REVIEW

INHALED NITRIC OXIDE IN THE MANAGEMENT OF PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN: A META-ANALYSIS

Carlos Augusto Cardim de Oliveira, Eduardo J Troster and Crésio R Pereira

RHCFAP/3017

OLIVEIRA CAC et al. - Inhaled nitric oxide in the management of persistent pulmonary hypertension of the newborn: a meta-analysis. **Rev. Hosp. Clín. Fac. Med. S. Paulo 55** (4):145-154, 2000.

Objectives: To evaluate the use of inhaled nitric oxide (NO) in the management of persistent pulmonary hypertension of the newborn. **Methods:** Computerized bibliographic search on MEDLINE, CURRENT CONTENTS and LILACS covering the period from January 1990 to March 1998; review of references of all papers found on the subject. Only randomized clinical trials evaluating nitric oxide and conventional treatment were included. **Outcomes studied:** death, requirement for extracorporeal membrane oxygenation (ECMO), systemic oxygenation, complications at the central nervous system and development of chronic pulmonary disease. The methodologic quality of the studies was evaluated by a quality score system, on a scale of 13 points. **Results:** For *infants without congenital diaphragmatic hernia*, inhaled NO did not change mortality (typical odds ratio: 1.04; 95% CI: 0.6 to 1.8); the need for ECMO was reduced (relative risk: 0.73; 95% CI: 0.60 to 0.90), and the oxygenation was improved (PaO_2 by a mean of 53.3 mm Hg; 95% CI: 44.8 to 61.4; oxygenation index by a mean of -12.2; 95% CI: -14.1 to -9.9). For infants *with congenital diaphragmatic hernia*, mortality, requirement for ECMO, and oxygenation were not changed. For all infants, central nervous system complications and incidence of chronic pulmonary disease did not change. **Conclusions:** Inhaled NO improves oxygenation and reduces requirement for ECMO only in newborns with persistent pulmonary hypertension who do not have diaphragmatic hernia. The risk of complications of the central nervous system and chronic pulmonary disease were not affected by inhaled NO.

DESCRIPTORS: **Nitric oxide. Newborn. Pulmonary hypertension. Extracorporeal membrane oxygenation (ECMO). Meta-analysis.**

At birth, a disturbance of oxygenation leads to persistence of elevated pressure of the pulmonary circulation. Some arteries do not have a complete vasodilation, and others remain closed. Gersony[1] described and named this syndrome *persistence of fetal circulation*.

Persistent pulmonary hypertension of the newborn (PPHN) is the common final pathway of pathologic conditions of circulatory and respiratory systems, including: respiratory distress syndrome, pneumonia with or without sepsis, pulmonary hypoplasia associated with congenital diaphragmatic hernia and cardiac malformations. The increased vascular tone of pulmonary circulation persists even after the precipitating insult is removed. A higher pressure of the pulmonary artery leads to right-to-left shunting at the ductus arteriosus and/or foramen ovale, resulting in hypoxemia. Pulmonary parenchymal disease intensifies the uneven ventilation-perfusion ratio, which worsens the hypoxemia, increasing vasospasm[2-11].

The true incidence of PPHN is unknown because of non-uniform diagnostic criteria and the lack of systematic population-based studies. The described ratio ranges from 1 in 500 to 1 in 1400 live births, and morbidity is expressive, including neurological deficits and chronic pulmonary disease. PPHN is one of the most serious illnesses in newborn intensive care units[3,11-14].

The conventional treatment of

From the Department of Pediatrics, Hospital das Clínicas, Faculty of Medicine, University of São Paulo.

PPHN includes: optimized ventilation with high fractions of inspired oxygen, induced respiratory and metabolic alkalosis, systemic vasodilators, hemodynamic support, correction of metabolic disorders, and the maintenance of a quiet environment[15-20].

Nitric oxide is a free amphiphilic radical that acts as an intracellular and intercellular messenger, increasing the levels of c-GMP, which reduces the intracellular concentration of calcium, inducing vasodilation[21,22].

Although the infusion of vasodilator agents has been shown to decrease pulmonary vascular resistance, its use is limited because of a concomitant decrease in systemic vascular tone, worsening the intrapulmonary shunt. The high affinity of NO to ferrous ion heme proteins results in its rapid inactivation by blood hemoglobin, giving to inhaled NO the property of selectivity to the pulmonary vascular bed[22-27].

Clinical evidence has demonstrated that inhaled NO improves oxygenation in PPHN, but until now, trials have been too small to give reliable answers. The outcomes measured are not meaningful regarding mortality or quality of life, but rather are meaningful regarding surrogate outcomes like oxygenation1[4,28].

The objective of this review was to estimate more precisely the effects of inhaled NO in the management of PPHN.

METHODS

Study Identification: All clinical trials concerning NO and PPHN published from January 1990 to March 1998 were retrieved. This pool of studies was identified by cross-referencing the following medical subject heading terms using MEDLINE, CURRENT CONTENTS and LILACS: *nitric oxide and infant; nitric oxide and newborn; nitric oxide and pulmonary hypertension; pulmonary hypertension and infant; pulmonary hypertension and newborn.* In addition, we reviewed manually the reference lists of each retrieved article obtained from the electronic databases, from other non-systematic reviews, and from congress chronicles. Only randomized clinical trials published in English, French, Spanish, and Portuguese were selected. We excluded incomplete studies and those from the same authors with the same population.

