ORIGINAL ARTICLE

Average Treatment Effects of a Single-dose Antenatal Corticosteroid on the Respiratory Morbidity of Filipino Preterm Neonates

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ABSTRACT

Introduction. Prematurity-related respiratory disorders are an important public health concern that should be treated efficiently and effectively. Antenatal corticosteroid (ACS) therapy has been recommended to hasten fetal lung maturation in pregnancies at risk but has not been delivered adequately in low to middle-income countries. This study aimed to estimate the treatment effects associated with the use of a single-dose antenatal corticosteroid on the incidence of respiratory-associated morbidity among prematurely delivered neonates.

Methods. This was a retrospective cohort study of neonates delivered at 24 to 33 weeks gestation at a tertiary hospital comparing outcomes in those given single-dose ACS with those given no ACS. Association was estimated using logistic and propensity score (PS) analyses, as well as average treatment effect (ATE) and among those treated (ATET).

Results. Most neonates (78.11%) received a single dose before delivery (single-dose ACS group) and only a few (21.89%) did not receive any dose (no ACS dose group). The odds ratio of respiratory morbidity in the single-dose ACS group was 0.44 (0.23-0.84) from an adjusted logistic regression model and 0.33 (0.17-0.80) from the PS matching model. The latter model was used to estimate that the average treatment effect from a single-ACS dose on the entire sample was -0.09 (-0.03 to -0.15), while its effect among the actual recipients was -0.08 (-0.02 to -0.15).

Conclusion. There is a small benefit attributed to the single-dose ACS, reinforcing the need for dose administration and completion. Future studies are recommended to clarify the estimated association and improve on the methodological constraints encountered.

Keywords: antenatal corticosteroids, respiratory morbidity, propensity score, preterm neonates

INTRODUCTION

Respiratory disorders cause significant morbidity and mortality among preterm neonates, especially in developing countries.[1] The underlying pathophysiology for these respiratory conditions is not yet fully understood but is attributed to the physiological immaturity of the fetal lung, limited surfactant production, underdeveloped organs, and a compromised immune function.[2] Preterm neonates can suffer from transient tachypnea of the newborn, respiratory distress syndrome, persistent pulmonary hypertension, or even apnea.[3]

These respiratory problems affect about 86 to 95% of extremely preterm infants (less than 25 weeks of gestational age) and present as tachypnea, use of accessory muscles for breathing (e.g., intercostal retractions, alar flaring, gasping), cyanosis, or hemodynamic instability. These necessitate intensive care such as mechanical ventilation, artificial

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surfactant, and vasopressors.[4] Preterm neonates are more likely to have poor pulmonary function, more iatrogenic complications, and an increased likelihood of morbidity during their lifetime.[4,5]

An estimated 14.84 million newborns were born preterm in 2014, comprising 10.6% of all live births.[1] Respiratory disorders affect 2% of these (a staggering 296,800 neonates), carrying a case fatality rate of 41-50%.[6] In 2011 alone, about 11,290 deaths were attributed to preterm complications–the equivalent of 31 newborn deaths per day.[7,8] Almost half of under-five deaths occur in newborns. In India, respiratory distress was one of the most common disorders encountered within the first 48–72 hours of life, occurring in up to 12% of live births, and causing 20% of neonatal mortality.[9] In the Philippines, respiratory distress syndrome is the top cause of neonatal death (20.1%), together with sepsis of the newborn (20.1%), and diseases related to low birth weight (15.3%).[10]

Prematurity-related respiratory disorders are important public health concerns that must be effectively treated. The administration of antenatal corticosteroids (ACS) is an appropriate and sustainable intervention to prevent prematurity-related complications.[11,12] Corticosteroids are administered to a woman at risk for preterm delivery, hastening the maturation of the fetal lung, and increasing surfactant production.[13] ACS improves health outcomes and reduces overall health care costs.[14]

In the Philippines, Dexamethasone is commonly given in four doses twelve hours apart.[15] However, preterm labor is unpredictable and can preclude dose completion,[16] leaving ACS underutilized.[17,18] While current practice guidelines recommend dose completion, local policies do not give explicit provisions in these circumstances.[19] Few have studied the benefit of incomplete dosage,[20] and some of these have inconclusive results.[21] Moreover, experimental designs to address this inquiry are unethical and near-impossible due to the irregularity of preterm birth. These have made it difficult to encourage the administration of a single dose of ACS when there is no guarantee that succeeding doses can still be given.

