The Egyptian Journal of Hospital Medicine (October 2017) Vol. 69 (8), Page 3144-3153

Postnatal Corticosteroids to Treat or Prevent Bronchopulmonary Dysplasia in Preterm Infants

Alsuhaymi Zuhair Hamdan A [1], Zamil Mufleh Al-Wahbi [2], Abdulmohsen Abdulkarim Alanazi [3], Zayed mohammed Z Al Almathlma [4], Samar Osama Mohamed Mahmoud Kassem [5], Faisal Ali A Alotaibi [6], Ghadi abdullah Aljehani [7], Mushari Aber F Alonazi [8], Abdulrahman Sulaiman I Alshudokhi [9], Alanoud Thamer Al Drasouny [10], Fatimah Fayiz Alghanim [11], Toqa Eissa Aljowaid [7]

1- Mikhwah General Hospital, 2- Khamis Mushait Maternity & Children Hospital (KMMCH), 3- King Abdullah Bin Abdulaziz University Hospital, 4- Mohayil General Hospital , 5- Umm Al Qura University , 6- Taif University , 7- Ibn Sina College , 8- Aljouf University , 9- Alfaisal University , 10- Almaarefa Colleges For Science And Technology , 11- Imam Abdulrahman Bin Faisal University

ABSTRACT

Background: The lungs of particularly newborn are fragile and can be easily damaged. With injury, scarring may follow which is translated into difficult breathing and increased oxygen needs, a condition called bronchopulmonary dysplasia (BPD) or Chronic Lung Disease (CLD). Since inflammation plays an important role in the pathogenesis of CLD, corticosteroids, especially dexamethasone, have been extensively used to avert or treat CLD. Thus, several studies suggest that systemic corticosteroids decrease the duration of ventilator dependence.

Aim of the Study: investigate the beneficial and harmful effects of the use of steroid in the prevention and treatment of BPD.

Methods: A systematic review and meta-analysis of observational studies and randomized controlled trials was conducted. A review of the scientific literature. Pubmed, Embase and Central were searched to identify randomized controlled trials that investigated postnatal corticosteroids treatment for BPD were the primary endpoints. Identification of papers and data extraction were performed by two independent researchers. We searched for relevant trials in the Cochrane Library, MEDLINE (from 1955), Embase (from 1970), the Transfusion Evidence Library (from 1980), and ongoing trial databases; all searches current to September 2017.**Results:** The search yielded seven RCTs which enrolled a total of 1862 participants eligible for inclusion in the present review. There were significant beneficial outcomes such as lower rates of failure to extubate and decreased risks of chronic lung disease at both 28 days (RR 0.84, 95% CI 0.83 to 0.87) and 36 weeks' postmenstrual age (RR 0.77, 95% CI 0.72 to 0.84), death or chronic lung disease at 28 days (RR 0.9, 95% CI 0.85 to 0.96) and 36 weeks' postmenstrual age (RR 0.91, 95% CI 0.87 to 0.96). Nevertheless, there were no significant differences in the rates of neonatal mortality (RR= 1.06, 95% CI 0.93, 1.26), periventricular leukomalacia (RR 1.16, 95% CI 0.9 to 1.46), necrotizing enterocolitis or pulmonary haemorrhage (RR 1.21, 95% CI 0.83 to 1.62). In contrast, gastrointestinal bleeding (RR 2.13, 95% CI 1.41 to 2.84) and intestinal perforation (RR 1.77, 95% CI 1.46 to 2.1) were imperative adverse effects. Moreover, many adverse neurological effects were found at follow-up examinations, including developmental delay (RR 1.72, 95% CI 1.4 to 2.05) and cerebral palsy (RR 1.56, 95% CI 1.03 to 2.1). Additionally, the rates of the combined outcomes of death or cerebral palsy (1.92, 95% CI 1.18 to 2.67), or of death or major neurosensory disability (RR 1.25, 95% CI 0.98 to 1.53), were not significantly increased. In subgroup analyses by type of corticosteroid, most of the advantageous and disadvantageous effects were related chiefly to dexamethasone whilst hydrocortisone had slight effect on any of the outcomes except for an increase in intestinal perforation and a borderline reduction in patent ductus arteriosus. The overall risk for bias was low as all were RCTs using robust methods.

Conclusion: despite the fact that early corticosteroid treatment can have beneficial outcome for BPD management through facilitation of extubation and decreasing the risk of chronic lung disease and patent ductus arteriosus, it ,on the other hand, results in short-term adverse effects including gastrointestinal bleeding, intestinal perforation, hyperglycaemia, hypertension, hypertrophic cardiomyopathy and growth failure.

Clinicians should carefully assess the risks of a short course of glucocorticoid therapy to mitigate BPD for premature neonates such that an individualized decision should be made in conjunction with the infant's parents.

