CYPRUS UNIVERSITY OF TECHNOLOGY

FACULTY OF HEALTH SCIENCE

DEPARTMENT OF NURSING

Dissertation

THE SHORT-TERM EFFECTS OF THE POSTNATAL USE OF CORTICOSTEROIDS IN THE PREVENTION AND TREATMENT OF BRONCHOPULMONARY DYSPLASIA IN PRETERM INFANTS

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Supervisor: Dr. Anastasios Merkouris

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I want to sincerely express my appreciation to my supervisor Dr Anastasios Merkouris for this professional guidance mentorship and personal support during the entire process of my degree project.

ABSTRACT

Introduction: Bronchopulmonary Dysplasia, a type of chronic lung disease, is a common complication in premature infants. Corticosteroids, as anti-inflammatory drugs, can be used for the prevention or treatment of Bronchopulmonary Dysplasia (BPD). Despite their effectiveness, the use of corticosteroids has become a center of dispute, due to the side effects associated with them.

Aim: The aim of this study was to review the academic literature related to the short term effects of the use of Corticosteroids for the prevention and treatment of BPD

Material and method: A critical review of the literature published between 2003 –2013 was performed. Literature collection was performed by the use of PubMed, Cinahl, Medline and Science Direct databases. Filtering of results was done by following key-words: Bronchopulmonary Dysplasia, postnatal corticosteroids, premature or preterm infants.

Results: Ten studies were included which med the criteria. Infants had a mean Gestational Age range of 24 to 29.6 weeks and with mean Birth Weight range 652 to 1092g, all on mechanical ventilator. Three types of corticosteroids were investigated (Dexamethasone, Hydrocortisone, and Betamethasone). The short-term effects of the using corticosteroids vary, depending on the specific medication employed, dosage and time. The beneficial effects on premature infants were lower mortality and morbidity rate, lower incidence of Bronchopulmonary Dysplasia (BPD), facilitating extubation and better ventilation score. Short side effects include reduction of Growth, Intestinal Perforation, Total Cerebral and Cortical Tissue, lower Motor Optimality Score (MOS), impaired General Movements (GMs), Periventricular Leykomalacia (PVL), Intraventicular Hemorrhage (IVH) & Retinopathy of Prematurity (ROP)

Conclusions: Corticosteroid treatment in prematurity for treatment or prevention of Bronchopulmonary Dysplasia has many beneficial results, but at the same time is associated with many short – term side effects. Very selective treatment for the highest risk infants with low dose of corticosteroid for as much short as possible duration, after the first week of life is safer.

Keywords: Bronchopulmonary Dysplasia, postnatal corticosteroids, premature, preterm, infants.

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Η Βρογχοπνευμονική Δυσπλασία, ως ένα είδος χρόνιας πνευμονικής νόσου, είναι μία συχνή επιπλοκή που εμφανίζεται στα πρόωρα νεογνά. Η θεραπευτική προσέγγιση των Κορτικοστεροειδών στοχεύει τόσο στην πρόληψη όσο και στην αντιμετώπιση της ασθένειας. Ωστόσο άμεσες ανεπιθύμητες επιδράσεις μπορούν να εμφανιστούν.

Σκοπός: Η διερεύνηση άμεσων επιδράσεων των Κορτικοστεροειδών στη πρόληψη και θεραπεία της Βρογχοπνευμονικής Δυσπλασίας στα πρόωρα νεογνά.

Υλικό και μέθοδος: Πραγματοποιήθηκε συστηματική ανασκόπηση της βιβλιογραφίας που δημοσιεύτηκε μεταξύ 2003 – 2013. Η βιβλιογραφική αναζήτηση πραγματοποιήθηκε στις βάσεις δεδομένων Pubmed, Cinahl, Medline and Science Direct, με τη χρήση των λέξεων κλειδιών: Bronchopulmonary Dysplasia, Postnatal Corticosteroids, Premature of Preterm Infants.

