The Effect of Betamethasone on the Consequences of Late Preterm Pregnancy: A Double-Blind Randomized Clinical Trial

Fatemeh Bahadori[1], Zahra Fakour[2]* , Roghayeh Redaei[3], Hamid Reza Khalkhali[4], Zahra Sahebazzamani

1. Associate Professor, Maternal and Childhood Obesity Research Center, Urmia University of Medical Sciences, Urmia, Iran
2. Associate Professor of Neonatology Department of Pediatric Disease, School of Medicine Shahid Motahari Hospital, Urmia University of Medical Sciences. Urmia, Iran
3. Obstetrician-Gynecologist, Taleghani Hospital, Chalous, Iran
4. Associate Professor, Department of Biostatistics and Epidemiology, Patient Safety Research Center, Urmia University of Medical Sciences, Urmia, Iran
5. Master of Midwifery Maternal and Childhood Obesity Research Center, Urmia University of Medical Sciences, Urmia, Iran

Article Info

Corresponding Information:
Zahra Fakour,
Associate Professor of Neonatology Department of Pediatric Disease, School of Medicine Shahid Motahari Hospital, Urmia University of Medical Sciences. Urmia, Iran
Email: z.fakour@yahoo.com

ABSTRACT

Background & Objective: This study aimed to assess the effect of betamethasone on neonatal and maternal complications of late preterm labor.

Materials & Methods: The women at the gestational age of 34 weeks to 36 weeks and 6 days who referred to Shahid Motahari Hospital, Urmia, Iran for premature labor or had a maternal indication of pregnancy termination were selected for this study. The participants were classified into the case group receiving two doses of 12 mg intramuscular betamethasone every 24 h or the control group who did not receive betamethasone. The incidence of respiratory distress syndrome (RDS), need for mechanical or noninvasive ventilation, days of stay in Neonatal Intensive Care Unit (NICU) or Neonatal Ward, umbilical arterial blood gases, maternal hyperglycemia, and wound infection were evaluated.

Results: A total of 200 pregnant women were enrolled with a mean age of 27.06±6.55 years. Out of 200 neonates, 52 cases had RDS of which 21 received betamethasone. The first-minute Apgar score was 6.96±0.75 in the control and 7.57±0.67 in the case groups (*P*<0.001). The incidence of RDS, need for surfactant administration, noninvasive ventilation, and days of stay at NICU or Neonatal Ward were significantly different between the study groups. However, because of the low number of cases (2 cases), we did not find a significant difference in the need for mechanical ventilation between the two groups (*P*=0.041). There was maternal hyperglycemia in 65% of women in the test group.

Conclusion: Administration of betamethasone in late premature pregnancies can be effective in the reduction of neonatal complications without any increase in maternal complications.

Keywords: Betamethasone, Preterm labor, Respiratory distress syndrome

Introduction

Late preterm birth or near-term birth can be among the causes of death and disability around the birth time **(1)** and these infants are more prone to acute and chronic complications of preterm birth than term infants. Late preterm infants are defined as babies delivered between 34, 0/7 weeks and 36, 6/7 weeks of gestation. The prevalence of preterm labor worldwide is 9.6% resulting in the death of more than one million infants annually **(2)**. Preterm birth rates have increased by 14% over the past decade in the United States, among which, more than 70% were late preterm **(3)**.

The cause of the elevation in late preterm births is unknown. However, the factors augmenting late preterm include increased survival and treatment interventions, the misjudgment of gestational age, changes in demographic characteristics, and maternal

health. Due to the rise in high-risk pregnancies, the probability of giving birth to infants during the late preterm period is increasing **(4)**. The type and time of delivery affect short-term and long-term neonatal complications. During hospitalization, these newborns are more likely to have difficulty in feeding (32% vs. 7%), hypoglycemia (16% vs. 5%), jaundice (54% vs. 38%), body temperature instability (10% vs. 0 %), apnea (6% vs. 0.1%), and respiratory distress syndrome (RDS) (29% vs. 4%) **(5)**.

According to Batterbee, late preterm neonatal hospitalization in the NICU varies from 20% to 50%, and this difference in intensive care hospitalization makes it difficult to advise on betamethasone administration. However, this difference in the NICU hospitalization of these infants could be attributed to the differences in the treatment methods of each medical center or other obstetric characteristics of high-risk mothers. The main problem of preterm infants with low birth weight is their immature lungs accompanied by a need for intubation and mechanical ventilation. Breathing with slightly higher vital capacity can lead to surfactant inactivation and activation of a chain of inflammatory reactions in the medium and small airways **(3)**.

