

Evaluation of Cortisol Level in Premature Neonates: Are There any Correlations between Prevalence of Patent Ductus Arteriosus and Prenatal Administration of Betamethasone?

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ABSTRACT

Background: The results of previous studies suggested that there is an increased risk of patent ductus arteriosus (PDA) in the neonates with lower serum cortisol levels. This study aimed to assess the association between serum cortisol values and PDA and investigate if there is an association between PDA and the antenatal administration of betamethasone.

Methods: The present study was carried out on the neonates with gestational age between 28 to 35 weeks. The prenatal administration of betamethasone to the mothers was extracted from the records. A pediatric cardiologist performed an echocardiographic assessment on the second day of life (DOL) and fifth DOL and the infants were evaluated for the presence of PDA. The blood samples were obtained on the second and fifth DOL and serum cortisol levels were measured. We evaluated the association between serum cortisol levels and PDA. Also, the correlation between PDA and the antenatal administration of betamethasone was assessed.

Results: The mean scores of serum cortisol levels on the second DOL in the neonates with and without PDA were 4.99 ± 2.69 ($\mu\text{g/dl}$) and 7.23 ± 2.87 ($\mu\text{g/dl}$), respectively that were significantly lower in the first group, compared to those of the second group. However, the mean levels of serum cortisol in the neonates with and without the prenatal administration of betamethasone were not significant ($P=0.522$).

Conclusion: We have concluded that lower serum cortisol level was associated with the increase in the risk of PDA and the prenatal administration of glucocorticoids may not reduce the occurrence of PDA.

Keywords: Betamethasone, Cortisol, Patent ductus arteriosus, Prematurity

Introduction

Patent ductus arteriosus (PDA) is one of the most common congenital heart defects that results in the persistent left-to-right shunt between the descending aorta and pulmonary artery (1, 2). The functional closure of the ductus arteriosus in term infants happens in the first 72 h of life, although its closure may be delayed in premature neonates (3, 4).

The results of the previous studies suggested that there is an increased risk of PDA in the

neonates with lower serum cortisol levels (5). It has been proposed that ill premature infants may have lower serum cortisol levels due to insufficient adrenal response to stress because of immaturity in the development of the hypothalamic-pituitary-adrenal axis (6).

The findings of several studies have demonstrated the benefits of antenatal administration of glucocorticoids (7, 8). Based on the previous animal studies, it has been proposed

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that prenatal corticosteroids have a constrictive effect on the ductus arteriosus of the fetus (9, 10) that may be due to a change in the response of the ductus muscle to the prostaglandin E2 (PGE2) (11). Therefore, it has been suggested that PDA may be less frequent in the neonates whose mothers have been prenatally treated with corticosteroids (12). This study aimed to assess the association between serum cortisol levels and PDA and investigate the association between PDA and the antenatal administration of betamethasone.

Methods

The Institutional Review Board/Ethics Committee of Iran University of Medical Sciences approved this observational cross-sectional study. The present study was conducted on all the neonates with a gestational age of 28 to 35 weeks, regardless of their birth weight admitted to neonatal intensive care unit in Akbar Abadi hospital over a one-month period between December 2016 and January 2017. The infants with neonatal sepsis, major congenital anomalies, and major heart defects, except for PDA, were excluded from this study. The parents signed an informed consent form.

The related previous history was reviewed and the prenatal administration of betamethasone to the mothers was extracted from the records. A pediatric cardiologist who was masked from the study protocol performed an echocardiographic assessment on the second and fifth days of life (DOL) and the infants were evaluated for the presence of PDA. No infants received treatment for PDA since none of them showed any signs of overt congestive heart failure or cardiovascular instability.

Two blood samples were obtained in the mornings on the second and fifth DOL and serum cortisol levels were measured in a single laboratory setting using cortisol RIA kit (IMMUNOTECH s.r.o, Czech Republic). We evaluated the association between serum cortisol levels and PDA. Also, the correlation between PDA and the antenatal administration of betamethasone was assessed. We also evaluated whether the prenatal corticosteroid administration has an effect on serum cortisol level in the first week of life in infants.

Statistical Methods

To present the quantitative data, we used mean and standard deviation, and the qualitative data were reported in percentage. To evaluate the subject's parameters between the groups we used t-test and Chi-square test. All statistical analyses were performed by SPSS software (IBM Corp. Released 2013. IBM SPSS statistics for windows, version 22.Armonk, NY: IBM Corp.). P-value less than 0.05 was statistically considered significant.

