The Thai Journal of Pharmaceutical Sciences

Volume 45
Issue 5 *2021*

Article 12

1-1-2021

Short-term antenatal corticosteroid increases risk of respiratory morbidity in late preterm infants

Nithipun Suksumek

Pithi Chanvorachote

Amuchou Soraisham

Abhay Lodha

Albert Akierman

See next page for additional authors

Short-term antenatal corticosteroid increases risk of respiratory morbidity in late preterm infants

Authors

Nithipun Suksumek, Pithi Chanvorachote, Amuchou Soraisham, Abhay Lodha, Albert Akierman, and Carlos Fajardo

Original Article

Thai Journal of Pharmaceutical Sciences

Short-term antenatal corticosteroid increases risk of respiratory morbidity in late preterm infants

Nithipun Suksumek[1], Pithi Chanvorachote[2], Amuchou Soraisham[3], Abhay Lodha[3], Albert Akierman[3], Carlos Fajardo[3]

[1]Department of Pediatrics, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand, [2]Department of Pharmacology and Physiology, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand, [3]Department of Pediatrics, Faculty of Medicine, University of Calgary, Alberta, Canada

Corresponding Author:
Nithipun Suksumek, Department of Pediatrics, Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok 10400, Thailand.
Phone:+6627634109.
E-mail: drnithipun@hotmail.com

Received: Jan 18, 2021
Accepted: Mar 12, 2021
Published: Nov 04, 2021

ABSTRACT

Background/Aim: Although antenatal corticosteroid (ANCS) is beneficial for preventing respiratory distress in preterm infants, the effect of ANCS on late preterm infants (LPI) is still unknown. This study aimed at investigating the effect of ANCS on respiratory morbidity of LPI. **Materials and Methods:** In matched cohort study, LPI of mothers who received ANCS (ANCS group) at 24–34 weeks of GA were matched with LPI of no ANCS (non-ANCS group) by gestational age and birth weight. **Results:** During 2 years, the ANCS group was 10.6% (191/1,810) in LPI and only 177 neonates met the criteria for inclusion and were ANCS group. The mean gestational age was 34.6 ± 0.7 weeks in both groups. Birth weights were 2270 ± 405 g and 2265 ± 401 g in ANCS and non-ANCS groups, respectively. Of the 177 infants whose mothers received ANCS, overall respiratory morbidities were 31.6% comparing to 30.5% in non-steroid group. Although decrease trend toward of RDS (4% vs. 8.5%, $P = 0.07$) and surfactant administration (3.4% vs. 6.2%, $P = 0.21$) was observed in steroid group, administration of steroid < 24 h before gestation significantly increase RDS compared with non-treatment (33.3% vs. 8.5%, $P = 0.04$). **Conclusions:** ANCS did not decrease risk of respiratory morbidity. Nevertheless, treatment with ANCS for a short period (<24 h) may increase RDS in LPI.

Keywords: antenatal corticosteroids, late preterm infant, respiratory morbidity

INTRODUCTION

Prematurity rate is increasing in the past 10 years in North America.[1] Late preterm infant (LPI) accounts for approximately seventy-five percent of all preterm infants. LPIs are infants born between 34 weeks and 36 weeks and 6 days.[2] Although LPIs appear to have general physiological and metabolic features similar to those of term infants, there are concerns regarding increased risk of morbidity and mortality.[3-6] There are several respiratory morbidities usually found in LPI including respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), and pulmonary hypertension.[7-9] These respiratory complications found to be related to gestational age, as 50% of infants born at 34 weeks gestation were found with complications; the incidence of such complications declines to 15% and 8% at 35- and 36-weeks' gestation, respectively.[10]

There is a standard treatment of antenatal corticosteroids (ANCS) administration for prevention of respiratory morbidities in preterm infants (24–34 weeks of gestation). ANCS was proved to increase synthesis and secrete of surfactant resulted in fetal lung maturation.[11] Such beneficial effect of ANCS use was demonstrated in a large randomized control trial of preterm pregnancy, and the results showed that RDS and mortality rate were significantly decreased after a single course of ANCS administration.[12] Furthermore, the administration of ANCS was shown to reduce the use of surfactant use.[13] Although the benefits of ANCS in preterm infants are known, the effect of ANCS administration on LPI (34–36 weeks of gestation) is largely unknown. Therefore, this study aimed at investigating either beneficial or adverse effects of ANCS administration on respiratory morbidity of LPI.

