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ORIGINAL PAPER

Inhaled nitric oxide therapy during the transport of neonates with persistent pulmonary hypertension or severe hypoxic respiratory failure

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Abstract Our aim was to determine whether starting inhaled nitric oxide (iNO) on critically ill neonates with severe hypoxemic respiratory failure and/or persistent pulmonary hypertension (PPH), at a referring hospital at the start of transport, decreases the need for extracorporeal membrane oxygenation (ECMO), lessens the number of hospital days and improves survival in comparison with those patients who were started on iNO only at the receiving facility. The study was a retrospective review of 94 charts of neonates that had iNO initiated by the transport team at a referring hospital or only at the tertiary neonatal intensive care unit (NICU) of the receiving hospital. Data collected included demographics, mode of transport, total number of hospital days, days on inhaled nitric oxide and ECMO use. Of the 94 patients, 88 were included. Of these, 60 were started on iNO at the referring facility (Field-iNO) and 28 were started at the receiving NICU (CHLA-iNO). All patients survived transport to the receiving NICU. Death rates and ECMO use were similar in both groups. Overall, patients who died were younger and had lower birth weights and Apgar scores. For all surviving patients who did not require ECMO, the length of total hospital stay (median days 22 versus 38, P=0.018), and the length of the hospital stay at the receiving hospital (median days 18 versus 29, P=0.006), were significantly shorter for the Field-iNO patients than for the CHLA-iNO patients, respectively. Earlier initiation of iNO may decrease length of hospital stay in surviving neonates with PPH not requiring ECMO.

Keywords Transport medicine · Inhaled nitric oxide · Neonates · Persistent pulmonary hypertension · Hypoxemia

Abbreviations

ABG	arterial blood gas
CDH	congenital diaphragmatic hernia
CHLA	Children's Hospital Los Angeles
CHLA-iNO	patients receiving inhaled nitric oxide at the receiving hospital
ECMO	extracorporeal membrane oxygenation
Field-iNO	patients started on inhaled nitric oxide at the referring hospital
IND	investigation new drug
iNO	inhaled nitric oxide
NICU	neonatal intensive care unit
$PaCO_2$	partial pressure of carbon dioxide
PaO_2	partial pressure of oxygen
PPHN	persistent pulmonary hypertension of the newborn
p.p.m.	parts per million

Introduction

Persistent pulmonary hypertension of the newborn (PPHN) results from sustained or recurrent elevation of the

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pulmonary vascular resistance in the immediate postnatal period. Affecting over 10,000 term and near-term infants in the United States of America annually, PPHN has primarily been associated with conditions such as meconium aspiration, sepsis and pneumonia. Each of these conditions may cause increases in extra- and intra-pulmonary shunting, limited lung volume, decreased compliance or a combination of these pathologic presentations. As a result, hypoxemia, hypercarbia, acidosis and increased right-to-left shunting occur and characterize the clinical condition. In addition, in patients with congenital diaphragmatic hernia (CDH), pulmonary vascular hypoplasia contributes to the increased pulmonary vascular resistance and the development of pulmonary hypertension.

In recent years, inhaled nitric oxide (iNO) has been used as a selective pulmonary vasodilator in the treatment of critically ill neonates with PPHN and severe hypoxemic respiratory failure. Multiple studies have demonstrated that iNO is effective in improving oxygenation [4, 11, 12, 16, 17, 19, 20, 22] and decreasing the need for extracorporeal membrane oxygenation (ECMO) [1, 2, 8–10, 15, 20] in patients with PPHN. These treatment modalities have primarily been used in tertiary/quaternary care centers that have the capability to provide specialized care such as ECMO. The initial stabilization and transfer of these patients from a referring medical facility to a tertiary care hospital are challenges for a transport team.

There have been few studies looking at iNO treatment in patients transported to a tertiary care facility [6, 7, 13, 14, 18, 21]. Although each study concluded that iNO used in transport is safe and effective, each of these studies had a small sample size. Furthermore, the question of whether starting iNO at the referring hospital versus the receiving hospital makes a difference in the management and outcome of the severely hypoxic neonate has not been addressed in previous studies.

