Chronology and Determinants of Respiratory Function Changes Following Administration of Systemic Postnatal Corticosteroids in Extremely Preterm Infants

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Objective To describe the effect of systemic corticosteroids administered to treat evolving bronchopulmonary dysplasia on oxygen diffusion and ventilation efficiency.

Study design This was a retrospective cohort study of ventilated infants who received a 9-day course of dexamethasone in a tertiary neonatal unit. We calculated the transcutaneous oxygen saturation–to–fraction of inspired oxygen (F_iO_2) ratio (SFR), the ventilation perfusion ratio (V_A/Q), and the ventilation efficiency index (VEI) before, during, and after the course of corticosteroids. The response to corticosteroids was calculated as the difference between the F_iO_2 percentage before starting steroids and the lowest F_iO_2 value during the course of steroid treatment.

Results Seventy infants (38 males) with a median gestational age (GA) of 25.0 weeks (IQR, 24.3-26.0 weeks) and a median birth weight of 0.70 kg (IQR, 0.63-0.82 kg) were studied at a median postnatal age of 39 days (IQR, 29-48 days). The median SFR before treatment was 1.42 (IQR, 1.19-1.72), and the highest SFR was 2.35 (IQR, 1.87-2.83) after 9 days of treatment. The median V_A/Q before treatment was 0.14 (IQR, 0.11-0.18) and was significantly higher at 72 hours after the start of treatment (0.22; IQR, 0.15-0.29; $P < .001$). The median VEI was 0.06 (IQR, 0.04-0.08) before treatment and was highest, 0.10 (IQR, 0.07-0.13) at 48 hours after starting treatment. The median rate of response to corticosteroids was 28% (IQR, 20%-37%). GA was significantly related to the response to corticosteroids ($\rho = 0.283$; $P = .019$).

Conclusions Oxygen diffusion continues to improve throughout the entire duration of a 9-day course of systemically administered corticosteroids in ventilated extremely preterm infants. More immature infants are less responsive to corticosteroids. *(J Pediatr 2019;215:17-23)*.

Postnatal corticosteroids are commonly administered systemically to prevent and treat evolving or established bronchopulmonary dysplasia (BPD) in mechanically ventilated preterm-born infants. Late administration of systemic corticosteroids (after 7 days) reduces neonatal mortality and the risk of BPD without increasing the risk of necrotizing enterocolitis or the combined risk of death and cerebral palsy.[1] The mechanism of action of postnatal corticosteroids is thought to be related to their potent anti-inflammatory properties because they inhibit proinflammatory cytokines, decrease lung neutrophil recruitment, and improve pulmonary edema,[2] possibly via a diuretic effect causing fluid offload from the lungs.[3]

Although some studies have described a temporal effect of corticosteroids on the respiratory function of preterm infants,[3,4] these studies were conducted more than 20 years ago, in more mature infants, and in an era when the use of antenatal corticosteroids and postnatal surfactants was not mainstream clinical practice. In the current era of the "new BPD,"[5] the timeline of respiratory function changes following administration of systemic corticosteroids is important, because it could indicate the optimal timing for extubation. It is also not known if, and if so, how quickly any beneficial effect on respiratory function is lost following the completion of a course of corticosteroids.

Numerous trials have proven the clinical utility of postnatal corticosteroids,[1,6,7] and recently published guidelines have reiterated their role in the

BPD	Bronchopulmonary dysplasia	PVL	Periventricular leukomalacia
F_iO_2	Fraction of inspired oxygen	SFR	Transcutaneous oxygen saturation–to–fraction of inspired oxygen ratio
GA	Gestational age		
IVH	Intraventricular hemorrhage		
MAP	Mean airway pressure	SpO_2	Transcutaneous oxygen saturation
$PaCO_2$	Arterial carbon dioxide pressure	V_A/Q	Ventilation perfusion ratio
PDA	Patent ductus arteriosus	VEI	Ventilation efficiency index
PMA	Postmenstrual age	V_T	Tidal volume

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prevention and treatment of BPD,[8] but their effect on oxygenation and ventilation efficiency has not been described in the current era. We report a novel, noninvasive method for calculating the ventilation- perfusion ratio (V_A/Q) and right-to-left shunt in extremely preterm-born infants diagnosed with BPD[9] or pulmonary interstitial emphysema,[10] as well as in healthy term infants.[11]

The primary aim of the present study was to describe the timeline of changes in respiratory function and composite gas exchange indices, such as the V_A/Q and right-to-left shunt, before, during, and after administration of systemic corticosteroids in extremely preterm-born infants. In addition, we wished to determine whether any demographic factors determined the magnitude of these infants' response to systemic corticosteroids.

