

Comparison of Intravascular Versus Intramuscular Betamethasone Phosphate on Neonatal Outcomes in the Cases of Imminent Preterm Birth

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Article Info

doi [10.30699/jogcr.9.2.125](https://doi.org/10.30699/jogcr.9.2.125)

Received: 2023/10/14;

Accepted: 2024/01/09;

Published Online: 13 Mar 2024;

Use your device to scan and read the article online



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ABSTRACT

Background & Objective: Preterm birth is the most important cause of neonatal mortality and morbidity. Finding the best treatment regimen, of antenatal corticosteroids, has been under serious concern. To compare the efficacy of intravascular versus intramuscular betamethasone phosphate on neonatal outcomes in the cases of imminent preterm birth.

Materials & Methods: A double-blind randomized clinical trial was performed on 136 eligible pregnant women with gestational age of 26- 34 weeks and imminent preterm birth (delivery within 24 hours). They were randomly assigned into two groups. Group A received intramuscular betamethasone phosphate, and group B received a similar dose of betamethasone phosphate intravenously. Women were followed up to delivery, and their neonatal outcomes were compared.

Results: Women of the two groups (68 women in each group), did not show a significant difference in maternal age, BMI, gravidity and parity, gestational age at the time of admission and delivery, history of miscarriage and assisted reproductive techniques, delivery route, sex and weight of newborns, and Apgar score in minutes 1 and 5. The need for NICU admission, duration of hospitalization, neonatal respiratory distress syndrome, surfactant requirement, and intubation were lower in the IV betamethasone group. There were no significant differences between the two groups according to necrotizing enterocolitis, intraventricular hemorrhage, and neonatal death.

Conclusion: Using IV betamethasone, in cases where there is no enough time to complete the 24-hour betamethasone course due to the possibility of impending delivery, may reduce neonatal complications due to quicker onset of action.

Keywords: Preterm Delivery, Betamethasone Phosphate, Neonatal Respiratory Distress Syndrome, Necrotizing Enterocolitis, Intraventricular Hemorrhage



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Introduction

Preterm birth is the most important cause of neonatal mortality and morbidity. Irrespective of many new modalities for reducing the number of preterm deliveries and lowering the neonatal morbidities and mortalities, it is still the most common cause of serious neonatal morbidity and neonatal deaths. At the same time, it causes a concerning financial burden on the health economy (1-5).

In 1972, corticosteroids were introduced, to reduce the neonatal respiratory distress syndrome (RDS), which is the primary cause of early neonatal mortality and disability (6). Using corticosteroids could

considerably reduce neonatal RDS, morbidity and mortalities due to prematurity. In spite of its widespread use, there are debates on types of corticosteroids to use; the dosage, frequency, timing of use and the route of administration (7-11). Over-treatment with corticosteroids is a major concern which happens due to attempts to prevent preterm birth but can cause neonatal and maternal risks and is costly to the health economy (12). Imminent deliveries, when there is no enough time to administer the full course of corticosteroids, are another case of concern. In such conditions, neonatal RDS and deaths are expected to be higher than the cases where the course of

corticosteroids was administered in full. Therefore, finding a solution to reduce prematurity adverse problems can minimize complications. Shortening the interval between two doses of betamethasone to 12 hours instead of 24 hours has been proposed in some studies (13-16). Another option is to administer betamethasone intravenously instead of the intramuscular route, to have quicker onset of action and consequently more beneficial effects on lung maturity. In cases of imminent birth, IV betamethasone phosphate is expected to result in a quicker onset of action, hence this method of administration, may have beneficial effects on reducing neonatal morbidity and deaths. To the best of our knowledge, no study has been performed on intravenous administration of betamethasone in human pregnancies (17). The purpose of this study was to compare the efficacy of intravenous versus intramuscular betamethasone phosphate on neonatal outcomes in the cases of imminent preterm birth.

Methods

The study was conducted as a double-blind randomized clinical trial in the labor ward of Akbarabadi Teaching Hospital, Tehran, Iran, from April 2018 to August 2020.

A written informed consent was obtained from all participants, and they were fully informed about the study. Institutional review board approval and institutional ethics committee approval was obtained.

Inclusion criteria were pregnant women with a gestational age between 26-34 weeks (according to a reliable LMP and ultrasound confirmation of the first trimester of pregnancy), singleton, regular uterine contractions, cervical dilatation of 3-4 centimeters and more, and imminent delivery (delivery in less than 24 hours).

Exclusion criteria were fetuses with intrauterine growth retardation, any fetal abnormalities, known allergy to betamethasone, history of known maternal diseases such as hypertension, diabetes, liver disease, renal failure, heart disease, neoplastic diseases, and maternal medications other than common supplements (iron, multivitamins, and folic acid).

136 eligible pregnant women were randomly assigned into two groups (Figure 1). Group A received intramuscular betamethasone phosphate in a dose of 12 mg, and group B received a similar dose of betamethasone phosphate intravenously with slow injection. Distilled water was used in both groups in order to blind the study. Women were followed up to delivery, and their neonatal outcomes were compared. Imminent preterm birth was defined as birth within less than 24 hours after admission.