We hypothesized that the initiation of iNO treatment in neonates at a referring facility rather than the delaying of treatment until the neonate arrives at a receiving hospital improves tertiary care therapy by bringing the tertiary care modalities to the referring hospital. Therefore, the goal of this retrospective cohort study was to determine whether the initiation of iNO prior to transport decreases the need for ECMO, decreases the number of total hospital days and improves survival rates.

Subjects and methods

Patient population

The Children's Hospital Los Angeles (CHLA) neonatal intensive care unit (NICU) is a 36-bed level III C unit [3] that serves as a large referral center for southern and central California and receives over 400 admissions a year and averages approximately 75 ECMO referrals annually. The majority of the ECMO referrals are for PPHN and severe hypoxemic respiratory failure. The children's emergency transport team at CHLA transported each patient in this study. The transport team is a free-standing unit that performs over 1,500 neonatal and pediatric transports annually. The majority of patients in this study was transported from hospitals located in the Los Angeles Metropolitan area that covers a total area of 12,562 km^2 (4,850 square miles). In addition to continuous nursing and respiratory therapy coverage, one of the unique aspects of the transport team is the availability of dedicated transport attending coverage 24 h a day, 7 days a week. Therefore, with a transport attending physician physically in attendance at each transport, and with communication with the CHLA attending neonatologist on service, immediate therapeutic decisions on critically ill neonates can be made at the referring hospital and throughout the transport to the receiving hospital. We reviewed all neonatal patients that were transported to CHLA via the transport team with a diagnosis of either PPHN with or without peripheral lung disease or severe hypoxemic respiratory failure, from 1996 to early 2002. All patients received iNO therapy; however, iNO may have been started at the referring facility (Field-iNO) by the transport team or iNO may have been withheld until the patient had arrived at the CHLA (CHLA-iNO). During the study period, the transport team had the capabilities to administer iNO during all modes of transport after 1998. Locations of referring hospitals ranged from a facility located across the street from CHLA (0.8 km/0.5 miles) to a NICU located in Las Vegas, Nevada (434.5 km/270 miles). Transported patients were given NO via a delivery system that incorporated a gas-powered, pressure-limited, continuous-flow transport flow ventilator (Biomed MVP-10). From an external source tank, NO was bled through a regulator and low-flow flowmeter into the inspiratory limb of the ventilatory circuit. iNO dose monitoring was performed by cells of an NO analyzer (Pulmonox II) placed inline with the inspiratory line approximately 12 in. from the patient's endotracheal tube. Dosing of iNO was adjusted by changes of the input flow of NO via the flowmeter. The dosing of iNO ranged from 10 parts per million (p.p.m.) to 80 p.p.m. Prior to 2000, iNO dosing was at the discretion of the transport team, as iNO had an investigation new drug (IND) status. A dose no greater than 20 p.p.m. was standardized in patients transported after 2000. Guidelines for initiation of iNO would include a partial pressure of oxygen (PaO_2) of less than 80 Torr on 100% inspired oxygen or an oxygen saturation of less than 90% with a disease associated with PPHN.

Definitions

For the purposes of this study, hypoxia was defined as a reduction of oxygen supply to the tissues below physiologic levels despite adequate tissue perfusion. Hypoxemia was defined as a Partial pressure of oxygen in arterial blood (PaO_2) of less than 60 mm Hg on 100% oxygen. Mode of transport was defined as the type of vehicle used during the transport of patients. Three modes were used: ground ambulance, rotor wing (helicopter with an unpressurized cabin) and fixed wing (Lear jet with a pressurized cabin). In all cases the transport team consisted of the transport attending physician, nurse and respiratory therapist. The transport team determined the mode of transport, based upon patient acuity, weather conditions, the referring hospital's distance from CHLA, time of day and the traffic conditions for ground transport. For arterial blood gases (ABGs) obtained for monitoring purposes, "pre-iNO ABG" was defined as being obtained prior to the initiation of iNO; "post-iNO ABG" was defined as the first ABG obtained after the initiation of iNO; "post-transport iNO ABG" was defined as the first ABG obtained after the patient had arrived at CHLA and was receiving iNO. Mode of ventilation included conventional ventilation, high-frequency oscillatory ventilation, high-intensity/jet ventilation and bag valve mask ventilation at the referring facilities. During transport of the patients to CHLA, conventional mechanical or bag valve mask ventilation was used.