Methods

We performed a retrospective review of the electronic and written medical and nursing notes of all infants who received a course of postnatal corticosteroids between January 1, 2009, and December 31, 2018, at King's College Hospital NHS Foundation Trust, London. Infants born at <30 weeks of gestational age (GA) who received systemic postnatal corticosteroids for the prevention or treatment of BPD were identified via the BadgerNet Neonatal Electronic Patient Record (Clevermed, Edinburgh, United Kingdom). Infants with congenital anomalies, such as congenital diaphragmatic hernia or congenital pulmonary airway malformations, were excluded from the study. The study was registered with the Clinical Governance Department of King's College Hospital NHS Foundation Trust. The Health Research Authority Toolkit of the UK National Health System confirmed that the study was not considered research and thus did not need regulatory approval by a Research Ethics Committee.

All infants were ventilated on pressure-limited time cycled or volume-targeted ventilation with an SLE6000 neonatal ventilator or SLE5000 infant ventilator (SLE, South Croydon, United Kingdom). Patient-triggered ventilation was the standard mode of ventilation. The targeted tidal volume (V_T) for infants with evolving BPD was 6-7 mL/kg.[12] All ventilated infants with respiratory distress received surfactant at birth,[13-15] and all infants <34 weeks postmenstrual age (PMA) received caffeine at a maintenance dose of 5 mg/kg/day. The infants had hourly recording of ventilatory measures, fraction of inspired oxygen (F_iO_2), inspiratory tidal volume (V_T), and transcutaneous oxygen saturation (SpO_2), as well as arterial blood gas analysis every 4-6 hours. A flow sensor was placed between the endotracheal tube and ventilator circuit, and V_T was measured by integration of the flow signal.

Systemic corticosteroids were administered to facilitate weaning from mechanical ventilation after the first week after birth in infants with evolving BPD and no evidence of ongoing infection.[1] Evolving BPD was defined as the requirement for mechanical ventilation at 1 week of age, given our previous demonstration that the use of invasive ventilation at this time point is 99% sensitive in predicting the development of BPD in infants born at GA <32 weeks.[16] Potential candidates for systemic corticosteroids included infants who remained ventilator-dependent with an F_iO_2 requirement >0.60 and a mean airway pressure (MAP) >10 cmH_2O.[17] Intravenous dexamethasone was given over a 9-day course in 3 steps: 0.25 mg/kg twice daily for 3 days, 0.15 mg/kg twice daily for 3 days, and 0.05 mg/kg twice daily for 3 days, for cumulative dose of 2.7 mg/kg.[17] Infants with a hemodynamically significant patent ductus arteriosus (PDA) were treated medically or surgically before the administration of postnatal corticosteroids in accordance with local protocol. Extubation was considered in infants with an F_iO_2 <0.5, pH >7.25, MAP <10 cmH_2O, and a respiratory rate above the set ventilator rate.[18]

The following variables were collected from the medical notes: full course of antenatal corticosteroids (at least 2 doses; yes/no), sex, GA (weeks), birth weight (kilograms), birth weight *z*-score,[19] postnatal age (days) and PMA (weeks), postnatal age at initiation of corticosteroid treatment, total duration of corticosteroid treatment (days), days from the start of treatment to extubation, reintubation within 72 hours after extubation (yes/no), cumulative dose of dexamethasone (mg/kg), total days ventilated, BPD at 36 weeks corrected GA (yes/no),[20] intraventricular hemorrhage (IVH) grade 3 or 4 or periventricular leukomalacia (PVL) (yes/no), survival to discharge from neonatal care (yes/no), discharge on home oxygen (yes/no), and PMA at discharge (weeks).

