Variability in the response to dexamethasone treatment in term neonates with respiratory failure

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Submitted: 20 April 2009
Accepted: 26 May 2009

Arch Med Sci 2009; 5, 3: 427-433

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Abstract

Introduction: We aimed to evaluate the effect of a short course of dexamethasone on pulmonary function and mechanics in term newborn infants with respiratory failure utilizing patient monitoring devices.
Material and methods: We conducted a retrospective review of term newborn infants, supported with conventional mechanical ventilation, and treated with pressors and short courses of dexamethasone (≤ 48 h) within the first week of life. Using a quasi-experimental design, where each patient served as his own control, we evaluated changes following the first dose of dexamethasone. We analyzed data from 36 newborn infants (gestational ages 39 ±0.6 weeks, birth weight 3.6 ±0.6 kg, oxygenation index 15 ±10). The first dexamethasone dose was given at 23 (17-30, median; IQR) h.
Results: Significant improvements in pulmonary function and mechanics and a significant decrease in the doses of pressors used were noted 12 h after the first dexamethasone dose. These improvements were sustained for the duration of data analysis. A subgroup of newborn infants subsequently treated with inhaled nitric oxide (iNO subgroup) had slower improvement in their oxygenation and ventilation than newborn infants who did not need iNO (CMV subgroup). The two subgroups had similar changes in mean arterial pressure and doses of pressors at the analyzed time points following the first dexamethasone dose.
Conclusions: Improvement in lung function and mechanics and a decrease in doses of pressors could be detected within 12 h of initiation of dexamethasone therapy. Changes observed in this study can be useful in designing future randomized controlled trials.

Key words: hypotension, neonate, respiratory failure, steroids, meconium, nitric oxide.

Introduction

Term newborn infants with critical respiratory failure and hypotension are frequently treated with corticosteroids. In a controlled study using inhaled nitric oxide for term infants with hypoxemic respiratory failure, 8% were also treated with corticosteroids [1]. Systemic glucocorticoids are also used in pediatric cardiac intensive care units for persistent hypotension [2]. A controlled steroid trial in ECMO-treated patients reported decreased enrollment, in part, related to the prevalence of treating eligible newborn infants with steroids [3]. It is believed that these newborn infants have inadequate adrenal responses associated with severe illness which might be steroid-responsive [4].

Although treating ventilator-dependent premature infants and adults with acute respiratory distress syndrome (ARDS) [5] with glucocorticoids improves the pulmonary condition [6], the pulmonary effects of term newborn infants treated with systemic glucocorticoids for respiratory failure or hypotension have not yet been defined. The purpose of this study is to describe the timeline and magnitude of pulmonary and hemodynamic changes following systemic steroid therapy in term newborns with respiratory failure. We also hypothesized that pulmonary response to steroid therapy would vary by the underlying disease leading to respiratory failure.