Received: 11/09/2017 DOI: 10.12816/0042866
Accepted: 21/09/2017

Keywords: Bronchopulmonary dysplasia, chronic lung disease, premature neonates, infants, corticosteroids, BPD, dexamethasone.

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is pathological condition interchangeably used with chronic lung disease (CLD) that develops in preterm neonates treated with oxygen and positive-pressure ventilation. The pathogenesis of this condition remains complex and poorly understood; however various factors can not only injure small airways but also interfere with alveolarization (alveolar septation), leading to alveolar simplification with a reduction in the overall surface area for gas exchange. The developing pulmonary microvasculature can also be injured [(1)](**Figure 1).**

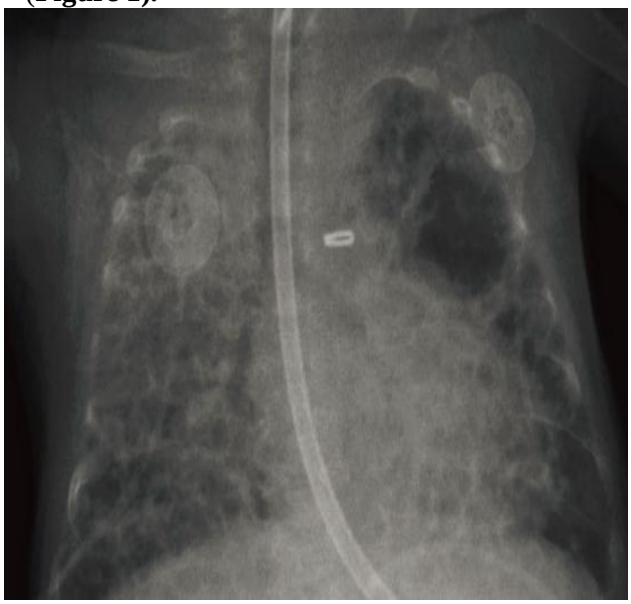

Figure 1: Chest radiograph of infant with bronchopulmonary dysplasia[(1)].

CLD was in the past defined as oxygen requirements beyond 28 days with abnormal x-ray [(2)]. However, a more meaningful definition in the current era is respiratory support (supplemental oxygen or CPAP in air) beyond 36 weeks post-conceptual age [(3)].

CLD is associated with low lung compliance, increased pulmonary resistance and increased energy used for breathing result in: exacerbations due to respiratory infections in first year of life, especially with RSV resulting in increased incidence of rehospitalisation , pulmonary hypertension if adequate oxygen is not maintained (with subsequent cor pulmonale and death), Increased incidence of bronchial hyper-reactivity [(4)], Minimal functional abnormalities at long term follow up [(5)]. Longer stay in hospital, persistent oxygen and ventilation requirements.

BPD have significantly worse developmental outcomes including poorer cognitive outcomes, more developmental delays and higher rates of learning disabilities even after adjustment for confounding[(6)]. It is not clear to what extent CLD causes the sequelae, or to what extent the problem leading to CLD (eg infection) caused the sequelae [(6)].

Increased incidence of growth failure (weight and stature) as a consequence of increased energy expenditure, abnormal sucking patterns and iatrogenic limitation of fluids [(4)].

New bronchopulmonary dysplasia (new BPD) is characterized, in part, by arrested alveolar and vascular development of the immature lung [(7)].Affected infants suffer from long-term pulmonary and nonpulmonary sequel. The pulmonary sequels include reactive airway disease and asthma during childhood and adolescence [(8)].Nonpulmonary long-term sequels include poor coordination and muscle tone, difficulty in walking, vision and hearing problems, delayed cognitive development, and poor academic achievement [(9)].
The proposed etiology of new BPD is the initiation of inflammatory mediators that cause impairment of alveolarization and vasculogenesis [(10)].The lacking anti-inflammatory mediators in the preterm neonate may be inundated easily by the proinflammatory cascade. A difference in the release of pro- and anti-inflammatory cytokines, occurring as a result of intrauterine/postnatal infection (sepsis), ventilator trauma, oxidants, pulmonary edema, or sepsis, damages the immature lung.

Corticosteroids are potent drugs which may improve lung function in infants with chronic lung disease by a number of different mechanisms. It has been suggested that they might have a role to play in the prevention of chronic lung disease by suppressing the inflammatory response in the lungs of infants at risk [(11)].It has also been shown that infants who develop chronic lung disease have low cortisol levels following adrenocorticotrophic hormone (ACTH) stimulation during the first week of life [(12)].To be effective in preventing chronic lung disease corticosteroids may have to be given within the first few days of life.

