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Neonatal outcomes based on antenatal corticosteroid exposure time for infants delivered between 23 and 34 weeks gestation

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Summary

Objective: To determine the minimal time interval required after antenatal corticosteroid treatment to see improvement in neonatal outcomes. *Study design:* A retrospective cohort analysis was performed on all women who delivered an infant between 23 0/7 weeks and 33 6/7 weeks gestational age from January 1, 2009 to August 31, 2013. Maternal data collected: maternal race, parity, mode of delivery, indication for delivery, infant birth weight, antenatal corticosteroid (ACS) administration, and time from ACS until delivery. Neonatal data collected: respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), sepsis, retinopathy of prematurity (ROP), intubation, surfactant administration, length of hospitalization, and mortality. *Results:* Infants were grouped by ACS exposure time before delivery. Gestational age at delivery was similar between the groups. There was not a statistically significant difference in the rate of RDS between the groups. Infants delivered 24 to 47 hours of ACS had the lowest rates of surfactant, intubation, and IVH. There appears to be a larger impact of ACS on infants delivered at 29 to 34 weeks *vs*. 23-28 weeks gestation. *Conclusions:* Improvement in neonatal outcomes are seen after any amount of ACS exposure but are generally most significant 24 to 47 hours after administration and between 29 to 34 weeks gestation.

Key words: Antenatal corticosteroids; Preterm delivery; Neonatal outcome.

Introduction

The neonatal benefits of antenatal corticosteroid (ACS) administration to women at risk for preterm delivery are well known [1]. While benefits are seen, it is unclear exactly how long after ACS are given that fetal benefits are observed. In most trials the treatment intervals were based on work from Liggins and Howie [2] in 1972 who found optimal fetal benefit at 48 hours to seven days after ACS exposure. Many of these studies are outdated and there have been many advances in neonatal medicine since that time, such as surfactant.

Women at risk for preterm delivery are not always stable enough to receive 48 hours of ACS prior to delivery. No recent studies exist which examine outcomes for infants unable to receive a full course (≥ 48 hours to seven days) of ACS prior to delivery. With advances in both obstetrical and neonatal medicine, the present authors sought to determine a current minimal interval required from ACS administration to delivery to see an improvement in neonatal outcomes. Their primary hypothesis was that neonatal outcomes are improved prior to 48 hours after ACS administration.

Materials and Methods

This was a retrospective cohort study of all infants that delivered between 23 0/7 weeks and 33 6/7 weeks gestational age between January 1, 2009 and August 31, 2013 at a tertiary level hospital, Hartford Hospital. The policy at the present facility is to

Table 1. — *Demographic and delivery characteristics.*

	Interval from steroid therapy to delivery					
Variable	Group A: None (n=58)	Group B: 1-23 hours (n=116)	Group C: 24-47 hours (n=26)	Group D: 2-7 days (n=190)	Group E: >7 days (n=158)	*p* value
Birth weight (grams)	1599 ± 569	1529 ± 512	1558 ± 599	1408 ± 542	1607 ± 542	0.0091*
Interval, first dose to delivery (days)	N/A	N/A	1.4 ± 0.3	4.0 ± 1.5	17.5 ± 11.8	0.0001*
Gestational age (first dose – weeks)	N/A	30.1 ± 3.1	30.0 ± 3.2	29.3 ± 3.1	28.0 ± 2.9	0.0001*
Gestational age (delivery – weeks)	30.2 ± 3.1	30.2 ± 3.1	30.3 ± 3.2	29.9 ± 3.1	30.5 ± 2.8	0.4903

**p* values considered statistically significant.

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Table 2. — *Neonatal outcomes.*

Outcome	Interval from steroid therapy to delivery					*p* value
	Group A: None (n=58)	Group B: 1-23 hours (n=116)	Group C: 24-47 hours (n=26)	Group D: 2-7 days (n=190)	Group E: >7 days (n=158)	
Composite neonatal outcome (n)	42 (72%)	71 (61%)	11 (42%)	116 (61%)	89 (56%)	0.0860
RDS (n)	39 (67%)	64 (55%)	10 (38%)	106 (56%)	79 (50%)	0.0945
Surfactant (n)	31 (53%)	47 (41%)	6 (23%)	81 (43%)	49 (31%)	0.0101*
Intubation (n)	36 (62%)	54 (47%)	8 (31%)	93 (49%)	61 (39%)	0.0134*
IVH (n)	7 (12%)	13 (11%)	0 (0%)	13 (7%)	6 (4%)	0.0446*
NEC (n)	2 (3%)	2 (2%)	2 (8%)	11 (6%)	10 (6%)	0.2939
Sepsis (n)	1 (2%)	5 (4%)	0 (0%)	16 (8%)	8 (5%)	0.2340
ROP (n)	6 (10%)	5 (4%)	3 (12%)	21 (11%)	8 (5%)	0.0914
Neonatal death (n)	4 (7%)	6 (5%)	0 (0%)	8 (4%)	5 (3%)	0.6163