Data collection

Patients with the diagnoses of PPHN and severe hypoxic respiratory disease were identified from the Excel database program of the CHLA neonatal intensive care unit. Data were collected from medical records of patients with these diagnoses using a standardized data sheet. The CHLA Institutional Review Board for this study granted an exemption for patient consent. The following data were recorded: time of birth, birth weight, Apgar scores, the referring hospital and mode of transport. Other data points recorded included CHLA hospital days, total hospital days (CHLA hospital days plus subsequent hospital days if the patient was transferred back to the home hospital), days on iNO, whether ECMO was initiated, and diagnoses at the time of transport and at the time of hospital discharge. Arterial blood gases were recorded at three time periods: before iNO, after iNO (irrespective of the timing of the initiation of iNO) and after transport. The mode of ventilation at each ABG draw was noted.

Statistical analysis

The outcome variables investigated were patient death, the use of ECMO, length of hospital stay and the partial pressure of oxygen in arterial blood. The primary grouping variable was denoted by FIELD and was coded as 0 = iNO started at CHLA and 1 = iNO started in the field. For univariate analysis, simple 2 by 2 tables were analyzed with Fisher's exact test, while comparisons of continuous variables were made using either the *t*-test or non-parametric rank sum tests if the distributions were highly skewed. For patient death and the use of ECMO a multivariate logistic regression analysis was used to adjust for possible differences between the patients starting iNO in the field versus those starting at CHLA. Since early death affects length of hospital stay, the relationships with hospital stay were evaluated for survivors only. In addition, the hospital stay was analyzed separately for patients having and not having ECMO. The hospital days were analyzed both as days while at CHLA and as the total days (CHLA days plus subsequent days at the home hospital if the patient was transferred back for ongoing care). Paired *t*-tests were performed on the changes in PaO_2.

Results

Of 131 patients transported for potential ECMO during 1994 to 2002, a total of 94 charts was reviewed. Thirty-seven charts were either unable to be retrieved or were incomplete. Six patients were excluded from the study because iNO had already been started by the referring hospital prior to the arrival of the transport team. No patients died in transport to CHLA. Of the remaining 88 patients, 60 (68%) were started on iNO at the referring hospital (Field-iNO) and 28 (32%) were started at CHLA after arrival (CHLA-iNO).

Table 1 summarizes the baseline characteristics of the two groups as well as the mode of transport. The patients differed significantly in that more CHLA-iNO patients were transported by ground (82% versus 52%, $P=0.010$) and more of the Field-iNO patients were transported by helicopter (42% versus 18% $P=0.019$) and given the diagnosis of hypoxia (18% versus 4%, borderline significance, $P=0.060$). Transport times were considerably longer in the Field-iNO patients (52.9 min versus 34.6 min, $P=0.019$).

Patient death

The death rates for CHLA-iNO and Field-iNO patients was not different (21% versus 18%, $P=0.732$). Patients were at higher risk of death if they had a lower 1 min Apgar score ($P=0.034$), 5 min Apgar score ($P=0.001$), birth weight ($P=0.013$), pH ($P=0.003$) and PaO_2 ($P=0.004$), higher $PaCO_2$ ($P=0.004$) or did not have meconium aspiration ($P=0.029$) as a diagnosis. Multivariate logistic analysis indicated that lower birth weight, lower pH, and the absence

Table 1 Baseline characteristics of Field-iNO patients and CHLA iNO patients (*NSVD* normal spontaneous vaginal delivery, *HFOV* high-frequency oscillatory ventilation)

