Rescue therapy with inhaled nitric oxide in critically ill patients with severe hypoxemic respiratory failure (Brief report)

[Thérapie de secours par l'inhalation d'oxyde nitrique chez de grands malades atteints d'insuffisance respiratoire hypoxémique]

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Purpose: To evaluate the efficacy of inhaled nitric oxide (iNO) on oxygenation, shunt, and pulmonary vascular resistance index (PVRI) in severely hypoxemic, ventilated patients.

Methods: In a two-period double-blind crossover design, 14 critically ill, hypoxemic, ventilated patients were randomized to receive iNO 10 ppm in 100% oxygen or no iNO in 100% oxygen for 30 min followed by a 30-min washout period and then crossed over to the other intervention. Responders to iNO then received iNO, which was increased from 5 ppm to 25 ppm in 5 ppm increments. Severity of illness scores and cardiorespiratory variables were measured.

Results: Nitric oxide decreased shunt ($P=0.002$) and PVRI ($P=0.033$) and increased oxygenation ($P=0.011$) although the latter two were not statistically significant after adjustment for multiple comparisons. Treatment by period interactions were observed.

Conclusion: Our findings suggest that iNO improves oxygenation to a clinically significant extent in critically ill patients who are severely hypoxemic.

Objectif : *Évaluer l'efficacité de l'inhalation d'oxyde nitrique (iNO) sur l'oxygénation, le shunt et l'index de résistance vasculaire pulmonaire (IRVP) chez des sujets atteints d'hypoxémie sévère et placés sous ventilation.*

Méthode : *Une étude de type croisée, à double insu et en deux temps a été réalisée auprès de 14 grands malades hypoxémiques placés sous ventilation. On les a répartis au hasard pour recevoir 10 ppm de iNO dans 100 % d'oxygène ou 100 % d'oxygène sans iNO pendant 30 min suivies d'une élimination de 30 min et de la permutation des interventions. Les sujets répondants à l'iNO ont alors reçu de l'iNO qui a été augmenté de 5 ppm à 25 ppm par paliers de 5 ppm. La sévérité de la maladie et des variables cardio-respiratoires a été mesurée.*

Résultats : *L'oxyde nitrique a réduit le shunt ($P = 0,002$) et l'IRVP ($P = 0,033$) et augmenté l'oxygénation ($P = 0,011$) bien que ces deux dernières modifications n'étaient pas statistiquement significatives à la suite d'un ajustement pour comparaisons multiples. Le traitement par période d'interactions a été étudié.*

Conclusion : *Nos résultats indiquent que l'iNO améliore l'oxygénation clinique de façon significative chez les grands malades souffrant d'hypoxémie sévère.*

INHALED nitric oxide (iNO) acutely improves oxygenation and decreases pulmonary artery pressure (PAP) in patients with severe acute respiratory distress syndrome (ARDS) but improvement in arterial oxygen tension (PaO_2) may not be beyond 24 hr[1–3] and survival in ARDS patients may be unchanged.[2–5] In this report, we present the results of a blinded study designed to assess the efficacy of iNO 10 ppm on oxygenation, shunt, and pulmonary vascular resistance in severely hypoxemic, ventilated patients and to determine the optimal dose, in terms of improvement in PaO_2, to five doses of iNO.

Methods

This study was approved by our Ethics Review Board. Eligibility criteria were age greater than 15 yr,

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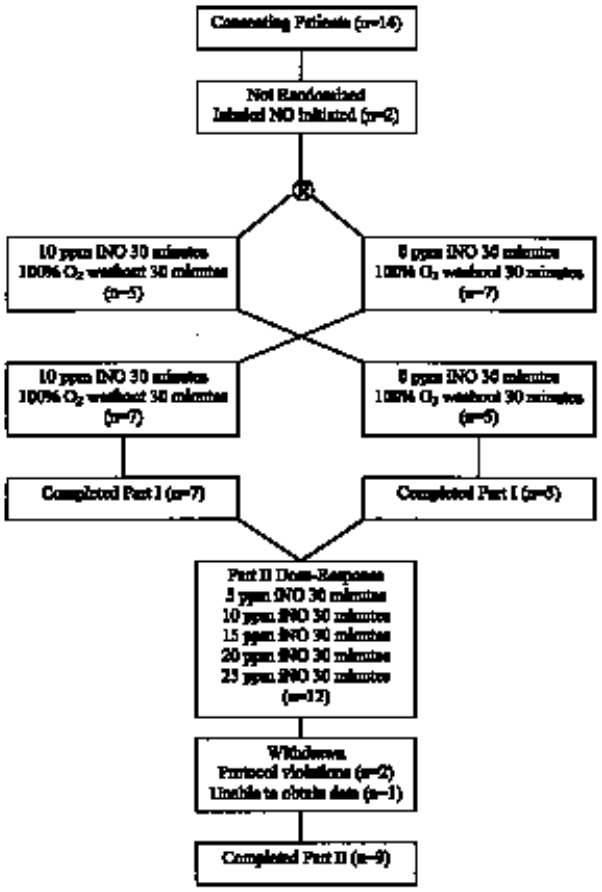

