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Comparison of the effect of single versus double doses of Betamethasone on the outcome of preterm neonates: A Clinical Trial Study

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ABSTRACT

Betamethasone is prescribed for accelerating fetal lung maturation in at risk pregnancies for preterm delivery. It is used to reduce the incidence of fetal distress syndrome, prevention of death from intracranial hemorrhage, necrotizing enterocolitis, and also to increase life expectancy.The aim of this study was to compare the effect of one versus double doses of Betamethasone on the outcomes of preterm neonates. In this clinical trial quasi-experimental study total of 100 women were selected and divided into two intervention and control groups. For intervention group a single dose of 12 mg Betamethasone and in control group double doses of 12 mg Betamethasone was injected intramuscularly with an interval of 24 hours. Data were entered into "SPSS". Chi-square and Mann Whitney U tests were used. Kolmograph-Smirnov test showed that data distribution was not normal. The results showed that mean and standard deviations of gestational age of the study population were 31.34 ± 2.44 weeks with a minimum of 24 and maximum of 35 weeks. Mean and Standard Deviations of women were 29.75 ± 7.01 years with a minimum of 16 and a maximum of 48 years. There were 48 male and 55 female neonates. There was no significantly different between the two groups in terms of Neonatal Respiratory Distress Syndrome (p=0.689), fetal death (p=0.525), or the need for hospitalization (p=0.394). There were no significantly different on the neonate outcomes between two groups according to single or double doses of Betamethasone.

Keywords: Betamethasone, Infant, Premature, Newborn Outcome, Respiratory Distress Syndrome, Newborn.

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INTRODUCTION

Betamethasone is prescribed for accelerating fetal lung maturation in at risk pregnancies for preterm delivery. In preterm neonates, Betamethasone is used to reduce the incidence of fetal distress syndrome, prevention of death from intracranial hemorrhage, necrotizing enterocolitis, and also to increase the life expectancy [1-3]. Multiple doses of Betamethasone may result in chorioamniotic and microcephaly [4, 5]. Neonatal respiratory distress syndrome (RDS) is an acute respiratory syndrome found in premature neonates who have surfactant production defects or immaturity of lungs structures [6]. It causes perinatal deaths in 44% of the cases [7]. The incidence of this disease is inversely correlated with gestational age. Much of the pulmonary surfactant is produced after 30 weeks of pregnancy. RDS occurs in 60% of pregnancies with less than 28 weeks of gestational age; however, it decreases in late pregnancies. The incidence of the disease is reduced 15 to 30% in deliveries with 32 to 36 weeks of gestational age [8].

Some studies have reported that maternal factors such as kidney problems, cardiovascular disease, hypertensive disorders, addiction to heroin and fetal factors such as fetal growth restriction, placental abnormalities, chorioamniotic separation, premature rupture of membranes may influence fetal lung maturity; but, more recent studies have not confirmed this [1]. Use of corticosteroids and postponing the childbirth are among preventive measures of neonate respiratory distress syndrome or hyaline membrane disease. Producing surfactant proteins and increasing the synthesis of phospholipids, glucocorticoids reduce the incidence and severity of neonatal distress syndrome [9]. Use of corticosteroids in preterm labor reduces the respiratory complication and mortality by 50% and 40% respectively [10]. Administration of corticosteroid to mothers reduces the risk of cerebral hemorrhage, necrotizing enterocolitis, and several other major complications. It reduces hospitalization time and costs as well [11, 12]. Administration of Betamethasone to mothers at risk of preterm birth is effective in hyaline membrane disease or respiratory distress in neonates [13, 14]. Lower doses of this medication are used to prevent neonate distress syndrome without any special side effects [15]. Preventive interventions have been effective in preterm births of less than 34 weeks of gestation. Therefore, use of glucocorticoids in women who are at risk of preterm birth with gestational age of less than 34 weeks is highly recommended [16]. Administration of Betamethasone is prescribed by a specialist if there is a risk for low birth weight [10]. However, it is recommended to conduct more studies in the field [17, 18]. The aim of this study was to determine the effect of single dose of Betamethasone versus double doses of the same medication on the outcomes of preterm neonates.

