Comparison of the Effect of Corticosteroid Therapy and Pre-natal Single-period Treatment on Birth Size and Neuronal Development in Preterm Infants With one Year Follow up in Yasuj Hospitals in 2015-2017

Comparación del efecto de la terapia con corticosteroides y el tratamiento prenatal de período único sobre el tamaño al nacer y el desarrollo neuronal en neonatos prematuros con un año de seguimiento en los hospitales de Yasuj en 2015-2017

*Razieh Vanda**

**corresponding author: Razieh Vanda, Assistant professor of Obsthetric and gynecology, Fellowship of Perinathology, Social Determinants of Health Research Center, Yasuj University of Medical sciences, Yasuj, Iran. E-mail: ra.vanda@yahoo.com*

Abstract

Since the first reported benefits of corticosteroid prescribing in 1972, many studies have shown that pre-natal corticosteroid can reduce morbidity and mortality in preterm infants. But the ideal diet for prescribing corticosteroids is still uncertain. Because corticosteroid efficacy has not been well established before 7 days, some doctors use prenatal corticosteroid therapy on a weekly basis when the risk of preterm delivery is still present. There is evidence that repeated embryonic contact with corticosteroids may not only be unprofitable, it is also dangerous, and there are worries about the adverse effects of birth rates especially on the head circumference, followed by impaired nervous evolution. A case-control study was conducted in a prospective study from 2015 to 2017. The study was performed on single-parent mothers who were referred only to preterm delivery in the 28th to 33rd weeks of gestation. These mothers were treated with corticosteroids in order to prevent complications of preterm delivery in two groups of 23 patients. Mothers who visited weekdays received a betamethasone course, and mothers who visited couples on weekdays received betamethasone at weekly intervals if they continued to receive remission and failed to deliver. At birth, the height, head circumference and weight of the newborns were measured and compared, and also the complications of obesity were assessed. At one year, growth parameters were measured and compared in two groups, and in addition the neurodevelopmental condition was tested CLAMS / CAT were reviewed and compared. The results of this study did not show the inhibitory effect of corticosteroid therapy on birth rates, which, unlike many animal and human studies, showed a significant reduction in the subsequent growth indices in the Crotone group. Although one of the goals of prenatal corticosteroid treatment is to achieve more beneficial pulmonary effects, this study did not improve the administration of recurrent prognosis in premature infants. Concerns about the association between smaller head sizes due to corticosteroid treatment and impaired brain development in animal models and some human studies have been shown. But there is still no evidence to support this hypothesis. Our study also did not address frequent pre-natal coronary events, along with an increase in the incidence of neurodegenerative disorders. In this study, the effect of repeated administration of corticosteroid on the time of birth and some complications of obesity have been investigated and a one-year follow-up examines the effect of weekly treatment on neurodevelopmental parameters and compares them between the two groups. In the present study, the sex composition of neonates was similar at birth and at one year of age, and there was no significant difference.

