for individual patient and physician variablilty.

Keywords

iNO, nitric oxide, weaning nitric oxide, neonate, pulmonary hypertension.

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Background

Nitric oxide (NO) has been found to be an important inter- and intracellular messenger in virtually every organ within the body [1]. Inhaled NO (iNO) is important in regulating vascular muscle tone. iNO is a selective pulmonary vasodilator. Studies of newborn lambs with persistent pulmonary hypertension (PPHN), caused by hypoxia, showed that inhaling 40-80 ppm of iNO decreased pulmonary vasoconstriction without systemic circulatory effects [2]. The use of iNO improves oxygenation in severely hypoxemic neonates, showing both acute and sustained improvement [3]. It is important to note that not all neonates will respond to iNO therapy. The mechanism for non-responders in not clear, but it is clear that some neonates, regardless of the etiology of hypoxic respiratory failure (HRF) will not have an efficacious reponse to iNO. iNO has a therapeutic role in neonates with HRF. In conjunction with ventilatory support, and other appropriate agents, iNO is indicated for the treatment of term and near term (now late-preterm) infants with HRF associated with clinical or echocardiographic evidence of pulmonary hypertension. The use of iNO in these settings improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO) [1, 4, 5, 6]. iNO started at 20 ppm was associated with improved oxygenation acutely and a reduced median duration of mechanical ventilation – these improvements were significant across all severity-of-illness strata, with a positive impact on PaO_2 within 30 minutes, regardless of the initial severity of illness [7]. Although there are numerous publications on the efficacy and use of iNO for HRF and/or pulmonary hypertension of the full term newborn, and emerging literature about iNO use in preterm neonates, many of them lack a detailed description of the weaning methods. Optimal weaning of iNO is important as it has been shown that rebound pulmonary hypertension after withdrawal of iNO is a significant risk. This rebound pulmonary hypertension is likely due to iNO down regulation of endogenous NO production [8].

Methods

Literature review of published articles on the use of iNO in the neonate. This literature review was based on Medline and PubMed search using terms such as “iNO”, “nitric oxide”, “neonate”, “weaning nitric oxide”. Articles were included for review if they were published in English, within the years 1995-2015, and included a specific protocol for weaning of iNO.

Results

An electronic search revealed 2,124 articles. From these 2,124 results, articles were eligible for review if they included the search criteria terms, described use of iNO in neonates, and had a specific description of the method used to wean iNO use. Based on this inclusion criteria, articles were

identified and reviewed. Case reports and surveys were not included in this review. There were 16 studies that met the inclusion criteria and included a clear description of the weaning method used for iNO. These 16 studies were retrieved in full text and reviewed. **Tab. 1** and **Tab. 2** show a summary of the studies included, the demographics, and maximum iNO dosage. The studies had enrolled a total of 1,735 (n = 7-248) neonates either at term either preterm and with mean birth weight of 3.3 kg (± 2 kg).

Main diagnoses included meconium aspiration syndrome (MAS), congenital heart disease (CHD) (total anomalous pulmonary venous return [TAPVR], d-transposition of the great vessels [DTGV], atrial septal defect [ASD], pulmonary atresia [PA], hypoplastic left heart syndrome [HLH]), pneumonia, respiratory distress syndrome (RDS), HMD, PPHN, congenital diaphragmatic hernia (CDH), sepsis, pulmonary hypoplasia, pulmonary hemorrhage, hydrops fetalis, and other congenital anomalies. The average dose of iNO was 20 ppm (range = 2-80 ppm). The duration of exposure to iNO was on average 2 + 2 days (range = 15 min - 7 days). Weaning protocols were highly varied from duration of treatment, duration of time in between iNO decreases, initial dose, adjunctive medications used to wean, and increasing FiO_2 used to wean iNO. The weaning parameters were based on multiple variables including FiO_2, PaO_2, O_2 sats, and pulmonary arterial pressure.

