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ORIGINAL ARTICLE

Effects of antenatal corticosteroids in very low birth weight preterm infants

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Abstract

Introduction: The benefits of antenatal corticosteroid (AC) to preterm infants are well established. Its action in multiple tissues promotes maturity of fetal structures, with significant impact in the reduction of neonatal morbimortality. **Objective:** Evaluate the effects of AC in very low birth weight preterm infants (VLBWPI). **Methods:** Data from the Rede Gaúcha de Neonatologia of those VLBWPI born between 01/01/2008 and 12/31/2014 at the Fêmina Hospital in Porto Alegre was used. The exposure to AC (one or two doses of intramuscular 12mg betamethasone) and its relation to mortality and following comorbidities were analyzed: respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), patent ductus arteriosus (PDA), and bronchopulmonary dysplasia (BPD). **Results:** A total of 496 patients were obtained, of whom 68% received at least one dose of CA and 32% received none. A significant reduction in the incidence of RDS was obtained in the group that exposed to AC (OR 0.468, $p = 0.001$). A 60% reduction in IVH (OR 0.401, $p < 0.001$) was noted. A reduction in the incidence of BPD was also observed with the use of AC (OR 0.296-0.903, p = 0.018). No statistical difference was observed in the incidence of PVL ($p = 0.3$), PDA ($p = 0.68$), NEC ($p = 0.44$) or ROP ($p = 0.58$). Neonatal death was significantly reduced by 78% in those treated with AC (OR 0.22, $p < 0.001$). **Conclusion:** exposure to AC, regardless of the number of doses, confers lower morbidity and lower mortality to VLBWPI.

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INTRODUCTION

Preterm births are births that occur before 37 incomplete weeks of gestation. The immaturity of the organism at the time of delivery leads to several consequences in newborns (NBs).

According to the Born Too Soon report of the World Health Organization (WHO), 15 million children are born preterm annually[1]. The prevalence of preterm birth has consistently been increasing[2–4], ranging from 5% to 25% in countries with different sociodemographic characteristics[4]. In Brazil, a study conducted in Ribeirão Preto reported an increase in the prevalence of prematurity from 6% in 1992 to 15% in 2004[3].

Such an increase has a direct impact on health indicators and child healthcare. Lawn et al. reported that neonatal mortality accounts for 42% of deaths in children aged below 5 years and that the complications of prematurity are the crucial direct cause of this mortality[4]. Data from the Brazilian Ministry of Health indicate that neonatal mortality accounts for 60%–70% of infant mortality in all regions of the country[5], reaching up to 77% in 2014[6].

In addition to mortality, the long-term morbidities resulting from preterm birth, including cerebral palsy, cognitive deficit, chronic lung disease, cardiac and gastrointestinal disorders, and auditory and visual loss, are noteworthy. These complications tend to increase with increasing survival of NBs with lower gestational age[1].

Improved care may reduce neonatal deaths caused by the complications of prematurity by up to three-fourth1. Considering the increasing need to improve preterm care, interventions have been sought to reduce mortality and morbidity in this population.

In 1972, Liggins and Howie's study revolutionized perinatal care and demonstrated the beneficial effects of antenatal corticosteroid (AC) use on fetal maturation[7]. Since then, several studies have been conducted on this topic; administration of ACs to pregnant women at risk of preterm birth has been established as an effective intervention in the literature[8–12].

The beneficial effects of ACs with its low cost and high availability have led to the widespread use of this intervention, which prevents approximately 370,000 neonatal deaths annually worldwide. The WHO considers ACs to be a priority intervention in the care of pregnant women at risk of preterm birth[1].

The present study aimed to evaluate the use of an AC in very low birth weight preterm infants (VLBWPIs) born at Hospital Fêmina in Porto Alegre, Brazil, and its association with neonatal mortality and the following morbidities: hyaline membrane disease (HMD), patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), periventricular leukomalacia (PVL), and/or intracranial hemorrhage (ICH) on imaging examination and retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD).

METHODOLOGY

This was a cross-sectional, retrospective study. The data provided by the Neonatal Intensive Care Unit ((NICU) of Hospital Fêmina (NICU-HF) to the Rio Grande do Sul Neonatology Network (RGN) were used. RGN performs epidemiological surveillance of the morbidity and mortality of very low birth weight infants in Rio Grande do Sul, Brazil[13]. Using a standard data collection record, the participating NICUs feed the RGN database annually.

