الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Post-Market Evaluation Study for the Safety and Effectiveness of Inhaled Nitric Oxide Therapy

BACKGROUND

Inhaled nitric oxide (iNO) therapy systems are a newly-developed technology for pulmonary vasodilation. This technology is used in several pulmonary conditions to improve the oxygenations as a rescue technique, beside the usage as a diagnostic approach in the pulmonary artery measurements. The aim of this study is to evaluate the safety of the iNO therapy in general, giving a closer look at the recent studies that investigate the roles of NO in the various medical conditions. The study also aims to enlighten the healthcare community about the current international practices in the iNO therapy at the one hand, and to define the known use problems and side effects associated with the technique on the other hand.

CLINICAL BURDEN

INO therapy

Nitric Oxide, or simply NO, is a colorless, odorless gas, which is known to be a potent and selective pulmonary vasodilator [1] –*Vasodilators are the agents that aid in the dilation or widening of the blood vessels, which decreases blood pressure, due to the relaxation of smooth muscle cells within the vessel walls as shown in* ***figure 1***- [2]. NO is considered as an ideal pulmonary vasodilator for two reasons. First, it is a gas, and thus provides the ideal way to be delivered to the target blood vessels in the lung with avoiding systemic hypotension. Secondly, NO has high affinity for heme protein, and as a result of this, any excess inhaled NO in the lung would rapidly binds to hemoglobin, eliminating the potential for systemic vasodilatation. Therefore, this feature enables NO to be a pulmonary-specific vasodilator. [3]

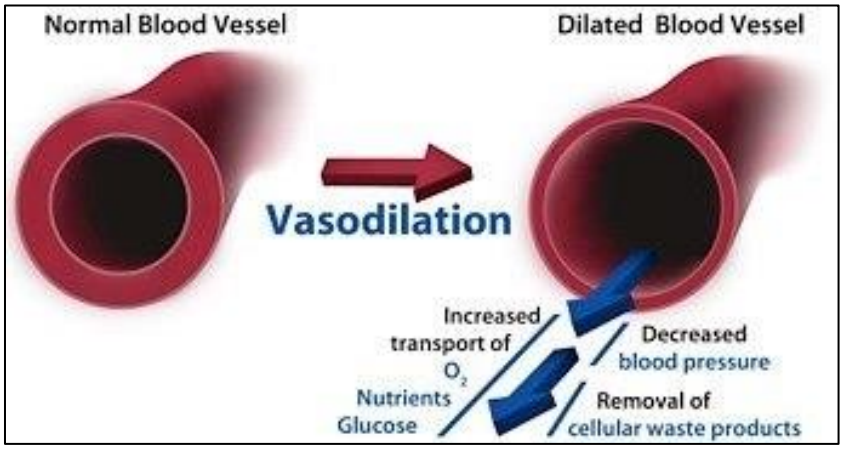

Figure 1: Illustration of the vasodilation mechanism in the blood vessels [2].

Alternative approaches for INO therapy

Abrupt discontinuation of vasodilators is reported by the US FDA to cause rebound pulmonary hypertension, [4] which reflect the necessity behind the suggestions of using delivery systems to administer the gas, in order to supply the patients with constant dosage, and to ensure the continuous delivery. [5] Even though INO is the only pulmonary vasodilator approved by the US Food and Drug Administration for the treatment of persistent pulmonary hypertension (PPHN), the off-label use of other inhaled pulmonary vasodilators systems has been reported, [5] such as the inhaled aerosolized pulmonary vasodilators using prostacyclins, epoprostenol, [6] iloprost, [7] [8] and prostaglandin. While prostacyclins, epoprostenol, and iloprost have been approved to treat the pulmonary arterial hypertension (PAH), prostaglandin is approved for palliative therapy to maintain patency of the ductus-arteriosus in neonates. [5] However, these vasodilators are still not approved for the use with PPHN because they are supplied through nebulizers, and thus, lack the consistency in the drug delivery, which do not fulfill the requirement of preventing the rebound pulmonary hypertension. [5]