In looking at the 7 studies that included preterm neonates there was 1 study that included babies with a postnatal age of 22.8 weeks [9], 1 study that included neonates ≤ 34 weeks GA [4], 1 study including babies 32-42 weeks GA [10], 1 study including infants ≥ 34 weeks GA [11], 1 study including babies < 33 weeks GA and ≥ 33 weeks GA [12], 1 study that was 35-42 weeks GA [13], 1 study including neonates 23-29 weeks GA [14], and 1 study that studied infants with birth weight less than 1,250 grams [5].

In the 7 studies that focused on full term neonates, the average birth weight, where it was included, was 3.3 kg [1, 6, 8, 15-19].

Table 1. Summary of studies regarding pre-term infants or pre-term plus term infants with iNO weaning protocols. Also a study with not reported GA is included.

Study	Type of study	Number of patients	Age (range)	Birth weight (range)	Diagnosis	iNO dose: initial (min-max)
Lee et al. [9]	retrospective, post-operative, chart review	7	PNA: 22.8 weeks (3 days-21 months)	not recorded	DORV, DTGV, HLH, PA, TAPVR, ASD	10, 20, 40 ppm (max: 20, 40, 60, 80)
Kinsella et al. [4]	randomized, multicenter	80	GA: 27 weeks (± 2.5)	1 kg (± 0.4)	severe hypoxemia despite surfactant and mechanical ventilation	5 ppm
Carriedo et al. [10]	retrospective, chart review	68	GA: 32-42 weeks	not recorded	patients enrolled in NINOs study	20 ppm (20-80)
Clark et al. [11]	randomized, placebo control	248	GA: ≥ 34 weeks, PNA: < 4 days old	3.3 kg (± 0.6)	MAS, pneumonia, PPHN, RDS, CDH, pulmonary hypoplasia	20 ppm (5-20)
Franco Belgium Collaborative [12]	randomized, multicenter	192	two groups: GA: < 33 weeks, GA: ≥ 33 weeks	not recorded	RDS, PPHN, MAS	10 ppm (5-20)
Wessel et al. [13]	prospective, randomized, single center	49	GA: 35-42 weeks	3.4 kg (± 1.5)	PPHN, MAS, pneumonia, sepsis, hydrops fetalis, pulmonary hemorrhage, RDS	80 ppm (5-80)
Banks et al. [14]	phase II open label, non-controlled	16	GA: 25.5 weeks (23-29)	0.78 kg	BPD	20 ppm (?-20)
Ballard et al. [5]	randomized, double blind, placebo-controlled	294	GA: 26 weeks (± 1.5)	0.76 kg (± 0.16)	RDS	20 ppm (2-20)

GA: gestational age; DORV: double outlet right ventricle; DTGV: d-transposition of the great vessels; HLH: hypoplastic left heart syndrome; PA: pulmonary atresia; TAPVR: total anomalous pulmonary venous return; ASD: atrial septal defect; PNA: postnatal age; MAS: meconium aspiration syndrome; PPHN: persistent pulmonary hypertension; RDS: respiratory distress syndrome; CDH: congenital diaphragmatic hernia; BPD: bronchopulmonary dysplasia.

Table 2. Summary of studies of full term infants with iNO weaning protocols.