The study used the data of all VLBWPIs born between January 1, 2008, and December 31, 2014, who met the following criteria: gestational age < 37 weeks at birth, birth weight ≤ 1,500 g, and medical record presenting information on AC use ("yes, complete," "yes, incomplete," or "no"). The exclusion criteria were gestational age ≥ 37 weeks at birth, birth weight > 1,500 g, incorrect filling of the field regarding AC use (a numerical record that does not correspond to any of the recommended alternatives), and absence of records regarding AC use.

The following variables were analyzed: maternal AC use; gestational age at birth; and presence of HMD, PDA, NEC, PVL, and/or ICH on imaging examination and of ROP, BPD, and death in NICU-HF.

For the diagnosis of BPD, the criterion adopted was the use of supplemental oxygen at 36 weeks of corrected gestational age or at 28 days of chronological age. ICH was diagnosed by transfontanellar ultrasonography, regardless of the degree. Other diagnoses were established by attending physicians according to the clinical and laboratory findings of patients and were entered in the data collection sheet, which does not have specific completion criteria.

The incidence of the morbidities included in this study and that of mortality were compared among the groups that received a complete course of an AC (two doses of 12 mg betamethasone), an incomplete course (one dose of 12 mg betamethasone), and no course of the AC.

The chi-squared test was used as a measure of association and, when necessary, Fisher's exact test was used. An alpha significance level of 0.05 was adopted, with a confidence interval of 95%.

RESULTS

During the data collection period, a total of 647 patients were identified. Of these, 139 were excluded because their records did not have data on AC use and 13 were full-term NBs; thus, a total of 495 VLBWPIs were included.

Of these, 337 were exposed to the AC, of whom 259 received two antenatal doses of betamethasone.

For analysis, the study NBs were divided into three groups (Table 1): extreme preterm (gestational age ≤ 30 weeks), intermediate (gestational age = 31–33 weeks), and late preterm (gestational age ≥ 34 weeks).

The outcomes of the group exposed to at least one dose of the AC compared with those of the group that did not receive any dose are shown in Table 2. Table 3 describes the findings of the comparison of two doses of betamethasone with a single dose of betamethasone.

Regarding HMD, 312 VLBWPIs had this morbidity (68.6%). In the group exposed to at least one dose of betamethasone, a reduction of 54% was observed in its incidence

Table 1. Characteristics of the study newborns.

Characteristics	AC	Without AC
	(N = 337)	(N = 158)
Maternal age (years)	27.2 ± 7	25.9 ± 6.9
Gestational age (weeks)		
≤30	190	103
31–33	124	39
≥34	23	8
Male	165	82
Birth weight (g)	1099 ± 257	990 ± 308
Apgar < 7 (1 min)	140	103
Apgar < 7 (5 min)	37	47

Table 2. Incidence of morbidities and death in very low birth weight preterm infants following the administration of at least one dose of antenatal corticosteroid (AC) versus no dose.