Αποτελέσματα: Βρέθηκαν δέκα μελέτες οι οποίες τηρούσαν τα κριτήρια. Τα νεογνά είχαν μέση ηλικία κύησης 24 to 29.6 εβδομάδες και μέσο βάρος γέννησης 652 to 1092g. Όλα τα νεογνά ήταν σε μηχανική υποστήριξη. Η Ντεξαμεθαζόνη, η Υδροκορτιζόνη και η Μπεταμεθαζόνη ήταν τα είδη των κορτικοστεροειδών που μελετήθηκαν. Οι άμεσες επιδράσεις ποικίλουν, ανάλογα με το είδος, τη ποσότητα και τη χρονική στιγμή στην οποία δόθηκε. Οι επιθυμητές άμεσες επιδράσεις περιλαμβάνουν μείωση της θνησιμότητας και της νοσηρότητας, μείωση επίπτωσης της Βρογχοπνευμονικής Δυσπλασίας, γρηγορότερη αποσωλήνωση. Οι ανεπιθύμητες άμεσες επιδράσεις περιλαμβάνουν μείωση ανάπτυξης των νεογνών, διάτρηση εντέρου, αλλαγές στην εγκεφαλική δομή, διαταραχή στις κινήσεις σώματος, Περικοιλιακή Λευκομαλακία, Ενδοκοιλιακή Αιμοραγία, Αμφιβληστροειδοπάθεια,

Συμπεράσματα: Η χορήγηση Κορτικοστεροειδών στη πρόληψη ή θεραπεία της ΒροχγοπνευμονικήςΔυσπλασίας στα πρόωρα νεογνά σχετίζεται τόσο με επιθυμητα όσο και με ανεπιθύμητα αποτελέσματα. Πιο ασφαλής θεραπευτική προσέγγιση θεωρείται η λιγότερη δυνατή δόση, στη λιγότερη δυνατή διάρκεια μετά τον πρώτη εβδομάδα ζωής των νεογνών.

Λέξεις- κλειδιά: : Bronchopulmonary Dysplasia, Postnatal Corticosteroids, Premature of Preterm Infants

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ABBREVIATIONS

BPD: Bronchopulmonary Dysplasia

BW: Birth Weight

GA: Gestational Age

GH: Growth Hormone

GMs: General Movements

HC: Head Circumference

IH: Hydrocortisone companied with Indomethacin

IP: Intestinal Perforation

MAP: Mean Arterial Pressure

MOS: Motor Optimality Score

NICU: Neonatal Intensive Care Unit

1. Introduction

Preterm birth, defined as a neonate being born in a period of under thirty seven weeks of pregnancy, present one of the most significant problems of perinatology (Martin, & Osterman, 2013). About 15 million neonates were born preterm worldwide in 2005 (Beck, et al., 2010). The last 30 years have seen a significant improvement care provision in Neonatal Intensive Care Unit (NICU) and as a result there is an increase on survival of very low birth weight and gestational age of preterm (Chinese Society of Parenteral and Enteral Nutrition, 2013). Despite this, premature infants continue to be at a high risk of morbidity and mortality, especially for respiratory disorders.

The most common complication in preterm infants is Bronchopulmonary dysplasia (BPD) which is a chronic lung disease. In 1967 Northway and colleague first described BPD as a lung injury in preterm infants with Birth Weight (BW) lower than 1500gr and Gestational Age (GA) lower than thirty two weeks, as a result from high concentrations of oxygen (FiO_2 >80%) and mechanical ventilation (more than 150 hours). This was the first historical definition which included necrotizing bronchiolitis and alveolar septal injury.

Increased quality of nursing care that resulted from improved pharmacological interventions, lead in the increased survival rate of preterm infants. This contributed to the change of definition of BPD. A new proposed definition is an infant less than thirty weeks of GA and with BW lower than 1200g, who has reached thirty six weeks of postmenstrual age, was treated with oxygen greater than twenty eight days, and requires oxygen or positive pressure at thirty six weeks of postmenstrual age (Groothuis & Makari, 2012). The revised definition of BPD does not include necrotizing bronchiolitis nor alveolar septal fibrosis.

