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ORIGINAL ARTICLE

Prenatal rescue dose of betamethasone in the preterm infant with intrauterine growth restriction

Dosis prenatal de rescate de betametasona en el prematuro con restricción del crecimiento intrauterino

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What do we know about the subject matter of this study?

Rescue cycles of prenatal corticosteroids are used to decrease respiratory morbidity in those preterm deliveries occurring 7-14 days after the initial cycle of corticosteroids. The rescue regimens and the type of corticosteroid administered are not standardized and there is not enough evidence of its use in special populations such as those with intrauterine growth restriction (IUGR).

What does this study contribute to what is already known?

The rescue dose of prenatal corticosteroids administered 21 days after initial maturation does not reduce morbidity and mortality. PTNB ≥30 weeks and IUGR exposed to 3 prenatal corticosteroid doses do not improve their respiratory outcome. At 2 years, the rescue cohort had lower scores on the ASQ®-3 scale. These results question the benefits of the rescue dose in this group of patients in the short- and long term.

Abstract

Antenatal corticosteroids reduce mortality and respiratory distress syndrome (RDS) in preterm newborns. These benefits decrease after a week of administration, recommending a rescue therapy if there is a new threat of premature delivery. Repeated administration of antenatal corticosteroids may have deleterious effects and their benefits are controversial in intrauterine growth restriction (IUGR). **Objective:** to verify the effects in the IUGR population of antenatal betamethasone rescue therapy on neonatal morbidity and mortality, RDS, and neurodevelopment at 2 years. **Patients and Method:** Retrospective study including ≤ 34 weeks and ≤ 1,500g preterm newborns divided according to antenatal betamethasone exposure: Single-cycle (2 doses) vs Rescue therapy (3 doses). Subgroups were created for those ≥ 30 weeks. Both cohorts were followed up to 24 months of corrected age. The Ages & Stages Questionnaires (ASQ)® was administered to assess neurodevelopment. **Results:** 62 preterm infants with a diagnosis of IUGR were included. The rescue therapy group compared with the

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single-dose group showed no differences in morbidity and mortality and less intubation rate at birth (p = 0.02), with no differences in respiratory support at 7 days of life. Preterm newborns ≥ 30 weeks exposed to rescue therapy showed higher morbidity and mortality (p = 0.03) and bronchopulmonary dysplasia (BPD) (p = 0.02), showing no differences in RDS. The rescue therapy group showed worse mean scores on the ASQ-3 scale, with no significant differences in cerebral palsy or sensory deficits. **Conclusions:** Rescue therapy reduces intubation at birth but does not reduce morbidity and mortality. However, at ≥ 30 weeks, this benefit is not observed and the IUGR population exposed to rescue therapy presented more BPD and lower scores on the ASQ-3 scale at 2 years. Future studies should be aimed at the individualization of antenatal corticosteroid therapy.

Introduction

Intrauterine growth retardation (IUGR) is defined as a fetal growth rate lower than normal for the growth potential of a fetus according to race and sex[1]. The newborn diagnosed with IUGR may have a low or normal birth weight for gestational age at birth but during the fetal period has a slowing of growth due to a perinatal insult[2].

The IUGR implies significant morbidity and mortality at the fetal, perinatal, and neonatal levels. In addition, it predisposes to other long-term morbidities such as short stature, metabolic syndrome, cardiovascular disease, neurodevelopmental disorders, and endocrine abnormalities.[3-7]

The diagnosis of IUGR is a challenge for the obstetrician who must decide the ideal time for delivery, assessing gestational age in addition to multiple ultrasound patterns to evaluate the severity of the IUGR status.[8]

On numerous occasions, in cases of IUGR, the delivery is performed before reaching the gestational age considered at term. In these situations, below 35 weeks of gestational age, the administration of prenatal corticosteroids has been recommended to accelerate lung maturation[9].

