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Review Article

Role of Postnatal Corticosteroids in the Treatment or Prevention of Bronchopulmonary Dysplasia

Ali Bulbul, Tolga Bacak, Hasan Avsar

Department of Pediatrics, Division of Neonatology, University of Health Sciences Türkiye, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Türkiye

ABSTRACT

As the frequency of viable low birth weight preterm babies increases, bronchopulmonary dysplasia (BPD), one of the most important morbidities in these babies, also increases. Using postnatal steroids to reduce the development of BPD has not been fully enlightened. Besides all prevention strategies for reducing the development of BPD, it is known that steroid therapy used in the 1st week of life could induce negative neuromotor development according to current data. It may be recommended to administer low-dose dexamethasone between 8 and 49 days in infants dependent on mechanical ventilators in the postnatal period. It is seen that the use of hydrocortisone in the early period does not cause negative neuromotor development, but it cannot prevent the development of BPD as much as dexamethasone. All intensive care units must have their steroid protocol for BPD and use steroids in cases when the BPD development scale score is >60–65% and should have a goal of trying to keep the cumulative dose at the lowest level.

Keywords: Bronchopulmonary dysplasia, dexamethasone, hydrocortisone, mortality, steroids

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The mortality rate of premature babies has been significantly reduced by advances in the diagnosis, treatment, and care of newborn babies. Especially, low birth weight premature babies who can be survived have many morbidity risks in the later period. Bronchopulmonary dysplasia (BPD), which is an important morbidity detected in premature babies, negatively affects the neuromotor development of the baby as well as adversely affects the respiratory system, causing rehospitalization, asthma, and chest wall deformities in the long term.[1] BPD was first reported in 1967 by Northway et al.[2] and still stands before us as an important morbidity in preterm infants in today's modern medicine. When the definition of BPD is made classically, it is known as a chronic lung disease characterized by alveolar fibroproliferation, cystic changes, dysplasia in the airways, and an increase in the muscle tissue in the bronchial structure, triggered by inflammation due to oxygen damage in preterm infants dependent on mechanical ventilation. With the survival of babies with smaller gestational age and birth weights, babies with low oxygen and respiratory support, but with a pause of alveolar development and vascular growth were later defined as "new BPD".[3,4]

BPD is not a stand-alone entity but should be accepted and evaluated multifactorial disease which affected by many

Address for correspondence: Ali Bulbul, MD. Department of Pediatrics, Division of Neonatology, University of Health Sciences Türkiye, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Türkiye
Phone: +90 505 265 44 25 **E-mail:** drbulbul@yahoo.com

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factors. It should be known that a single intervention will not be sufficient to prevent or treat the development of BPD.[3] There has been a significant decrease in mortality rates of preterm babies in the last 50 years, but no change in the frequency of BPD has been observed.[5]

When the frequency of BPD is examined in detail, it is seen that the incidence of BPD increases in these survivable babies, especially as the gestation period is reduced to lower weeks. It is reported that the frequency of BPD decreases with babies who are >28 gestational weeks; however, it is also seen that the frequency of BPD increases with babies who are <28 gestational weeks, especially <26 gestational weeks.[6-8] While the incidence of BPD does not change in total, the detection time of BPD is shifted at smaller weeks of gestation, and this situation can be called the left shift in BPD frequency.[5,9]

The frequency of BPD may vary between countries and even between intensive care units, depending on the health services provided. In general, it is reported that 50% of viable preterm babies with a gestational week of <27 weeks have BPD problems, and this rate rises to 80% in those with a gestational week of 25 weeks and below.[10,11] It has been reported that BPD develops with a frequency of 30–50% in babies with a birth weight of fewer than 1000 g.[12] In general, babies with extremely low birth weight, male gender, intrauterine infection, chorioamnionitis, prolonged invasive respiratory support, prolonged exposure to high concentrations of oxygen, perinatal asphyxia, sepsis, patent ductus arteriosus (PDA), and genetic factors are known to cause high risk in the development of BPD.[3]

