FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2014/2015

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Prenatal Corticosteroids and Respiratory Distress Syndrome Prevention in Infants less than 35 Weeks of Gestational Age

março, 2015

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Mestrado Integrado em Medicina

Área: Neonatologia

Tipologia: Dissertação

Trabalho efetuado sob a Orientação de:

Professora Doutora Maria Hercília Ferreira Guimarães Pereira Areias

E sob a Coorientação de:

Dr. Gustavo Marcondes Duarte Rocha

Trabalho organizado de acordo com as normas da revista:

Journal of Pediatric and Neonatal Individualized Medicine

março, 2015

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR
PROJETO DE OPÇÃO
DISSERTAÇÃO / MONOGRAFIA

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200907048	2015

DESIGNAÇÃO DA ÁREA DO PROJECTO

Neonatologia

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Prenatal Corticosteroids and Respiratory Distress Syndrome Prevention in Infants less than 35 Weeks of Gestational Age

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Prenatal Corticosteroids and Respiratory Distress Syndrome Prevention in Infants less than 35 Weeks of Gestational Age

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Abstract

Introduction: Preterm delivery is associated with an increased risk of newborn morbidity and mortality. Respiratory distress syndrome (RDS) is the most common comorbidity. It has been proven that this syndrome can be prevented with the administration of prenatal corticosteroids to women at threat of preterm delivery before 35 weeks of gestational age.

Aim: To evaluate the risk factors, severity, co-morbidities and mortality of this condition in newborns less than 35 weeks of gestational age and to assess the association between the elapsed time since the administration of the last dose of a full cycle of corticosteroids and the frequency and severity of RDS.

Methods: In this descriptive retrospective study were included all newborns below 35 weeks of gestational age born at our center between January 1, 2012 and December 31, 2014 and admitted in Neonatal Intensive Care Unit (NICU). We excluded newborns with major malformations, chromosomopathies, hydrops or congenital TORCH infection.

Results: A total of 234 newborns were studied. Eighty-three (35.5%) newborns had RDS and 151 (64.5%) remained without RDS. Prenatal corticosteroids were used in 90.1% of all newborns. When adjusted to the severity of RDS, a higher birth weight and a higher gestational age were associated with a significant reduction in mortality. The use of vasopressor support was significantly associated with an increase of mortality.

Conclusion: Clinical chorioamnionitis, placental abruption, abnormal umbilical flow, and caesarean section were more frequent in infants with RDS. The use of peripartum antibiotics was significantly less frequent in infants with RDS. The last dose of a full cycle of prenatal corticosteroids must be given at least 10.5 hours before the delivery to prevent RDS.

Keywords: Respiratory distress syndrome, prenatal corticosteroids, preterm birth, newborn, neonatal intensive care unit, risk factors

Introduction

Preterm delivery is associated with an increased risk of newborn morbidity and death. Respiratory distress syndrome (RDS) is its most common consequence and cause of morbidity in these newborns. [1-3]

The administration of prenatal corticosteroids to women at threat of preterm delivery before 35 weeks of gestational age has been proved to prevent RDS by increasing maturation of fetal lung and other tissues. [4, 5]. Prenatal corticosteroids have also been associated to a diminished risk of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), early sepsis and neonatal death. [2, 4]

The major benefit of prenatal corticosteroids is observable when delivery occurs between 24 hours and seven days after the beginning of therapy, but the effect seems to be diminished 14 days after the administration. [2-4, 6]

The most recent evidences showed that multiple courses were not recommended due to associations with reduced fetal growth, increased risk of adrenal suppression and due to failure to reduce the risk of death. [2, 7, 8] However, according to the 2013 *Update of the European Consensus Guidelines on the Management of Neonatal RDS in Preterm Infants*, a rescue course can be administered if more than two to three weeks have passed since the first course, in women at threat of preterm delivery and gestational age below 33 weeks. [6]

The natural progression of RDS consists of a state of pulmonary insufficiency, caused by a deficiency of surfactant production in fetal lungs with structural immaturity, starting at delivery and followed by an increase in severity throughout the first two days of life. [2, 6]. If not treated, the disease can progress to respiratory failure and sometimes to death of the newborn. [6]

Risk factors for this pathology are multiple gestation, maternal diabetes, chorioamnionitis, caesarean section, male sex, fifth minute Apgar score lower than seven, low birth weight and low gestational age. [9, 10] Prenatal corticosteroid therapy and preterm rupture of membranes reduce the risk of RDS. [10]

This study aims to evaluate the risk factors, severity, co-morbidities and mortality of RDS in newborns less than 35 weeks of gestational age and to assess if the elapsed time from administration of the last dose of a full cycle of corticosteroids influences the frequency and severity of RDS.

Methods

The authors performed a descriptive retrospective study of all newborn infants less than 35 weeks of gestational age born between January 1, 2012 and December 31, 2014 at Hospital São João, admitted to the Neonatal Intensive Care Unit (NICU). Those with major malformations, chromosomopathies, hydrops or congenital TORCH (Toxoplasmosis; Others such as syphilis, varicella-zoster or parvovirus B19; Rubella; Cytomegalovirus; and Herpes) infection were excluded.

The demographic, prenatal, delivery, and placental data, as well as information regarding evolution in NICU, treatment at discharge and necropsy results of deceased newborns were collected from clinical charts and retrospectively analyzed.