Study Population: Term (>37 weeks of gestational age), or near term (>34< 37 weeks of gestational age) newborns (< 28 days of age at the beginning of the study) with hypoxemia and diagnosis of PPHN done by echocardiography were studied. Infants with intracardiac shunting due to structural heart disease (except ductus arteriosus) were excluded.

Interventions: The treated group received administration of inhaled NO by tracheal cannula. The control group was managed with conventional treatment.

Outcomes: Death, requirement for ECMO, systemic oxygenation, disturbances of the central nervous system (hemorragic disorders and convulsions), and development of chronic pulmonary disease during hospitalization were the outcomes studied.

Assessment of methodologic quality: The quality pattern of each study was assessed according to the Heyland score system[30], with a maximum of 13 points.

Data analysis: Using the *REVIEW MANAGER* software, *version 3.1, The Cochrane Collaboration, March 1998,* data were combined to estimate, for categorical outcomes, the typical odds ratio, relative risk, relative risk reduction, absolute risk redution and number needed to treat. Outcomes were measured on a continuous scale, and typical estimates for weighted mean difference were calculated, as well as their correspondent 95% confidence intervals. The heterogeneity of treatment effects across the studies was ascertained by a chi-square analysis, using the null hypothesis that results were similar, where $p>0.05$ for the test of homogeneity is consistent with the assumption that differences in study results are due to chance. Relative risk, and not odds ratio, was calculated if the outcome rate measured was higher than 0.2.

RESULTS

Study selection: From January 1990 to March 1998, 261 publications were found that dealt with NO and PPHN. Eight randomized clinical trials fulfilled the inclusion criteria. The characteristics of these studies are described in Table 1.

The meta-analysis of results for infants without congenital diaphragmatic hernia included seven studies (548 newborns). Only two trials were selected for meta-analysis for infants with congenital diaphragmatic hernia (70 newborns).

Validity criteria and quality score of selected clinical trials are listed in Table 2.

The tests for homogeneity were non-significant, meaning homogeneous results in all analyses, except for "oxygenation index at 30 min".

PPHN without congenital diaphragmatic hernia

A) Death during hospitalization. The meta-analysis included 5 studies (513 newborns) [30,32,34,36,37]. There were 31 (11%) deaths in the NO group, and 26 (12%) in the control group. There

Table 1 - Characteristics of selected clinical trials.

Authors/year (reference)	Multicentric	Study Population	Gestational age(weeks)	Hypoxemia and Mechanical Ventilation	Co-interventions: Surfactant and/or HFOV [a]
Barefield [30]	No	17 [b]	>35	Yes	Not Accepted
Cornfield [31]	Yes	23	Mean:37,3 [c]	Yes	Not Accepted
Davidson [32]	Yes	155	>37	Yes	Not Accepted
Day [33]	No	22	-[c]	Yes	Accepted
NINOS [34]	Yes	235	>34	Yes	Accepted
NINOS [35]	Yes	53 [d]	>34	Yes	Accepted
Roberts [36]	Yes	58	>37	Yes	Accepted
Wessel [37]	Yes	49	>34	Yes	Accepted

a High frequency oscillatory ventilation
b Population studied 24, but only 17 were randomized
c Minimal gestational age not mentioned
d Study interrupted because of suggestion of worse outcome

Table 2 - Methodologic quality assessment of eight selected trials[a] .

Author/yr (reference)	Barefield 1996 [30]	Cornfield 1997 [31]	Davidson 1998 [32]	Day 1998 [33]	NINOS 1997 [34]	NINOS 1997 [35]	Roberts 1997 [36]	Wessel 1997 [37]
Randomization	2	2	2	2	2	2	2	2
Blinding	1	1	1	1	1	1	1	0
Analysis	2	2	2	2	2	2	2	2
Patient selection	1	1	1	1	1	1	1	1
Comparability of groups at baseline	1	1	1	0	1	1	1	1
Extent of follow-up	1	1	1	1	1	1	1	1
Treatment protocol	1	1	1	1	1	1	1	1
Co-interventions	1	1	1	1	1	1	1	1
Crossovers	2	1	1	2	2	1	2	2
TOTAL	12	11	11	11	12	11	12	11

[a] Score system according to Heyland[29].

was no difference in mortality between groups (odds ratio: 1.04; 95% CI: 0.59 to 1.82) (Table 3; Fig. 1).

B) Requirements for extracorporeal membrane oxygenation (ECMO). Five studies [30-32,34,36,37] were selected, including 537 newborns. Fewer patients from the NO group needed ECMO, 101/305 (33%), compared to 115/232 (50%) controls (relative risk: 0.73; 95% CI: 0.6 to 0.9) (Table 4 and Fig. 2).

C) Systemic oxygenation. This outcome was analyzed in 7 trials[30-34,36,37], but the unity of measures was not always the same. In all the studies except one [32], it was concluded that NO improved oxygenation. The meta-analysis data was consistent with the analyzed measurement. The weighted mean differences showed better results for the oxygenation index and PaO_2 for those treated with NO (Table 5; Fig. 3).

D) Disturbances of the central nervous system. Three studies [32,34,37] were selected, with 420 newborns. There was no difference between NO-treated and control groups (odds ratio: 0.83; 95% CI: 0.50 to 1.37) (Table 6; Fig. 4).

