Accepted February 2014

REVIEW

Postnatal corticosteroids for the prevention of bronchopulmonary dysplasia

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Keywords – **Bronchopulmonary dysplasia (BPD), postnatal corticosteroids**

Abstract

Bronchopulmonary dysplasia (BPD) remains a common complication of preterm birth with long term substantial consequences. The administration of postnatal corticosteroids in an attempt to attenuate the chronic lung injury is still a matter of ongoing debate after more than 30 years of research. Systematic reviews of the available randomised controlled trials (RCTs) have shown that administration of the main investigated corticosteroid, dexamethasone, is beneficial for short term pulmonary morbidity and mortality, but concerns about long term neurodevelopmental sequelae have resulted in recommendations of restricted use. Although these systematic reviews pool the results of the RCTs as they were homogeneous, they are hampered by clinical heterogeneity in terms of investigated cumulative dosage regimens. In this review, we will discuss the clinical consequences of the changes in prescribing postnatal steroids in this high risk population and provide new evidence on the modulating effects of the heterogeneity within the trials. Finally, we will discuss alternative strategies for the administration, the subtypes of postnatal corticosteroids and future research perspectives.

Introduction

Bronchopulmonary dysplasia

The implementation of antenatal glucocorticoids, postnatal surfactant therapy, new modalities of respiratory support and nutritional intervention in perinatal and neonatal care have led to increased survival in the lowest birth weight infants. However, this improved survival is associated with high rates of short term morbidities and long term neurodevelopmental sequelae, of which bronchopulmonary dysplasia (BPD) continues to be the most important complication.[1,2] Despite the above advances in neonatal care, the prevalence of BPD has shifted little, although both the etiology and clinical picture of BPD have changed over recent decades.

The first description of BPD by Northway et al. in 1967 was one of severe lung injury in relatively mature preterm infants, who were ventilated with high pressures and high concentrations of oxygen, before the advent of surfactant therapy.[3] This so-called classical BPD is characterized by profound lung parenchymal inflammation, fibrosis and muscle hypertrophy and diffuse airway damage.[4]

The classical form of BPD is rarely seen in infants exceeding a birth weight of more than 1200 grams and 30 weeks of gestational age.[5,6] Treatment and survival of the very young has led to a new pattern of lung injury.[7,8] This so-called new BPD is mainly seen in very preterm infants with a gestational age of less than 30 weeks. It is characterized by an arrest in lung development with fewer and larger alveoli, and less striking fibrosis and inflammation.[9,10]

Due to the recognition of this new entity, the timing of assessment of BPD diagnosis shifted from 28 days postnatal age to 36 weeks postmenstrual age.[11] Cohort studies showed that the latter timing of diagnosis determined the long term pulmonary and neurological outcome superior to the old definition.[12]

Incidence and health burden of BPD

In the Netherlands, less than one percent of live born infants are born with a gestational age under 30 weeks and/or a birth weight less than 1250 g, resulting in more than 1000 of these preterm infants at the highest risk of developing BPD each year.[13,14] Unfortunately, exact data on the incidence of BPD in the Netherlands are lacking, but published international cohort studies show incidences of approximately 23% in infants born at 28 weeks, increasing to 73% in infants born at 23 weeks.[1,15]

BPD is characterized by extended respiratory support, a compromised lung function during a prolonged primary hospitalization for several months and recurrent respiratory infections during the first years of life, as well as long term

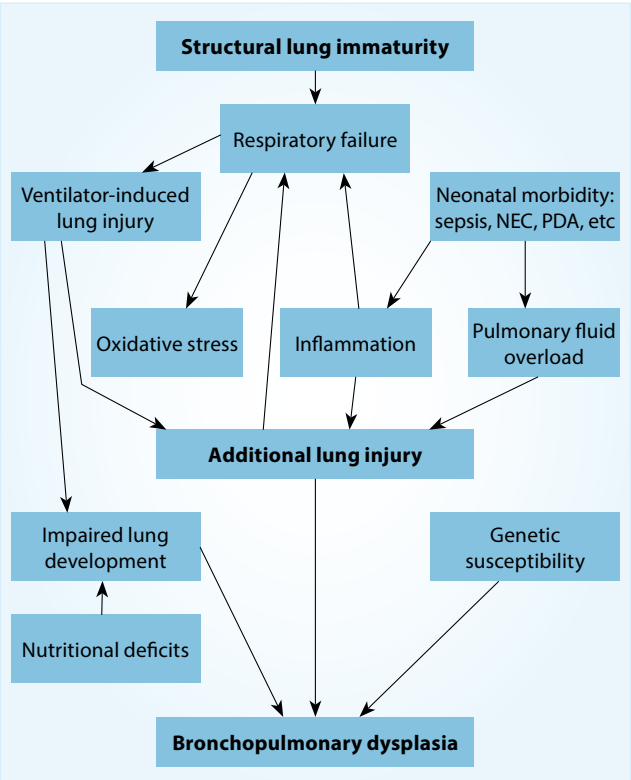
pulmonary morbidity into adolescence.[16-19] Furthermore, and of even more importance, patients with established BPD are at high risk of cerebral palsy (CP) and developmental delay as BPD has repeatedly been shown to be an independent risk factor for adverse neurodevelopmental outcome with a high correlation between these adverse outcomes and the severity of the condition.[12,20-22]

BPD is considered a multifactorial disease, where as well as genetic susceptibility, intrauterine growth restriction, nutritional deficits, direct mechanical injury caused by artificial ventilation, oxygen toxicity and pulmonary inflammation have been identified as important causes of its development, thus explaining the rationale of using antenatal and postnatal corticosteroids (*figure 1*).[5,6,23,24]

Evidence for postnatal corticosteroid therapy

Pulmonary inflammation plays a central, modulating role in the pathogenesis of BPD and glucocorticoids have a strong anti-inflammatory effect, making them an ideal candidate for attenuating the inflammatory response associated with BPD: the rationale of glucocorticoids seems justified. However, after 30 years of research, the administration of corticosteroids for the prevention and treatment of BPD in preterm infants is still one of the most controversial and ongoing hot topics in neonatology.

Figure 1. Pathogenesis of bronchopulmonary dysplasia. NEC necrotising enterocolitis; PDA persistent ductus arteriosus.



International recommendations

In the mid 1990s RCTs clearly showed that systemic corticosteroids, mainly dexamethasone, significantly reduced the incidence of BPD and the combined outcome BPD and death, in preterm infants at risk.[25,26] Systematic reviews including all these RCTs divided the therapy according to the timing of starting administration, being early (<96 hr), moderately early (7-14 days) or late (>3 weeks) onset.[27-29]

All these reviews showed a significant reduction in the combined outcome mortality and BPD at 28 days postnatal age and 36 weeks PMA in the group of patients receiving systemic corticosteroids compared to placebo, regardless of the timing of administration. Furthermore, the treated infants could be extubated earlier. However, these beneficial effects were at the cost of short term transient adverse effects, such as hyperglycemia, gastrointestinal bleeding, gastrointestinal perforation and hypertension.

This led to the belief that glucocorticoids could be the "magic bullet" for the treatment of preterm infants at high risk of BPD. As a consequence, 25-50% of all extreme preterm infants were treated with glucocorticoids in the late 1990s.[30,31]

However, the international view on postnatal corticosteroids changed after the publication of the first reports on long term neurodevelopmental outcome into a stigma of "misguided rockets" for these trials showed an association with increased risk of abnormal neurological development.[32,33] The results of the systematic reviews divided by the timing of administration were not as consistent on this outcome as they were on the beneficial pulmonary outcome.[34,35] The meta-analysis of trials investigating glucocorticoid therapy at an early onset showed a significant increase in adverse long term neurological development, such as cerebral palsy (CP), neurological exams and developmental delay.[34] In contrast, the reviews on moderately early and late administration (>seventh day of life) did not show any difference between the treated patients and the placebo group.[35]

