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ARTICLE

Early use of combined exogenous surfactant and inhaled nitric oxide reduces treatment failure in persistent pulmonary hypertension of the newborn: a randomized controlled trial

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Abstract

Objective To evaluate whether combined surfactant with inhaled nitric oxide (iNO) use will prevent newborns with hypoxemic respiratory failure (HRF) from developing an Oxygenation Index (OI) > 40.

Methods 100 term newborns with acute HRF (OI ≥ 20) were randomized to: Surfactant+iNO: received iNO plus up to two doses of surfactant or iNO-Controls: received iNO+placebo. Main outcome was the development of severe HRF (OI > 40) despite iNO use.

Results Baseline mean ± SD OI was 37.4 ± 14 for the Surfactant+iNO group and 38.2 ± 16 for the controls. Infants receiving surfactant+iNO improved their oxygenation faster, resulting in lower OI at 24 h: 12.9 ± 9 vs 18.7 ± 11 of controls, $p < 0.05$; and a lower proportion developing OI > 40: 24%(12/50) vs 50%(25/50) of controls, $p < 0.02$. Fewer infants receiving surfactant+iNO presented the combined outcome of death or ECMO: 16%(8/50) compared to 36%(18/50) of controls, $p < 0.05$.

Conclusions Early use of combined surfactant+iNO improves oxygenation preventing the progression to severe HRF. This may reduce mortality and ECMO need.

Introduction

Hypoxemic respiratory failure (HRF) and/or persistent pulmonary hypertension (PPHN) significantly contribute to morbidity and mortality in the newborn period [1–4]. Several randomized controlled trials (RCT) have demonstrated that inhaled nitric oxide (iNO) improves oxygenation and decreases the need for ECMO or death in term newborns with HRF [5–7]. However, the response to iNO can be inconsistent with only 50–60% of infants showing improvements in their oxygen levels. This may be due to the presence of severe lung disease with decreased lung recruitment, and/or severe lung and vascular injury [8, 9].

There is evidence of surfactant deficiency in several lung diseases that leads to HRF in the term newborn [9–11]. In two RCT high doses of exogenous surfactant therapy improved oxygenation and decreased ECMO use in newborns with HRF [12, 13]. However, there was no impact in mortality nor other outcomes, and some adverse events have been associated with surfactant administration in these critically ill patients [13]. To date, we are not aware that the use of surfactant has been tested in conjunction with iNO in a large RCT. There is some physiological basis for using this combination: exogenous surfactant would enhance iNO distribution to the pulmonary circulation by improving alveolar recruitment. In a RCT of early iNO use in HRF, the overall use of surfactant was nearly 70%, this fact may have contributed to the low incidence of ECMO and death observed in this trial [14]. In the same way, we also observed a lower incidence of severe HRF in a group of

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infants with early iNO use in which 65% had received surfactant previously [15].

We hypothesize that early and combined use of exogenous surfactant and iNO in the treatment of newborns with moderate to severe respiratory failure [Oxygenation Index (OI) ≥ 20] and pulmonary hypertension will improve oxygenation and prevent them from developing severe HRF (OI > 40), despite iNO use.

Design & methods

This was a prospective, randomized, double-blind, placebo-controlled, multicenter trial, comparing the early addition of up to two doses of exogenous surfactant versus placebo to iNO treatment in newborns with HRF. The study was performed in five NICUs in Chile, between March 2009 and April 2014 and was approved by the Ethics Committee of each of the five hospitals. Written informed consent was required from the parents before entry.

Study population

Term and near-term newborns (≥35 weeks' gestation) with birthweights >2000 g and less than 72 h after birth were eligible. We included infants requiring mechanical ventilation with HRF reaching an OI ≥ 20 and echocardiographic signs of pulmonary hypertension (a tricuspid insufficiency jet with an estimated pulmonary artery pressure ≥2/3 of systemic blood pressure and/or evidence of right-to-left shunting through foramen ovale or ductus arteriosus). Oxygenation Index calculation was based on two consecutive measurements of post ductal arterial blood gases. Infants were not enrolled if they had life-threatening congenital malformations, congenital heart disease, diaphragmatic hernia, and other forms of lung hypoplasia. Patients in critical condition (severe acidosis with pH < 7.0), recent surfactant use (<4 h), and lack of parental consent were excluded from the study.

