Commentary

Inhaled nitric oxide: another weapon in our armamentarium in the battle against acute hypoxic respiratory failure in preterm infants

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Abstract

Acute hypoxic respiratory failure (AHRF) remains a significant cause of death in intensive care units. With the realization that pathophysiologic abnormalities in AHRF involve surfactant abnormalities as well as inflammatory and vascular changes, it is not surprising that nitric oxide (NO) has been investigated as an adjunct to the multiple ventilatory strategies adopted in the management of this disorder. Since the enthusiastic reports of Roussaint in 1993 showing improved survival with inhaled NO in the management of AHRF, several well-designed studies have been published, all designed to investigate the utility of NO in neonatal, pediatric and adult patients. Michael Schreiber and colleagues evaluated 207 preterm infants with AHRF in a randomized, double-blind placebo-controlled study. Inhaled NO was administered at a constant low dose for up to 6 days in the NO group. Patients were further randomized to conventional ventilation and to high-frequency oscillatory ventilation. The patients showed a statistically significant improvement in their primary endpoint of the incidence of chronic lung injury and death in the inhaled NO group. There was no increase in the incidence of intraventricular hemorrhage between the study and placebo groups. Schreiber and colleagues concluded that early treatment with inhaled NO would improve long-term pulmonary outcomes in premature infants with respiratory distress syndrome, decreasing the incidence of chronic lung disease and death. Prior to this study no prospective randomized trial had demonstrated any benefits in clinical outcomes such as the length of hospital stay or death. This study supports the belief that the majority of patients will experience, at a minimum, a short-term benefit from inhaled NO therapy, but also suggests that inhaled NO may influence clinical outcomes as well. The recognition that AHRF is often the result of a multifactorial process makes it unlikely that one treatment modality will have a major beneficial effect on mortality and morbidity.

Keywords acute hypoxic respiratory failure, acute respiratory distress syndrome, inhaled nitric oxide, preterm infants

Introduction

Since the landmark article of Palmer and colleagues in 1987 identifying nitric oxide (NO) as the vascular endothelial relaxing factor [1] and the primary pathway to vasodilatation, NO has made the journey from bench use to clinical use very rapidly.

NO is an ideal transcellular messenger. It is a small lipophilic free radical with a very short half-life. NO is rapidly oxidized to nitrates and nitrite in the blood, combining with hemoglobin to form methemoglobin. NO activates soluble guanylate cyclase by combining with the heme moiety of the enzyme. This enzyme increases conversion of guanosine 5′-triphosphate to guanosine 3′,5′-monophosphate, which is associated with reduced intracellular calcium and vascular relaxation [2].

There is abundant evidence that endogenous NO also plays a key role in physiologic regulations of airway functions and is implicated in airway disease. NO derived from constitutive

ARHF = acute hypoxic respiratory failure; iNO = inhaled nitric oxide; NO = nitric oxide.

NO synthase is involved in physiologic regulation of airway function, whereas NO derived from inducible NO synthase is involved in inflammatory disease of the airway and in host defense mechanisms [2].

Acute hypoxic respiratory failure (AHRF) encompasses acute respiratory distress syndrome and acute lung injury and remains a significant cause of death in the intensive care unit. With the realization that AHRF is a combination of surfactant abnormality as well as an inflammatory disorder that transcends pulmonary lesions and includes involvement of the microvasculature of multiple organ systems, it is not surprising that NO has been investigated as an adjunct to the multiple ventilatory strategies adopted in the management of AHRF.

Since the enthusiastic reports of Roussaint and colleagues [3] in 1993 showing improved survival with inhaled nitric oxide (iNO) in the management of AHRF, several excellent studies have been published, all designed to investigate the utility of NO in neonates [4,5], in children [6] and in adults [7,8] with AHRF.

The prospective randomized, double-blind placebo-controlled study conducted at the University of Chicago by Michael Schreiber and colleagues [9] provides additional ammunition for the proponents of NO use in neonates with AHRF.