The etiology of BPD is multifactorial. Commonly associated factors include Acute Lung Injury, inflammation from Chorioammniotis before delivery and oxygen toxicity (Groothuis & Makari, 2012). Attempts to prevent or treat BPD involve lower dose of oxygen supplementation, and administration of diuretics, bronchodilators, caffeine, Vitamin A, Steroids, Mast Cell Stabilizers, Antioxidants, Erythromycin, Nitric Oxide and Inositol (Baveja & Christou, 2006). Postnatal corticosteroids can be used for the treatment of preterm infants in critical condition due to BPD (Gupta, Chen, Yeh, & Prasanth, 2012). Past studies suggest that

early postnatal corticosteroids (less than eight days) can reduce the incidence of BPD and promotes earlier extubation. Other studies associate corticosteroids to better gas exchange and facilitates weaning from mechanical ventilation. Administration of Corticosteroids during infancy also seems to reduce the need for therapies associated with the disease during childhood, in which case the regiments followed would be both more lengthy and costly (Halliday, Ehrenkranz, & Doyle, 2010).

Due to the effectiveness of Corticosteroids on BPD, the anti–inflammatory drugs have seen extended use in 1990s for both the prevention and treatment of BPD (Wilson-Costello, et al., 2009). During the period 1990 -1995 the use of postnatal corticosteroids increased by 41% (Hack & Fanaroff, 1999). By 1997, at least 23% of preterm infants received postnatal corticosteroids as indicated by studies conducted by Vermont Oxford Network and for the NICHD Neonatal Research Network (Jobe, 2009). Dexamethasone was most commonly used drug for prevention and treatment of BPD. Extensive use of Dexamethasone has declined since 2002, due to the joint recommendation made by the American Academy of Pediatrics and Canadian Pediatric Society. The recommendation focused especially in the first week of life, due to the appearance of short-term effects (Canadian Pediatric Society: Joint statement with the American Academy of Pediatrics, 2002). Such short-term effects include Systemic Arterial Hypertension, hyperglycemia, gastrointestinal bleeding or perforation, Hypertrophic Cardiomyopathy, reduced Head Circumference (HC) and general bone growth alterations were increased by early corticosteroid treatment. This resulted in a 20% reduction of the use of Dexamethasone in preterm infants with BPD. In 2010 Committee on Fetus and Newborn of America also reported the need for avoiding Dexamethasone (American Academy of Pediatrics, Canadian Paediatric Society, 2002). In reviewing the past empirical data, the Committee noted the strong correlation between Corticosteroid dosage and adverse effects.

The use of postnatal corticosteroids and the adverse effects for BPD on premature neonates is a major issue for Health Sciences and governments because of the economic costs associated with the repeated hospitalizations. The effects of BPD extend beyond the first months, as evidenced by the strong association of the disease with chronic respiratory conditions and the related healthcare costs (Fawke, et al., 2010). The mean cost of BPD was $43,312 higher than infants without BPD (Johnson, Patel, Jegier, Engstrom, & Meier, 2013).

This it can be attributed to the use of specialized equipment such as mechanical ventilation and oxygen. In the United States the cost of hospitalization for every infant who had BPD in 2001 was estimated at $116.000 (Russel, et al., 2007).

2. Aim

The aim of this study is to review data collected from conducted between 2003 and 2014 that involve the investigation of short effects on premature infants that may result from the use of corticosteroids in relation to BPD.

3. Materials and methods

The sources from the studies taken under consideration were MEDLINE, SCIENCE DIRECT, PUBMED and CINAHL. To be included in the review, the trials had to meet the following criteria:

1. To be studying the short effects of corticosteroids related to the treatment or prevention of Bronchopulmonary Dysplasia (BPD) on prematurely born infants.
2. Language limited to English
3. Keywords used were: Bronchopulmonary Dysplasia, Postnatal Corticosteroids, and Premature or Preterm Infants.
4. Limited to recent studies (2003 – 2013)
5. Limited to prematurely born infants (less than 37 weeks)
6. Limited to postnatal corticosteroids.
7. Limited to short effects.

