Critical analysis of the use of corticosteroids in the neonatal period

Marcia Antunes,1 Jaques Belik2

Abstract

Objective: to review the use of corticosteroids in the treatment of newborns with chronic lung disease, adrenal insufficiency and upper airway edema.

Sources: review of the available medical literature on the use of corticosteroids in newborns.

Summary of the findings: although there is evidence of short-term clinical improvement of chronic lung disease with the administration of dexamethasone, the available literature did not show significant reduction in neonatal morbidity and mortality associated with this condition.

Conclusions: the use of corticosteroids must be carefully analyzed and restricted to the treatment of severe cases, since these drugs may produce irreversible effects on the nervous system and neurological development of newborns.


Introduction

The first extracts of adrenocortical hormones to present a reasonable degree of activity were synthesized circa 1930; but it was only in 1949 that Hench et al. showed the dramatic effects of the therapeutic use of cortisone and of ACTH on rheumatoid arthritis.1 The contribution of Hench and the seminal research by Kendall and Reichstein on steroid synthesis produced such an impact on the medical world that they were awarded the 1950 Nobel Prize of Medicine.

Haddad et al. published the first study reporting postnatal use of steroids in premature newborn babies. The authors concluded that there was no significant reduction on the incidence of hyaline membrane disease in 32 newborns from diabetic mothers.2 In 1972, Liggins and Howie published the first study demonstrating the importance of antenatal corticosteroid administration.3 The authors reported lower morbi-mortality rates in premature babies.

In 1978, Kramer and Hutzen carried out the first study reporting the use of corticosteroids in the treatment of pulmonary chronic disease in babies. Since then, numerous studies have evaluated perinatal use of steroids.

1. Pharmacological action

a) Anti-inflammatory and bronchodilator

The powerful anti-inflammatory effect of corticosteroids is the main reason for its clinical use. Corticosteroids can suppress the manifestation of inflammations through inhibition of specific leukocyte functions (migration, phagocytic activity), and stabilization of cellular membranes of capillaries and of dilution - allowing for reduction of the edema. In the lung, the glucocorticoids reduce the
concentration of inflammatory markers in tracheobronchial secretions. Moreover, prolonged use reduces the proliferation of capillaries, the production of fibroblasts, and excessive deposition of collagen and fibrin, consequently promoting cicatrization.

Corticosteroids are efficient in the handling of bronchial hyperresponsiveness. They revert the obstruction of small airways by relaxing bronchial smooth muscle in older children and adults with asthma. The bronchodilator effect is also evident on newborns with chronic pulmonary pathologies. This beneficial effect is, partially, the result of an increase in beta-adrenergic activity because steroids cause an increase in density of beta-adrenergic receptors.

b) Metabolism of nutrients

In addition to the anti-inflammatory effect, corticosteroids alter carbohydrate, protein, and lipid metabolism. In relation to carbohydrates, corticosteroids stimulate the production of glucose reducing its peripheral utilization, induce deposition of glycogen in organs such as the liver and the heart, and promote gluconeogenesis.

The use of glucocorticoids leads to an important reduction of the endogenous production of proteins. Glicocorticoids, the most potent catabolic hormones, act primarily by increasing protein breakdown, both in muscle and at the whole-body level and inhibit appropriate growth. Associated to this process, there is the elevation of plasma levels of amino acids that further enhances the potential for gluconeogenesis. Finally, corticosteroids cause redistribution of body fat and induce lipolysis from adipose tissue triglycerides.

c) Hydroelectrolytic balance

In adults, the mineralocorticoids act on the distal tubule and kidney collecting duct, increasing sodium reabsorption and urinary excretion of both potassium and hydrogen. The existence of this process in children or newborns is unknown.

d) Cardiovascular system

The glucocorticoids induce hypertension by mechanisms that are still not well understood. Others have indicated that sodium retention may play a role in the etiology of this effect.

e) Muscle and skeleton system

The prolonged use of corticosteroids in older children and adults leads to a weakness of the muscles through a mechanism that still is not well understood, though possibly related to inadequate perfusion of striated muscle. Steroid miopathy is well known in adult patients with Addison’s disease, Cushing’s disease, cancer, autoimmune disease and when associated with the use of neuromuscular blockers.