The study randomized 207 preterm infants, delivered before 34 weeks of gestation and weighing less than 2000 g. To ensure that the birth weight distribution was similar among the groups, five 250-g birth weight categories were randomized. All the neonates randomized to the study group received NO at a constant initial dose of 10 parts per million for 24 hours and then 5 parts per million for up to 6 days or until exit from the study, whichever was earlier. The infants were further randomized to a conventional intermittent mandatory ventilatory group or to a high-frequency oscillatory ventilatory group. Subsequent ventilatory decisions were left to the managing physicians, but data from infants in whom ventilatory switches were made were still analyzed on an intent-to-treat basis. No crossover was allowed.

Although the primary hypothesis was that iNO would decrease the incidence of chronic lung disease and death among preterm infants undergoing mechanical ventilation for respiratory distress syndrome, *post hoc* analysis was performed to assess the influence of ventilator strategy on the incidence of chronic lung disease. The effect of iNO on the incidence of intraventricular hemorrhage was also investigated.

The authors reported a statistically significant decrease in death and chronic lung disease between the study group and the placebo group (48.6% versus 63.7%, $P = 0.03$). Schreiber and colleagues also found that the overall incidence of intraventricular hemorrhage did not differ in the groups and that the type of ventilation had no significant effect on outcome.

The authors concluded that “early treatment with iNO improved long-term pulmonary outcomes in premature infants with respiratory distress syndrome, decreasing the incidence of chronic lung disease and death”. In addition, “iNO decreased the incidence of severe intraventricular hemorrhage and periventricular leucomalacia” [9].

Although the combined endpoints were significantly different between the two groups, the incidence of death as a single primary endpoint was not statistically different between the two groups (15.5% versus 22.5%, $P = 0.18$). The baseline data also show a difference in the duration of mechanical ventilation between the study group and the placebo group (16 days versus 28.5 days) and in the incidence of early sepsis (4.8% in the iNO group versus 11.8% in the placebo group). Although these factors have be documented to influence the mortality and morbidity of acute respiratory distress syndrome [10], this degree of difference is unlikely to be responsible for the improvements noted in the iNO group.

So what does this work add to the body of knowledge about the utility of iNO and how it affects our practice with respect to management of AHRF? iNO therapy has been shown to acutely lower pulmonary artery pressures and to improve gas exchange in neonates, children and adults [11,12]. Other effects of NO on the respiratory system, such as enhanced expression of surfactant protein and diminished pulmonary inflammation, may also contribute to its beneficial effects. Cogent reasons thus exist to suggest a potential benefit of iNO in patients with AHRF.

Prior to this study, no prospective randomized trial had demonstrated any benefit in clinical outcomes such as days on the ventilator, total days either in the intensive care unit or in the hospital, or death. A meta-analysis of all randomized controlled trials on the use of iNO for the treatment of AHRF from 1966 to 2002 concluded “iNO transiently results in improved oxygenation in AHRF, with no discrepancy between small and large doses, but that it has not demonstrated a significant effect on mortality” [13].

The concern in the neonatal literature that iNO may induce intracranial bleeding in preterm infants was not supported in this study. Disturbances in platelet aggregation and prolongation of bleeding time have been demonstrated in neonates [14,15]. In the present study there was no evidence of increased intraventricular hemorrhage in the iNO group. The mechanism by which NO inhibits platelet function might be through a NO-induced increase in platelet cyclic guanosine monophosphate-dependent protein kinases [16].

The majority of patients will experience, at a minimum, short-term clinical benefit from iNO therapy, and the present study suggests that iNO may influence clinical outcomes as well. This should be a consideration in our armamentarium in the battle against AHRF. The recognition that AHRF is often the

result of multifactorial processes makes it unlikely that one treatment modality will have a major beneficial effect on mortality and morbidity.

Competing interests

RPD is a consultant for INO Therapeutics.

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