Gestational age (weeks)	AC	Without AC	OR	95% CI	p-value
Hyaline membrane disease					
≤30	136 (77%)	86 (22.7%)	0.277	0.119–0.646	0.02
31–33	60 (51.7%)	26 (68.4%)	0.495	0.228–1.073	0.07
≥34	3 (15%)	1 (8.3%)	1.941	0.178–21.199	1.00
Total	199 (63.8%)	113 (36.2%)	0.468	0.294–0.744	0.01
Intracranial hemorrhage					
≤30	47 (30.7%)	29 (52.7%)	0.398	0.212–0.747	0.004
31–33	13 (14.1%)	11 (36.7%)	0.284	0.110–0.732	0.015
≥34	2 (14.3%)	0	0.857	0.692–1.062	1.00
Total	62 (23.9%)	40 (44%)	0.401	0.243–0.663	<0.001
Periventricular leukomalacia					
≤30	11 (9.6%)	4 (11.1%)	0.854	0.254–2.868	0.75
31–33	4 (5.6%)	2 (10.5%)	0.507	0.086–3.006	0.60
≥34	1 (8.3%)	0	0.917	0.773–1.087	1.00
Total	16 (8.1%)	6 (10.3%)	0.766	0.285–2.057	0.59
Bronchopulmonary dysplasia					
≤ 30	25 (19.2%)	7 (23.3%)	0.782	0.302–2.027	0.61
31–33	15 (14.6%)	12 (35.3%)	0.313	0.128–0.762	0.01
≥ 34	1 (5.6%)	2 (20%)	0.235	0.018–2.993	0.28
Total	41 (16.3%)	21 (28.4%)	0.493	0.269–0.903	0.02
Patent ductus arteriosus					
≤30	51 (31.3%)	37 (41.6%)	0.634	0.371–1.084	0.09
31–33	23 (20.4%)	10 (27%)	0.690	0.293–1.627	0.49
≥34	2 (10%)	0	0.900	0.778–1.042	0.51
Total	76 (25.6%)	47 (34.1%)	0.666	0.430–1.032	0.08
Necrotizing enterocolitis					
≤30	22 (14.5%)	12 (15.4%)	0.931	0.434–1.997	0.85
31–33	9 (8.2%)	0	0.918	0.868–0.971	0.11
≥34	3 (15.8%)	0	0.842	0.693–1.023	0.27
Total	34 (12.1%)	12 (9.5%)	1.308	0.653–2.619	0.50
Retinopathy of prematurity					
≤30	56 (56%)	12 (41.4%)	1.803	0.780–4.168	0.20
31–33	20 (32.3%)	11 (42.3%)	0.649	0.253–1.667	0.46
≥34	3 (60%)	2 (40%)	0.750	0.038–14.972	1.00
Total	79 (47.3%)	25 (43.1%)	1.185	0.649–2.163	0.64
Deaths					
≤30	35 (21.9%)	60 (65.9%)	0.145	0.082–0.257	<0.001
31–33	10 (9.4%)	4 (11.4%)	0.807	0.236–2.757	0.74
≥34	2 (11.1%)	1 (8.3%)	1.375	0.111–17.093	1.00
Total	47 (16.5%)	65 (47.1%)	0.223	0.141–0.352	<0.001

Table 3. Incidence of morbidity and death in very low birth weight preterm infants according to the administration of two doses of the antenatal corticosteroid (AC) (complete AC) versus one dose of the AC (incomplete AC)

Gestational age (weeks)	Complete AC	Incomplete AC	OR	95% CI	*p*-value
Hyaline membrane disease					
≤30	100 (73%)	36 (92.3%)	0.255	0.065–0.776	0.01
31–33	42 (48.8%)	18 (60%)	0.636	0.274–1.480	0.39
≥34	2 (10.5%)	1 (100%)	0.105	0.028–0390	0.15
Total	144 (59.5%)	55 (78.6%)	0.401	0.214–0.749	0.003
Intracranial hemorrhage					
≤30	34 (28.6%)	13 (38.2%)	0.646	0.291–1.435	0.29
31–33	10 (14.7%)	3 (12.5%)	1.207	0.303–4.814	1.00
≥34	1 (7.7%)	1 (100%)	0.077	0.012–0.506	0.14
Total	45 (22.5%)	17 (28.8%)	0.717	0.373–1.379	0.38
Periventricular leukomalacia					
≤30	6 (6.5%)	5 (22.7%)	0.237	0.065–0.855	0.03
31–33	4 (7.5%)	0	0.925	0.856–0.998	0.56
≥34	0	1 (100%)	–	–	0.08
Total	10 (6.4%)	6 (14.6%)	0.400	0.136–1.173	0.10
Bronchopulmonary dysplasia					
≤30	17 (16.3%)	8 (30.8%)	0.440	0.165–1.173	0.10
31–33	11 (14.7%)	4 (14.3%)	1.031	0.229–3.552	1.00
≥34	1 (5.9%)	0	0.941	0.836–1.060	1.00
Total	29 (14.8%)	12 (21.8%)	0.622	0.293–1.319	0.22
Patent ductus arteriosus					
≤30	38 (29.9%)	13 (35.1%)	0.788	0.363–1.710	0.54
31–33	16 (19%)	7 (24.1%)	0.739	0.269–2.030	0.59
≥34	2 (10.5%)	0	0.895	0.767–1.044	1.00
Total	56 (24.3%)	20 (29.9%)	0.756	0.414–1.383	0.42
Necrotizing enterocolitis					
≤30	17 (14.5%)	5 (14.3%)	1.02	0.347–2.996	1.00
31–33	4 (5%)	5 (16.7%)	0.263	0.066–1.057	0.06
≥34	2 (11.1%)	1 (100%)	0.111	0.030–0.410	0.15
Total	23 (10.7%)	11 (16.7%)	0.599	0.275–1.305	0.20
Retinopathy of prematurity					
≤30	39 (50.6%)	17 (73.9%)	0.362	0.129–1.017	0.058
31–33	15 (33.3%)	5 (29.4%)	1.200	0.357–4.038	1.00
≥34	3 (75%)	0	0.250	0.046–1.365	0.40
All	57 (45.2%)	22 (53.7%)	0.713	0.352–1.447	0.37
Deaths					
≤30	25 (20%)	10 (28.6%)	0.625	0.266–1.496	0.35
31–33	10 (12.8%)	0	0.872	0.801–0.849	0.06
≥34	2 (11.8%)	0	0.882	0.742–1.050	1.00
Total	37 (16.6%)	10 (15.6%)	1.092	0.510–2.338	1.00