FIGURE 1 Flow diagram of the various stages of this trial. The "R" indicates randomization.

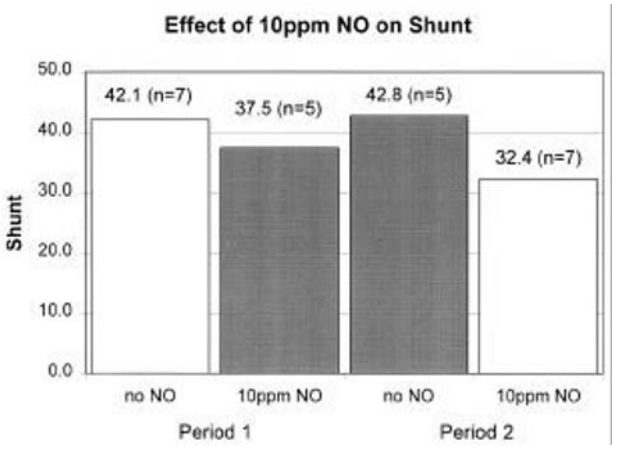

FIGURE 2 Bar graph of the effect of inhaled nitric oxide (iNO)10 ppm on cardiac shunt. The dark bars denote Group A (iNO then no iNO); the white bars denote Group B (no iNO then iNO). The mean value for each group by period and intervention is listed above the respective bar.

$PaO_2 \cdot FIO_2^{-1}$ ratio <200 despite mechanical ventilation with 100% oxygen, and a mean PAP greater than 20 mmHg. Exclusion criteria were pregnancy, sustained hemodynamic instability, moribund state, history of prior home oxygen use, liver cirrhosis, known intracardiac shunt, or an absolute contraindication to anticoagulation. Written informed consent was obtained from the next-of-kin.

All patients were ventilated with a Puritan-Bennett 7200 ventilator with NO 800 ppm in nitrogen introduced through the ventilator air intake after further blending with nitrogen or air. A Pulmonox II electrochemical monitor in the inspiratory limb continuously monitored iNO and NO_2.

The study consisted of a two-period crossover trial and a dose-finding study. All patients remained on 100% oxygen during the entire study. Aside from the respiratory therapist who applied the study intervention, patients, caregivers, and trial participants were blinded.

Using computer generated random numbers, we randomized patients to receive either iNO 10 ppm for 30 min followed by a 30-min washout period on 100% oxygen without iNO (group A) or 100% oxygen without iNO for 30 min followed by a second 30-min period on 100% oxygen (group B). Patients then crossed over to the alternate intervention for 30 min followed by a 30-min washout period on 100% oxygen. We defined a positive response as a 10 mmHg increase in PaO_2. Patients with positive responses then received iNO 5 ppm 30 min followed by 5 ppm increases after each 30-min period until a final dose of 25 ppm was attained (Figure 1).

We measured the following variables at the end of each period: PaO_2, venous oxygen tension, arterial and venous oxygen saturation, hemoglobin level, systolic, diastolic and mean arterial pressures, pulmonary artery occlusion pressure, and cardiac output. Oxygenation index ($PaO_2 \cdot FIO_2^{-1}$), cardiac shunt ($Qs \cdot Qt^{-1}$), cardiac index, PVRI, and systemic vascular resistance index (SVRI) were calculated.