Characteristic	FIELD (n=60)	CHLA (n=28)	P
Birth delivery			
C-section	52%	46%	0.647
NSVD	48%	54%	
Gestational age (weeks)	38.9	39.9	0.067
Age at transport (h)	25 (±34)	16 (±19)	0.259
Weight at transport (g)	3368 (±657)	3304 (±782)	0.691
Apgar 1 min	5.6 (±2.4)	4.7 (±2.8)	0.201
Apgar 5 min	7.4 (±1.7)	6.4 (±2.3)	0.040
Diagnosis			
Respiratory failure	45%	50%	0.661
PPHN	58%	64%	0.595
Meconium aspiration	47%	46%	0.983
Hypoxia	18%	4%	0.060
Sepsis	32%	29%	0.769
Pre-nitric ventilator type			
Conventional	34%	44%	0.387
HFOV	64%	37%	0.023
Changed back to HFOV at CHLA	42%	78%	0.149
Jet ventilation	0%	0%	–
Hand bagging	2%	19%	0.005
Pre-nitric ABG			
pH	7.4 (±0.19)	7.3 (±0.19)	0.952
$PaCO_2$ (Torr)	42 (±18)	46 (±26)	0.375
PaO_2 (Torr)	51 (±30)	60(±29)	0.279
HCO_3 (mmol/l)	22 (±5)	23 (±5)	0.614
Base excess (mmol/l)	−0.5 (±15)	−2 (±9)	0.596
Oxygen saturation (%)	83 (±12)	78 (±24)	0.273
Pre-nitric ventilatory parameters			
Mean airway pressure	18.4	16.1	0.351
Oxygen index	42.2	41.7	0.958
$A-aDO_2$	606.7	590.9	0.108
Transport mode	18.5	16.1	0.351
Ground	31 (52%)	23 (82%)	0.010
Helicopter	25 (42%)	5 (18%)	0.019
Fixed wing	4 (6%)	0 (0%)	
Transport time (min)	52.9	34.6	0.019

of meconium aspiration were all somewhat independently related to patient death. After adjustment for these variables, there was no association found between patient death and location of iNO initiation. Analysis by other diagnoses, such as hypothermia, hypoglycemia or idiopathic PPHN, showed no significant association. There still was no significant difference in the death rates (odds ratio= 0.819, P=0.775, 95% confidence interval 0.209 to 3.210). Table 2 summarizes these results. The duration of transport did show significant difference in death outcome. Patient death occurred more frequently if transport times were fewer than 29.9 min compared with increased survival rates if transport times were greater than 49.8 min (P<0.014).

ECMO

Thirty-seven patients received ECMO (13 CHLA-iNO, 24 Field-iNO). The use of ECMO was more likely if the 1 min Apgar score was less (P=0.021) and meconium aspiration was diagnosed (P=0.005). The use of ECMO was not related to the location of iNO initiation (odds ratio=0.914, P=0.865). After adjustment for 1 min Apgar score and diagnosis there was still no significant relationship between ECMO and starting the iNO in the field versus at CHLA [odds ratio (OR) =1.075, P=0.900].

Table 2 Multivariate logistic regression evaluating patient deaths after adjustment for weight, pH, and meconium aspiration diagnosis

Died	Odds ratio	$P>\|z\|$	95% Confidence interval	
Weight	0.998	0.034	0.997	0.999
pH	0.002	0.003	0.0	0.120
Meconium aspiration	0.190	0.029	0.043	0.841
iNO in Field	0.819	0.775	0.209	3.210

Hospital stay

The length of hospital stay was analyzed in terms of the length of stay at CHLA, the quaternary treating hospital, and the total hospital stay based on the length of stay at CHLA plus the subsequent stay at the home hospital. Because the event "death" affects the length of hospital stay and the death rates were similar for the Field-iNO and CHLA-iNO patients, the length of hospital stay was analyzed for survivors only.