Mechanical ventilation is associated with an increased risk of bronchopulmonary dysplasia. Prenatal corticosteroids are currently recommended in women with a gestational age of 24-34 weeks who are at risk for preterm delivery **(6)**. Over the past 20 years, steroid administration to women at risk for preterm labor has resulted in improved outcomes for newborns **(4)**. According to the American College of Obstetricians and Gynecologists, prenatal administration of corticosteroids in women at risk for preterm labor significantly reduced neonatal mortality, intracranial hemorrhage, and necrotizing enterocolitis, compared to the neonates of mothers who did not receive the medicine **(7)**.

Another study showed that the administration of even a single dose of betamethasone at 34 and 35 weeks of gestation augmented fetal lung maturation and was effective in diminishing RDS and NICU hospitalization **(1)**. Corticosteroids are not routine in pregnancies for over 34 weeks. Various investigations have demonstrated that antenatal betamethasone administration can be influential in reducing RDS in late preterm infants **(6)**. However, this impact has not been observed in other studies **(8, 9)**. Although the benefits of corticosteroids before 34 weeks are well specified, comprehensive information on the effects of corticosteroids after 34 weeks is not available. Considering that Shahid Motahari Educational and Medical Center in Urmia, Iran is a referral center for many cases of preterm infants to receive care in intensive care units, corticosteroid administration for imminent early and late preterm deliveries seems necessary. Therefore, due to the inconsistency of various studies on this subject, the effect of betamethasone on late preterm labor and its outcomes was studied in Shahid Motahari Medical Center in Urmia.

Materials and Methods

This double-blind randomized clinical trial was performed on 200 pregnant women who referred to Shahid Motahari Educational and Medical Center in Urmia during 2015. The information of this study was registered in the Iran Clinical Trial Registration Center with the IRCT number of IRCT2014050217365N2.

The inclusion criteria entailed being pregnant with a gestational age of 34-36 weeks at the time of hospitalization, being at the risk of spontaneous preterm delivery or recommended preterm delivery by a physician due to maternal or fetal problems or both, and signing informed consent regarding the treatment. The gestational age was determined based on the last menstrual period if sure or by ultrasound before the 20th week of pregnancy.

The exclusion criteria were multiple pregnancies, major congenital malformations, clinical evidence of chorioamnionitis, previous use of corticosteroids, need for the urgent termination of pregnancy due to maternal or fetal factors, insulin-dependent diabetes, maternal smoking and use of narcotics, contraindications to use a corticosteroid, and being pregnant at the time of discharge from hospital and referring to another hospital for terminating the pregnancy.

The sample size was calculated as 200 based on previous studies **(10)**. The random sampling method was simple or purpose-based and pregnant women with a gestational age of 34-37 weeks and at risk of preterm delivery who were admitted to this center were evaluated. Patients were randomly assigned to two groups of 100 to receive betamethasone or not. The method of selection was to put 100 A cards (betamethasone injection) and 100 B cards (no injection) in the envelope and mix them thoroughly. Next, the patients were selected for one of the two study groups blindly. Therefore, a double-blind study was performed. Consent was obtained from patients in the case and control groups. In the case group, 2 doses of 12 mg betamethasone were injected, which was repeated 24 h later. Patients were not injected with betamethasone in the control group. Nifedipine was prescribed in both groups to delay delivery and the course treatment completion according to the treatment protocol. Infants were followed up by the neonatal specialist and their information was recorded in a questionnaire. Patients who gave birth before receiving the second dose were analyzed in the treatment group.

Neonatal outcomes encompassed neonatal RDS (i.e., tachypnea, grunting, chest retractions, flaring, cyanosis, and increased need for oxygen) or transient tachypnea of the newborn, type of delivery, gestational age at birth, birth weight, neonatal Apgar score, need

for surfactant administration and respiratory support, duration and type of respiratory support, and the length of hospital stay and death. The information of participants was confidential and provided anonymously.

Statistical Analysis

Descriptive statistics, including mean, standard deviation, and percentage were used to describe the data. In addition, the paired t-test and chi-square test were applied to compare the means between the two groups and examine the relationship between variables and qualitative scale, respectively. P-value<0.05 was considered statistically significant. All the analyses were performed by the SPSS software version 16 (IBM SPSS, Armonk, NY, USA).