Study	Type of study	Number of patients	Age (range)	Birth weight (range)	Diagnosis	iNO dose: initial (min-max)
Roberts et al. [1]	multicenter, double blind, placebo-controlled	58	GA: 39.8 weeks (± 1.5)	3.44 kg (± 0.62)	PPHN	80 ppm (10-80)
NINOS [6]	prospective, randomized, multicenter	53	GA: 38 weeks (± 2.2)	3.05 kg (± 0.5)	CDH	20 ppm (20-80)
Davidson et al. [8]	randomized, placebo-controlled, double blind	155	GA: 39.7 weeks (± 1.8)	3.4 kg (± 0.5)	MAS, sepsis, idiopathic PPHN, RDS	5, 20, 80 ppm final dose: 1, 4, 16
Kinsella et al. [16]	randomized, HFOV iNO	205	GA: 38.9 weeks (± 0.2)	3.2 kg (± 0.6)	Pneumonia, RDS, MAS, PPHN, pulmonary hypoplasia, CDH	20 ppm (6-40)
Atz et al. [15]	post-operative, non-randomized	9	PNA: 11.8 days (± 20.3)	3.5 kg (± 1)	TAPVR	80 ppm (10-80)
Sadiq et al. [17]	randomized, controlled, multicenter	85	GA: 39 weeks (± 2)	3.48 kg (± 0.42)	MAS, HMD, pneumonia, PPHN, congenital anomalies	10 ppm (10-80)
Aly et al. [19]	infants with hypoxemia refractory to optimal ventilatory and cardiotropic support with ECHO evidence of Pumonary Hypertension	16	GA: 39.2 weeks (± 3.7)	3.2 kg (± 0.8)	MAS, CHD, HMD, sepsis, CDH, pirimary PPHN,	25 ppm (5-25)
Wang et al. [18]	multicenter, non-randomized, controlled	200	GA: 39.3 weeks (± 2.2)	3.2 kg (± 0.68)	HRF	10 ppm (10-20)

iNO: inhaled nitric oxide; GA: gestational age; PPHN: persistent pulmonary hypertension; CDH: congenital diaphragmatic hernia; MAS: meconium aspiration syndrome; RDS: respiratory distress syndrome; HFOV: high frequency oscillatory ventilation; PNA: postnatal age; TAPVR: total anomalous pulmonary venous return; HMD: hyaline membrane disease; CHD: congenital heart disease; HRF: hypoxic respiratory failure.

Discussion

Numerous studies have proven the efficacy of the use of iNO for neonatal conditions including PPHN, secondary pulmonary hypertension caused by CHD, CDH, MAS, pneumonia, RDS, and other pathologies. However, how, and when, to wean iNO has not been extensively studied and there are very few studies that clearly discuss the protocol used to wean iNO within the study. Since it is clear that abrupt discontinuation of iNO leads to rebound pulmonary hypertension, it is important to look at the weaning protocols that have been described and encourage further research into safe and appropriate protocols for how and when to wean iNO.

The studies described below were filtered from an electronic database search of iNO and neonates and these were a selection of the studies which discuss specific weaning protocols. Within these groups of studies, 14 weaned iNO without specific use of adjuncts. Two studies used adjuncts to wean iNO: FiO_2 and sildenafil.

Studies regarding pre-term infants or pre-term plus term infants treated solely with iNO

We will first describe the 7 studies that included preterm neonates, and did not use any medications as adjunct to their iNO weaning protocols.

Wessel et al., in 1997 [13], looked at improved oxygenation in a randomized trial of iNO for PPHN of the newborn. There were 49 patients with GA 35-42 weeks. Mean birth weight was 3.4 kg. Patients had PaO_2 100 mmHg, FiO_2 1.0, maximum ventilatory and pharmacologic support and evidence of PPHN on echocardiography (ECHO).

Patients in the iNO group were started at 80 ppm. After 1 hour at this dose, the iNO was lowered to 40 ppm. If this change was tolerated, 40 ppm was continued for up to 12 hours. Dose decreases of 5 ppm were attempted each morning. iNO was discontinued if the dose could be reduced to 5 ppm and tolerated for at least 12 hours with a PaO_2 60 mmHg, and $FiO_2 \leq 0.5$. iNO was discontinued, but not a treatment success if the subject was cannulated for ECMO, or the clinical

team converted from conventional ventilator to HFOV. The change from 80 ppm to 40 ppm has previously been shown to be well tolerated as doses above 20 ppm are not shown to be significantly more effective. The approach of decreasing by 5 ppm per attempt, and allowing 24 hours between changes for adjustment to the new dose was well tolerated.

In 1999, Kinsella et al. [4] performed a multicenter randomized trial looking at iNO in premature neonates with HRF. There were 80 patients with mean GA 27 weeks and mean birth weight of 1 kg. All infants had severe HRF despite surfactant and mechanical ventilation.