Lung maturation with prenatal corticosteroids has been shown to reduce mortality, respiratory distress syndrome, and intraventricular hemorrhage when administered in the complete regimen, maintaining these effects from 24 h after completing the regimen until the following 7 days[10,11]. After this period, their efficacy diminishes, and it is recommended to repeat the administration of prenatal corticosteroids if there is a new risk of premature delivery[11-13].

There is currently concern about the possible deleterious short- and long-term effects of prenatal corticosteroid administration[14]. Neurodevelopmental[15-17], cardiovascular, metabolic[18,19], and endocrine[20-22] effects have been described. Further studies are currently recommended to find the optimal dose, timing, and patient for its administration[14,23].

There is a lack of sufficient evidence for the administration of prenatal corticosteroids in the IUGR population in a single cycle or the administration of repeated cycles[24]. In current practice, prenatal corticosteroids are administered given the current evidence of their effects in a singleton pregnancy and without a diagnosis of IUGR.

The objective of this study is to test the effects on neonatal morbidity and mortality in the IUGR population according to whether one or two cycles of prenatal corticosteroid therapy are administered, i.e., one complete cycle and one rescue dose.

Patients and Method

Retrospective cohort study carried out from January 1, 2015, to December 31, 2020, which included preterm newborns < 35 weeks and ≤ 1500 g with prenatal diagnosis of IUGR seen at an IIIC level Neonatal Unit. Patients with major malformations and/or genetic syndromes were excluded. The NEOSOFT database was used for the collection of results and the review of medical records.

Two cohorts of patients were established according to the prenatal corticosteroid therapy received. The first cohort, which received a single cycle, included patients receiving two prenatal doses of betamethasone at 12mg and that birth > 21 days after the first dose. The second cohort, which received a rescue dose in addition to the initial cycle, received a rescue dose of prenatal betamethasone at 12mg, 21 days after the first cycle.

The population characteristics of both cohorts were defined by the following variables: maternal age, singleton birth, multiple gestations, presence of gestational diabetes, hypertension stages (including pre-eclampsia, eclampsia, and HELLP syndrome), chorioamnionitis clinically defined by the presence of at least two of the following parameters: fever >38.5 ºC, tachycardia (maternal heart rate >100 bpm/fetal heart rate > 80 bpm), leukocytosis (> 18,000 µ/L), uterine tenderness or foul-smelling discharge, and third-trimester bleeding (placental abruption, placenta previa, uterine rupture, vasa previa). Also, data on the percentage of

cesarean sections, gestational age (GA), anthropometry at birth, and sex were collected. The stage of IUGR was defined prenatally according to the Figueras classification which includes fetal Doppler assessment and the percentage of severe IUGR (above stage III) in each cohort was determined[26] as well as the gestational age of the first and last dose.

The primary outcomes (morbidity and mortality) included deceased and survivor patients with severe morbidities such as severe intraventricular hemorrhage (IVH), grades III-IV in the Papile classification; periventricular leukomalacia (PVL), either cystic or non-cystic, defined as changes in signal intensity or echogenicity of the periventricular white matter, detected by ultrasound or MRI; bronchopulmonary dysplasia (BPD) defined as moderate (need for supplemental O2 for ≥ 28 days and FiO2 < 30% at 36 weeks of corrected age or at discharge) or severe (need for supplemental O2 for ≥ 28 days, FiO2 > 30%, and/or continuous positive airway pressure (CPAP) or mechanical ventilation (MV) at 36 weeks of corrected age or at discharge); enterocolitis (NEC) ≥ 2 grade, or retinopathy of prematurity (ROP) requiring treatment.

As secondary outcomes, respiratory distress syndrome was determined according to maximum FiO2 at admission, need for MV, and surfactant administration.

Data on days of respiratory support were collected as MV, noninvasive ventilation (NIV), CPAP, high-flow nasal cannula (HFNC) oxygen therapy, and the need for respiratory support at 7 days of life.