Various mechanisms have been described for beneficial effect of steroids on lung mechanics in infants with BPD. Various steroids of different potency have been studied at various timings; in different dosing regimens; for different duration; in different forms (including intravenous, inhalational, intratracheal, and recently intratracheal with surfactant as a vehicle). Amongst systemically used steroids, dexamethasone comes as the most potent and most studied one. It has been studied in early (<7 days), moderately early (7–14 days) and late/delayed (>14 days), postnatal periods and dosing ranging from 0.1 mg/kg/day to 0.5 mg/kg/day and duration ranging from 3 days to 42 days. Hydrocortisone comes second. Beclomethasone is the most commonly used inhalational steroid for BPD. Recently, budesonide has been tried as intratracheal instillation with or without surfactant as a vehicle and shown to reduce inflammatory marker in tracheal aspirates in initial clinical trials [(13)].

Corticosteroids are given either parenterally or enterally. It is not clear if early use of corticosteroids provides long-term benefits; nor is it clear that adverse neurological outcomes found in animal studies do not apply to the immature human newborn infant.

The present review is intended to examine the relative benefits and adverse effects of postnatal corticosteroids commenced to preterm infants at risk of developing chronic lung disease.

MATERIALS AND METHODS

Search methods

We carried out a systematic review for RCTs including postnatal corticosteroid therapy in neonates diagnosed as with BPD/CLD.

Data sources: Cochrane Library, MEDLINE (from 1955), Embase (from 1970), the Transfusion Evidence Library (from 1980), and ongoing trial databases; all searches current to September 2017. The search terms were used in combinations and together with the Boolean operators OR and AND. Search terms used were: "POSTNATAL CORTICOSTEROIDS", "BRONCHOPULMONARY DYSPLASIA", "C HRONIC LUNG DISEASES" ,"PRETERM INFANTS", "NEONATES". 782 articles initially matched the stipulated criteria and were included in the current review.

Study selection and criteria

Search results were screened by scanning abstracts for the following:

Inclusion Criteria

1. Randomized controlled trials (RCTs)and controlled clinical trials (RCTs)
2. Preterm infants at risk of developing chronic lung disease, including those who are ventilator-dependent.
3. Intravenous or oral corticosteroids versus control (placebo or no treatment). Trials of inhaled corticosteroids were not included in this review.

Exclusion criteria

1. Suspicion of congenital heart diseases, sepsis or pneumonia, chromosome abnormalities and those infants who received an exchange transfusion.
2. Incomplete outcome data.
3. Cased of deaths before 10 days of age.

STUDY OUTCOMES

Primary outcomes

- Chronic lung disease (including at 28 days, at 36 weeks' postmenstrual age and at 36 weeks' postmenstrual age in survivors)
- Mortality; death or chronic lung disease (at 28 days and 36 weeks' postmenstrual age)
- Long-term outcomes (including blindness, deafness, cerebral palsy and major neurosensory disability)

Secondary outcomes

- Failure to extubate
- Late rescue with corticosteroids (all infants and in survivors)
- Need for home oxygen therapy
- Complications during the primary hospitalisation (including infection, hyperglycaemia, hypertension, pulmonary air leak, patent ductus arteriosus, severe intraventricular haemorrhage, periventricular leukomalacia, necrotizing enterocolitis, gastrointestinal bleeding, intestinal perforation and severe retinopathy of prematurity)

Data extraction

Two reviewers independently reviewed studies, abstracted data, and resolved disagreements by consensus. Studies were evaluated for quality. A review protocol was followed throughout.

We sought information regarding the method of randomization, blinding, stratification, reporting of

the outcome of all the infants enrolled and whether the trial was single or multicentre. Information on the trial participants included birth weight, gestational age, severity of respiratory distress syndrome, need for mechanical ventilation and surfactant, and gender. We analyzed information on clinical outcomes for mortality, survival without chronic lung disease, chronic lung disease defined at 28 days and 36 weeks' postmenstrual age, failure to extubate, pneumothorax, infection, hyperglycaemia, hypertension, severe retinopathy of prematurity, patent ductus arteriosus, severe intraventricular haemorrhage, periventricular leukomalacia, necrotizing enterocolitis, gastrointestinal bleeding, intestinal perforation and need for late corticosteroid treatment, as well as long-term outcomes including blindness, deafness, cerebral palsy and major neurosensory disability.

For each study, one review author entered the final data into Review Manager (RevMan) 5 software (RevMan 2012) [14] and then a second review author checked for accuracy. We resolved discrepancies through discussion or by involving a third assessor.

We attempted to contact authors of the original reports to provide further details when information regarding any of the above was unclear.

Assessment of risk of bias in included studies

We used the standard method of the Cochrane Neonatal Group for assessing the methodological quality of the studies. The authors independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [15]. We resolved any disagreement by discussion or by including a third assessor.

The study was done according to the ethical board of King Abdulaziz university.

Statistical synthesis

Fixed-effect model was used for all meta-analyses [16].

We performed the analysis using RevMan 5 [14], supported by The Cochrane Collaboration. We used the Mantel-Haenszel method for estimates of typical risk ratio and risk difference. No continuous outcomes were included in this review. We analyzed continuous measures using the inverse variance method, if included.