The study looked at whether low dose iNO would improve survival of premature neonates with severe HRF and would not increase frequency or severity of intracranial hemorrhage or CLD.

Patients were stratified by study center and GA (≤ 28 wks or > 28 wks GA). Infants were randomized into iNO at 5 ppm or no iNO therapy. During the first 60 minutes of the trial there were no changes in ventilator device or ventilator settings. The groups were treated for 7 days and then there was a period of no gas administration for both groups. If there was a ≥ 15% increase in oxygenation index (OI), iNO was restarted. If iNO was restarted periods of trial off gas were every 2 days, with a maximum treatment time of 14 days. This was an on/off method of weaning with a prolonged period in between trials off iNO. Decreasing doses more gradually compared to having a prolonged period in between attempts off iNO is also a safe method of weaning iNO.

In 1999, the Franco-Belgium Collaborative NO trial [12] looked at early vs. delayed iNO in moderately hypoxemic neonates with respiratory failure. The primary endpoint of the study was a decrease in OI at 2 hours. It was a randomized multicenter trial, where 192 patients were divided into 2 groups; < 33 weeks and ≥ 33 weeks GA. In the < 33 week group, neonates were included if they had 2 OI measurements one hour apart that were 12.5-30. For the ≥ 33 week group, neonates were included if they had 2 OI measurements, an hour apart, that were 15-40.

Neonates were then randomized to iNO or no iNO therapy. Those on iNO were not masked. The iNO groups received 10 ppm of iNO. There was no change in ventilatory support other than FiO_2 during the first 2 hours of the trial, unless there was acute deterioration of the subject. If the control group reached the upper limit for age of OI measurement, the subject was given iNO at 20 ppm, exogenous surfactant, or had mode of ventilation changed. Those subjects in the iNO group who reached the upper limit of OI for age were given surfactant and/or had mode of ventilation changed. After 2 hours of the trial, therapeutic decisions were at the discretion of the clinical team. When able, iNO was weaned to 5 ppm and slowly tapered. Though this study allowed for weaning at the discretion of the clinical team, there was an attempted protocol for weaning iNO.

Clark et al., in 2000 [11], looked at low dose iNO for PPHN in newborns. They performed a randomized placebo controlled trial of 248 patients who were greater than or equal to 24 weeks GA, and less than 4 days old. The patients had diagnoses of MAS, pneumonia, idiopathic PPHN, RDS, CDH or pulmonary hypoplasia. Patients were included in the study if they required assisted ventilation, had an OI = 25 or higher, or had clinical or ECHO evidence of pulmonary hypertension without structural heart disease.

The study protocol was that iNO was started at 20 ppm, and continued for 4 hours. At 4 hours, arterial blood gas (ABG) and methemoglobin were measured. The dose was decreased to 5 ppm if the neonate's condition was stable, PaO_2 was at least 60 mmHg, and the pH was 7.55 or lower.

If these criteria were not met, study gas was kept at 20 ppm, and the neonate was evaluated every 4 hours until the criteria were met or the neonate had been treated for 24 hours. During the first 24 hours, the dose of study gas could be returned to 20 ppm if the PaO_2 fell below 60 mmHg when the FiO_2 was 1.0. After 24 hours of treatment, the dose was decreased to 5 ppm. Treatment was continued at 5 ppm until the FiO_2 was less than 0.7. If the neonate had been treated for 96 hours, or the neonate was 7 days old, and treatment could not be discontinued, the subject was considered a treatment failure. This study shows that 4 hours between attempted weaning steps was a safe duration of iNO treatment for adjustment to the dose, or if the subject required return to the previously tolerated dose.

Carriedo et al., in 2003 [10], performed a retrospective chart review of 68 patients looking at the safety of withdrawing iNO in patients considered non-responders following a brief exposure to iNO. The patients were between 32-42 weeks GA. The subjects were a subset of patients enrolled in the NINOS trial.

The weaning protocol was that patients were initially started on iNO at 20 ppm for 30 minutes.