RISKS AND COMPLICATION

NO is described to associate with minimal toxicity, especially when administered in dosage of 20 ppm, and up to 40 ppm. [9] Yet, the main concerns involved with iNO toxicity include the excess production of NO2 and the elevated formation of methemoglobin. [3] [9] NO2 is a cytotoxic molecule, and can cause pulmonary injury at concentrations greater than 5 ppm. Its production is susceptible to occur when NO react with O2 in high oxygen concentration in the ventilator circuit. However, studies show that iNO at doses less than 80 ppm is not associated with significant NO2 productions. Methemoglobin can also be formed, due to the high affinity of NO to bind to the heme protein, and thus, methemoglobin levels should be measured frequently and kept at a level below 2.5%. Nevertheless, studies show that when iNO doses is maintained below 20 ppm, methemoglobin level is rarely raised above 2.5%. [3] [9]

INO therapy is approved by the US FDA for the treatment of term and near-term (>34-weeks gestation) neonates with hypoxic respiratory failure associated persistent pulmonary hypertension PPHN. [1] Nonetheless, there are many other off-label uses of iNO, [10] including acute respiratory distress syndrome (ARDS) in infants and adults, [11] mitral stenosis and severe PH following cardiac surgery, [12] severe acute submissive pulmonary embolism, [13], beside other conditions. It is also used in several

pulmonary conditions to improve the oxygenations as a rescue technique, beside the usage as a diagnostic approach in the pulmonary artery (PA) measurements.

EVALUATION OUTCOMES

Part 1: Clinical paper review

1.1 An overview of the search criteria

A literature review was conducted, with intention to acquire the most relevant papers that discuss the safety of iNO. A total of 82 articles were obtained and screened, which resulted in 38 articles, as shown in **figure 2**.