Subgroup analysis and heterogeneity

We included subgroup analyses by the type of corticosteroid used (dexamethasone or hydrocortisone) where there were sufficient numbers of trials to make such subgroup analyses meaningful.

Sensitivity analysis

Sensitivity analyses were intended for situations where this might affect the interpretation of significant results (risk of bias related with the quality of some of the included trials or missing outcome data). We concluded that none were necessary in the present review.

RESULTS

Searches identified 782 publications in addition to another 16 publications that were found through manual research. After removal of duplicates, abstracts and titles 301 publications were assessed as identified from title and abstract, and 173 papers were excluded. 13 papers full text could not be retrieved and another 91 papers with the same cohort. There were also 69 papers excluded because they did not meet the study outcomes. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting the results

Finally, 7 studies were included and detailed as the focus for the present study. **Figure 1**

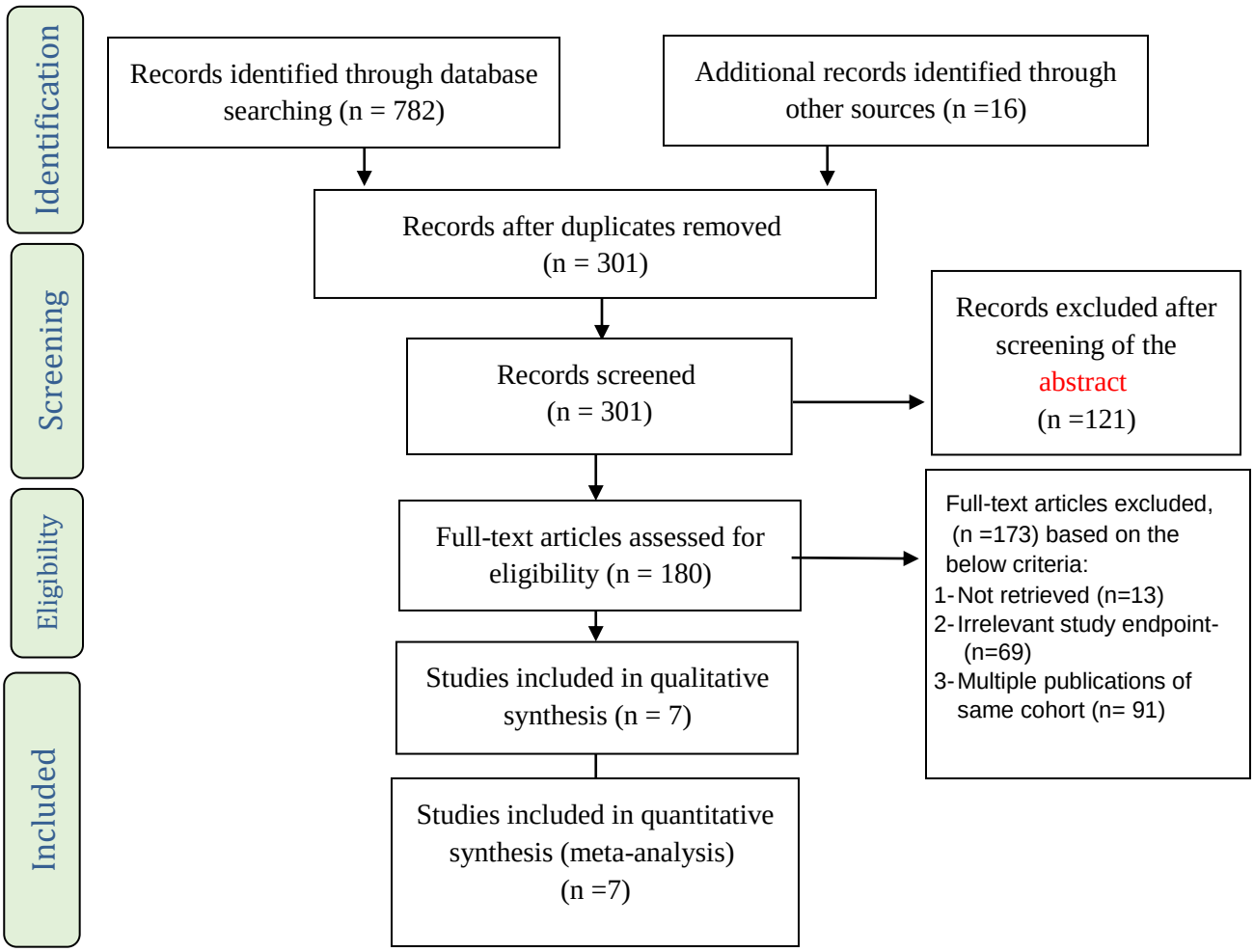

Figure 1: PRISMA flow diagram showing the selection criteria of the assessed studies [17].