As shown in Table 3, the surviving patients receiving iNO in the field and not receiving ECMO (n=30) had shorter lengths of stay at CHLA (median 18 days versus 29 days; P=0.006, rank-sum test) than those receiving iNO only at CHLA (n=13). However, patients receiving ECMO had similar lengths of stay (median 16 days versus 17 days; P=0.980), irrespective of the institution where iNO administration was initiated. The same result is seen when total hospital days (CHLA days plus subsequent home hospital days) were taken into account, with the combined length of stay being shorter for the Field-iNO group than for the CHLA-iNO group when ECMO was not given (median 21 days versus 38 days, respectively; P=0.019), but similar in both groups if ECMO was given (median 34 days versus 36 days; P=0.622). Thus, these findings indicate that, for the patients who did not require ECMO, the use of iNO in the field shortened the overall length of stay by approximately 17 days and the CHLA length of stay by about 11 days.

Changes in PaO_2 during Transport

Among the Field-iNO patients, PaO_2 from the pre-iNO ABG to the post-iNO ABG (P=0.038) improved significantly (Table 4). However, there was no statistically significant improvement noted for the post-transport ABG (P=0.37). There were no differences found in the PaO_2 values of the CHLA-iNO group. Furthermore, no differences could be documented in the other components of the ABG (pH, $PaCO_2$, HCO_3, base excess and oxygen saturation) in each of the groups. Finally, when the CHLA-iNO and Field-iNO groups were compared, there was no statistical difference between the changes in PaO_2.

Discussion

Our study is the largest retrospective review of the use of iNO therapy in neonatal transports to date. Multiple diagnoses contributed to the presentation of severe hypoxemic respiratory failure, including PPHN, sepsis, meconium aspiration and congenital diaphragmatic hernia. Of these patients, 70% were started on iNO at the referring hospital by the transport team. Consistent with prior studies, all patients survived transport. Not all referring NICUs have the capabilities and infrastructure to care for these critically ill patients, especially since they do not have an ECMO program to offer for maximal therapeutic intervention and optimal survival [13]. Furthermore, it has been shown that suddenly discontinuing iNO may be detrimental [5, 14]. Our transport set-up minimizes this risk, because iNO therapy can be continued en route. Our data indicate that our transport set-up delivers iNO in an effective manner, because arterial oxygen pressures improved during transport and were sustained during transport. Although iNO initiated in the field did not affect mortality rates and the need for ECMO therapy, we found a substantially shorter hospital stay for patients who survived in the Field-iNO group. In a different perspective, the cost of a hospital bed in the CHLA NICU is $1,974 per day (in 2005). Thus, estimated savings of $21,174 per patient at CHLA were realized in the Field-iNO patients. This amount is considerably larger when one takes into account other hospital costs (physician, nursing and ancillary fees, medications, examinations, etc.) and the number of days of the total hospitalization stay. This finding suggests that the utilization of iNO therapy during neonatal transports is a cost-saving modality.

A few earlier studies addressed the impact of iNO administration during neonatal transport on smaller patient populations. The findings of those studies suggest that critically ill, mechanically ventilated patients can be safely

Table 3 Length of hospital stay of surviving neonates at CHLA and total hospital stay based on presence of ECMO and location of initiation of iNO

Location	CHLA hospital stay				Total hospital stay			
	Mean	Standard deviation	Median	P	Mean	Standard deviation	Median	P
NO ECMO								
CHLA	34.7	19.8	29	<0.009	42.6	22.3	38	0.019
FIELD	18.8	12.9	18		25.8	15.5	21	
ECMO								
CHLA	25.2	20.9	16	0.980	42.6	16.3	36	0.622
FIELD	25.3	20.3	17		39.1	16.5	34	

Table 4 Arterial blood oxygen concentrations of iNO transport patients

Variable	Observed	Mean	Standard deviation	Minimum	Maximum
Pre-iNO CHLA PaO_2	27	60.4	50.8	9	236
Post-iNO CHLA PaO_2	27	81.9	95.3	16	427
Pre-iNO Field PaO_2	57	52.2	31.0	10	241
Post-iNO Field PaO_2	60	62.8	48.1	11	232
Post-transport Field PaO_2	42	60.8	36.6	18	200

transported on iNO [7, 21], that iNO may provide a therapeutic bridge during transport to a tertiary center [14], and that iNO facilitates the transport of ill neonates by stabilizing the oxygen liability characteristic of PPHN [13].