RDS was diagnosed by a combination of clinical and radiographic features according to the criteria of the 2013 *Update on the European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome in Preterm Infants*. [6] These criteria are: (1) PaO_2 < 50 mmHg or central cyanosis in room air or a need for supplemental oxygen to maintain PaO_2 > 50 mmHg or to maintain oxygen saturation > 85% within the first 24 hours of life and; (2) a chest radiography consistent with RDS (reticulogranular appearance to lung fields with or without low lung volumes and air bronchograms) within the first 24 hours of life. [6] For practical purposes, we classified RDS in grades I to III according to the radiographic results (I - light, slight reticulogranular appearance; II - moderate, reticulogranular appearance with air bronchograms; III – severe, unclear cardiac borders or white lung). [11]

Gestational age (completed weeks) was determined by menstrual age in women with regular menstrual cycles, by ultrasonography when a discrepancy of two or more weeks between menstrual age and ultrasonographic age occurred or in the absence of a menstrual date, or by the New Ballard Score in the absence of obstetrical indexes. [12] Intrauterine growth restriction was defined as a birth weight below the 3rd centile of Fenton`s growth charts. [13] Histological chorioamnionitis classification was made according to the method proposed by Blanc WA (stage I: intervilositis, stage II: chorionitis, stage III: chorioamnionitis). [14] Funisitis was defined as polymorphonuclear leukocytes in the wall of umbilical vessels or in Wharton's jelly. [15] Villitis was diagnosed by the presence of a mononuclear infiltrate in the villous tree. [16] Vasculitis was defined as a polymorphonuclear leukocytes infiltrate in the chorionic or umbilical vessel walls. [17]

Bronchopulmonary dysplasia (BPD) was diagnosed when a requirement for supplementary oxygen persisted for at least 28 days after delivery associated to characteristic radiographic features. Classification was according to the National Institutes of Health consensus criteria. [18] Patent *ductus arteriosus* (PDA) was confirmed by echocardiography with Doppler. [19, 20] NEC was defined by clinical findings, such as feeding intolerance longer than 24 hours and abdominal distention, the presence of radiological features such as intramural air, perforation or meconium plug syndrome or by definitive surgical findings. NEC was classified according to modified Bell staging criteria. [21] IVH was diagnosed when transfontanellar ultrasound showed intraventricular bleeding confined to the periventricular area (grade 1), without ventricular dilatation (grade 2), with ventricular dilatation (grade 3) or with parenchymal involvement (grade 4). [22] Periventricular leukomalacia (PVL) was diagnosed when a hypoechoic cyst in the periventricular white matter was observable in the ultrasound. [22] Retinopathy of prematurity (ROP) was diagnosed and graded by ophthalmologists according to the International Classification of Retinopathy of Prematurity revised. [23] Sepsis was suspected in the presence of positive laboratory findings in patients with suggestive clinical features and diagnosed when a blood culture turned out to be positive. [22] Pneumonia was diagnosed by a combination of clinical and laboratory findings, and a chest radiographic showing patchy infiltrate, granularity, air bronchogram or consolidation. [24] Pneumothorax was suspected by clinical findings and confirmed by a chest radiographic showing air in the pleural space. [25]

According to the Protocol of Gynecology and Obstetrics Department of our hospital, the prenatal therapy with corticosteroids is performed in mothers with 34 or less weeks of gestational age at threat of preterm labor. Betamethasone (2 doses of 12mg separated by 24 hours) was used until February of 2014. Dexamethasone (4 doses of 6mg every 12 hours) was used since March of 2014. A rescue cycle is given to mothers who maintain criteria for corticosteroids therapy after a medical team decision.

Surfactant therapy, poractant alfa, was given to newborns according to the protocol of our unit, in an initial dose of 200 mg/kg and, if needed (RDS with a persistent need of $FiO_2 > 0,4$), subsequent doses of 100 mg/kg.

Postnatal intravenous corticosteroids were administrated according to DART protocol when indicated. [26]

The statistical analysis was performed using SPSS® for Windows, version 20. Continuous variables were characterized by mean (± standard deviation) or median (medium-maximum) if they had symmetric or asymmetric distribution respectively and categorical variables by absolute and relative frequencies. To compare continuous variables parametric tests (independent t test and One-Way ANOVA) or non-parametric tests (Mann Whitney-U test and Kruskal Wallis test) were used if they had two or more than two categories, and Chi-Squared or Fisher's exact test to compare categorical variables, the latter for expected values less than 5. A multivariate analysis by logistic regression was performed to evaluate predictive factors of severity and mortality. Receiver operating characteristic (ROC) curve was performed to study the time between last dose of a full cycle of corticosteroids and delivery and the risk of RDS. A p value less than 0.05 was considered statistically significant.

This study protocol has been approved by the ethics committee of our hospital.

Results

Two hundred and thirty-four newborns were included in this study. Eighty-three (35.5%) newborns had RDS and 151 (64.5%) remained without RDS. Seventeen (7.3%) infants deceased during the stay in NICU.