Other secondary outcomes analyzed were hypotension in the first week of life, ductus requiring treatment, and early and late sepsis. Weight at 36 weeks of corrected gestational age (cGA) was determined.

All variables were defined according to the criteria established by the Vermont Oxford Network[27].

A sub-analysis was established for the gestational age group of 30 weeks or more.

Finally, both cohorts were followed up to 24 months of corrected age. The validated Ages & Stages Questionnaires®, Third Edition (ASQ®-3) was used to assess neurodevelopment[28]. The presence of infantile cerebral palsy, defined as a chronic non-progressive impairment of motor skills, posture, balance, coordination, muscle tone, or reflexes, was also determined. The presence of sensory deficits such as visual (need for corrective lenses or mono/bilateral blindness) and auditory (need for hearing aids or mono/bilateral hearing loss was analyzed.

Contingency tables and the chi-square test were used to contrast the possible differences between the groups in the qualitative variables and the 2 x 2 tables, with a low number of observations (n < 5), Fisher's exact test was calculated, showing the Odd Ratio in both cases. For quantitative variables, Student's t-test or Mann-Whitney's U test was used, depending on the distribution of the variable, in pairwise comparisons. For variables showing an association with a $p < 0.05$, a multivariate model adjusted for the following confounders was performed: GA, third-trimester bleeding, chorioamnionitis, hypertensive stages, Apgar score < 5 at 5 minutes of life, and sex. Using the backward selection method, variables with p values ≥ 0.15 for the Wald statistic were removed one by one from the model until the adjusted OR estimate was obtained. In all cases, a statistically significant difference was considered when the p-value < 0.05. The SPSS v25.0 software (IBM Corp., Armonk, NY) was used for this analysis.

This study was approved by the Provincial Ethics Committee of Malaga on November 12, 2020.

Results

Of 65 preterm infants, 62 were < 35 weeks and weight ≤ 1500 g with prenatal diagnosis of IUGR were included in the study, divided into 25 for the single-cycle cohort and 37 for the rescue cohort. Three preterm infants (2 in the single-cycle cohort and 1 in the rescue cohort) were excluded due to associated malformations, one esophageal atresia, one Timothy syndrome, and one gastroschisis.

Table 1 summarizes the population characteristics and shows equivalency to each other in their perinatal conditions. The causes of preterm delivery (chorioamnionitis, third-trimester bleeding, and hypertensive stages, among others) were similar in both populations. There were differences in the gestational age at which the last dose of prenatal corticosteroid was administered, due to the characteristics of each cohort.

Table 2 shows the results of the comparison of both cohorts. No significant differences in morbidity and mortality or severe morbidities of prematurity were observed in both cohorts. At the respiratory level, the rescue cohort showed a lower percentage of intubation at birth [adjusted OR (95%CI): 0.06 (0.005-0.7)] and a trend towards less need for MV. However, this did not correlate with fewer days of MV, NIV, CPAP, or HFNC oxygen therapy. There were no differences in maximum FiO2 during admission, nor in the need for surfactant. Also, no differences were found between the two cohorts in the number of preterm infants requiring respiratory support at 7 days of life.

Since 83% of the sample population had a gestational age equal to or greater than 30 weeks of gestational age, a sub-analysis was performed in this population to avoid the biases of more extreme gestational ages.

Table 3 shows the analysis of preterm infants ≥30

Table 1. Characteristics of the cohorts according to the regimen of prenatal corticosteroids received.