Characteristics of included studies

Seven Studies met the inclusion criteria [18,19,20,21,22,23,24]

Most of the trials enrolled low birth weight infants with respiratory distress syndrome who were receiving mechanical ventilation. **Table 1**

Table 1 : baseline characteristics of the included studies

Authors	Year of study	Participants	Methods
Biswas *et al.* [18]	2003	253 infants < 30 weeks' gestation, within 9 hours of birth at entry; all mechanically ventilated	Multi-centre, placebo-controlled, randomised trial
Anttila *et al.* [19]	2005	109 infants with birth weight 500g to 999 g, gestation < 32 weeks, need for mechanical ventilation and supplemental oxygen by 4 hours of age. Stratified by weight (500 g to 749 g versus 750g to 999 g)	Multicentre, double-blind, placebo-controlled, randomised trial
Efird *et al.* [20]	2005	34 infants of gestation > 23 weeks and < 29 weeks, and birth weight > 500 g and < 1000 g enrolled by 2 hours of age Exclusions: major malformations, chromosomal abnormalities and congenital heart disease	Randomised, double-blind, placebo-controlled trial
Peltoniemi *et al.* [21]	2005	51 infants with birth weight 501 g to 1250 g, gestation 23 to 29 weeks, needing mechanical ventilation before age of 24 hours. The subgroup 1000 g to 1250 g had to need supplemental oxygen and mechanical ventilation > 24 hours despite surfactant Exclusions: lethal malformations or suspected chromosomal abnormalities	Multi-centre, double-blind, randomised controlled trial
Ng *et al.* [22]	2006	48 infants of gestation < 32 weeks and birth weight < 1500 g who had systemic hypotension despite treatment with volume expanders and dopamine within the first 7 days of life. Infants also had to have an indwelling arterial catheter for continuous BP monitoring	Double-blind, randomised controlled trial
Bonsante *et al.* [23]	2007	70 infants either < 1000 g birth weight or < 28 weeks' gestation, ventilator-dependent after 7 days of age and considered to be a candidate for corticosteroids	Two-centres, randomized, double-blind, placebo-controlled trial
Batton *et al.* [24]	2012	366 Infants 23 to 26 completed weeks' gestation with study-defined low blood pressure	Multicentre, randomized, placebo-controlled trial

The corticosteroid administered was usually dexamethasone and the most common treatment regimen was 0.50 mg/kg/day for three days followed by 0.25 mg/kg/day for three days, 0.12 mg/kg/day for three days and 0.05 mg/kg/day for three days. There was, however, considerable variation in treatment regimens, including short courses of one to two days and longer courses of up to four weeks. Nine studies used hydrocortisone.

Table 2: Studies' Intervention and Outcome

Authors	Year study	Interventions	Outcome
Biswas *et al.* [18]	2003	Hydrocortisone 1 mg/kg/day as continuous infusion for 5 days, then 0.5 mg/kg/day for 2 days. Also given tri-iodothyronine 6 µg/kg/day for 5 days, halving to 3 µg/kg/day for 2 days Controls given equal volume infusion of 5% dextrose	The primary outcome was death or ventilator dependence at 7 days, or death or oxygen dependence at 14 days Secondary outcomes included durations of ventilation, oxygen dependence and hospitalisation, oxygen dependency at 36 weeks, IVH, PVL, PDA and NEC
Anttila *et al.* [19]	2005	Exclusions: life-threatening congenital anomalies or known chromosomal anomaly	Survival to 36 weeks without IVH (grade III-IV), PVL (echodensities after 1st week or periventricular cysts on ultrasound) or BPD (oxygen at 36 weeks), growth, duration of assisted ventilation and oxygen, late corticosteroid treatment, infection, hyperglycaemia, hypertension, ROP, PDA, GI bleeding and perforation and NEC
Efird *et al.* [20]	2005	Hydrocortisone intravenously at dose of 1 mg/kg every 12 hours for 2 days, followed by 0.3 mg/kg every 12 hours for 3 days Control infants received an equivalent volume of normal saline as placebo	Blood pressure, urine output, hyperglycaemia, mortality, durations of mechanical ventilation and hospital stay, CLD (oxygen at 36 weeks), infection, NEC, intestinal perforation, PDA, IVH, PVL and cortisol levels
Peltoniemi *et al.* [21]	2005	Hydrocortisone 2.0 mg/kg/day intravenously 8-hourly for 2 days, 1.5 mg/kg/day 8-hourly for 2 days, 0.75 mg/kg/day 12-hourly for 6 days Control infants received isotonic saline as placebo. The first dose was given before 36 hours. Use of open-label corticosteroids was discouraged	Survival without BPD (oxygen at 36 weeks), IVH (grades III or IV), cystic PVL, durations of ventilation, oxygen and hospital stay, sepsis, hyperglycaemia, hypertension, PDA, GI bleeding, GI perforation, NEC, ROP and cortisol levels. Long-term outcomes: neurosensory impairments (blindness, deafness, developmental delay assessed by MDI on Bayley scales, cerebral palsy) and disabilities (severe - any of severe cerebral palsy (not likely to walk), blindness or severe developmental delay (MDI < 55, moderate - moderate cerebral palsy (not walking at 2 years but likely to do so), deafness, moderate developmental delay (MDI 55 to < 70), mild - mild cerebral palsy (walking at 2 years) or mild developmental delay (MDI 70 to < 85)
Ng *et al.* [22]	2006	Exclusions: major or lethal congenital or chromosomal abnormalities, congenital heart defects, previous postnatal systemic or inhaled corticosteroids, proven infection or NEC	BP, use of vasopressors, durations of ventilation, oxygen and hospital stay, PIE, pulmonary haemorrhage, pneumothorax, hyperglycaemia, glycosuria, IVH (grades III or IV), PVL, NEC, GI perforation, sepsis, ROP (> stage II) and mortality
Bonsante *et al.* [23]	2007	Exclusions: major anomaly likely to affect long-term neurological outcome Active treatment – total dose of hydrocortisone 10.5 mg/kg over 10 days	Placebo group - equal volume of 0.9% saline Primary outcomes: survival free of disability at 2 years of age, mortality up to 2 years of age and neurological outcome after discharge
Batton *et al.* [24]	2012	Hydrocortisone 1 mg/kg loading, then 0.5 mg/kg at 12-hourly intervals for 6 doses	Short-term outcomes during the primary hospitalisation of death, BPD (not defined), IVH grade III or IV, PVL and NEC requiring surgery