(OR: 0.294–0.744, $p = 0.001$). In the group of extreme preterm infants, this reduction was 73% (OR: 0.119–0.646, $p = 0.002$). The use of two doses of betamethasone presented a negative association with HMD (OR: 0.214–0.749, $p = 0.003$) compared with the use of only one dose.

ICH was observed in 102 patients, and the use of AC was a protective factor. The total reduction was 60% (OR: 0.243–0.663, $p < 0.001$); in extreme preterm infants, this reduction was 61% (OR: 0.212–0.747, $p = 0.004$), whereas in intermediary preterm infants, it was 72% (OR: 0.110–0.732, $p = 0.007$). Notably, no statistically significant difference was observed between those who received complete AC treatment and those who received incomplete AC treatment (OR: 0.373–1.379, $p = 0.31$).

PVL was observed in 22 patients. Exposure to AC at any dose was not shown to reduce its incidence in any group (OR: 0.285–2.057, $p = 0.382$).

In total, 62 patients persistently needed supplemental oxygen at 36 weeks of gestation and were diagnosed with BPD. However, a significant benefit was observed with the use of the AC (OR: 0.269–0.903, $p = 0.018$) primarily in the group of preterm newborns (OR: 0.128–0.762, $p = 0.011$), but without distinction between one or two AC doses (OR: 0.293–1.319, $p = 0.15$).

AC use was not associated with a reduction in the incidence of PDA (OR: 0.43–1.03, $p = 0.68$), NEC (OR: 0.653–2.619, $p = 0.44$), and ROP (OR: 0.784–1.536, $p = 0.58$).

During the study period, a total of 122 deaths occurred; the use of the AC was associated with a significant reduction in mortality in the VLBWPIs (OR: 0.141–0.352, $p < 0.001$), particularly in those with gestational age ≤ 30 weeks (OR: 0.082–0.257, $p < 0.001$). However, no difference was observed between the groups receiving one or two doses of the AC.

DISCUSSION

HMD is the main cause of early neonatal death[12], with prematurity being its primary risk factor. According to Ballard et al.[14], corticosteroids promote acceleration of structural maturity of the epithelium and pulmonary mesenchyme and stimulate pneumocyte maturation, which leads to a greater surfactant production. A preterm NB exposed to ACs for up to 7 days after birth has a greater lung volume and compliance, lower pulmonary vascular permeability, and better response to postnatal surfactant treatment[12]. In agreement with the abundant available evidence[15–17], the present results demonstrated a significant reduction in this morbidity.

ICH and PVL are related to the immaturity of cerebral microvascularization and its mechanisms of self-regulation[18]. Changes in systemic blood pressure due to the events common during the neonatal period, such as sepsis, have important consequences in cerebral perfusion. While ICH is associated with germinal matrix hemorrhage, PVL appears to be related to white matter ischemia. These morbidities have a considerable impact on child development because PVL is an important cause of cerebral palsy[18,19] and ICH is an important risk of hydrocephalus[20]. ACs are believed to interfere with the pathogenesis of these diseases through their vasoconstrictive effect[21] and the stimulation to myelination and functional maturation of nerve tissue cells[14]. The benefit of AC use was demonstrated in the present study; the AC had a highly relevant impact on the reduction of ICH, consistent with the findings in the current literature[12,18,22]. However, the present study failed to observe similar results regarding PVL. Considering that the highest incidence of PVL was observed in the group with gestational age < 30 weeks, the risks inherent to gestational age may have contributed to this result.