Pathology of BPD

The inflammatory source should be evaluated as multidimensional in the development of BPD. Inflammatory cell formation may begin with chorioamnionitis in the intrauterine period. Inflammatory processes such as postpartum sepsis, mechanical ventilation, oxygen exposure, and necrotizing enterocolitis appear as important factors in the development of BPD.[8,12] With these factors, the inflammation process starts, especially in polymorphonuclear leukocytes and macrophages causing damage in the lungs of premature babies. As a result, the histopathological event results in epithelial necrosis, fibrosis, inappropriate alveolar septation, and simplified dysregulated microvascular growth.[8] Alveolarization is a complex and developmental process in which many cells interact. In this process, the "alveolar microenvironment" formed together by the signal pathways, cells, and extracellular matrix that provides communication plays an important role in normal alveolar development.

Intra-alveolar tension, pulmonary microvascular development, and extracellular matrix have different roles in the alveolarization process. While interalveolar physiological tension ensures the differentiation of the epithelium, excessive tension prevents the proliferation of the alveolar epithelium.[9] In the case of hyperoxia, apoptosis and necrosis occur in the alveolar epithelium. Today, the interaction of TGF-β/fibroblast/extracellular matrix triad is thought to play an important role in the pathology of BPD.[9]

Mediators

Transforming growth factor TGF-β superfamily signaling: Type 2 TGF-β receptor stimulation plays a key role in the development of BPD in experimental animal studies. A positive correlation exists between increased TGF-beta protein and impaired lung alveolarization.[13] It has been observed that the use of TGF-beta inhibitors can limit impaired alveolarization in experimental animals whose BPD has been created with hyperoxia.[14]

Oxidative Stress

Decreased antioxidant capacity is associated with an increased risk of BPD in preterm infants.[5] In animal studies, it is known that alveolar development improves when oxidized glutathione is given, and alveolarization worsens in animals with superoxide dismutase 3 enzyme gene loss.[15]

Inflammatory Cells and Matrix Structure

Inflammation and inflammatory pathways play an important role in the development of BPD. It has been shown that alveolarization is completely stopped in case of excessive secretion of nuclear factor-kappa B kinase subunit beta inhibitor.[16] While the decrease in regulatory T-cells and CD11b cells and increase in CD8a+ effector T-cell functions are effective in the development of BPD, it is emphasized that alveolar macrophages play a role as the main regulatory cell in the arrest of alveolarization.[5] It has been reported that elastin, laminin, and cross-linked collagen in the extracellular matrix may be effective in the development of BPD, and lysyl oxide release is impaired after hyperoxia, which may cause fibrosis.[17] It has been shown that the decrease in tissue inhibitor of metalloproteinase in the extracellular matrix is associated with BPD.[18]

Non-coding RNA

It is thought that microRNA (miR) products show different distributions in the diagnosis of BPD and these miR products may play an important role in the development of BPD. In contrast to the decrease in miR-17, miR-489, miR-150, and miR-29b values according to the human and animal studies, increased miR-34a value is associated with the

development of BPD.[5] It has been shown that the decrease in miR-29 level increases the severity of BPD.[19]

Alveolar Epithelial Plasticity

Type 1 and type 2 alveolar cells develop with cell interaction between epithelial cells as transition from the canalicular stage to the saccular stage. It is thought that the mediators involved in the plasticity of this pathway may be effective in the development of BPD.[5]