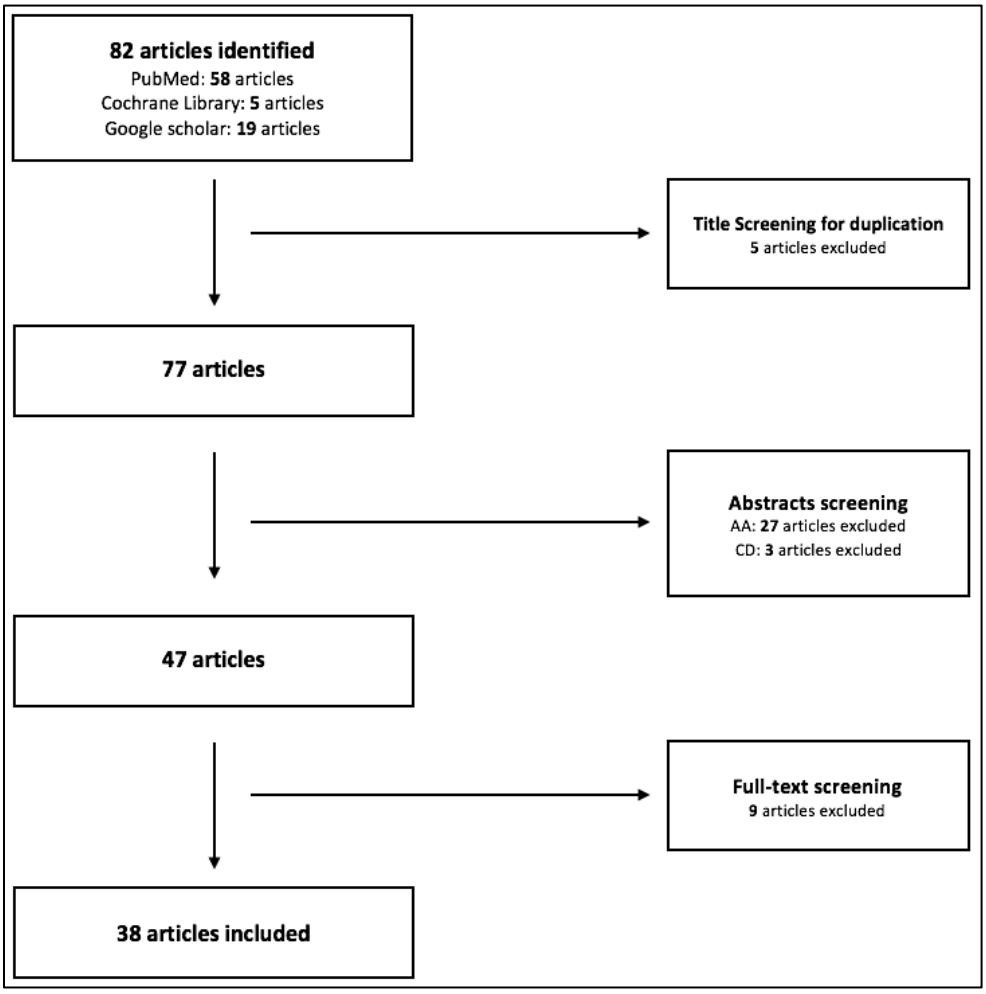

Figure 2: Schematic representation of the search findings.

2.2 Results of the clinical paper review

INO therapy was found to be administered to patients with different medical conditions and different populations (part I: preterm infants, part II: full-term infants, and part III: adults), as highlighted in **table 1.** Overall, it is clearly noticed that the use of iNO is mostly safe, and does not lead to severe side effects when used in tertiary care settings with strict administration protocols and careful monitoring. However, minimal toxicity might occur due to the formation of NO2 and methemoglobin when higher than recommended doses are administered, especially with preterm infants. [14] [15] Also, there is a strong evidence that iNO is associated with increasing the risk of the renal dysfunction with adult patients. [16] On the other hand, and with respect to the effectiveness of iNO therapy, it greatly varies based on the targeted patient populations.

The overall results of are presented in table 1, and can be summarized in the following points:

First: Current-evidence in the efficacy of iNO therapy with preterm infants:

- Generally speaking, iNO does not seem to be effective either as a rescue treatment option or as a routine treatment option for preterm infants who require ventilation assistant, where multiple studies (Ref. 17, 4, 18, 19, 20, and 21) have shown that iNO did not correspond to survive the respiration support without developing BPD, and showed no effect on reducing mortality.

Secondly: Current-evidence in the efficacy of iNO therapy with full-term infant and kids:

- Overall, iNO therapy is effective as a rescue treatment in full-term infants with hypoxemic respiratory failure associated with PPHN who have not responded to other methods of support, where it increases levels of oxygenation, and reduce the need to ECMO, but no evidence in infants with CDH, (Ref. 22, 24, and 25). Also it aids in decreasing the probability of developing severe hypoxemic respiratory failure in full-term infants with moderate respiratory failure (Ref. 24, 25)
- Similarly, iNO therapy is effective as a rescue treatment in full-term infant and children with ARDS just for the short-term improvement in the oxygenation (Ref. 26 and 14).

Thirdly: Current-evidence in the efficacy of iNO therapy with adults:

- Overall, iNO therapy improves oxygenation, but without any decrease of mortality in adults with ARDS. Hence, it should be used as a rescue treatment, and as a bridge to improve oxygenation while other therapies are considered (Ref. 13 and 14)
- Also, iNO shows a promising outcomes in reducing pulmonary arterial pressure in adult. (Ref. 28)

Table 1: Clinical paper review for the INO therapy in preterm infants, full term infants and adult patients