2. Perinatal use

Perinatal use of corticosteroids involves prenatal and neonatal administration. Prenatal administration of dexamethasone or betamethasone is indicated only to stimulate fetal lung maturation. The maturation process occurs through an increase in the production of surfactant and yields substantial reduction in neonatal morbidity and mortality.

In newborn babies, corticosteroids are indicated for the treatment of numerous clinical conditions, including bronchopulmonary dysplasia, postextubation upper airway obstruction, adrenal insufficiency, and treatment of hemangiomas. In this review, we will limit our discussion to antenatal corticosteroid administration, including its pharmacological effects, clinical benefits, types of administration, duration of treatment, risks, and our recommendations.

3. Chronic lung disease

a) Clinical effects

The use of oxygen combined, or not, with mechanical ventilation in the treatment of respiratory diseases of the newborn can affect the pulmonary parenchyma. This can ultimately lead to chronic lung disease (CLD). In most cases, therapeutic application of corticosteroids in newborns with bronchopulmonary dysplasia results in significant, short-term improvement of patient clinical status. The beneficial effects of corticosteroids are secondary to improvement of lung compliance and resistance in ventilator-dependent babies.

Different clinical studies have shown that the use of corticosteroids allows for reduction of ventilator settings, for reduction of supplementary oxygen, and for increase in successful extubation. Despite the referred short-term clinical effects, and contrary to what was expected, the use of steroids did not reduce neonatal morbidity and mortality.

b) Therapeutic notes

The most widely used corticosteroid in systemic treatment and prevention of CLD of the newborn is dexamethasone (endovenous or oral administration). One clinical trial has reported the combined use of dexamethasone and hydrocortisone.

c) When to start

The matter of deciding when steroid treatment should start with ventilation-dependent newborns is controversial. Mammal et al., Noble-Jamieson et al., and Harkavy et al. reported the use of steroids after the fourth week of life. In turn, Bourchier et al., Kazzi et al., and a Collaborative...
Trial Group\textsuperscript{42} recommended starting treatment on the third week of life. Moreover, still, Avery et al.,\textsuperscript{17} Gladstone et al.,\textsuperscript{43} Papagallo et al.,\textsuperscript{44} Cummings et al.,\textsuperscript{34} and Merz et al.\textsuperscript{45} suggested administration on the second week of life, whereas Benini et al.\textsuperscript{46} reported the use after the eighth day of life.

The metanalysis carried out by Halliday et al. was aimed at assessing early postnatal corticosteroids (less than 96 h), moderately early postnatal corticosteroids (7-14 days), or delayed corticosteroids (more than 3 weeks) in prevention and/or treatment of CLD. The authors concluded that moderately early corticosteroids reduces neonatal mortality and CLD. However, short- (infection, hyperglycemia, hypertension, gastrointestinal bleeding) and long-term (cerebral palsy and poor neurodevelopment) also were described\textsuperscript{25-27}.

Data from different studies suggest that early dexamethasone administration (24 to 48 hours after delivery) could prevent chronic lung disease.\textsuperscript{47,48} Prophylactic use of the drug, however, does not seem to be justified considering potential adverse effects of the treatment, such as hypertension, hyperglycemia, gastrointestinal perforation,\textsuperscript{49} growth restriction\textsuperscript{12} and small head circumference.\textsuperscript{19}

d) Dosage

Traditionally, initial dexamethasone dosage is of 0.5 mg/kg/day;\textsuperscript{17} 0.6 mg/kg/day was the highest dosage described.\textsuperscript{42} More recently, lower doses have been suggested with the objective of reducing adverse steroid effects.\textsuperscript{50} Moreover, a recent study applied 0.15 mg/kg for 3 days followed by 0.1 mg/kg for 3 days, 0.05 mg/kg for 2 days, and 0.02 mg/kg for the last 2 days.\textsuperscript{19}

e) Duration of treatment

The different regimens suggested in the literature can be divided according to duration into short (less than 2 weeks) and prolonged (2 to 6 weeks) treatment. Typically, the regimen presented by Avery et al.\textsuperscript{17} is the most widely used in cases of prolonged treatment. Avery et al.\textsuperscript{17} administered dexamethasone intravenously for 3 days at 0.5 mg/kg/day, followed by 3 days at 0.3 mg/kg/day, and 3 days in tapering (10\%) doses down to 0.1 mg/kg/day. Next, a daily dose was administered for 1 week, yielding a total 20 days of treatment. Kazzi et al. described a therapy with dexamethasone for 7 days followed by hydrocortisone for a total of 17 days of therapy.\textsuperscript{38}

