

ORIGINAL ARTICLE

IMPACT OF ANTENATAL CORTICOSTEROIDS ON FREQUENCY AND MORTALITY DUE TO RESPIRATORY DISTRESS SYNDROME IN PRETERM NEONATES

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Background: Prematurity is still a major problem for health care services throughout the world. Before the late 1980s, respiratory distress syndrome (RDS) was the primary cause of morbidity and mortality in preterm new-borns. Frequency of RDS and ensuing mortality in infants treated with antenatal steroid is less than those delivered without this therapy. Many pregnant females deliver before term or 37 weeks, hence may be advised this prophylactic therapy without creating significant maternal or foetal side effects. **Method:** It was a descriptive case-series conducted in the department of obstetrics and gynaecology, unit II of Jinnah Hospital Lahore for a period of 6 months. **Results:** The study sample of 230 was divided into two groups on the basis of exposure to dexamethasone. RDS was reported 76 (33.0%) cases (preterm neonates) in the study, out of these 26 (22.4%) cases belonged to exposed group and 50 (43.9%) cases belonged to non-exposed group. Mortality due to RDS among all preterm neonates with RDS occurred in total 29 (12.6%) preterm neonates in the study, out of these 5 (4.3%) cases belonged to exposed group and 24 (21.1%) belonged to non-exposed group. **Conclusion:** Frequency of RDS and mortality due to this disease in group of infants treated with antenatal steroid is far less than the group of preterm new-borns delivered without this therapy.

Keywords: Antenatal dexamethasone; effectiveness period; preterm new-borns; RDS; neonatal outcome

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INTRODUCTION

Prematurity is still a major problem for health centres throughout the world. The incidence of preterm birth in the developed world is between 7–12%.¹ Respiratory distress syndrome (RDS), also known as hyaline membrane disease was the primary cause of morbidity and mortality in preterm new-borns before 1980's. Neonatal respiratory distress syndrome (RDS) is one of the major problems in modern obstetrics. Maturation of foetal lungs is dependent on surfactant, which is a complex molecule. The prime factor for insufficient surfactant production and pulmonary immaturity is birth of a new-born before reaching the term. For more than thirty years antenatal corticosteroids are in use for foetal lung maturation. The incidence of RDS is 1–2%.² Liggins and Howie first introduced steroid therapy in 1972.³ After the first consensus conference of National Institutes of Health (NIH) in 1994, it was proved that antenatal corticosteroids decrease the incidence of RDS in infants born between 29 to 34 weeks of gestation. They recommended giving a single course of corticosteroids to every pregnant woman between 24 and 34 weeks gestation who is at risk of preterm delivery within next seven days.¹

Since the introduction of steroid therapy in clinical practice, many randomized controlled studies have concluded the positive maturational effects of antenatal corticosteroids on foetal lungs, which decrease incidence and severity of hyaline membrane disease, reduce incidence of intra-ventricular haemorrhage, and overall reduce neonatal mortality.⁴ The maximum

benefit of steroids is seen if the babies are born after 48 hours but within 7 days from first dose of steroid course. So they are not useful in every case of preterm pregnancy. When prescribing the steroid therapy to the preterm pregnant women they may be informed that a single course of antenatal corticosteroid therapy is not associated with any significant side effects on the mother or foetus.⁵ Steroid therapy decreases the risk of hyaline lung disease in 50% cases and mortality risk of a premature by almost 40%.^{6,7} The incidence of RDS has an indirect relationship with the gestational age, meaning that it is high at early gestation and reduce with advancing gestation, from about 50% in babies born at 26–28 weeks to about 25% at 30–31 weeks and 5% at 35 weeks.^{8,9} It is a leading cause of mortality in preterm infants and accounts for 30% of all neonatal deaths.¹⁰ The major complications of RDS are air leaks (pneumothorax and pulmonary emphysema), bronchopulmonary dysplasia, and death.¹¹ In a study conducted in Imam Hospital Complex, Tehran Medical University, Iran in 2005, new-borns delivered preterm and within 48 hours or after 7 days of antenatal dexamethasone were 50.2%, and frequency of RDS in this group of preterm neonates was 35.9% and mortality due to RDS was 14.9% in this group (without effectiveness of steroid therapy). Similarly in second group of preterm new-borns delivered preterm and after 48 hours or before 7 days of antenatal dexamethasone were 49.7%, and frequency of RDS in this group of preterm neonates was 18.1% and mortality due to RDS was 5.7% (with effectiveness of steroid therapy).¹² The symptoms of respiratory distress develop within four

