



Research article

Betamethasone or dexamethasone as the preferred antenatal corticosteroid to decrease neonatal morbidities: a randomized controlled clinical trial

Minoo IROMLOO¹, Nargess GHAZALEH², Ehsan ABOLHASANI²¹ Imam Hussein Hospital, Shaheed Beheshti University of Medical Sciences, Iran² Faculty of Medicine, Hamadan University of Medical Sciences, Iran³ Faculty of Medicine, Shaheed Beheshti University of Medical Sciences, Iran

Address for Correspondence:
Ehsan ABOLHASANI, MD
Apartment No:7, No:18, East 28th Street, Sa'adat
1997977313 Abad, Tehran, Iran
Tel: +98 912 3114571
E-mail: ehsanabolhasani1979@gmail.com

ABSTRACT

Objective: Comparing antenatal betamethasone and dexamethasone in decreasing morbidities related with preterm labor in neonates.

Materials and methods: Randomized, double-blind, comparator-controlled study comparing the effect of antenatal betamethasone with dexamethasone in preventing three major preterm labor morbidities; respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC) in neonates of mothers with preterm labor between 29 and 34 weeks at Imam Hussein Hospital, Iran. One hundred-fifty singleton pregnant women with preterm labor were recruited to the study according to eligibility criteria. Patients were randomized to receive either betamethasone or dexamethasone.

Results: There was no significant difference between the groups with regard to baseline characteristics. The rates of RDS were 26 (36.6%) in betamethasone and 25 (34.3%) in dexamethasone (RR= 1.07, 95% CI: 0.69-1.66), IVH were 7 (9.9%) in betamethasone and 6 (8.2%) in dexamethasone (RR= 1.20, 95% CI: 0.42-3.39), NEC was 5 (7.04%) in betamethasone and 2 (2.7%) in dexamethasone (RR= 2.57, 95% CI: 0.51-12.82) groups. Neonatal mortality was 8 (11.3%) in betamethasone and 13 (17.8%) in dexamethasone (RR= 1.08, 95% CI: 0.94-1.23) groups.

Conclusion: Betamethasone and dexamethasone are comparable in reducing the rate of morbidities and mortality of preterm neonates.

Key words: Betamethasone; dexamethasone; intraventricular hemorrhage; necrotizing enterocolitis; respiratory distress syndrome.

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Introduction

Antenatal corticosteroid administration between 24 and 34 weeks of gestation for fetal lung maturation has beneficial effect when administered at least 24 hours before preterm delivery [1-4]. It was shown that a single course of antenatal steroids decreases neonatal morbidity and mortality by reducing the risk of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and death of premature infant [1, 5-6].

Betamethasone and dexamethasone are preferred corticosteroids for this purpose. They readily cross placenta and have weak immunosuppressive and mineralocorticoid effects. In addition, their duration of action is longer compared with other widely used corticosteroids, methylpred-

nisolone and cortisol [7]. Although they seem to have identical biological activity, different studies report dissimilar effectiveness of betamethasone and dexamethasone in terms of neonatal morbidities and mortality [6, 8].

In this clinical trial, we aimed to compare the effectiveness of antenatal betamethasone and dexamethasone in decreasing mortality and morbidity in preterm labor.

Patients and Methods

Patients and setting

A randomized, double-blind, comparator-controlled clinical trial was conducted at Imam Hussein University Hospital from March, 2007, through March, 2009.



Study diagram and eligibility criteria were presented in **Figure 1**. Residents, who performed the primary screening, explained the study to subjects who met the inclusion criteria and then consent was taken from all participants. Consent form was approved by University's Committee on Research and Ethics. By using computer-generated random numbers, subjects were allocated randomly in each medication group (i.e. group A and B for betamethasone and dexamethasone respectively).

Patients in betamethasone group received 12 mg medication intramuscularly at 0 and 24 hours and intramuscular placebo with the same appearance at 12 and 36 hours. The other medication group received 6 mg dexamethasone intramuscularly at 0, 12, 24, and 36 hours. Patients delivered before completing the steroid doses were excluded from the study (**Figure 1**).

Syringes were covered by an opaque material and only physician responsible for blinding was aware of the content. All patients and physicians were blinded to the type of drug assigned to each subject. After delivery, neonates were admitted in NICU of our hospital and a specialist in pediatric field, blinded to the group assignment, evaluated the neonates' status and complications of preterm labor. We focused on three complications of preterm neonates including RDS, IVH, and NEC.