*p value < 0.05

Table 3. — *Neonatal outcomes by logistic regression.*

Outcome	Group	Odds ratio (95% CI)	*p* value
Composite neonatal outcome (n)	B	0.60 (0.30, 1.19)	0.1463
	C	0.28 (0.11, 0.74)	0.0098*
	D	0.60 (0.31, 1.14)	0.1177
	E	0.49 (0.26, 0.95)	0.0339*
RDS (n)	B	0.60 (0.31, 1.16)	0.1284
	C	0.31 (0.12, 0.80)	0.0154*
	D	0.62 (0.33, 1.14)	0.1233
	E	0.49 (0.26, 0.92)	0.0255*
Surfactant (n)	B	0.59 (0.31, 1.12)	0.1072
	C	0.26 (0.09, 0.75)	0.0121*
	D	0.65 (0.36, 1.17)	0.1488
	E	0.39 (0.21, 0.73)	0.0029*
Intubation (n)	B	0.53 (0.28, 1.01)	0.0549
	C	0.27 (0.10, 0.73)	0.0097*
	D	0.59 (0.32, 1.07)	0.0817
	E	0.38 (0.21, 0.71)	0.0025*
IVH (n)	B	0.92 (0.35, 2.45)	0.8666
	C	N/A	N/A
	D	0.54 (0.20, 1.41)	0.2065
	E	0.29 (0.09, 0.90)	0.0315*
NEC (n)	B	0.49 (0.07, 3.58)	0.4830
	C	2.33 (0.31, 17.55)	0.4104
	D	1.72 (0.37, 8.00)	0.4887
	E	1.89 (0.40, 8.91)	0.4198
Sepsis (n)	B	2.57 (0.29, 22.50)	0.3945
	C	N/A	N/A
	D	5.24 (0.68, 40.40)	0.1119
	E	3.04 (0.37, 24.85)	0.2997
ROP (n)	B	0.39 (0.11, 1.34)	0.1345
	C	1.13 (0.26, 4.92)	0.8702
	D	1.08 (0.41, 2.81)	0.8796
	E	0.46 (0.15, 1.40)	0.1709
Neonatal death (n)	B	0.74 (0.20, 2.72)	0.6461
	C	N/A	N/A
	D	0.59 (0.17, 2.05)	0.4087
	E	0.44 (0.11, 1.70)	0.2351

Odds ratio compared to reference group A (no ACS).

administer two doses of 12 mg of betamethasone intramuscularly 24 hours apart for women at risk of preterm delivery prior to 34 weeks gestation. Gestational age was recorded as completed weeks. Infants with known fetal anomalies and intrauterine fetal demise were excluded. Institutional review board approval was obtained from Hartford Hospital. A cooperative institutional review board agreement with Connecticut Children's Medical Center was also obtained.

Maternal and delivery data collected included maternal race, parity, mode of delivery, indication for delivery, infant birth weight, ACS administration (yes/no), and time from administration of ACS until delivery. The time from ACS until delivery was determined from both the electronic medication administration record and progress note documentation. The time was rounded down to the closest hour. The neonatal data collected included respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), administration of surfactant, intubation, culture proven sepsis, retinopathy of prematurity (ROP), length of NICU stay, and death. In addition, individual neonatal outcomes were combined to evaluate a composite neonatal outcome. Chi-square, Fisher Exact, and logistic regression analysis were performed when appropriate. *P* values < 0.05 were considered statistically significant.

Results

There were 612 infants that delivered during the study period. There were 53 infants with known anomalies or intrauterine demise. There were an additional 11 infants (five singletons and six twins) that were excluded due to unclear timing of their ACS administration. The remaining 548 infants were included in the analysis. The reason for preterm delivery was classified as preterm labor, premature preterm rupture of membranes (PPROM), or indicated. Infants were then grouped by ACS exposure.

The policy at the present facility is to administer two doses of 12 mg of betamethasone intramuscularly 24 hours apart for women at risk of preterm delivery between $23^{0/7}$ and $34^{0/7}$gestation. Group A did not receive any ACS. Infants that did receive ACS were grouped by ACS to delivery interval as follows: group B, one to 23 hours after ACS administration; group C, 24 to 47 hours; group D, 48 hours to seven days; group E, eight or more days.