Ref	Design	Subjects	condition	Safety	Efficacy	Comments
Part I: Evaluating the safety and effectiveness of INO therapy in *preterm infant patients*						
17	RCT	451 neonates <30 weeks' gestation, <1250 g receiving mechanical ventilation or positive pressure resp. support on days 5 to 14. 222 infants (control), 229 (iNO).	BPD (survive resp. support without BPD)	Safe	Not effective	INO did not improve survival without BPD at 36 weeks' PMA or respiratory and neurodevelopmental outcomes at 18 to 24 months' PMA.
4	CCT	402 Preterm <34 weeks infants, 162 (INO) and 240 (control).	BPD (survive resp. support without BPD)	Safe	Not effective	INO didn't decrease the risk of developing BPD and death in preterm infants receiving resp. support.
18	Review of 14 RCTs	Preterm infants	BPD (survive resp. support without BPD)	Safe	Not effective	iNO as rescue therapy for the very ill preterm infant does not appear to be effective. Early routine use of iNO in preterm infants with respiratory disease does not improve survival without BPD
19	RCT	800 preterm infants (24-28 weeks), <500 g, requiring surfactant or continuous positive airway pressure for ARDS within 24 h of birth. 399 infants (INO) and 401 (placebo)	BPD (survive resp. support without BPD)	Safe	Not effective	Early use of low-dose INO in very premature infants did not improve survival without BPD or brain injury, suggesting that such a preventive treatment strategy is unsuccessful.
20	Prospectiv e study	60 infants, with a gestational age of <32 weeks and a birth weight of less than 1500 g.	BPD (survive resp. support without BPD)	Safe	Moderately effective.	35 neonates survived the respiratory support without developing BPD, while 25 neonate developed BPD
21	Review of 12 RCTs	3298 infants < 37 weeks gestation with CLD	CLD	Safe	Not effective	INO did not show a statistically significant effect on death or chronic

						lung disease (CLD) for infants <37 weeks.
Part II: Evaluating the safety and effectiveness of INO therapy in full-term *infant patients*						
1	RCT	43 infant patients (2-11 months), 21 treated sample (160 ppm for 30min, 5X a day) and 23 control sample (O2).	Bronchiolitis	Safe	Not effective	The use of INO to treat bronchiolitis in infants was not effective, but, the length of hospitalization was slightly encouraging.
22	Review of 17 RCTs.	Infants born at or near term with hypoxic respiratory failure.	Respiratory Failure	Safe	Moderately effective.	INO therapy is effective in full-term infants with respiratory failure who have not responded to other methods of support. It increases levels of oxygenation, and reduce the need to ECMO, but no evidence in infants with CDH
23	Review of 14 RCTs	1275 infants and adult patients with acute respiratory failure	Respiratory Failure	Safe	Not effective	INO therapy didn't improve survival rate, and associated with kidney function impairment.
24	RCT	56 newborns with moderate respiratory failure. Early iNO, n=28, with 20 ppm, and conventional mechanical ventilation (Control, n=28).	Moderate Respiratory Failure	Safe	Effective	Early use of iNO in newborns with moderate respiratory failure improves oxygenation and decreases the probability of developing severe hypoxemic respiratory failure.
25	Post-hoc analysis	299 term/late preterm infants.	Moderate Respiratory Failure	Safe	Moderately effective.	Decreased ECMO/death rates, and decreased the progression of respiratory failure. The results suggest that early use of surfactant and iNO in moderate respiratory failure may improved outcomes.
26	Prospectiv e study	33 children (2-9 years old) with ARDS	ARDS	Safe	Effective for a short term oxygenation	iNO improves short- term oxygenation, but there was no difference in mortality and duration of mechanical ventilation between iNO and control group.

14	Review of 14 RCTs	1303 infant and adult patients	ARDS	Safety concerns	Not effective	INO improve oxygenation only in the first 24 hours, also iNO might lead to methemoglobin or NO2 formation
27	Retrospective study	29 infants who had undergone iNO therapy for PH due to CDH, 8 (iNO) and 21 (control)	PH due to CDH	Safe	Effective	INO therapy seems to increase survival in PH due to CDH. ** Limited number of patients.*
15	Retrospective study	163 neonates, 81 premature and 82 term and near-term infants, with 452 MetHb measurements.	MetHb Formation	Safe	NA	Toxic levels of MetHb rarely occur if doses of <20 ppm for near-term and <10 ppm for preterm infants are respected.
Part III: Evaluating the safety and effectiveness of INO therapy in *adults patients*						
13	Review of 9 RCTs	1142 patients	ARDS	Safe	Not effective	INO therapy improves oxygenation, but without any decrease of mortality. Hence, it shouldn't be routinely used in ARDS patient, but as a bridge to improve oxygenation while other therapies are considered.
16	Review of 10 RTCs	1363 adult ARDS patients.	ARDS	Safety concerns	Not evaluated	iNO therapy is expected to increase the risk of renal dysfunction, especially with prolonged use and in patients with ARDS
14	Review of 14 RCTs	1303 infant and adult patients	ARDS	Safety concerns	Not effective	INO improve oxygenation only in the first 24 hours, also iNO might lead to methemoglobin or NO2 formation, and possible renal impairment
23	Review of 14 RCTs	1275 infants and adult patients with acute respiratory failure	Respiratory Failure	Safe	Not effective	INO therapy didn't improve survival rate, and associated with kidney function impairment.
28	RCT	185 adult CHDs with severe PAH (iloprost, n=127; NO, n=58)	Pulmonary Arterial Hypertension	Safe	Effective	INO help reducing pulmonary arterial pressure, also pulmonary vascular resistance were observed.
29	RCT	29 patient, iNO (n = 14) or oxygen (n	Mitral Stenosis and	Safe	Effective	Effective in improving hemodynamics for patient