Material and methods

We conducted a retrospective review of medical records for newborn infants cared for in the Neonatal Intensive Care Unit (NICU) at the University of Michigan Health System between January 1, 1998 and June 30, 2001. The Institutional Review Board approved the study. Newborn infants were identified for analysis if they were born beyond 37 weeks' gestation, required mechanical ventilation for respiratory distress, were treated with pressors (dopamine and/or dobutamine), and received intravenous dexamethasone (DXM) 0.5 mg/kg within the first 7 days of life. Neonates were excluded if they had major congenital heart or chest anomalies. Those who were supported by high frequency ventilation and treated with surfactant or extracorporeal membrane oxygenation (ECMO) within 36 h of the first steroid dose were also excluded from the analysis, since these treatments introduce confounding variables. Patients supported with ECMO commonly experience pulmonary edema that affects the measured pulmonary function and mechanics parameters. The bedside pulmonary monitoring device cannot be used reliably when patients are supported with high frequency ventilation. The time points of hemodynamic and pulmonary data extraction were the time of the first dose of DXM, and then at 6-h intervals up to 72 h post-treatment. Newborn infants with hypoxemia and manife-stations of persistent pulmonary hypertension (PPHN) were commonly treated with pressors to elevate systemic blood pressure and decrease right-to-left shunting, even if these newborn infants were not remarkably hypotensive, with the goal to keep mean arterial pressure from 45-55 mm Hg. Local practice during this period was to treat term infants with respiratory failure with pressors and with DXM, if necessary. We were unable to find infants with a similar degree of respiratory dysfunction that were not treated with steroids and thus we could not identify a control group. Treatment with inhaled nitric oxide (iNO) was initiated if ventilated infants could not maintain PaO_2 > 50 mm Hg in 1.0 FiO_2 with indications of right-to-left shunting by echocardiography or a pre-to-post ductal gradient on dual site pulse oxymetry. Inhaled nitric oxide was discontinued if PaO_2 failed to increase by at least 20 mm Hg. We further stratified infants for the severity of respiratory failure into two groups: those who responded to iNO (NO group) and those who infants who were not treated with iNO [Conventional Mechanical Ventilation (CMV) group]. Collected data included demographics; timing and doses of DXM; complications of steroid therapy such as hypertension, hyperglycemia, intestinal perforation, and sepsis; and other medications received during the study period. Peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), mean airway pressure (Paw), FiO_2, respiratory rate (RR), inspiratory tidal volume (V_t), and minute ventilation were recorded from the Bird Graphic Monitor (Viasys Healthcare, Palm Springs, CA, U.S.A.) as long as the newborn infant remained on mechanical ventilation (V.I.P. BIRD Infant/Pediatric Ventilator, Viasys Healthcare, Palm Springs, CA, U.S.A.). The ventilation efficiency index (VEI) (ml/kg/cm H_2O) was calculated as: 3800/(PIP – PEEP) × RR × $PaCO_2$ [7]. The oxygenation index (OI) was calculated as: Paw × FiO_2 × 100/PaO_2. The alveolar-arterial oxygen gradient (A-a DO_2) was calculated as A-a (O_2) = (FiO_2%/100) × (713 mm Hg) – ($PaCO_2$/0.8) – PaO_2. Dynamic compliance (C_L) was calculated as: V_t/PIP – PEEP. C_L, VEI, and V_t were normalized to birth weight [kg]. These respiratory parameters were collected retrospectively from the respiratory therapy data sheets that are part of the medical record. Respiratory therapists in the study site obtain these respiratory parameters from the bedside monitoring device and record them at least every 6 h or more frequently if a blood gas is obtained or whenever they change the ventilator settings. Doses of pressors are reported as the subsequent administration of dopamine and dobutamine in µg/kg/min. Newborn infants were diagnosed as having meconium aspiration syndrome (MAS) if there was meconium stained amniotic fluid and the infant had respiratory failure with a compatible chest radiograph. Infants were considered to have congenital pneumonia if they had respiratory failure and radiographic findings compatible with pneumonia and clear amniotic fluid. Hyperglycemia was defined as elevated blood glucose requiring treatment with insulin.

Management of conventional mechanical ventilation consisted of flow-triggered, pressure-limited, assist-control with settings adjusted to deliver a tidal volume of 4-7 ml/kg. Pressures (PIP and PEEP) were adjusted to maintain tidal volume delivery while attempting to achieve physiologic gas exchange on blood gas measurements.

Statistical analysis

We used a convent sample of patients and did not estimate the needed sample size because changes in pulmonary mechanics and function using monitoring tools available to clinicians have yet to be reported. This was a pilot trial, utilizing a quasi-experimental study design, with each patient serving as his own control. Statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA, 2002). Analyses involved both continuous and dichotomous variables. Continuous variables were compared using the Student *t*-test, paired *t*-test, and non-parametric analysis when appropriate. Bonferroni *post-hoc* analysis for pre versus post dose observation for each time period was done. Dichotomous variables were analyzed using χ^2 analysis or Fisher's exact test for small sample sizes. A *p*-value of < 0.05 was used to identify statistically significant differences between groups for each variable of interest.