Nine time points were selected to describe the timeline of respiratory function and ventilation changes: immediately before initiation of the corticosteroid course (pre-steroids) and 12 hours, 24 hours, 48 hours, 72 hours, 7 days, 9 days (completion of the course), 14 days, and 21 days after initiation of the course. For these time endpoints, data on F_iO_2, peak inflation pressure, arterial CO_2 pressure ($PaCO_2$), ventilatory rate, positive end-expiratory pressure, inflation time, and SpO_2 were collected. The average values of 3 recordings around each time point (1 hour earlier, exact time, and 1 hour later) were used in our analyses.

The response to corticosteroids was calculated as the difference between the F_iO_2 before the start of corticosteroid treatment and the lowest F_iO_2 achieved during the 9-day course of treatment. The noninvasive pulse oximetry–based SpO_2-to-F_iO_2 ratio (SFR) was calculated to characterize oxygen diffusion,[21] because it has been shown to better describe oxygen diffusion in preterm infants compared with F_iO_2 alone and is a reliable surrogate for the arterial oxygen–to–inspired oxygen concentration ratio in a variety of clinical settings.[22,23] To calculate the SFR, both SpO_2 and F_iO_2 are expressed as percentages, meaning that the highest possible value for the index in an infant with an SpO_2 of 100% in 21% oxygen would be 4.76.

The ventilation efficiency index (VEI) was used to describe the efficiency of ventilation. It is calculated as $VEI = 3800/(\Delta P \times RR \times PaCO_2)$, where 3800 is a constant for the production of CO_2 (mL mmHg kg^{-1} min^{-1}) and ΔP is the

difference between peak inflation pressure and positive end-expiratory pressure (in mmHg).[24,25] The VEI was calculated only for mechanically ventilated infants.

Using 2 paired values of SpO_2 and F_iO_2, a oxyhemoglobin dissociation curve was constructed for each infant and compared with an ideal reference neonatal oxyhemoglobin dissociation curve. Using the paired values of F_iO_2 and SpO_2, the ventilation perfusion ratio (V_A/Q), the right shift of the oxyhaemoglobin dissociation curve, and the percentage of right-to-left shunt were calculated for 3 time points: before the start of corticosteroid treatment, at 72 hours after the start of treatment, and at the completion of treatment (9 days).[9] V_A/Q, shift, and right-to-left shunting were derived using software based on the Lockwood algorithm, which derives results for each dataset from a 2-compartment model: shunt, shift, and V_A/Q for a single homogeneous ventilated compartment.[26] The hemoglobin level at the time of assessment was used in the calculations.

Statistical Analyses

The data were tested for normality using the Kolmogorov–Smirnoff test and found to be nonnormally distributed, and thus are presented as median and IQR. To exclude bias due to missing data, the GA, birth weight, and survival to discharge of the included infants were compared with those of nonincluded infants using the nonparametric Mann–Whitney *U* test and the Pearson χ^2 test, respectively. The V_A/Q, right shift of the oxyhemoglobin dissociation curve, and right-to-left shunt were compared at the 3 selected time points using Kruskal–Wallis 1-way ANOVA and the Mann–Whitney *U* test as a post hoc test to detect differences between groups. The relationships between the response to corticosteroids and continuous variables, such as GA age, birth weight *z*-score, age, body weight, and MAP at corticosteroid administration, were examined using Spearman ρ correlation analysis, and the differences in the response to corticosteroids in binary conditions, such as sex, full course of antenatal corticosteroids, presence of PDA, and presence of grade 3-4 IVH or PVL, were examined using the nonparametric Mann–Whitney *U* test. Statistical analyses were performed using SPSS for Windows, version 24.0 (IBM, Armonk, New York).

Results

During the study period, 488 infants were born at GA <30 weeks and admitted to the neonatal unit at King's College Hospital, with a median GA of 26 weeks (IQR, 25-28 weeks) and median birth weight of 0.88 kg (IQR, 0.69-1.03 kg). Eighty-one of these infants (17%) received a course of postnatal systemic corticosteroids. Complete medical and nursing notes were available for 70 of the infants (Table I), who composed our study cohort. The median GA was 25.0 weeks (IQR, 24.3-26.0 weeks) and median birth weight was 0.70 kg (IQR, 0.63-0.82 kg) in the included infants, compared with 26.0 weeks (IQR, 23.5-26.0 weeks) and 0.71 kg (IQR, 0.56-0.80 kg) in the nonincluded infants (P = .928 and .603, respectively). Sixty of the 70 included infants and 10 of the 11 nonincluded infants survived to discharge from the neonatal unit (P = .640).