	Single Cycle N = 25	Rescue N = 37	p value
Maternal age (years)	33.4 ± 6.4	32.4 ± 6.6	0.55
Multiple gestation	8 (32%)	14 (37.8%)	0.63
Primiparity	14 (56%)	21 (56.8%)	0.95
Gestational diabetes	2 (10%)	5 (15.6%)	0.56
Hypertesion stages	13 (52%)	10 (27%)	0.13
Chorioamnionitis	1 (4%)	2 (5.4%)	0.80
Premature rupture of membranes	4 (16%)	4 (10.8%)	0.55
Third-trimester bleeding	2 (8%)	2 (5.4%)	0.68
IUGR stage III-IV	10 (40%)	11 (29.7%)	0.40
Cesarean	25 (100%)	35 (94.6%)	0.23
Gestational age at first dose	27.7 ± 2.1	26.1 ± 1.9	0.14
Gestational age at last dose	27.8 ± 0.4	31.4 ± 0.3	< 0.001
Gestational age (weeks)	31.7 ± 2.4	31.7 ± 1.8	0.95
Birth weight (g)	1110.8 ± 282.5	1093.9 ± 262.3	0.81
Height at birth (cm)	35.9 ± 4.2	36.5 ± 3.2	0.52
Head circumference at birth (cm)	27.3 ± 3.1	27.1 ± 2.5	0.70
Female gender	14 (56%)	17 (45.9%)	0.43

The results of the continuous variables are expressed as mean ± standard deviation. The qualitative variables show the total number and the percentage with respect to their cohort . IUGR = intrauterine growth restardation.

weeks of gestational age. A higher morbidity and mortality ($p = 0.03$) were observed in the rescue cohort due to a higher proportion of moderate-severe BPD ($p = 0.02$). Adjusted analysis was not possible as there were no cases of moderate-severe BPD or morbidity and mortality in the single-cycle cohort. No cases of PVL or IVH grades III-IV or NEC ≥ 2nd grade were observed in the population of ≥ 30 weeks of gestational age. Regarding respiratory outcomes, there were no differences between the two cohorts in the need for MV or the days of respiratory support for each of the modalities or in the need for support at 7 days of life. There were also no differences in the need for surfactant treatment.

Finally, Table 4 shows the neurodevelopmental results at follow-up at 2 years of corrected age, with 20 preterm infants in the single-cycle cohort and 28 in the rescue cohort completing this assessment. No differences were observed between the two cohorts in the presence of infantile cerebral palsy or sensory deficits. A higher proportion of cases below the lower limit of normal was observed in the rescue group in the ASQ®-3 scale items: Communication, Gross Motor Skills, and Social, however, significance was not reached. Figure 1 shows the distribution of scores according to prenatal corticosteroid exposure, highlighting worse mean scores in the rescue group in all items of the ASQ®-3 scale, bordering on statistical significance in the Social item with a $p = 0.07$.

Discussion

The administration of rescue doses of prenatal corticosteroids is aimed at reducing the decrease in the efficacy of prenatal corticosteroids, observed from the week it was administered[13,29,30].

Our study found no benefit in mortality or severe morbidity in the cohort receiving a rescue dose 21 days after initial maturation. Also, this cohort presented less intubation at birth without reaching differences in the need for MV since, in their evolution, patients not

Table 2. Results of the comparison between cohorts according to the pattern of lung maturation