The demographic and prenatal data of newborns are shown in table 1. Both mean birth weight and median gestational age were significantly lower in the RDS group ($p<0.0001$). There were no differences in maternal diseases between the two groups. However, pregnancy complications, such as clinical chorioamnionitis, placental abruption and abnormal umbilical flow, were significantly higher in newborns with RDS ($p=0.002$, $p=0.030$ and $p=0.007$, respectively). Prenatal corticosteroids were administered in 90.2% of the newborns with RDS and in 90.1% of those without RDS. The first corticosteroid cycle was completed in 67.6% of the newborns with RDS and in 70.6% of those without RDS. Betametasone was the most used corticosteroid (76.2%). The median time between the last dose of a full cycle of corticosteroids and delivery in infants with RDS was lower than in infants without RDS (59.0 hours and 81.5 hours, respectively). Peripartum antibiotics were prescribed in 47.7% mothers of newborns without RDS and in 32.5% mothers of newborns with RDS ($p=0.025$). Regarding the placental histology, there were no statistically significant differences between newborns who had RDS and those without RDS.

The delivery and evolution in neonatal intensive care unit are represented in table 2. Caesarean section was the preferred method of delivery (68.7% in infants with RDS and 54.3% in those without). The difference of the percentage of caesarian section between infants with and without RDS was significant, being higher in newborns with RDS ($p= 0.032$). The vaginal delivery was significantly more frequent in newborns without RDS ($p=0.032$). An Apgar score at first and fifth minutes lower than seven was significantly more common in infants with RDS (both with $p<0.0001$). Resuscitation and early invasive ventilation were significantly more frequent in infants who had RDS (both with $p<0.0001$). Early nasal CPAP was slightly more used in newborns with RDS, but the difference was not significant. With the exception of periventricular leukomalacia and hydrocephalus, all of the neonatal morbidities were significantly more frequent in newborns with RDS. The most common neonatal morbidities in all infants were PDA and anemia with red blood cells transfusion need (25.2% and 24.8%, respectively). Hydrocephalus and seizures were the least frequent neonatal morbidities and only occurred in infants with RDS (0.4% and 1.3%, respectively). Vasopressor support was significantly more needed in newborns with RDS ($p<0.0001$) with a median of 2.5 days of vasopressor support in infants with RDS and 1.0 in infants without RDS. Infants who had RDS had a significant higher need for oxygen therapy and invasive ventilation ($p<0.0001$), with a median duration of 6.0 and 5.0 days, respectively. Parenteral nutrition was used significantly more frequently and for a higher median number of days in newborns with RDS (both with $p<0.0001$). Parenteral nutrition was administrated in 93.8% and for a median of 14.0 days in infants with RDS and in 66.7% and for a median of 7.0 days in infants without RDS. Newborns with RDS had a significantly higher need for surfactant, bronchodilators and inhaled corticosteroids ($p<0.0001$). None of the infants without RDS needed any of these therapies. Postnatal intravenous corticosteroids were administrated in seven infants with RDS (8.4%) and in none without RDS ($p=0.001$). The total median number of days of stay in NICU was 15.0 and it was significantly higher in infants with RDS, who stayed a median of 33.0 days ($p<0.0001$). Fifty nine (25.2%) infants were transferred to another NICU to continue treatment. The percentage of transferred patients was significantly higher in the group of infants without RDS (12.0% in infants with RDS and 32.5% without RDS; $p=0.001$). The newborns had a median of 6.0 days in our unit until transference, being the median number of days higher in those with RDS (9.5 days). Bronchodilators, inhaled corticosteroids and oxygen therapy were prescribed as treatment at discharge only to the group with RDS. Inhaled corticosteroids were the most commonly used (14.5%). All of the 17 deceased newborns had RDS (20.5%) and the global mortality rate was 7.3% ($p<0.0001$). The most common causes of death were grade IV

intraventricular hemorrhage and multiorgan dysfunction. Each of these pathologies caused the death of six newborns with RDS. There was also one newborn deceased due to arrhythmia, one due to extreme prematurity, two due to pulmonary hypoplasia and one due to pulmonary hemorrhage. Eight of the deceased newborns were autopsied (47.1%). Pulmonary pathology findings were present in seven autopsies. Two newborns had BPD, two showed respiratory distress syndrome findings, two had bilateral pneumonia and one had massive pulmonary hemorrhage.

Table 3 reports the differences in demographics and clinical characteristics according to severity of RDS. Thirty-five infants had mild RDS, 32 had moderate RDS and 16 had severe RDS. Gestational age was lower in more severe forms of RDS (p=0.014). Multiple gestation was significantly more frequent in infants with more severe grades of RDS (p=0.025). A full first cycle of corticosteroids was less frequent in infants with severe RDS (p=0.013). In more severe stages of RDS, the newborns needed early invasive ventilation more frequently (p=0.010). Patent *ductus arteriosus* with surgical treatment, periventricular leukomalacia and thrombocytopenia with platelet transfusion were more frequent in more severe stages of RDS. The need for vasopressor support, oxygen therapy and invasive ventilation were significantly higher (p=0.003, p=0.032 and p=0.016, respectively) in infants with higher grades of RDS. The surfactant was given according to the severity of RDS (p=0.001).

Higher request for invasive ventilation and higher median number of surfactant doses were predictive factors of severity of RDS, when adjusted to birth weight and gestational age [OR= 3.0, 95% CI (1.04-8.67) and OR= 3.2, 95% CI (1.46-6.97)].

