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Original Research

Shorter Intervals of Antenatal Corticosteroid Administration Can Influence Short- and Long-Term Outcomes in Premature Infants

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Abstract

Background: Studies examining shorter intervals between antenatal corticosteroid administration (ACS) and delivery are limited. This study analyzed effects of the timing of ACS on short-term and long-term outcomes in premature infants. **Methods**: This retrospective cohort study analyzed 534 deliveries between $22^{0/7}$ and $29^{6/7}$ gestational weeks, from January 2008 through December 2015, at the Department of Obstetrics and Gynecology of the University Hospital in Ulm, Germany. The initiation of antenatal corticosteroids to delivery was categorized using cutoffs of $>/\leq$24 hours. The study reported on gestational age, birthweight, the time interval between the first ACS and delivery, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score, umbilical pH, delivery mode, incidences of retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), the use of surfactant, as well as the neurodevelopment after 2 years (mental development index (MDI) and psychomotor development index (PDI)), and mortality. **Results**: Gestational ages were significantly advanced in the >24 hours group ($p < 0.001$). The incidences of BPD and IVH were significantly higher in neonates with less than 24 hours to delivery (BPD: 51.0% *vs.* 41.2%, $p = 0.045$; IVH: 10.5% *vs.* 3.0%, $p = 0.001$). There were no significant differences in ROP ($p = 0.083$), NEC ($p = 0.856$), or neurodevelopment after 2 years (MDI: $p = 0.465$, PDI: $p = 0.116$). **Conclusions**: Complications such as NEC and ROP, along with long-term neurological outcomes, do not seem to be influenced by shorter ACS intervals. In contrast, BPD, IVH, and surfactant administration appear to occur more frequently with ACS <24 hours.

Keywords: antenatal corticosteroid administration; premature infants; respiratory distress syndrome; bronchopulmonary dysplasia; intraventricular hemorrhage

1. Introduction

Despite numerous advances in modern medicine, the medical community has been unable to substantially impact the number of worldwide preterm deliveries or mitigate the resulting morbidity, mortality, and long-term complications. In 2012, Liu *et al.* [1] estimated that approximately 1.1 million neonates die annually as a result of complications associated with preterm delivery. In 2018, an estimated 35% of neonatal deaths were attributed to complications of preterm delivery [2]. In high-income countries, the mortality rate for newborns born under 32 weeks is estimated to be 10–15%, with approximately 5–10% suffering from cerebral palsy [3].

As the rate of preterm deliveries continues to rise, the need for proven preventative interventions becomes increasingly essential in reducing of morbidity and mortality. Liggins and Howie [4] were responsible for the revolutionary introduction of corticosteroids as a preventive measure in the incidence of respiratory distress syndrome (RDS) among preterm infants in 1972. Since its introduction, the application has been researched multiple times in an effort to optimizing its use during childbirth. The 2006 Cochrane review of 21 studies including 3885 women and 4269 infants confirmed the efficacy in reduction of intraventricular hemorrhage (IVH), RDS, neonatal mortality, necrotizing enterocolitis (NEC), and need for respiratory support without an increased risk of chorioamnionitis, maternal death, or puerperal sepsis [5]. The updated 2017 Cochrane review (30 studies, 7774 women, 8158 infants) and the subsequent Cochrane review in 2020 (27 Studies, 11,272 women, 11,925 infants) both reconfirmed the risk reductions [6,7].

The antenatal corticosteroid administration (ACS) has been integrated into standards for preterm delivery worldwide. The maximal benefit of corticosteroids can be ob-

served 24 hours after antenatal administration and are considered most effective when delivery occurs within seven days of administration [8,9]. It is widely accepted and reported that there is a significant reduction in neonatal brain injury after 48 hours [10]. Additional benefits include the reduction of infant mortality, RDS, IVH, and NEC [11–13].

There are limited studies examining narrower intervals between ACS and delivery. The Effective Perinatal Intensive Care in Europe (EPICE) Cohort reported an immediate and rapid decline in mortality after ACS. They reported a 20.6% mortality rate in infants unexposed to antenatal corticosteroids and observed a risk reduction of more than 50% with an interval between 18 and 36 hours. The authors concluded that ACS may be effective even with a short interval to delivery, suggesting a simulated reduction in mortality by 26% with administration 3 hours before delivery [10].