Mechanism of Glucocorticoids

When glucocorticoids enter the cell, they exert their effects in genomic and non-genomic ways. In the non-genomic pathway, glucocorticoids first stimulate Annexin A1 synthesis. Increased Annexin A1 reduces prostaglandin synthesis by inhibiting phospholipase A2, COX-1, and COX-2. As a secondary nongenomic effect, glucocorticoids reduce vasodilation and capillary permeability by providing cell membrane stabilization, thus reducing leukocyte migration into the alveolar area.[3] Genomically, glucocorticoids prevent proinflammatory transcription (nuclear factor-kappa B and activator protein-1) by transrepression, and increase the production of anti-inflammatory cytokines (interleukin-10) by transactivation.[8] Inflammation triggered by low serum cortisol levels contributes to the development of BPD.[20] In studies conducted, it has been reported that serum cortisol values in the first 48 h of life in preterm infants are in the range of 300–450 nmol/L.[21,22] It was found that cortisol value did not change according to weeks in babies born below the 28th gestational week.[23] It has been reported that gender, multiple pregnancies, perinatal infection, epidural analgesia, delivery method, and administration of antenatal steroids affect serum cortisol levels in newborn babies.[23] It should be kept in mind that steroids are potent inhibitors of DNA synthesis and therefore may have reduced effects on the growth and repair of lung damage.[3]

Effect Of Glucocorticoids on the Development of BPD

For the first time in 1972, Liggins GC et al.[24] reported a reduction in respiratory distress syndrome (RDS) and mortality with antenatal glucocorticoid use. Antenatal steroid administration significantly reduces mortality, the incidence of RDS, and intraventricular hemorrhage in preterm infants.[3] However, the effect of antenatal steroid administration on reducing the frequency of BPD has not been fully determined.[25] To reduce the frequency of BPD and intubation, the use of glucocorticoids increased gradually in the postnatal period, and the frequency of steroid use increased to 25% in babies with a gestational age of <28 weeks in the 1990s. As a result of the data obtained in this process, the negative effects of steroids on neuromotor development and growth values were observed.

Therefore, in the 2002 statement of the American Academy of Pediatrics (AAP), it was not recommended to use postnatal steroids to prevent or treat BPD in preterm infants, especially because of the development of cerebral palsy (CP) and negative neuromotor development effects.[26] After this statement, a significant decrease was observed in the use of postnatal steroids in the prophylaxis and treatment of BPD.[11] However, the AAP updated its recommendation in 2010 after the frequency of BPD did not change over time, and even some publications reported an increase in the frequency of BPD. The AAP reported that low-dose (<0.2 mg/kg/day) dexamethasone treatment increases the chance of survival without BPD, but steroids should not be used routinely because there is insufficient knowledge about the side effects of long-term steroid use.[26] Since there are not enough studies on the efficacy of low-dose hydrocortisone (1 mg/kg/day) in the early period and high-dose (2–3 mg/kg/day) hydrocortisone administration in the later weeks of life in the same report, its routine use is not recommended in the prevention of BPD.[26] Although the use of steroids has decreased in the last 10 years to prevent the development of BPD, the use of steroids has come to the fore again due to both increasing the success of extubation and positive effects on lung respiratory parameters. Systemic corticosteroids are widely used in the prevention and treatment of BPD because they increase surfactant synthesis and antioxidant enzymes in the lung, reduce proinflammatory cells and infiltration, as well as reduce pulmonary edema.[27]

Hydrocortisone

Early Period (First 7 days) Use of Hydrocortisone

It is known that systemic hydrocortisone treatment in the first 7 days of life prevents the development of BPD. In the case of early adrenal insufficiency prophylaxis with low-dose hydrocortisone in babies with extremely low birth weight, the incidence of BPD and the need for PDA closure are reduced.[28] Late-onset sepsis and intestinal perforation (especially in those receiving indomethacin due to PDA) were found to be increased in these infants receiving hydrocortisone. In the meta-analysis of 12 studies evaluating the effect of hydrocortisone in the early period, it was reported that early hydrocortisone treatment was moderately effective in preventing the development of BPD in preterm infants, there were no negative effects on neuromotor development, but it increased the frequency of intestinal perforation.[29] According to the meta-analysis, 18 babies should be given early hydrocortisone treatment (NNT: numbers needed to treat) for a BPD-free life. The need

for PDA treatment (NNT: 11) and moderate-severe neuromotor developmental retardation (NNT: 14) decreased with early hydrocortisone treatment; on the contrary, it was found that the frequency of intestinal perforation (NNT:30) increased.[29]