Among short-term regimens, it is possible to emphasize that by Mammel et al.,\textsuperscript{4} with 3-day intravenous dexamethasone at 0.5 mg/kg/day.\textsuperscript{55} The collaborative trial group administered dexamethasone to newborns at dosages of 0.6 mg/kg/day endovenously for 7 days, followed by optional tapering of the dose in the next 9 days.\textsuperscript{42} Cummings compared 42 to 18-day corticosteroid treatments\textsuperscript{34} and concluded that weaning was significantly faster in the 42-day treatment group than in the 18-day treatment group.

An alternative to the administration of these drugs is pulse therapy. Brozanski administered dexamethasone at 0.5 mg/kg/day for 3 days at 10-day intervals until babies no longer required supplemental oxygen, assisted ventilation, or reached 36 weeks of postmenstrual age.\textsuperscript{18}

f) Inhaled steroids

In addition to endovenous and oral administration, inhaled steroids have also been used in babies with CLD or with high risk for development of dysplasia. Though inhaled steroids cause significantly less side-effects than systemic steroids, its efficacy is still arguable. The available inhaled steroids are beclomethasone dipropionate, triamcinolone, flunisolide, dexamethasone, budesonide, and fluticasone propionate.

The studies differ in terms of the drug, dosage, and duration of treatment (7-28 days). Papagallo administered 1 mg/kg/day of dexamethasone for 7 days and 0.5 mg/kg/day for 3 days through nebulization. LaForce and Brudno administered beclomethasone at 50 micrograms/day for 2 weeks.\textsuperscript{51} Pokriefka administered flunisolide for 28 days and Konig flunisolide at 187-250 micrograms/day.\textsuperscript{52}

In a metanalysis for the Cochrane Revision,\textsuperscript{53} the comparison of systemic and inhaled steroids showed that the latter takes longer to start acting and patients only begin to present clinical improvements after the first week of treatment. It is proven that inhaled steroids lead to an improvement in extubation rates; results with nonventilated babies, however, are inconclusive.\textsuperscript{53} This last study confirms the results of a 1999 publication that suggests a more rapid response with the use of systemic steroids, but no significant differences in the rate of CLD at either 28 days or 36 weeks.\textsuperscript{54}

A recent study compared early (before 3 days) with delayed (after 15 days) steroid therapy and dexamethasone with inhaled budesonide\textsuperscript{55} in terms of mortality, incidence of CLD, neurological abnormalities, and complications of prematurity. Results indicated that babies treated with early dexamethasone had improved survival without chronic lung disease in comparison to those given delayed treatment and inhaled steroids; but results for survival to discharge were in the opposite direction. Dexamethasone was associated with increased risk for hypertension when compared to inhaled steroids.\textsuperscript{55}

g) Recommendations

Despite proven beneficial short-term effects, caution is recommended when using corticosteroids. Prudence is based on the lack of evidence indicating that the use of these drugs reduces long-term morbidity and mortality in chronic lung disease. Moreover, there is an apparent increase in incidence of neurological sequelae associated with the therapy.\textsuperscript{55} As
suggested by others, indication of dexamethasone in the treatment of chronic lung disease should be limited to newborns requiring high concentrations of oxygen and ventilator settings.

Empirically, the use of dexamethasone should be recommended when oxygenation index remains greater than 20 for over 72 hours in babies aged more than 7 days of life and with clinical status typical of CLD. Before starting the treatment, the presence of infection, patent ductus arteriosus, cor pulmonale, and surfactant deficiency should be excluded.

It is recommended to start dexamethasone at 0.1 mg/kg endovenously at every 12 hours and for 3 days. If the patient improves with dexamethasone, the dosage should be tapered 10% every day for 10 days (total treatment = 13 days). Treatment with dexamethasone should be interrupted on the third day if patient does not present at least 25% FiO₂ reduction.

The dose of dexamethasone should be lowered (25-50%) in case the baby presents arterial hypertension (systolic arterial pressure less than 85 mmHg). At last, it is also important to underscore that if patient clinical status worsens during weaning of dexamethasone, the procedure should be interrupted. The baby should be administered the dosage used before deterioration.