Diagnosis of RDS was made by a pediatrician blinded to group allocation. RDS was diagnosed in case of necessity of at least 48 hours mechanical ventilation and presence of radiologic findings in chest x-ray. IVH was diagnosed by transcranial ultrasound and was confirmed by computed tomography if necessary. An expert radiologist who also was blinded to group allocation reviewed all data for IVH diagnosis and had graded them according to description of Papile *et al.* [9]. For diagnosing NEC, samples were investigated clinically and radiologically and confirmed by surgery or autopsy by a pathologist. Follow-up for the occurrence of these complications patients were followed for 2 weeks after birth.

Other data including maternal age, gestational age, mode of delivery, first and fifth minute Apgar scores, and gender of fetus were also recorded.

Analysis

It was assumed that approximately 65% of our patients would not develop respiratory disorders by receiving each drug, and detecting a difference of at least 20% in medication groups outcome ($e=0.2$), with $\alpha=0.05$ and $\beta=0.2$. According to following formula sample size in each group (n_1 and n_2) were calculated as 70.

$$n_1 = n_2 = \frac{(z_{\alpha/2} + z_{\beta})^2 (p_1(1-p_1) + p_2(1-p_2))}{e^2}$$

At the time of delivery, all data regarding the timing of labor onset, along with maternal and neonatal complications, were documented. The primary outcome measure was all deliveries before 34 weeks of gestation. The secondary outcome measures were preterm birth between 34 and 37 weeks of gestation and neonatal outcomes including birth weight, neonatal death, and the need for admission to neonatal intensive care unit (NICU).

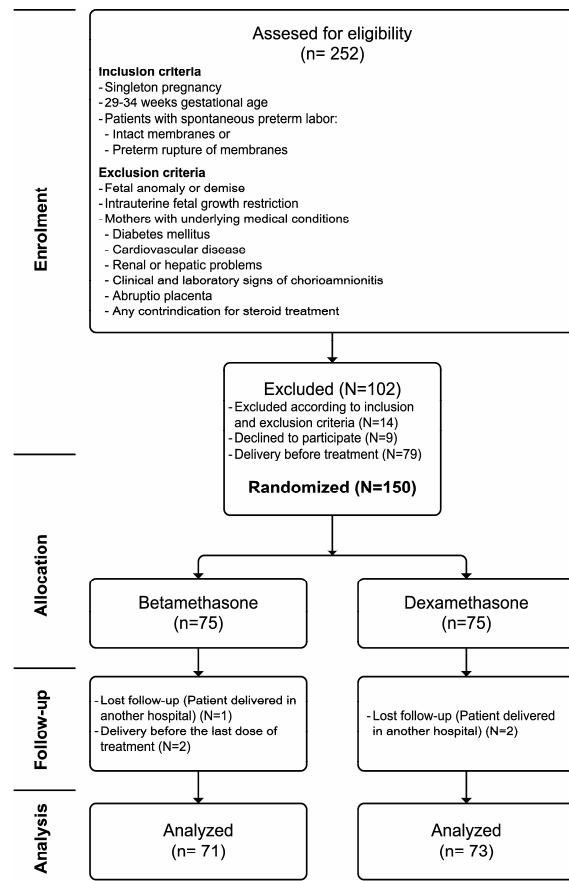


Figure 1. Study diagram.

Student's t test and Chi square test were used for continuous and categorical variables, respectively. When expected cell frequency was equal to or less than 5, Fisher's exact test was used. In all calculations statistical significance level was set to 0.05. SPSS for Windows version 12 (SPSS Inc., Chicago, IL).

Results

Amongst 252 mothers who were screened for eligibility 150 mothers, who met the inclusion criteria, were assigned randomly to one of the study groups to receive either betamethasone or dexamethasone. Seventy five women were allocated in each group. Finally, 71 cases in betamethasone group and 73 cases in dexamethasone group were included in the final analysis. Enrollment process and final sample size is illustrated in **Figure 1**. Demographic information of mothers and neonates is summarized in **Table 1**.

Outcome measures of the study were presented in **Table 2**. There was no significant difference with respect to RDS, IVH and NEC among both groups.

Intracranial hemorrhage was diagnosed in 7 neonates (9.9%) whose mothers had received betamethasone (2 patients [2.8%] with grade III/IV) and in 6 neonates (8.2%) in dexamethasone group (RR=1.20, 95% CI: 0.42-3.39, P=0.73) with 3 patients (4.1%) with grade III/IV. Only one patient (1.4%) in dexamethasone group had IVH alone and

comorbidity of IVH with RDS was found in 5 patients (7.4%) in betamethasone and 5 patients (6.9%) in dexamethasone groups (RR=1.03, 95% CI: 0.31-3.40, P>0.05).

NEC comorbidity with RDS and IVH was found in 2 (2.8%) patients in betamethasone group but not in dexamethasone patients (P=0.24).