The PREMILOC study is instructive in determining the dose of hydrocortisone to be given in the early period. In the PREMILOC study, it was reported that the chance of surviving without the development of BPD increased significantly in preterm infants who were given 1 mg/kg/day for the first 7 days and 0.5 mg/kg/day hydrocortisone for the next 3 days (cumulative dose: 8.5 mg/kg for 10 days).[30] It has been reported that when hydrocortisone is given at a physiological dose in the early period, the success of extubation increases on the 7th day of life, and the oxygen requirement decreases at the corrected 36th week.[30] When the PREMILOC study was examined, it was found that babies who were treated for PDA in the first 24 h of life, SGA babies, and babies with asphyxia (pH <7.0) were not included in the study, and the effect of hydrocortisone could prevent the development of BPD at a higher rate in female gender (NNT:7).[30] In the subgroup analyses of the PREMILOC study, no correlation was found between the basal cortisone level measured before treatment and the development of BPD. The frequency of spontaneous intestinal perforation and intraventricular bleeding (grades 3 and 4) was higher in the group with high basal cortisone levels and hydrocortisone administered.[23] Therefore, it is emphasized that the balance of hydrocortisone therapy's benefits and harms should be considered in the early period. A study involving the same infants for 2 years reported that neuromotor development was significantly better in infants who were given early hydrocortisone at 24 and 25 weeks of age.[31]

Mild-early Period (7–14 Days) Use of Hydrocortisone

The STOP-BPD study aimed at the effect of systemic hydrocortisone on the development of BPD and was designed as follows: in-babies with a gestational ae of <30 weeks and/or a birth weight of <1250 g, who were on mechanical ventilator between the 7th and 14th days of life were randomized in a double-blind manner; infants given systemic hydrocortisone 5 mg/kg/day (divided into 4 doses) for 7 days, 3.75 mg/kg/day (divided into 3 doses) for 5 days, then reduced by 1 dose every 5 days for a total of 22 days (cumulative dose 72.5 mg/kg) compared with infants given placebo mannitol. In the case of progressive severe pulmonary deterioration (respiratory index >10) after at least 10 days of treatment in the follow-up, a study was opened (open-label) and hydrocortisone was given to the infants. According to the study, hydrocortisone treatment did not affect death or the development of BPD.[32] It has been reported that the success of extubation on the 3rd, 7th, and 14th days was higher and the respiratory index was better in the group given hydrocortisone.[32] When subgroup analysis was performed in the study, it was found that mortality decreased in infants below 27 weeks of gestational age in the group receiving hydrocortisone treatment.[32] It was reported that the frequency of death and/or neuromotor development disorder did not change in the 2-year follow-up of 356 preterm infants included in the study.[33] This study is important in proving that hydrocortisone treatment does not negatively affect neuromotor development in the first 2 years of life. It should be known that when hydrocortisone is used at physiological doses (8–10 mg/m^2/day), it does not have a mineralocorticoid effect (it does not cause hypertension by keeping sodium) but has a mineralocorticoid effect at doses higher than the physiological dose.[8] It has been shown that hydrocortisone treatment applied for BPD in preterm infants has no negative effects on brain volume and neurodevelopment.[34] In the magnetic resonance imaging study performed between 73 preterm infants given hydrocortisone and the control group, no change was observed in total brain tissue and cerebellar volume.[34] Although hydrocortisone has a significant anti-inflammatory inhibitory effect on the lung without a negative effect on brain development, it has been shown that it is not as effective as dexamethasone in preventing the development of BPD.[30,32] As a result, there is no consensus about the time interval and dose of hydrocortisone to prevent or treat the development of BPD. Current findings show that low doses of hydrocortisone will not cause adverse neuromotor development in the future.