	Single Cycle N = 25	Rescue N = 37	OR (95%CI)	p value	Ajusted OR (95%CI)	Ajusted P-value
Primary outcomes	4 (16%)	9 (24.3%)	1.6 (0.4- 6.2)	0.43		
Death	1(4%)	1 (2.7%)	0.6 (0.04-11.1)	0.77		
Intubation at birth	6 (24%)	1 (2.7%)	0.08 (0.01-0.78)	0.01	0.06 (0.005-0.7)	0.02
Apgar 5 min, < 5	0	0	-	-		
IVH grades III-IV	1 (4%)	0	0.6 (0.2-1.4)	0.22		
PVL	1 (4%)	0	0.6 (0.2-1.4)	0.22		
NEC ≥ 2	0	0	-	-		
ROP treated	2 (8%)	1 (2.7%)	0.3 (0.2-3.7)	0.34		
Hypotension 1st week	2 (8%)	3 (8.1%)	1.01 (0.1-6.5)	0.98		
PDA treated	1(4%)	1 (2.7%)	0.6 (0.04-11.1)	0.77		
Early sepsis	0	0	-	-		
Late sepsis	8 (32%)	9 (24.3%)	0.6 (0.2-2.1)	0.50		
BPD	3 (12.5%)	7 (19.4%)	1.6 (0.3-7.3)	0.23		
Need for Surfactant	6 (24%)	9(24.3%)	1.01 (0.3-3.3)	0.97		
Need for MV	6 (24%)	6 (16.7%)	0.6 (0.1-2.2)	0.47		
Need for respiratory support at 7 days of life	8 (32%)	13 (35.1%)	1.1 (0.3-3.3)	0.79		
Máximum FiO_2	30.9 ± 4.3	28.1 ± 2.4		0.57		
VM time (d)	10.7 ± 4.2	0.9 ± 4		0.81		
NIV time (d)	1 ± 0.6	0.3 ± 0.2		0.25		
CPAP time (d)	4.7 ± 1.2	4.6 ± 0.9		0.95		
HFNC time (d)	3.1 ± 1.2	4.1 ± 1.2		0.57		
Weight at 36 weeks cGA	1649.3 ± 260.5	1652.4 ± 229.6		0.96		

The qualitative variables are expressed in n(%) within each cohort, the quantitative ones in mean ± standard deviation. IVH: intraventricular hemorrhage; PVL: periventricular leukomalacia; NEC: Necrotizing enterocolitis; ROP: retinopathy of prematurity; PDA: patent ductus arteriosus; BPD: bronchopulmonary dysplasia; MV: mechanical ventilation; NIV: non-invasive ventilation; CPAP: Continuous Airway Pressure; HFNC: high-flow nasal cannula; GAc: corrected gestational age.

intubated in the delivery room subsequently required MV. Likewise, the need for support at 7 days of life is similar in both cohorts. These results are in line with the literature[13]. Pulmonary function has been studied during rescue, finding better compliance in the first 72 hours compared with placebo; however, both groups presented similar results at discharge. According to these observations, the effect of a rescue dose at the respiratory level is limited in time; however, this study does not refer to the IUGR population, its sample size is limited, and it does not subdivide according to GA. In our sample, those preterm infants with IUGR and ≥ 30 weeks of gestational age exposed to a third dose of betamethasone do not present less intubation at birth or less need for MV.

It is also noteworthy that, in the overall comparison, the rescue group does not show differences with respect to the single-cycle group in the need for surfactant or BPD, obtaining worse results when subdivided above 30 weeks of gestational age.

According to the study by Jobe et al. (2021) in primates, maturation with prenatal corticosteroids increases surfactant production, but at the same time, they can induce apoptosis and suppress the immune response and pulmonary developmental pathways at the usual doses compared with a lower dose formula-

Table 3. Results of the comparison ≥ 30 weeks according to the lung maturation pattern

	Single Cycle N = 20	Rescue N = 32	OR (95%CI)	p value*
Primary outcomes	0	7 (21.9%)	0.5 (0.4- 0.7)	**0.03**
Death	0	1 (3.1%)	1.5 (0.4-5.1)	0.42
Intubation at birth	2 (10%)	1 (3.1%)	0.3 (0.02-3.4)	0.55
ROP treated	0	1 (3.1%)	1.5 (0.4-5.1)	0.42
Hypotension 1st week	0	2 (6.5%)	1.1 (0.5-2.5)	0.52
PDA treated	1 (5%)	0	0.4 (0.2-1.2)	0.36
BPD moderate/severe	0	5 (16.1%)	2.1 (1.2-3.9)	**0.02**
Need for Surfactant	3 (15%)	6 (18.8%)	1.3 (0.2-5.9)	0.72
Need for MV	1 (5%)	3 (9.7%)	2 (0.2-21.1)	0.54
Need for respiratory support at 7 days of life.	3 (15%)	10 (31.3%)	2.5 (0.6-10.8)	0.32
Máximum FiO_2	27.6 ± 18.1	25.6 ± 11.7		0.66
VM time (d)	20	8.1 ± 6.8		0.18
NIV time (d)	0.7 ± 3.1	0.2 ± 6.4		0.92
CPAP time (d)	2.6 ± 2.8	3.3 ± 3.8		0.61
HFNC time (d)	2.5 ± 6.4	3.6 ± 7.3		0.45
Weight at 36 weeks cGA	1714.85 ± 249.8	1678 ± 2268		0.51