E) Development of chronic pulmonary disease during hospitalization. This meta-analysis included 2 trials[32,34] totaling 378 infants. There was no difference between groups for this outcome. Forty-six cases of chronic pulmonary disease were found, 30/217 (11%) in the NO-treated group, and 17/161 (14%) in the control group (odds ratio: 1.3; 95% CI: 0.69 to 2.46) (Table 7, Fig. 5).

PPHN with congenital diaphragmatic hernia

A) Death or ECMO requirement: These outcomes were analyzed in only one trial[35], and both were considered as a single outcome. From the 53 patients studied, 28 were in the control group and 25 were in the NO-treated group. The rate for the control group was 0.82 and for those treated with NO was 0.96 (relative risk: 1.17; 35% CI: 0.97 to 1.41) (Table 8).

B) Systemic oxygenation: Two trials [33,35] were selected, but the authors have published their data differently, so we could not assemble them in a unique meta-analysis. In one trial [35], a subgroup of 10 patients with pulmonary hypoplasia did not have an improvement of oxygenation when com-

Table 3 - Nitric oxide vs Conventional treatment: Death during hospitalization.

	Results (%)	95% Confidence interval
Control group	0.12 (12)	-
NO group	0.11 (11)	-
Relative risk	1.03	0.62 to 1.72
Odds ratio	1.04	0.59 to 1.82

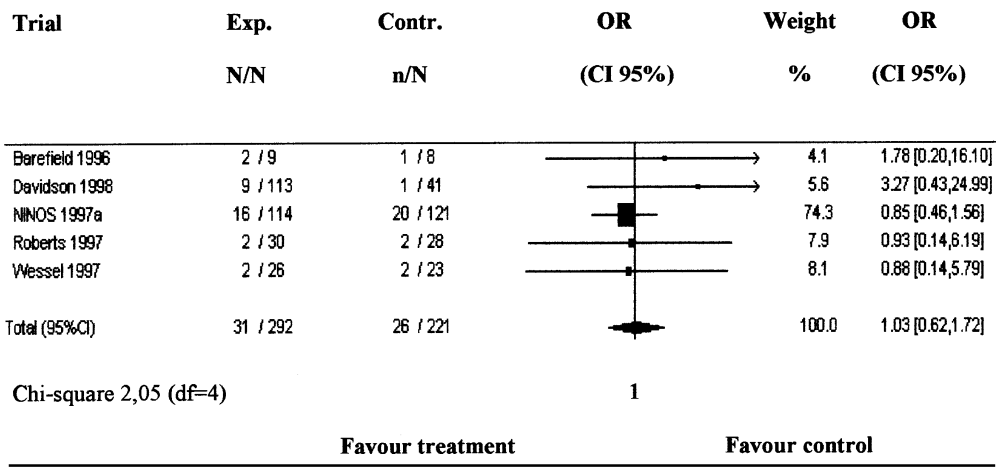

Figure 1 - Nitric oxide vs conventional treatement: death during hospitalization.

Table 4 - Nitric oxide vs Conventional treatment: Requirement for ECMO during hospitalization.

	Results (%)	95% Confidence interval
Control group	0.50 (50)	-
NO group	0.33 (33)	-
Relative risk	0.73	0.60 to 0.90 *
Absolute risk reduction	0.13 (13)	0.05 to 0.21
Relative risk reduction	0.26 (26)	0.10 to 0.40
Number needed to treat	8	4.74 to 22.22

* $P < 0.05$

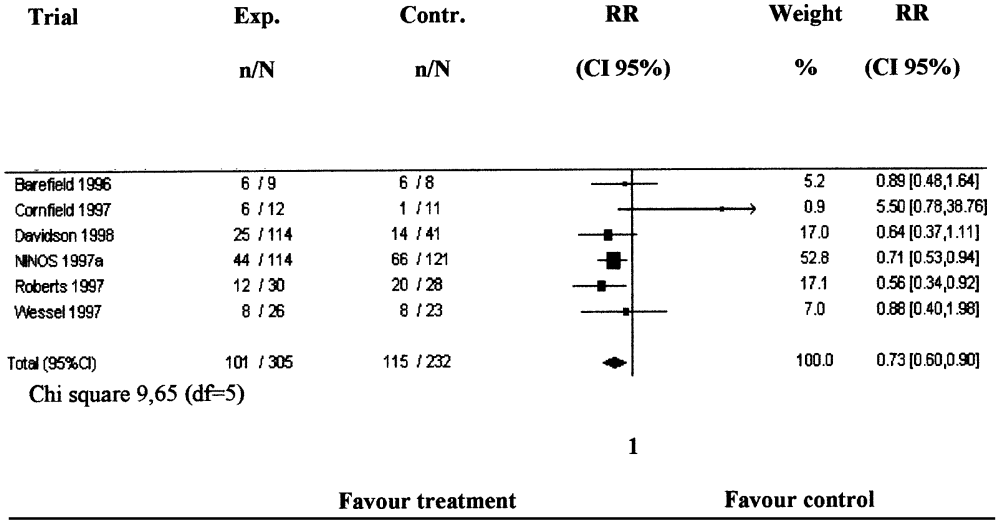

Figure 2 - Nitric oxide vs conventional treatement: requirement for ECMO during hospitalization.

Table 5 - Measurements of systemic oxygenation of the seven selected studies.

