European Journal of Molecular & Clinical Medicine (EJMCM)
ISSN: 2515-8260 Volume 09, Issue 01, 2022

Original research article

Study of Effect of Betamethasone in Preterm Fetus on Heart Rate

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Abstract

Background: To recognize and understand the short term effects of administration of prophylactic betamethasone, to the mother, on the foetal heart rate pattern.

Material and methods: This study was a cross sectional study. It was conducted over two years in department of Obstetrics and Gynaecology, at Patna medical college and Hospital, Patna. After admission, a baseline Electronic Foetal Monitoring (FEM) test was done and repeated at 12 hourly intervals for the next 84 hours. Two doses of betamethasone intramuscularly were given at 24 hours interval. Foetal Heart Rate pattern like baseline, beat to variability, acceleration and deceleration were monitored. If FHR pattern showed any non-reassuring findings, EFM was repeated after 1 hour and followed up with Biophysical Profile (BPP).

Conclusion: betamethasone, induces changes in foetal physiology. These changes are not brought about by foetal hypoxia. Knowledge of the transient effects of betamethasone, will avoid unnecessary preterm delivery of babies. This will also reduce the number of caesarean sections in future pregnancies.

Keywords: Preterm labour, Effect of betamethasone.

Introduction

Preterm Labour is defined by the World Health Organization (WHO) as 'Onset of labour, prior to the completion of 37 Weeks of gestation, in a pregnancy beyond 20 weeks of gestation According to the WHO, 9.6% of all live births are preterm. Developing countries like Africa (11.9%) and south Asia (11.4%) contribute the highest burden in terms of absolute number. A high rate was also observed in North America(10.6%)[3]. Morbidityand mortality of the babies are dependent on the gestational age at delivery. Even though early preterm birth constitutes 1-2% of all live births, it contributes to 60% of perinatal mortality and a majority of the morbidity, mainly in the form of neurologicaldeficits. Preterm labour resulting in preterm delivery is catastrophic and ultimately ends in perinatal mortality and morbidity. Both obstetricians and the neonatologists are looking for research advances that would predict, prevent and treat preterm labour in addition to improving neonatal care. Preterm delivery is responsible for three-fourths of all neonatal deaths not associated with congenital anomalies.[6] Preterm delivery rate varies from 6 to 15% of all deliveries; of these, 40-50% occurs spontaneously, whereas 25% occur following PPROM (Preterm premature rupture of membrane). The remaining 25% of

iatrogenic preterm labour is due to obstetric interventions that are done to avoid maternal or foetal compromise.[7] It is a major determinant of serious neonatal morbidity, including Respiratory Distress Syndrome (RDS), Necrotizing Enterocolitis (NEC), Intra- Ventricular Haemorrhage (IVH) and long term neurological problems. Prevention of preterm labour is a step of utmost importance. If successful, it can stopa foetus from being stripped of his or her comforts in the womb and being pushed intothe harsh world at a time when she or he is still not ready for it. Prevention of preterm labour requires identification of women at risk and then instituting measures to prevent it. A recent meta-analysis concluded that antenatal corticosteroid administration before preterm delivery was associated with a significant reduction not only in neonatal death but also in RDS, IVH and NEC. Although the side effects of the treatment areminor compared to its benefits[13], proper care must be taken before the administration of the drug. The effects of betamethasone on FHR (Foetal Heart rate) patterns have been documented in various studies. Katz et al, in their study, have reported a cessation of foetal movement after the administration of betamethasone accompanied by an increase in nonreactive FHR pattern which was a transient phenomenon, with the foetal movement returning to normal within 24 hours of steroid administration. A study, by Damien Subtil et al, reports that during treatment (day 0 to day 1) the foetal heart variability increased, whereas it decreased significantly after the treatment(day 2 to day3). A trial by Mulder et al in two of their studies confirmed a decreasein foetal heart variability after betamethasone, which returned to its previous level after stopping the treatment. Magee et al demonstrated an initial increase in the long and short term foetal heart variability and decreased foetal movements on the first day after the steroid administration followed by a decreased in foetal heart variation on the second day. Their observations were matched those of Dawes et al by showing that there was a small increase in short term variability on the first day after steroid administration. The studies quoted above provide conflicting results and lead to no common conclusion concerning the effects of Betamethasone. Hence, this prospective analysis has been undertaken to evaluate these effects with an adequate sample and a stringent methodology.