Keywords: Corticosteroid, Neural evolution, premature babies

Resumen

Desde los primeros beneficios informados de la prescripción de corticosteroides en 1972, muchos estudios han demostrado que los corticosteroides prenatales pueden reducir la morbilidad y la mortalidad en los recién nacidos prematuros. Pero la dieta ideal para la prescripción de corticosteroides todavía es incierta. Debido a que la eficacia de los corticosteroides no ha sido bien establecida antes de los 7 días, algunos médicos usan la terapia prenatal de corticosteroides semanalmente cuando el riesgo de parto prematuro todavía está presente. Existe evidencia de que el contacto embrionario repetido con corticosteroides no solo no es rentable, sino que también es peligroso, y existe preocupación por los efectos adversos de las tasas de natalidad, especialmente en la circunferencia de la cabeza, seguida de una evolución nerviosa alterada. Se realizó un estudio de casos y controles en un estudio prospectivo de 2015 a 2017. El estudio se realizó en madres monoparentales que fueron derivadas solo a partos prematuros en las semanas 28 a 33 de gestación. Estas madres fueron tratadas con corticosteroides para prevenir las complicaciones del parto prematuro en dos grupos de 23 pacientes. Las madres que visitaron los días de la semana recibieron un curso de betamethasone, y las madres que visitaron parejas los días de la semana recibieron betamethasone a intervalos semanales si seguían recibiendo la remisión y no cumplían. Al nacer, se midieron y compararon la altura, la circunferencia de la cabeza y el peso de los recién nacidos, y también se evaluaron las complicaciones de la obesidad. Al año, los parámetros de crecimiento se midieron y compararon en dos grupos y, además, se evaluó la condición de desarrollo neurológico, se revisaron y compararon las CLAMS / CAT. Los resultados de este estudio no mostraron el efecto inhibitorio de la terapia con corticosteroides en las tasas de natalidad, que, a diferencia de muchos estudios en animales y humanos, mostró una reducción significativa en los índices de crecimiento posteriores en el grupo de Crotone. Si bien uno de los objetivos del tratamiento con corticosteroides prenatal es lograr efectos pulmonares más beneficiosos, este estudio no mejoró la administración del pronóstico recurrente en los bebés prematuros. Se han mostrado inquietudes acerca de la asociación entre tamaños de cabeza más pequeños debido al tratamiento con corticosteroides y al desarrollo cerebral deficiente en modelos animales y algunos estudios en humanos. Pero todavía no hay evidencia para apoyar esta hipótesis. Nuestro estudio tampoco abordó los eventos coronarios prenatales frecuentes, junto con un aumento en la incidencia de trastornos neurodegenerativos. En este estudio, se investigó el efecto de la administración repetida de corticosteroides en el momento del nacimiento y algunas complicaciones de la obesidad, y un seguimiento de un año examina el efecto del tratamiento semanal en los parámetros del desarrollo neurológico y los compara entre los dos grupos. En el presente estudio, la composición sexual de los neonatos fue similar al nacer y al año de edad, y no hubo diferencias significativas.

Palabras clave: corticosteroide, evolución neural, prematuros.

Introduction

Preterm labor is defined as the birth of a baby before 37 weeks or 259 days. This situation complicates 12% of births in the United States, accounting for 85% of birth-related deaths. Approximately 20% of cases are intentional preterm deliveries due to maternal or fetal indices such as intrauterine growth restriction, preeclampsia, peripheral placenta, fetal abnormal tests, among other cases 20-30% due to amniotic fluid infection, and 20 to 30% are without cause[1].

Economic Impact of Early Labor: The financial resources used to maintain low birth weight infants are one of the economic losses due to early childbirth. Many causes can be cited for early childbirth. Studies show that 28% of births below 37 weeks are due to medical or pregnancy outcomes. Specific gestational periods are from 6 to 13 weeks of gestation; whether mild and spotting or severe, such as menstruation, with loss of gestation Before 24 weeks, premature delivery and placental separation are associated[1].

The mental and physical stress of the mother is rarely examined, but it seems to be significant. Stress followed by high levels of maternal cortisol with unexplained preterm labor. Repeated, familial and racial preterm births have led to the role of genetic causes in the development of this disease. In addition to painful or painless uterine contractions, symptoms such as pressure in the pelvis, cramps such as menstrual cramp, watery or vaginal discharge and pain in the lower back of the womb is associated with preterm labor. Because these symptoms are also seen in normal pregnancies as well as symptoms much earlier than the onset of the early delivery process, the diagnosis of preterm delivery is often not timely by the patient or doctor. In some studies, genital tract infection has been reported as a cause of early delivery, and in some with trichomoniasis or candidiasis of the vagina at 24-28 weeks of gestation, the risk of preterm labor was not increased. In various studies, it was found that gingival infection caused 7 times the risk of preterm delivery in women with a healthy age group[1].

The use of corticosteroids 24 hours before birth can reduce the incidence and severity of intraventricular hemorrhage, and studies have shown that corticosteroid premature use of mortality rate, respiratory distress and intraventricular hemorrhage in preterm neonates born between It reduces 24 to 33 weeks, and its beneficial effect increases with surfactant therapy. Positive effects of corticosteroids in premature infants who develop rupture of the embryo

are also proven. The type of corticosteroid used may be important, although both betamethasone and dexamethasone pass through the active forms in their forms, but the half-life of betamethasone is longer because the betamethasone release volume is larger and is much more slowly cleared. In addition, although both compounds reduce respiratory distress, it is only betamethasone that reduces mortality and dexamethasone has no positive effect on third and fourth degree bleeding in infants[1].