	Study Population	Results (95% confidence interval)
PaO_2 (torr) at 30 and 60 min	Control group: 53 NO group: 57	WMD [b]: 53.18 (44.8 a 61.4)
OI [c] at 30 and 60 min	Control: 94 NO group: 171	WMD: -12.17 (-14.4 a –9.9)
Number of improved cases at 30 and 60 min	Control group: 28 NO group: 30	RR [d]: 7.47 (1.9 a 29.6) OR [e]: 8.34 (2.8 a 25.1) ARR [f]: -0.46 (-0.6 a –0.2) RRR [g]: -6.47 (-28.6 a –0.9) NNT [h]: -2.16 (-3.8 a –1.5)
PaO_2 variation at 30 and 60min	Control group: 121 NO group: 114	WMD: 48.50 (30.3 a 66.6)
OI [c] variation at 30 and 60 min	Control group: 121 NO group: 114	WMD: -14.90 (-20.3 a –9.5)
OI [c] reduction after end of treatment	Control group: 13 NO group: 13	WMD: -9.50 (-11.51 a –7.49)

a) Partial pressure of arterial oxygen; **b)** weighted mean difference; **c)** oxygenation index; **d)** relative risk; **e)** odds ratio; **f)** absolute risk reduction; **g)** relative risk reduction; **h)** number needed to treat.

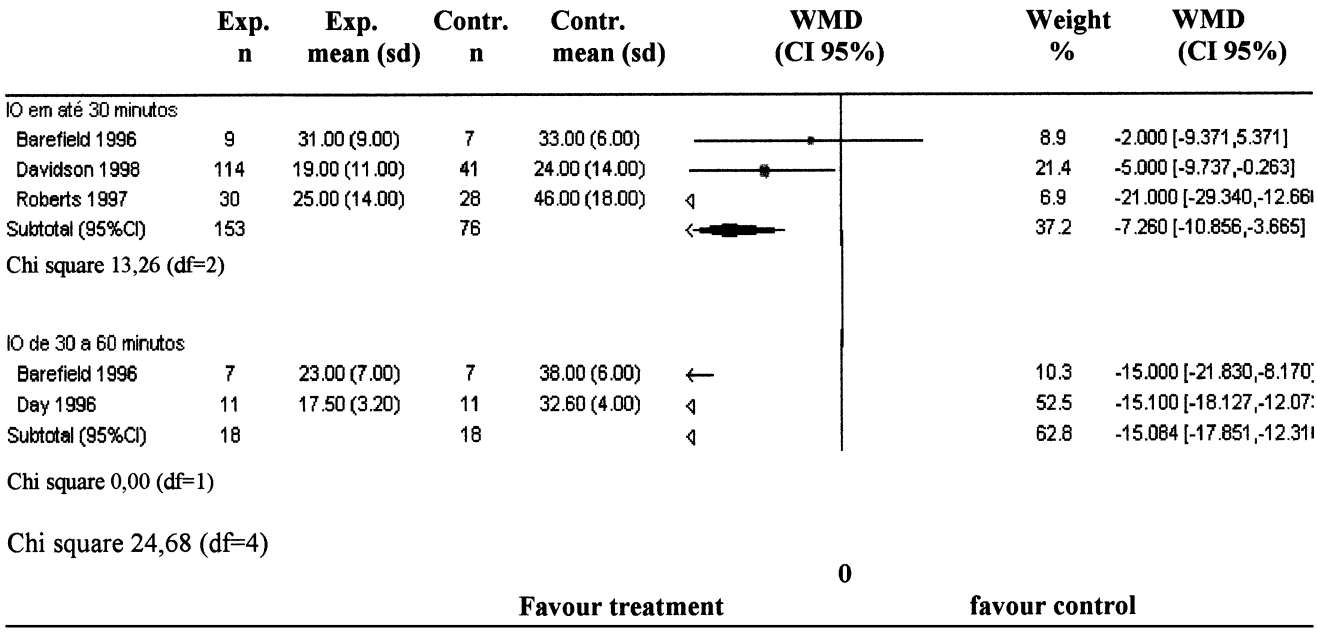

Figure 3 - Nitric oxide vs conventional treatement: systemic oxygenation.

pared with the control group; but considering only the NO-treated group, the measurements were better after treatment in comparison with the baseline (PaO_2: 29 ±± 3 mm Hg vs 45 ±± 10 mm Hg; P<0.05). In the larger trial[37], the authors did not find an improvement for this outcome (Table 9).

C) Disturbances of the central nervous system: The only study found[37] showed no difference between the groups: 4/28 (14%) events in control group and 4/25 (16%) in NO-treated group (odds ratio: 1.14; 95% CI: 0.26 to 5.07)

D) Development of chronic pulmonary disease: The same trial[37] was again the only one to study this end-

Table 6 - Nitric oxide and Conventional treatment: disturbances of the central nervous system.