Protocol

Infants were randomized to two study groups:

(1) Surfactant+iNO group: received up to 2 doses of 100 mg/kg of poractant alfa (Curosurf®; Chiesi Farmaceutici, Italy) along with the initiation of 20 parts per million (ppm) of iNO (iNOmax®; Ikaria, NJ).
(2) Control-iNO group: which received up to 2 doses of placebo (air) and was started on iNO at 20 ppm.

Infants were randomized using sequentially sealed opaque envelopes from a computer-generated randomization list. This allocation sequence was generated centrally by an independent statistician, and sealed envelopes were sent to each center.

Surfactant and placebo administration

Blinded and slow intra-tracheal instillation of Curosurf® 100 mg/kg birthweight (1.25 ml/kg) or equivalent sham air through a side-port of the endotracheal tube. A second dose was given between 6 and 12 h after the first dose if the patient persisted with an OI > 20. This procedure was done by an unblinded nurse not involved in patient care and was given behind a screen.

Inhaled NO was given from a sealed tank (INOmax®) and administered using the INOvent® device [Ikaria, NJ (currently Mallinckrodt, NJ)]. iNO was started at 20 ppm in both groups and ventilator variables were not changed during the first 30 min unless acute deterioration occurred. This initial dose was kept constant for 4 h; after that, attempts were done to perform a stepwise reduction by 5 ppm every 2–4 h until 5 ppm dose was reached. Once stabilized, the dose was kept for at least 24 h. Attempts were then made to discontinue iNO if the patient stayed 24 h stable with a dose of ≤5 ppm and with an OI < 10.

Patient monitoring and follow-up

An indwelling arterial line was kept monitoring systemic blood pressure and to draw serial blood gases at baseline, 2, 6, 12, and 24 h and at least every 12 h while the patient was receiving iNO. Patients were kept on conventional mechanical ventilation, which settings were adjusted to keep PaO_2 between 60 and 100 and $PaCO_2$ between 40 and 60 mmHg. Inotropic drugs were given to keep systemic arterial blood pressures ≥45 mmHg. Sodium bicarbonate was given if necessary, to keep an arterial pH > 7.25. Sedation was used in all infants, initially with fentanyl or morphine infusion. Paralysis was not used routinely but was used in some infants with difficult ventilation. Infants who persisted with an OI > 30 despite iNO were treated with high-frequency oscillatory ventilation (HFOV) plus iNO using the Sensormedics® Ventilator.

The primary outcome measure was considered as the proportion of infants developing *treatment failure*, defined as presenting an OI > 40 despite iNO use within 48 h. Patients in both groups who reached an OI > 40 during study treatment could be treated with a rescue dose of open-label surfactant according to the treating neonatologist criteria. Infants who persisted with an OI > 40 despite iNO and HFOV were considered for ECMO in absence of a major intracranial hemorrhage or an uncontrollable bleeding. ECMO was performed in one of the centers (Hospital Universidad Católica) and when indicated, patients were attempted to be transferred to that center.

Other measures of treatment efficacy were considered: ECMO rate; mortality during hospital stay and the combined adverse outcome death or need for ECMO. Days of oxygen therapy and mechanical ventilation during the hospital stay were also registered. In terms of safety variables, tolerance to surfactant administration was observed closely, based on the incidence of any of the following events: episodes of oxygen desaturation (drop in O_2 saturation to <80% for more than 1 min); bradycardia episodes <100 beats/min; and the need for increasing FiO_2 and/or ventilator requirements by >10% of pretreatment values. The incidence of other complications related to surfactant administration as the presence of air-leaks and/or pulmonary hemorrhage within the 48 h of study treatment was also recorded.

Data collection

All these variables along with the clinical data of patients including pregnancy history and delivery, birthweight, and the presence of other complications of the neonatal period were registered onto standardized forms.

Statistical analysis

Sample size was estimated based on iNO RCT [5–7] and data previously published by our centers [15, 16]. Assuming that 50% of control group patients could develop an OI ≥ 40, we determined that ~50 patients per arm were needed to detect a reduction in treatment failure to 25% in the Surfactant+iNO group, achieving a statistical power of 80% and an alpha error of 0.05.

Clinical and demographic characteristics were compared using the Student's *t* test and ANOVA for continuous variables. Categorical variables were compared using chi-squared test and if the expected number of observations was less than five, Fisher's exact test was used. A p value ≤ 0.05 was considered significant.

For safety reasons an interim analysis by an independent team was assessed when half of the needed sample size was recruited. This was used to determine the possible early termination because of safety: if the rate of adverse events or complications increased; or early efficacy if the primary endpoint was better in 1 of the 2 groups at a more stringent level of significance. A recommendation to continue study enrollment was made at that time.