Dexamethasone

Among glucocorticoids, its potency is 25 times higher than hydrocortisone.[8] It is transported in plasma by binding to albumin (other steroids bind to transcortin). It does not bind to mineralocorticoid receptors. The dose of dexamethasone applied in the treatment of BPD was gradually reduced over time; while the initial dose was 0.6 mg/kg/day, it was reduced to 0.3 mg/kg/day and then to 0.15 mg/kg/day over time.[10] In randomized controlled studies, the administration of dexamethasone in the 1st week of life reduces the frequency of BPD, the frequency of death, and the need for oxygen support in the postnatal 36th week.[35] However, it has been shown that the use of dexamethasone in the early period causes short-term side effects (gastrointestinal bleeding, intestinal perforation, hyperglycemia, hypertension, hypertrophic cardiomyopathy, and growth failure) and negative neuromotor development.[36-38] Therefore, steroids should be reserved for those with difficulties in weaning preterm babies older than 7 days

from the mechanical ventilator, also called extubation.[10] Due to its short- and long-term side effects, the use of dexamethasone is not recommended in the 1st week of life to prevent the development of BPD.[8] Considering its use in this period, it has been reported that the curing period should be kept as short as possible and it can be given in <3 days.[39] The DART protocol published in 2006 on the use of dexamethasone in the postnatal period has led to significant improvements in the strategy for preventing the development of BPD.

In the study, 70 preterm infants who were monitored on a mechanical ventilator after the 1st week of life were randomly given low-dose (cumulative dose 0.89 mg/kg) dexamethasone therapy and it was shown that oxygen demand decreased in the ventilator, intubation time decreased, and there was no negative effect on neuromotor development during a 2-year follow-up.[40] In studies published successively, it has been shown in meta-analyses that dexamethasone administration after the 1st week of life reduces BPD, BPD or death, extubation failure, and the need for second-cure steroids.[41] However, information about the negative effect of dexamethasone therapy on neuromotor development during this period is contradictory. Traditionally, high-dose use of dexamethasone (up to 8 mg/kg per 42 days) and longer-term administration (21–42 days) are considered to be the main cause of adverse neuromotor development results.[8,42,43] Finally, in a meta-analysis review evaluating the use of dexamethasone, it was suggested that the cumulative dose of dexamethasone should be 2–4 mg/kg and starting at a mild early stage (between the 8th and 14th days) is the most appropriate treatment model.[44] The most important problem related to steroid use in the treatment or prevention of BPD is the concern of adverse neuromotor development (neurodevelopmental impairment: NDI) in the long term and the increase in the frequency of CP. In the reported studies, when the risk factor for developing BPD is <33%, the frequency of CP and NDI increases with steroid use, and when the risk factor for developing BPD is >60%, steroid use reduces the frequency of NDI and CP.[8] For this reason, it is necessary to evaluate every premature baby for the risk factor of developing BPD. Widely Neonatal BPD Outcome Estimator Program (pregnancy, weight, gender, ethnicity, and created depending on respiratory support) is used, but it is emphasized that each country should implement their calculation program based on their clinical data.[8,45]

Early Period (First 7 Days) Steroid Use

Steroid use in preterm infants within the 1st week of life reduces the rates of extubation failure, PDA, and severe retinopathy. However, it increases the frequency of hyperglycemia, hypertension, hypertrophic cardiomyopathy, intestinal perforation, gastrointestinal bleeding, and growth failure in the following period of a lifetime.[36] While many complications develop due to the use of dexamethasone, it is known that the frequency of intestinal perforation increases with the use of both dexamethasone and hydrocortisone.

What is the Effect of Steroid Administration in The First 6 Days of Life on the Development of BPD and Mortality?

In a review evaluating 32 randomized controlled studies (including 4395 infants) on the subject: When all steroid applications were evaluated in a single group, it was reported that early steroid initiation in the first 6 days of life did not reduce mortality and BPD separately, the frequency decreased when mortality and BPD were evaluated together, and the frequency of intestinal perforation and the development of CP increased.[46] When dexamethasone was evaluated alone, it was found that dexamethasone had no effect on the frequency of mortality, significantly reduced the frequency of BPD, and increased the frequency of intestinal perforation and CP. It has been shown that early administration of hydrocortisone is effective in reducing the incidence of mortality and BPD and increasing the frequency of intestinal perforation and has no effect on the frequency of CP.[46] While steroids given in the early period of life significantly reduce the frequency of BPD, it is seen that this effect is especially dependent on dexamethasone.[36] While the effect of steroid use on mortality in the early period was not determined, it was observed that hydrocortisone use decreased the mortality rate in subgroup analyses.[36] The summary of steroid use in the early period and its reflections in the future is presented in Table 1.