		= 15) for 48 hours immediately after surgery.	severe PH following cardiac surgery			with Mitral Stenosis and Severe Pulmonary Hypertension (PH) After Mitral Valve Surgery.
30	Phase I RCT	8 patients with CT-demonstrated, submassive PE and moderate to severe dyspnoea.	Pulmonary Embolism	Safe	Effective	iNO reduced dyspnoea without adverse events in 8 patients with severe submassive PE.

Part 2: Clinical experience review

This section aims to present the recommendations of some specialized international associations including: The National Institute of Health, The American Academy, The American Association for Respiratory Care, and The Canadian Pediatric Society. These parties published numerous guidelines to define the best practices in the utilization of the INO therapy, as summarized in **Table 2.**

Table 2: A complementary material addressing certain recommendations for the best-practices in using NO

	The National Institute of Health (NIH) recommendations (2010)	The American Academy of Pediatrics (AAP) recommendations (2014)
Preterm Infants	1. Taken as a whole, the available evidence does not support use of iNO in early routine, early rescue, or later rescue regimens in the care of premature infants who require respiratory support. 2. There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants <34 weeks gestation. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties. 3. Basic research and animal studies have contributed to important understandings of iNO benefits on lung development and function in infants at high risk of BPD. These promising results have only partly been realized in clinical trials of iNO treatment in premature infants. Future research should seek to understand this gap. 4. Predefined subgroup and post hoc analyses of previous trials showing potential benefit of iNO have generated hypotheses for future research for clinical trials. Prior strategies shown to be ineffective are discouraged unless new evidence emerges. The positive results of one multicenter trial, which was characterized by later timing, higher dose, and longer duration of treatment, require confirmation. Future trials should attempt to quantify the individual effects of each of these treatment-related variables (timing, dose, and duration), ideally by randomizing them separately. 5. Based on assessment of currently available data, hospitals, clinicians, and the pharmaceutical industry should avoid marketing iNO for premature infants.	1. The results of randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study indicate that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure. 2. The preponderance of evidence does not support treating preterm infants who have respiratory failure with iNO for the purpose of preventing/ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities. 3. The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with iNO is similar to that of control infants. 4. The results of 1 multicenter, randomized controlled trial suggest that treatment with a high dose of iNO (20 ppm) beginning in the second postnatal week may provide a small reduction in the rate of BPD. However, these results need to be confirmed by other trials. 5. An individual-patient data meta-analysis that included 96% of preterm infants enrolled in all published iNO trials found no statistically significant differences in iNO effect according to any of the patient-level characteristics, including gestational age, race, oxygenation index, postnatal age at enrollment, evidence of pulmonary hypertension, and mode of ventilation. 6. There are limited data and inconsistent results regarding the effects of iNO treatment on pulmonary outcomes of preterm infants in early childhood.