Betamethasone decreases the incidence of localized lumbar spinal cord, but dexamethasone does not have this effect. Therefore, today a new debate has been made on the choice of the type of birth control corticosteroid and many studies are under way. The effects of other drugs, such as phenobarbital, vitamin k, vitamin E and indomethacin, on the reduction of intracranial hemorrhage, whether maternal or neonatal use, are still under discussion. Of course, some studies have shown that magnesium sulfate may have a lowering effect on intraventricular hemorrhage. Evolution is not determined solely by genetics and, on the other hand, is not only influenced by the environment[1]. At present, the bio psychosocial model demonstrates the importance of external and internal factors[2].

Materials and methods

A case-control study was conducted in a prospective study from 2015 to 2017. The study was performed on single-parent mothers who were referred only to preterm delivery in the 28th to 33rd weeks of gestation. These mothers were treated with corticosteroids in order to prevent complications of preterm delivery in two groups of 23 patients. Mothers who visited weekdays received a betamethasone course, and mothers who visited couples on weekdays received betamethasone at weekly intervals if they continued to receive remission and failed to deliver. Systemic diseases of the mother such as epilepsy, diabetes and hypertension, and the description of the use of certain medications, as well as the presence of complications of pregnancy, limited intrauterine growth and apparent abnormalities of the embryo removed the study. At birth, the height, head circumference and weight of the newborns were measured and compared, and also the complications of obesity were assessed. At one year, growth parameters were measured and compared in two groups, and in addition the neurodevelopmental condition was tested CLAMS / CAT were reviewed and compared[3,4].

Results

This case-control study was performed on 32 preterm infants in the control group (18 boys and 14 girls) and 23 preterm infants in the case group (13 males and 10 females). The two groups were compared in terms of sex composition with K2 test, which according to Pv = 0.98, there was no significant difference between the two groups. In the control group, follow-up was not possible after one year in a newborn, and seven other infants died in this group; in the case group, two infants died due to sepsis. Finally, in the control group, 14 boys and 11 girls were re-visited after one year. In the case group, 11 boys and 10 girls were examined. After one year, there was no significant difference in gender composition between the two groups. (Pv = .08).

The mean age of mothers in the control group was 26 ± 4 and in the case group was 26.76 ± 4.5, which was not significantly different between the two groups using t-test. (Pv = 0.54). The mean weight of mothers in the control group was 70.6 ± 3.3 and in the case group was 72.4 ± 3.2, which was not significantly different between the two groups. (Pv = .07).

The mean gestational age at the time of receiving the first course of corticosteroid in mothers treated with a corticosteroid period (control group) was 30.84 ± 2.2 weeks, and in the mothers treated with more than one course of corticosteroid (case group) 29.3 ± 1.4 weeks. Regarding the distribution of these data, the normal distribution of these data was compared with T.test test. According to the value of Pv = 0.01, there was a significant difference between the two groups. In this way, the gestational age was significantly lower for corticosteroid therapy in mothers receiving repeated courses than mothers receiving corticosteroids.

The mean age of gestational age in the control group was 31.45 ± 2.1 and 32.7 ± 1.2 weeks in the case group, with respect to pv =9% no significant difference was found between the two groups and the two groups of opinion. The mean pregnancy was consistent at birth.

Mean Apgar score of 5 neonates in the control group was 7.44 ± 1.6 and in the case group was 8.13 ± 0.9, and, due to the non-normal distribution of the data in the two groups, as well as the independence of the data, Mann-Whitney test used. But there was no significant difference between the two groups. The mean birth weight of the infants in the control group was 1543.13 ± 4.8 grams and 18887.8 ±311grams in the case group, respectively. Using t-test with respect to pv =0.001, there was a significant difference between the birth weight of the newborns in the two groups Was obtained. The birth weight of the infants in the case group was significantly higher than the control group. Considering the fact that variable weight is

affected by various maternal, embryonic and environmental factors, this study attempts to homogenize the maternal and fetal factors affecting the mother, parity and sex of the infant, but it can not be the influence of other contributing factors that we did not control was not taken into account.