MATERIALS AND METHODS

In this clinical trial quasi-experimental study, 100 preterm women referring to Besat Hospital in Sanandaj in 2013 and their 103 neonates (three mothers had twin) were enrolled in the study. Inclusion criteria were 24 to 36 weeks of pregnancy and exclusion criteria were placental abruption, chorioamnionitis, severe preeclampsia, HELLP syndrome, and fetal distress syndrome. Based on previous published studies [14, 19] and considering the 95% confidence level and power of 80%, the sample size in each group were estimated 37 cases, but to increase the accuracy it was determined as 50 cases in each group. (Figure 1)

Samples were selected non-randomly (in order to comply with ethical issues) based on the mother's clinical condition and were divided into single-dose and double doses of Betamethasone (50 participants in each group). Informed consent was obtained from the participants in the study and information such as age, history of gestational age, and number of preterm neonates was recorded in the check list. For intervention group a single dose of 12 mg Betamethasone was injected intramuscularly and for Control group double doses of 12 mg Betamethasone were injected within 24 hours (standard procedure).Information about delivery and newborn including gender, weight and Apgar scores were determined and recorded in the check list. Then the neonatal respiratory distress syndrome, necrotizing enterocolitis, cerebral hemorrhage and neonatal mortality was examined by a neonatologist and evaluations were recorded.

Respiratory distress syndrome was diagnosed based on symptoms of respiratory distress syndrome or Hyaline membrane disease including: intercostals and subcostal retraction, nasal flaring, tachipnea, granting (groan) with or without peripheral or central cyanosis. Specific radiological features included: reticulonodular pattern and classic ground glass in both lungs with an “Air bronchogram" view. Then other causes of respiratory distress were ruled out and the diagnosis was confirmed by specialist. Diagnosis of Necrotizing enterocolitis were made based on clinical examination by a specialist and other diagnostic factors including:

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increase of food remains in the stomach, bilious vomiting, abdominal distension, bloody stools, episodes of apnea and bradycardia, lethargy and poor skin perfusion, and radiograph of the abdomen in the supine position. Cross-table lateral view shows distension of the small intestine. Intestinal cystic pneumatosis and gas appears in the portal vein. Detected bleeding in the brain was determined by clinical examination of a pediatrician. Diagnosis of neonatal deaths was determined according to expert opinion on the death of newborn babies. In order to reduce bias and blinding the data collection process, data were collected and recorded in the check list by a fellow midwife who was not sensitive to study.To the end of the study researchers were unaware about patient grouping.Data were entered into SPSS software. Descriptive statistics were used to answer questions such as average and ratio. Kolmogorov-Smirnov test showed that Quantitative variables were not normally distributed. Hypotheses with respect to the measure and type of the variable and its distribution were made using “chi-square “and” Mann–Whitney U tests.

This study was approved by Ethics Committee of Kurdistan University of Medical Sciences, Sanandaj, Iran (Reference number: 14/40742 dated: 2013-09-28). It was registered in Iranian registry for Clinical Trials with the following registration code: IRCT2014090912789N6.