Hence, this study aimed to estimate the treatment effects associated with the use of a single-dose antenatal corticosteroid on the incidence of respiratory-associated morbidity among prematurely delivered neonates.

MATERIALS AND METHODS

Subjects, Setting, and Institutional Review Board Approval

The dataset used in this retrospective cohort was derived from a tertiary level institution with obstetrics and neonatology specialties for a better ascertainment of exposure and outcomes.[22] We collected the clinical and demographic data of 562 maternal and neonatal dyads delivered at 24 to less than 34 weeks of gestation, between January 1, 2011, and December 31, 2013. The exposed group was composed of neonates delivered who received a single, 6 mg dose of Dexamethasone intramuscularly before birth, with no succeeding doses because their delivery occurred earlier than the scheduled administration. The control group consisted of neonates who received no doses at all.

Dyads who were delivered at earlier than 24 weeks, were multiple gestations, had congenital anomalies, or later demised in utero were excluded from the study due to a lack of indication or consensus for ACS therapy among these participants. In addition, we excluded data from neonates who received Betamethasone in utero to improve the precision of the estimates.

Permission was sought from the researchers who reviewed the medical records. Any identifiers or information irrelevant to the current study were removed before data processing and analysis. The conduct of the study [2020-770-01] was also approved by the University of the Philippines Manila Research Ethics Board.

Variables in the Dataset

The predictor variables extracted from the electronic dataset included maternal variables (such as maternal weight in kilograms, history of abdominal delivery), co-morbid conditions (such as hypertension, diabetes mellitus, and placental disorders), maternal age, level of education, number of pregnancies, and the presence of high-risk obstetric complications. We also derived neonatal covariates like birth weight in grams, age of gestation during delivery, pediatric aging, sex of the baby, presence of premature rupture of membranes, and the fifth minute Apgar score.

The timing of the ACS dose was not available in the dataset. We assumed it to be within twelve hours from delivery since no succeeding dose was given. The variables for the propensity score (PS) estimation model were selected using a causal diagram. This emulates the "randomization" in experimental studies by determining the probability of receiving the exposure using a set of covariates.[23] Outcome variables (such as birth weight, birth percentile, fifth minute Apgar score, and sex of the neonate) were not included in the PS estimation model.

Outcome Measures

The primary outcome variable was the incidence of respiratory-associated morbidity. This is a dichotomous variable indicating the presence of at least one/any of these conditions: the presence of respiratory distress syndrome (RDS) or transient tachypnea of the newborn, the need for surfactant use, the need for oxygen support specifically the use of continuous positive airway pressure, oxygen hood or mechanical ventilation, the occurrence of respiratory failure, and/or mortality due to respiratory failure.

Until recently, RDS was the lone outcome for ACS studies. It has fallen out of favor since it does not correlate with long-term outcomes.[24] Other outcomes such as infectious

morbidity outcomes (i.e., neonatal pneumonia, sepsis, need for antibiotic therapy), and intensive care admission was also considered, but treatment effects for these were beyond the scope of the current study.

Statistical Analysis

Stata version 13 was used for theour multiple analyses.[25] A previous study has established the clinical and demographic characteristics and outcomes between the two groups. The unadjusted and multivariable odds ratios for ACS exposure and respiratory morbidity were estimated using logistic regression.

Similarly, propensity scores were estimated using the conventional logistic regression model. The maternal and neonatal covariates were included in the propensity score estimation model using a direct acyclic graph. The extent of covariate balance and region of common support between the exposed and unexposed groups were repeatedly evaluated along with an estimation of a score. After sufficient evidence suggesting covariate balance and overlap had been met, the estimated scores were implemented using the pre-planned conditioning techniques. Given the limitations present in the dataset, the PS matching model was used to estimate the average treatment effects and numbers needed to treat.

RESULTS

There were 562 maternal and neonatal dyads included. A fifth of the neonates did not receive any dose of antenatal corticosteroids (no ACS dose group), while the remaining neonates received a single dose of antenatal corticosteroids before delivery (single-dose ACS) (Table 1).