Late (≥7 Days) Steroid Use

In a meta-analysis of 23 randomized controlled trials in which steroids were given 7 days after birth, it was determined that the duration of treatment was between 2 and 42 days and the cumulative dose was between 0.65 and 8.5 mg/kg. It has been reported that the use of steroids in the late period reduces the rate of BPD, death rate, BPD, and death rate at the postconceptional 36th week.[41] Subgroup analyses have shown that the positive effects obtained with steroid use in the late period were due to dexamethasone.[36] The current data support that the use of hydrocortisone in the late period reduces mortality to a small extent, while the use of dexamethasone slightly increases the incidence of CP.[36]

Table 1. Types of steroid use in bronchopulmonary dysplasia and its effects on the development of mortality and morbidity

Form of steroid administration	Effect on mortality and morbidity	BPD	Recommends
Inhaled corticosteroid <14 day	Mortality and cerebral palsy increase	No change	Routine use is not recommended
Inhaled corticosteroid >7 day	Not enough data	–	–
Systemic early corticosteroid use ≤7 day	Mortality DM–not decrease HC–decrease	Decreasing DM–more Effective	DM–is not recommended HC–Wait for routine use
	DM–CP increase HC-CP no change		
	Extubation failure, PDA, and severe ROP decreased		
	Gastrointestinal bleeding, intestinal perforation, hypertension, hyperglycemia, hypertrophic cardiomyopathy, growth retardation increase		
Systemic late corticosteroid use >7 day	Mortality and morbidity decrease DM–more effective	Decrease	DM- Recommended if high-risk BPD HC–Wait for routine use
	CP slightly increased mortality plus CP not change		
Intratracheal surfactant+Budesonide	Mortality not change/slightly decreased	Decrease	Not enough data for routine use

BPD: Bronchopulmonary dysplasia; CP: Cerebral palsy; DM: Dexamethasone; HC: Hydrocortisone.

What should be the Timing of Steroid Administration? When should Steroids be Given?

Preterm infants who remain on a ventilator for more than 2 weeks are considered to have a high risk of developing BPD.[47] In addition to pulmonary problems in the long term, neurodevelopmental problems, CP, cognitive deficits, and deafness can be seen in children with BPD. It is known that CP and motor abnormalities were seen when dexamethasone is used, especially in preterm infants with a low risk of BPD.[48,49] The optimal timing of postnatal steroid administration is unknown. Steroids are generally administered after 4 weeks postnatally since there is concern about the negative effects of steroids on neurological development in the early period.[50] However, there are insufficient data on this time extension's safety and efficacy. In this case, the duration of mechanical ventilation and oxygen exposure of preterm babies increases, which can be associated with BPD and negative neuromotor development.[50] According to the study in which 951 babies with a gestational age below 27 weeks were evaluated, it was determined that steroids should be given to the babies with a high risk of developing BPD between the postnatal 8th and 49th days.[50] Delayed administration of steroid therapy may delay the desired anti-inflammatory effect and thus lead to less response in treatment.[50]

Inhaled Steroids

Currently, there is no accepted standard practice regarding the use of inhaled steroids to prevent or treat the development of BPD. In the NEUROSIS study published in 2015, which included the use of budesonide as an inhaled corticosteroid, 863 infants were randomized, starting from day 1, to one group given a placebo and another group inhaled budesonide (for 14 days-2 puff per day-200 mg per puff). Inhaled budesonide therapy was continued once a day until the infant had no oxygen support or positive pressure support or was 32 weeks of postconceptional age. It has been reported that the frequency of BPD decreased in the group given inhaled budesonide, there was no difference in neuromotor development, but the mortality rate increased slightly and the mortality rate remained high at the age of 2 years.[51] In different studies, it has been reported that inhaled budesonide treatment reduces the development of BPD, and no significant neuromotor developmental delay was found in the follow-up of infants given inhaled corticosteroids at the age of 2–3 years.[52,53] However, studies on inhaled budesonide's dose, duration, and efficacy are needed to recommend it as a routine application. Inhaled corticosteroids reduce the development of BPD, but since its relationship with mortality has not been fully elucidated, it is not recommended to be routinely used in the prevention of BPD in the early period.[8]