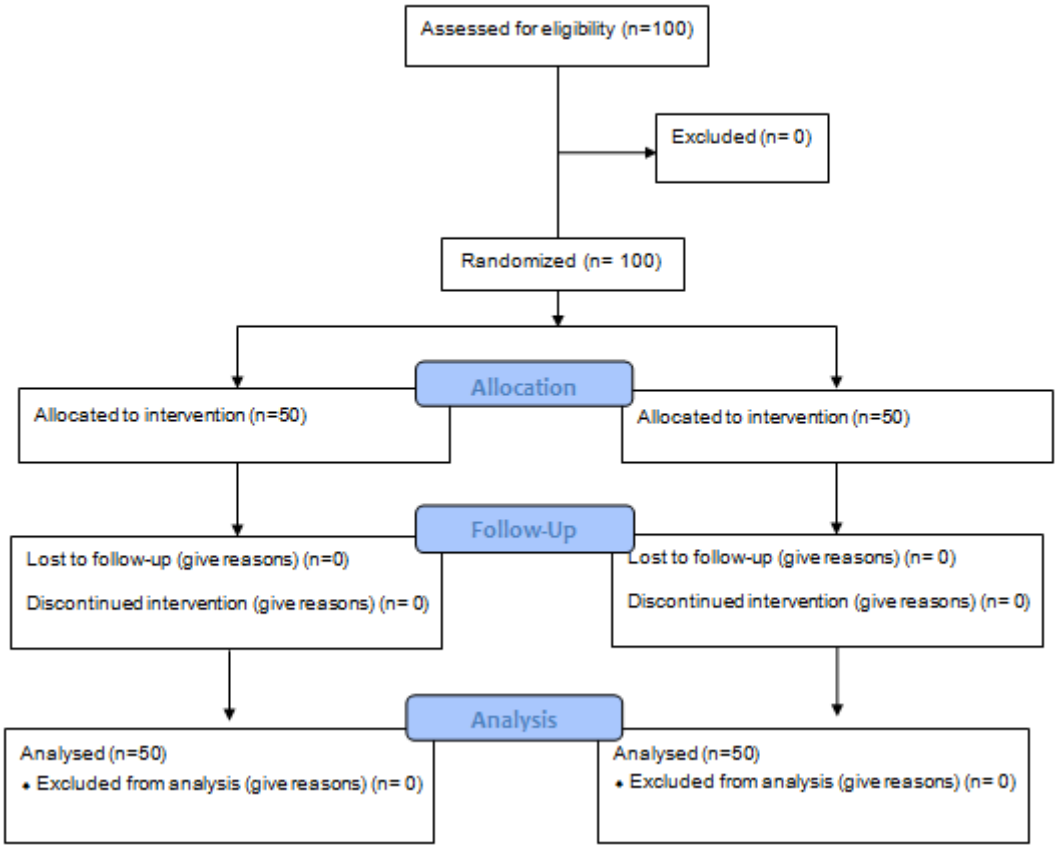

Figure 1) Flow diagram of the progress through the two groups

RESULTS

Results showed that mean gestational age of the study population were 31.34 ± 2.44 weeks (or at least 24 to 35 weeks). Mean age of mothers were 29.75± 7.01 years with a minimum of 16 to a maximum of 48 years. 48 neonates (6.46%) were male and 55 (4.53%) were female. Intraventricular hemorrhage occurred in 11 patients (10.7%); but, there were no sign of it in 92 of the patients (89.3%). Neonatal sepsis occurred in 7 cases (6.8 %); however, it did not happen in 96 of the cases (93.2%). Only one of the mothers who were in the double dose group had a history of premature birth (1%).

Given the maternal gestational age (P = 0.92), age (P = 0.87) and birth weight (P = 0.73), there was no significant difference between the two groups according to single dose and double medication doses. The two groups did not differ statistically according to their need to stay in the neonatal intensive care unit, need for respiratory support and neonate mortality (Table 1).

Table 1: Comparison of neonatal outcomes in both groups

Variable	Single dose group (50)		Double doses group (53)		P Value
	No.(%)	No.(%)	No.(%)	No.(%)	
Need for neonates hospitalization	8 (16%)	42 (84%)	12 (22.6%)	41 (77.4%)	0.394
Need for respiratory protection	42 (84%)	8 (16%)	44 (83%)	9 (17%)	0.893
Neonate mortality	38 (76%)	12) (24%	43 (81.1%)	10 (18.9%)	0.525
Incidence of enterocolitis	46 (92%)	4 (8%)	46 (86.8%)	7 (13.2%)	0.392
Respiratory distress	36 (72%)	14 (28%)	40 (75.5%)	13 (24.5%)	0.689
Intraventricular hemorrhage	46 (92%)	4 (8%)	46 (86.6%)	7 (13.2%)	0.689
Neonatal sepsis	49 (98%)	1 (2%)	47 (88.7%)	6 (11.3%)	0.060

Other findings related to enterocolitis, respiratory distress, intraventricular hemorrhage and neonatal sepsis showed no significant difference between the single dose and double dose groups (Table 2). Also, there was no significant difference between mean Apgar score of 1 (p = 0.889) and 5 (p = 0.336) and according to neonatal hospital stay in NICU (p = 0.695).

DISCUSSION

Many studies have proved the beneficial effect of Betamethasone and dexamethasone in improving the respiratory distress syndrome of preterm neonates [19-22]. This is due to the effect of glucocorticosteroid on surfactant-associated protein and increased synthesis of phospholipids resulting in the improvement of neonatal distress syndrome [9,10].

In our study on preterm neonates with a mean gestational age of 42.2 ± 34.31-weeks, there were no significant differences in both single and double dose groups according to gestational age, birth weight, and Apgar score in 1 and 5 minutes, and Gender distribution. Many studies have been conducted on the effects of standard treatment (administration of double doses of Betamethasone) and in most of the cases the effects have been confirmed by conducted studies [19-28]. Although, limited studies have compared the efficacy of single dose and double dose or multi-dose of Betamethasone [29-31], the results of our study showed that there was no significant difference in single and double doses on the occurrence of neonatal respiratory syndrome (p=0.689). The findings of this study matches the findings of Wang et al [29], in which a 10 years cohort study conducted in the Kaohsiung University of Taiwan, the effect of Betamethasone in three groups of single dose, multiple dose and a non Betamethasone group were investigated. In that study there was no significant difference between single and multiple dose groups ($p>0.05$); however, there was a statistical difference between non Bethamethasone and Betemethasone groups ($p<0.05$). Another study conducted by Khandelwal et al. [30] compared the effect of Betemethasone in a single and double dose groups. In this study, the difference was not significant and their results matched with our study. In a study by Peltoniemi et al [33], in single dose group compared to double dose group the respiratory distress was more prominent.