McDougall *et al*. [14] performed a systematic review in 2023 to examine studies researching other timing intervals for ACS. Across the ten trials included in the review (involving 4592 women, 5018 infants), a total of 37 different timing intervals were reported. The authors concluded that the studies were too heterogenous and the intervals with the best outcomes were too inconsistent to make generalized recommendations [14].

The purpose of this study was to analyze the effect ACS timing on short- and long-term outcomes in premature infants delivered between $22^{0/7}$ weeks and $29^{6/7}$ weeks of gestation.

2. Methods

Institutional Review Board approval was obtained through the Ethics Commission of the University of Ulm (Record Number 445/18, Accepted March 2019). This retrospective cohort study analyzed deliveries between $22^{0/7}$ and $29^{6/7}$ gestational weeks at the Department of Obstetrics and Gynecology of the University Hospital in Ulm, Germany, from January 2008 through December 2015. A total of 534 deliveries were analyzed. The study reported gestational age, birthweight, the time interval between the first ACS and delivery, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score, umbilical pH, delivery mode, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), IVH, NEC, the use of surfactant (as a marker for the presence of RDS), neurodevelopment after 2 years (mental development index (MDI) and psychomotor development index (PDI)), and mortality. An index score <70 (Bayley-II) has been widely used as a marker of moderate and/or severe disability [15,16]. The infants in our cohort were evaluated using the Bayley Scales of Infant Development II, in accordance with internal standards for prematurely born infants, as part of the neurological follow-up provided by the social-pediatric center.

Twin and multiple deliveries were not excluded. ACS was performed using 2 doses of 12 mg betamethasone (Celestan®, SP Labo N.V., Heist-op-den-Berg, Antwerp, Belgium) intramuscular 24 hours apart. Time from initiation of ACS to delivery was categorized using cutoffs of $>/\leq 24$ hours.

Statistical Analysis

Descriptive statistics for categorical variables were presented and summarized using absolute and relative frequencies, while ordinal and metric data were described using median, interquartile range, and range. Comparisons between groups regarding categorical variables were performed using the Chi-square test or Fisher's exact test (if expected frequencies in 2×2 cross tabulations were less than 5). Statistical comparisons between groups regarding ordinal data were performed by the non-parametric Mann-Whitney U test. Statistical analyses were performed with Statistical Package for Social Sciences (SPSS, IBM® Corp. Released 2020. IBM SPSS Statistics for Windows, Version 25.0., Armonk, NY, USA). All statistical tests were two-tailed, and a p value < 0.05 was considered statistically significant. There was no adjustment of the significance level for multiple comparisons.

3. Results

Median maternal age was 31 years (range 18 to 47 years). The newborn median weight at delivery was 820 grams (range 265 to 1780 grams). 470 (88.0%) of the newborns were delivered by caesarean section, 63 (12%) of the newborns were delivered vaginally. 331 (62.0%) of the deliveries were primigravidas. There were 170 multiple pregnancies (31.8% of the study population), consisting of 68 twin deliveries, 10 triplet deliveries, and 1 quadruplet delivery. An APGAR score below 5 at 5 minutes after delivery was reported in 18 (3.4%), while at 10 minutes after delivery, 4 (0.7%) infants had an APGAR score below 5. An umbilical artery pH $\geq$7.20 was observed in 453 (92%) of the newborns, while 40 (8%) newborns had a pH $<$7.20, which is indicative of acidosis. The umbilical artery pH was unknown for 41 (7.7%) newborns.

The most common diagnoses at admission were preterm labor (defined as birth before $36^{6/7}$ gestational weeks) and/or premature rupture of membranes, followed by preeclampsia, fetal growth restriction, and pathological fetal doppler [17].

According to internal standards, 45 patients in the $>$24 hours group received an additional single dose of 12 mg betamethasone, defined as a "boost", as the initial administration (2 doses of 12 mg betamethasone 24 hours apart) was given more than 14 days before delivery. 19 patients in the $>$24 hours group received a second cycle (additional 2 doses of betamethasone 24 hours apart) because their initial cycle occurred under $24^{0/7}$ weeks.