Results

The mean age of participating mothers was 27.06±6.55 years. The mean age of mothers in the intervention and control groups was 27.42±6.7 and 26.71±6.42 years, respectively. Mean gestational age, route of delivery, hypertension (BP>140/90), wound infection, and incision site infection in the control and intervention groups are shown in Table 1. There was no significant difference between the two groups in terms of the mentioned variables. RDS occurred in 52 newborns 21 of which received betamethasone.

The two groups were not significantly different concerning ABG. The mean Apgar score of the first and fifth minutes in the control group was significantly lower than the test group (Table 2). None of the 52 infants with RDS developed pneumothorax, intraventricular hemorrhage, or sepsis, and all neonates were discharged alive. The overall mean duration of hospitalization was 4.71±2.09 days with 3.38±1.16 days in the intervention group and 5.61±2.12 days in the control group indicating a significant effect for receiving betamethasone ($P<0.001$).

Two infants in the control group received mechanical ventilation and none of the newborns in the betamethasone group required mechanical ventilation. There was no significant relationship between receiving betamethasone and mechanical ventilation ($P=0.235$). Two of the neonates who received betamethasone needed noninvasive ventilation, while this number was 16 in the control group. This relationship was significant in evaluating the effect of betamethasone on reducing the need for CPAP ventilation ($P=0.002$) (Table 2). In the intervention group, only one infant received surfactant, while this number in the control group was ten, which was significantly different ($P=0.017$). The impact of betamethasone on tachypnea was not significant ($P=0.708$) (Table 2). In pregnant women in the betamethasone group, FBS increased by 64% (FBS>95) and 2hpp increased by 30% (2hpp>120). Out of 52 infants with RDS, none developed pneumothorax, intraventricular hemorrhage, or sepsis.

Table 1. Demographic characteristics and frequency distribution of maternal variables in control and intervention groups

Variables	Control group (n=100)	(n=100) Intervention group (receiving betamethasone(	P-value
Maternal age (year) mean and standard deviation	26.71 ±6.42	27.42±6.7	P=0.445
Gestational age (week)mean and standard deviation	34.99±0.82	35.20±0.08	P=0.075
Natural childbirth (frequency)	42	40	P=0.443
Cesarean delivery (frequency(	58	60	P=0.443
High blood pressure (number) (frequency(	14	9	P=0.188
Incision site infection (number) (frequency(	9	5	P=0.203

Table 2. Frequency distribution and mean of neonatal variables in control and intervention groups

Variables	Intervention group (receiving betamethasone((n=100)	Control group (n=100)	P-value
Hospitalization (frequency)	21	31	0.001
The first PH at the time of hospitalization	0.05±7.40	0.96±7.45	0.097
The first PCO2 at the time of admission	7.80±44.50	6.48±46.4	0.443