Results

We evaluated the records of 74 patients. Thirty-seven newborn infants were treated with surfactant or supported with HFOV within 36 h of the DXM treatment and one infant had inadequate baseline pulmonary data; they were excluded. The remaining 36 infants comprise the study group. Thirteen infants responded to treatment with iNO. We describe data for the whole group and for the two subgroups, with and without iNO treatment. All infants received morphine for pain and lorazepam for sedation, and 34 infants (94%) were also treated with pancuronium to improve the control of respiratory failure or to reduce oxygen consumption. None of the infants died during the NICU hospitalization. Demographic characteristics, primary conditions attributing to respiratory failure, dosing and timing of DXM treatment, baseline pulmonary variables, and doses of pressors are summarized in Table I.

Table I. Newborn infants characteristics

Variable	Total (*N* = 36)	CMV subgroup (*N* = 23)	iNO subgroup (*N* = 13)	*P* values
Birth weight [kg]	3.6 ±0.6	3.6 ±0.7	3.6 ±0.5	0.96
Gestational age [weeks]	39 ±1.5	39 ±1.3	39 ±1.8	0.31
Male gender [%]	67	61	76	0.50
White race [%]	53	57	46	0.55
Admission diagnosis:				
• MAS (%)	12 (33)	8 (35)	4 (31)	0.74
• Pneumonia (%)	18 (50)	11 (49)	7 (54)	0.82
• Sepsis (early onset) (%)	2 (6)	1 (4)	1 (8)	1.00
Apgar score at 5 min*	8 (6-9)	8 (6-9)	8 (7-9)	0.12
First dexamethasone dose [mg/kg]*	0.5 (0.5-0.5)	0.5 (0.5-0.53)	0.5 (0.5-0.5)	0.46
Timing of the first dexamethasone dose [h]*	23.4 (11.5-30.3)	23.4 (18.2-29.5)	23.4 (15.4-30.0)	0.66
Pulmonary parameters before first dose, mean (± 1 SD):				
• VEI ($\times 10^{-4}$)	2 (1)	2 (1)	2 (1)	0.30
• OI	15 (10)	14 (11)	15 (8)	0.73
• C_L/kg	0.36 (0.12)	0.36 (0.15)	0.36 (0.10)	0.73
• V_t/kg	8 (2)	7 (2)	8 (2)	0.24
• FiO_2	94 (12)	92 (14)	97 (6)	1.00
• A-a DO_2	501 (138)	484 (154)	530 (102)	0.343
• Paw	12 (2)	12 (3)	13 (2)	0.63
• Pressors	31 (11)	29 (12)	34 (8)	0.30
• MAP	49 (11)	49 (10)	49 (12)	0.21

1 SD – standard deviation, VEI – ventilation efficiency index, OI – oxygenation index, CL – dynamic compliance, V_t/kg – inspiratory tidal volume, Paw– mean airway pressure, A-a DO_2 – alveolar-arterial gradient, CMV subgroup – infants supported with conventional mechanical ventilation and not treated with iNO, iNO subgroup – infants supported with conventional mechanical ventilation and treated with iNO, MAS – meconium aspiration syndrome, MAP – mean arterial pressure [mm Hg], Pressors – combined dopamine and dobutamine doses (µg/kg/min)
**Median (25^{th}-75^{th} quartiles)*

Table II. Pulmonary function and mechanic and hemodynamic measurements for all patients (n = 36) by observation period