Results

From 30 premature neonates included in this study based on eligibility, 22 (73.33%) cases had serum cortisol levels lower than 6.5 $\mu\text{g}/\text{dl}$ in the primary evaluation on the second DOL and in this group, 19 neonates (86.36%) had PDA in the first echocardiography. From eight neonates with serum cortisol levels more than 6.5 $\mu\text{g}/\text{dl}$, 5 neonates (62.5%) had PDA.

The mean scores of serum cortisol levels in the second DOL in neonates with and without PDA were 4.99 ± 2.69 and 7.23 ± 2.87 ($\mu\text{g}/\text{dl}$), respectively that was significantly lower in the first group, compared to those of the second group ($P=0.044$) (Figure 1). It was shown that 19 out of

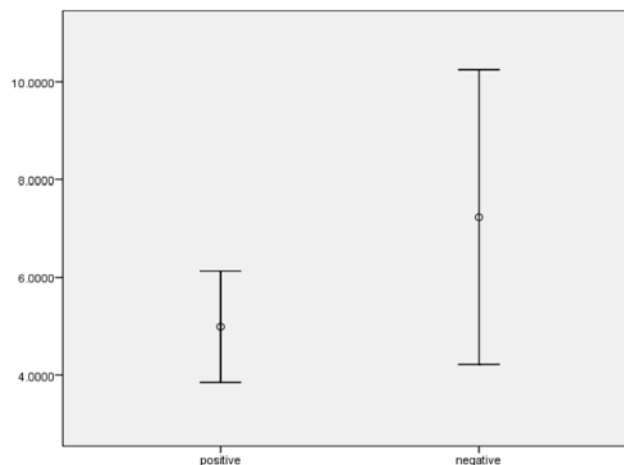


Figure 1. Mean cortisol level in the second day of life in neonates with and without patent ductus arteriosus

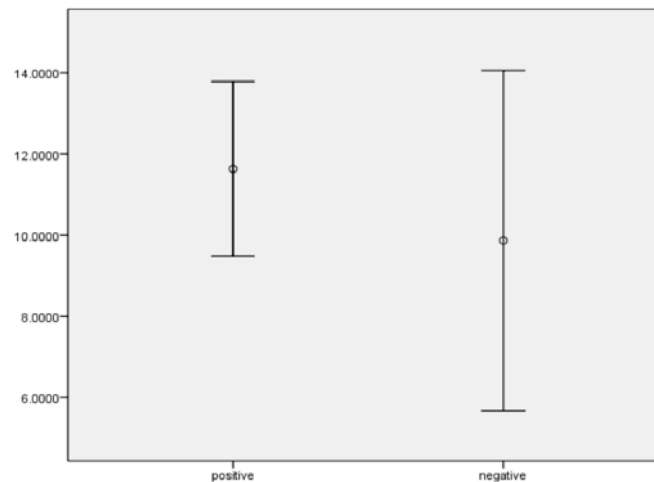


Figure 2. Mean cortisol level in the fifth day of life in neonates with and without patent ductus arteriosus

24 (79%) neonates with PDA and 3 out of 6 (50%) neonates without PDA had serum cortisol level less than 6.5 in the second DOL. Furthermore, the mean values of serum cortisol levels in the fifth DOL in the neonates with and without PDA were 11.63 ± 5.09 and 9.87 ± 3.99 ($\mu\text{g/dl}$), respectively that was not significant ($P=0.750$) (Figure 2).

In the fifth DOL, 12.5% and 16.7% of the neonates with and without PDA had serum cortisol values less than 6.5. The mean scores of serum cortisol difference between the second and fifth DOL were 6.63 ± 4.43 and 3.76 ± 2.63 in the neonates with and without PDA, respectively. This difference was significantly higher in the group of neonates with PDA, compared to the group of neonates without PDA ($P=0.025$).

Out of 30 premature neonates, 17 cases were born from mothers that have been antenatally given betamethasone. On the second DOL, the mean values of serum cortisol levels in the neonates with and without the prenatal administration of betamethasone were 5.15 ± 2.86 and 5.83 ± 2.86 ($\mu\text{g/dl}$), respectively, and the difference was not significant ($P=0.522$). Thirteen neonates with a history of prenatal betamethasone administration had serum cortisol levels less than 6.5 on the second DOL, although this level of serum cortisol was evident in 11 neonates without a history of prenatal betamethasone. Therefore, there was no significant difference between these two groups ($P=0.087$).