At that point they were divided into 2 groups, those who had an increase in PaO_2 less than 20 mmHg and those who had an increase in $PaO_2 \geq$ 20 mmHg. If there was less than 20 mmHg change in PaO_2, iNO was stopped for 15 minutes, and ABG was obtained and iNO was given at 80 ppm for 30 minutes. For those who had an increase in $PaO_2 \geq 20$ mmHg the gas could be increased to 40 ppm for 30 minutes. This was an on/off protocol. This protocol demonstrated that short exposure to iNO was not associated with rebound pulmonary hypertension as seen with longer exposure time. This is likely related to the short exposure not downregulating endogenous NO production.

In 1999 [14], Banks et al. performed a phase II open label, non-controlled trial to look at the safety and dosing for a future randomized study. In this trial infants had BPD, required MAP ≥ 10 cm H_2O, and $FiO_2 \geq 0.45$.

The protocol in this study was that all enrolled patients were treated with iNO at 20 ppm for 72 hrs. iNO was discontinued prior to 72 hrs if there was an increase in $FiO_2 > 10\%$, with no other explanation, $PaCO_2 > 70$ mmHg, increased opacification on chest x-ray, or methemoglobin > 5%. After 72 hrs, patients were determined to be responders if they had a > 15% reduction in inspired oxygen concentration. In the infants without apparent benefit from iNO, the therapy was discontinued by decreasing iNO by 5 ppm increments every 6 hours.

In those who were determined to have a response to iNO, every 3 days, an attempt to wean iNO dose by 20% was performed. If the oxygen saturation fell by > 5% and lasted > 10 minutes during the wean, the dose was returned to the previously tolerated level. In the 24 hours after a wean attempt, if the infants oxygen requirement increased by 10%, iNO was returned to the last tolerated dose. This protocol utilized both a percentage decrease and a specific ppm decrease for iNO and was well tolerated by study participants.

Ballard et al. in 2006 [5], studied 294 infant receiving iNO who were less than 1,250 g. This study looked at survival without BPD at 36 weeks postmenstrual age. iNO was given at 20 ppm for 48-96 hours and was decreased at weekly intervals to 10, 5 and 2 ppm, with a minimum total duration of treatment of 24 days. Monitoring parameters included goal oxygen saturations of 88-94% and expected PaO_2 ranges 40-70 mmHg. This was a very prolonged weaning protocol for iNO.

Studies regarding full term infants treated solely with iNO

There were 7 studies that focused on full term neonates that had specific iNO weaning protocols, but had no adjunct as part of the weaning protocol [1, 2, 5, 12-14].

Atz et al., in 1996 [15], performed a non-randomized study on 9 patients who were post-operative from TAPVR repair. Their average GA was 11.8 days with a mean birth weight of 3.5 kg.

The iNO weaning protocol was that all patients were on 80 ppm of iNO for 15 minutes and then the iNO was discontinued. If the mean pulmonary arterial pressure (mPAP) reached 35 mmHg or higher, or the cardiac index was less than 2.5 $L/min^{-1}/m^{-2}$, iNO was restarted at 20 ppm. It was kept this way for one day. iNO was weaned to 10 ppm on day 1. iNO was discontinued from 10 ppm when the mPAP remained less than systemic.

In all the patients iNO decreased mPAP. There were no significant changes in right or left atrial pressures, heart rate, cardiac index, systemic blood pressure or systemic vascular resistance

In all patients, mPAP rose transiently when iNO discontinued. The peak rebound pressures were, on average, at 7 min after withdrawal, with an average increase in mPAP of 10 mmHg at withdrawal. The new steady state baseline was achieved at an average of 28 min after withdrawal. This study was specific in measuring the time from decreasing the dose to the new steady state for the subjects, which is important when determining how long to allow transient responses to decreased dose before determining the wean is a failure.

Roberts et al., in 1997 [1], performed a multicenter double blind, placebo controlled trial of iNO and PPHN of the newborn. There were 58 patients with mean GA of 39.8 weeks, and a mean birth weight of 3.44 kg. All patients included in the study had a diagnosis of PPHN on ECHO, PaO_2 55 mmHg or less on 2 consecutive tests performed 30 minutes apart while on mechanical ventilation with FiO_2 requirement of 1.0.