The qualitative variables are expressed in n(%) within each cohort, the quantitative ones in mean ± standard deviation. *Chi squared; T-Student. ROP: retinopathy of prematurity; PDA:. persistent ductus arteriosus; BPD: bronchopulmonary dysplasia; MV: mechanical ventilation; NIV: non-invasive ventilation; CPAP: Continuous Airway Pressure; HFNC: high-flow nasal cannula; GAc: corrected gestational age.

Table 4. Results of the comparison at 2 years, according to pattern of lung maturation

	Single Cycle N = 20	Rescue N = 28	p value*
Cerebral palsy	0	0	-
Visual deficit	0	1 (3.6%)	0.39
Hearing impairment	1 (5%)	2 (7.1%)	0.76
Score below LLN			
ASQ-communication	1 (6.7%)	4 (21.1%)	0.24
ASQ-gross-motor	2 (13.3%)	4 (21.1%)	0.55
ASQ-fine-motor	2 (13.3%)	3 (15.8%)	0.84
ASQ-resolution	2 (13.3%)	2 (10.5%)	0.80
ASQ-social	2 (13.3%)	4 (21.1%)	0.55

Qualitative variables are expressed in n(%) within each cohort. LLN: lower limit of normal. *Fisher's exact test.

tion of betamethasone[33]. The higher incidence of BPD in the rescue group could be related to this deleterious effect on the pulmonary developmental pathways, in addition to other factors related to the pathology of IUGR itself.[34] Further studies would be needed to relate the presence of BPD to a higher number of doses of prenatal corticosteroids administered.

Grade III-IV IVH[10,12] was another of the morbid-

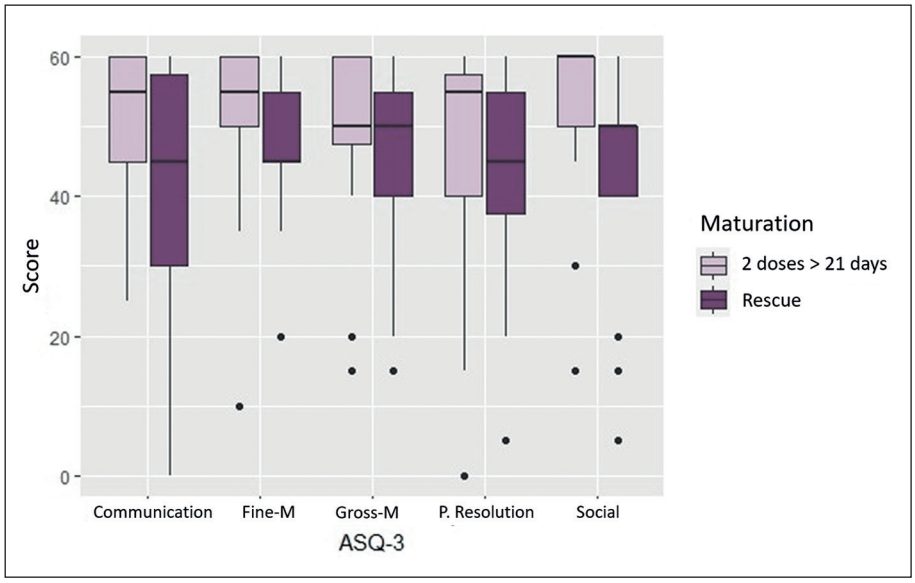

Figure 1. Distribution of scores on the ASQ-3 scale according to exposure to prenatal corticosteroids.

ities whose incidence decreases after the administration of a repeated cycle of prenatal corticosteroids. In our sample, we found no differences between the two cohorts; however, the population analyzed had a low incidence of severe IVH, with 1 case in the single-cycle group and no cases in the rescue group. In those ≥30 weeks of GA, we did not find any case of severe IVH. Given this low presence of severe IVH, the administration of a rescue dose cannot be related to its lower incidence.