Table I. Characteristics of the study infants (N = 70)

Characteristics	Value
Antenatal	
Full course of antenatal steroids, median (IQR)	43 (61)
GA, wk, median (IQR)	25.0 (24.3-26.0)
Birth weight, kg, median (IQR)	0.70 (0.63-0.82)
Birth weight *z*-score, median (IQR)	−0.77 (−1.44 to −0.21)
Male sex, n (%)	38 (54)
At corticosteroid initiation	
Age, d, median (IQR)	39 (29-48)
PMA, wk, median (IQR)	30.5 (29.3-32.9)
FiO_2, median (IQR)	0.69 (0.57-0.81)
MAP, cmH_2O, median (IQR)	12 (10-13)
Respiratory rate, per min, median (IQR)	45 (40-52)
PEEP, cmH_2O, median (IQR)	5 (5-6)
Inspiratory time, s, median (IQR)	0.40 (0.36-0.42)
Duration of corticosteroid treatment, d, median (IQR)	9 (7-10)
PDA, n (%)	5 (7)
Outcomes of corticosteroid treatment	
Days from starting steroids to extubation, median (IQR)	3 (2-4)
Cumulative dose, mg/kg, median (IQR)	2.66 (2.41-2.71)
Reintubated within 72 h, n (%)	14 (20)
Total days of mechanical ventilation, median (IQR)	48 (39-65)
BPD at 36 weeks PMA, n (%)	64 (91)
Home oxygen, n (%)	49 (70)
General outcomes	
Survival to discharge, n (%)	60 (86)
IVH grade III or IV or PVL, n (%)	19 (27)
PMA at discharge, wk, median (IQR)	44 (41-49)

PEEP, positive end-expiratory pressure.

The ventilatory and respiratory function measures at the selected time points are presented in Table II. Thirty-two infants received 1 dose of surfactant, 29 infants received 2 doses, and 9 infants received 3 doses. The median F_iO_2 decreased from 0.69 (IQR, 0.57-0.81) before corticosteroid treatment to a minimum of 0.41 (IQR, 0.35-0.53) at 9 days after the start of corticosteroid treatment (Table II). The median SFR increased from 1.42 (IQR, 1.19-1.72) before treatment to a maximum of 2.35 (IQR 1.87-2.83) at 9 days after the start of treatment (Figure 1, A). The median VEI increased from 0.06 (IQR, 0.04-0.08) before treatment to a maximum of 0.10 (IQR, 0.07-0.13) at 48 hours after the start of treatment (Figure 1, B). The median V_A/Q increased from 0.14 (IQR, 0.11-0.18) before treatment to 0.22 (IQR, 0.15-0.29) at 72 hours after the start of treatment (P < .001; Figure 2). The median degree of right-to-left shunt decreased from 10% (IQR, 7%-14%) before treatment to 7% (IQR, 4%-12%) at 72 hours after the start of treatment (P = .033). The median response to steroids (ie, decrease in F_iO_2) was 0.28 (IQR, 0.20-0.37).

The infants' response to corticosteroids was positively related to GA (ρ = 0.283; P = .019) but not to birth weight *z*-score (ρ = 0.066; P = .595), age at the start of steroid

Table II. Comparison of ventilatory measures before, during, and after the course of corticosteroids

