Efficacy of single dose antenatal corticosteroid on reducing the morbidity and mortality of preterm infants: a retrospective cohort study*

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ABSTRACT

Objective: To determine the efficacy of a single dose of antenatal dexamethasone on the neonatal morbidity and mortality of preterm infants born between 24 weeks to 33 weeks and six days age of gestation at a tertiary government hospital.

Methods: A detailed chart review of both maternal and neonatal records of all neonates born between 24 weeks and 33 weeks and 6 days age of gestation at a tertiary government hospital from January 1, 2011 to December 31, 2013 was done. Patients were grouped based on maternal exposure to antenatal dexamethasone. After which, rate of neonatal deaths and morbidities were recorded. Chi-square test for categorical variables, independent t-test for continuous data and logistic regression were used for analysis.

Results: Seven hundred and three maternal-neonatal dyads were included. Of these, 120 (17.1%) were not exposed to any antenatal corticosteroid prior to delivery, 347 (49.4%) were exposed to a single dose of 6-mg dexamethasone, and 236 (33.5%) received a complete course of four doses of 6-mg dexamethasone before preterm delivery. There were better neonatal outcomes from mothers who received completed doses of antenatal corticosteroids than those who received only a single dose, however in comparison to those who have not received any antenatal corticosteroids, the group that received only a single dose had significantly better neonatal outcome. Logistic regression analysis demonstrated that exposure to a single dose of dexamethasone before delivery was associated with reduction in neonatal mortality, and select neonatal morbidities.

Conclusion: It was observed that there was improved neonatal outcomes in neonates given a single dose dexamethasone compared to those who didn't receive any antenatal corticosteroid. Obstetrician gynecologists should not hesitate in administering antenatal dexamethasone even if completion may not seem feasible.

Keywords: antenatal corticosteroid, dexamethasone, incomplete doses, preterm neonates, single dose

INTRODUCTION

Preterm birth remains to be one of the biggest threats towards achieving the World Health Organization Millennium Development Goal of reducing infant mortality despite the advent of advanced medicine and technology.[1]

According to UNICEF Philippines, in the Philippines, 48% of children who die under the age of 5 years are newborns, and 39% of these are from preterm complications, such as respiratory distress syndrome, intraventricular hemorrhage and necrotizing enterocolitis, making this the leading cause of newborn mortality. In 2011, 11,290 deaths were attributed to preterm complications, equivalent of 31 newborn deaths every day.[2] The economic consequences of preterm birth not only affect their family, but also represent a significant societal burden.

As previously mentioned, various complications are observed among neonates born less than 37 weeks due to their physiological immaturity. Pediatric outcomes for those infants born within or after 32 weeks have similar outcomes for those born at term, while the most significant neonatal conditions are noted to occur among those infants who are born before 32 weeks of gestations and a much poor prognosis for those who were delivered before their 26th week.[3]

Despite the improved outcomes for preterm infants as a result of improved perinatal care and interventions aimed at hastening fetal lung maturity through antenatal corticosteroids and artificial surfactant use, preterm birth remains to become a significant cause of morbidity and mortality. Respiratory distress syndrome is one of the common complications experienced by preterm infants, from the lack of pulmonary surfactant which is produced after 30 to 32 weeks of gestation, and can lead to hypoxemia

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and impaired spontaneous ventilation.[4] Preterm infants are also susceptible to the development of cerebroventricular hemorrhage, ineffective thermoregulation, and necrotizing enterocolitis.[5]

The seminal work of Liggins and Howi[6] inspired 35 years of research on fetal lung maturity leading to the more recent studies of Crowley[7], Balci[8], and others that proved the efficacy of reducing neonatal complications from preterm birth through administration of corticosteroids prior to delivery. It is known to accelerate the maturation of developmentally regulated proteins and to stimulate cell differentiation, thus increasing the production of surfactant, improving lung compliance and protecting the intestinal mucosa from significant damage.[9]