4. Adrenal insufficiency (hypocortisolemia)

a) Physiology of cortisol during the perinatal period

The adrenal production of steroids can be detected as early as the ninth week of gestation. During the second half of the gestation term, the adrenal cortex appears as a distinct anatomical structure, and it starts to synthesize glucocorticoids and mineralocorticoids. These corticoids will be necessary for adequate adaptation to extraterine life. The plasma adrenocorticotropic (ACTH) hormone levels are relatively high on the fetus, the newborn, and the mother. There are limited data on plasma concentrations of cortisol during fetal life. In 1973, Beitins et al. reported an average value of 2.1 + or - 1.2 micrograms/dl in 3 to 6-week old fetuses. Fifty to 75% of fetal plasma cortisol is derived from the fetal adrenal and 25 to 50% from the mother through placental diffusion.

Fetal plasma cortisol levels are directly proportional to those of the mother, and their increase can be induced by stress during labor. These levels decrease after birth and the nadir occurs with 24 to 36 hours of life. Next, they increase rapidly to levels greater than or equal to those found later in childhood. The circadian rhythm of adults, with diurnal variation of increase in the morning and reduction at night, does not appear before age 1 to 3 years.

b) Therapeutic approach

Many premature babies with less than 1,000 grams have shown evidence of adrenal insufficiency during the first week of life. These babies seem to present an inability to secrete adequate amounts of cortisol in situations of increase in stress, which leads to hypocortisolemia and shock. The therapeutic use of corticosteroids is indicated for newborns with clinical evidence of adrenal insufficiency.

In 1989, Colasurdo et al. reported a case of 9 babies (average gestational age 26 weeks and average weight 711 g) who presented hypotension and low cortisol levels. All patients presented improvement of clinical status with administration of hydrocortisone endovenously (23-200 mg/m²/24 h; 1 to 4 times a day). In 1993, Helbock et al. described 6 hypotensive, premature babies (25 to 26 weeks' gestation) and treated initially with 0.1-1 mg of hydrocortisone endovenously, followed by 1.5 to 6 mg/day. All patients showed significant increase in arterial pressure.

In a retrospective study, Fauser et al., in the same year, showed that 8 hours after a single dose of dexamethasone (0.25 mg/kg) it was possible to terminate infusion of adrenaline in eight, 450-1,020-g babies. Reynolds and Hanna reported the use of dexamethasone in hypotensive babies at 0.2 mg/kg/day. These authors observed an increase in arterial pressure and urinary output (referência errada). In 1994, Derleth administered dexamethasone at doses as low as 0.03 mg in 12-hour intervals. Results indicated improvement in arterial pressure, diuresis, and pulmonary function of hypotensive newborns.

Bourchier and Weston, in 1997, compared the use of dopamine with hydrocortisone for the treatment of hypotensive very low birthweight infants (less than 1,500 g). The dosage administered was of 2 doses of 2.5 mg/kg with a 4-hour interval, subsequent doses at every 6 hours (for 48 hours), followed by 1.25 mg/kg for another 48 hours, and, finally, 0.625 mg/kg for the last 48 hours. The authors concluded that both dopamine and hydrocortisone are effective in the treatment of hypotensive very low birthweight infants. Sasidharan reported the use of dexamethasone in hypotensive adrenaline in eight, 450-1,020-g babies. Reynolds and Hanna reported the use of dexamethasone in hypotensive babies at 0.2 mg/kg/day. These authors observed an increase in arterial pressure and urinary output (referência errada). In 1994, Derleth administered dexamethasone at doses as low as 0.03 mg in 12-hour intervals. Results indicated improvement in arterial pressure, diuresis, and pulmonary function of hypotensive newborns.

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c) Recommendations

The administration of dexamethasone is recommended for newborns with hypotension associated with manifestations of adrenal insufficiency (hypoglycemia and hyponatremia). We recommend the use of dexamethasone for the treatment of these patients, both due to the proven efficacy of, and larger clinical experience with the drug as compared to hydrocortisone in the neonatal period. The initial dosage should be 0.1 mg/kg at every 12 hours for 3-5 days. There is no need for slow weaning if the drug is administered for less than 7 days.
5. Airway obstruction

The endotracheal tube is a foreign body that may injure the upper airway causing laryngeal edema. This in turn may result in failure of extubation in preterm infants. Tightly-fit endotracheal tubes, prolonged duration of mechanical ventilation, and repeated reintubations can lead to subsequent subglottic stenosis. Corticosteroids have been used prophylactically in order to reduce airway obstruction and facilitate extubation.