With these criteria in place, 193 articles were produced. From them, 183 were excluded in total, from which 35 concerned the investigation of long term effects. 44 were removed for being produced before 2003. Another 56 were excluded because of their focus on the effects of Corticosteroids on conditions unrelated that of Bronchopulmanory Dysplasia. Lastly, 48 were excluded because the infants under investigation did was not limited to premature infants (less than 37 weeks). This procedure leads to the remaining 10 studies, on which the present literature review is focused on.

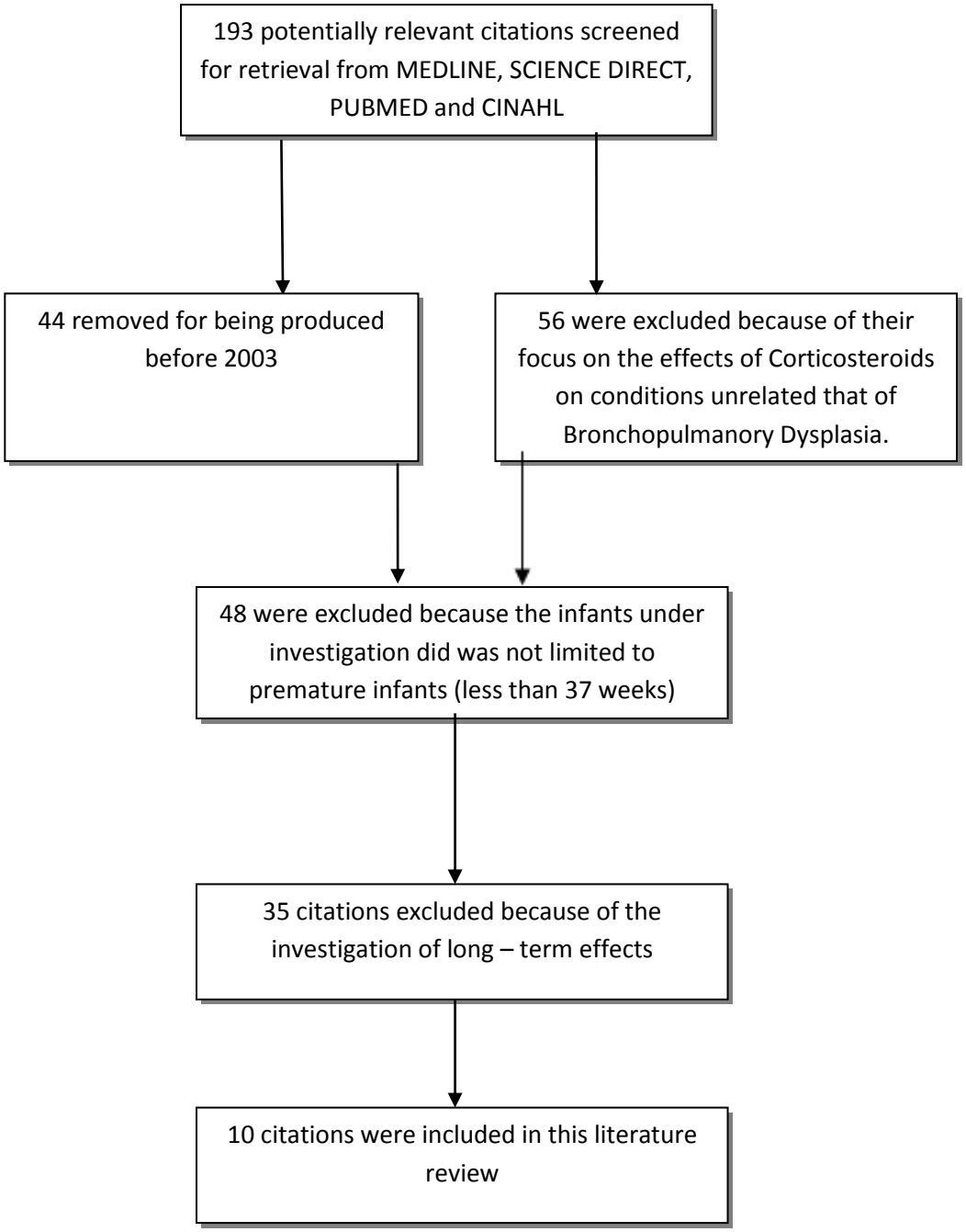

Figure 1: Process of study selection.

First Author/ year/ country	Aim	Design	Sample	Corticosteroids regimen – Duration days	Results
Huysman et al./ 2003/Netherlands	To evaluate the short – term effect of dexamethasone on the GH – IGF axis in ventilated very preterm infants developing bronchopulmonary dysplasia.	Interventional quasi experimental	Subjects: N=10 with BPD all treated with Dexamethasone. BW: mean 1092g GA: mean29.6 weeks Mechanical ventilator after 1st week of life.	Dexamethasone (dexa): 1 mg/kg/day for 3 days, then 0.3 mg/kg/day for 3 days and then tapered every 3 day to 0.1mg/kg/day every other day - 21 days	Ventilation score decreased on the 2d day of study ($p<0.05$). Growth hormone (GH) levels decreased after the start of Dexamethasone from median 12.0 μg/L to 4.4 μg/, (mean $p<0.01$).

Kristi L Watterberg et al./ 2004/ USA	To investigate the hypothesis that 1) preventing the development of adrenal insufficiency of prematurity would improve clinical outcomes, 2) dose of glucocorticoid intended to mimic cortisol concentrations seen in patients under stress and 3) glucocorticoid used Hydrocortisone, which is metabolism to the endogenous glucocorticoid cortisol.	Interventional Randomized Control Trial	Subjects: N= 360 – 180 infants treated with Hydrocortisone and 180 with placebo. BW: mean for Hydrocortisone treated infants 731g – for placebo treated infants 734g GA: mean for Hydrocortisone treated infants 25.2 – for placebo treated infants 25.3 weeks. Mechanical ventilator after 12- 48h of life.	