Descriptive characteristics of the cohort are summarized in Table 1.

Table 1. Cohort demographics and neonatal outcomes.

Age	Range 18–47 years	Median 31 years
Weight at Delivery	Range 265–1780 grams	Median 820 grams
Vaginal Delivery	63/534	11.8%
Caesarean Section	470/534	88.0%
Primigravida	331/534	62.0%
Twins n = 68	136/534	25.0%
Triplets n = 10	30/534	6.0%
Quadruplets n = 1	4/534	0.7%
APGAR <5 at 5 minutes	18/510[a]	3.5%
APGAR <5 at 10 minutes	4/510[a]	0.8%
Umbilical artery (UA) pH	Range 6.84–7.55	Median 7.34
UApH ≥7.20	453/493[b]	91.9%
UApH 7.10–7.19 (mild acidosis)	32/493	6.5%
UApH 7.00–7.10 (moderate acidosis)	6/493	1.2%
UApH <7.00 (severe acidosis)	2/493	0.4%
BPD	44.0% (223/507)[c]	
Mild	29.4% (149/507)	
Moderate	9.3% (47/507)	
Severe	5.3% (27/507)	
ROP	54.1% (216/399)[d]	
Stage 1	13.0% (52/399)	
Stage 2	13.8% (55/399)	
Stage 3	27.1% (108/399)	
Stage 4	0.3% (1/399)	
IVH	16.8% (85/507)[c]	
Grade 1	3.7% (19/507)	
Grade 2	6.9% (35/507)	
Grade 3–Grade 4	6.1% (31/507)	
PDA	32.0% (162/507)[c]	
NEC	3.9% (20/507)[c]	

[a]data missing for 24 neonates; [b]data missing for 41 neonates; [c]data missing for 27 neonates; [d]data missing for 135 neonates.

APGAR, Appearance, Pulse, Grimace, Activity, and Respiration; UA, Umbilical artery; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; IVH, intraventricular hemorrhage; PDA, persistent ductus arteriosus; NEC, necrotizing enterocolitis.

The time interval between ACS start and childbirth was less than 24 hours in 150 (28.1%) of the deliveries. Gestational ages were significantly more advanced in the >24 hours group (≤24 hours group: n = 150, median week of pregnancy = 25, interquartiles = 23–28, range = 22–29; >24 hours group: n = 384, median week of pregnancy = 26.5, interquartiles = 25–28, range = 22–29; Mann-Whitney U test, $p < 0.001$; Fig. 1).

Newborns in the ≤24 hours group were significantly less frequently delivered by caesarean section (with more vaginal deliveries) compared to newborns in the >24 hours group (79.9% *vs.* 91.4%, $p < 0.001$).

Newborns born within 24 hours after ACS initiation more frequently had a 5-minute APGAR score below 5 compared to newborns born later than 24 hours after ACS initiation (6.3% *vs.* 2.5%, Chi-Square test, $p = 0.035$).

The proportion of newborns with a 10-minute APGAR below 5 and with an umbilical artery pH <7.20 did not differ between the ≤24 hours group and the >24 hours group ($p = 0.210$ and $p = 0.183$, respectively).

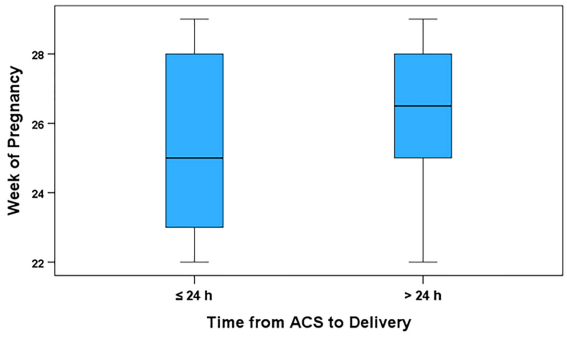

Fig. 1. ACS distribution by week of pregnancy. ACS, antenatal corticosteroid administration.