Most studies have reported a trend in reduction of reintubation in newborns, but they do not show a beneficial effect in relation to post-extubation stridor. This reduction is more evident in babies with prolonged duration of endotracheal intubation or who were repeatedly reintubated.

a) Therapeutic approach

The most commonly used therapeutic approach involves administration of at least one dose of dexamethasone prior to extubation. Ferreram et al. reported the use of a single dose of dexamethasone (0.25 mg/kg) before extubation. Couser et al. administered one 0.25 mg/kg dose of dexamethasone 4 hours before extubation. The authors followed with 3 other doses at 8-hour intervals and showed a reduction in stridor of patients treated with dexamethasone. Studies with older children reported the use of 0.5 mg/kg in 6-hour intervals for a total of 6 doses. These treatments were started 6 to 12 hours before extubation.

b) Recommendations

Considering the short- and long-term side-effects in premature newborns, we recommend that preextubation use of steroids be restricted to babies with high risk for upper airways lesion. In other words, for babies with repeated failed extubation due to proven airway edema. We recommend a 0.1 mg/kg dosage of dexamethasone in 12-hour intervals, for a total of 4 doses; treatment should be started 12 hours before extubation.

6. Adverse effects of the use of corticosteroids

a) Common side-effects

Metabolic side-effects are among the main short-term effects, out of which hyperglycemia is very important. The incidence of hyperglycemia in premature babies treated with dexamethasone can be as high as 52%. The need for insulin, in turn, can be as high as 30% of cases. Dexamethasone has also been associated with hypertriglyceridemia (with hyperinsulinemia) and increase in free fatty acid (FFA) levels in premature babies.

Finally, changes in arterial pressure have been frequently reported with the administration of corticosteroids. The incidence of hypertension in premature babies receiving dexamethasone can vary from 40 to 80%.

b) Neurosensorial development and steroids

Many neonatologists are surprised by the fact that the evidence indicating that use of corticosteroids is potentially malefic for newborns is older than the clinical use of the drug. In 1968, Howard showed the effects corticosterone therapy in the brain of rats when administered during the first 2 weeks of life. The author described interference in the synthesis of DNA, RNA, and proteins.

Currently, there are various studies describing the negative effects of these drugs on neurological development when administered to newborns. The sequelae observed are possibly secondary to the effect of glucocorticoids during critical periods of brain development. Among other things, corticosteroids can affect myelination and mitosis of neurons resulting in long-term effects.

Papile and colleagues reported a significant reduction in somatic growth and head circumference in premature babies treated with dexamethasone. Others have raised the hypothesis that learning difficulties and cognition in low birthweight newborns is related to neonatal corticosteroid treatment.

Various recent studies describe sequelae related to neonatal corticosteroids. The results indicated that physical growth, mental development, neuromotor function, and intelligence quotient were affected in babies submitted to postnatal administration of steroids.

Fitzhardinge and colleagues reported in a follow-up study with 24 babies that those who received steroids had an increased tendency to present neurological and electroencephalographic abnormalities and other neuropsychomotor development at 1 year of age. Yeh et al. concluded that babies who received dexamethasone during the neonatal period presented a higher incidence of neuromotor dysfunction and lower psychomotor development scores at 2 years of age. Doyle and colleagues showed a higher incidence of cerebral palsy, blindness, and low IQ in a group of 120 children examined at age 5 years. These children had received dexamethasone or hydrocortisone after the first week of life for approximately 4 weeks (average of 27 days).

b) Other effects

In addition to the discussed side-effects, the use of corticoids in newborns can result in gastrointestinal hemorrhage, perforated gastric ulcer, intestinal perforation, increase in risk for infection, hypernatremia, myocardial hypertrophy, poor weight gain, suppression of the hypothalamic-pituitary-adrenal (HPA) axis, which can last up to one month after the treatment.
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Correspondence:
Dr. Jaques Belik - Professor of Pediatrics
University of Calgary - Foothills Medical Center
Room C211, 1403 - 29th Street NW
Calgary, Alberta T2N 2T9 - Canada
Phone: (403) 670.1615 / Fax: (403) 670.4892
E-mail: jbelik@ucalgary.ca