Findings of the above mentioned studies indicate that in the majority of studies, administration of a single dose of Betamethasone can be effective in the reduction of respiratory distress syndrome. However, Inconsistencies in the results of some studies shows the importance of further studies in the field.

Despite the fact that, clinical significance of 5% difference could be important; however, neonatal mortality rate showed no statistical difference in both groups (p=0.525). This finding is consistent with results of a study conducted by Mazumder et al [31] in which they compared the effect of Betamethasone in single and multiple dose groups. There was no significant difference in the mortality rate between the double groups ($p> 0.05$) which is consistent with our study.

Studies conducted by Wang[29], Khandelwal [30] and Ay et al [32] were consistent with the study conducted by Peltoniemi et al [33] and no study found to be inconsistent with these finding. Also the studies

by Nayeri et al [28], Nanbakhsh et al [19] and Bontis et al [20] on studying the effects of Betamethasone in standard (double dose) administration compared to no Betamethasone group find out a significant decrease in the number of mortalities and was consistent with the results of our study.

Other findings revealed no significant difference (p = 0.392) in necrotizing enterocolitis in the both study groups. They also suggest an incidence of 0.8% in the single dose group and 2.13% in the double dose group. Though, single dose group was better (due to a 5% difference), which may be clinically important.

Findings of the study conducted by Khandelwal et al were inconsistent with the results of our study [30]. In this study necrotizing enterocolitis rate in the single dose group and double dose groups were 6.2% and 0% respectively and the difference was significant (p <0.05). These findings were consistent with findings of Mazumder et al [31], Wang [29] and Peltoniemi et al [33]. In all four studies both groups did not match; however, they confirmed that a single dose of Btamethasone could prevent necrotizing entrocolitis which requires more studies to confirm. Considering the need for respiratory support, hospitalization of neonates, and ensuing length of stay in NICU, no significant difference were seen between both groups (p>0.05). This finding is consistent with other relevant studies [29-32]. Administration of a single dose of Betamethasone has the same effects with that of double doses of the same medication in avoiding the need for respiratory support and NICU hospitalization. Therefore, studies on standard treatment with Betamethasone have proved that Betamethasone is effective in reducing the need for hospitalization [20, 21, 25.26].

In our study, there was no statistical difference between the incidence of sepsis in neonates (2%) in single dose versus double dose groups (P=0.06). However, the difference was not significant in the double dose group (the rate was 9.3% more than single dose group which is clinically important). These findings were consistent with the results of all the above studies [29-31].

Incidence of intraventricular hemorrhage in single and double dose were not statistically significant (p=0.689). This finding was consistent with previous studies in this area [29-31].

In conclusion, a dose of Betamethasone can be considered as an option in the prevention of adverse outcomes in preterm neonates and to reduce the side effects of Betamethasone. Results of other related studies showed a negative correlation between administration of Betamethasone and height and weight; although, further studies are necessary for getting a final conclusion.

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REFERENCES

[1] Cunningham FC, Leveno KJ, Bloom, Hauth JC, Windstorm LGKD, Williams obstetrics, 23nd ed, New York, McGraw Hill 2010; pp:819.
[2] Gamsu HR, Mulinger BM, Donnai P, Dash CH. Br J Obstet Gynecol 1989; 96(4):401-10.
[3] Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation, 4th Ed, Baltimore, Williams & Wilkins 1994; pp: 89-90.
[4] Vermillions, Soper D, Newiman R. Am J Obstet Gynecol 2000; 183(4):810-4. DOI: http://dx.doi.org/10.1067/mob.2000.108838
[5] Scheepens A, van de Waarenburg M, van den Hove D, Blanco C. The Journal of Physiology. 2003;552(1):163-175. doi:10.1113/jphysiol.2003.043414
[6] Rodriguez RJ, Martin RJ, Fanaroff AA. Respiratory distress syndrome and its management. In: Fanaroff AA, Martin RJ, Editors. Neonatal-perinatal medicine: Diseases of the fetus and neonate. 8th, Mosby: St. Louis. 2006; pp: 1001-11.
[7] Meneguel JF, Ginsburg R, Miyoshi MH, Peres CA, Russo RH, Kopelman BI, et al. Sao Paulo Med J 2003; 121(2): 45-52. doi.org/10.1590/S1516-31802003000200003
[8] Dudell GG, Stoll BJ. Respiratory tract disorders. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. Nelson Textbook of Pediatrics. 18th, Philadelphia: Saunders Co. 2007; pp: 728-53.
[9] Crowley P. Cochrane Database Cyst Rev 2000 ;2:CD000065.