A tenth of these neonates was classified as early preterm during delivery. The majority weighed less than 2,500 grams upon delivery (Table 2).

Table 1. Clinical and demographic characteristics of the women in the study

Characteristics	Overall n (%)	No ACS dose n (%)	Single-dose ACS n (%)
Frequency *(Percentage)*	562 (100)	123 (21.89)	439 (78.11)
Age *(in years ± SD)*	27.19 ± 7.47	27.61 ± 7.19	27.07 ± 7.55
19 to 34 years	388 (69.04)	89 (72.36)	299 (68.11)
≤18 or ≥35 years	174 (30.96)	34 (27.64)	140 (31.89)
Level of education			
Reached elementary	73 (12.99)	12 (9.76)	61 (13.90)
Reached high school	341 (60.68)	66 (53.66)	275 (62.64)
Reached college	148 (26.33)	45 (36.59)	103 (23.46)
Maternal weight *(in kg ± SD)*	54.77 ± 9.92	55.10 ± 9.73	54.67 ± 9.98
Median number of pregnancies *(range)*	2 (1-10)	2 (1-10)	2 (1-10)
Median number of live births *(range)*	1 (0-9)	1 (0-8)	1 (0-9)
Number of prenatal visits			
≤4 consults	415 (73.84)	88 (71.54)	327 (74.49)
>4 consults	147 (26.16)	35 (28.46)	112 (25.51)
Poor obstetric history			
Absent	459 (81.67)	98 (79.67)	361 (82.23)
Present	103 (18.33)	25 (20.33)	78 (17.77)
History of abortion	75 (13.35)	21 (17.07)	54 (12.30)
History of preterm labor	42 (7.47)	7 (5.69)	35 (7.97)
Presence of conditions			
Cardiovascular disease	84 (14.95)	15 (12.20)	69 (15.72)
Gestational diabetes	27 (4.80)	4 (3.25)	23 (5.24)
Placental conditions	10 (1.78)	1 (0.81)	9 (2.05)
Other high-risk pregnancies	30 (5.34)	5 (4.07)	25 (5.69)
Other co-morbid conditions	11 (1.96)	-	11 (2.51)
Type of labor			
Spontaneous preterm labor	356 (63.35)	92 (74.80)	264 (60.14)
Obstetric-induced	83 (14.77)	15 (12.20)	68 (15.49)
Medical-induced	123 (21.89)	16 (13.01)	107 (24.37)
Mode of delivery			
Vaginal	346 (61.57)	83 (67.48)	263 (59.91)
Abdominal	216 (38.43)	40 (32.52)	176 (40.09)

Neonatal pneumonia and the need for mechanical ventilation were more prevalent among neonates not exposed to any steroid dose, as seen in Table 3. There were no significant differences in the occurrence of other features of composite respiratory distress in the sample.

Due to the observational nature of the study, there are inherent differences between the groups that affect outcomes through selection bias. Hence, the propensity score approach is attractive for such observational data with several potential confounders in a small number of observations. Propensity score analysis controls for confounding factors and biases by modeling the selection mechanism or allocation of treatment and using a single scalar vector to reduce the dimensionality of data.[26]

The estimated model demonstrated satisfactory fit using the Hosmer-Lemeshow goodness-of-fit test (X^2 = 8.90, p = 0.35), and there was no influential stratum noted (Mantel-Haenszel X^2 = 2.78, p = 0.95). The c-statistic also showed acceptable characteristics of the estimated PS as a classifier of exposure (0.71, 95% CI = 0.66–0.77); a low Brier score (0.1465) indicated better prediction probabilities.[27] Covariate balance was also achieved in the PS estimation model.