Meta-analysis Results

There were significant beneficial outcomes such as lower rates of failure to extubate and decreased risks of chronic lung disease at both 28 days (RR 0.84, 95% CI 0.83 to 0.87) and 36 weeks' postmenstrual age (RR 0.77, 95% CI 0.72 to 0.84), death or chronic lung disease at 28 days (RR 0.9, 95% CI 0.85 to 0.96)and 36 weeks' postmenstrual age (RR 0.91, 95% CI 0.87 to 0.96) , patent ductus arteriosus and ROP, including severe ROP. Nevertheless, there were no significant differences in the rates of neonatal or subsequent mortality (RR= 1.06, 95% CI 0.93, 1.26), infection, severe intraventricular haemorrhage, periventricular leukomalacia(RR 1.16, 95% CI 0.9 to 1.46), necrotizing enterocolitis or pulmonary haemorrhage(RR 1.21, 95% CI 0.83 to 1.62). In contrast, gastrointestinal bleeding (RR 2.13, 95% CI 1.41 to 2.84) and intestinal perforation (RR 1.77, 95% CI 1.46 to 2.1) were important adverse effects. Moreover, several adverse neurological effects were found at follow-up examinations, including developmental delay (RR 1.72, 95% CI 1.4 to 2.05) and cerebral palsy (RR 1.56, 95% CI 1.03 to 2.1). Additionally, the rates of the combined outcomes of death or cerebral palsy (1.92, 95% CI 1.18 to 2.67), or of death or major neurosensory disability (RR 1.25, 95% CI 0.98 to 1.53), were not significantly increased. In subgroup analyses by type of corticosteroid, most of the advantageous and disadvantageous effects were related chiefly to dexamethasone whilst hydrocortisone had slight effect on any of the outcomes except for an increase in intestinal perforation and a borderline reduction in patent ductus arteriosus. The overall risk for bias was low as all were RCTs using robust methods.

DISCUSSION

As the pathogenesis of BPD is multifactorial, so are the mechanisms to respond to steroid therapy. Since inflammation seems to play a critical role in the evolution of BPD, benefit seen with glucocorticoids most likely mediates through its anti-inflammatory effect.

Lung inflammation is downregulated by dexamethasone therapy. Groneck et al. evaluated the tracheobronchial aspirate from preterm infants at high risk of BPD. The number of neutrophils and concentrations of leukotriene B4, interleukin-1, elastase-α1-protease inhibitor, and albumin were decreased after dexamethasone treatment[25]. It indicates that dexamethasone affects the release of inflammatory mediators and neutrophils influx into the airways of preterm infants who require mechanical ventilation and decreases the microvascular permeability. Pulmonary edema is the hallmark of BPD; dexamethasone has been shown to reduce the pulmonary edema in infants with BPD.

Corticosteroids are potent drugs which may improve lung function in infants with chronic lung disease by a number of different mechanisms. It has been suggested that they might have a role to play in the prevention of chronic lung disease by suppressing the inflammatory response in the lungs of infants at risk [11]. It has also been shown that infants who develop chronic lung disease have low cortisol levels following adrenocorticotrophic hormone (ACTH) stimulation during the first week of life [26]. To be effective in preventing chronic lung disease corticosteroids may have to be given within the first few days of life.

Dexamethasone is a potent, long-acting steroid with exclusive glucocorticoid effect. When compared to hydrocortisone, dexamethasone is 25–50 times more potent. The half-life is 36–54 hours. Dexamethasone has been extensively studied in neonatal medicine and has shown to improve pulmonary function, facilitate extubation, and decrease the incidence of BPD [27]. However, many associated adverse side effects prevent the routine use of dexamethasone. The short-term side effects include hyperglycemia, hypertension, hypertrophic cardiomyopathy, gastrointestinal bleeding, and perforation. The risk of gastrointestinal perforation increases with concomitant indomethacin treatment [28]. There is also a concern with the chronic suppression of the hypothalamic-pituitary-adrenal axis [29]. and long-term neurodevelopmental delay [30].

The present systematic review found that early (≤ 7 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants, in the regimens used, have significant short and long-term effects, both beneficial and harmful. A significant problem in interpreting the late follow-up data is that only 12 of the 28 trials of early postnatal

corticosteroids have reported follow-up results; therefore, the possibility of follow-up bias and publication bias must be considered. Potential limitations of the study with a significant increase in the rate of cerebral palsy are that only 84% of surviving infants were examined and the age of assessment was in early childhood [(31)]. It is important to remember that cerebral palsy had been diagnosed before the children were five years of age in most cases; diagnosing cerebral palsy with certainty before five years of age is problematic [(32)]. In the other study where the rate of cerebral palsy was significantly worse at two years of age, with 81% follow-up, the difference became non-significant at eight to nine years, an age when the diagnosis of cerebral palsy is more certain, and where the follow-up rate was much better (92%) [(33)] illustrating the importance of age of assessment and high follow-up rates. No study was designed primarily to test the effect of postnatal corticosteroids on adverse long-term neurosensory outcome and all were underpowered to detect clinically important differences in long-term neurosensory outcome.

CONCLUSION

Despite the fact that early corticosteroid treatment can have beneficial outcome for BPD management through facilitation of extubation and decreasing the risk of chronic lung disease and patent ductus arteriosus, it, on the other hand, results in short-term adverse effects including gastrointestinal bleeding, intestinal perforation, hyperglycaemia, hypertension, hypertrophic cardiomyopathy and growth failure.

Clinicians should carefully assess the risks of a short course of glucocorticoid therapy to mitigate BPD for premature neonates such that an individualized decision should be made in conjunction with the infant's parents.

REFERENCES

1. **Namasivayam Ambalavanan,Ted Rosenkrantz, Mary L Windle and Arun K Pramanik, (2014):** Bronchopulmonary Dysplasia. Medscape, Available at https://reference.medscape.com/article/973717-overview
2. **Northway-WH Jr; Rosan-RC and Porter-DY (1967):** Pulmonary disease following respirator therapy of hyalinemembrane disease. Bronchopulmonary dysplasia. **N Engl J Med**., 276: 357-68. 2.
3. **Shennan AT, Dunn MS, Ohlsson A*et al.*(1988):** Abnormal pulmonary outcomes in premature infants: prediction from oxygen requirement in the neonatal period. Pediatrics, 82: 527-32.
4. **Bhutani VK, Abbasi S(1998):** Long term pulmonary consequences in survivors with bronchopulmonary dysplasia. Clin Perinatol.,19: 649-671.
5. **Doyle LW, Chavasse R, Ford GW*et al.*(1999):** Changes in lung function between age 8 and 14 years in children with birth weight of less than 1,501 g. Pediatric Pulmonology,27: 185-90.
6. **Davis P, Thorpe K, Roberts R *et al.*(2001):** Evaluating "old" definitions for the "new" bronchopulmonary dysplasia (BPD). Pediatric Research, 49: 27A.
7. **Bhandari A and Bhandari V(2007):** Bronchopulmonary dysplasia: an update. Indian Journal of Pediatrics, 74(1): 73–77.
8. **Bhandari A and Panitch H (2006):** Pulmonary outcomes in bronchopulmonary dysplasia. Seminars in Perinatology, 30(4): 219–226.
9. **Anderson P and Doyle L (2006):**Neurodevelopmental outcome of bronchopulmonary dysplasia.Seminars in Perinatology, 30(4): 227–232.
10. **D'Angio C and Maniscalco W(2002):**The role of vascular growth factors in hyperoxia-induced injury to the developing lung. Frontiers in Bioscience, 7: 1609–1623.
11. **Groneck P, Speer CP*(1995):*** *Inflammatory mediators and bronchopulmonary dysplasia. Archives of Disease in Childhood. Fetal and Neonatal Edition ,73:F1-3.*
12. **Watterberg KL, Gerdes JS, Cole CH, Aucott SW, Thilo EH, Mammel MC *et al.(2004):*** *Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics,114:1649-57.*
13. **Gupta S, Prasanth K, Chen CM, Yeh TF(2012):** Postnatal corticosteroids for prevention and treatment of chronic lung disease in the preterm newborn. International journal of pediatrics, 4:212.
14. **nordic.cochrane.org/sites/nordic.cochrane.org/files/public/.../AnnRep2012.pdf**
15. **Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD *et al.* (2011):**Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* .,343:d5928.
16. **https://www.meta-analysis-workshops.com/download/bookChapterSample.pdf.**
17. **Moher D, Liberati A, Tetzlaff J, Altman DG (2009):** *P*referred *R*eporting *I*tems for *S*ystematic Reviews and

*M*eta-*A*nalyses: The PRISMA Statement. PLoS Med., 6(7): e1000097. doi:10.1371/journal.pmed1000097.