Both betamethasone and dexamethasone have shown benefits, and have been extensively studied as antenatal corticosteroid regimens. Since 1994, experts in maternal-fetal medicine and obstetrics have agreed on the use of antenatal corticosteroids.[10] According to clinical guidelines, there are two regimens: the first would be two doses of 12 mg betamethasone given 24 hours apart; and the other would be four doses of 6 mg dexamethasone given 12 hours apart[11]. The guidelines do not recommend one regimen above the other since both kinds of corticosteroids have been found to be of equal effectiveness in reducing the complications associated with preterm birth[12,13], but in our institution, the dexamethasone protocol is more commonly used due to its availability and ease of procurement.

Various meta-analysis and cohort studies evaluating the use of corticosteroids in women at increased risk of preterm birth has concluded that a single course of corticosteroids reduced a number of complications associated with prematurity such as perinatal mortality, respiratory distress syndrome, intraventricular hemorrhage, systemic infections, necrotizing enterocolitis, and cognitive delays among infants delivered before reaching term[7, 14 - 15].

Significant benefits were found in those who were administered with corticosteroids between 26 to 35 weeks age of gestation, and those born within one week of commencing treatment[8].

The completion of a single course of antenatal corticosteroids is not always feasible due to imminent deliveries, and the need to terminate pregnancy as a result of maternal and/or fetal indications. According to our hospital records, approximately 1,000 live preterm births occur annually – with less than half completing the recommended regimen. Although the use of antenatal corticosteroids in the prevention of adverse neonatal outcomes among preterm births has been widely implemented and practiced,only few studies evaluating the effectiveness of a single or incomplete course of antenatal steroid regimen have been made. In practice though, dexamethasone is still given even if only a single dose can possibly be given prior to delivery. It is highly believed that any exposure to antenatal steroids would result to better outcomes for the preterm infant[16-21].

The lack of sufficient data justifying the effectiveness of a single dose or incomplete course of antenatal steroids in reducing the disease and death burden among preterm neonates has made it difficult to create appropriate algorithms and pathways for situations such as imminent preterm delivery or emergency caesarian section during preterm labor. In addition, there has been no documented study in the Philippines that focuses on the effectiveness of a single dose antenatal steroids among women in preterm labor.

OBJECTIVES

General objectives

To determine the efficacy of a single dose of antenatal dexamethasone on the neonatal morbidity and mortality of preterm infants born between 24 weeks to 33 weeks and six days age of gestation at the department of obstetrics and gynecology at a tertiary government hospital.

Specific objectives

a. To compare the neonatal mortality rate between neonates exposed to a single dose of antenatal dexamethasone with those who completed a course of dexamethasone and those who were not exposed at all.

b. To determine the causes among preterm neonates death.

c. To compare the incidence of morbidities of neonates whose mothers were given a single dose of antenatal dexamethasone with those who completed a course of dexamethasone and those who were not exposed at all, based on the following parameters:

   • Respiratory distress syndrome
   • Systemic infections
   • Necrotizing enterocolitis
   • Intraventricular hemorrhage

d. To compare the length of hospital stay of neonates whose mothers were given a single dose of antenatal corticosteroids with those who completed a course of steroids and those who were not exposed at all.

MATERIALS AND METHODS

Study design

A retrospective cohort design was utilized to assess the efficacy of a single dose of dexamethasone in preventing neonatal morbidity and mortality.

Patient population

Singleton neonates who were born between 24 weeks to 33 weeks and six days age of gestation at the obstetric admitting section- labor and delivery room complex of a tertiary government hospital from January 2011 – December 2013 were included. The study population included 703 maternal and neonate dyad divided into three groups. The first group consisted of premature neonates whose mothers were exposed to a single dose of antenatal dexamethasone. Group two consisted of premature neonates whose mothers received a complete a course of antenatal dexamethasone and group three included premature neonates whose mothers were not exposed to antenatal steroids.