Parameter		Before 1st dose	6 h after 1st dose	12 h after 1st dose	24 h after 1st dose	36 h after 1st dose	48 h after 1st dose
VEI (× 10^{-4})	Mean (± 1SD)	2 (1)	3 (1)	4 (2)	4 (2)	4 (2)	3 (1)
	P = (pre vs. post)*	NA	0.823	0.003	0.007	0.001	0.031
OI	Mean (± 1SD)	15 (10)	10 (7)	9 (7)	9 (6)	8 (5)	8 (4)
	P = (pre vs. post)*	NA	0.085	0.019	0.036	0.001	0.002
C_L/kg	Mean (± 1SD)	0.36 (0.13)	0.41 (0.17)	0.43 (0.16)	0.43 (0.11)	0.46 (0.12)	0.45 (0.16)
	P = (pre vs. post)*	NA	1.000	0.442	0.502	0.042	0.109
V_t/kg	Mean (± 1SD)	8 (2)	8 (2)	8 (2)	7 (2)	7 (2)	7 (2)
	P = (pre vs. post)*	NA	1.000	1.000	1.000	1.000	1.000
FiO_2	Mean (± 1SD)	94 (12)	93 (13)	89 (14)	80 (19)	73 (23)	65 (24)
	P = (pre vs. post)*	NA	1.000	1.000	0.022	0.001	0.001
Paw	Mean (± 1SD)	12 (2)	12 (2)	11 (3)	11 (2)	10 (2)	10 (2)
	P = (pre vs. post)*	NA	1.000	0.526	0.041	0.001	0.001
$AaDO_2$	Mean (± 1SD)	501 (138)	464 (127)	451 (126)	417 (157)	370 (170)	341 (159)
	P = (pre vs. post)*	NA	1.000	1.000	0.269	0.004	0.001
Pressors	Mean (± 1SD)	31 (11)	26 (13)	22 (14)	15 (14)	7 (8)	3 (6)
	P = (pre vs. post)*	NA	1.000	0.024	0.001	0.001	0.001
MAP	Mean (± 1SD)	49 (11)	55 (10)	56 (9)	57 (10)	59 (8)	55 (9)
	P = (pre vs. post)*	NA	0.164	0.040	0.003	0.001	0.113
Extubated	N (%)	0 (0%)	0 (0%)	1 (3%)	2 (6%)	2 (6%)	5 (14%)

1SD – 1 standard deviation, VEI – ventilation efficiency index, OI – oxygenation index, CL – dynamic compliance, V_t/kg – inspiratory tidal volume, Paw – mean airway pressure, A-a DO_2 – alveolar - arterial gradient, Pressors – combined dopamine and dobutamine doses (μg/kg/min), MAP – mean arteria pressure [mm Hg]

**Bonferroni post-hoc analysis pre vs. post dose observation for each time period*

Table III. Percent change from baseline

Parameter		6 h after 1st dose			12 h after 1st dose			24 h after 1st dose			36 h after 1st dose			48 h after 1st dose		
		CMV	iNO	p*	CMV	iNO	p*	CMV	iNO	p*	CMV	iNO	p*	CMV	iNO	p*
VEI	Mean	41.4	27.5	0.736	93.3	54.3	0.141	115.9	39.9	0.043	156.0	35.5	0.002	146.9	36.6	0.007
(× 10^{-4})	(± 1SD)	(50.8)	(54.2)		(76.1)	(64.0)		(107.7)	(40.8)		(116.1)	(47.4)		(119.6)	(67.3)	
OI	Mean	–20.9	–21.7	0.116	–23.1	–33.3	0.151	–32.7	–27.7	0.854	–51.2	–31.0	0.088	–56.1	–20.2	0.045
	(± 1SD)	(29.2)	(75.4)		(43.2)	(59.6)		(26.1)	(41.8)		(19.4)	(33.9)		(16.6)	(55.6)	
C_L/kg	Mean	13.0	5.4	0.589	23.6	22.4	0.484	31.8	16.6	0.141	47.0	15.5	0.005	52.7	5.5	0.001
	(± 1SD)	(17.4)	(29.7)		(18.3)	(37.8)		(30.7)	(24.0)		(33.5)	(23.7)		(32.1)	(23.5)	
V_t/kg	Mean	9.6	–2.4	0.126	16.5	3.6	0.122	10.9	–11.8	0.007	10.2	–14.9	0.014	2.8	–24.8	0.010
	(± 1SD)	(15.1)	(23.5)		(21.8)	(27.9)		(27.8)	(18.1)		(27.4)	(20.5)		(28.0)	(23.5)	
FiO_2	Mean	–1.9	1.1	0.181	–8.2	–1.9	0.121	–20.9	–6.3	0.026	–31.1	–11.2	0.026	–40.2	–21.0	0.032
	(± 1SD)	(17.3)	(8.5)		(21.6)	(10.7)		(20.3)	(16.9)		(22.4)	(21.4)		(21.1)	(25.0)	
Paw	Mean	–1.5	–4.3	0.407	–6.4	–14.4	0.348	–12.6	–16.7	0.105	–18.4	–19.1	0.658	–24.8	–19.6	0.352
	(± 1SD)	(9.0)	(10.7)		(12.5)	(28.0)		(11.0)	(21.4)		(13.6)	(16.4)		(13.6)	(14.4)	
$AaDO_2$	Mean	2.3	–11.7	0.187	–10.6	–9.7	0.733	–26.9	–9.6	0.042	–39.3	–14.7	0.008	–45.5	–23.9	0.051
	(± 1SD)	(35.5)	(24.3)		(25.3)	(21.4)		(20.9)	(22.2)		(26.7)	(20.2)		(22.3)	(27.2)	
Pressor	Mean	–14.6	–17.4	0.868	–18.9	–29.7	0.960	–39.4	–61.0	0.679	–72.4	–83.5	0.418	–88.2	–92.6	0.602
	(± 1SD)	(49.9)	(26.4)		(87.1)	(27.3)		(74.2)	(36.0)		(33.9)	(19.2)		(24.2)	(14.8)	
MAP	Mean	13.6	13.9	0.754	17.0	19.7	0.987	19.4	23.1	0.934	24.5	26.3	0.934	13.1	23.0	0.422
	(± 1SD)	(17.3)	(20.5)		(22.4)	(33.7)		(21.3)	(33.2)		(25.6)	(33.2)		(25.3)	(31.3)	