Lower birth weight and lower gestational age, when adjusted to RDS severity, were predictive factors of mortality [OR= 0.990, 95% CI (0.98-0.99) and OR= 0.459, 95% CI (0.31-0.68)]. The need for vasopressor support, when adjusted to RDS severity, was also a predictive factor of mortality [OR= 14.4, 95% CI (3.2-63.6)].

The ROC curve identified a cut-off lower than 10.5 hours between the last dose of a full cycle of corticosteroids and the delivery as a higher risk of onset of RDS. The sensibility value of this cut-off was 80.0%. Another ROC curve also determined a cut-off lower than 6.5 elapsed hours between the last dose of a full cycle of corticosteroids and the delivery as a higher risk of onset of moderate to severe RDS. The sensibility value of this cut-off was 83.3%.

Discussion

The prevalence of RDS in newborns with less than 35 weeks of gestational age was 35.5% in our samples, which is similar to previous studies. [2] Lower gestational age, lower birth weight, clinical chorioamnionitis, placental abruption, abnormal umbilical flow, caesarean section, and first and fifth minutes Apgar score lower than seven were more frequent in infants with RDS, which is consistent with the literature. [9, 10, 27, 28]

Lower gestational age and multiple gestation were significantly more frequent in more severe grades of RDS, as it has been shown by others. [29]

It has been shown that prenatal corticosteroids reduce the risk of RDS. [6] However, in our study, because corticosteroids were used in a high percentage of cases (90.1%), we could not find a significant difference in the administration of corticosteroids between infants with or without RDS and between the different grades of severity of RDS. However, a full cycle was associated with less severe forms of the condition. These results show the importance of using complete corticosteroid cycles in the prevention of more severe grades of RDS.

Peripartum antibiotics were significantly less prescribed in infants with RDS, being consistent with what was found by Cousens, S. *et al*. [30] This could be because chorioamnionitis is reduced by peripartum antibiotics, leading to a higher gestational age and reducing the incidence of RDS. [31]

The newborns with RDS had a significantly higher need for resuscitation and early invasive ventilation. The latter one was also more needed according to the severity of RDS, as expected, since this is the management of infants with RDS.

BPD, a complication associated with the premature lung injury usually occurring after RDS and more frequent in more immature infants, also occurred in our study in newborns with RDS with an incidence of 18.1%. [32]

In our study, PDA was the most common neonatal morbidity, affecting 25.2% of all newborns and 50.6% of those with RDS, data according to the literature. [33] Surgical treatment for PDA was only needed in six infants with RDS, because most of PDA closes spontaneously or with pharmacological treatment.

Only newborns with RDS had pneumonia (7.2%). Invasive ventilation and chorioamnionitis in infants with RDS are two risk factors that increase the likelihood of pneumonia. [24] Pneumothorax only occurred in infants with RDS (9.6%), probably due to the higher incidence of clinical chorioamnionitis and resuscitation attempts, which are risk factors for this condition. [25]

Intraventricular hemorrhage (≥ grade 3) and sepsis had a significantly higher incidence in infants with RDS. This could be due to the differences found in the administration of a full cycle of prenatal corticosteroids in the different grades of RDS because, according to the literature, corticosteroids reduce the incidence of IVH and sepsis. [2, 4]

Periventricular leukomalacia was significantly more frequent in preterms with more severe grades of RDS. Infants with severe RDS had a higher need for oxygen therapy and invasive ventilation, known risk factors for periventricular leukomalacia, which could explain the association between leukomalacia and a higher severity of RDS. [6]

RDS was associated with a significantly higher incidence of ROP (≥ grade 2) in our study. The major risk factors to ROP are prematurity, low birth weight and oxygen therapy, which are common in newborns with RDS. [6]

Other observed morbidities, such as atelectasis, seizures, acute renal failure, thrombocytopenia with platelet transfusion, anemia with red blood cells transfusion and gastroesophageal reflux, were significantly more frequent in infants with RDS, justifying the necessity for RDS prevention.

Vasopressor support was more used in newborns with RDS, namely in more severe forms. It matched our expectations due to the higher morbidity that occurred in newborns with RDS and due to the higher severity of RDS in those newborns.

As we expected, oxygen therapy was significantly more used in infants with RDS and with more severe grades of RDS. It was also used for a significantly higher median number of days. Invasive ventilation was only needed on infants with RDS and this difference of requirement for invasive ventilation was significant. Fifty-seven (68.7%) infants with RDS needed invasive ventilation for a median of 5.0 days. When comparing the different grades of RDS, invasive ventilation was more frequent in the more severe grades. These results were expected due to oxygen therapy and invasive ventilation being the management for RDS. According to the literature, invasive ventilation is necessary in a significant number of preterm infants with RDS who fail on CPAP, despite this being injurious to lungs. [6]

Parenteral nutrition was significantly more used in infants with RDS and for a higher median number of days. These results were expected because infants with RDS had lower gestational age and birth weight, needing a longer parenteral nutrition. [6]