[10] Crowley P, Chalmers I, Keirse MJ. Br J Obstet Gynaecol. 1990;97(1):11-25.
[11] Asnafei N, Pourreza R, Miri S.M. Journal of Gorgon University of medical sciences 2005; (14): 57-60.
[12] Robert L Goldenberg, MD. Obstet Gynecol 2002; 100(5): 1020-1037. Doi:10.1016/S0029-7844(02)02212-3
[13] Schmitt BD, Todd J. Instructions for Pediatric Patients.2 en. Ed. Philadelphia, Saunders, 1999.
[14] Mansouri M, Seyedolshohadaei F, Company F, Setare Sh, Mazhari S. Journal of Gorgan University of Medical Sciences 2010; 12(3): 18-23
[15] Dalziel SR, Walker NK, Parag V, Mantell C, Rea HH, Rodgers A, et al. Lancet 2005 ; 365(9474):1856-62. doi:10.1016/S0140-6736(05)66617-2
[16] National Institutes of Health (NIH) Consensus Development, ETATS-UNIS (Commanditaire) Effect of corticosteroids for fetal maturation on perinatal outcomes. Am J Obstet Gynecol 1995 ; 173:246-52.
[17] Ventolini G, Neiger R, Mathews L, Adragna N, Belcastro M. Am J Perinatal. 2008; 25(2): 79-83. DOI: 10.1055/s-2007-1022470
[18] Costa S, Zecca E, De Luca D, De Carolis MP, Romagnoli C. Eur J Obstet Gynecol Reprod Biol. 2007; 131(2):154-7. doi:10.1016/j.ejogrb.2006.05.006
[19] Nanbakhsh F, Mohadesi H, Ordokhani A, Ghaderi J. Scientific Journal of Hamedan Nursing & Midwifery Faculty (Nasim-Danesh) 2011;19(2): 5-10
[20] Bontis N, Vavilis D, Tsolakidis D, Goulis DG, Tzevelekis P, Kellartzis D, Tarlatzis BC. Clin Exp Obstet Gynecol. 2011; 38(2)165-7 doi: 10.1136/adc.2008.137935.
[21] Bonanno C, Wapner RJ. Obstet Gynecol Clin North Am.2012; 39(1):47-63. doi: 10.1016/j.ogc.2011.12.006
[22] Meneguel J, Guinsburg R, Miyoshi M, Peres C, Russo R, Kopelman B et al. Sao Paulo Med J 2003;121(2). Doi:10.1590/S1516-31802003000200003
[23] Behrman R, Kliegman R, Jenson H. Nelson textbook of pediatrics. Philadelphia: W.B. Saunders Co.; 2007.
[24] Crowley PA. Amj Obstet Gynecol 1995; 173: 322-35 doi:10.1016/0002-9378(95)90222-8
[25] Fekih M, Chaieb A, Sboui H, Denguezliw, Hidars, Khairi H. Tunis Med 2002; 80(5): 260-5.
[26] Roberts D, Dalziel S. Cochrane Database Syst Rev 2006 ; 19(3): CD004454. DOI: 10.1002/14651858.CD004454.pub2
[27] Moraveji Asl M, Kashanian M, Ahangari Shirzi A. The Razi Journal of Medical Sciences 2005;12(45): 180-173
[28] Nayeri F, Movaghar-Nezhad K, Assar-Zadegan F. East Mediterr Health J 2005; 11(4):716-22. doi:10.1016/S0140-6736(06)68846-6
[29] Wang Y, Tseng H, Yang S, Lu C, Wu J, Dai Z et al. Pediatrics & Neonatology 2012;53(3):178-183. DOI: 10.1016/j.pedneo.2012.04.004
[30] Khandelwal M, Chang E, Hansen C, Hunter K, Milcarek B. American Journal of Obstetrics and Gynecology. 2012;206(3):201.e1-201.e11.
[31] Mazumder P, Sourabh D, Jaswinder K. Indian Pediatrics 2008 ; 45(8) : 661-7.
[32] Ay H, Tosun M, Malatyalıoğlu E, Aygün C, Bilge Çetinkay M. J Turkish-German Gynecol Assoc 2010; 11: 38-43.
[33] Peltoniemi O, Kari M, Tammela O, Lehtonen L, Marttila R, Halmesmaki E et al. Pediatrics 2007;119(2):290-298.