In response to these reports, the American Academy of Pediatrics, the Canadian Pediatric Society and the European Association of Perinatal Medicine, concluded that routine use of systemic dexamethasone in the treatment of BPD could no longer be recommended until further research had established the optimal type, dose and timing of corticosteroid therapy.[36,37] Furthermore, this recommendation was recently affirmed in a publication stating that current evidence is insufficient to recommend other corticosteroid doses and preparations.[38]

Changes in BPD incidence

The international neonatal community has discarded the use of early postnatal glucocorticoids completely for the above reasons and is therefore not a subject for this review. Regarding the use of moderately early or late postnatal systemic glucocorticoids, clinicians encounter a dilemma facing those

patients at high risk of BPD, since BPD is associated with an increased risk of adverse neurological outcome itself.[12] The debate is still ongoing that BPD is a direct cause of adverse long term neurological outcome or an indirect sign of increased systemic inflammatory status leading to that adverse outcome. A systematic review using meta-regression showed that the adverse effects of moderately early or late administrated postnatal glucocorticoids on long term neurodevelopmental outcome might be modified by the BPD risk.[39] However, in line with the current opinion of postnatal corticosteroids being "misguided rockets", clinicians postpone its administration until the third to fourth week of postnatal life, lowering the dosage schedule of dexamethasone or changing to alternative corticosteroids without knowing the effect of this policy change on the benefit to risk ratio.

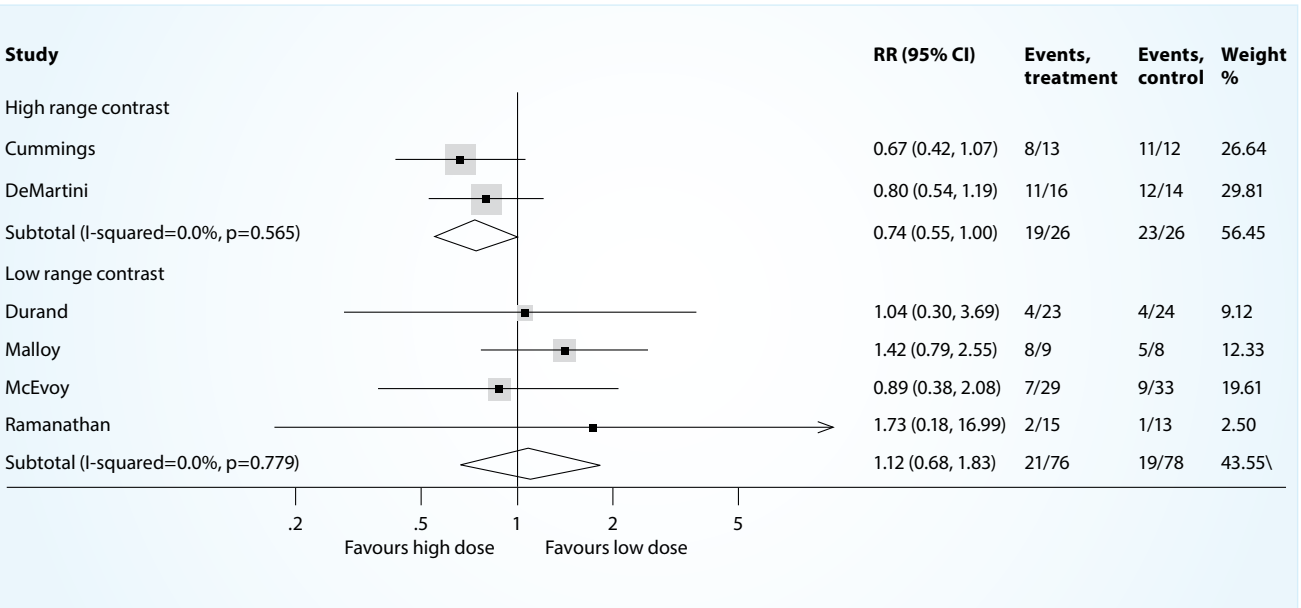
Several cohort studies have been performed including cohorts of high risk preterm infants divided in periods before and after the published international recommendations on the restricted use of postnatal corticosteroids.[40-42] These studies showed that with a decline in the use of postnatal corticosteroids, the incidence of BPD increased. Furthermore, approximately ten percent of preterm infants are still being treated with this therapy, where the clinician faces the dilemma on which treatment, with what cumulative dose (daily dose times duration of therapy) or duration itself, the patient will have the optimum benefit to risk ratio.[30]

New insights

Lowering the dose: head-to-head comparison

In order to determine what the effects are of lowering the cumulative dose of dexamethasone to minimize the adverse effects, we first performed a systematic review, of all RCTs comparing head-to-head a higher versus a lower dosage regimen of dexamethasone in ventilated preterm infants.[43] Patients who participated in these trials received steroids so that these were not placebo controlled trials. Six studies enrolling a total of 209 participants were included; two studies contrasted the cumulative dexamethasone dose in the higher ranges (>2.7 mg/kg in the higher dose regimen) and four in the lower ranges (≤2.7 mg/kg in the higher dose regimen). Meta-analysis revealed no effect of dexamethasone dose on mortality and neurodevelopmental sequelae in these two subgroups. Subgroup analysis of the studies contrasting the dexamethasone dose in the higher ranges showed that the highest dose of dexamethasone was more effective in reducing BPD than the lower dose (typical relative risk (TRR) 0.67; 95% confidence interval (CI) 0.45, 0.99; *figure 2*). These data suggested that a reduction in dexamethasone dose might increase the incidence of BPD without decreasing the risk for adverse neurodevelopmental outcome. However, the validity of this observation is compromised by the small sample of randomised children, heterogeneity on study populations and designs, the use of late rescue corticosteroids and the lack of long term neurodevelopmental data in some studies.[43]

Figure 2. Meta-analysis of the combined outcome death and BPD at PMA of 36 weeks. High-range contrast indicates trials using cumulative dexamethasone doses in the higher ranges (≥ 2.7 mg/kg in the higher-dosage regimen). Low-range contrast indicates trials using cumulative dexamethasone doses in the lower ranges (≤2.7 mg/kg in the higher-dosage regimen). Each dot is relative risk (RR) of one study. The size of the shaded square indicates the weight of the study in the meta-analysis. The horizontal line indicates the 95% confidence interval (CI). The diamond indicates the subtotal of the studies shown above (meta-analysis), the centre being the typical RR and the distance between the extremes (left and right) being the 95% CI. The arrow in the study by Ramanathan et al.[59] indicates that the 95% CI exceeds the scaling of the RR shown at the bottom. The vertical line indicates a RR of one (no difference).



Lowering the dose: revisiting the placebo controlled RCTs

To further determine the effects of lowering the dexamethasone, we re-analyzed the known placebo controlled dexamethasone trials initiating therapy after the first week of life. The known reviews stacked information from trials with tremendous clinical heterogeneity in their cumulative dose and duration of therapy, and timing of therapy onset.[35] Using this clinical heterogeneity, we divided the different RCTs into subgroups and performed meta-regression according to the used cumulative dexamethasone dose to determine the effect modification of these variables.

This systematic review included sixteen trials randomising 1,136 patients. Trials with a moderately early (7-14 days) or delayed (>3 weeks) postnatal treatment onset were analyzed separately.[44] Meta-analyses of the subgroup showed that higher dexamethasone doses reduced the TRR for the combined outcome mortality or bronchopulmonary dysplasia, with the largest effect in trials using a cumulative dose above 4 mg/kg (moderately early TRR 0.57; 95% CI 0.39,0.84; delayed TRR 0.75; 95% CI 0.60,0.93; *figure 3*). No effect was found of doses on the risk of neurodevelopmental sequelae in the delayed treatment studies, but in the moderately early treatment studies the risk of mortality or cerebral palsy decreased by 6.2% (95% CI -11.1%,-1.3%), and the risk of a mental developmental index below -2SD decreased by 6.6% (95% CI -13.0,-0.2) for each incremental mg/kg cumulative dexamethasone dose (*figure 4*). Higher cumulative dexamethasone doses administered after the first week of life may decrease the risk for BPD without increasing the risk for neurodevelopmental sequelae in ventilated preterm infants. Even more striking was the finding that in the moderately early treatment studies, the risk of neurodevelopmental sequelae was decreased for each incremental mg/kg cumulative dexamethasone dose.[44]

At present we can only speculate on the possible mechanisms for this time dependent effect of dexamethasone therapy on neurodevelopmental outcome. First, as suggested by animal data, the direct effect (beneficial or harmful) of dexamethasone on the brain might differ depending on the postnatal age of exposure.[45] Second, the effect of dexamethasone on the pulmonary condition and outcome (i.e. BPD), may also indirectly affect neurodevelopmental outcome. Protracted mechanical ventilation has been shown to be an independent risk factor for neurodevelopmental sequelae.[20] As starting dexamethasone in the moderately early time frame will almost certainly reduce the time on mechanical ventilation compared to delayed treatment, it may thus reduce the risk for CP. A recent study in preterm baboons showed that a difference as small as five days of mechanical ventilation already results

Figure 3. Overall and subgroup meta-analysis of the combined outcome mortality or BPD at 36 weeks PMA in the moderately early treatment studies. CD indicates cumulative dosage. A) Cummings et al.[60] dexamethasone arm with cumulative a dose of 3.0 mg/kg versus placebo; B) Cummings et al.[60] dexamethasone arm with a cumulative dose of 7.8 mg/kg versus placebo.

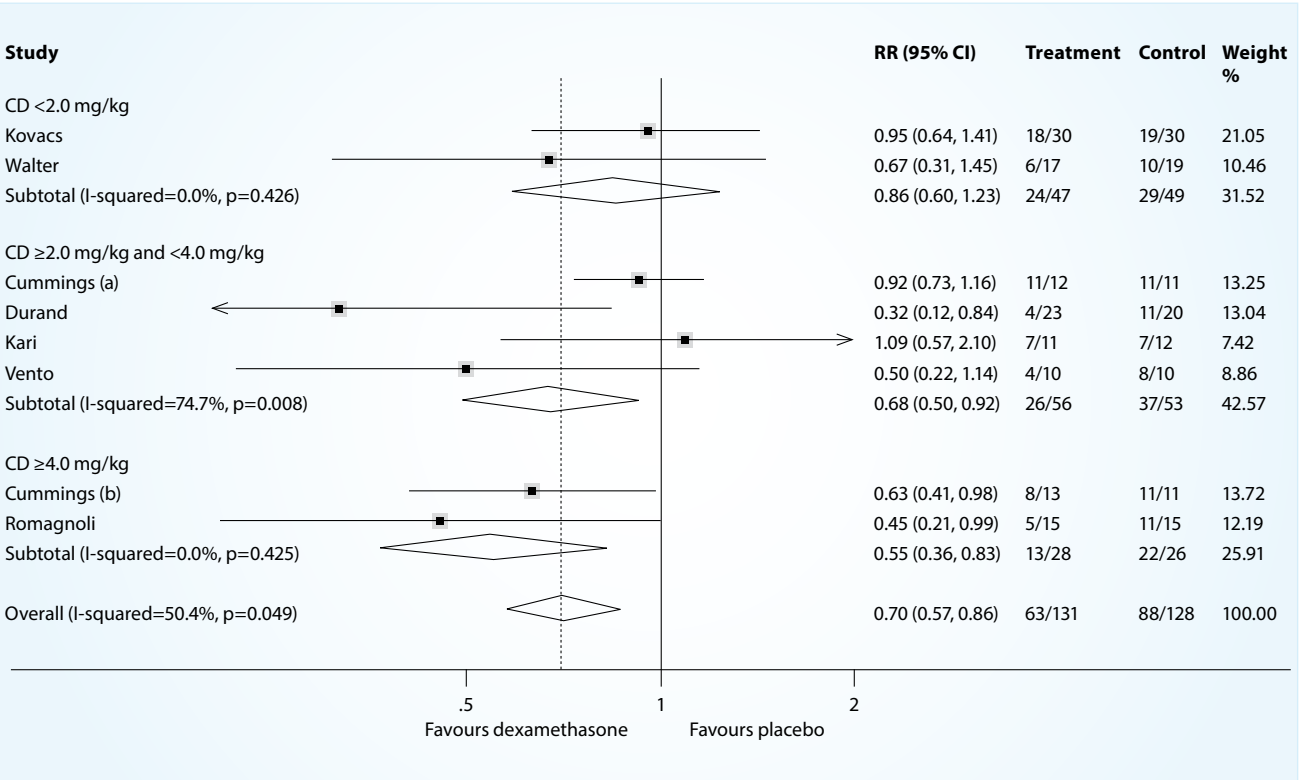
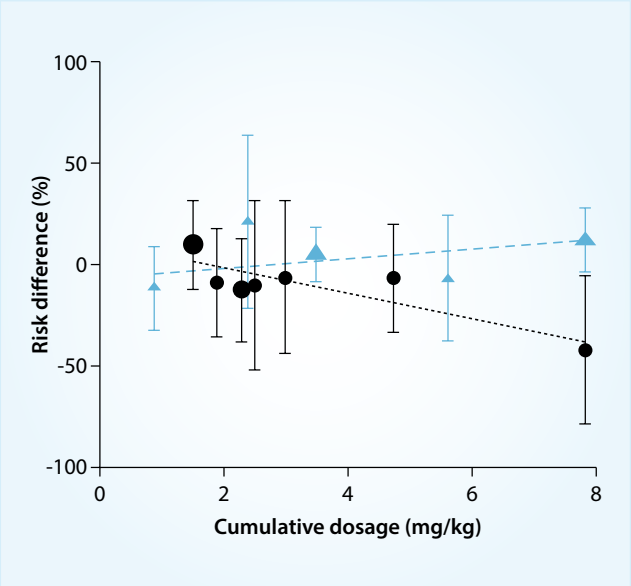


Figure 4. Meta-regression analysis and meta-analysis of the cumulative dexamethasone dose (CD) and the effect on the combined outcome mortality or CP. Shown are regression lines for moderately early (circles and dotted line) and delayed (triangles and hatched line) trials. The scale of the symbols represents the calculated weight in the pooled estimate.



in a decreased brain growth and the presence of subtle brain injury.[46]

In addition to mechanical ventilation, BPD itself is an important independent risk factor for CP.[47] Therefore, reducing the incidence of BPD, when starting dexamethasone treatment moderately early, might, in part, explain the time dependent (moderately early vs delayed) effect of dexamethasone on CP.

Considering these mechanisms in combination, it might well be that a direct negative effect of dexamethasone on the brain is overridden by the indirect beneficial effect mediated via a reduction in time on mechanical ventilation and the incidence of BPD.

Alternative administration corticosteroid therapy

Given the above mentioned concerns on adverse neurodevelopmental sequelae with systemic administration of corticosteroids, local administration via the inhalation route might be an effective and safe alternative. However, the updated Cochrane review, which identified eight RCTs initiating therapy ≥ seventh day of life, randomising 232 preterm infants showed a paucity of data on short term and long term adverse effects, and furthermore, the included trials differed considerably in patient characteristics, inhalation therapy and outcome definitions.[48] The sparse meta-analyses that could be done showed that inhaled glucocorticoids did not reduce the separate or combined outcomes of death or BPD, or have beneficial effects on short term respiratory outcomes such as failure to extubate and total duration of mechanical ventilation or oxygen dependency, although there was a trend to a reduced use of systemic glucocorticoids in favour of inhalation corticosteroids. Based on these results the use of inhalation glucocorticoids initiated at ≥7 days of life for preterm infants at high risk of developing BPD cannot be recommended at this point in time.[48]