1 SD – standard deviation, VEI – ventilation efficiency index, OI – oxygenation index, CL – dynamic compliance, V_t/kg – inspiratory tidal volume, Paw – mean airway pressure, A-a DO_2 – alveolar - arterial gradient, CMV subgroup – infants supported with conventional mechanical ventilation and not treated with iNO (n = 23 at time 0), iNO subgroup – infants supported with conventional mechanical ventilation and treated with iNO (n = 13 at time 0), MAS – meconium aspiration syndrome, MAP – mean arterial pressure [mm Hg], Pressors – combined dopamine and dobutamine doses (μg/kg/min)

**Mann-Whitney non-parametric analysis of two independent groups*

The frequencies of the variables in Table I were statistically different between the two subgroups (CMV vs. NO subgroups). Complications of DXM included hypertension in 3 (8%), hyperglycemia in 4 (11%), late onset sepsis in 1 (3%), and intestinal perforation in 1 (3%). All of these complications occurred in the CMV group; however, the differences in these frequencies between the two subgroups were not statistically significant. None of the patients in the NO subgroup was extubated during the 72 h data analysis period. However, in the CMV subgroup 2 (10%) were extubated by 24 h, 5 (22%) were extubated by 48 h, and 10 (43%) were extubated by 72 h.

Measured and calculated pulmonary parameters, mean arterial pressure, and pressor doses in the 48 h post-first DXM dose were compared to baseline values for all patients in the study and are shown in Table II. Statistically significant improvement in VEI, OI, pressor doses, and mean arterial pressure (MAP) could be detected by 12 h, and significant changes in Paw and FiO_2 by 24 h after the first DXM dose and were sustained for the duration of analysis. However, statistically significant changes in C_L and A-a DO_2 were detected only after 36 h from the first DXM dose.

Percent changes in pulmonary and hemodynamic parameters were compared between the two subgroups at several time points after DXM treatment and are summarized in Table III and selected variables are also displayed in Figures 1-3. There were no differences in the percent change in MAP and doses of pressors between the two subgroups at the analyzed time points as shown in Figure 1. There were, however, differences in percent changes between the two subgroups in pulmonary parameters following the first DXM dose. Greater percent changes in VEI in the CMV subgroup were detected at 24 h; however, greater percent increase in C_L in the CMV subgroup could be detected 12 h later (Figure 2). Greater percentage improvement in oxygenation was detected in the CMV subgroup