Regarding the 2-year follow-up results, no significant differences were found between the two groups, although the rescue cohort showed lower scores on the ASQ-3 scale, as well as a higher proportion of patients with a below-normal score for the Communication, Gross Motor Skills, and Social items. These results are striking since in the rescue group, there are no cases of grade III-IV IVH or PVL, which raises the hypothesis that this worse evolution could be related to the greater number of prenatal doses of betamethasone received. Some studies do not find alterations in neurodevelopment in premature infants who have received rescue cycles of prenatal corticosteroids[35]; however, other studies show concern in this regard[13, 16] describing adverse results in neurodevelopment and a greater incidence of mental and behavioral disorders[14-17, 23]. Repeated administration of prenatal corticosteroid cycles has been associated with reduced brain growth and alterations in myelination[36]. A lower neuronal density in the hippocampus after prenatal corticosteroid administration[23] has also been described, as well as a reduction in the concentration of neurotrophin-3 with possible consequences for neuronal growth, differentiation, and survival. In addition, the IUGR population is at risk for neurodevelopmental alterations that are increased in the case of prematurity or fetal circulatory redistribution[5]. This condition, added to the possible effect of repeated cycles of corticosteroids, could explain the worse outcome on the ASQ®-3 scale of PTNB with IUGR who received 3 doses of prenatal corticosteroids.

The current controversy about the short- and long-term effects of prenatal corticosteroids calls for a search for the target population, the minimum effective dose, and the appropriate interval to optimize their efficacy and reduce such adverse effects.[14,19,20,38,39].

Based on current evidence, it might be reasonable to decrease the administration of repeated prenatal corticosteroids in PTNB with IUGR, especially ≥30 weeks of GA, since morbidity and mortality in this population are lower than that occurring at lower gestational ages and the potential benefit of repeated cycles of prenatal corticosteroids is not as evident or as relevant, as we have observed in our sample. In addition, these populations are frequently exposed to repeated cycles of prenatal corticosteroids, with preterm infants ≥ 30 weeks accounting for more than 72% of our population.

Our study has several limitations. Since it is a retrospective cohort study, its conclusions have less evidence than the meta-analyses published on the subject. The minimum sample size to find a 5% difference in morbidity and mortality would be 86 PTNB in each cohort. Also, our study has not gathered a sufficient sample size to validate its results externally. The results of the IUGR subgroup with ≥ 30 weeks of gestational

age could not be adjusted by multivariate analysis due to the null presence of cases in some variables.

As strengths of our study, we can mention its single-center nature with homogeneous diagnostic and therapeutic criteria; the population characteristics, similar in both cohorts, making them comparable; the analysis of a little-studied population such as fetuses with IUGR and the separation according to gestational age, as well as the neurodevelopmental assessment at 2 years of age, which provides relevant information on the use of prenatal corticosteroids in little studied populations.

Multicenter randomized clinical trials would be necessary to confirm our results.

Conclusions

The rescue dose of prenatal corticosteroids administered 21 days after initial maturation does not reduce morbidity and mortality. PTNB ≥30 weeks and IUGR exposed to 3 prenatal corticosteroid doses do not improve their respiratory outcome. At 2 years, the rescue cohort had lower scores on the ASQ®-3 scale. These results question the benefits of the rescue dose in this group of patients in the short- and long term. Future studies should be aimed at individualizing prenatal corticosteroid therapy.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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