hours of birth in new-borns with RDS. The clinical course is of gradual deterioration for the first 2–3 days with worsening of hypoxia, hypercapnia and acidosis. The chest X-Ray has a typical ground glass appearance throughout the lung fields.⁸ Dexamethasone and betamethasone are the corticosteroids recommended for antenatal therapy.^{13,14} The recommended regimen of steroid therapy according to National Institutes of Health Consensus is either of these: two doses of 12 mg betamethasone given intramuscularly 24 hours apart or four doses of 6 mg dexamethasone given intramuscularly 12 hours apart between 24 and 34 weeks of gestation in pregnancies at risk for preterm delivery.^{15,16} Any significant risk of single course of steroids is not proven on human studies. There is only one study which followed the new-borns after birth till the age of 12 and whose mothers were given steroids during that pregnancy. That study proved that there were no adverse effects of single dose of steroids on the physical growth or development of children.⁶ There are no absolute contraindications to the antenatal use of steroid prophylactic therapy but few relative contraindications. These are in women with active or suspected chorioamnionitis.

Women with diabetes (both long-standing and pregnancy-related) will need careful blood sugar monitoring for about three to four days after getting steroids because blood sugar levels control might be difficult. Steroids when given together with a beta-mimetic drug e.g., terbutaline, they can be even more hazardous.⁶ There can be risk of flare up of tuberculosis after steroid therapy but this risk can be minimized by the newer and more rapidly acting anti-tubercular drugs if available.¹⁷ Whatever is the gender or race of the foetus and situation of availability of surfactant therapy, the decision to use antenatal corticosteroids should not be changed. Every pregnant woman who is eligible for tocolytic therapy should also be eligible for antenatal steroid therapy.¹⁴

Significant benefit of steroid therapy can be seen 24 hours after the first dose and before 7 days. If the delivery occurs before 24 hours of initiation of regimen, there, even then significant reductions in neonatal mortality, RDS, and IVH is seen. So antenatal corticosteroids should be given in all cases of preterm birth except in a situation when delivery is imminent.¹⁴ As it is proven that the frequency of RDS and mortality due to this disease in group of infants treated with antenatal steroid is far less than the group of preterm new-borns delivered without this therapy and many pregnant females deliver before term or 37 weeks in our hospital so this study is conducted to formulate recommendations to give antenatal steroid therapy to all preterm labour women and increase awareness about it and thus try to reduce the morbidity and mortality in preterm neonates due to RDS.

MATERIAL AND METHODS

It was a descriptive case series conducted in the department of Obstetrics and Gynaecology (unit II), Jinnah Hospital, Lahore for a period of Six months on a sample of 230 cases selected by non-probability purposive sampling. Patients were recruited from emergency & out patients department after permission from hospital authorities and ethical review board. Antenatal corticosteroid prophylaxis i.e., 6 mg dexamethasone 1/M two doses 12 hours apart was given along with other specific treatment (like tocolysis with salbutamol or nifedipine). The patients were counselled regarding the objective and importance of steroid therapy. Informed consent was taken in every case. The demographic information was recorded (name, age, parity, gestational age). Then after giving antenatal corticosteroid therapy to all preterm pregnant females, patients were followed for next 7 days to determine the frequency of those who deliver with effectiveness period of steroid therapy.

Then patients fell in either of these two groups depending on the time of delivery after complete course of steroid therapy. Group “A” consisted of those patients who were administered 6 mg dexamethasone 1/M four doses 12 hours apart and who delivered after 48 hrs but before 7 days of corticosteroid therapy. Group B consisted of the patients who were delivered without effectiveness of steroid therapy, i.e., before 48 hrs or after 7 days. Then patient were followed for next 7 days till delivery of the neonate. If delivery occurred then neonate were followed from time of birth till first 7 days of life for development of RDS. If death of neonate occurred, then leading cause of death, directly related to RDS was obtained from Paediatric department of Jinnah Hospital, Lahore. SPSS-16.0 was used to analyse data.

RESULTS

The study sample was divided into two groups on the basis of exposure to dexamethasone and delivery of neonate after or before the period of effectiveness of dexamethasone. Group I consist of subjects who were exposed to antenatal dexamethasone and delivered a neonate after the period of effectiveness of dexamethasone. Group II consist of those subjects who were also exposed to antenatal dexamethasone but delivered a neonate outside the effectiveness period of dexamethasone. Mean gestational age of the patients was 33.35±2.41 weeks ranging from 28–36 completed weeks of gestation. Respiratory distress syndrome was found in 76 (33.0%) cases (preterm neonates) in the study, out of these 26 (22.4%) cases belonged to exposed group and 50 (43.9%) cases belonged to non-exposed group. (Table-1) Mortality due to Respiratory distress syndrome among all preterm neonates with RDS occurred in total 29 (12.6%) preterm neonates in the study, out of these 5 (4.3%) cases belonged to exposed group and 24 (21.1%) belonged to non-exposed group ($p=0.00$).

Table-1: Frequency of Respiratory Distress Syndrome and Mortality due to RDS

		Delivery period		Total	p-value
		Group A (>48 hours - <7 Days)	Group B (<48 hours - >7days)		
Perinatal Outcome 1: Respiratory Distress Syndrome	Yes	26 (22.4%)	50 (43.9%)	76 (33%)	0.001*
	No	90 (77.6%)	64 (56.1%)	154 (67%)	
Perinatal Outcome 2: Mortality due to RDS	Yes	5 (4.3%)	24 (21.1%)	29 (13%)	
	No	111 (95.7%)	90 (78.9%)	201 (87%)	
Total cases		116	114	230	

DISCUSSION

A leading cause of respiratory distress in preterm new-borns is hyaline membrane disease or RDS. The lungs of preterm new-borns do not have sufficient pulmonary surfactants which normally forms a thin layer on alveolar surfaces. The main function of these surfactants is to increase the surface tension at the air-liquid interface in the alveoli and terminal airways and prevent alveoli to collapse. The aetiology of RDS is surfactant deficiency which leads to atelectasis, impairment of gas exchange, and cause secondary lung damage. Surfactant deficiency is due to prematurity of lungs. The condition usually deteriorates for 2–4 days after birth with slow improvement thereafter. Severe respiratory distress syndrome can lead to death of new-born, although this is least likely to happen on the day 1 of life. Mortality usually occurs between days 2–7. Long-term complications of RDS may develop due to oxygen toxicity, high pressures delivered to the lungs, the severity of the disease itself, or periods when the brain or other organs did not receive sufficient oxygen.¹⁸ Prematurity is one of the most important factors predisposing a neonate to RDS. Thus single most intervention to prevent RDS is by prevention of preterm delivery.¹² Antenatal steroid treatment for women who are at risk of preterm delivery has evolved as the most effective treatment for the prevention of RDS, reducing early neonatal morbidity and mortality.^{16,19} Steroids bind with the specific receptor proteins in the target tissue which regulate the expression of the particular genes which respond to steroids. In this way, steroids alter the levels of the proteins synthesized by the different target tissues. Steroids recommended for antenatal therapy are dexamethasone and betamethasone.³

Many human studies prove that the benefits of antenatal steroids are greatest after 24 hours of initiation of regimen and last for 7 days after treatment. Treatment regimens recommended are either two doses of 12 mg betamethasone 24 hours apart intramuscular or four doses of 6 mg dexamethasone given intramuscularly 12 hours apart. The current recommendation is to give them intramuscularly. All foetuses between 24 and 34⁶ weeks' gestation at risk of preterm delivery should be considered for antenatal treatment with corticosteroids. Follow up of such new-borns till age

of 12 years in studies has proven that there are no adverse effects of steroids on the physical growth or development of children. There are no absolute contraindications to the antenatal use of steroid prophylactic therapy. The effectiveness of steroids varies with the time between administration of steroids and delivery of the foetus, and it was suggested that treatment was most effective in babies born between 1–7 days after administration.^{20,21}

In our study with regards to efficacy of dexamethasone, it shows greater effects if delivery occurs after 24 hours of last dose of dexamethasone and before 7 days, which is proved.

In a Cochrane meta-analysis of 18 RCT's, conducted by Oxford University in 2010 on behalf of International Epidemiological Association and published in Oxford Journals 2010, there is a clear evidence that antenatal steroid therapy is effective in preventing neonatal mortality (31% reduction) and morbidity (34% reduction in RDS), but it still remains at low coverage in low and middle-income countries.¹⁶ In 1997, a large epidemiological study showed a significant increase in antenatal corticosteroid therapy from 61–87%. So this is evident that, increase in the use of this prophylactic therapy has reduced perinatal morbidity and mortality.²²

CONCLUSION

The results of this study conclude that antenatal dexamethasone prophylaxis for prevention of respiratory distress syndrome in preterm neonates is very effective. This study also proves that respiratory distress syndrome is quite common among preterm new-borns and antenatal dexamethasone causes not only prevention of this disease but also significantly reduces its severity along with early neonatal mortality due to this disease in preterm new-borns. This effect is more marked if new-born delivers after a period of effectiveness of dexamethasone. So it is proven that a single course of dexamethasone to a woman in preterm labour is highly cost-effective and gives promising results. Steroid therapy can lead to a drastic change in the profile of complications for preterm babies in developing countries like of ours, where preterm labour is a significant cause of neonatal mortality and where care for preterm babies is still not up to the mark, and the use of antenatal

steroids remains a missed opportunity in many health centres and hospitals.

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AUTHORS' CONTRIBUTION

FZ performed literature search, data collection and analysis and produced the first draft of article. NU gave input in literature search, did critical appraisal and proof reading of article, helped in making final version.

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