The mean of head circumference at birth was 29.54 ± 1.8 cm in the control group and 30.28 ± 1.5 in the case group, and no significant difference was found between the two groups by the t-test. The mean height of the infants At birth, the control group was 41.3 ± 3.7 cm in the control group and 44.2 ± 3.7 in the case group, and using t-test and p = 0.006, the difference was significant. Thus, the height of infants in the case group is significantly higher than the height of infants in the control group.

From the above information, it is shown that in addition to birth weight, height of infants in the group receiving repeated treatment (case) was significantly higher than the control group, but the size of the round head was not significantly different between the two groups. In newborns with a higher weight and height, it is expected that the two headings are more suitable for them. In this study, the difference between the two groups was not achieved and the head circumference did not follow the weight and height. All of these newborns were re-visited after one year. The mean height, head circumference and weight were measured and compared by t-test. The mean weight of the one-year-olds in the control group was 9138 ± 632 g and in the case group was 8872 ± 500 g. According to P =0.1, the difference between the two groups was not significant. The mean head circumference in one year old infants was 42.9 ± 1.5 and 42.3 ± 0.8 in case group, and according to pv =0.1, the difference between the two groups was not significant. The mean height at one year of age in infants in the control group was 79.2 ± 2.7 and in the case group was 77.8 ± 1.8 cm. According to pv =0.04, the difference between the two groups was statistically significant.

The results of this study indicated that the lambs of the control group at one year of age were significantly higher than the infants of the case group and this difference was statistically significant. In case group weights and head circumference were significantly higher in the control group Most of the infants were case group, but there was no significant difference. In general, it can be indicative of a long-term reductive effect on growth indices for the treatment of corticosteroid recurrence.

The mean of children under 10th percentile of growth chart for each growth parameter at one year was obtained in two groups and compared with k^2 test. The two groups were compared with children under 10 years of age at one year of age with chi square test, which according to pv = 0.0, there was a significant difference between the two groups. Two groups were compared in terms of frequency of children with head circumference below the 10th percentile at the age of one with Fisher's test, which according to pv =0.03, there was a significant difference between the two groups.

Finally, two groups were compared with the k^2 test for children under 10 percentiles at one year of age. According to pv =0.04, there was a significant difference between the two groups. It can be seen from the above information that the prevalence of lactation under the 10th percentile for all growth parameters in case group at one year was significantly higher than that in the control group. To evaluate the status of neural evolution in CLAMS / CAT groups. This test provides a quantitative assessment of evolution in the field of verbal and verbal skills. In other words, it evaluates the cognitive branch of evolution. The CLAMS method is used to assess verbal abilities, and the CAT includes examining skills equal to or greater than 70 normal, and score less than 70 as abnormal.

In this study, 7 infants in the control group (28%) and 7 infants in the case group (33.3%) scored less than 70. These findings were analyzed by K^2 test and, according to PV = 0.06, the difference between the two groups was not significant. In this study, contact with frequent prenatal cortex was not associated with an increase in the incidence of developmental-neurological disorders in the first year of life.

Table 1: Frequency distribution of natural and abnormal nerve development in the control and case groups

	normal	abnormal	Total
Witness	18 72%	7 28%	25 100%
Case	14 66.7%	7 33.3%	21 100%

Frequency of complications due to prematurity among infants in two groups:

Respiratory Distress Syndrome (RDS)): One of the cases that was compared among the infants in the two groups, the information on which is given in Table 2.

Table 2: Relative frequency of RDS in neonates born in both control and control groups

	NO RDS	Mild RDS	Sever RDS
Witness	7	17	8
Case	9	11	3

This information was analyzed by k^2 test and according to PV =0.3, no significant difference was found between the two groups. Of course, it should be noted that three of the infants in the control group died from severe RDS. All 3 newborns had a gestational age of less than 32 weeks, and two of them were boys and girls. The Apgar score was less than 7 in every 3 infants.