There were no significant differences regarding the incidence of ROP (60.7% *vs.* 51.3%, $p = 0.083$) or NEC

Table 2. Neonatal outcomes after ACS ≤24 hours and >24 hours.

	≤24 hours	>24 hours	*p* value
Gestational age (weeks)	Median 25 interquartiles = 23–28, range = 22–29	Median 26.5 interquartiles = 25–28, range = 22–29	***p* < 0.001**
5 min APGAR <5	9/143 (6.3%)	9/367 (2.5%)	***p* = 0.035**
10 min APGAR <5	0/143 (0.0%)	4/367 (1.1%)	*p* = 0.210
UApH <7.20	15/140 (10.7%)	25/353 (7.1%)	*p* = 0.183
Caesarean Section	119/149 (79.9%)	351/384 (91.4%)	***p* < 0.001**
BPD	73/143 (51.0%)	150/364 (41.2%)	***p* = 0.045**
NEC	6/143 (4.2%)	14/364 (3.8%)	*p* = 0.856
IVH (Grade IV)	15/143 (10.5%)	11/364 (3.0%)	***p* = 0.001**
ROP	74/122 (60.7%)	142/277 (51.3%)	*p* = 0.083
Surfactant	103/143 (72.0%)	225/364 (61.8%)	***p* = 0.030**
Death	1/143 (0.7%)	6/364 (1.6%)	*p* = 0.410
MDI			*p* = 0.465
>70	91/124 (73.4%)	239/303 (78.9%)	
50–70	16/124 (12.9%)	32/303 (10.6%)	
<50	17/124 (13.7%)	32/303 (10.6%)	
PDI			*p* = 0.116
>70	92/115 (80.0%)	237/281 (84.3%)	
50–70	8/115 (7.0%)	25/281 (8.9%)	
<50	15/115 (13.0%)	19/281 (6.8%)	

ACS, antenatal corticosteroid administration; APGAR, Appearance, Pulse, Grimace, Activity, and Respiration; UA, Umbilical artery; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; ROP, retinopathy of prematurity; MDI, mental development index; PDI, psychomotor development index. Bold is used to show significance under $p < 0.05$.

(4.2% *vs.* 3.8%, $p = 0.856$) between newborns of the ≤24 hours group and the >24 hours group. However, the incidences of BPD and IVH were significantly higher in neonates with less than 24 hours of delivery (BPD: 51.0% *vs.* 41.2%, $p = 0.045$; IVH: 10.5% *vs.* 3.0%, $p = 0.001$). In addition, the ≤24 hours group received surfactant more often than the >24 hours group (72.0% *vs.* 61.8%, $p = 0.030$).

There were no significant differences in mortality, MDI, or PDI, between newborns of the ≤24 hours group and the >24 hours group ($p = 0.410$, $p = 0.465$, and $p = 0.116$, respectively (Table 2)).

75.0% of the newborns between $22^{0/7}$–$22^{6/7}$ weeks of pregnancy and 60.4% of newborns between $23^{0/7}$–$23^{6/7}$ weeks of pregnancy received ACS less than 24 hours before childbirth (Table 3).

Table 3. Number of deliveries distributed by week of pregnancy.

Weeks of pregnancy	≤24 hours	>24 hours	Total
$22^{0/7}$–$22^{6/7}$	6	2	8
$23^{0/7}$–$23^{6/7}$	32	21	53
$24^{0/7}$–$24^{6/7}$	19	42	61
$25^{0/7}$–$25^{6/7}$	20	70	90
$26^{0/7}$–$26^{6/7}$	21	57	78
$27^{0/7}$–$27^{6/7}$	13	68	81
$28^{0/7}$–$28^{6/7}$	26	54	80
$29^{0/7}$–$29^{6/7}$	13	70	83
Total	150	384	534

4. Discussion

This study shows that 75% of newborns between $22^{0/7}$–$22^{6/7}$ weeks of pregnancy and 60% of newborns between $23^{0/7}$–$23^{6/7}$ weeks of pregnancy received ACS administration less than 24 hours before childbirth, allowing us to conclude that they received a single dose of betamethasone. We also showed a statistically significantly higher rate of BPD, IVH, and surfactant administration in the <24 hours group. The population born between $22^{0/7}$ weeks and $23^{6/7}$ weeks are especially vulnerable to BPD and IVH, with reported BPD estimates as high as 80% [18–20].