Results

During the study period, 142 eligible ventilated newborns with HRF were screened for enrollment. Of them, 41 were excluded due to: lack of parental consent ($n = 20$); severe instability ($n = 12$); surfactant administration within the period of exclusion ($n = 4$) and 5 for other reasons. Therefore 101 patients were randomized, however, 1 was excluded post-randomization, due to congenital heart disease. Then, 100 infants were analyzed (Fig. 1), their mean ± SD birthweight was 3478 ± 545 g, and gestational age 39 ± 1.6 weeks. Infants were enrolled at 26.3 ± 17.1 h after birth. As shown in Table 1, demographic and clinical characteristics, including diagnoses and severity of respiratory diseases were similar between both groups at randomization. Baseline median OI (range) was 35 (20–67) for the Surfactant+iNO group and 36 (20–77) for the controls.

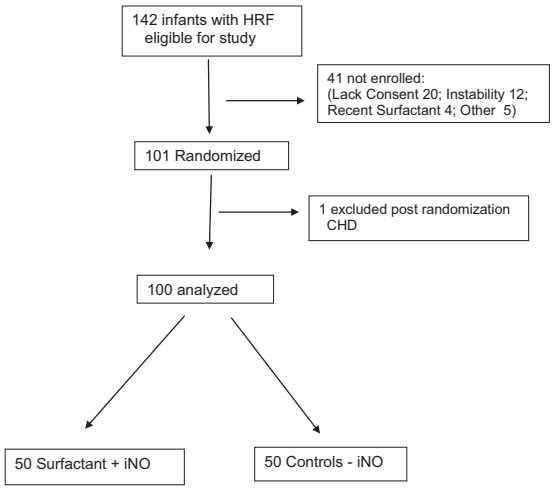

Fig. 1 Consort diagram of eligible study infants. Flow of participants in the study, from screening to group allocation.

Table 1 Patient characteristics.

	Controls-iNO ($n = 50$)	Surfactant + iNO ($n = 50$)	p value
Gestational age (mean ± SD weeks)	38.8 ± 2.3	39.1 ± 1.5	NS
Birth weight (mean ± SD grams)	3486 ± 622	3424 ± 463	NS
Male gender, *n* (%)	26 (52%)	28 (56%)	NS
5 min Apgar score, median (range)	8 (0–10)	8 (4–10)	NS
Outborn, *n* (%)	37 (74%)	36 (72%)	NS
Oxygenation Index (mean ± SD OI)	38.2 ± 16.0	37.4 ± 13.8	NS
Age at enrollment (mean ± SD h)	25.3 ± 16.3	27.1 ± 17.8	NS
Primary diagnosis	*n* (%)	*n* (%)	
Meconium aspiration	29 (58)	24 (48)	NS
Pneumonia-sepsis	10 (20)	13 (26)	
RDS	9 (18)	9 (18)	
PPHN-other	2 (4)	4 (8)	

As shown in Fig. 2, infants receiving the combination of surfactant+iNO improved their oxygenation faster than the iNO-control group, and this was sustained for the 48 h study period, resulting in a significantly lower OI ($p < 0.05$). In terms of the primary outcome, infants in the combined Surfactant+iNO group presented a significantly lower treatment failure (OI > 40): 24% (12/50) compared to 50% (25/50) of the iNO-control group, $p < 0.02$. Of interest, less than half of the infants required a second dose of treatment during the study period: 18 (36%) of the surfactant+iNO group and 23 (46%) of the iNO control group.

Table 2 illustrates other respiratory and efficacy outcomes, we highlight that fewer infants from the surfactant +iNO group reached the combined adverse outcome of death or ECMO: 16% (8/50) compared to 36% (18/50) of the iNO-control group, $p < 0.05$. Of the 8 infants who died, 3 came from the 52 infants that were initially treated at the ECMO center, and the other 5 infants came from the 48 infants that were treated at non-ECMO centers. Of the 18 newborns who persisted with an OI > 40 despite iNO treatment at non-ECMO centers, 15 were transferred for ECMO, however, the other 3 deteriorated quickly and died before ECMO could be installed. Only 1 of 19 infants that received ECMO died, this was not different between groups: 1/12 infants of the control group and 0/7 infants of the treatment group.

Length of ventilator support, oxygen therapy, and hospital stay were not different between the groups. Most infants used inotropes during the study period: 47 (94%) of the control group and 44 (88%) of the surfactant group. We did not observe differences in the rate of adverse events nor other morbidities evaluated, including IVH, pneumothorax, pulmonary hemorrhage, and tolerance to surfactant/placebo administration (Table 3).