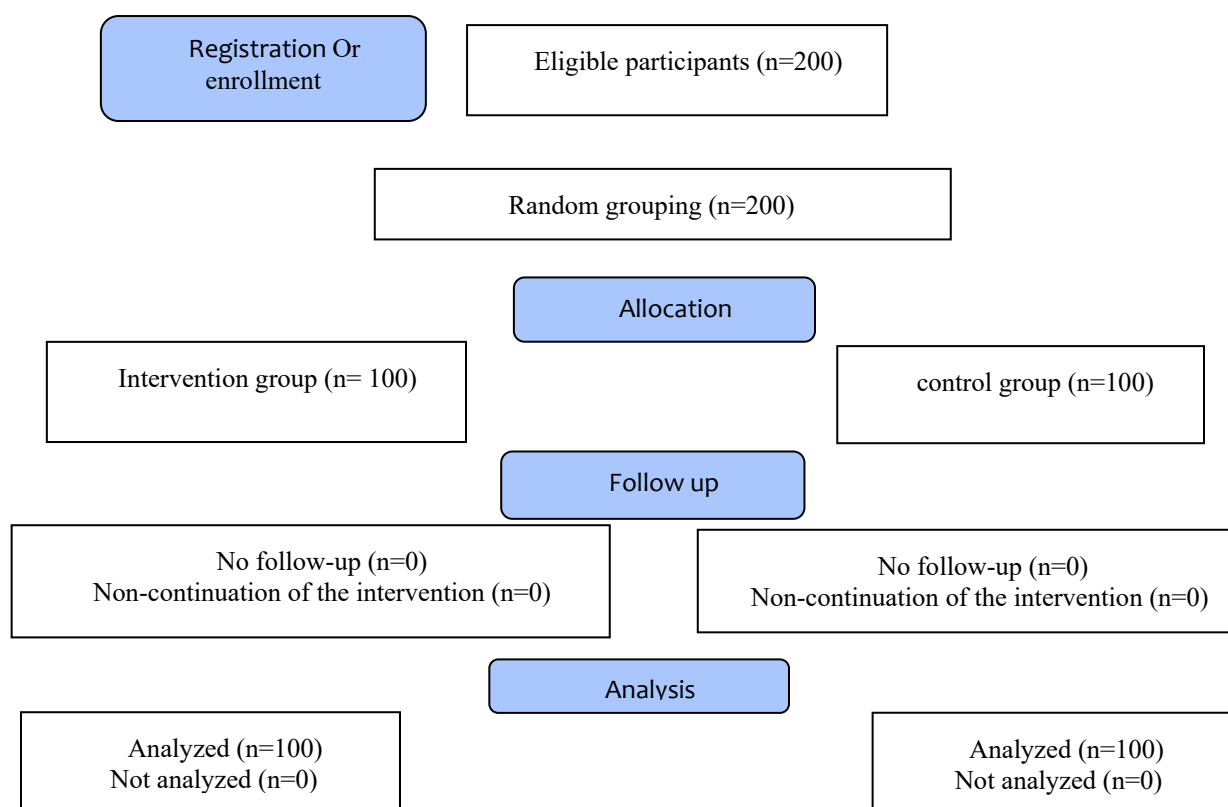| Variables	Intervention group (receiving betamethasone) (n=100)	Control group (n=100)	P-value
The first PO2 at the time of admission	13.46±36.06	6.48±33.70	0.402
The first HCO3 at the time of admission	3.35±28.12	3.03±28.43	0.736
Birth weight (grams)	499.28±2235.71	423.91±2193.87	0.749
Receiving surfactant	1	10	0.017
First minute Apgar score	0.67±7.57	0.75±6.96	<0.001
Fifth minute Apgar score	0.67±8.42	0.96±7.45	0.005
Number of hospitalization days for infants	1.16±3.38	2.12±5.61	<0.001
NICU admission	1	7	0.016
Mechanical Ventilation	0	2	0.235
Non-invasive mechanical ventilation (CPAP)	2	16	0.002
Respiratory Distress Syndrome (RDS)	21	31	<0.001

Figure 1. The CONSORT Flow Diagram 2010

Discussion

In the present study, betamethasone administration in late preterm patients decreased the need for surfactant and increased the first and fifth minute Apgar scores, and finally, reduced neonatal hospitalization in the NICU. According to Vijaya Ontela (2018), betamethasone administration did not affect Apgar score **(8)**. Mirzamoradi *et al.* in 2018 showed that betamethasone administration diminished the need for surfactant, which was consistent with the results of the present study **(2)**. An increase in Apgar score is a sign of improvement in the infant's condition. The effect of betamethasone intake on improving the infant's general condition should be considered and we can predict a reduction in the complications and negative consequences. However, there can be no discussion about the effect of taking betamethasone because we did not have any deaths in either group. Our study demonstrated that betamethasone intake was effective in reducing RDS (P=0.041). This decrease was also evident in the administration of surfactant and mechanical ventilation, which overall indicated an enhancement in the general condition of infants who had received betamethasone. The latter finding was in line with a study conducted in Sanandaj, Iran by Mansouri *et al.* **(11)**.

Our study was also consistent with the results of Porto in terms of the influence of betamethasone on diminishing hospital stay. Due to the difference in sample size and regional differences between these two studies, the effect of receiving betamethasone on reducing the length of hospital stay can be considered. This is especially important in centers with high neonatal admission rates, which can lead to better neonatal care, as well as a decrease in nosocomial infections in neonates due to shorter hospitalization. The need for surfactant administration was lower in the betamethasone group than the control group (P=0.017), which can be very important in reducing the economic burden imposed on the system and parents **(12)**.

In line with Ventolini *et al.* who showed a decrease in RDS and the need for oxygen therapy, the results of our investigation revealed that receiving betamethasone could diminish the need for noninvasive ventilation without any effect on mechanical ventilation. This variation in the influence can be attributed to the error that infants who need mechanical ventilation have more immaturity in their respiratory system. Following betamethasone administration according to the method of our study, no impact was found in them. In this regard, studies with a larger statistical population are recommended taking into consideration the factors influencing RDS development **(13)**.