The inclusion criteria for the study were:

a. Singleton preterm deliveries
b. A complete neonatal record
c. Corticosteroid administered was dexamethasone

The criteria for exclusion from the study were:

a. Early preterm births (less than 24 age of gestation)
b. Stillbirths
c. Multiple gestations
d. Neonates with fetal congenital anomalies
e. Mothers being given a second or third dose of antenatal dexamethasone
f. Use of Betamethasone as antenatal corticosteroid

Methodology

A detailed chart review of both maternal and neonatal records of all neonates born between 24 weeks and 33 weeks and 6 days age of gestation at the department of obstetrics and gynecology at a tertiary government hospital from January 1, 2011 to December 31, 2013 was done. Medical records of the mothers were reviewed and data were extracted and recorded in a patient data form. The charts of neonates were likewise reviewed and recorded in the patient data form. The neonates were divided into three groups: Group 1 consisted of premature neonates whose mothers were exposed to a single dose of antenatal dexamethasone. Group 2 consisted of premature neonates whose mothers received a complete a course of antenatal dexamethasone and group 3 included the premature neonates whose mothers were not exposed at all to antenatal steroids. Occurrence of neonatal mortalities and morbidities among the three groups were compared.

When there was incomplete data, a further search was done using the department's masterlists of admissions and outcome, the computerized database of the department's perinatology section, and the annual reports.

The data were then entered manually into a spreadsheet and sorted using Excel computer software. The spreadsheet consisted of the maternal and neonatal characteristics, the indications for delivery, and neonatal outcome.

Data Analysis

Descriptive statistics such as mean, mode and frequency were used for the categorical or continuous data variables. A Chi-square test for categorical variables and independent t-test for continuous data were used to determine if any statistical significant difference existed between the groups in terms of maternal factors and neonatal outcomes.

Adjusted differences in survival and neonatal outcomes between the groups were estimated using multiple logistic regression models. These models were adjusted for significant and clinically important baseline population characteristics such as maternal age, gestational age, and birth weight. Cut-off for entry to and removal from models was set at $p<0.05$ and $p>0.10$. The level of significance for all sets of analysis was set at $p<0.05$ using 2-tailed comparisons. Significance levels were not adjusted for multiple comparisons performed.

RESULTS

During the period from January 1, 2011 to December 31, 2013, there were 703 maternal-neonatal dyads that met the inclusion criteria for this study. From the dyads, 120 (17.1%) were not exposed to any antenatal corticosteroid prior to delivery, 347 (49.4%) were exposed to a single dose of 6-mg dexamethasone, and 236 (33.5%) received a complete course of four doses of 6-mg dexamethasone before preterm delivery.

Table 1 shows the baseline characteristics of the study population categorized on the number of antenatal corticosteroids administered to them. The baseline demographic variables between the groups were generally similar except for those that received college education,

Table 1. Baseline Maternal Characteristics of the Study Population

Comparison between those who did not receive any antenatal corticosteroid and those that received a single dose			
	No ACS (n=120)	**Single ACS (n=347)**	***p-value***
Maternal age (years)	28±7.26	27±7.41	.33
Gravidity	3±1.87	3±1.65	.97
Body weight (kilograms)	55.13±9.77	54.05±9.45	.28
Birth weight (grams)	1566.34±670	1822.33±633	.00**
College education (n=210)	44 (36.67%)	57 (16.43%)	.01*
Prenatal consults	3.22±2.51	3.15±2.29	.80
Vaginal delivery (n=381)	70 (58.33%)	177 (51.01%)	.17
Premature rupture of membranes (n=69)	6 (5.00%)	33 (9.51%)	.12
Gestational diabetes mellitus (n=41)	4 (3.33%)	11 (3.17%)	.93
Pre-eclampsia and eclampsia (n=104)	12 (10.00%)	49 (14.12%)	.25
Placental problems (n=11)	1 (9.09%)	4 (36.36%)	.62
Gravidocardiac conditions (n=7)	3 (2.50%)	2 (0.58%)	.11
Other medical conditions (n=257)	28 (23.33%)	114 (32.85%)	.05