Measures	Pre-steroids	12 hours	24 hours	48 hours	72 hours	7 days	9 days	14 days	21 days
Ventilated infants, n	70	68	64	53	35	25	25	23	19
F_IO_2, median (IQR)	0.69 (0.57-0.81)	0.62 (0.49-0.76)	0.57 (0.44-0.75)	0.50 (0.40-0.63)	0.48 (0.37-0.60)	0.42 (0.33-0.51)	0.41 (0.35-0.53)	0.53 (0.45-0.65)	0.50 (0.40-0.66)
PIP, cmH_2O, median (IQR)	24 (21-26)	24 (21-27)	23 (19-26)	21 (17-25)	20 (18-26)	21 (19-25)	20 (18-24)	22 (20-25)	23 (20-25)
$PaCO_2$, mmHg, median (IQR)	753 (49 - 63)	647 (41 - 54)	541 (37 - 50)	43 (39 - 48)	44 (39 - 52)	51 (48 - 58)	50 (46 - 61)	55 (50 - 59)	56 (49 - 61)

PIP, peak inflation pressure.

treatment ($\rho = -0.079$; $P = .523$), body weight at the start of steroid treatment ($\rho = 0.173$; $P = .159$), or MAP at the start of steroid treatment ($\rho = -0.022$; $P = .860$). The response to steroids was not significantly different in male infants compared with female infants ($P = .534$), in infants who received a full course of antenatal steroids compared with those who did not receive antenatal steroids or received an incomplete course ($P = .897$), in infants with a PDA at the start of steroid treatment compared with infants with no PDA ($P = .794$), or in infants with grade 3-4 IVH or PVL compared with those without IVH grade 3-4 or PVL ($P = .800$). In addition, the response to steroids was not significantly different between infants who were successfully extubated and those who were reintubated within 72 hours of extubation ($P = .184$) or between infants who received 1 dose of surfactant and those who received more than 1 dose ($P = .121$).

Discussion

After starting a course of postnatal corticosteroids, preterm infants exhibited a gradual improvement in oxygen diffusion that lasted for the 9-day duration of the course. This improvement was characterized by an increase in the ventilation/perfusion ratio and a decrease in intrapulmonary right-to-left shunting. The only determinant of the response to treatment was GA, with more mature infants having a greater decrease in oxygen requirement.

Some previous studies have described the chronology of events following administration of postnatal corticosteroids in preterm-born infants. Greenough et al reported that administration of dexamethasone was associated with improvements in diuresis and respiratory system compliance after 36 hours of treatment.[3] Kovacs et al studied the effect of inhaled corticosteroids after 3 days of systemic corticosteroids on pulmonary function and reported an increase in compliance at 10 days but a loss of effect by 17 days after the initiation of treatment.[4] Those studies were conducted in more mature infants in an era when synchronized ventilation and volume-targeted ventilation did not constitute standard clinical care and thus describe a different population of infants.

In the present study, we found median V_A/Q values in the range of 0.14-0.24. These are severely abnormal values compared with the mean V_A/Q of 0.84 that we previously reported in healthy term infants.[11] Because our present cohort consists of a selected subpopulation of critically ill infants, our results are not surprising and not dissimilar to V_A/Q values in infants with pulmonary interstitial emphysema[10] or BPD diagnosed at 28 days after birth.[9] Svedenkrans et al reported mean V_A/Q values in the range of 0.42 using similar prospective methodology in convalescent infants diagnosed with severe BPD at 36 weeks PMA.[27]

We did not find a significantly different response to steroids in infants who were successfully extubated compared with those who were reintubated within 72 hours. This likely reflects the fact that independent breathing is dependent not only on the diffusion capacity of the lungs, but also on the functional integrity of the respiratory muscles.[28] Our findings also suggest that postnatal corticosteroids might have little effect on respiratory drive and respiratory muscle function. In our study, according to local practice, the majority of infants did not have a PDA at the initiation of corticosteroid treatment, and thus the major component of the right-to-left shunt was intrapulmonary rather than intracardiac. Although there was a significant reduction in the percentage of shunting within 72 hours of starting steroids, this effect was not sustained at 9 days into the course of treatment. This might be explained by the initial diuretic action of steroids, which might have caused a reduction in right-to-left shunting, but following this, fluid input was optimized to promote growth, which might have reduced any ongoing effect on the intrapulmonary shunt.[3] More mature infants responded better to the course of corticosteroids, possibly as a result of more mature enzyme systems, which were therefore more receptive to treatment.[2]

Compared with the DART protocol with a cumulative dose of 0.89 mg/kg,[29] in our unit postnatal corticosteroids are administered relatively later and at a dose of 2.4 mg/kg. The later administration is explained by our policy of administering postnatal corticosteroids only after treating hemodynamically significant PDAs and might affect the generalizability of our results. Higher dexamethasone doses have been shown to reduce the relative risk of mortality or BPD with no effect on the risk of neurodevelopmental sequelae.[30] A recent meta-analysis concluded that a higher dose of dexamethasone was more effective in reducing the risk of BPD, with no significant difference in death or cerebral palsy[31]; of note, in that study, "high dose" was defined

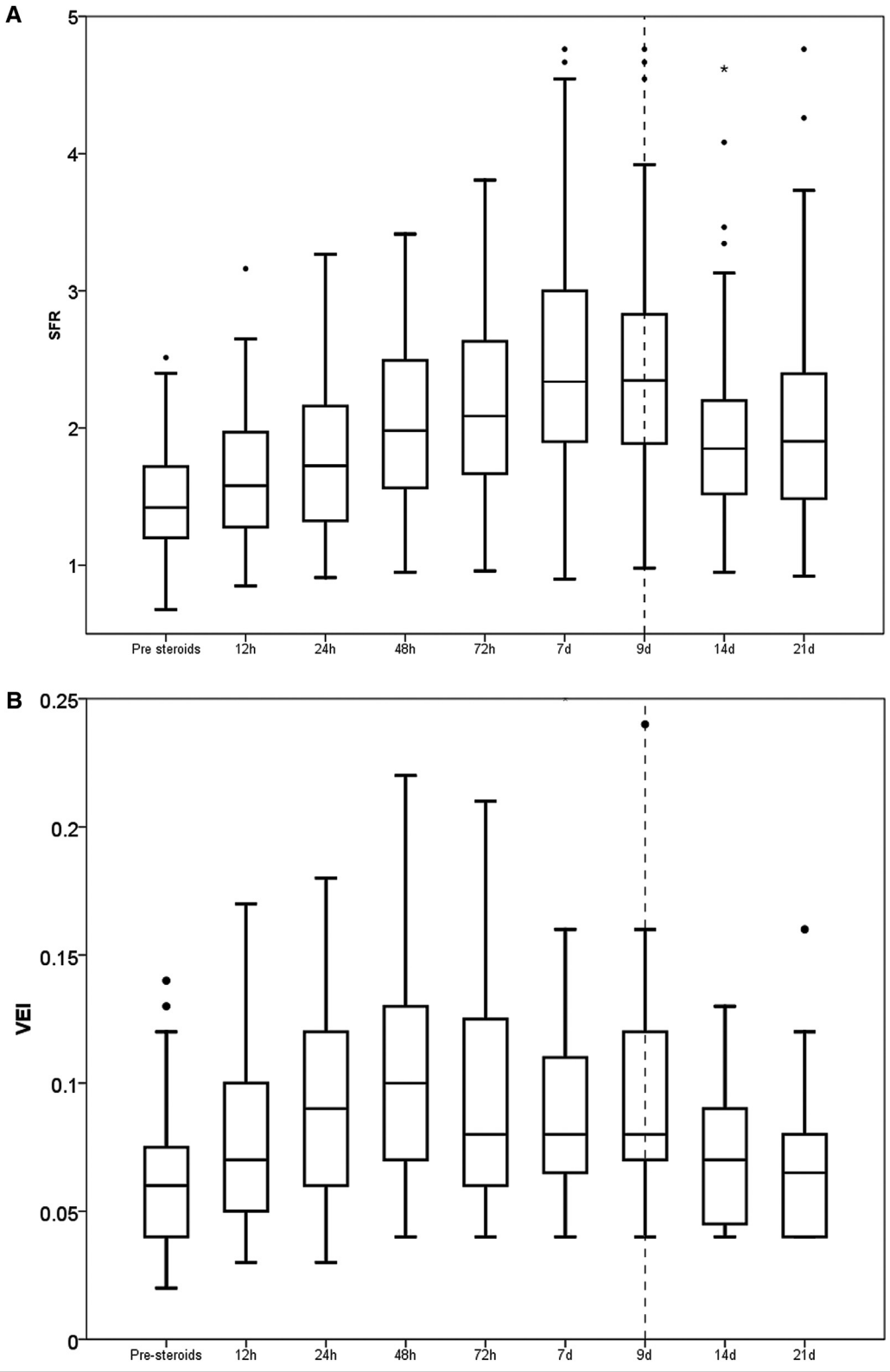

Figure 1. Changes in **A,** SFR and **B,** VEI before, during, and after the administration of corticosteroids. Boxes represent the 25th, 50th, and 75th percentiles; whiskers show the 5th and 95th percentiles; and points are outliers. The vertical dashed line indicates completion of the course of treatment.