	Results (%)	95% Confidence interval
Control group	0.20 (20)	-
NO group	0.19 (19)	-
Odds ratio	0.83	0.50 to 1.37

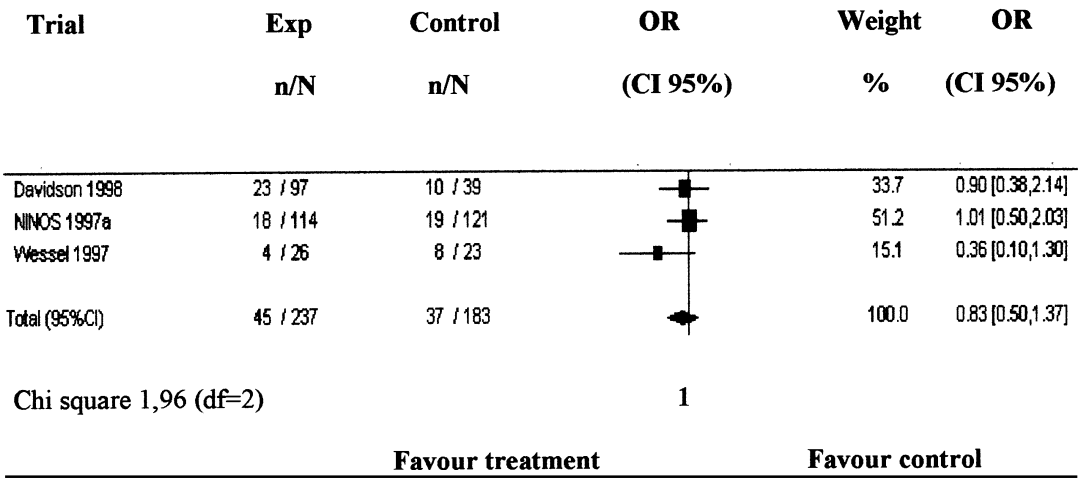

Figure 4 - Nitric oxide vs conventional treatement: disturbances of the central nervous system.

Table 7 - Nitric oxide vs Conventional treatment: Development of chronic pulmonary disease during hospitalization.

	Results (%)	95% Confidence interval
Control group	0.11 (11)	-
NO group	0.14 (14)	-
Relative risk	1.26	0.72 to 2.24
Odds ratio	1.30	0.69 to 2.46
Absolute risk reduction	0.02 (2)	-0.97 to 0.04
Relative risk reduction	0.27 (27)	-1.24 to 0.28
Number needed to treat	Not significant	-

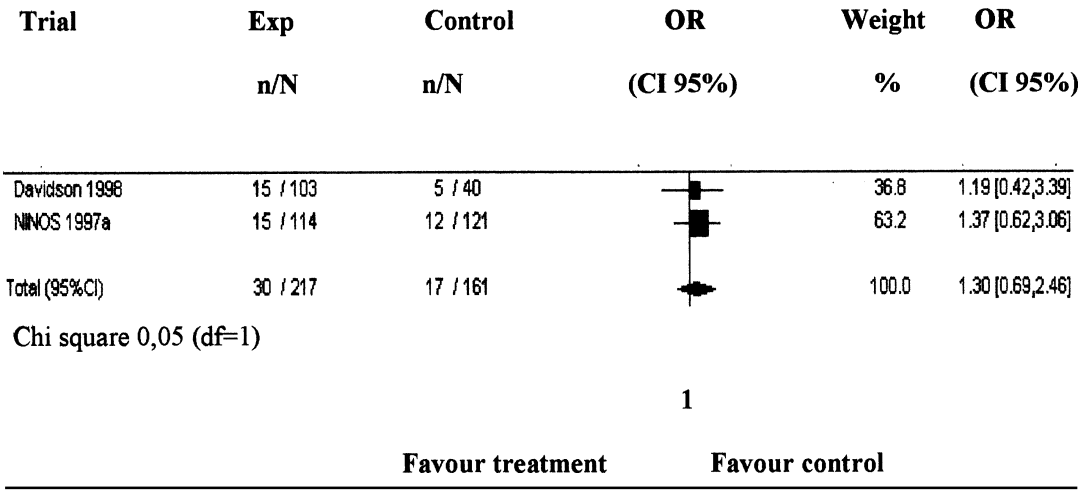

Figure 5 - Nitric oxide vs conventional treatement: development of chronic pulmonary disease during hospitalization.

Table 8 - PPHN with congenital diaphragmatic hernia: Death or ECMO requirement.

	Results (%)	95% Confidence interval
Control group	0.82 (82)	-
NO group	0.96 (96)	-
Relative risk	1.17	0.97 to 1.41
Absolute risk reduction	0.14 (14)	-0.02 to 0.30
Relative risk reduction	0.17 (17)	0.03 to 0.41
Number needed to treat	7.19	3.33 to 43.48

Table 9 - PPHN with congenital diaphragmatic hernia: Systemic oxygenation.

	Increase in PaO_2 torr	Decrease in oxygen index
NO group[a]	7.80 (± 19.80)	-2.70 (± 23.40)
Control group[a]	1.10 (± 7.60)	4.00 (± 14.80)
P value	0.22	0.27
WMD [b] (95% confidence interval)	6.70 (-1.55 to 14.95)	-6.70 (-17.38 to 3.98)

[a] Media (±standard deviation)
[b] Weighed mean difference

point, and no benefit was demonstrated with inhaled NO (relative risk: 0.62; 95% CI: 0.24 to 1.61).

DISCUSSION

Infants without congenital diaphragmatic hernia

For the majority of intensive care unit trials, mortality is the most meaningful outcome because it is easily measured and clinically important[38].

The results of this meta-analysis, involving 531 patients without diaphragmatic hernia, may appear to exclude any possible benefit from inhaled NO in reducing the mortality of infants with persistent pulmonary hypertension.