Values expressed as either mean±sd or n(%); * - p>0.05, ** - p>0.01

Comparison between those who received a single dose antenatal corticosteroid and those with a complete course			
	Single ACS (n=347)	**Complete ACS (n=236)**	***p-value***
Maternal age (years)	27±7.41	28±7.34	.06
Gravidity	3±1.65	3±1.87	.56
Body weight (kilograms)	54.05±9.45	55.69±11.14	.06
Birth weight (grams)	1822.33±633	1897.20±544	.13
College education (n=210)	57 (16.43%)	109 (46.19%)	.00**
Prenatal consults	3.15±2.29	2.97±2.38	.35
Vaginal delivery (n=381)	177 (51.01%	134 (56.78%)	.17
Premature rupture of membranes (n=69)	33 (9.51%)	30 (12.71%)	.22
Gestational diabetes mellitus (n=41)	11 (3.17%)	26 (11.02%)	.00**
Pre-eclampsia and eclampsia (n=104)	49 (14.12%)	43 (18.22%)	.18
Placental problems (n=11)	4 (36.36%)	6 (54.55%)	.20
Gravidocardiac conditions (n=7)	2 (0.58%)	2 (0.85%)	.70
Other medical conditions (n=257)	114 (32.85%)	115 (48.73%)	.00**

Values expressed as either mean±sd or n(%); * - p>0.05, ** - p>0.0

which was higher among the group that completed their course of antenatal corticosteroids, which shows that the treatment arms are comparable to each other.

Table 2 summarized the neonatal status and their need for additional therapeutic management. It was observed that there were improved neonatal outcomes among those newborns whose mothers received at least a single dose of antenatal corticosteroid compared to those who did not received any dose of dexamethasone.

The initial APGAR score was significantly better in the neonates that received a single dose dexamethasone (8.34 ± 1.45) compared to the group that did not receive any (7.45 ± 2.26). There was also a significant difference between development of neonatal pneumonia (31.70% vs 49.17%), seizures (0.58% vs 8.33%), systemic infections (25.65% vs 50%) and subsequent need for antibiotic regimen (37.45% vs 62.50%) between the two groups.

In terms of neonatal mortality, there were a significant number of deaths, 35 of the 347 neonates (10.09%), from the group that received a single dose antenatal dexamethasone as compared to the group that did not receive any dexamethasone, 30 of 120 neonates (25%). The major cause of death is from sepsis. Although there was a significant difference between the neonatal mortality from the single dose dexamethasone group and the group that just received a single dose (1.27% vs 7.49%), there is still a big difference between those that did not receive any dexamethasone (7.49% vs 22.50%). Lastly, the length of hospital stay was not statistically significant between the three groups.

Logistic regression analysis, as shown in Table 3, demonstrated that exposure to a single dose of

Table 2. Neonatal outcome

Comparison between those who did not receive any antenatal corticosteroid and those that received a single dose	**No ACS (n=120)**	**Single ACS (n=347)**	*p-value*
Neonatal deaths (n=70)	30 (25.00%)	35 (10.09%)	.00**
Gestational age (weeks)	30.57±3.96	31.92±2.77	.00**
Initial Apgar score <7 (n=122)	39 (32.50%)	58 (16.71%)	.00**
Initial Apgar score	7.45±2.26	8.35±1.45	.00**
5" Apgar score	8.12±1.68	8.78±0.71	.00**
Small for gestational age (n=31)	9 (7.50%)	17 (4.90%)	.27
Direct rooming in (n=281)	30 (25.00%)	151 (43.52%)	.00**
Respiratory distress syndrome (n=117)	29 (24.17%)	117 (33.72%)	.05
Neonatal pneumonia (n=272)	59 (49.17%)	110 (31.70%)	.00**
Seizures (n=12)	10 (8.33%)	2 (0.58%)	.00**
Transient tachypnea of the newborn (n=46)	11 (9.17%)	17 (4.90%)	.09
Bronchopulmonary dysplasia (n=11)	3 (2.50%)	7 (2.02%)	.75
Systemic infections (n=245)	60 (50%)	89 (25.65%)	.00**
Respiratory failure (n=5)	2 (1.67%)	3 (0.86%)	.46
Need for antibiotic regimen (n=323)	75 (62.50%)	130 (37.46%)	.00**
Need for mechanical ventilation (n=34)	13 (10.83%)	19 (5.48%)	.05*
Need for oxygen modalities (n=190)	35 (29.17%)	119 (34.29%)	.30
Retinopathy of prematurity (n=124)	13 (10.83%)	57 (16.43%)	.14
Death due to sepsis (n=56)	27 (22.50%)	26 (7.49%)	.00**
Death from congenital anomalies (n=18)	4 (3.33%)	14 (4.03%)	.73
Length of hospital stay (days)	10.50±10.68	10.73±10.50	.86