Overall 21 (14.6%) neonates died due to these three complications with 8 neonates (11.3%) in betamethasone and 13 (17.8%) in dexamethasone groups (RR = 1.08, CI 95%: 0.94-1.23, P=0.26). All mortalities in betamethasone group had RDS while 3 neonates (4.2%) had RDS and IVH and 2 neonates (2.8%) had RDS and IVH synchronously, 1 (1.4%) had RDS and NEC. Two patients who had all 3 morbidities at the same time were died. In dexamethasone group, only one infant (1.4%) death was due to isolated IVH alone, 9 (12.3%) neonates because of RDS alone and three (4.1%) died because of RDS and IVH.

Discussion

The advantages of corticosteroids in preterm labor were first reported by Liggins *et al.* [1] in 1972. They demonstrated improvement in respiratory status of preterm neonates by prescribing corticosteroids in 7 days. It is evident now that prescribing a single course of antenatal corticosteroid not only decreases neonatal mortality and morbidities but also decrease health care expenses. Due to their ability to pass placenta, partially low mineralocorticoid and immunosuppressive effects, betamethasone and dexamethasone are preferred by most physicians. However, cost, availability, and ease of administration affects the choice medications prescribed by physicians [10].

In our study, we compared the effects of betamethasone and dexamethasone on three complications (RDS, IVH and NEC) and mortality of preterm labor. We found no difference in RDS, IVH, and NEC morbidities and mortality between these corticosteroids and they had the same effect on these preterm labor complications of neonates. Our findings are in consistent with previous reports that reported no difference between betamethasone and dexamethasone in RDS incidence [11]. Our results are also compatible with the findings of Eliman *et al.* (Betacode trial) who found no difference in RDS and NEC rate [10]. These findings are compatible with the results from Bar-Lev *et al.* who find no differences in IVH incidence [11]. However, lower IVH incidence with dexamethasone in Betacode trial [10] was not seen in our study.

Table 1. Patients characteristics and study parameters.

	Betamethasone (n=71)	Dexamethasone (n=73)	P
Age (yr)	24.9±4.9	24.5±4.9	0.63
Duration of pregnancy (days)	220±14	223±12	0.17
Fetal birthweight (g)	1604±397	1612±284	0.89
<i>Apgar score</i>			
1 st minute	6.7±1.6	6.9±1.73	0.50
5 th minute	9.1±1.2	8.9±1.3	0.38
<i>Mode of delivery</i>			
Vaginal	32 (45.7%)	26 (36.6%)	0.25
Cesarean section	39 (54.9%)	47 (64.4%)	
<i>Neonatal gender</i>			
Female	33 (46.5%)	35 (47.9%)	0.86
Male	38 (53.5%)	38 (52.1%)	

Numbers are presented as mean ± standard deviation or N (%).

In a meta-analysis by Crowley the effect of different corticosteroids on preterm labor morbidity and mortality was evaluated [6]. He did not find any difference between betamethasone and dexamethasone in RDS and IVH incidence but he reports betamethasone as the more effective medication in decreasing mortality rate. The equal efficacy of these corticosteroids was observed in our study. In addition, the rate of mortality was not significantly different in our results.

Dexamethasone nongenomic effects are more potent (about five times) than betamethasone and a methyl group at position 16 of ring D makes it different from betamethasone molecule [12-13]. In a study by Derks *et al.*, after betamethasone administration a more rapid rise in serum cortisol levels of fetal sheep in comparison with dexamethasone was observed [13]. They also described continuous rise in cortisol levels at 72 hours postexposure in fetal sheep of dexamethasone-treated group. The physiologic response to these corticosteroids demonstrates some differences in different studies and the reason is not exactly known yet.

Table 2. Outcome measures.

	Dexamethasone (n=73)	Betamethasone (n=71)	RR (95% CI)	P
<i>Major morbidities (at least one of the following)</i>	28 (38.4%)	27 (38.0%)	0.99 (0.65-1.50)	0.97
Respiratory distress syndrome (RDS)	25 (34.3%)	26 (36.6%)	1.07 (0.69-1.66)	0.76
Intraventricular hemorrhage (IVH)	6 (8.2%)	7 (9.9%)	1.20 (0.42-3.39)	0.73
Necrotizing enterocolitis (NEC)	5 (6.9%)	2 (2.7%)	2.57 (0.51-12.82)	0.27
Neonatal death*	13 (17.8%)	8 (11.3%)	1.08 (0.94-1.26)	0.26

*Attributed to complications presented in this table.
Values are expressed as ratio (%)

Conclusion

To put in a nutshell, we found no differences between antenatal dexamethasone and betamethasone in decreasing RDS, IVH, and NEC morbidity and mortality. Nevertheless, assessing their effect on more complications involving long-term morbidities on greater population can help to choose the proper corticosteroid. We recommend administration of both medication but the choice is still based on cost, availability, ease of administration.

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