Consistent with Shelto *et al.*, who observed an increase in fasting blood glucose, we showed a 65% increase in glucose in the test group. However, no conclusion can be made because the glucose was not checked in the control group **(14)**. Finally, according to the obtained results and the efficacy of betamethasone in reducing RDS, the need for non-mechanical ventilation, and surfactant usage, it could be recommended in late preterm infants. Furthermore, considering the possibility of the impact of betamethasone on the development of the nervous system of infants, betamethasone administration should be further examined in the future in this regard.

Conclusion

According to the findings of the current study, the administration of betamethasone in late premature pregnancies can be effective in reducing neonatal complications without any increase in maternal complications.

Acknowledgments

Conflict of Interest

The authors declared no conflict of interest.

References

1. Almassinokiani F, Sabouteh M, Soheilipour F, Kashanian M, Akbari P, Rahimzadeh N. Does antenatal Betamethasone improve neonatal outcome in late preterm births?. Int J Child Adolesc health. 2016;2(3):11-5.

2. Mirzamoradi M, Hasani Nejhad F, Jamali R, Heidar Z, Bakhtiyari M. Evaluation of the effect of antenatal betamethasone on neonatal respiratory morbidities in late preterm deliveries (34-37 weeks). J Matern.-Fetal Neonatal Med. 2020;33(15):2533-40. [DOI:10.1080/14767058.2018.1554051] [PMID]

3. Battarbee AN, Glover AV, Vladutiu CJ, Gyamfi-Bannerman C, Aliaga S, Manuck TA, et al. Risk factors associated with prolonged neonatal intensive care unit stay after threatened late preterm birth. J Matern.-Fetal Neonatal Med. 2019:1-6. [DOI:10.1080/14767058.2019.1623777] [PMID] [PMCID]

4. Moore H, Venugopalan V. Antenatal betamethasone prevented respiratory distress

syndrome in late preterm infants. Arch Dis Child. 2018;103(4):218-. [DOI:10.1136/archdischild-2017-313632] [PMID]

5. Engle WA, Kominiarek MA. Late preterm infants, early term infants, and timing of elective deliveries. Clin Perinatol. 2008;35(2):325-41. [DOI:10.1016/j.clp.2008.03.003] [PMID]

6. Hillman NH, Pillow JJ, Ball MK, Polglase GR, Kallapur SG, Jobe AH. Antenatal and postnatal corticosteroid and resuscitation induced lung injury in preterm sheep. Respiratory research. 2009;10(1):124. [DOI:10.1186/1465-9921-10-124] [PMID] [PMCID]

7. Gyamfi-Bannerman C. ACOG CO™™ I™™ EE OPINION SUMMARY. 2017.

8. Ontela V, Dorairajan G, Bhat VB, Chinnakali P. Effect of antenatal steroids on respiratory morbidity of late preterm newborns: a randomized controlled trial. J Trop Pediatr. 2018;64(6):531-8. [DOI:10.1093/tropej/fmy001] [PMID]

9. Movahed F, Baricany A, Jafari M. Effect of betamethasone on neonatal respiratory failure in late preterm pregnancies. Journal of Gorgan University of Medical Sciences. 2015;17(4):16-20.

10. Sheldon B, Korones M. Complications En: Goldsmith J, Karotkin E. Assisted ventilation of the neonate United States of America: Saunders-Elsevier Inc. 2011:389-425. [DOI:10.1016/B978-1-4160-5624-9.00023-8]

11. Mansouri M, Seyedolshohadaei F, Setare S, Mazhari S. Effect of antenatal Betamethasone on prevention of respiratory distress syndrome among neonates with gestational age of 35-36 weeks. Journal of Gorgan University of Medical Sciences. 2010;12(3).

12. Porto AMF, Coutinho IC, Correia JB, Amorim MMR. Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants: randomised clinical trial. Bmj. 2011;342:d1696. [DOI:10.1136/bmj.d1696] [PMID] [PMCID]

13. Ventolini G, Neiger R, Mathews L, Adragna N, Belcastro M. Incidence of respiratory disorders in neonates born between 34 and 36 weeks of gestation following exposure to antenatal corticosteroids between 24 and 34 weeks of gestation. Am J Perinatol. 2008;25(02):079-83. [DOI:10.1055/s-2007-1022470] [PMID]

14. Shelton S, Boggess K, Smith T, Herbert W. Effect of betamethasone on maternal glucose. J Matern.-Fetal Neonatal Med. 2002;12(3):191-5. [DOI:10.1080/jmf.12.3.191.195] [PMID]

How to Cite This Article: