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Association of postnatal dexamethasone use in the development of retinopathy of prematurity in low birth weight infants

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低体重早产儿使用地塞米松与视网膜病变发展进程的相关性

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摘要

目的:评价地塞米松疗法对早产儿视网膜病变(retinopathy of prematurity,ROP)的发生率和严重程度的影响。ROP 是导致婴幼儿视力损害的重要原因之一,甚至导致失明。近年来,由于新生儿护理技术的提高,能够存活的(极)低出生体重儿不断增加,导致发生 ROP 高危人群的产生。产前和产后类固醇(postnatal steroids,PNS)的使用对 ROP 发生率的影响尚有争议,并且该制剂与 ROP 严重程度的相关性尚未评估。

方法:选取儿童医院 2012-04/2013-06 出生体重不足 1500 克并胎龄不足 29 周的 115 例新生儿进行双盲对照研究。随机分为病例组和对照组,病例组内给予 8~14d 的新生儿静脉滴注地塞米松,对照组不予注射。从出生后 6wk 开始进行眼科检查并持续至病症消退。

结果:收入新生儿重症监护室、出生体重不足 1500 克的新生儿的存活率为 69% (80/115)。新生儿胎龄越低(≤25 周和 26~28 周)ROP 发生率越高。参加此项研究的 58 例婴幼儿中,ROP (二期或二期以上)的发生率为 8.6%。在接受 PNS 的 28 例新生儿中,2 例(7.4%)发生严重的早产儿视网膜病变。而在没有接受 PNS 的 30 例新生儿中,有 3 例(9.7%)确诊为 ROP。接受 PNS 婴幼儿与对照组婴幼儿 ROP 的发生率无显著差异($P=0.35$)。此外,病例组(7.4%)和对照组(9.7%)比较,严重 ROP(二期以上)发生率也无显著差异 ($P=0.36$)。

结论:此研究表明,接受地塞米松静脉滴注的新生儿与未接受地塞米松滴注的新生儿在早产儿视网膜病变的发生率和严重程度上无显著差异。因此,注射地塞米松治疗早产儿慢性肺病通常不会增加 ROP 发生的危险性。

关键词:早产儿视网膜病变;严重程度;低出生体重;产后地塞米松疗法;早产儿

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Abstract

• AIM: To evaluate the impact of postnatal dexamethasone therapy (PNS) on incidence and severity of retinopathy of prematurity (ROP) in premature infants. ROP is one of the most important causes of visual impairment in infants which can lead to blindness. The increased survival of extremely low birth weight and low birth weight (LBW) infants in recent years due to advances in neonatal care has produced a population of infants at very high risk of developing ROP. Not only there are controversies around the effect of antenatal and postnatal steroids (PNS) on the incidence of ROP in premature infants, the association of this agent and severity of ROP has not yet been assessed.

• METHODS: A total of 115 neonates with birth weight less than 1500g and gestational age less than 29wk were selected from Children Hospital between April 2012 and June 2013 who met the criteria for entering this double blind control study. Patients were divided randomly into case and control groups and intravenous dexamethasone 0.25mg/kg/12h was administered from day 8 to day 14 of age for case group and the control group received no dexamethasone. Ophthalmologic examinations were started at 6th week and followed until resolution.

• RESULTS: Of the neonates with ≤1500g birth weight admitted to neonatal intensive care unit, 69% (80/115) survived. Neonates of lower gestational age (≤25wk and 26-28wk) had an increased incidence of ROP. The incidence of ROP (stage II or higher) was 8.6% among all 58 infants enrolling this study. Severe retinopathy of prematurity was detected in 2 (7.4%) of 28 neonates received PNS and 3 (9.7%) of 30 neonates who did not received PNS. No significant difference was observed for ROP incidence between postnatal dexamethasone receiving versus control group infants ($P=0.35$). Beyond that the incidence of severe ROP (stage>II) did not have significant difference between cases (7.4%) and control (9.7%) group too ($P=0.36$).

• CONCLUSION: Our study demonstrated that there is no marked difference between neonates received post natal dexamethasone and no receiving neonates on incidence and severity of retinopathy of prematurity. Therefore, dexamethasone which was useful in treatment of chronic lung disease in preterm infants seems be safely administered without concern about increasing risk of ROP.

• KEYWORDS: retinopathy of prematurity; severity; low birth weight; postnatal dexamethasone therapy; premature infants
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INTRODUCTION

Retinopathy of prematurity (ROP) is one of the most important causes of visual impairment in premature infants which can lead to blindness. ROP is responsible for up to 15% of all causes of blindness in developed countries and up to 60% in middle income countries[1]. Oxygen is known to disturb the production of angiogenic factors and therefore perturbing normal vessel development (Lois Smith and others). Various risk factors have been described in developing ROP in premature infants such as respiratory distress syndrome (RDS), apnea, patent ductus arteriosus (PDA), sepsis, acidosis, anemia, shock, blood transfusion, intra ventricular hemorrhage (IVH), asphyxia, hypothermia, vitamin A and vitamin E deficiencies and connection to ventilator[2-4]. Incidence of ROP has a reverse relation with gestational age and birth weight. ROP prevalence in gestational age of 26-28wk is about 70% and in 29-30wk is about 45%[5]. The increased survival of extremely low birth weight (LBW) and LBW infants in recent years, due to advances in neonatal care, has produced a population of infants at very high risk of developing ROP[6]. Administration of antenatal steroids (ANS) to reduce the risk of respiratory distress syndrome (RDS) is a common neonatal care. However, postnatal steroids (PNS) have been used increasingly for the prevention and treatment of chronic lung disease (CLD) in LBW infants[7]. There several studies concerning the association between postnatal dexamethasone (PNS) use and the incidence of ROP, but not only there are controversies around the effect of postnatal steroids on the incidence of ROP in premature infants, the association of this agent and severity of ROP has not yet been assessed[8-11]. Hence, the primary focus of this study was to evaluate the impact of postnatal dexamethasone therapy (PNS) on incidence and severity of ROP in premature infant.

MATERIALS AND METHODS

A total of 115 neonates, who met the criteria for entering this double blind case- control study were selected from Children Hospital of Bandarabbas (affiliated to Bandarabbas University of Medical Sciences) between April 2012 and June 2013. The inclusion criteria were preterm infants with birth weight less than 1500g and gestational age less than 29wk and also preterm infants with gestational age of 29-34wk who were unstable and dependent to oxygen therapy. The exclusion criteria were infants with lethal anomalies, infants with severe drug complications such as gastrointestinal bleeding and hypertension and infants died along with study. Antenatal steroids were administered prenatally based on 1994 NIH Consensus Statement to women with threatened preterm labor at 24-34wk gestation. Birth weight was measured using a digital scale (Tefal Company, France, capacity: 20kg, least count: 10g, with LED display) and gestational age was determined by either the last menstrual period or ultrsound biparietal diameter (BPD), and femur length (FL) and confirmed by neonatal examination. The study was explained for infant's parents and consent were taken from all of them. Then patients were divided into 2 case-control randomized groups. Intravenous dexamethasone was administered 0. 25mg/kg/12h from 8th to 14th day of age for case group and the control group received no dexamethasone. All infants were checked up daily by a neonatologist and medical conditions were assessed precisely and all infants with one of the risk factors for sepsis; prolonged rupture of membranes >18h, colonization with group B streptococci (GBS), or maternal chorioamnionitis and infants exhibit abnormal signs in the first 24h of life underwent a sepsis work up. Supportive oxygen therapy was performed for infants demanding oxygen with low pulse oximetry 3-5L/min. Surfactant was given as a rescue treatment to infants who met clinical and radiologic criteria for RDS. Echocardiography was done for diagnosis of suspective patients for PDA and treated per protocol. Also, serial cranial ultrasound studies was done for suspective patients with intraventricular hemorrhage (IVH) and CLD was defined as chest x-ray changes consistent with CLD along with a requirement for supplemental oxygen at 36wk postconceptional age. Usually 1-2wk after delivery, postnatal dexamethasone treatment was initiated at the discretion of the individual neonatologist for the treatment of CLD, for high oxygen need, or inability to wean infant from respiratory support. After exclusion of deaths, demographic and clinical data of 58 patients were collected. ROP was diagnosed by pediatric ophthalmologist according to criteria of International Classification of Retinopathy of Prematurity (ICROP)[12]. The first ophthalmologic examination was conducted at 6th week of age and subsequent examinations were done at the discretion of ophthalmologist based on first ophthalmoscopic results.

All infants were followed until ROP regressed or required the laser therapy

Statistical Analysis We grouped continuous variables for determining whether the incidence of ROP was increased in the control group for determining: gestational age ≤25wk, 26-28wk and >28wk, exposure to PNS: no, 0.5, 1, 2, ≥3 courses, duration of ventilation: no, 1, 2, ≥3wk, exposure

to ANS : no, 1, 2, ≥3wk. We assessed all risk factors for ROP. The case and control patients' data were evaluated by SPSS statistical package (Version 15).

The*t*-test was used to compare quantitative variables and chi square test for qualitative parameters. Meanwhile, this study was approved by the Ethics Committee of Bandarabbas University