Hydrocortisone:1 mg/kg/day for 12 days, then 0,5mg/kg/day for 3 days - 15 days	Infants treated with Hydrocortisone had significantly improved survival without BPD (38%, 28 of 73) compared with placebo (24%, 18 of 76) and significantly lower mortality rate (12%, 9 of 73) than placebo treated infants (21%, 16 of 76). Infants receiving indomethacin had more Intestinal Perforations (IP) than group who received only Hydrocortisone or placebo receiving Indomethacin or placebo alone ($p<0.01$). Neither weight nor Head Circumference (HC) were decreased in the treated infants.

Huysman et al./ 2005/ Netherlands	The aim of this study was to evaluate whether recombinant growth hormone (GH) overcomes the growth – inhibiting effects of Dexamethasone treatmetnt.	Interventional Randomized Control Trial	Subjects: N=30 – all treated with Dexamethasone. At the same time within 4 -6h after start of Dexamethasone, Growth Hormone (GH) (N=15) or Placebo (N=15) was started. BW: mean for GH treated infants 889g – for placebo treated infants 847g GA: mean for GH treated infants 27.2 – for placebo treated infants 27.3 weeks. Mechanical ventilator.	Dexamethasone: 1mg/kg/day for 3 days, then 0,3mg/kg/day for 3 days and then the dosage was tapered to 0.3mg/kg/day for 3 days and then tapered every 3 days to 0.1mg/kg/day every other day over a 24 day period. GH: 0.3mg/kg/day for 6 weeks	During high dose Dexamethasone treatment no gain in HC, weight, crown heal length and knee heal length occurred in the GH and placebo groups. Growth, during the 6 week period, was not different between the GH and placebo group. During high dose of Dexamethasone there was stunting of head growth, whereas after the discontinuation HC and weight where higher. No difference in adverse effects in two groups. High dose of GH treatment did not improve growth.
Mataloun MMGB et al./ 2005/ Brazil	To analyze the effects of corticosteroids on bronchopulmonary dysplasia, length of	Observational Retrospective Cohort Study	Subjects: N= 38 – 16 treated with dexamethasone and 22 without BW: mean for	Dexamethasone: 0.3mg/kg/day for 3 days, then 0.2mg/kg/day for 3 days and then	Reduction on growth in Dexamethasone group (change in weight: treated group – 47g/week, control group – 85.5g/week, p=0.06; change in HC: treated group – 0.75cm/week, control group – 1cm/week, p=0.05).