Objectives

To study the short term effects of maternal betamethasone administration on the foetalheart rate variability using Foetal Heart Rate trace from the Electronic Foetal Monitoring (EFM) in preterm labour.

Review of Literature

Preterm labour (PTL) is defined as the onset of painful uterine contraction with progressive effacement and dilatation of cervix after the gestation of viability and before 37 completed weeks or 259 days of pregnancy. The rate of preterm delivery among single term pregnancies has risen from 9.7% in 1990 to 11% in 2005. Spontaneous preterm birth before 37 weeks of gestation occurs in 7-11% of pregnancies and before 34 weeks of gestation in 3-7% of pregnancies. The latter are more likely due to pathological than physiological causes. The pathway of parturition has the following three components: cervical ripening, activation of myometrium, and activation of foetal membranes. In preterm birth one of the components predominates. For example, in women with incompetent cervix premature cervical ripening occurs, while in premature rupture of membranes there is premature activation of membranes. Inflammation promotes inflammatory reactants like endotoxin and cytokines [Interleukin 1 (IL 1) & Tumour necrosis factor (TNF)]. These will enhance prostanoidexpression in the decidua. IL-6 expression may be associated with ascending amnio-chorionic- decidual infection. This may trigger uterine contractions. Maternal and foetal stress can result in the release of various adrenal and hypothalamic stress hormones, which enhance placental, decidual, and amnio-chorionCorticotrophin Releasing Hormone (CRH) expression. Acting as a paracrine effector,

CRH enhances amnio-chorionic decidual prostanoid production and stimulates uterine contractions. The contribution of preterm delivery to adverse outcome is related to the gestational age at delivery more than the birth weight. Preterm delivery particularly that before 34weeks of gestation accounts for three quarters of neonatal mortality and one half of long term neurological impairment in children, including developmental delay visual and hearing impairment, chronic lung disease, cerebral palsy etc. In contrast stimulation of sympathetic nervous system produces slow rise in FHR andit improves myocardial contractility. Thus baseline FHR at any time is under the influence of both parasympathetic and sympathetic activity. Foetal heart rate is also controlled by neural reflexes mediated via baroreceptors and chemoreceptors present in the arch of the aorta and carotid sinus respectively. The reflexes are modified in thebrain stem where central chemoreceptors are present. Betamethasone belongs to class C among drugs which can be administered during pregnancy, and is associated with both risks and benefits. Beneficial effect is brought about by its action on glucocorticoid receptors on the type II pneumocytes which stimulate the production of surfactant. However, the undesirable non-pulmonary effects are not well studied. Corticosteroid are widely used anti-inflammatory and immunosuppressive drugs which are used in treatment of a wide range of medical disorders, both for maternal and for foetal reasons. One of the most important uses is to enhance foetal lung maturity in preterm labour, which in turn decreases the risk of RDS, IVH, NEC and neonatal mortality. These side effects do not appear to be clinically significant in appropriately grown foetuses. However foetal heart variation or variability can be affected by Glucocorticoids. The decrease in foetal heart variability has been reported with betamethasone and the reverse was found with dexamethasone. Dexamethasone is metabolized quicker than betamethasone, and the shorter plasma half-life of dexamethasone is the reason for the different dosage regimens for betamethasone and dexamethasone. The affinity of betamethasone for the glucocorticoid receptors in the foetal lungs is higher than dexamethasone and it has also been observed that a significant reduction in neonatal mortality, as opposed to reduction in RDS alone, has only been found for betamethasone. This sometimes leads to assumption that betamethasone is better or more effective than dexamethasone. Liggins and Howie published their results of a randomised controlled trial of betamethasone administration in women who were expected to deliver preterm. They demonstrated a significant reduction in RDS. Crowley et al drew conclusions that convinced obstetricians and paediatricians that corticosteroids led to statistically and clinically significant reductions in neonatal morbidity and mortality and that these benefits overweigh the risk. Crothers et al in his study provided that high-level evidence of direct relevance for clinical practice. If one drug clearly results in significantly fewer deaths and fewer disabled children then it should be used consistently in women at risk of preterm birth and would be of great importance to women at risk of preterm birth, their children, health services and communities.