Table 4. — *Neonatal outcomes, gestational age 23-28 weeks.*

	Interval from steroid therapy to delivery					
Outcome	Group A: None (n=15)	Group B: 1-23 hours (n=28)	Group C: 24-47 hours (n=6)	Group D: 2-7 days (n=57)	Group E: >7 days (n=34)	*p* value
Composite neonatal outcome (n)	15 (100%)	28 (100%)	6 (100%)	56 (98%)	34 (100%)	1.0000
RDS (n)	15 (100%)	28 (100%)	6 (100%)	54 (95%)	32 (94%)	0.7692
Surfactant (n)	14 (93%)	28 (100%)	6 (100%)	50 (88%)	28 (82%)	0.1477
Intubation (n)	14 (93%)	28 (100%)	6 (100%)	53 (93%)	31 (91%)	0.5670
IVH (n)	6 (40%)	8 (29%)	0 (0%)	13 (23%)	6 (18%)	0.3017
NEC (n)	2 (13%)	1 (4%)	2 (33%)	8 (14%)	5 (15%)	0.2568
Sepsis (n)	0 (0%)	3 (11%)	0 (0%)	10 (18%)	7 (21%)	0.3044
ROP (n)	6 (40%)	4 (14%)	3 (50%)	18 (32%)	8 (24%)	0.1830
Neonatal death (n)	4 (27%)	5 (18%)	0 (0%)	6 (11%)	4 (12%)	0.6163

Table 5. — *Neonatal outcomes, gestational age 29-34 weeks.*

	Interval from steroid therapy to delivery					
Outcome	Group A: None (n=43)	Group B: 1-23 hours (n=88)	Group C: 24-47 hours (n=20)	Group D: 2-7 days (n=133)	Group E: >7 days (n=124)	*p* value
Composite neonatal outcome (n)	27 (63%)	43 (49%)	5 (25%)	60 (45%)	55 (44%)	0.0662
RDS (n)	24 (56%)	36 (41%)	4 (20%)	52 (39%)	47 (38%)	0.0902
Surfactant (n)	17 (40%)	19 (22%)	0 (0%)	31 (23%)	21 (17%)	0.0027*
Intubation (n)	22 (51%)	26 (30%)	2 (10%)	40 (30%)	30 (24%)	0.0057
IVH (n)	1 (2%)	5 (6%)	0 (0%)	0 (0%)	0 (0%)	0.0047*
NEC (n)	0 (0%)	1 (1%)	0 (0%)	3 (2%)	5 (4%)	0.6607
Sepsis (n)	1 (2%)	2 (2%)	0 (0%)	6 (5%)	1 (1%)	0.4146
ROP (n)	0 (0%)	1 (1%)	0 (0%)	3 (2%)	0 (0%)	0.5107
Neonatal death (n)	0 (0%)	1 (1%)	0 (0%)	2 (2%)	1 (1%)	1.0000

*p value < 0.05

Group A consisted of 58 infants (10.6%), group B of 116 infants (21.2%), group C of 26 infants (4.7%), group D of 190 infants (34.6%), and group E of 158 infants (28.8%). There were 27 patients that received an additional "rescue" course of betamethasone. They were classified according to the most recent time after ACS administration, with all but two patients receiving a complete (48 or more hours) of rescue steroids.

The average gestational age at time of first ACS was significantly different, but the gestational age at delivery was not (Table 1). Infant birth weight was significantly lower in group D (Table 1). Infants delivered as a result of preterm labor were more likely to receive between one and 23 hours ACS (85% of patients in group B were delivered due to preterm labor, *vs*. 12% to 41% in the other groups, $p = 0.001$) Infants whose delivery was indicated were more likely to receive between 24 hours and seven days of ACS (42.3% in group C and 40.5% in group D *vs*. 20.7% to 32.8% in the other groups, $p = 0.0063$). Indicated deliveries were predominately due to severe preeclampsia/HELLP syndrome or suspected intrauterine growth restriction.

There was no statistically significant difference in the rate of RDS between the groups. The highest rate of RDS was in infants not exposed to ACS (group A) and the lowest rate was in infants delivered 24 to 47 hours after ACS (group C). Group C had the lowest rates of surfactant, intubation, or IVH (Table 2). When neonatal outcomes were evaluated using logistic regression using group A for comparison, group C had the lowest odds ratio for neonatal outcome, RDS, surfactant use, and intubation (Table 3).

Infants were also separated into groups based on gestational age (23 to 28 weeks and 29 to 34 weeks) to determine the impact of early *vs*. late preterm delivery on ACS benefits. For infants delivered at 23 to 28 weeks, there were no differences in neonatal outcome. Table 4 shows that RDS, surfactant, and intubation were very common among all infants in this age group. For infants delivered at 29-34 weeks, there were lower rates of surfactant and intubation in group C and lower rates of IVH in infants that received 24 hours or more of ACS (groups C, D, and E), see Table 5. While not significant, the rate of RDS was lowest in group C and highest in group A. The rate of RDS was similar for groups B, D, and E. When neonatal outcomes for infants 29 to 34 weeks were evaluated using logistic regression, group C again had the lowest odds ratio for neonatal outcome, RDS, and intubation (Table 6). The rate of IVH, NEC, sepsis, ROP, and neonatal death was very low or zero in all groups in the 29-34 week subset, therefore statistical analysis was limited.