However the lower bound of the 95% confidence interval—the one which suggests the largest benefit from treatment—was 0.59, showing that clinically important benefits fall within the confidence interval, so the trial cannot definitely rule out the possibility that the treatment is beneficial for this outcome. Furthermore, although a population of 531 patients may seem expressive, the power of this meta-analysis would be nearest 30% (Type II error: 0.7) if the expected reduction in death rate with the use of NO was 30%. This means that there would be a 70% chance that we wrongly accepted the null hypothesis and that we could not have detected the effect of inhaled NO on mortality, even if it may exist. The power would be greater if the baseline mortality was higher or if the sample was larger.

Therefore, it would be premature to definitely rule out inhaled NO from the management resources for PPHN because we have not found a reduction in mortality. In doing so, we might be giving up a "gray zone" intervention with great potential benefits[38,39].

Mechanisms for suboptimal inhaled NO responses are: unsuspected structural heart disease; left ventricular dysfunction, decreased lung volume in association with pulmonary parenchymal disease, pulmonary edema, low concentrations of NO for the severity of the disease, paradoxical response to NO, worsening of the ventilation/perfusion ratio, cytotoxicity of NO and its metabolites, structural abnormalities of the pulmonary vascular tree, undiagnosed alveolar capillary dysplasia or pulmonary hypoplasia, non-optimized hemodynamic and ventilatory support, and undetected biochemical abnormalities[23,31,32,36,37,40,42,43].

If we estimate mortality in the control group as 12%, this means that 88% of the infants would survive. Therefore direct measures of quality of life have also clinically meaningful outcomes. In the same way, a lower requirement for invasive, potentially harmful, and expensive therapeutic procedures such as ECMO is also beneficial[44;45].

Systemic arterial oxygenation improved with NO treatment. Although physiologically relevant, to be considered a valid outcome, this response should correlate to a true clinical outcome and fully capture the treatment effect.

The pathophysiologic mechanisms of PPHN associated with CDH and the pharmacological actions of inhaled NO help to explain the reasons for the poor responses of these infants. In some patients, there was temporary improvement of systemic oxygenation, but even this positive result was not significant.

Implications for Clinical Practice

Inhaled NO appears to improve the outcome in hypoxemic-term and near-term infants with PPHN. We do not consider it as the "magic bullet", but rather as a part of a strategy addressing the complex cardiopulmonary interactions that characterize this syndrome. One of the possible co-interventions is a rescue treatment with high frequency ventilation and/or exogenous surfactant, allowing the NO to contact most pulmonary areas, improving the ventilation/perfusion rate. Adjunctive therapy of hemodynamic support is also useful in the maintenance of systemic arterial pressure, an essential condition to change the right to left intracardiac shunting. Patients selected

for inhaled NO treatment cannot have high degrees of structural pulmonary abnormalities (hypoplasia or alveolar capillary dysplasia) that could prevent the action of the gas. An adequate concentration of inhaled NO (probably between 5 and 20 ppm) must be used to achieve the best response in each clinical situation and to prevent the cytotoxic effects. The treatment must be initiated before structural pulmonary changes have developed[40-43].

More clinical trials considering the above mentioned considerations must be performed.

With concentrations from 5 to 20 ppm, the potential toxic effects including methemoglobinemia and lung injury caused by NO_2 , peroxynitrite, and hydroxyl radical formation are minimal. Inhalation therapy with NO is less costly than ECMO; the cost for treating 3 patients with ECMO is equivalent to the costs of the system to deliver NO to several more patients.

In congenital diaphragmatic hernia, NO remains an unproved treatment. For these infants, when ECMO criteria are fulfilled, time must not be wasted with therapeutic treatments with NO that could postpone ECMO. Inhaled NO may be effective in neonates with hypoplastic lungs who need to be transported to an ECMO center. Some infants seem to have a better response when NO was used after a period with ECMO or in cases that developed postoperative pulmonary hypertension[44,45].

CONCLUSIONS

In the management of persistent pulmonary hypotension (PPHN) of term and near-term newborns without congenital diaphragmatic hernia (CDH) or pulmonary hypoplasia, inhaled nitric oxide (NO) reduces requirements for extracorporeal membrane oxygenation (ECMO) and improves systemic oxygenation, but does not change mortality.

For infants with CDH or pulmonary hypoplasia, there were no differences between NO-treated and untreated groups in mortality, need for ECMO, or oxygenation.

The incidence of disturbances of the central nervous system (convulsions or hemorrhagic disorders) and development of chronic pulmonary disease during hospitalization were the same for the NO-treated group and the control group, regardless of whether the PPHN was or was not associated with CDH or pulmonary hypoplasia.

RESUMO

RHCFAP/3017

OLIVEIRA CAC e col. - Avaliação do uso do óxido nítrico no tratamento da hipertensão pulmonar persistente do recém-nascido: uma metanálise. **Rev. Hosp. Clín. Fac. Med. S. Paulo 55** (4):145-154, 2000.