Furthermore, the mean scores of serum cortisol levels in the neonates with and without the prenatal administration of betamethasone were 11.74 ± 5.36 and 10.68 ± 4.31 ($\mu\text{g/dl}$), respectively in the fifth DOL, and the difference

was not significant ($P=0.565$).

In the fifth DOL, three neonates with a history of prenatal betamethasone administration had a serum cortisol level less than $6.5 \mu\text{g/dl}$ that was reported only in one neonate with no history of prenatal administration of betamethasone ($P=0.132$). The mean scores of serum cortisol difference between the second and fifth DOL in the neonates with and without prenatal administration of betamethasone were 6.59 ± 4.84 and 4.85 ± 4.09 , respectively, and the difference was not significant ($P=0.603$).

The diagnoses of PDA in the first and second echocardiographic assessments were observed in 24 (80%) and 5 (16.7%) cases, respectively that was significantly higher in the first assessment, compared to the second one ($P=0.033$). Based on echocardiographic findings, PDA was resolved in 19 out of 24 neonates with PDA in the primary assessment.

The mean values of cortisol levels on the second DOL in the neonates with PDA without change, PDA that resolved spontaneously, and without PDA were 5.38 ± 3.05 , 4.89 ± 2.67 , and 7.23 ± 2.87 ($\mu\text{g/dl}$), respectively, and there was no significant difference between these groups ($P=0.216$). Moreover, the mean scores of serum cortisol levels on the fifth DOL in the neonates with PDA without change, PDA that resolved spontaneously, and without PDA were 7.86 ± 3.91 , 12.62 ± 4.97 , and 9.87 ± 3.99 ($\mu\text{g/dl}$), respectively ($P=0.109$).

The mean values of serum cortisol level difference between the second and fifth DOL in the neonates with PDA without change, PDA that resolved spontaneously, and without PDA were 2.84 ± 1.81 , 7.73 ± 4.28 , and 5.83 ± 4.54 ($\mu\text{g/dl}$),

respectively. These differences between the second and fifth DOL were significantly higher in the neonates with PDA that was spontaneously resolved, compared to other cases ($P=0.006$). In the neonates born from mothers that were given prenatal betamethasone, PDA remained without any changes in 80% of the cases, although PDA was spontaneously resolved in 47.7% of the neonates and 66.6% of the cases had no sign of PDA, and the difference was not significant ($P=0.364$).

Discussion

In this study, we assessed the association between serum cortisol values and PDA and between PDA and the antenatal administration of betamethasone. Moreover, it was investigated whether prenatal corticosteroid administration has an effect on serum cortisol level in the first week of life in premature infants. It was observed that lower serum cortisol values were associated with higher risk of PDA in the second DOL but not in the fifth DOL suggesting a compensatory increase in serum cortisol levels during the first week of life.

Watterberg et al. have also demonstrated that lower cortisol levels are associated with higher risk of PDA (5). They have found a reduction in serum cortisol values in the first week of life whereas in the present study there was an increase in serum cortisol level in the second and fifth DOL that was associated with spontaneous closure of PDA. Also, it was found that the difference between serum cortisol in the second and fifth DOL was significantly higher in the neonates with PDA, compared to those without PDA suggesting the previous statement on the negative correlation between serum cortisol and PDA.

Although in the previous studies, it has been proposed that prenatal administration of corticosteroids might affect the neonatal level of serum cortisol (13). In this study, there was no correlation between prenatal corticosteroids and neonatal serum cortisol levels in the second and fifth DOL. In the present study, there was no association between the prenatal administrations of betamethasone and PDA incidence in the infants whereas Waffarn et al. and Eronen et al. have proposed in different studies that prenatal corticosteroids reduce the risk of PDA (8, 12).

This association may be caused by the effects of the glucocorticoids on the sensitivity of the ductus arteriosus muscle to PGE2 (14). The results

of other studies also stated that the administration of prenatal corticosteroids might improve the cardiovascular system and lower the risk of PDA (7, 15). This difference between the results of the present study and mentioned studies is maybe due to later administration of betamethasone to some of the mothers that caused a reduction in the effectiveness of this drug.

There were some limitations in the present study. Since the study population was small, the results might have low generalizability. Another limitation was the observational nature of this study. It is recommended to carry out further studies with a larger population and with clinical trial design to evaluate the mentioned associations.

Conclusion

In the end, it was concluded that lower serum cortisol level was associated with the increase in the risk of PDA, and the prenatal administration of glucocorticoids had no effect on serum cortisol level in the first week of life and did not reduce the occurrence of PDA.

Conflicts of interests

The authors declare that there is no conflict of interest.

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