Intratracheal Steroids

Studies have been reported on the efficacy of intratracheal steroid applications in preterm infants, either by the intratracheal alone or in addition to surfactant treatment in the treatment of RDS (52–55). In a study involving 265 infants who were given intratracheal budesonide (0.25 mg/kg) together with surfactant in the treatment of RDS in preterm infants, it was reported that the frequency of BPD decreased by 40%, the frequency of BPD and the death by 43%, and there was no difference in the frequency of NDI in the 2-year follow-up.[52] However in another retrospective study which designed as: surfactant alone in the treatment of RDS and surfactant with budesonide (0.25 mg/kg) given in 68 babies with a gestational week <28 weeks, birth weight <1500 g were evaluated and reported that the frequency of BPD, BPD at 36 weeks, or death frequency was not affected.[54] It was found that the frequency of inotrope requirement for hypotension decreased in the first 5 days in the group given intratracheal budesonide, and the need for re-hospitalization for respiratory reasons was lower in the 1st year.[54] Discussions about the routine administration of surfactant with budesonide continue because there is not enough current data.[8,56]

Second-Cure Steroid Use

In cases where extubation success cannot be achieved with a single cure in postnatal steroid use, a second cure could be applied. It has been reported that the second-cure steroid requirement is higher in babies with SGA and twins.[47] It was found that the success of extubation decreased in babies who received the second cure of dexamethasone treatment; while an extubation success could be achieved in the first cure around 50%, it was found that the extubation success rate in the second cure was around 35%.[47] It has been reported that there is no difference between the increase in weight, height, and head circumference when babies who receive a single cure and those who receive two cures are compared according to their anthropometric measurements at discharge.[47,57] However, it was observed that there was a significant difference in terms of weight, height, and head circumference between babies who received two cures and those who did not receive any steroid therapy.[47]

Prednisolone

It has been shown in animal studies that the transition of prednisolone to the cerebrospinal fluid is lower than dexamethasone.[58] With this feature, it is hypothesized that prednisolone has a lower negative effect on neurological development compared to dexamethasone.[58] In a study on prolonged use of prednisolone in premature infants older than 30 days diagnosed with BPD, it was found that prednisolone treatment, which was started at a dose of 1–2 mg/kg/day in the 1st week and reduced by 0.5 mg/kg every week for a total of 4 weeks, had a positive effect on pulmonary functions. It has been reported that no negative effect was found on weight, head circumference, and height development z scores.[58] Large-scale, controlled prospective studies are needed to decide whether to use prolonged prednisolone in preterm infants with BPD. It has been reported that after prednisolone is given for BPD treatment in preterm infants diagnosed with BPD postconceptional after 36 weeks, the need for mechanical ventilation support and oxygen support decreases significantly, but the 1-week treatment period is sufficient, and when the treatment is extended to 4 weeks, it has negative effects on linear growth.[59] In a study conducted with 385 preterm infants with a postmenstrual age >36 weeks of gestation and diagnosed with oxygen-dependent BPD, it was reported that prednisolone was 63% effective in weaning the infant from oxygen in the group receiving single-dose oral prednisolone treatment.[60]

Different Studies on Steroids in the Treatment of BPD

In studies evaluating the efficacy of inhaled steroids (budesonide, beclomethasone, and fluticasone) after the postconceptional 36th week in babies with BPD, it has been shown that while inhaled steroids reduce coughing and wheezing episodes in infants, they are not effective in reducing the need for mechanical ventilation and oxygen support.[61]