Necrosis colitis (NEC): In the neonates, the two groups were evaluated. In the control group, 3 infants were infected with NEC, while in the case group NEC cases were not observed. These results were analyzed by Fisher test

and, with respect to PV =0.2, no significant difference was found between the two groups. All 3 cases of NECs died. All of whom had gestational age less than 30 weeks, and two of them were boys and one girl.

It can be seen from this review that in this study, the administration of recurrent courses of corticosteroid had no effect on the incidence of complications, and no significant difference was found between the two groups. Perhaps prescribing recurrent corticosteroids before and after birth has a negligible but significant effect on reducing the severity of the complications studied in this study, with 3 of the severe RDS cases in the control group and 3 of those who died due to NEC in the same group, but the RDS in the case group received Corticosteroid recurrence did not cause death before birth and there was no case of NEC in the group.

Of course due to the lower gestational age in infants who died due to RDS and NEC, prematurity may have put them at higher risk of death. In this study, 3 infants were diagnosed with RDS due to RDS, 3 were due to NEC, and one died from sepsis. In the case group, 2 people died due to Sepsis.

Discussion and conclusion

In this study, the effect of weekly repeated administration of corticosteroid on the amount of birth time and a series of complications of obesity was investigated and compared with the one-year follow-up of weekly treatment on growth parameters and neurodevelopmental parameters. In the present study, the sex composition of neonates was similar at birth and at one year of age, and there was no significant difference. Because some of the complications of obesity, especially the neonatal respiratory distress syndrome in men are higher, the effect of gender has been eliminated as a confounding factor. The mean gestational age at birth was similar between the two groups, and no statistically significant difference was found between the two groups. The mean of Apgar 5 minutes was similar between neonates in both groups. Therefore, the neonatal characteristics of the two groups were similar in terms of gestational age at birth, sex, and Apgar score of 5 minutes. The maternal characteristics of the two groups in terms of age, weight, parity and socioeconomic status were similar between the two groups, and no statistically significant difference was found. In this study, gestational age was significantly lower when receiving the first course of corticosteroid in mothers undergoing recurrent corticosteroid therapy than the mothers receiving corticosteroid therapy. Potential variables may already be responsive to this relationship, for example, the unfavorable history of previous pregnancies, such as a history of preterm delivery or frequent abortions, encourages the physician to prescribe corticosteroids from the lower gestational age to follow complications.

In our study, the mean birth weight of infants in the case group was significantly higher than that in the control group (receiving a course of corticosteroid). The results from our study are quite contradictory with the results of most animal and human studies, including Bank and French (5 and 6), and they question the effect of corticosteroid suppression on growth. In an observational study in Australia, French and his colleagues it was reported that birth weight and head circumference decreased with increasing the number of corticosteroids. In this study, women who received corticosteroid courses had long-term complications of pregnancy, and the underlying conditions may have affected fetal development, and the study could not have been between the potential growths constraints of these conditions and the potential effects of corticosteroid treatment. In this study, in addition to birth weight, height of the infants in the receiving group was significantly higher than the control group, but the size of the round head did not differ between the two groups. In the study of Bank[5], there was no difference in head circumference but indicated a lower birth weight in the corticosterone recipient group. In the studies of Haas and Stephen (7 and 8), the birth weight was similar between two groups (receiving a course and receiving courses of corticosteroid). In a study by Kumar[4], a study was conducted to evaluate the association between prognosis of neurodegenerative development and recurrent corticosteroid treatment. Also, birth rates (height, weight, and head circumference) are similar between the two groups. In these studies, similar to our study, we did not show a reduction in the effect of duplicate corticosterone therapy on birth-timing. This study shows that repeated cortisone has a long-term effect on growth indices, and the lacerations of the repeat treatment group, although initially weighted and taller, were smaller after one year. Of course, for the definitive conclusion, follow-up of these infants should be carried out at an early age, which is hoped to be considered in other studies. The result of our study is to evaluate growth parameters at one year with the results of previous studies with a different course of corticosteroid. In two recent follow-up studies of children receiving a prenatal corticosteroid, a follow-up group of up to 12 years old[7] and another group of 20 years of age[9] showed a difference in mean physical growth between the treated group and the untreated group. Not yet the study did not address frequent pre-natal coronary events, along with an increase in the incidence of neurodevelopmental disorders in the first year of life. The result of the present study is similar to previous studies, both the study of corticosteroid course and most of the studies related to the many courses of corticosteroids.