Surfactant was required by 67 (80.7%) of the newborns with RDS, with a median of one dose. These results were expected because surfactant (prophylactic or as rescue therapy) is used as management of RDS and reduces the risk of pneumothorax and neonatal death in infants with RDS or at risk of developing it. [6] Surfactant was significantly more administrated in infants with more severe grades of RDS. The median surfactant dose was one in mild and moderate RDS and two in severe RDS. This matched our expectations, since the management of ongoing RDS includes a rescue therapy with two or more doses of surfactant. [6]

Postnatal intravenous corticosteroids were used in seven (8.4%) newborns with RDS, because they facilitated the extubation procedure and reduced BPD. [6]

Bronchodilators and inhaled steroids were both used in 11 (13.3%) of the newborns with RDS during the hospitalization in NICU. These therapies are used in a late period of the management of RDS or in an early period of BPD. [32] At discharge, eight (9.6%) newborns with RDS were medicated with bronchodilator, 12 (14.5%) with inhaled corticosteroids and 8 (9.6%) with oxygen. These results could be due to more severe forms of BPD in those infants.

Infants with RDS had a significantly higher median number of days of hospitalization in NICU. Infants with RDS were hospitalized for a median of 33 days, with a number of hospitalization days between one and 191. Infants without RDS had a median of only 11 days of hospitalization in NICU, with a minimum of one day and a maximum of 61 days. Probably the infants with lower median number of days of hospitalization were transferred to another NICU to continue the treatment. Infants without RDS were significantly more transferred to another NICU to continue the treatment. The median number of days until transference was lower in infants without RDS. These results were expected due to the lower morbidity in those infants.

As expected, the mortality rate was significantly higher in newborns with RDS. This could be because those infants have more risk factors for the death causes. Probably the deceased infants were those with the most severe grades of RDS, which also are those that had a significantly lower completion of the cycle of prenatal corticosteroids. Twelve deceased infants with RDS died due to grade IV intraventricular hemorrhage and multiorgan dysfunction, probably because they were not given corticosteroids before birth, or the given corticosteroids did not have an appropriated therapeutic effect due to several causes, including suboptimal administration timing or incomplete cycles. [6] Arrhythmia, extreme prematurity, pulmonary hypoplasia and

pulmonary hemorrhage are associated with immaturity, low birth weight and low gestational age, explaining the death of the other four infants with RDS. [34]

As we expected, a higher request for invasive ventilation and a superior median number of surfactant doses, when adjusted to birth weight and gestational age, were associated with a significantly higher severity of RDS. This could be due to these therapies, used more frequently in newborns with more severe disease, being the management of RDS. [6]

When adjusted to the severity of RDS, a higher birth weight and a higher gestational age were associated with a significant reduction in mortality. These results were compatible with the literature, according to which gestational age is the most important predictor of survival. The lower the gestational age and birth weight, the higher the risk of death. [35] The opposite occurred with the need for vasopressor support, which was significantly associated with an increased mortality. This result could be due to the higher morbidity that occurred in newborns with RDS.

In our study, a time between the last dose of a full cycle of prenatal corticosteroids and the delivery lower than 10.5 hours was associated with a higher risk of onset of RDS, with a sensibility of 80%. An elapsed time between the last dose of a full cycle of prenatal corticosteroids and the delivery lower than 6.5 hours was associated with a higher risk of onset of moderate to severe RDS, with a sensibility of 83.3%. According to the literature, it was determined that the optimal interval between the start of corticosteroid treatment and the delivery is more than 24 hours and less than seven days, which is consistent with the time periods found in our study. [6]

Our study had some limitations. Firstly, as a descriptive retrospective study, it probably has biases, including misclassification bias. Secondly, prenatal corticosteroid administration regimens changed since March 2014, which may have been a confounding factor in the type of prenatal management. However, it was not our aim to compare the effect of both drugs used in prevention of RDS, which have shown a similar effect. Prospective studies with adequate sample sizes could be useful to a better understanding of the morbimortality in these preterm newborns.

Conclusion

Clinical chorioamnionitis, placental abruption and abnormal umbilical flow are risk factors for RDS. Peripartum antibiotherapy is indirectly related to prevention of RDS.

Newborns with RDS have more frequently neonatal co-morbidities, namely BPD, PDA, IVH (≥ grade 3), ROP (≥ grade 2), sepsis, pneumonia, pneumothorax, acute renal failure, thrombocytopenia with platelet transfusion, anemia with red blood cells transfusion and gastroesophageal reflux.

A full cycle of prenatal corticosteroids was fundamental to prevent higher grades of severity of RDS.

Higher gestational age and birth weight were associated with a significant reduction in mortality. Vasopressor support, on the other hand, was associated with an increased mortality.

Delivery in less than 10.5 hours since the last dose of a full cycle of prenatal corticosteroids was associated with a higher risk of onset of RDS, with a sensibility of 80%. A higher risk of onset of moderate to severe RDS occurred in newborns born in less than 6.5 hours since the last dose of a full cycle of prenatal corticosteroids, with 83.3% of sensibility.