Antenatal corticosteroid administration significantly reduces mortality, moderate RDS, severe RDS, and the need for mechanical ventilation in infants with low gestational weeks.[1] The effect of antenatal glucocorticoid use on BPD cannot be fully explained. While a decrease in the frequency of BPD is expected with all the positive effects of antenatal steroids, it was found that the frequency of BPD did not change in studies.[62] When antenatal glucocorticoid is given, the frequency of BPD or death is low, although statistically significant.[63]

Adrenal Suppression

Adrenal suppression status should be evaluated in the use of glucocorticoids for BPD. Since adrenal suppression may develop in cases where the treatment period exceeds 14 days, glucocorticoids should not be discontinued abruptly but should be tapered and discontinued.[8] The hydrocortisone equivalent of the given glucocorticoid should be

calculated. It has been reported that adrenal suppression did not develop in infants given a dose of 8–10 mg/m^2/day (approximately 1 mg/kg/day) of hydrocortisone.[29] Hydrocortisone dose should be tapered and discontinued in infants receiving a daily hydrocortisone equivalent dose of >20 mg/m^2. In these babies, the dose is reduced by 50% every 3 days. When it comes to a daily dose of 15–20 mg/m^2 hydrocortisone, the drug is divided into 2 doses per day and given for 3 days. When the hydrocortisone dose is 8–10 mg/m^2, the hydrocortisone dose is divided into 2/day and continued for 2 more weeks and then discontinued. The baby is followed closely in terms of adrenal insufficiency symptoms (hypoglycemia, hyponatremia, and hypotension) during reduction and cessation.[8]

Anthropometric Measurements

In a comprehensive study examining the effect of postnatal steroid therapy on postnatal anthropometric measurements in preterm infants with BPD, it has been reported that postnatal weight gain and head circumference z scores were not affected in a single-cure (5 days) systemic glucocorticoid (hydrocortisone or dexamethasone) use with 6104 preterm babies younger than 28 weeks in 5 years.[57] No difference was found in weight gain and head circumference growth in babies who received more than one steroid cure.[57]

Effect of Standardization Training

In a study conducted to reduce the differences within the clinic in postnatal steroid applications to prevent the development of BPD in preterm infants, it was shown that steroid use increased from 50% to 80% with the education of the monitoring standards established within the clinic, and the rates of recurrent steroid use did not change. It was observed that while compliance with the recommended guidelines was 71% in the pre-training period, it increased to 96% in the post-training period.[64] To prevent or treat the development of BPD in preterm infants in neonatal intensive care units, it is recommended to standardize postnatal steroid administration and ensure compliance with in-clinic training. It is recommended that each neonatal unit makes statistics of BPD frequencies. It has been reported that the use of postnatal steroids at optimal doses in units where the local BPD frequency is over 46% reduces the frequency of BPD.[65] Neonatal units should have a goal of trying to keep the cumulative dose at the lowest level.[65]

Conclusion

The use of steroids is an important milestone in the treatment of BPD or in the strategy of preventing the development of BPD. The advantages of steroid use have been proven in preterm infants at high risk of developing BPD. In steroid treatment, which steroid should be given, when it should be given, in what dose it should be given, in which way it should be given, and for how long it should be given are the questions that must be explained. In addition to all these questions, the steroid to be given should not have a negative effect on the growth and neuromotor development of the baby. Evidence of the absence of adverse neuromotor development with hydrocortisone given early in life slightly pushes the use of hydrocortisone. Evidence of the absence of adverse neuromotor development with hydrocortisone given early in life brings the use of hydrocortisone to the fore. However, it has been clearly shown that hydrocortisone is not as effective as dexamethasone.

The clinician should first identify babies at high risk for the development of BPD, and consider the use of physiological doses of hydrocortisone in the early period. Dexamethasone use should be planned for babies older than 7 days of life, who need invasive ventilation support, and who are considered to be at high risk of developing BPD. In infants with a high risk of developing BPD, steroid use should not be left after 7 weeks. When the decision to use steroids is made, steroid-related side effects and drug interactions should be evaluated, especially infants given PDA closure therapy should be careful in terms of intestinal perforation.

Disclosures

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