In a follow-up study of 12 year-old women, corticosteroids had no significant effect on neurodegenerative status[10].

In another study, up to the age of 20, corticosteroid had no adverse effect on the pre-natal development, and the

difference between the control and the control group Patients treated with betamethasone was not in the capacity of cognitive capacity and intelligence[7].

The lack of correlation between pre-natal corticosteroid therapy and the development of neurodevelopmental disorders in this study were similar to that of the French[6] and Kumar[4] studies, but contrary to the findings of Hock's review[11].

There is still no evidence to support the hypothesis that multiple postpartum corticosteroid periods can cause neurodevelopmental disorder and, given that the number of children surveyed and the duration of follow-up in studies are low, more detailed studies are needed and Prolonged[12]. In this study, the administration of recurrent corticosteroids before birth did not affect the incidence of premature complications, and no significant difference was found between the two groups.

Our result was similar to the failure to improve the complications of premature corticosteroid therapy with the results of the study by Bank[5] and Kumar[4]. But contrary to the results of the investigations, French[6] and Stephan[8] are. Finally, in this prospective study, the administration of recurrent course of coronary prognosis in premature infants has not improved, and in the long run, it reduces height, weight and head circumference. In addition, contact with repeated courses of corticosteroid was not associated with an increase in the incidence of developmental-neurological disorders in the first year of life.

Suggestions: Due to the fact that the natural state of developmental-neurotics in the first years of life can not guarantee the natural evolution in later years, for the better and more complete evaluation, the infants examined in this study have been followed up by the end of puberty and adolescence. Consider various variables such as physical growth and different evolutionary fields. In addition, in order to evaluate the results of this study with the population (term of life and the absence of pre-natal cortex), it is suggested that these infants are compared with those of age, gender, race, and socioeconomic status the results are related to physical, evolutionary and mental development.

References

1. cunningham F.G, Leveno K.J, Bloom SL, et al. preterm birth. In: Cunningam FG. Leveno K.J, Bloom SL, et al. Williams obstetrics. 22 nd edition. New york: McGRAW – HILL;2005.P.855-800
2. Robert D. need Iman. Growth and development. IN: Behrman R, kliegman R, jenson H. NELSON text book of pediatrics. 17 th edition Philadelphia. SANDERS; 2004. P 21-37
3. REnay walker. Development and Behavior. In: Robertson J, shilk of skin. The haiet lane handbook. 17 th edition. U.S of America. ELSEVIER MOSBY; 2006. P. 231-44.
4. Praveen K, Roo pas, William A. Neurodevelopmental out come of ALBW infant aftr multiple couses of antenatal corticosteroids. J matern fetal med 2004.
5. Bank BA, chaan A, morgan MA, parer JT. Multiple courses of antenatal corticoisteroids and outcome od premature neonates, AM J obstet Gynecol 1999;181:709-17.
6. French NP, Hagan R, Evan SF. Repeated antenatal corticosteroids. Size at birth and subsequent development. AM J obstet Gynecol 1999; 180: 114-21.
7. Smolders-de Hass H, Neuvel J. physical development and medical history of children who were treated antenatally with corticosteroids to prevent RDS A: 10 to 12 year follow up. Ped 1990;86:65-70
8. Vermillion ST, Bland M, soper D. Effectiveness of a rescue does of antenatal betamethasone after an initial single course. Am J of obstet and Gynecol 2001.
9. Dessens AB, Haas HS. Twenty year follow up of antenatal corticosterois. ped 2000; 105: e77.
10. Doyle LW, Ford GW, Richard AL. Antenatal corticosteroids and out come at 14 years of age in children with birth weight less than 1500gr. Ped 2000; 106:e2.
11. Soorani-Lunsing RJ. Neurobehavioral relationships and puberty: another transformation? Early Hum dev. 1993; 34:59-67.
12. Lewis H, Modi N. The effects repeated Antenatal glucocorticoid therapy on the developing brain. Br J obstet Gynecol 2001.