Values expressed as either mean±sd or n(%); * - p>0.05, ** - p>0.01

Comparison between those who received a single dose antenatal corticosteroid and those with a complete course	**Single ACS (n=347)**	**Complete ACS (n=236)**	*p-value*
Neonatal deaths (n=70)	35 (10.09%)	5 (2.12%)	.00**
Gestational age (weeks)	31.92±2.77	30.39±2.91	.00**
Initial Apgar score <7 (n=122)	58 (16.71%)	25 (10.59%)	.04*
Initial Apgar score	8.35±1.45	8.42±1.30	.59
5" Apgar score	8.78±0.71	8.78±0.72	.99
Meconium stained delivery (n=14)	5 (1.44%)	9 (3.81%)	.07
Small for gestational age (n=31)	17 (4.90%)	5 (2.12%)	.09
Direct rooming in (n=281)	151 (43.52%)	100 (42.37%)	.78
Respiratory distress syndrome (n=117)	117 (33.72%)	31 (13.14%)	.00**
Neonatal pneumonia (n=272)	110 (31.70%)	103 (43.64%)	.00**
Transient tachypnea of the newborn (n=46)	17 (4.90%)	18 (7.63%)	.17
Bronchopulmonary dysplasia (n=11)	7 (2.02%)	1 (0.42%)	.10
Systemic infections (n=245)	89 (25.65%)	96 (40.68%)	.00**
Need for antibiotic regimen (n=323)	130 (37.46%)	118 (50.00%)	.00**
Need for mechanical ventilation (n=34)	19 (5.48%)	2 (0.85%)	.00**
Need for oxygen modalities (n=190)	119 (34.29%)	36 (15.25%)	.00**
Retinopathy of prematurity (n=124)	57 (16.43%)	54 (22.88%)	.06
Death due to sepsis (n=56)	26 (7.49%)	3 (1.27%)	.00**
Length of hospital stay (days)	10.73±10.50	11.25±11.17	.66

Values expressed as either mean±sd or n(%); * - p>0.05, ** - p>0.01

Table 3. Usefulness of a single dose ACS on perinatal outcomes using logistic regression

	OR	95% CI	R^2	*p-value*
Intensive care admission	0.43	(0.27, 0.69)	.038	.00**
Respiratory distress syndrome	1.59	(0.99, 2.56)	.012	.05
Transient tachypnea of the newborn	0.51	(0.23, 1.12)	.015	.09
Bronchopulmonary dysplasia	0.80	(0.20, 3.16)	.001	.75
Neonatal pneumonia	0.48	(0.31, 0.73)	.033	.00**
Sepsis or systemic infections	0.35	(0.22, 0.53)	.068	.00**
Need for mechanical ventilation	0.48	(0.23, 1.00)	.020	.05
Need for oxygen therapy	1.26	(0.81, 1.99)	.003	.30
Need for antibiotic therapy	0.36	(0.23, 0.55)	.063	.00**
Overall survival	0.34	(0.20, 0.58)	.057	.00**

Hosmer–Lemeshow and Omnibus tests at the last step, $p > 0.05$

dexamethasone before delivery was associated with reduction in neonatal mortality, intensive care admissions, need for antibiotic therapy and select neonatal morbidities such as systemic infections and bronchopulmonary dysplasia. Based on this study, neonates that received a single dose of dexamethasone will be 2.08 less likely to develop neonatal pneumonia, 2.86 times less likely to develop systemic infections and 2.78 less likely to subsequently need antibiotic therapy.