ROP is caused by an abnormal retinal neovascularization due to hyperoxia and, in its most advanced stages, can lead to blindness due to retinal detachment. Some studies suggest that AC is a protective factor against more severe degrees of ROP[23,24]. This mechanism is not well established; in rabbit fetuses, dexamethasone decreases physiological and pathological neovascularization[24]. The relationship between ROP and AC is controversial, and most current studies demonstrate a lack of benefit from AC administration[12], a finding also observed in the present population.

The number of cases of NEC has increased with the survival of younger and consequently more severely affected preterm NBs, and it is a significant cause of mortality. Its etiology is multifactorial and remains unclarified. Despite being an inflammatory bowel disease, a decrease in its incidence was not observed. Some studies suggest that exposure to AC increases the risk of NEC[25].

PDA may cause hemodynamic repercussions and serious complications such as pulmonary hemorrhage[26]. Although there is some evidence of AC being beneficial, accelerating maturation of the ductal endothelial cells and reducing channel sensitivity to the vasodilatory effects of prostaglandins[27,28], the present study, in agreement with the current literature, failed to demonstrate such an association[29].

BPD is a frequent and worrisome complication because its incidence has remained practically unchanged over the years[17,30]. Through a synergy of pre- and postnatal factors, changes in the development and maturation of the fetal lung occur, culminating in this chronic disease with its classic pattern of alveolar simplification15. Contrary to the more recent evidence[12,15,30–32], a significant decrease was observed in VLBWPIs exposed to the AC, particularly in those with gestational age between 30 and 33 weeks. This discrepancy may be explained by the heterogeneity of BPD definitions and difficulty in establishing its diagnosis, particularly in a retrospective analysis.

Undoubtedly, the main outcome of the present study is the impact of AC use on reducing neonatal mortality. The decrease in mortality is related to the reduction observed in the studied morbidities and stimulation of the maturation

of fetal structures. This beneficial effect was observed in all gestational age groups and at all AC doses.

The optimal time for AC therapy is between 24 h and 7 days before delivery[7,22,33]. The literature presents conflicting results regarding the administration of corticosteroids outside this period with respect to its efficacy and possible side effects[22]. However, Dalziel et al. observed that there is a reduction in neonatal mortality even when delivery occurs 24 h after the administration of the first dose of ACs[12].

The most recent protocols recommend routine use of only one dose of ACs for pregnant women at risk of preterm birth[34,35]. A recent meta-analysis suggested the use of a single dose of ACs owing to the lack of evidence about the safety and possible long-term consequences of repeated-dose AC administration[12]. Several studies have attempted to clarify the optimal therapy to obtain the maximum benefit from AC therapy. In a cohort of 447 children with gestational age of <33 weeks, Lampe et al. observed that an exposure to repeated doses of ACs was associated with lower weight, shorter stature, and lower cephalic perimeter at birth[33]. However, Crowther et al. found that preterm NBs with gestational age of <32 weeks exposed to multiple AC doses presented less incidence of HMD and BPD, with no alterations in the anthropometric measurements[39]. In agreement with the findings of most current studies, the present study failed to demonstrate the benefit of repeated AC use[27,36–38].

Considering the >30 years of abundant evidence regarding the benefit of AC therapy, it is alarming that one-third of the pregnant women in this study did not receive the therapy. The result of this study is consistent with a WHO report indicating that in Latin America, the use of ACs in pregnant women at risk of preterm birth ranges from 4% to 71%1. Healthcare professionals should be aware of the possibility of AC administration considering its inexpensiveness and extreme effectiveness in reducing neonatal mortality.

Among the limitations of this study, its retrospective nature is noteworthy. The used data sheet does not establish the diagnostic criteria, which is the responsibility of attending physicians. Therefore, there is a possible heterogeneity in the sample. Moreover, the interval between AC administration and delivery was not reported. Nonetheless, this sample included a considerable number of VLBWPIs.

CONCLUSION

The evidence of the benefits of AC use in reducing neonatal morbidity and mortality is abundant and reliable. In the present study, a reduction in the incidence of mortality, HMD, BPD, and ICH was observed in VLBWPIs exposed to an AC. Further studies should be conducted to assess the long-term effects of ACs, such as changes in growth, the hypothalamic–pituitary–adrenal axis, and neuropsychomotor development.

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