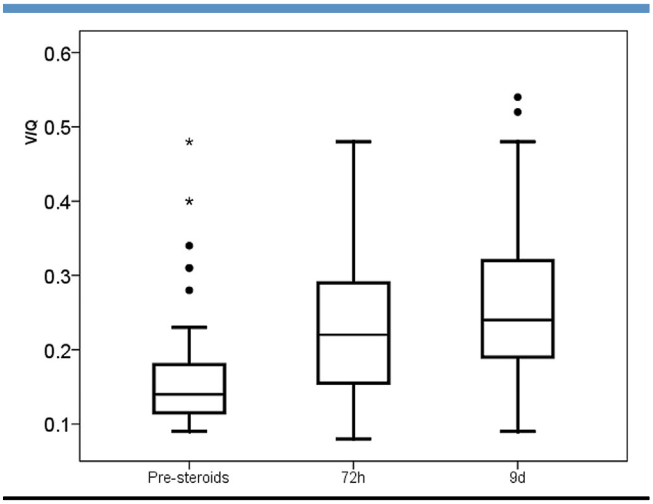

Figure 2. V_A/Q before, at 72 hours after initiation, and at completion of the course of corticosteroids. Boxes represent the 25th, 50th, and 75th percentiles; whiskers show the 5th and 95th percentiles; and points are outliers. The asterisks on SPSS graphs are extreme outliers which represent cases that have values more than three times the height of the boxes.

as a cumulative dose >3 mg/kg, which is higher than the dose that we used. However, the same meta-analysis highlighted that early (≤7 days) initiation of corticosteroids was associated with a lower risk of cerebral palsy compared with later (>7 days) regimens. Given the limitations of the currently available evidence and evidence showing both benefits and harms of treatment,[1] we reiterate that it may be prudent to reserve the use of late corticosteroid treatment for infants who cannot be weaned from mechanical ventilation, and to minimize both dose and duration.

Our study has some strengths and limitations. We described gas exchange abnormalities in a moderately sized group of preterm-born infants in the current era of the "new BPD".[5] We conducted an extensive respiratory assessment at numerous time points, rather than focusing only on F_iO_2 and ventilatory measures,[29] and we used physiological indices that described both the efficiency of ventilation and oxygen diffusion. We acknowledge the retrospective nature of our study as a limitation, but given the rarity of the treatment, a prospective study might have been logistically unfeasible. In calculating the relative position of the F_iO_2 vs SpO_2 curve in our cohort, we used 2 paired points of SpO_2 and F_iO_2 measurements, whereas some previous neonatal studies in sick infants have used 3-5 paired points.[32] Two paired samples should be sufficient, however, with the higher SpO_2 value predominantly defining the degree of shunting and the lower value defining the V_A/Q ratio. This methodology has been applied in previous studies.[10,11]

In conclusion, our evaluation of the chronology of respiratory function changes following systemic corticosteroid treatment in a contemporary cohort of mechanically ventilated preterm infants may influence decision making regarding the optimal timing for extubation and inform clinicians about the anticipated sequence of events during and following completion of the course of treatment. Improvements in respiratory function were sustained throughout the entire duration of a course of systemic corticosteroids, with significant improvements evident within 48-72 hours, suggesting that the optimal time for extubation is between 48-72 hours and 7 days after starting treatment. Administration of corticosteroids was associated with significant improvements in oxygen diffusion and V_A/Q and with decreased intrapulmonary shunting. The main determinant of the response to steroids was GA, with more mature infants exhibiting a greater decrease in oxygen requirement. ■

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