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Tables and Figures

Table 1 – Demographic and prenatal data

	Total (n=234)	RDS (n=83)	Without RDS (n=151)	p
Gender, n (%)				
Male	134 (57.3)	44 (53.0)	90 (59.6)	0.330*
Female	100 (42.7)	39 (47.0)	61 (40.4)	0.330*
Birth weight (grams), mean (±SD)	1658 (±578)	1225 (±516)	1896 (±462)	<0.0001§
Gestational age (weeks), median (min-max)	32 (23-34)	30 (23-34)	33 (27-34)	<0.0001¥
Intrauterine growth restriction, n (%)	39 (16.7)	18 (21.7)	21 (13.9)	0.127*
Multiple gestation, n (%)	81 (34.6)	24 (28.9)	57 (37.7)	0.174*
Maternal diseases, n (%)				
Chronic hypertension	23 (9.8)	12 (14.5)	11 (7.3)	0.078*
Human Immunodeficiency Virus infection	1 (0.4)	0	1 (0.7)	0.999∞
Hepatitis B infection	2 (0.9)	1 (1.2)	1 (0.7)	0.999∞
Pregnancy complications, (%)				
Gestational diabetes	21 (9.0)	10 (12.0)	11 (7.3)	0.223*
Gestational hypertension	13 (5.6)	3 (3.6)	10 (6.6)	0.390∞
Pre-eclampsia	46 (19.7)	17 (20.5)	29 (19.2)	0.814*
HELLP syndrome**	7 (3.0)	4 (4.8)	3 (2.0)	0.249∞
Clinical chorioamnionitis	13 (5.6)	10 (12.0)	3 (2.0)	0.002∞
Placental abruption	21 (9.0)	12 (14.5)	9 (6.0)	0.030*
Abnormal umbilical flow	34 (14.5)	29 (22.9)	15 (9.9)	0.007*
Hydramnios	7(3.0)	3 (3.6)	4 (2.6)	0.701∞
Oligoamnios	9 (3.8)	5 (6.0)	4 (2.6)	0.286∞
Prenatal Steroids, n (%)	210 (90.1)	74 (90.2)	136 (90.1)	0.965*
Betametasone	160 (76.2)	52 (70.3)	108 (79.4)	0.137*
Dexametasone	50 (23.8)	22 (29.7)	28 (20.6)	0.175*
Full first cycle	146 (69.5)	50 (67.6)	96 (70.6)	0.650*
Full rescue cycle	8 (3.8)	2 (2.7)	6 (4.4)	0.715∞
Time between the last dose of a full cycle of steroids and delivery (hours), median (min-max)	75 (1-1148)	59 (1-1148)	81.5 (1-1096)	0.271¥
Positive group β streptococcus screening, n (%)	11 (45.8)	5 (55.6)	6 (40.0)	0.675∞
Premature membrane rupture, n (%)	49 (21.1)	13 (16.0)	36 (23.8)	0.166*
Peripartum antibiotics, n (%)	99 (42.3)	27 (32.5)	72 (47.7)	0.025*
Placental histology, n (%)				
Chorioamnionitis	54 (24.3)	25 (30.5)	29 (20.7)	0.101*
Funisitis	7 (3.2)	4 (4.9)	3 (2.1)	0.428∞
Vilitis	14 (6.3)	3 (3.7)	11 (7.9)	0.263∞
Vasculitis	18 (8.1)	9 (11.1)	9 (6.4)	0.220*
Hemorrhage	1 (0.5)	0	1 (0.7)	0.999∞
Ischemia	97 (43.7)	34 (41.5)	63 (45.0)	0.608*

*Chi-square test, ∞Fisher's exact test, §Independent t test, ¥Mann-Whitney U test