Alternative type of corticosteroids

The same concerns for the long term neurodevelopmental outcomes for administrating dexamethasone have led to the introduction of alternative anti-inflammatory corticosteroids, such as hydrocortisone. Animal studies have suggested that, in contrast to dexamethasone, hydrocortisone has no detrimental effect on the brain.[49] Historical cohort studies have suggested that hydrocortisone treatment is equally effective in reducing death or BPD compared with infants treated with dexamethasone without causing an increased risk of adverse neurological outcome.[50,51,52,53]

To date, eight RCTs including 880 infants have investigated a low hydrocortisone dose started within <72 hours after birth (early treatment onset) without a clear reduction in the incidence of death or BPD.[54] Only one of these trials reported long term follow-up, showing no differences in adverse neurodevelopmental sequelae.[55]

No placebo controlled randomised trials have investigated the use of hydrocortisone after the first week in life in ventilator-dependent preterm infants. However, more and more NICUs in the Netherlands are switching from using dexamethasone to hydrocortisone, despite the lack of evidence that hydrocortisone is effective and safe. For that reason, the SToP-BPD trial was designed and is currently recruiting.[56] It is a randomised double blind placebo controlled study in preterm infants, who are ventilator-dependent at a postnatal age of 7-14 days and have a suspected diagnosis of developing BPD. Compared to the early RCTs using a low dosage regimen, the investigated regimen of hydrocortisone has a cumulative dose 72.5 mg/kg and will be administered during a 22 day tapering schedule. Randomising patients into placebo seems justified, since at a global level, neonatologists are not willing to initiate steroids in the second week of life, but only as a rescue therapy in the third or fourth week of life. At the end of 2015 this trial will have determined the role of postnatal hydrocortisone administration at a moderately early onset in ventilator-dependent preterm infants.

Future perspectives based on current evidence

The cohort studies showing an increase of BPD incidence with the decreasing use of postnatal corticosteroids, the findings of the above-mentioned head-to-head comparison of a higher versus lower dosage regimen, as well as the subgroup and meta-regression analyses of the placebo controlled trials all

suggest that the current recommendations of lowering the dose and the duration of postnatal corticosteroids might not be in the best interest of preterm infants at high risk of BPD. However, we would like to emphasize that these underpowered or indirect suggestions of evidence should be confirmed in randomised controlled trials.

A large multicenter study, comparing a higher cumulative dexamethasone dose (≥4 mg/kg) with a lower dose (≤2 mg/kg) using a comparable duration of treatment at moderately early onset, is urgently needed. The clinical community should decide if there is still room for a placebo arm in such a trial. Such a trial should be adequately powered to detect small but clinically relevant treatment effects. Dilution of treatment effect due to the use of corticosteroids outside the study protocol, or crossing over between trial arms should be avoided as much as possible. Data should be analyzed on an intention-to-treat basis, per-protocol, and in an adherers-only analysis in order to accurately estimate the true effect of dexamethasone treatment on the clinical outcome parameters.

Second, future research should focus on the optimal aerosol delivery system for the administration of inhaled glucocorticoids in ventilated and non-ventilated infants, which is quite a challenge since preterm infants have low tidal volumes and functional residual capacity, high respiratory rates, a shortened particle residence time and in general smaller airway diameters.[57] A large RCT administrating inhaled corticosteroids at an early onset is currently recruiting patients,[58] whereas in the Netherlands and Belgium the SToP-BPD trial will provide data on the use of hydrocortisone at a moderately early onset in the near future.

Conclusions

These new systematic reviews on postnatal corticosteroids using subgroup meta-analyses and meta-regression show that the current practice of lowering the cumulative dose of dexamethasone in preterm infants does not result in a better benefit to risk ratio, but instead diminishes the positive effects on the incidence of the combined outcome death or BPD without lowering the adverse neurodevelopmental sequelae. Furthermore, it confirms that the optimal timing of therapy onset is between seven and fourteen days of postnatal life.

Finally, we show that there is no evidence to support the use of the alternative method of administration (i.e. inhalation glucocorticoids) or alternative drugs, namely hydrocortisone to prevent the development of BPD in high risk preterm infants.

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