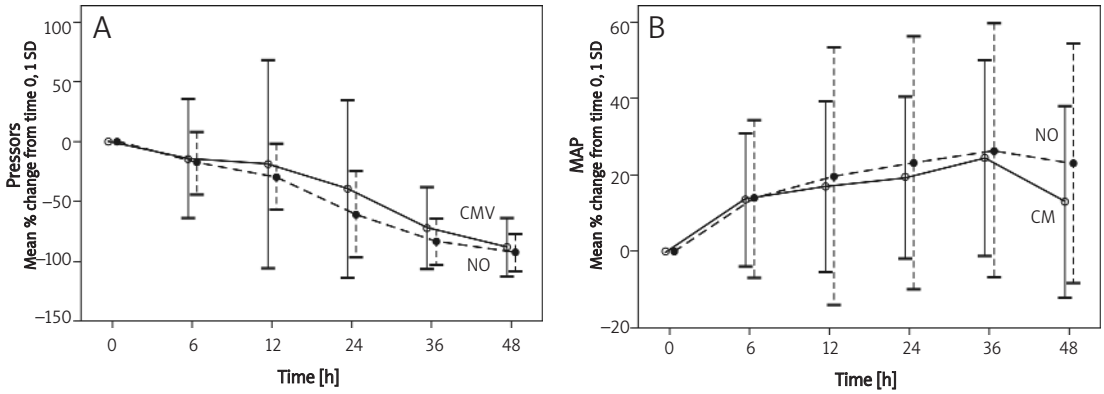

Figure 1. Percent changes in pressor doses (**A**) and mean arterial pressure (MAP) (**B**) from baseline at dexamethasone treatment

CMV – CMV subgroup, NO – iNO subgroup

**p < 0.05 comparing CMV and iNO subgroups at each time point with Bonferroni correction for multiple comparisons*

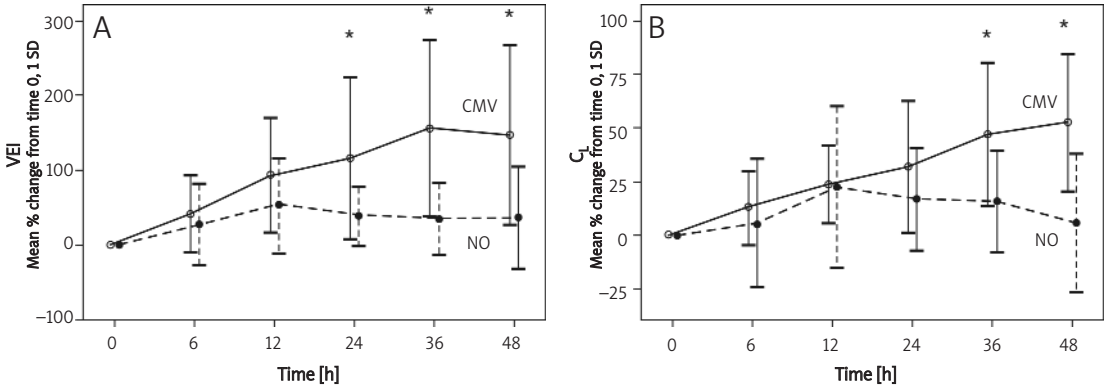

Figure 2. Percent changes in ventilation efficiency index (VEI) (**A**) and dynamic compliance (C_L) (**B**) from baseline at Dexamethasone treatment