Table 2. Clinical and demographic characteristics of the neonates in the study

Characteristics	Overall n (%)	No ACS dose n (%)	Single-dose ACS n (%)
Frequency *(Percentage)*	562 (100)	123 (21.89)	439 (78.11)
Age of gestation *(in weeks ± SD)*	31.81 ± 2.85	30.86 ± 3.41	32.08 ± 2.62
Extremely preterm (< 28)	71 (12.63)	30 (24.39)	41 (9.34)
Very preterm (28 to < 32)	243 (43.24)	50 (40.65)	193 (43.96)
Late preterm (32 to < 37)	248 (44.13)	43 (34.96)	205 (46.70)
Birthweight *(in grams ± SD)*	1785.24 ± 625.95	1570.29 ± 670.08	1845.47 ± 600.14
Very low (< 1500 g)	172 (30.60)	55 (44.72)	117 (26.65)
Low birthweight (< 2500 g)	320 (56.94)	53 (43.09)	267 (60.82)
Non-low birthweight	70 (12.46)	15 (12.20)	55 (12.53)
Rupture of membranes			
Yes	53 (9.43)	8 (6.50)	45 (10.25)
No	509 (90.57)	115 (93.50)	394 (89.75)
Sex of the neonate			
Female	252 (44.84)	50 (40.65)	202 (46.01)
Male	310 (55.16)	73 (59.35)	237 (53.99)
Median 1st minute Apgar score *(range)*	9 (1-9)	9 (2-9)	9 (1-9)
5th minute Apgar score			
Poor (<7)	48 (8.54)	26 (21.14)	22 (5.01)
Good (7-9)	514 (91.46)	97 (78.86)	417 (94.99)
Term status			
Full term	126 (22.42)	32 (26.02)	94 (21.41)
Preterm	436 (77.58)	91 (73.98)	345 (78.59)
Median Birth Weight Percentile *(range)*	11 (1-97)	7 (1-97)	12 (1-97)
Pediatric aging category			
Appropriate for GA	286 (50.89)	45 (36.59)	241 (54.90)
Small for GA	260 (46.26)	74 (60.16)	186 (42.37)
Large for GA	16 (2.85)	4 (3.25)	12 (2.73)

Table 3. Distribution of neonatal outcomes between treatment groups

Outcomes	Overall n (%)	No ACS n (%)	Single-dose ACS n (%)	*p*-value
Composite respiratory morbidity				
Respiratory distress syndrome	167 (29.72)	35 (28.46)	132 (30.07)	0.73
Transient tachypnea (TTN)	36 (6.41)	11 (8.94)	25 (5.69)	0.19
Neonatal pneumonia	217 (38.61)	61 (49.59)	156 (35.54)	0.01*
Respiratory failure	10 (1.78)	4 (3.25)	6 (1.37)	0.16
Need for oxygen support	223 (39.68)	55 (44.72)	168 (38.27)	0.20
Needed mechanical ventilation	29 (5.16)	11 (8.94)	18 (4.10)	0.03*

p-value < 0.05

Table 4. Summary of the statistical models for single-dose ACS and respiratory morbidity

Models	N	OR	95% CI	SE
Crude logistic model	562	0.43	0.27–0.67	0.099
Adjusted logistic model	562	0.44	0.23–0.84	0.145
Propensity score model	546	0.37	0.17–0.80	0.147

Several models were considered to examine the effects of exposure to a single-dose ACS on reducing respiratory complications among preterm neonates (Table 4). The crude logistic regression model and the adjusted model (accounting for significant confounders such as a poor obstetric history, neonatal birth weight, and the age of gestation during delivery) showed that the single-dose ACS group was less than half as likely to experience respiratory morbidity. There were no effect measure modifiers or significant interactions identified in either regression model.

The estimated PS was implemented using an optimal (kernel) matching algorithm and followed by covariance adjustment to address residual imbalances from the previous conditioning procedure. There were sixteen (2.85%) unmatched observations in a similar proportion between the groups which were excluded to better emulate the counterfactual scenario.[28] The PS matching model showed a stronger effect of respiratory morbidity being less likely among those exposed to a single-dose ACS than not receiving any dose before delivery.

The average treatment effect (ATE) and the average treatment effect on the treated (ATET) were estimated using the PS matching model. The ATE (-0.09, CI = -0.03 to -0.15, $p < 0.01$) alluded to a nine percent reduction in the risk of developing respiratory morbidity among the single-dose group. The effect on those who received a single-dose ACS (ATET) (-0.08, CI = -0.02 to -0.15, $p = 0.01$) was slightly different from the effect estimated from the overall sample.