Material and methods

This study was a cross sectional study. It was conducted over two years in department of Obstetrics and Gynaecology, at Patna medical college and Hospital, Patna, Bihar. After admission, a baseline Electronic Foetal Monitoring (FEM) test was done and repeated at 12 hourly intervals for the next 84 hours. Two doses of betamethasone intramuscularly were given at 24 hours interval. Foetal Heart Rate pattern like baseline, beat to variability, acceleration and deceleration were monitored. If FHR pattern showed any non-reassuring findings, EFM was repeated after 1 hour and followed up with Biophysical Profile (BPP). All antenatal primigravidas between 28 to 34 weeks of gestation with preterm labour, and a singleton pregnancy in vertex presentation.

Inclusion Criteria
Primigravida, Singleton pregnancies, Gestational age between 28-34 weeks with preterm contractions whoare clinically stable

Exclusion Criteria
Multiple Pregnancy, Multigravida, Polyhydramnios, Pregnancy complicated by Pre-ecclampsia, Gestational Diabetes, Antepartum Haemorrhage- Placenta Previa, Abruptio Placenta, Cervical Incompetence.
The study protocol was explained to the patient and written informed consent was taken prior to recruitment in the study. Each potential participant for the study received a unique code. Following recruitment, blood samples was drawn for routine standard of care in preterm labour. The patient then received the second dose of Injection Betamethasone Intramuscularly24 hours from the time of administration of first dose.

Results
A Prospective clinical and descriptive study consisting of 62 pregnant women was undertaken to study the effect of betamethasone administration on foetal heart rate pattern in preterm labour. Among the 62 women 3 did not deliver with us and hence were excluded from the study. So, only 59 women delivered In PMCH, Patna Bihar. Their ages ranged from 18 to 37 years with a mean of 24.9 ± 4.27. Most of the women were between 21 and 25 years of age. There was a transient decrease in the baseline FHR noted at 36 hours after betamethasone administration, which returned to normal at 60 hours which was statistically significant($P<0.05$), The same observation was found when the study population was analysed at different gestational ages except in those whose gestational age was less than 30wks. ($P<0.0001$), There was transient decrease in the beat to beat variability noted at 24 to 48 hours of betamethasone administration, which returned to normal at 72 hourswhich was statistically significant ($P<0.05$) The same observation was found when the study population was analysed at different gestational ages.($P< 0.05$)

GA AT ADMISSION	NO. OF PATIENTS	GESTATIONAL AGE AT DELIVERY									
		28	29	30	31	32	33	34	35	36	>37
28	12				1		1	1			9
29	3			1							2
30	8									1	7
31	6					1					5
32	10					1					9
33	20						1		1	3	15

The median Gestational age at the time of admission was 31 weeks and at the time ofdelivery was 38 weeks. 13 out of 18 underwent emergency LSCS. The most common indication was foetal distress (44%). Other indications included Cephalo Pelvic Disproportion (CPD), Meconium Stained Liquor (MSL), Abruptio placentae and Antepartum Ecclampsia (APE). The relatives of one of the stillborn babies (28weeks) refused LSCS and NICUcare due to financial constraints. The second foetus (30weeks) had a scan showing a cardiac anomaly. Both

patients opted for Preterm Vaginal Delivery despite the presence of foetal distress and the babies were stillborn. Both babies weighed <1000gms. 4% of the babies had a birth weight of < 1.5 Kg.(extremely low birth weight)21% of the babies weighed between 1.5 to 2.5 kg at the time of birth (low birthweight),The remaining 75% of the babies had Birth weight >2.5 Kg. The mean APGAR score at 1 minute was 7.41 (+/- 1.74) and was 8.31 (+/- 1.85) at 5minutes, which is an indicator of good neonatal outcome. 70% of the patients had vaginal delivery: labour was either induced orspontaneous in onset. 30% of the patients delivered by caesarean section. Among those who had vaginal delivery 58% were term neonates and 12%were preterm. Among the LSCS (Lower Segment Caesarean Section) 22% were termneonates and 8% preterm.