Our study provides the first preliminary evidence that earlier initiation of iNO during transport may decrease length of hospital stay in surviving neonates with severe hypoxemia and respiratory failure not requiring ECMO. However, there are several limitations in our study. Although we reviewed 73% (94/131) of all cases between 1996 and 2002, we were unable to obtain either complete data or charts on 37 patients. Furthermore, six patients were excluded from the study because iNO had been initiated by the referral hospital prior to the transport team's arrival. There is the possibility that our data would be different if we had been able to obtain all of the charts and included all of the data in our analysis. Because each transport mission is different in terms of mode of transport, time duration, and distance between the referring and receiving hospitals, there was significant variability in the amount of iNO delivered to each patient. When the two groups were compared, the Field-iNO patients were more likely to be transported by air but had longer transport times. The starting and administering of iNO sooner and for a longer period may have led to a more beneficial outcome for these patients. The death rate was higher in patients with shorter transport times. These patients may have been more critically ill and may have needed faster transport to the referring hospital. However, because we could not control all factors that determine mode of transport (distance, geography, weather, traffic, and patient acuity), we could not make a decision on whether this made a difference between the two patient groups.

During the time period studied, there was no existing standardized protocol for the dose of iNO administered. Although the majority of patients were started and maintained at 20 p.p.m. (47 of 60 Field-iNO patients), others received iNO in the 10 p.p.m. to 80 p.p.m. range. Transport team members may have intuitively thought higher doses of iNO could lead to an improvement in the patients' respiratory status. Conversely, variability in lower iNO doses could have had an impact on outcomes. Prior to transport, the mode of ventilation could also have affected the response to iNO and therefore outcomes as well. The change from a high-frequency oscillatory ventilator or jet ventilator to the conventional ventilator during transport may have had an effect on the delivery of oxygen to a severely damaged lung. Although this change in the mode of ventilation could have affected gas exchange, we did look at patients that were changed back to high-frequency oscillator ventilation and found no differences between the Field-iNO and CHLA-iNO groups. We did control for the mode of ventilation used in transport, since we only use a conventional ventilator in our neonatal transports.

Discharge criteria at the referring hospitals may have played a factor on the total length of hospitalization. Since many of these referring institutions are not tertiary centers, the criteria for patients' discharge may be different and stricter than those at CHLA. Not only can these factors influence total hospitalization stay, but they also influence total hospitalization costs.

We also noted that a small number of patients (14) during the study period had a discharge diagnosis of congenital diaphragmatic hernia. These patients may have been diagnosed with "respiratory failure" without an admission CDH diagnosis. Even though not very effective, iNO is used widely for CDH. Patients with CDH typically have prolonged hospitalization; thus, this may also have had an impact on our data with regard to hospitalization days. However, our data did show that surviving Field-iNO patients with CDH and not requiring ECMO had shorter hospitalization.

Another weakness of the study was the ABG values that were collected before iNO, after iNO and after transport. Some patients did not have their ABG values recorded immediately after transport to CHLA. Since no protocol was established for the transport of these patients, the interval between pre-iNO and post-iNO ABGs may have been hours. Therefore, it is difficult to estimate the actual improvement in PaO_2. Finally, since this was a non-randomized study, the results are also based on a successful adjustment for baseline covariate thorough a multivariate analysis. Therefore, there could be some bias based on some variables that were not measured.

Conclusions

While limited by the retrospective nature of this study, our findings suggest that initiating iNO at a referring hospital

and continuing the administration during transport decreases the number of hospital days for those neonates with severe respiratory failure who survive and do not require ECMO. Overall death rates and the need for ECMO therapy do not appear to be affected. A prospective, controlled study is warranted to validate and challenge our findings.

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