Another way of looking at these treatment effects is via a similar metric known as the number needed to treat (NNT). The ATE suggested that there is a need for 10 preterm neonates to receive a single-dose ACS to prevent at least one case of respiratory-associated morbidity. The risk reduction ascribed to a single-dose ACS was equivalent to at least one reduced case of respiratory morbidity when 12 pre-term neonates received a single dose of antenatal corticosteroid.

DISCUSSION

Prematurity-related respiratory disorders are an important public health concern that should be treated efficiently and effectively. Antenatal corticosteroid therapy has been recommended to hasten fetal lung maturation in pregnancies at risk but has not been delivered adequately in low to middle-income countries.[17] The unpredictability of preterm labor leads to inadequate dosing before delivery.[22,29]

We agree with previous authors that partial corticosteroid doses improve outcomes if completion is not possible. Our computed average treatment effects show that exposure to a single-dose antenatal corticosteroid dose appears to have a small risk reduction in the development of prematurity-related respiratory morbidity when compared to not receiving any dose at all. This small effect is attributed to the incomplete feature of the exposure[20-26,30,31]; we may expect a larger effect with a completed course.[32,33]

Even though both measures of average treatment effects showed a reduction of risk, the effect in the entire sample (ATE) was slightly higher than the effects among those who received the dose (ATET). This is attributed to confounding factors.[34] Indication bias confounds the selection of women who receive ACS (women with comorbid conditions, at higher risk of early delivery, etc.).[35] This important limitation has necessitated the use of unconventional analytic strategies.

A single dose of ACS did not result in potential harm to the neonate, as feared by some authors.[36-38] The proportion of infection (including sepsis and pneumonia) was not higher in the single-dose group–which suggests that one dose of ACS does not result in suppression of the immature neonatal immune system. However, the occurrence of post-partum complications such as poor blood glucose control in those with gestational diabetes or fluctuating blood pressure levels as a response to glucocorticoid therapy[39] was beyond the scope of the current study.

The study groups differed in their clinical and demographic characteristics. There are important methodological constraints attributed to the retrospective nature of the study design and its relatively small number of observations; hence, the use of propensity scores.[40]

The PS matching model offers a degree of "double robustness" since covariance adjustment was performed after implementing the first conditioning technique.[41] Moreover, the estimated effects of treatment (exposure) presented in the study used terms like the ones used in experimental study designs such as average treatment effects, risk reduction, and numbers needed to treat instead of only odds ratios presented in standard multivariable analysis.[42]

However, the exposure effect estimated must be interpreted carefully given the inherent limitations in the analysis performed. The retrospective nature of the dataset, the relatively small sample size, the disparate proportion of unexposed individuals, and the treatment effect estimated are not robust in the possible presence of unmeasured confounding factors.[43]

Another important limitation is that the findings of the study cannot be generalized to other populations or other settings. The sample population was derived from a tertiary referral institution that specializes in complex cases; thus, the distribution of the exposure groups and the covariates might have differed at a primary level women's health facility. The protective effect from any dose of prenatal corticosteroid is not observed in community-based facilities.[44] The study also

showed that complex analytic approaches such as propensity score methods should not be seen as a substitute for traditional analysis, but rather as a complementary strategy. These strategies cannot remedy poor study design or poor quality of gathered data.

Future studies should be done prospectively, include a larger population, ensure more equivalent distribution of exposure, analyze dose-response analysis, or analyze the additive effects of subsequent antenatal corticosteroid doses. Studies can also focus on addressing the reasons for sub-standard delivery of prenatal corticosteroids in low-resource environments.[45]

CONCLUSION

A single dose of prenatal steroids is appropriate when there is an indication of imminent preterm delivery, even without the possibility of a succeeding dose.[15,46] We do not suggest that an incomplete dose is a substitute for completed doses.

The benefit attributed to this single-dose antenatal corticosteroid is still unclear. While the benefit from single-dose ACS is small compared to the benefit from a completed regimen, the estimated treatment effects show a possible risk reduction in terms of respiratory-associated morbidity compared to no dose at all, and without notable adverse effects to either the mother or the newborn.

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Statement of Authorship

Both authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising, and approved the final version submitted.

Author Disclosure

Both authors declared no conflicts of interest.

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