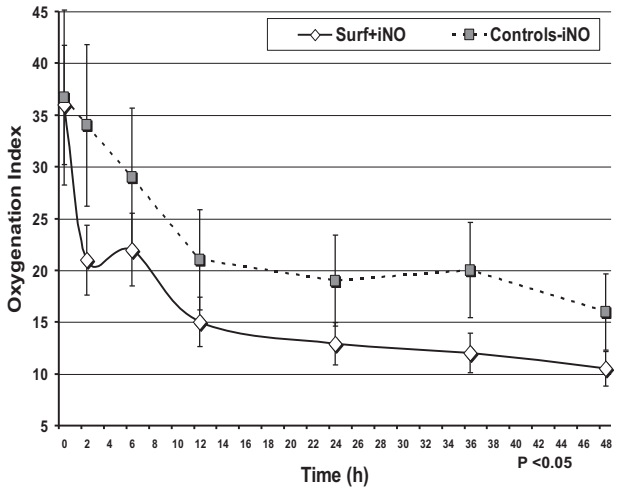

Fig. 2 Change in Oxygenation Index. Variation of OI during the study period (means ± SD): infants treated with surfactant+iNO improved their oxygenation faster resulting in a significant lower OI compared to control group, $p < 0.05$.

Discussion

In the present study, we compared the early and combined use of surfactant with iNO versus standard iNO therapy in newborns with moderate to severe HRF. In this population, we demonstrate that the addition of exogenous surfactant to iNO therapy, leads to faster improvement and better oxygenation, preventing the progression to severe HRF. In the same way, this combination of therapies ensured a significant reduction in the combined outcome of death or ECMO requirement.

Table 3 Adverse events associated to study treatment administration:.

	Controls-iNO ($n = 50$)	Surfactant+iNO ($n = 50$)	p value
Desaturation < 80%: n (%)	4 (8%)	5 (10%)	NS
Obstruction ETT: n (%)	0 (0%)	1 (2%)	NS
Pneumothorax: n (%)	3 (6%)	1 (2%)	NS
Pulmonary hemorrhage: n (%)	1 (2%)	0 (0%)	NS
Arterial hypotension: n (%)	1 (2%)	1 (2%)	NS

Table 2 Respiratory and other outcomes.

	Controls-iNO ($n = 50$)	Surfactant+iNO ($n = 50$)	p value
Treatment failure: n (%) (OI > 40)	25 (50%)	12 (24%)	0.02
Treated with ECMO: n (%)	12 (24%)	7 (14%)	NS
Death: n (%)	7 (14%)	1 (2%)	0.07
ECMO or death: n (%)	18 (36%)	8 (16%)	<0.05
HFOV use: n (%)	42 (84%)	37 (74%)	NS
Received rescue surfactant	7 (14%)	2 (4%)	NS
M.Ventilation days, median (range)	9 (2–54)	8 (2–62)	NS
Oxygen therapy days, median (range)	16 (3–57)	14 (3–68)	NS
Length of hospital stay days, median (range)	22 (5–54)	19 (5–83)	NS

In the nineties, two RCT showed that high doses of surfactant improved oxygenation and decreased ECMO use in newborns with HRF [12, 13]. However, in a meta-analysis of studies evaluating surfactant use in MAS, despite ECMO reduction there was no impact on mortality or other outcomes [17, 18]. On the other side, adverse events have been associated with surfactant such as endotracheal tube obstruction and hypoxemic events in 21 and 33% of patients, respectively [13]. In some cases, these events precipitated respiratory deterioration and ECMO connection. Similarly, studies evaluating lung lavage with surfactant in MAS, reported also adverse events [19]. None of the patients included in these studies received iNO. Consequently, in the last recent meta-analysis update for surfactant use in MAS [18], the authors conclude: "The relative efficacy of surfactant therapy compared to, or in conjunction with other approaches to treatment including iNO …remains to be tested". Although surfactant is a common therapy in the NICU and may be considered standard of care for PPHN in current days, at the time this study was designed and run, the evidence for its use was not clear. On the other hand, it is expensive, especially considering the large doses required to treat term newborns, and at that time, its use was restricted to preterm infants with RDS by the Ministry of Health Neonatal Guidelines [3]. Therefore, physicians, nurses, and parents did not have ethical concerns about surfactant randomization. This study was reviewed and approved by the 5 hospital's Ethics Committees.