RESULTS

During the observation period from April 2012 to June 2013, 150 LBW neonates were admitted to the Neonatl Intensive Care Unit (NICU). A total of 115 infants (76.7%) were eligible for this study. Of these, 80 (69.6%) survived until hospital discharge. However, 13 infants were lost to follow up and 4 infants had severe drug complications and were excluded. The eye examination was performed and followed up on the remaining 58 infants that were divided into 2 case-control study groups; 27 in case group and 31 in control group. The case group consisted of 13 boys (48.1%) and 14 girls (51.9%) and the conrol group, 18 boys (58.1%) and 13 girls (41.9%) with $P=0.31$. The mean birth weight of case group was 1434g (±30g) and was l479g (±42g) in control group ($P=0.56$). The ranges of gestational age and birth weight shown in Table 1. Other risk factors did not have marked difference between case and control groups, as shown in Table 1. Overall, 19 infants (32.8%) had ROP in both groups, 10 (37.0%) in case group and 9 (29.0%) in contol group. Of these, 14 (73.7%) were stage I and 5 (26.3%) stage≥II. The incidence of severe ROP (stage II or higher) was 8.6% among all 58 infants. Gender, respiratory distress syndrome, oxygen treatment at 36 weeks post-conceptional age and prenatal use of steroids were not significantly associated with severe ROP, but the incidence of severe ROP clearly decreased with increasing gestational age in both case-control group. Our statistical analysis showed that ROP incidence in case group was 37.0% (10 infants) and in control group was 29.0% (9 infants); therefore no significant difference was observed for ROP incidence between postnatal dexamethasone receiving versus control group infants ($P=0.35$). Moreover, a 7d dexamethasone therapy; a total cumulative dose of ≤3.5mg, did not increase the risk of developing ROP (data not shown). Beyond that, incidence of severe ROP (stage ≥ II) didn't have significant difference between cases (7.4%) and control (9.7%) groups too ($P=0.36$, Table 2).

Table 1 Frequency distribution of demogaphic characteristics and risk factors in case and control groups

Variables	Groups		*P*
	Case	Control	
Sex (%)			
Male	13 (48.1)	18 (58.1)	0.31
Female	14 (51.9)	13 (41.9)	
Mean birth weight (g)	1434±30	1479±42	0.56
Mean 5th min Apgar	7.04	7.52	0.34
Mean supplement oxygen (d)	5.22	3.77	0.09
Maternal ANS consumption	9M	12M	0.44
Mean gestational age (wk)	30.07±2.01	30.8±2.17	0.17

M: Mothers. $P<0.05$ demonstrates significancy.

Table 2 Severity of retinopathy with or without postnatal dexamethasone therapy *n*(%)

ROP stage	PNS exposure (*n*=10)	Non PNS exposure (*n*=9)	All
0	17 (63.0)	22 (71)	39 (67.2)
I	8 (29.6)	6 (19.4)	14 (24.1)
II, III	2 (7.4)	3 (9.7)	5 (8.6)

PNS: Post natal dexamethasone.

DISCUSSION

This study was conducted to evaluate the association of postnatal dexamethasone on incidence and severity of ROP in LBW (w≤1500g) neonates. The overall incidence of ROP was 32% in this study. As it was expectab1e, the incidence of ROP was not correlated significantly with gestational age and days on supplemental oxygen. Our study demonstrate that, there is no marked difference between received post natal dexamethasone in case group and no dexamethasone receiving neonates in control group on incidence and severity of retinopathy of prematurity.

Conflicting retrospecive studies have been published in assessing the association of PNS and ANS with ROP. In retrospective studies, postnatal steroid administration has been shown to either have a protective effect on the incidence of severity of ROP (case-control study with 58 newborns)[6], no effect (retrospective review with 147 newborns)[7] or on the contrary, increases the severity of ROP and need for cryotherapy (case-control study with 52 newborns)[8]. On the other hand, two observational studies have reported an effect on duration and dose. Termote *et al*[13] reported that in VLBW infants only prolonged use of postnatal hydrocortisone was associated with an increased risk for severe ROP. Haroon Parupia and Dhanireddy[14] suggested that a higher cumulative dose of PNS was a risk factor for severe ROP, controlling for other risk factors. Consistent with these reports, our findings have demonstrated that a 7d dexamethasone therapy period which corresponds to a total cumulative dose of ≤3.5mg, does not increase the risk of developing ROP; therefore, this duration and cumulative dexamethasne dose may be the golden considering items in administration of this agent, which can subside its adverse effects, particularly on ROP development. Albeit this study has demonstrated that dexamethasone does not have an increasing effect on ROP incidence and severity, all undesirable consequences of corticosteroid therapy in preterm infants may not be fully known; therefore, caution use of these potent pharmacologic agents seems well advised. Our study has some limitations such as the small number ofpatients having ROP in this study, especially those with what the authors define as severe ROP, final outcome of infants with the most severe ROP, assessment of disability events in case of very low mortality rate on the overall population and the follow-up period is not long enough to indicate long-term effects. However, in our study the results are in agreement to those studies that accentuated duration and

cumulative dexamethasne dose may play a role on ROP development[13,14].

Inconclusion, our study demonstrates that, there is no marked difference between neonates received post natal dexamethasone and no receiving neonates on incidence and severity of retinopathy of prematurity with a duration period of 7d and cumulative dose of ≤3.5mg; therefore, dexamethasone which was previously a useful agent in treatment of chronic lung disease in preterm infants appears to be safely administered without concern about increasing risk of ROP. However, future studies with larger numbers of patients would be needed to confirm our findings.

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