MATERIALS AND METHODS

Study Population

This retrospective matched cohort study was conducted in LPI (gestational age between $34^{0/7}$ weeks and $36^{6/7}$ weeks), who were born at three neonatal intensive care units (NICU) at Calgary (Foothills Medical Centre, Peter Lougheed Centre, and Rockyview General Hospital), Alberta between January 1, 2010 and December 31, 2011.

The ANCS group was LPIs who were born to mothers received complete doses of ANCS therapy at 24–34 weeks of gestational age as per ACOG recommendation. Non-ANCS group was matched with ANCS group by gestational age and birth weight (± 100 g). The interval of ANCS given prior to delivery are < 24 h, 24-48 h, 48 h–1 week, 1–2 weeks, and >2 weeks before delivery in steroid group. We excluded infants with major congenital anomalies and chromosomal disorders.

Data Collection

The research protocol was submitted to Child Health Research Office for Scientific review and then to the Conjoint Health Institute Research Ethics Board at the University of Calgary committee for approval to review the medical records. Patient confidentiality was maintained throughout the study by coding each patient with a unique identity number and the data entry also maintained. We performed chart review for all eligible infants. We collected maternal and neonatal demographic characteristics, antepartum morbidity, and neonatal outcomes. These included gestational age, birth weight, gender, multiple births, gestational hypertension, gestational diabetes, smoking, prolonged rupture of amniotic membrane (more than 18 hours), intrauterine growth restriction (<10^{th} percentile), antepartum hemorrhage, antenatal antibiotics, mode of delivery, meconium stained amniotic fluid, positive pressure ventilation during resuscitation. We collected neonatal respiratory outcomes included RDS (known as hyaline membrane disease is inadequate pulmonary surfactant due to preterm birth), TTN (known as wet lung is observed clinically as a relatively mild, self-limited disorder most commonly affecting infants who are born at or near-term gestation), and pneumothorax (air-leak in pleural space diagnosed by chest x-ray). The need for surfactant (will be administered if respiratory distress presence when oxygen needed more than 30% with nasal continuous positive pressure ventilation), ventilation support, hypoglycemia, jaundice requiring phototherapy, postnatal antibiotics, and length of hospital stayed, and mortality rate were also collected.

Statistical Analysis

We compared the demographics and neonatal outcome between the two groups. Categorical variables (rate of respiratory morbidity, surfactant administration, complication, gender, maternal complication) were analyzed using chi-square. Continuous variables (gestational age, birth weight) were analyzes using t-test. The difference in comparison of the proportion respiratory morbidity in different period of ANCS were analyzed using comparing two proportions analysis with level of significant of 0.05. Statistical analyzes were performed using IBM SPSS Statistics Version 22. All *P* values were based on two-sided test results, and a value <0.05 was considered statistically significant.

RESULTS

A total of 1810 LPI were admitted during study period. One hundred and ninety-one (10.6%) infants were exposed to ANCS. Fourteen infants were excluded because of major congenital or chromosomal anomalies. Remaining 177 infants exposed to antenatal steroids were matched to 177 infants without exposure to antenatal steroid.

Of the 177 infants exposed to ANCS, 32 (18.1%) infants received steroids within 1 week of delivery, 11 (6.2%) infants within 1–2 weeks prior to delivery and 134 (75.7%) infants received more than 2 weeks before delivery.

The mean gestational age was 34.6 ± 0.7 weeks in both groups. Birth weights were 2270 ± 405 g and 2265 ± 401 g in steroids group and non-steroids groups, respectively. There were no differences between the two groups in baseline characteristics except for multiple births and antepartum hemorrhage. ANCS exposure groups were more likely to be of multiple gestations and more likely to have antepartum hemorrhage as presented in Table 1.

The rate of RDS was lower in ANCS group but not statistically significant (4.5% vs. 8.5%, $P = 0.13$). Similarly, there was a statistically non-significant increased rate of TTN among infants of steroid group. There was a significant decrease in RDS ($P = 0.03$) in comparing among various periods of steroid administration (<24 h, 24–48 h, 48 h–1 week, 1–2 weeks, and >2 weeks). There was no difference in infants without RDS and TTN.