	The American Association for Respiratory Care recommendations for the use of iNO for full-term neonates (2010)
Full-term infants	1. It is recommended that INO therapy be instituted early in the disease course, which potentially reduces the length of mechanical ventilation, oxygen requirement, and stay within the intensive care unit. 2. It is recommended that INO should not be used routinely in newborns with congenital diaphragmatic hernia. 3. It is suggested that INO therapy should not be used routinely in newborns with cardiac anomalies dependent on right-to-left shunts, congestive heart failure, and those with lethal congenital anomalies. 4. It is suggested that there are insufficient data to support the routine use of INO therapy in postoperative management of hypoxic term or near-term infants with congenital heart disease. 5. The recommended starting dose for INO is 20 ppm. 6. It is recommended that response to a short trial (30–60 min) of INO should be judged by an improvement in PaO2 or oxygenation index (OI); if there is no response, INO should be discontinued. 7. For the newborn with parenchymal lung disease, it is recommended that optimal alveolar recruitment be established prior to initiation of INO therapy. 8. For newborns with a response to INO therapy, it is recommended that the dose should be weaned to the lowest dose that maintains that response. 9. It is recommended that INO should not be discontinued until there is an appreciable clinical improvement; that the INO dose should be weaned to 1 ppm before an attempt is made to discontinue; and that the FIO2 should be increased prior to discontinuation of INO therapy. 10. It is recommended that FDA-approved INO delivery systems should be used to assure consistent and safe gas delivery during therapy. 11. During conventional mechanical ventilation, it is suggested that the INO gas injector module should be placed on the dry side of the humidifier. 12. During conventional ventilation, it is suggested that the sampling port be placed in the inspiratory limb of the ventilator, downstream from the site of injection, no greater than 15 cm proximal the patient connection/interface. 13. It is suggested that the FIO2 be measured downstream from the injection of INO into the circuit. 14. It is suggested that the patient/ventilator system be continuously monitored for changes in ventilation parameters, with adjustments to maintain desired settings during INO therapy. 15. It is suggested that the lowest effective doses of INO and O2 be used, to avoid excessive exposure to NO, NO2, and methemoglobinemia. 16. It is suggested that the INO delivery system be properly purged before use to minimize inadvertent exposure to NO2 17. It is suggested that the high NO2 alarm be set at 2 ppm on the delivery system to prevent toxic gas exposure to the lungs. 18. It is suggested that methemoglobin be monitored approximately 8 hours and 24 hours after therapy initiation and daily thereafter. 19. It is suggested that the INO dose be weaned or discontinued if methemoglobin rises above 5%. 20. It is suggested that continuous pulse oximetry and hemodynamic monitoring be used to assess patient response to INO therapy. 21. It is suggested that scavenging of exhaled and unused gases during INO therapy is not necessary
	The Canadian Pediatric Society recommendations for the use of iNO for full-term neonates (2017)
	• iNO use in the term infant with severe hypoxic respiratory failure improves oxygenation and decreases the combined outcome of death or need for ECMO, mainly by decreasing the use of ECMO. • iNO use is not effective for most infants with congenital diaphragmatic hernia. Its role in the management of the preterm infant has yet to be established. • iNO use is safe when administered in tertiary care NICUs under strict protocols and monitoring. • The starting dose in term infants is 20 ppm, with gradual reduction of the dose following improvement of oxygenation. At the recommended doses, iNO is associated with minimal toxicity.

SFDA RECOMMENDATIONS

1. It is suggested that inhaled nitric oxide (INO) be delivered through delivery systems to assure consistent and safe gas delivery during therapy, as the conventional way of delivering the gas through regulators and flowmeters are neither accurate, nor safe to the operators and the surrounding area.
2. It is suggested that INO intended department adapts a clear policy and procedures for the administration of nitric oxide, to ensure that clinical staff understand and acquire the skills to administer the INO.
3. INO should be used in a well-ventilated area, to avoid the possible build-up of NO2 in the area, as NO2 is cytotoxic and can cause pulmonary injury at concentrations >5 ppm. Also, while the INO systems are in use, a routine monitor of the NO2 level using NO2 detector should be considered, with an attention to maintain the level below 2.5 ppm.
4. INO is reported to associate with minimal toxicity when used as recommended. However, there is an evidence that the treatment could lead to the following potential adverse events whenever misused:
    a. Rebound Pulmonary Hypertension, which can be caused by the abrupt discontinuation of INO.
    b. Increased level of methemoglobin, which can be caused when doses > 20 ppm of INO is used.
    c. Increased levels of NO2, which can be caused when doses > 80 ppm of INO is used.
    d. Increase the risk of renal dysfunction, especially with prolonged INO use in adults with ARDS

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