18. **Biswas S, Buffery J, Enoch H, Bland M, Markiewicz M, Walters D(2003):** Pulmonary effects of triiodothyronine (T3) and hydrocortisone (HC) supplementation in preterm infants less than 30 weeks gestation: Results of the THORN trial - Thyroid Hormone Replacement in Neonates. Pediatric Research,53:48-56.
19. **Anttila E, Peltonemi O, Haumont D, Herting E, ter Horst H, Heinonen K *et al.*(2005):** Early neonatal dexamethasone treatment for prevention of bronchopulmonary dysplasia. Randomised trial and meta-analysis evaluating the duration of dexamethasone therapy. *European Journal of Pediatrics*,164:472-81.
20. **Efird MM, Heerens AT, Gordon PV, Bose CL, Young DA(2005):** A randomized-controlled trial of prophylactic hydrocortisone supplementation for the prevention of hypotension in extremely low birth weight infants. *Journal of Perinatology* ,25:119-24.
21. **Peltoniemi O, Kari A, Heinonen K, Saarela T, Nikolajev K, Andersson S *et al.*(2005):** Pretreatment cortisol values may predict responses to hydrocortisone administration for the prevention of bronchopulmonary dysplasia in high-risk infants. *Journal of Pediatrics*,146:632-7.
22. **Ng PC, Lee CH, Bnur FL, Chan IH, Lee AW, Wong E *et al.* (2006):**A double-blind randomized controlled study of a stress dose of hydrocortisone for rescue treatment of refractory hypotension in preterm infants. *Pediatrics*,117:367-75.
23. **Bonsante F, Latorre G, Iacobelli S, Forziati V, Laforgia N, Esposito L *et al*.(2007):** Early low-dose hydrocortisone in very preterm infants: a randomized placebo-controlled trial. *Neonatology*,**91**(4):217-21.
24. **Batton BJ, Li L, Newman NS, Das A, Watterberg KL, Yoder BA *et al.*(2012):** Feasibility study of early blood pressure management in extremely preterm infants. *Journal of Pediatrics*,**161**(1):65-9.
25. **Groneck P, Reuss D, Gotze-Speer D and Speer C(1993):**The effects of dexamethasone on chemotactic activity and inflammatory mediators intracheobroncheal aspirates of preterm infants at risk for chronic lung disease," Journal of Pediatrics, 122(6): 938–944.
26. **Watterberg KL, Gerdes JS, Gifford KL, Lin H-M*(1999):*** Prophylaxis against early adrenal insufficiency to prevent chronic lung disease in premature infants. Pediatrics, 104:1258-63.
27. **Garland J, Alex C, Pauly T *et al*.(1999):** A three-day course of dexamethasone therapy to prevent chronic lung disease in ventilated neonates: a randomized trial. Pediatrics, 104 (1I): 91–99.
28. **Stark A, Carlo W, Tyson J *et al.* (2001):**Adverse effects of early dexamethasone in extremely-low-birth-weight infants: National Institute of Child Health and Human Development Neonatal Research Network. The New England Journal of Medicine, 344: 95–101.
29. **Karemaker R, Kavelaars A, Wolbeek M *et al*.(2008):**Neonatal dexamethasone treatment for chronic lung disease of prematurity alters the hypothalamus-pituitary-adrenal axis and immune system activity at school age," Pediatrics, 121(4): e870–e878.
30. **Yeh T, Lin Y, Lin H *et al*.(2004):**Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity.The New England Journal of Medicine, 350(13): 1304–1313.
31. **Shinwell ES, Karplus M, Reich D, Weintraub Z, Blazer S, Bader D *et al*.(2000):** Early postnatal dexamethasone treatment and incidence of cerebral palsy. *Archives of Disease in Childhood Fetal and Neonatal Edition*,83:F177-81.
32. **Stanley FJ (1982):**Using cerebral palsy data in the evaluation of neonatal intensive care: a warning. *Developmental Medicine and Child Neurology*,24:93-4.
33. **Lin YJ, Lin CH, Wu JM, Tsai WH, Yeh TF(2005):** The effects of early postnatal dexamethasone therapy on pulmonary outcome in premature infants with respiratory distress syndrome: a two-year follow-up study. *Acta Paediatrica*,94:310-6.