Main outcome variables included neonatal respiratory distress syndrome. Secondary outcomes were intraventricular hemorrhage, necrotizing enterocolitis, neonatal death, NICU admission and duration of NICU admission, and neonatal sepsis, which were compared in the two groups. Neonatal complications were assessed in 24 hours' intervals up to discharge from the hospital. The collected data was analyzed using SPSS software version 16 (IBM, USA). The normality of the data was evaluated using the Kolmogorov-Smirnov test. An independent t-test and chi-square test were employed to compare the data of the two groups. P value of 0.05 was considered significant.

Results

Women in both groups (68 women in each group), did not show significant difference according to maternal age, BMI, gravidity and parity, gestational age at the time of admission and delivery, history of miscarriage and assisted reproductive techniques, delivery route, sex and weight of newborns, and Apgar score in minutes 1 and 5 (Table 1). The duration between admission and delivery was longer in the IV group, but such difference was not statistically significant between the two groups (about 8.75 hours versus 10.14 hours) (Table 1). The need for NICU admission, duration of hospitalization, neonatal respiratory distress syndrome, surfactant requirement, and neonatal intubation were lower in the intravenous betamethasone group (Table 2). There were no significant differences between the two groups for necrotizing enterocolitis, intraventricular hemorrhage (IVH) and neonatal death (Table 2).

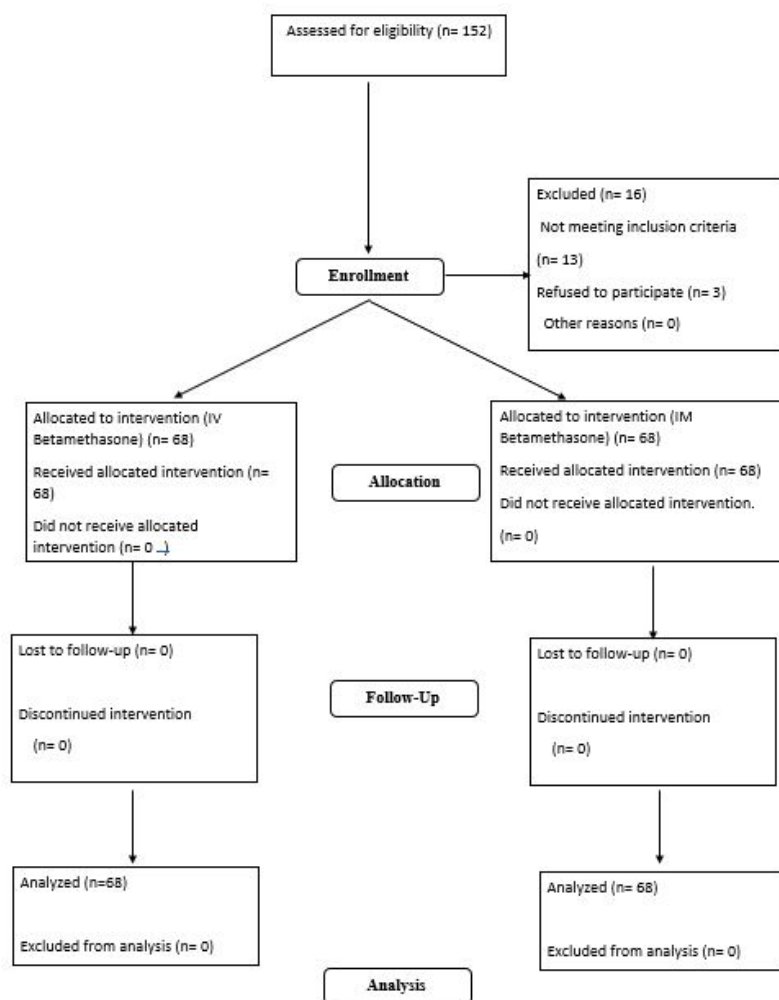


Figure 1. The Consort E-Flowchart

Table 1. Characteristics of patients in two groups.

Characteristics	IM betamethasone N=68	IV betamethasone N=68	P Value
Age (year) M±SD	30.51 ± 5.77	29.38 ± 6.48	0.29
BMI M±SD	27.18± 4.35	28.32 ± 4.55	0.62
Primigravid N (%)	25 (36.8%)	29(42.6%)	0.48
Primipara N (%)	28 (41.2%)	34(50,0%)	0.30
History of miscarriage N (%)	20 (29.4%)	12 (17.6%)	0.10
Living child N (%)	38 (55.9%)	33 (48.5%)	0.39
History of ART N (%)	4 (5.9%)	2(2.9%)	0.40
Gestational age at the time of admission (days, weeks) M±SD	225,20± 12,36 32.17±1.76	226.0 3±12.32 32.29±1.76	0.74
Cervix dilatation (CM) M±SD	3.95 ±1.12	3.73 ±0.89	0.55
Effacement (%) M±SD	35.63±16.87	34.70 ±17.99	0.43
Ruptured membranes N (%)	21 (30.9%)	31 (45.6%)	0.08
Gestational age at the time of delivery (days, weeks) M±SD	225.63 ±12.57 32.23±1.79	226.38 ±12.28 32.34±1.75	0.80

Characteristics	IM betamethasone N=68	IV betamethasone N=68	P Value
Interval to delivery (h) M±SD	8.75±6.75	10.14±8.68	0.07
Cesarean delivery N (%)	34 (50.0%)	30 (44.1%)	0.49
Sex (boy) N (%)	38 (55.9%)	41(60.3%)	0.60
Neonatal weight (gr) M±SD	1916.83 ±442.07	1985.88 ±502.07	0.22

Table 2. Neonatal outcomes in two groups.