The iNO protocol was that patients were randomly assigned to control or iNO of 80 ppm with FiO_2 0.9 for 20 minutes. They were considered a treatment success if the PaO_2 increased to greater than 55 mmHg, OI decreased to less than 40, and systemic blood pressure did not drop below 40 mmHg. The iNO wean began 20 minutes after the period when the patient was determined to be a treatment success or not. iNO was weaned twice

per day if the PaO_2 was greater than 55 mmHg. At that time the gas was weaned by 10 ppm. During wean, the FiO_2, ventilatory therapy, and medical therapy remained unchanged. If the PaO_2 decreased by 15% or was equal to or less than 55 mmHg, 10 minutes after the iNO wean, the gas was raised to the previous level. The results of this study showed that half the infants required iNO for less than 2 days. This shows that iNO can safely be weaned with changes in dosage twice per day.

In 1997, the NINOS study group [6] looked at iNO and HRF in infants with CDH. It was a prospective, multi-center, randomized trial. There were 53 patients with a mean GA of 38 weeks and a mean birth weight of 3.05 kg.

In this trial iNO was started at 20 ppm. There was a positive response if there was an increase in arterial PaO_2 above baseline at 30 minutes after beginning study gas. If less than a full response, study gas was stopped for 15 minutes if tolerated, ABG was obtained, iNO was increased to the max of 80 ppm. Those infants who had a full response to the maximal concentration remained on this increased concentration; if the response was partial, subjects continued at the lowest study gas concentration to which there was a partial response. iNO was discontinued if there was no response at either 20 ppm or 80 ppm. After the initial study gas dosing, which was specified by the protocol, study gas management was at the discretion of the centers. Weaning of study gas was only attempted if the PaO_2 was more than the acceptable baseline established by each participating center (the minimal criteria being an oxygen saturation > 92% and/or a PaO_2 > 50 Torr). This study differed in that it used specific clinical criteria instead of amount of time at a dose to determine when to attempt to wean iNO.

Kinsella et al., in 1997 [16], performed a multicenter trial of iNO and high frequency oscillatory ventilation (HFOV) in newborns with severe PPHN. They looked at 205 infants with mean GA 38.9 wks, and mean birth weight of 3.2 kg. The subjects had diagnoses of pneumonia, RDS, MAS, PPHN, pulmonary hypoplasia or CDH. They were randomly assigned to one of 2 study groups. The groups were iNO and conventional ventilation or HFOV without iNO therapy. Treatment failure, which was defined as PaO_2 < 60 mmHg, resulted in crossover to the alternative treatment; treatment failure after crossover led to combination treatment with HFOV plus iNO. Treatment response with the assigned therapy was defined as sustained PaO_2 of 60 mmHg or greater.

The iNO group was started on a dose of 20 ppm for 4 hours, at which time the dose was decreased to 6 ppm. If PaO_2 was < 60 mmHg while the iNO was at 20 ppm a trial of 40 ppm was allowed, though no duration was clearly defined. At 24 hours of treatment, the iNO was discontinued. If there was an increase in OI after the discontinuation of the gas, iNO was restarted for 24 hours. This protocol was continued until iNO could be discontinued without an associated decline in oxygenation.

The results of the study showed no significant difference between the study groups. This iNO weaning protocol was on/off from 6 ppm of iNO. While there were multiple attempts to go from 6 ppm to off over multiple days, a stepwise approach to weaning from 6 ppm may have shown a difference between the 2 groups, in specific parameters such as days on mechanical ventilation.

Davidson et al., in 1999 [8], performed a double blinded, randomized placebo controlled trial of 155 patients looking at the safety of withdrawing iNO from patients with PPHN. The patients in this study had diagnoses of MAS, sepsis, idiopathic PPHN, and RDS. They were included in the study if they were a term neonate, had ECHO evidence of PPHN, FiO_2 1.0, MAP ≥ 10, and postductal PaO_2 40-100.

The patients were split into 4 different treatment groups with iNO doses of 0, 5, 20 or 80 ppm. Patients were considered a treatment failure if the PaO_2 was 40 mmHg for 30 minutes and FiO_2 was 0.95 on a conventional ventilator. Patients were also considered treatment failures if they had refractory hypotension, defined as mean systemic arterial pressure of < 35 mmHg independent of oxygenation. Patients were grouped as a treatment success if PaO_2 > 60 mmHg, FiO_2 < 0.6, and mean airway pressure < 10 cm H_2O.

In this study the protocol for weaning iNO was initially to determine treatment success or failure as described above. Immediately after that determination, iNO was decreased by 20%. An ABG was obtained 15-30 minutes later. Anytime in the following 4 hours, another 20% decrease of iNO could be made by the clinical team. 15-30 minutes after the decrease in iNO, an ABG was obtained. With each step in the process, no change was made immediately before a decrease in iNO, or within the 15-30 minutes until the ABG was obtained. This process was continued until the gas was completely discontinued. If a rapid wean was being attempted, the post change ABG could be used as the pre-change ABG. If the patient had PaO_2 < 40 during a wean step, the iNO could be increased by 20%

as well as an increase in FiO_2. The final dose prior to discontinuation of the gas was 20% of the initial dose (0, 1, 4, 16 ppm). This study again showed that up to 30 minutes to allow for calibration to the new steady state was a reasonable amount of time for exposure to the new dose of iNO before determining if this step was a success or failure.

In 2003, Sadiq et al. [17], looked at iNO in the treatment of moderate PPHN of 85 newborns. This was a randomized, controlled, multicenter trial. The neonates had a mean GA of 39 weeks, and a mean birth weight of 3.48 kg. They were mechanically ventilated with FiO_2 1.0, and presented ECHO evidence of pulmonary hypertension. iNO was started at 10 ppm. There were stepwise increases of 10-20 ppm every 30 minutes until no further increases in PaO_2 occurred or until a maximum iNO concentration of 80 ppm was reached. At that point, ventilatory support was weaned as tolerated to maintain $PaCO_2$ 40-50 Torr, and $PaO_2 \geq 50$ Torr. iNO was weaned when the subject was on minimal ventilator settings and FiO_2 was 0.3-0.5. iNO was also weaned if methemoglobin was > 5%. The mean duration of iNO therapy was 96 hours. This study utilized iNO to wean ventilator settings prior to weaning iNO, and with this, the average amount of iNO use was 3 days, which is not a prolonged exposure to iNO.

Wang et al. in 2011 [18], performed a non-randomized, open, controlled study on the efficacy of iNO. They compared 107 term and near term infants with iNO therapy with 93 control patients. Patients were enrolled in they were in HRF with an oxygenation index > 15 that persisted for at least 48 hours.

iNO was started at 10 ppm. Treatment response was evaluated by PaO_2. If PaO_2 > 20, 10-20 or < 10 mmHg from baseline were determined to be full, partial, or no response. If there was not a full response at 10 ppm, iNO was increased to 20 ppm. If no response at 20 ppm, iNO was decreased to 10 ppm. Concentration of iNO was weaned by 1-2 ppm every 6-12 hours until weaned off as long as there was no deterioration in oxygenation. This study again showed that 6-12 hours was a safe amount of time between decreases in iNO.

Other studies, with adjunct medication beyond iNO

The last 2 studies used an adjunct medication in the protocol to wean iNO. The first study used sildenafil [9] and the second study used increased oxygen [19] to wean iNO.