Objetivos: Avaliar o papel do óxido nítrico inalatório no tratamento da hipertensão pulmonar persistente do recém-nascido. **Material e método:** Busca bibliográfica informatizada para janeiro de 1990 a março de 1998 (MEDLINE, CURRENT CONTENTS e LILACS) complementada manualmente. Apenas ensaios clínicos controlados e randomizados foram selecionados. **Intervenção:** tratamento com óxido nítrico inalatório comparado com tratamento convencional. **Desfechos:** morte, necessidade de ECMO, oxigenação sistêmica, complicações em sistema nervoso central e doença pulmonar crônica. Qualidade metodológica: critério de escores, sendo treze a pontuação máxima. **Resultados:** Nos não portadores de hérnia diafragmática o óxido nítrico inalatório não reduziu a mortalidade, OR: 1,04 (IC 95%: 0,59 a 1,82), mas diminuiu a necessidade de indicação de ECMO, RR: 0,73 (IC 95%: 0,6 a 0,9) e melhorou a oxigenação sistêmica, diferença média ponderada (DMP) para PaO2 em 30 e 60min: 53,18 (IC 95%: 44,8 a 61,4) e DMP para IO em 30 e 60min: -12,17 (IC 95%: -14,4 a -9,9). Nos portadores de hérnia diafragmática, não houve melhora da oxigenação arterial, nem redução da mortalidade ou da necessidade de ECMO, RR: 1,17 (IC 95%: 0,97 a 1,41). A incidência de complicações neurológicas e de doença pulmonar foram semelhantes para os dois grupos.

DESCRITORES: **Oxido nítrico. Recém nascido. Hipertensão pulmonar. ECMO. Metanálise.**

REFERENCES

1. GERSONY WM, MORISHIMA HO, DANIEL SS et al. - The hemodynamic effects of intrauterine hypoxia: an experimental model in newborn lambs. **J Pediatr** 1976; **89**: 631-5.

2. ABMAN SH & KINSELLA JP - Inhaled nitric oxide therapy of pulmonary hypertension and respiratory failure in premature and term neonates. **Adv Pharmacol** 1995; **34**:457-75.

3. WALSH-SUKYS MC - Persistent pulmonary hypertension of the newborn. The black box revisited. **Clin Perinatol** 1993; **20**:127-43.

4. CORNFIELD D - Effects of birth-related stimuli on L-arginine-dependent pulmonary vasodilatation in ovine fetus. **Am J Physiol** 1992; **262**:1474-81.

5. FURCHGOTT RF - Introduction to EDRF research. **J Cardiovasc Pharmacol** 1993; **22**:supl.7, p.s1-2.

6. HAMMERMAN C LASS N & STRATES E - Prostanoids in persistent pulmonary hypertension. **J Pediatr** 1987;**39**:470-2.

7. KINSELLA JP & ABMAN SH - Recent developments in the pathophysiology and treatment of persistent pulmonary hypertension of the newborn. **J Pediatr** 1995; **126**:853–64.

8. ROBERTS JD & SHAUL PW - Inhaled nitric oxide for treatment of pulmonary artery hypertension in the newborn and infant. **Crit Care Med** 1993; **21** suppl: s374.

9. RUSS DR. & WALKER RB - Role of nitric oxide in vasopressinergic pulmonary vasodilatation. **Am J Physiol** 1992; **262**:743-7.

10. SOIFER SJ - Pulmonary hypertension: physiologic or pathologic disease? **Crit Care Med** 1993; **21**(suppl):s370-4.

11. SPITZER AR, DAVIS J, CLARCKE WT - Pulmonary hypertension and persistent fetal circulation in the newborn. **Clin Perinatol** 1988; **15**:389-413.

12. BALLARD RA & LEONARD CH - Developmental follow-up of infants with persistent pulmonary hypertension of the newborn. **Clin Perinatol** 1984; **11**:737-44.

13. DAVIDSON D - Inhaled nitric oxide for neonatal pulmonary hypertension. **Am Rev Respir Dis** 1993; **147**:1078-9.

14. DAVIDSON D - Inhaled nitric oxide trials: “Vive la différence”. **Pediatrics** 1996; **97**: 4389.

15. GEGGEL RL & REID LM - The structural basis of PPHN. **Clin Perinatol** 1984; 11:525-49.

16. FERRARA B, JOHNSON DE, CHANG P-N et al. - Efficacy and neurologic outcome of profound hypocapneic alkalosis for treatment of persistent pulmonary hypertension**. J Pediatr** 1984; **105:**457-61.

17. HAMMERMAN C, YOUSEFZADEH D, CHOI J-H et al. - Persistent pulmonary hypertension of the newborn: managing the unmanageable. **Clin Perinatol** 1989;**16**:137-56.

18. MILNER DA - Nitric oxide. **Eur J Pediatr** 1994**; 153**:7-11.

19. FURCHGOTT RF & ZAWADZKI JV - The obligatory role of endothelial cells in the relaxation of arterial muscle by acetylcholine. **Nature** 1980; **288**:376-6.

20. DUSTING GJ, READ MA & STEWART AG - Endothelium-derived relaxing factor released from cultured cells: differentiation from nitric oxide. **Clin Exp Pharmacol Physiol** 1988; **15**:83-91.

21. KIECHLE FL & MALINSKI T - Nitric oxide. Biochemistry, pathophysiology, and detection. **Am J Clin Pathol** 1993; **100**: 567-75.

22. MONCADA S - The firs Robert Furchgott lecture: from endothelium-dependent relaxation to the L-arginine: NO pathway. **Blood Vessels** 1990**; 27**:208-17.

23. CORNFIELD D & ABMAN HS - Inhalation nitric oxide in pulmonary parenchymal and vascular disease. **J Lab Clin Med** 1996;**127**:530-9.