Table 6. — *Neonatal outcomes by logistic regression (gestational age 29-34 weeks).*

Outcome	Group	Odds ratio (95% CI)	*p* value
Composite neonatal outcome (n)	B	0.57 (0.27, 1.19)	0.1353
	C	0.20 (0.06, 0.65)	0.0074*
	D	0.49 (0.24, 0.99)	0.0459*
	E	0.47 (0.23, 0.96)	0.0391*
RDS (n)	B	0.55 (0.26, 1.15)	0.1097
	C	0.20 (0.06, 0.69)	0.0111*
	D	0.51 (0.25, 1.02)	0.0564
	E	0.48 (0.24, 0.98)	0.0425*
Surfactant (n)	B	0.42 (0.19, 0.93)	0.0329*
	C	N/A	N/A
	D	0.47 (0.22, 0.97)	0.0401
	E	0.31 (0.14, 0.67)	0.0030*
Intubation (n)	B	0.40 (0.19, 0.85)	0.0172*
	C	0.11 (0.02, 0.51)	0.0053*
	D	0.41 (0.20, 0.83)	0.0131*
	E	0.31 (0.15, 0.63)	0.0013*
IVH (n)	B	2.53 (0.29, 22.36)	0.4037
	C	N/A	N/A
	D	N/A	N/A
	E	N/A	N/A
NEC (n)	B	N/A	N/A
	C	N/A	N/A
	D	N/A	N/A
	E	N/A	N/A
Sepsis (n)	B	0.98 (0.09, 11.08)	0.9848
	C	N/A	N/A
	D	1.98 (0.23, 16.96)	0.5313
	E	0.34 (0.02, 5.58)	0.4510
ROP (n)	B	N/A	N/A
	C	N/A	N/A
	D	N/A	N/A
	E	N/A	N/A
Neonatal death (n)	B	N/A	N/A
	C	N/A	N/A
	D	N/A	N/A
	E	N/A	N/A

Odds ratio compared to reference group A (no ACS).

Discussion

While there have been multiple studies showing the benefit of antenatal corticosteroids for infants that are delivered preterm [2-4], the details regarding optimal dosing, interval, and length of drug effect are not clear. Multiple other studies have found no difference in ACS benefit based on time from drug exposure to delivery [5-8]. In addition, other studies also found incomplete ACS doses to be beneficial [9-12].

The present study showed that infants delivered 24 to 47 hours after ACS exposure had lower rates of surfactant, intubation, and IVH *vs*. no ACS, one to 23 hours or 48 or greater of ACS exposure. All infants exposed to ACS, regardless of time interval, showed non-significant improvement in overall outcome, RDS, surfactant, and intubation rates. Infants exposed to 24 hours or greater of ACS had lower rates of IVH. Similar improvement in outcome (lower surfactant, intubation, and IVH) 24 to 47 hours after ACS was seen in infants delivered between 29 to 34 weeks but there was no difference in outcome seen based on ACS exposure for infants delivered between 23 to 28 weeks.

Infant birth weight is known to contribute to neonatal outcomes. The lower birth weight in group D may have contributed to higher rates of neonatal complications than would have otherwise been observed in a similar birth weight group. The lower birth weight in this group may be explained by the increased number of infants in this group that had an indicated preterm delivery, which was almost exclusively due to suspected intrauterine growth restriction or severe pre-eclampsia/HELLP syndrome, known risks for poor intrauterine fetal growth.

A limitation to the present study is the small number of infants delivered 24 to 47 hours after ACS administration. Another limitation is that there are differences in the indication for delivery between the groups. For example, infants in group B were more likely to have been delivered preterm due to preterm labor versus pre-eclampsia or intrauterine growth restriction. These limitations may bias the present results.

The present results support the authors' hypothesis that neonatal outcomes are improved in less than 48 hours after antenatal corticosteroid administration compared to no ACS. The optimal way to improve neonatal outcome would be to delay delivery. That is not also a feasible option. The present data support counseling patients that any amount of ACS may improve neonatal outcomes. With similar, in some instances improved, neonatal comes after 24 hours of ACS *vs*. 48 or more hours of ACS the present data supports that indicated deliveries may be performed sooner than 48 hours after ACS administration without increasing adverse neonatal outcomes.

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