** HELLP syndrome: Hemolysis, elevated liver enzymes and low platelet count Syndrome

Table 2 - Delivery and evolution in neonatal intensive care unit

	Total (n=234)	RDS (n=83)	Without RDS (n=151)	p
Delivery, n (%)				
Vaginal	95 (40.6)	26 (31.3)	69 (45.7)	0.032*
C-section	139 (59.4)	57 (68.7)	82 (54.3)	0.032*
Apgar score, n (%)				
1st min <7	74 (31.6)	47 (56.6)	27 (17.9)	<0.0001*
5th min <7	22 (9.4)	17 (20.5)	5 (3.3)	<0.0001*
Resuscitation, n (%)	96 (41.0)	62 (74.7)	34 (22.5)	<0.0001*
Early nasal CPAP, n (%)	75 (32.1)	28 (33.7)	47 (31.1)	0.682*
Early invasive ventilation, (%)	42 (18.1)	40 (48.8)	0	<0.0001∞
Neonatal morbidities, n (%)				
Bronchopulmonary dysplasia	15 (6.4)	15 (18.1)	0	<0.0001∞
Patent *ductus arteriosus*	59 (25.2)	42 (50.6)	17 (11.3)	<0.0001*
Surgical treatment	6 (10.2)	6 (14.3)	0	0.002∞
Necrotizing enterocolitis (≥ grade 2A)	0	0	0	-
Intraventricular hemorrhage (≥ grade 3)	9 (3.9)	7 (8.5)	2 (1.3)	0.010∞
Hydrocephalus	1 (0.4)	1 (1.2)	0	0.355∞
Periventricular leukomalacia	5 (2.2)	3 (3.7)	2 (1.3)	0.346∞
Retinopathy of prematurity (≥ grade 2)	12 (5.2)	11 (13.4)	1 (0.7)	<0.0001∞
Sepsis	27 (11.5)	22 (26.5)	5 (3.3)	<0.0001*
Pneumonia	6 (2.6)	6 (7.2)	0	0.002∞
Pneumothorax	8 (3.4)	8 (9.6)	0	<0.0001∞
Atelectasis	7 (3.0)	7 (8.4)	0	0.001∞
Seizures	3 (1.3)	3 (3.6)	0	0.044∞
Acute renal failure	15 (6.4)	14 (16.9)	1 (0.7)	<0.0001∞
Thrombocytopenia with platelet transfusion	16 (6.8)	16 (19.3)	0	<0.0001∞
Anemia with red blood cells transfusion	58 (24.8)	44 (53.0)	14 (9.3)	<0.0001*
Gastroesophageal reflux	24 (10.3)	17 (20.5)	7 (4.6)	<0.0001*
Vasopressor support, n (%)	15 (6.4)	14 (16.9)	1 (0.7)	<0.0001∞
Vasopressor support (days), median (min-max)	2 (1-25)	2.5 (1-25)	1 (1-1)	0.308¥
Oxygen therapy, n (%)	82 (35.2)	64 (78.0)	18 (11.9)	<0.0001∞
Oxygen therapy (days), median (min-max)	4 (1-191)	6 (1-191)	1.5 (1-6)	<0.0001¥
Invasive ventilation, n (%)	57 (24.4)	57 (68.7)	0	<0.0001∞
Invasive ventilation (days), median (min-max)	5 (1-88)	5 (1-88)	-	-
Parenteral nutrition, n (%)	175 (76.1)	75 (93.8)	100 (66.7)	<0.0001*
Parenteral nutrition (days), median (min-max)	9 (1-90)	14 (1-90)	7 (1-20)	<0.0001¥
Surfactant, n (%)	67 (28.6)	67 (80.7)	0	<0.0001∞
Doses, median (min-max)	1 (1-5)	1 (1-5)	0	<0.0001¥
First dose of surfactant (hours), median (min-max)	1 (0-24)	1 (0-24)	0	0.441¥
Postnatal iv steroids, n (%)	7 (2.9)	7 (8.4)	0	0.001∞
Bronchodilators, n (%)	11 (4.7)	11 (13.3)	0	<0.0001∞
Inhaled steroids, n (%)	11 (4.7)	11 (13.3)	0	<0.0001∞
Stay in NICU (days), median (min-max)	15 (1-191)	33 (1-191)	11 (1-61)	<0.0001¥
Transferred to another NICU, n (%)	59 (25.2)	10 (12.0)	49 (32.5)	0.001*
Days until transference, median (min-max)	6 (1-25)	9.5 (2-25)	5 (1-22)	0.092¥
Treatment at discharge, n (%)				
Bronchodilator	8 (3.4)	8 (9.6)	0	<0.0001∞
Inhaled steroids	12 (5.1)	12 (14.5)	0	<0.0001∞
Oxygen	8 (3.4)	8 (9.6)	0	<0.0001∞
Deceased, n (%)	17 (7.3)	17 (20.5)	0	<0.0001∞
Causes of death, n (%)				
Intraventricular hemorrhage grade IV	6 (35.3)	6 (35.3)	0	0.647∞
Multiorgan dysfunction	6 (35.3)	6 (35.3)	0	0.647∞
Arrhythmia	1 (5.9)	1 (5.9)	0	0.941∞
Extreme prematurity	1 (5.9)	1 (5.9)	0	0.941∞
Pulmonary hypoplasia	2 (11.8)	2 (11.8)	0	0.882∞
Pulmonary hemorrhage	1 (5.9)	1 (5.9)	0	0.941∞

*Chi-square test, ∞Fisher's exact test, §Independent t test, ¥Mann-Whitney U test

Table 3 - Demographic and clinical characteristics according to severity of RDS

	Mild RDS (n=35)	Moderate RDS (n=32)	Severe RDS (n=16)	p
Gestational age (weeks), median (min-max)	33 (27-34)	31 (24-34)	29 (23-34)	0.014¥
Multiple gestation, n (%)	7 (20.0)	8 (25.0)	9 (56.2)	0.025*
Prenatal Steroids, n (%)	33 (94.3)	25 (80.6)	16 (100)	0.082∞
Full first cycle	26 (78.8)	18 (72.0)	6 (37.5)	0.013*
Early invasive ventilation, (%)	11 (31.4)	17 (53.1)	12 (75.0)	0.010∞
Neonatal morbidities, n (%)				
Patent *ductus arteriosus* with surgical treatment	3 (8.6)	0	3 (18.8)	0.044∞
Periventricular leukomalacia	0	1 (3.2)	2 (12.5)	0.043∞
Thrombocytopenia with platelet transfusion	5 (14.3)	4 (12.5)	7 (43.8)	0.035∞
Vasopressor support, n (%)	1 (2.9)	7 (21.9)	6 (37.5)	0.003∞
Oxygen therapy, n (%)	24 (68.6)	24 (75.0)	16 (100)	0.032∞
Invasive ventilation, n (%)	18 (51.4)	25 (78.1)	14 (87.5)	0.016¥
Surfactant, n (%)	22 (62.9)	29 (90.6)	16 (100)	0.001∞
Doses, median (min-max)	1 (1-2)	1 (1-5)	2 (1-4)	0.044¥

*Chi-square test, ∞Fisher's exact test, §One-Way ANOVA, ¥Kruskal-Wallis test

Agradecimentos

À Professora Hercília Guimarães, pela incansável orientação científica, disponibilidade e apoio, fundamentais para a concretização desta dissertação.