Discussion

The National Institute of Health Consensus Conference recommend that short term antenatal steroids are effective in preventing neonatal Respiratory Distress Syndrome (RDS) and appear to have no detrimental effect on the adrenal function in newborn infants. Synthetic glucocorticoids have been administered for the past 20 years to enhance the foetal lung maturation. Pregnancies with preterm contraction and threatened preterm delivery constitute a great majority of high risk and low risk pregnancies, requiring steroids. Steroid induced effects are mediated by glucocorticoid receptors located diffusely throughout the body both in adults and foetuses. Zarqa Saif et al (2015) recently examined the term and preterm placentae from human pregnancies. They identified that there are 8 known isoforms of the glucocorticoid receptor present in the preterm placenta GRα (94 k Da), GRβ (91 k Da), Grα C (81 k Da), GR P (74 k Da), GR A (65 k Da), GRα D1-3(50-55 k Da). Expression varied between preterm and term placentae with a greater expression of Grα C in preterm placentae relative to term placentae. We studied 59 antenatal women belonging to the low risk group. While monitoring such patients, the surveillance of foetal well-being becomes essential and is most commonly achieved by inspecting the foetal heart rate pattern produced by the Electronic Foetal Monitor. This method was employed in our study. There was a transient decrease in the baseline FHR noted at 36 hours after betamethasone administration, which returned to normal at 60 hours which was statistically significant($P<0.0001$) There was transient decrease in the beat to beat variability noted at 24 to 48 hours of betamethasone administration, which returned to normal at, 72 hours. This observation was statistically significant. ($P<0.05$) The number of accelerations reached a peak at 36hrs and returned to normal by 60 hours. This finding was statistically significant($P<0.05$), Magee et al demonstrated an initial increase in the long and short term foetal heart variability and decreased foetal movements on the first day after the steroid administration followed by decreased foetal heart rate variation on the second day. Our study, as well as the studies done by Dukes and Mulder et al have found that the decrease in the foetal heart rate and variability, were statistically significant at 48 hours of betamethasone administration ($P <0.05$). This observation was similar when the study population was analysed as a whole and for different gestational age groups.These changes were only transient and returned to normal on the 3rd day (60-72 hours) of betamethasone administration. Dawes et al however reported a substantial but transient and unexplained increase in the FHR variation after the steroid (Dexamethasone) administration. Sigi Rotmensch et al, in their study concluded that betamethasone causes profound but transient variation in FHR parameters. Baseline FHR was elevated, FHR variability was decreased on day one and on day 2 the number of accelerations decreased after betamethasone injection. Damien Subtil, et al, studied the immediate and delayed effects of antenatal corticosteroids on the foetal heart rate. It was a randomized trial which compared the action of betamethasone acetate, betamethasone phosphate, and dexamethasone Phosphate on the foetal heart rate when given for preterm labour. Juan Piazze, Kathleen Comalli Dillon, and Cerekja Albana noted that maternal

corticosteroid administration between 26- 34 weeks may be related to higher foetal reactivity when these foetuses reach term (>37wks). A recent study conducted by Shamsi et al found that after injection of corticosteroid, there was a transient increase in embryonic movement but index of BPP (Biophysical profile) and AFI(Amniotic fluid Index) did not show any change So large scale, case-controlled studies may be needed in the future to evaluate the whole range of effects of betamethasone and its clinical outcome in detail. But the present study emphasizes on the need to be aware of the transient changes in the foetal heart physiology which are reflected in foetal heart rate after betamethasoneadministration in order to avoid iatrogenic premature delivery.

Conclusion

In pregnancies with preterm contraction, it is essential to administer antenatalcorticosteroids to avoid complications of prematurity such as RDS, NEC and IVH. The use of antenatal corticosteroids causes a transient decrease in baseline FHR and beat to beat variability which are possibly due to changes in foetalphysiology and not due to foetal hypoxia. Knowledge of these transient changes of betamethasone, especially on FHRpatterns (baseline FHR and beat to beat variability) will avoid unnecessary premature interventions resulting in iatrogenic preterm deliveries.

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Received :09-11-2021. Revised:26-11-2021. Accepted:28-12-2021