DISCUSSION

Preterm birth is one of the most common causes of neonatal mortality, causing more than 1 million deaths each year worldwide. The Philippines ranks 8th out of 184 countries for the number of babies born prematurely, and ranks 17th for the total number of deaths due to complications from preterm birth.[2]

Preterm delivery was associated with multiple neonatal complications such as hyaline membrane disease, higher risk for systemic infections, necrotizing enterocolitis, and intraventricular hemorrhage, as well as need for respiratory support and prolonged hospital stay, even death. Although our results showed a difference in the development of respiratory distress syndrome, neonatal pneumonia, systemic infections, need for antibiotic therapy and mechanical ventilator and oxygen between the neonates that received a full courseand only a single dose dexamethasone, there was a significant difference between those that received a single dose compared to those that didn't receive any dexamethasone. Comparing those who weren't given any dexamethasone, those who received a single dose were directly roomed in more often, developed less neonatal pneumonia and seizures, and had significantly less systemic infections and thus needed less antibiotic treatment.

In this study, newborns from mothers given a single dose of antenatal dexamethasone had a significant decrease in neonatal care admission, development of neonatal pneumonia and other systemic infections and had an overall better survival as compared to those who did not receive any antenatal dexamethasone. Our findings were similar to a published article regarding the efficacy of a single dose antenatal betamethasone in morbidity and mortality of infants. Chee-Ming Huang et al[18] reviewed 134 premature infants, of which 33 received a single dose betamethasone and 101 were in the control group. The requirement for exogenous surfactant therapy and vasopressors were significantly lower among preterm neonates who are exposed to a single antenatal dose of betamethasone compared to those who were not given any steroids. On this basis, they recommended that there should be no hesitation in giving antenatal corticosteroids even if the completion of the regimen is not feasible due to imminent delivery or fetal distress.

In another study by Costa et al[16], that revealed variable results, there was no significant difference observed among those between 28 to 34 weeks, while infants 25-27 weeks age of gestation had the most benefit in decreasing morbidity, need and duration of mechanical ventilator and oxygen support, while infants in the 32-34 weeks subgroup failed to show any differences.

This research was also similar to a retrospective cohort study was conducted by Elimian, et al[17], where the need for vasopressors, the rate of intraventricular hemorrhage and neonatal mortality were approximately two times higher among those not exposed to antenatal corticosteroids compared those whose mothers were given an incomplete dose prior to delivery. Another cohort study yielded a similar result supporting that there is no significant difference with the neonatal outcomes of whether the preterm neonates were exposed to a complete or incomplete course of corticosteroids[19].

Similar observations were also noted in an Australian study showing that the outcomes for receiving an incomplete regimen is more favorable compared to those who were not exposed to steroids at all.[20] However, it can also be noted that exposure to steroids, incomplete or complete, decreased the need for exogenous surfactant

therapy and mechanical ventilation compared to those preterm infants who are not exposed to steroids.

Compare single vs complete. Emphasize importance complete but compared single to none showed with benefit.

CONCLUSION

This study showed that a single dose of dexamethasone administered to women in preterm labor decreased neonatal care admission, development of neonatal pneumonia and other systemic infections and had an overall better survival as compared to those who did not receive any antenatal dexamethasone. Obstetrician gynecologists should therefore not hesitate in administering antenatal dexamethasone even if completion may not seem feasible.

LIMITATION / RECOMMENDATION

Since our study a retrospective cohort, it is limited to the accuracy of record keeping. Future studies may involve a larger population or focus on specific maternal characteristics that influence the clinical outcomes.

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