CMV – CMV subgroup, NO – iNO subgroup

**p < 0.05 comparing CMV and iNO subgroups at each time point with Bonferroni correction for multiple comparisons*

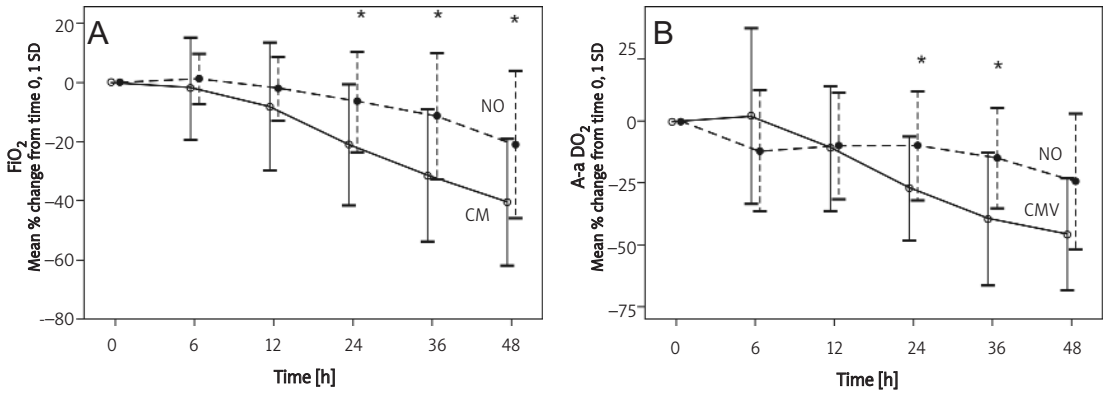

Figure 3. Percent changes in FiO_2 (**A**) and alveolar-arterial oxygen gradient (A-a DO_2) (**B**) from baseline at Dexamethasone treatment

CMV subgroup, NO – iNO subgroup

**p < 0.05 comparing CMV and iNO subgroups at each time point with Bonferroni correction for multiple comparisons*

at 24 h, characterized by decreases in FiO_2 and A-a DO_2 (Figure 3).

Discussion

Significant changes in pulmonary mechanics and function were detected as early as 12 h following the first dose of DXM in a population of term newborn infants with severe respiratory failure. The pulmonary improvement was sustained for at least 48 h. The rates of extubation at 48 and 72 h in infants not requiring nitric oxide suggests that they may have had less severe lung disease than the subgroup requiring nitric oxide, although the two subgroups had similar OI at the outset. This potential difference in severity of respiratory failure must be considered in interpreting the difference in pulmonary changes between subgroups. Adjusting ventilatory pressures (PIP and PEEP) and rates to achieve adequate gas exchange and maintaining V_t in a targeted range could have affected the pattern of change in V_t. However, VEI is a good indicator of early improvement in ventilation in this group of patients, especially for those infants treated with iNO. Since there was no specific protocol to wean FiO_2, the decrease in A-a DO_2 might be a better indicator of respiratory improvement.

Pulmonary effects of treatment of preterm infants with DXM have been demonstrated in controlled prospective studies [6, 8]. These improvements were also reported as early as 12 h following treatment with DXM in ventilator-dependent infants after two weeks of life [9]. Controlled studies for ventilator-dependent term infants have not been reported.

The decrease in pressor need and the improvement in blood pressure in this case series were detected at similar times as those reported in Noori's prospective evaluation following treatment with hydrocortisone [10]. The rapid steroid response was speculated to be secondary to reduction in interstitial fluid, alteration of membrane permeability [9], and upregulation of alveolar fluid clearance [11].

A controlled study of term infants with meconium aspiration and mild respiratory distress (22% required mechanical ventilation) [12], and a controlled study in an animal model of meconium aspiration (not intubated) suggested decreased survival with no significant histopathologic benefits of glucocorticoid treatment [13]. These reports raised serious concerns over the use of steroids in sick newborn infants. However, subsequent reports of both animal and human steroid treatments did not support these concerns. A controlled study of intubated and ventilated neonatal piglets subjected to endotracheal instillation of meconium reported beneficial effects of treatment with DXM on oxygenation and pulmonary function [14, 15]. A case series of sick newborn infants with respiratory failure and persistent pulmonary hypertension [16] and a small controlled study of infants with Meconium Aspiration Syndrome (MAS) [17] reported clinical improvements and no increase in mortality with systemic steroid treatment. A recent prospective controlled study of infants supported with ECMO who received DXM did not shorten the ECMO course, but also was not associated with increased mortality. That study, as in our report, showed increased risks for hypertension and hyperglycemia associated with DXM treatment [3].

While studies of steroid use in preterm infants raised concerns for later cerebral palsy, the developmental outcomes of term infants treated with steroids have not yet been described [18]. Further study of both short and long term efficacy and safety is warranted.

While we cannot attribute the pulmonary and cardiovascular changes in our study to the DXM alone in the absence of a control group, there appears to be a differential effect according to the

severity of the underlying respiratory disease. In conclusion, our findings may help in choosing appropriate short term outcome variables and in calculating sample sizes needed for a prospective randomized trial to evaluate the use of systemic steroids to treat refractory respiratory failure in term newborn infants.

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