Aly et al., in 1997 [19], did a cohort study of 16 patients looking at the weaning strategy of iNO in the treatment of PPHN of the newborn. The subjects had a mean GA of 39.2 weeks, and a mean birth weight of 3.2 kg.

iNO was started at 25 ppm. The gas was weaned in increment decreases of 5 ppm, at 4 hour intervals, when FiO_2 was less than 0.5 with insignificant gradient between pre- and post-ductal oxygen saturation, and mean airway pressure was less than 10 mmHg. When patients were considered stable on 5 ppm of iNO, the gas was discontinued. If the subject had a decrease in oxygen saturation by 10%, or if oxygen saturation was less than 85%, iNO was restarted at 5 ppm and the patient allowed to stabilize for 30 minutes. After the 30 minutes period, FiO_2 was increased to 0.4, and discontinuation from iNO was attempted again. Allowing transient increases in FiO_2 can be utilized in weaning iNO. Combining transient increases in FiO_2 as well as allowing for transient (30 minutes) changes in PaO_2 and $PaCO_2$ can help weaning iNO and achieve a new steady state between weaning steps.

Lee et al., in 2008 [9], studied the use of sildenafil for facilitating weaning of iNO in neonates with pulmonary hypertension following surgery for CHD. This was a retrospective post operative chart review of 7 patients with mean postnatal age of 22.8 weeks. All the patients included in the study had failed to tolerate an iNO wean prior to the use of sildenafil.

Sildenafil was given with an average dose of 0.3 mg/kg orally 4 times daily. iNO was weaned based on the dose at initiation of wean. For those on 20-40 ppm, iNO was weaned in 5 ppm increment decreases, for those receiving iNO 10-20 ppm, the wean increment was 2 ppm. For those receiving 2-10 ppm, the wean increment decrease was 1 ppm, and for those receiving 0-2 ppm the wean increment decrease was 0.5 ppm. The dose was weaned every 1-2 hours. Adjunct medication such as Sildenafil has a role in weaning iNO, though it is not essential in being able to wean iNO successfully.

Global remarks

The prescribing information from iNOmax® includes discussion on the indication for use, how to administer iNO including dosage, but there is no specific recommendation made by the manufacturer for weaning of iNO.

This subset of studies described above show a wide variation in the use and weaning of iNO in neonates.

Conclusions

There are many studies regarding the dosage and efficacy of iNO, but very few of them actually discuss a weaning protocol in detail. Understanding that there is, indeed, a wide variation in the use and administration of iNO in babies, we believe it to be very important to describe these patterns, and describe more in depth an "optimal" weaning protocol for iNO. Based on this review, we propose a strategy for those patients determined to be iNO responders, to wean iNO in a stepwise approach from 20 ppm in increments of 5 ppm per decrease until 5 ppm; and stepwise by 1 ppm from 5 ppm to off while monitoring O_2 saturations and predetermined blood gases parameters. Each weaning step should be performed after a minimum of 4 hours at the current dose while allowing transient increases in FiO_2 while adjusting to the new dose. This weaning is recommended both for invasive and non-invasive modes of ventilation. This is not a protocol that is appropriate for every patient pathology, but is a safe starting point with allowance for individual patient and physician variability.

Creating a standard protocol to weaning iNO is an important first step, however, we expect that any protocol will vary depending on multiple factors, including, for example, the use of adjunctive medications to wean the dose of iNO, the decision to wean iNO vs. FiO_2 vs. mechanical ventilation settings first and, perhaps more importantly, the underlying pathology of the neonate.

Abbreviations

ABG: arterial blood gas
ASD: atrial septal defect
BPD: bronchopulmonary dysplasia
CDH: congenital diaphragmatic hernia
CHD: congenital heart disease
DORV: double outlet right ventricle
DTGV: d-transposition of the great vessels
ECMO: extracorporeal membrane oxygenation
FiO_2: fraction of inhaled oxygen
GA: gestational age
HFOV: high frequency oscillatory ventilation
HLH: hypoplastic left heart syndrome
HRF: hypoxic respiratory failure
HMD: hyaline membrane disease
iNO: inhaled nitric oxide
MAS: meconium aspiration syndrome
NO: nitric oxide
OI: oxygenation index
PA: pulmonary atresia
PPHN: persistent pulmonary hypertension
RDS: respiratory distress syndrome
TAPVR: total anomalous pulmonary venous return

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