Ao Dr. Gustavo Rocha e à Dra. Filipa Flor-de-Lima pela orientação científica e apoio na realização deste projeto.

Aos restantes elementos da Unidade de Cuidados Intensivos Neonatais do Centro Hospitalar de S. João pelo acolhimento e simpatia demonstrados.

À família e amigos por terem demonstrado apoio ao longo de todo o processo de realização deste trabalho.

ANEXOS

Normas da Revista
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- **chapter within a book**: Eyben E. Fathers and sons. In: Rawson B (Ed.). Marriage, divorce and children in ancient Rome. Oxford: Clarendon Press, 1991.
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Parecer

Título do Projecto: "Prenatal corticosteroids and respiratory distress syndrome prevention in infants less than 34 weeks of gestational age"

Nome do Investigador Principal: Patrícia Isabel Azevedo Campos

Serviço onde decorrerá o Estudo: Serviço de Neonatalogia do Centro Hospitalar de S. João

Objectivo do Estudo:

Esta investigação tem como objectivos estabelecer a prevalência da administração de corticosteróides pré-natais em caso de ameaça de parto pré-termo, avaliar a relação entre o tempo decorrido desde a administração de corticosteróides maternos e a prevenção da síndrome de dificuldade respiratória. Procura ainda determinar o tempo a partir do qual se deve considerar a repetição de corticosteróide ante-natal, caso a ameaça de parto prematuro persista.

Concepção e Pertinência do Estudo:

Este estudo visa a elaboração de uma Tese de Mestrado da FMUP, cuja orientação é da responsabilidade da Doutora Hercília Guimarães.

Não haverá qualquer envolvimento directo ou indirecto de doentes neste Estudo, já que se trata de um estudo de natureza retrospectiva.

Benefício/risco: NA

Respeito pela liberdade e autonomia do sujeito de ensaio: NA

Confidencialidade dos dados: Questionada a investigadora sobre a forma de garantir a confidencialidade dos dados obtidos, foi indicado que aos mesmos será atribuída uma codificação de acesso exclusivo da investigadora e dos médicos que vierem a ser envolvidos no estudo.

Elo de ligação: Prof.ª Doutora Hercília Guimarães

Indemnização por danos: NA

Continuação do tratamento: NA

Propriedade dos dados: Visando este projecto de investigação a construção de uma Tese de Mestrado, os dados obtidos serão objecto de apreciação pública.

Curriculum do investigador: Adequado ao perfil da investigação preconizada.

Data previsível da conclusão do estudo: Janeiro 2015

Conclusão: Considerados os objectivos do Estudo, o sentido do parecer inicial aprovado em reunião plenária e os esclarecimentos ora prestados pela investigadora, não se levantam reservas éticas à realização deste projecto de investigação, na sua actual definição metodológica.

Porto e C.H.S.João, 2014-12-18

O Presidente da CES

Doutor Filipe Almeida

CES 254-14

Exmo. Senhor

Presidente do Conselho de Administração do

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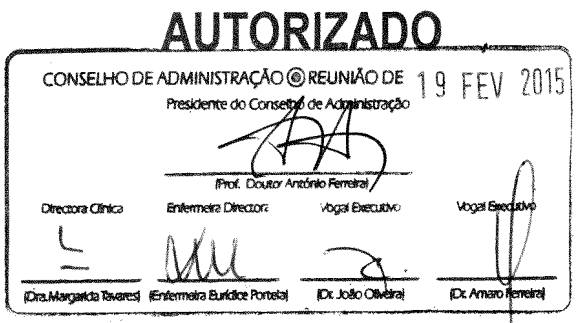

Assunto: Pedido de autorização para realização de estudo/projecto de investigação

Nome do Investigador Principal: Patrícia Isabel Azevedo Campos

Título do projecto de investigação: Prenatal Corticosteroids and Respiratory Distress Syndrome Prevention in Infants less than 34 Weeks of Gestational Age

Pretendendo realizar no(s) Serviço(s) de Neonatologia do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, autorização para a sua efectivação.

Para o efeito, anexa toda a documentação referida no dossier da Comissão de Ética do Centro Hospitalar de S. João respeitante a estudos/projectos de investigação, à qual endereçou pedido de apreciação e parecer.

Com os melhores cumprimentos.

Porto, 30 / Outubro / 2014

O INVESTIGADOR/PROMOTOR

Patrícia Isabel Azevedo Campos

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☐
NÃO APLICÁVEL ☑

8. TERMO DE RESPONSABILIDADE

Eu, Patrícia Isabel Azevedo Campos,

abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 10 / Novembro / 2014

A Comissão de Ética para a Saúde tendo aprovado o parecer do Relator, aguarda que o Investigador/Promotor esclareça as questões nele enunciadas para que possa emitir parecer definitivo.

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética
2014·XII·03

Patrícia Isabel Azevedo Campos
O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de / /

Considerando que foram satisfatórios os esclarecimentos prestados pelo investigador,

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

A Comissão de Ética [illegible] realização deste projecto de investigação.

Prof. Doutor Filipe Almeida
Presidente da Comissão de Ética
2014·12·18