The main admission diagnoses for the <24 hours group were labor, followed by premature rupture of membranes with labor (including infection), eclampsia, bleeding (including placental abruption), and hemolysis, elevated liver enzymes, and low platelets (hemolysis, elevated liver enzymes, and low platelet count (HELLP)). Differences in long term neurological outcomes, NEC, and ROP were not statistically significant when comparing ACS > or ≤24 hours.

One of the largest studies researching ACS in very preterm infants concluded that even ACS given only hours before delivery may be effective. The EPICE research group published data from 4594 infants born between 24

and 31 gestational weeks. Approximately 40.7% of the women received ACS within the optimal time frame of 24 hours to seven days before delivery [10]. Our percentages of surfactant use were lower than those reported in the EPICE cohort (<24 hours group 31.4% *vs.* 48.4%). Additionally, there were differences in cohort gestational age, with 11% of our cohort delivering under $23^{6/7}$ weeks.

The original dosing regimen of betamethasone (12 mg injections intramuscularly, 24 hours apart) leads to a maternal plasma concentration of approximately 100 ng/mL 1 hour after treatment and a fetal concentration of 20 ng/mL 2 hours after administration. The half-life in fetal plasma was estimated to be 12 hours [21,22]. Our data confirmed a protective effect when administered under 24 hours.

While it is known that corticosteroids support surfactant production, leading to decreased respiratory distress in fetal lungs (*in vivo* and in animal models), it is important to note that surfactant is not the sole factor in preventing RDS [22–24]. There are other molecular mechanisms triggered by ACS that aid in fetal lung processes. BPD, for instance, is a complex pulmonary complication that may be reduced in newborns with optimal ACS timing. In our cohort the highest BPD incidences were in the $\leq$24 hours group (51%). Since the introduction of surfactant, the mortality rate due to RDS has significantly decreased, resulting in an estimated 25% reduction in overall infant mortality and 56% reduction in RDS-related deaths [25,26]. For newborns without optimal ACS, surfactant can be a lifesaving intervention. The surfactant administration rate was 72% in the $\leq$24 hours group. This result may be influenced by gestational age, as 38% of the $\leq$24 hours group was delivered before $24^{6/7}$ weeks of pregnancy.

Our study features several strengths, including a large cohort size, long-term follow-up (including MDI and PDI), and a low gestational age (beginning at $22^{0/7}$ weeks of pregnancy). Limitations of our study include its retrospective nature. Prospective randomized studies in this vulnerable population have been and remain ethically challenging.

5. Conclusions

We are limited in prevention of preterm delivery and have seen, in spite of technological advances, that the rate of preterm delivery is not decreasing. Optimal timed ACS is effective in prevention of numerous adverse outcomes. Gestational age at delivery plays a substantial role in short- and long-term outcomes, such as BPD and IVH. Although more studies are needed, the current study showed that the rate of neonatal outcomes, such as NEC, neurodevelopment at 2 years of age, and ROP, are not negatively influenced by shorter ACS intervals.

Abbreviations

ACS, antenatal corticosteroids administration; BPD, bronchopulmonary dysplasia; ROP, retinopathy of prematurity; NEC, necrotizing enterocolitis; IVH, intraventricular hemorrhage; MDI, Mental Development Index; PDI, Psychomotor Development Index; EPICE, Effective Perinatal Intensive Care in Europe.

Availability of Data and Materials

Available upon written request through the corresponding author.

Author Contributions

KK was responsible for conceptualization, data curation, formal analysis, writing—original draft, review, and editing. LS was responsible for conceptualization, data curation, writing—review and editing. TF was responsible for formal analysis, writing—critical review and editing. JE, MD, AP, HB, SC, WJ, PS and BH were responsible for acquisition and interpretation of data, writing—review and editing. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the University of Ulm (Record number 445/18, accepted March 2019). Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

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Conflict of Interest

The authors declare no conflict of interest.

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