For the first part of this study, the data for each group were summarized by period due to the crossover design. Treatment by period interactions (residual effects from crossover) were analyzed as described by Willan and Pater.[6,7] In the absence of period effects and treatment interactions, data from both groups were pooled by intervention (no iNO, 10

ppm iNO); two-sided paired t tests were used for comparisons. In the presence of treatment by period interactions, modified paired t tests were used for comparisons. Linear regression was used to examine for the presence or absence of a dose-response in the second part of this study. Bonferroni correction for multiple comparisons was used. A *P*-value <0.01 was considered to be significant.

Results

Fourteen ventilated patients with severe hypoxemia were enrolled in the study but two patients were started on 10 ppm iNO before randomization occurred due to the severity of their hypoxemia; they were excluded from the analysis. The Table highlights patient characteristics by group at time of randomization.

Two patients received assist-control ventilation; ten patients received pressure control inverse ratio ventilation at the time of randomization. Mean positive end-expiratory pressure was 6.9 ± 3.2 cm H_2O. Mean PVRI was 560.1 ± 178.9 dyne·sec^{-1}·cm^{-5}·m^2. Responders received iNO for four to 29 days.

Figure 2 summarizes the effect of iNO 10 ppm on $PaO_2 \cdot FIO_2^{-1}$ Treatment by period interactions were found; therefore, the data have been summarized separately for each group. All twelve randomized patients responded to iNO 10 ppm, which decreased $Qs \cdot Qt^{-1}$ (P=0.002) and PVRI (P=0.033) and increased $PaO_2 \cdot FIO_2^{-1}$ (P=0.011). No adverse hemodynamic effects were noted.

Nine of the 12 responders completed the dose-finding study. Maximal increase in PaO_2 was found at 5 ppm in five patients, 10 ppm in two patients, 15 ppm in one patient and 20 ppm in one patient.

For all patients, NO_2 levels remained below 2 ppm. Methemoglobin levels did not exceed 1.6%. No acute hemorrhage occurred during iNO administration.

Discussion

Our intention was to assess the utility of iNO in critically ill hypoxemic patients. NO was reserved for rescue therapy after other options commonly used in our practice had failed to improve oxygenation to a satisfactory level.

Because we planned to study a severely ill subset of critically ill patients and anticipated a small number of participants, we deliberately chose a two-period crossover design to permit all study participants an opportunity to receive iNO. In the absence of treatment by period interactions, the crossover trial compares interventions within each patient, minimizes between-subject variability, and results in an increased power with a reduced sample size.[6] In the presence of interactions, first period data may still be used to draw inferences. Modified paired t tests may be used to make comparisons between interventions using data from both periods.[7]

TABLE Description of patients at time of enrollment

Patient characteristic	*Group A (n=5)*	*Group B (n=7)*
Age (yr)	71.2 ± 5.2	58.7 ± 14.9
APACHE II score	29.2 ± 2.5	24.9 ± 6.5
LIS	3.10 ± 0.31	2.64 ± 0.45
$PaO_2 \cdot FIO_2^{-1}$	57.4 ± 8.4	64.4 ± 9.5
PEEP (cm H_2O)	8.5 ± 2.2	5.7 ± 3.4
PVRI (dyne·sec^{-1}·cm^{-5}·m^2)	450.6 ± 61.1	638.3 ± 197.6

APACHE=acute physiology and chronic health evaluation; LIS=lung injury score; PEEP= positive end-expiratory pressure; PVRI=pulmonary vascular resistance index. All values are expressed as means ± standard deviations.

Our patients had a mean $PaO_2 \cdot FIO_2^{-1}$ of 61.5 before study entry, with a mean APACHE II score of 26.6, making this one of the most compromised groups yet studied. Mortality was 20%, which is comparable with recent ARDS mortality data.[8] The majority (10/12, 83%) of these patients responded with a clinically significant increase in PaO_2. This increase corroborates the findings of other investigators that iNO produces an acute increase in PaO_2 in most patients with severe hypoxemic respiratory failure.[9,10] Current evidence suggests that the beneficial effects of iNO in terms of improvement in PaO_2 may last only 24 to 48 hr;[1–3] however, in some patients with borderline oxygenation, iNO may buy valuable time and may permit improvement in lung function without incurring organ damage from prolonged hypoxemia. Thus, while current data do not support the routine use of iNO, it may be useful as rescue therapy in patients who are severely hypoxemic despite aggressive ventilator strategies.

We conclude that our data demonstrate the ability of iNO to raise PaO_2 to a clinically significant extent in patients who are severely hypoxemic. Studies are still required to determine the optimum dose and method of administration.

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