24. PEPKE-ZABA J, HIGENBOTTAM TW, DINH-XUAN AT et al. - Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension. **Lancet** 1991;**338**:1173-4.

25. FROSTELL CG, FRATACCI M-D, WAIN JC et al. - Inhaled nitric oxide: a selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction (published erratum appears in circulation). **Circulation** 1991; **83**:2038–47.

26. KINSELLA JP, TOWES WH, HENRY D et al. - Selective and sustained pulmonary vasodilation with inhalational nitric oxide therapy in a child with idiopathic pulmonary hypertension. **J Pediatr** 1993; 122: 803-6.

27. KINSELLA PJ, NEISH SR, DUNBAR D et al. - Clinical responses to prolonged treatment of persistent pulmonary hypertension of the newborn with low doses of inhaled nitric oxide. **J Pediatr** 1993; **123**:103-8.

28. ABMAN SH & KINSELLA JP - Inhaled nitric oxide for persistent pulmonary hypertension of the newborn: the physiology matters. **J Pediatr** 1995;**11**: 53–5.

29. HEYLAND DK, COOK DJ, BMATH DK et al. - Maximizing oxygen in critical ill patients: a methodological appraisal of evidence. **Crit Care Med** 1996; **24**:*517*-24.

30. BAREFIELD SE, KARLE VA, PHILIPS JB et al. - Inhaled nitric oxide in term infants with hypoxemic respiratory failure. **J Pediatr** 1996; **129**:279-86.

31. CORNFIELD ND, GUIANG S, DE REGNIER et al. - Randomized controlled trial of low dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. **Pediatr Res** 1997; **41**:144A.

32. DAVIDSON D, BAREFIELD ES, KATTWINKEL J et al. - Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the term newborn: a randomized, double-masked, placebo-controlled, dose-response, multicenter study. **Pediatrics** 1998; **101**:325-34.

33. DAY RW, LYNCH JM, WHITE KS et al. - Acute response to inhaled nitric oxide in newborns with respiratory failure and pulmonary hypertension. **Pediatrics** 1996; **98**:698-705.

34. THE Neonatal Inhaled Nitric Oxide Study Group - Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. **N Engl J Med** 1997;**336**:597-604.

35. THE NEONATAL INHALED NITRIC OXIDE STUDY GROUP - Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. **Pediatrics** 1997; **99**:.838-45.

36. ROBERTS JD, FINEMAN JR, MORIN FC et al. - Inhaled Nitric Oxide Study Group. Inhaled nitric oxide avaliação do uso do óxido nítrico no tratamento da hipertensão pulmonar persistente do recém-nascido: uma metanáliseand persistent pulmonary hypertension of the newborn**. N Engl J Med** 1997;**336**:605-10.

37. WESSEL LD, ADATIA I, VAN MARTER LJ et al. - Improved oxygenation in a randomized trial Of Inhaled nitric oxide for persistent pulmonary hypertension of the newborn. **Pediatrics** 1997;**100**:1-14.

38. DOIG G - Interpreting and using clinical trials. **Crit Care Clin** 1998;**14**:513-24.

39. CASSIERE HA, GROTH M & NIEDERMAN MS - Evidence-based medicine: the Wolf in sheep's clothing. **Yr Bk Intens Care Emerg Med** 1997; 744-9.

40. SHAH NS, NAKAYAMA DK & JACOB TD - Efficacy of inhaled nitric oxide in oleic acid-induced acute lung injury. **Crit Care Med** 1997;**25**(1):153-8.

41. KINSELLA JP & ABMAN SH - Controversies in the use of inhaled nitric oxide therapy in The newborn. **Clin Perinatol** 1998;**25**:203-17.

42. STEINHORN RH, COX PN, FINEMAN JR et al. - Inhaled nitric oxide Enhances oxygenation but not survival in infants with alveolar capillary dysplasia. **J Pediatr** 1997;**130**:417-22.

43. TURBOW R, YANG L, SILLS J et al. - Variable oxygenation response to inhaled nitric oxide in severe persistent pulmonary hypertension of the newborn. **Acta Paediatr** 1995;**84**:1305-8.

44. KANTO WP - A decade of experience with neonatal extracorporeal membrane oxygenation. **J Pediatr** 1994;**124**:335-47.

45. SMITH J & KIRSTEN GF - Persistent pulmonary hypertension of the neonate in a developing country – does extracorporeal membrane oxygenation have a role to play. **S Afr Med J** 1993; **83**:742–5.

Received for publication on the 03/07/00

NEWS

31º CONGRESSO BRASILEIRO DE PEDIATRIA

07 to 13/10/00
Centro de Convenções de Fortaleza-CE
Tel: (85) 2615849
E-mail: socep@roadnet.com.br

6º CONGRESSO PAULISTA DE OBSTETRÍCIA E GINECOLOGIA DA SOGESP

11 to 14/11/00
Centro Têxtil de São Paulo-SP
Phone: (11) 8847654

XIII CONGRESSO MUNDIAL DE PSIQUIATRIA DINÂMICA II PRÊMIO GÜNTER AMMON

13 to 17/03/01
Berlin – Germany
Tel: 0049/89/6427230
Fax: 0049/89/64272395

32nd ANNUAL MEDICAL-SCIENTIFIC CONFERENCE AMERICAN SOCIETY OF ADDICTION MEDICINE (ASAM)

19 to 22/04/01
Los Angeles, CA
Web site: www.asam.org