iNO improves oxygenation and decreases the need for ECMO or death in term infants with HRF [5–7]. However, the rate of response varies widely and a percentage close to 50% died or required ECMO [20]. Given this evidence, it was necessary to look for new alternatives that combined with iNO improve these outcomes. There are potential benefits of using surfactant in combination with iNO: surfactant for alveolar recruitment added to iNO for pulmonary vasodilation. In the same way that HFOV has shown to enhance iNO efficacy [21], surfactant may magnify iNO action when lung recruitment is optimized. Similarly, changes in methemoglobin levels have been shown as an indicator of iNO delivery and better lung recruitment, and have been associated with a positive response to iNO in PPHN [22]. An early use of these therapies, optimizing lung volume and oxygenation, can avoid the adverse effects of oxygen toxicity and barotrauma. The use of iNO in PPHN models led to preservation of mitochondrial function in the lungs [23] and decreased hyperoxia-induced surfactant dysfunction [24].

To date, we are not aware that surfactant has been tested in conjunction with iNO in large RCT. In a pilot study, Gadzinowski et al. [25] observed that administration of surfactant before starting iNO, improved oxygenation and may have decreased PPHN severity. After that, Dargaville et al. [26] in an un-blinded RCT reported that lung lavage with diluted surfactant decreased the combined outcome of death or ECMO in infants with MAS. In this study, infants received standard care, which included iNO and HFOV in most of them, but at the discretion of treating clinicians.

Recently, Konduri et al. [27] did a retrospective post-hoc analysis of his early iNO RCT which enrolled infants with HRF. Although surfactant use was not randomized in this trial, 64% of the infants received this therapy prior to study entry allowing the analyses. The post-hoc analysis revealed that surfactant use before iNO initiation at an OI of 15–25, was associated with a significant decrease in the incidence of ECMO/mortality (surfactant 13.5%, vs no treatment 26%, $p = 0.008$). Additionally, surfactant treated infants had a shorter duration of ventilator therapy and hospitalization. The present study confirms Konduri's observations.

Of interest, infants receiving combined surfactant+iNO in our trial showed faster and consistent improvement in oxygenation and only 36% required a second dose. This is significantly less than the 3–4 doses given in the earlier reported studies where surfactant was used without iNO. In terms of adverse events, only 10% presented hypoxic events and 2% ETT obstruction during surfactant administration, which is considerably less than the rate reported in Lotze's study (33 and 21%, respectively). This can be explained by the surfactant used in our study (poractant alfa) that has a higher concentration of phospholipids per volume unit. The lower volumes administered (1.2 vs. 4–6 ml/Kg) probably determined a better tolerance to the procedure.

There are some limitations to our study. We intended to enroll patients early in the evolution of the disease. However, since most patients were outborns from study centers, many were randomized after the first day of life. Having included our patients later and possibly more seriously ill could have influenced the effectiveness of our intervention, showing less impact than if treatment had started earlier. We also had problems recruiting patients and, as a result, it took us five years to achieve the number needed in our design. However, our research team remained constant and the associated therapies had no significant changes during this period. Eventually, we were able to complete patient recruitment and follow up, and the results are very consistent. As mentioned, ECMO was only performed in one of the centers, and if needed, patients had to be transferred to that center. However, transport was not easily accessible for all patients, and although most patients were transferred, some deteriorated and died while waiting to be transferred to the ECMO center. This could have influenced the effectiveness of tested therapies and explain our mortality rate despite our ECMO availability, but this was equivalent for both groups. This is the reality of our region, ECMO and appropriate critical transport are unavailable in many regions outside the developed world. Taking this scenario

into account, our results gain relevance, because they support that combining less invasive therapies as surfactant and iNO prevents disease progression and reduces mortality and ECMO use in infants with HRF.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Appendix 1: Collaborators

The following members from the centers are non-author contributors to this study. They contributed with data collection and provided clinical care for study patients:

Hospital Clínico Universidad Católica de Chile, Santiago: Katherine Flores, Rodrigo Lagos, Claudia Miralles, María Eugenia Pérez, Solange Rojas, Angélica Vives.

Hospital Guillermo Grant, Concepción: Lilian Cifuentes, Andrea Saldías, Claudia Aburto.

Hospital Dr. Luis Tisné, Santiago: María Lidia Poblete, Paula Vasquez.

Hospital San José, Santiago: Ana María Pacheco, Paula Ponce.

Hospital Dr. Sótero del Rio, Santiago: Mónica Ahumada, Patricia Mena, Claudia Toro.

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