Characteristics	IM betamethasone N=68	IV betamethasone N=68	P Value
Apgar minute 1 M±SD	7.56 ±1.96	7.72 ±1.87	0.92
Apgar minute 5 M±SD	9.15 ±1.39	9.31 ±1.14	0.69
NICU admission N (%)	55 (80.9%)	38 (55.9%)	0.001
duration of hospitalization (days) M±SD	11.20 ±7.61	4.68±5.82	0.05
Intubation N (%)	28 (41.2%)	15(22.1%)	0.02
Surfactant administration N (%)	24 (35.3%)	13(19.1%)	0.03
RDS N (%)	45 (66.2%)	31 (45.6%)	0.02
NEC N (%)	0	0	-
IVH N (%)	14 (20.6%)	9 (13.2%)	0.25
Sepsis N (%)	0	0	-
Neonatal death N (%)	7 (10.3%)	3 (4.4%)	0.19

Discussion

The present study suggests that use of the intravenous form of betamethasone in cases where there is not enough time to complete the 24-hour course of betamethasone due to the possibility of impending delivery, could be beneficial. Since 1972, corticosteroids have been used widely to reduce respiratory distress syndrome and other complications of prematurity (10-13). Since then, many studies compared different corticosteroid administration protocols, including the type of corticosteroids, duration of administration, using single or multiple doses, as well as the need for additional doses in case of continuation of pregnancy. In 1983, Petersen et al. compared the pharmacokinetics of intravenous and intramuscular betamethasone phosphate (BP), as a solution (Celestine Injection) and a mixture of BP (4.0 mg/ml) in solution and betamethasone acetate (BA) (3.1 mg/ml) in suspension (Celestone Chronodose), in pregnant women in their late pregnancy (18). They showed that betamethasone phosphate, which is a soluble ester of betamethasone, and may be administered either intravenously or intramuscularly, has the same or even better effect than a mixture of betamethasone phosphate and betamethasone acetate in suspension. Also, in other studies (19, 20), authors proposed that in pregnant women, betamethasone reached a peak plasma concentration during 5-37

minutes after IV betamethasone phosphate (10-36 minutes in non-pregnant women ;), with a mean terminal half-life of 262 minute (about 4 hours) (6.5 hours in non-pregnant women). Neonatal benefit from corticosteroids begins within a few hours after administration (21). An incomplete course of corticosteroids is associated with lower neonatal death in the cases of imminent preterm delivery (21). Since preterm delivery is unpreventable in some cases, efforts to reduce complications of prematurity are necessary. According to previous studies, intramuscular use of betamethasone has had beneficial effects in reducing respiratory distress syndrome, NEC, IVH, NICU admission and duration of NICU admission, and neonatal death (13-18). According to pharmacokinetic studies, intravenous betamethasone reaches the serum therapeutic level faster than intramuscular form and, as a result, reaches the target organs sooner (19, 20). Dexamethasone-phosphate and the combination of betamethasone-phosphate + betamethasone-acetate are the most widely used corticosteroids for fetal lung maturity in different parts of the world (22, 23). In a meth-analysis in 2017, the authors proposed that new studies are required to determine the optimal dose-to-delivery interval and the best choice of corticosteroids. Another study suggests that a drug containing betamethasone-

acetate is not ideal for antenatal corticosteroid therapy because the slowly released betamethasone-acetate results in prolonged fetal exposure (24, 25).

Conclusion

Betamethasone-phosphate can be used both intramuscular and intravenously, and to the best of our knowledge there are no studies on the use of intravenous betamethasone-phosphate in human pregnancy, which has quicker onset of action. Therefore, in imminent delivery, intravenous betamethasone might be more effective than intramuscular form. Future studies are required to reach robust conclusions on this matter.

Acknowledgments

This work has been supported by Iran University of Medical Sciences, Deputy of Research and Technology, Project No. 3588.

Ethics approval

The ethical approvals were obtained from the ethics committee of the Iran University of Medical Sciences (IRCT ID: IRCT201705052624N23) and Ethics committee reference number is IR.IUMS.REC.1396.27410.

Conflict of Interest

All authors declare no conflict of interest.

Funding

None.

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How to Cite This Article:

Kashanian, M., Eshraghi, N., Kalani, M., Bordbar, A., Eshraghi, N., Kalati, M., et al. An efficacy comparison of intravascular versus intra muscular betamethasone phosphate on neonatal outcomes in the cases of imminent preterm birth. *J Obstet Gynecol Cancer Res*. 2024;9(2):125-30.

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