In sub-group, analysis by gestational age comparing between both groups revealed no significant difference. This study revealed decreased trend toward in RDS in overall gestational age ($P = 0.07$). Descriptive analysis regarding respiratory morbidities was classified by the duration of last dose of ANCS before delivery and gestational age. Regarding secondary outcome, the rates of exogenous surfactant treatment were found to be slightly higher in non-steroid group compared with steroid group (3% vs. 6%, $P = 0.21$). No statistically difference in mode of ventilation including nasal prong, nasal continuous positive airway pressure (CPAP), or biphasic CPAP, and mechanical ventilation as shown in Table 2.

Table 3 reveals that RDS in non-steroid control was significantly lower than that of infants received steroid <24 h before delivery (*8.5*% vs. 33.3%, $P = 0.04$). There was no difference in other period of ANCS administration.

DISCUSSION

Treatment of ANCS was clinically proved to benefit neonatal outcome in terms of lung function and decrease mortality rate. To recently, the beneficial effect of ANCS on neonates of more than 34 weeks of gestation is still elusive.[14] Here, we have shown that treatment with ANCS had no preventive effect on respiratory morbidity in LPI. Interestingly, administration of ANCS for short period (<24 h) increased the incidence of RDS in LPI.

Table 1: Comparison of demographic parameters between ANCS group and non-ANCS group

Data	Steroids (*n*=177)	No Steroids (*n*=177)	*P*
Gestational age (weeks), mean±SD*	34.6±0.74	34.6±0.74	1.00
Birth weight, grams, mean±SD*	2270±405	2265±401	0.90
Male gender, *n* (%)	81 (46)	90 (51)	0.33
Gestational hypertension, *n* (%)	35 (20)	35 (20)	1.00
Gestational diabetes, *n* (%)	14 (8)	19 (11)	0.70
Smoking, *n* (%)	13 (7)	21 (12)	0.14
Prolonged rupture of membrane>18 h, *n* (%)	32 (18)	21 (12)	0.10
Intrauterine growth restriction<10th centile, *n* (%)	23 (13)	27 (15)	0.71
Oligohydramnios, *n* (%)	8 (5)	2 (1)	0.06
Antepartum hemorrhage, *n* (%)	27 (15)	12 (7)	0.01
C-section, *n* (%)	92 (52)	78 (44)	0.13
Intermittent positive pressure ventilation, *n* (%)	40 (23)	31 (18)	0.23

*Data presented as mean±SD: using unpaired *t*-test. Data presented as *n* (%): using Chi-square test

Table 2: Primary and secondary outcome

Data *n* (%)	ANCS group (*n*=177)	Non-ANCS group (*n*=177)	*P*
Overall RD	56 (31.6)	54 (30.4)	0.81
- GA 34 weeks	29 (16.4)	33 (18.6)	0.58
- GA 35 weeks	15 (8.4)	13 (7.3)	0.69
- GA 36 weeks	12 (6.8)	8 (4.5)	0.36
RDS	7 (4)	15 (8.5)	0.07
- GA 34 weeks	6 (3.4)	10 (5.6)	0.31
- GA 35 weeks	0 (0)	4 (2.3)	NA
- GA 36 weeks	1 (0.6)	1 (0.6)	1.00
TTN	45 (25.4)	37 (21)	0.31
- GA 34 weeks	21 (11.9)	21 (11.9)	1.00
- GA 35 weeks	14 (7.9)	9 (5.1)	0.28
- GA 36 weeks	10 (5.6)	7 (4.0)	0.45
Pneumothorax	1 (0.6)	2 (1.1)	0.45
- GA 34 weeks	0 (0)	2 (1.1)	NA
- GA 35 weeks	0 (0)	0 (0)	NA
- GA 36 week	1 (0.6)	0 (0)	NA
Surfactant	6 (3.4)	11 (6.2)	0.21
Nasal prong	29 (16.4)	24 (13.6)	0.45
Nasal CPAP/Biphasic CPAP,	28 (15.8)	24 (13.6)	0.54
Mechanical ventilation,	8 (4.6)	11 (6.2)	0.47
Antibiotic	76 (42.9)	67 (37.8)	0.33
Death	0 (0)	0 (0)	1.00
Using Chi-square			

ANCS: antenatal corticosteroid, RD: respiratory distress, RDS: Respiratory distress syndrome, TTN: transient tachypnea of newborn, GA: gestational age

The findings of our study reveal 18% (32 of 177 infants) received ANCS within 1 week before late preterm delivery. We found that younger GA infants (34 weeks of gestation) receiving steroids >2 weeks before delivery have a trend to show more RDS compared to those receiving them <2 weeks (8.9% vs. 5.8%) before delivery. There is also a trend to more TTN, and combined respiratory morbidity in infants that received steroids >2 weeks before delivery in overall gestational ages (21% vs. 27%, and 25% vs. 31%, respectively).

Our study is unique in providing an additional information of delivery room resuscitation (positive pressure ventilation) requirement, and NICU respiratory management. The common underlying mechanism in respiratory distress in these LPIs might be due to delay in the absorption of lung fluid, leading to reduced pulmonary compliance. We expected the reduction in transient tachypnea of newborn because ANCS could augment the elimination of lung fluid through the mechanism of sodium channel activation and ion transportation.[15] In addition, our study showed a significant decrease in RDS from 9% in non-steroid group to 5% in steroid group and also a decreased administration of exogenous surfactant in the latter group. However, we found a trend toward greater rate of RDS in non-steroid use group especially at 34 and 35 weeks while Joseph *et al*., study demonstrated reduction at 33 and 34 weeks.[16]

Hence, we were able to account in latency between corticosteroid expose and timing of delivery and shown increasing in rate of RDS in which received steroid given more than 2 weeks before delivery. In this study, we found that the administration of steroid <24 h before delivery could increase the respiratory complications of RDS compared with non-steroid group. Consistent with mentioned results, we found that the incidences of healthy infants (with no respiratory complications) in the ANCS <48 h groups were significantly lower than those of the non-steroid control. The supportive ideas of ANCS potentially caused neutral or negative respiratory effects may be explained by the finding of Liley *et al*[17]. indicating that glucocorticoids could have both stimulatory and inhibitory effects on surfactant protein production. This inhibitory effect of ANCS on lung maturation was also supported by the study of Alan HJ[18] reporting that inflammation not only causes lung injury, but it also stimulates fetal lung maturation. Both ANCS and inflammation affect lung development, however, many factors including appropriate period of administration may influence the balance of such regulations on fetal lung development.

Table 3: Comparison of respiratory outcome between ANCS and non-ANCS group in each period of administration

	No steroid (*n*=177), *n* (%)	Steroid group (*n*=177), *n* (%)				
		<24 h (*n*=6)	24–48 h (*n*=6)	48 h–1 week (*n*=20)	1–2 weeks (*n*=11)	>2 week (*n*=134)
No RD, *n* (%)	123 (69.5)	4 (66.7)	4 (66.7)	16 (80)	7 (63.6)	90 (67.1)
P	NA	0.89	0.89	0.33	0.68	0.65
RDS, *n* (%)	15 (8.5)	2 (33.3)	0 ((0)	3 (15)	0 (0)	5 (3.7)
P	NA	0.04	0.46	0.34	0.31	0.09
TTN, *n* (%)	37 (20.9)	0 (0)	2 (33.3)	1 (5)	4 (36.4)	36 (26.9)
P	NA	0.21	0.46	0.09	0.22	0.22

Using comparing two proportions

Our study shows no difference in antenatal and postnatal antibiotic administration. The interesting concerns about the possible risk of an incomplete course of ANCS.[19,20] Our data show no difference in rate of positive pressure ventilation, rate of RDS or perinatal death at the delivery room when comparing between steroids and non-steroids groups. Apparently, our study did not show any differences in adverse neonatal outcomes including hypoglycemia which is different from Gyamfi- Bannerman's study.[13] Mortality rate was neither different in both groups in every gestational age, in contrast to Joseph *et al*. 's study[16] that showed the reduction of infant mortality at 33 and 34 weeks in those receiving steroids.

The strength of our study is a well matched and controlled study and high validity due to same standard neonatal management in 3 NICUs. However, there were limitations to our study including. maternal factor (e.g., antenatal hemorrhage, multiple gestation) may affect RDS in LPIs and few participants enrolled in the subgroup analysis. We included only LPIs admitted to the NICUs and we did not include LPI admitted to post-partum unit.

CONCLUSIONS

ANCS was not associated with decrease risk of overall respiratory morbidity. RDS tends to be lower in ANCS group. Treatment with ANCS at <24 h may increase the incidence of RDS in LPI. Further study of LPIs whose mother received ANCS within 48 hours before delivery or further case-control study with matched antepartum and peripartum factors.

ACKNOWLEDGMENTS AND FUNDING

This study was supported by grants from Phramongkutklao Hospital and Phramongkutklao College of Medicine, Bangkok, Thailand.

CONFLICT OF INTETEST

The authors declare that they have no competing interests.

REFERENCES

1. Davidoff MJ, Dias T, Damus K, Russell R, Bettegowda VR, Dolan S, *et al*. Changes in the gestational age distribution among US singleton births: Impact on rates of late preterm birth, 1992 to 2002. Semin Perinatol 2006;30:8-15.
2. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Osterman MJ. Birth: Final data for 2006. Natl Vital Stat Rep 2009;57:1-104.
3. Young PC, Glasgow TS, Li X, Guest-Warnick G, Stoddard G. Mortality of late-preterm (near-term) newborns in Utah. Pediatrics 2007;119:e659-65.
4. Kramer MS, Demissie K, Yang H, Platt RW, Sauvé R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. Fetal and infant healthstudy group of the Canadian perinatal surveillance system. JAMA 2000;284:843-9.
5. Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical outcomes of near-term infants. Pediatrics 2004;114:372-6.
6. Tomashek KM, Shapiro-Mendoza CK, Weiss J, Kotelchuck M, Barfield W, Evans S, *et al*. Early discharge among late preterm and term newborns and risk of neonatal morbidity. Semin Perinatol 2006;30:61-8.
7. Escobar GJ, Greene JD, Hulac P, Kincannon E, Bischoff K, Gardner MN, *et al*. Rehospitalisation after birth hospitalisation: Patterns among infants of all gestations Arch Dis Child 2005;90:125-31.
8. Clark RH. The epidemiology of respiratory failure in neonates born at an estimated gestational age of 34 weeks or more. J Perinatol 2005;25:251-7.
9. Roth-Kleiner M, Wagner BP, Bachmann D, Pfenninger J. Respiratory distress syndrome in near-term babies after caesarean section Swiss Med Wkly 2003;133:283-8.
10. Picone S, Paolillo P. Neonatal outcomes in a population of late-preterm infants. J Matern Fetal Neonatal Med 2010;23 Suppl 3:116-20.
11. Liggin GC. Premature delivery of foetal lambs infused with glucocorticoids. J Endocrinol 1969;45:515-23.
12. Liggins GC, Howie R. A controlled trial of antenatal glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. Pediatrics 1972;50:515-25.
13. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita AT, Reddy UM, Saade GR, *et al*. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med 2016;374:1311-20.
14. American College of Obstetrician and Gynecologist. Antenatal Corticosteroid Therapy for Fetal Maturation. Committee Opinion Number 273. American College of Obstetrician and Gynecologist; 2002.
15. Stutchfield P, Whitaker R, Russell I. Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: Pragmatic randomised trial. BMJ 2005;331:662.
16. Joseph KS, Nette F, Scott H, Vincer MJ. Prenatal corticosteroid prophylaxis for women delivering at late preterm gestation. Pediatrics 2009;124:e835-43.
17. Liley HG, White RT, Benson BJ, Ballard PL. Glucocorticoids both stimulate and inhibit production of pulmonary surfactant

protein A in fetal human lung. Proc Natl Acad Sci U S A 1988;85:9096-100.
18. Jobe AH. Glucocorticoids, inflammation and the perinatal lung. Semin Neonatol 2001;6:331-42.
19. Elimian A, Figueroa R, Spitzer AR, Ogburn PL, Wiencek V, Quirk JG. Antenatal corticosteroids: Are incomplete courses beneficial? Obstet Gynecol 2003;102:352-5.
20. Sen S, Reghu A, Ferguson SD. Efficacy of a significant dose of antenatal steroid in surfactant-treated babies under 31 weeks' gestation. J Matern Fetal Neonatal Med 2002;12:298-303.