	stay, mortality, growth, as well as the adverse effects in very low birth weight newborns between 10 – 14 days of life and dependent on mechanical ventilation.		Dexamethasone treated infants 1082g – for untreated infants 970g GA: mean for Dexamethasone treated infants 28.9 – for untreated infants 29 weeks Mechanical ventilator after 10 – 14 days of life	0.1 mg/kg/day for 3 days - 9 days	The incidence of BPD in Dexamethasone group was 6.5% and 30% in group without Dexamethasone.
Doyle et al./ 2006/ Australia	To determine the short - term effects of low dose dexamethasone treatment among chronically ventilator dependent neonates.	Interventional Randomized Control Trial	Subjects: N=70 – 35 infants treated with Dexamethasone and 35 with placebo. BW: mean for Dexamethasone treated infants 652g – for placebo treated infants 700g GA: mean for Dexamethasone treated infants 24 – for placebo treated infants 25 weeks Mechanical ventilator 7 days or after of life	Dexamethasone: 0.15mg/kg/day for 3 days, then 0.10/kg/day for 3 days, then0.05mg/kg/day for 2 days and then 0.02 mg/kg/day for 2 days - 10 days	More infants were extubated successfully by 10 days of treatment in Dexamethasone group (60%, 21 of 35) compared with placebo group (12%, 4 of 34), (p<0,001). Little reduction on mortality rate in Dexamethasone group (11%, 4 of 35) compared with placebo group (20%, 7 of 35). No obvious effects of Dexamethasone on blood glucose, blood pressure (p>0.23). The weigh change over the 10 days of treatment which was lower in Dexamethasone group. But, by the time of discourage weight, length and HC were not different. Non intestinal perforation.

Parikh et al./ 2007/ USA	To relate postnatal dexamethasone therapy in extremely low birth weight infants to their total and regional brain volumes.	Interventional Randomized Control Trial	Subjects: N= 41 – 11 treated with Dexamethasone and 30 did not – had MRI studies BW: mean for Dexamethasone treated infants 740g – for untreated infants 808g GA: mean for Dexamethasone treated infants 25.1 – for untreated 26.2 weeks Mechanical ventilator	Dexamethasone:the mean cumulative dose was 2.8mg/kg (1.2 – 5.9mg/kg) - mean duration therapy was 6.8 days (2- 14 days).	Smaller total cerebral (10.2%, p=0.03) and cortical tissue (8.7%, p=0.06) volume in Dexamethasone group. Decrease in sub cortical gray matter (19.9%) in Dexamethasone group and smaller cerebellum (20.6%).
Aucott et al/ 2008/ USA	To evaluate the relationship between cortisol concentrations and short – term outcomes.	Interventional Randomized Control Trial	Subjects: N= 311 – 158 treated with Hydrocortisone and 153 with placebo. BW: mean for all 734g GA: mean for all 25.3 weeks Mechanical ventilator after 12 – 48h	Hydrocortisone:1 mg/kg/day for 12 days, then 0.5 mg/kg/day for 3 days - 15 days	Day 5 to 7 low cortisol values at baseline is not associated with increase morbidity and mortality. High concentrations associated with Intraventicular Hemorrhage (IVH) Extremely high concentrations associated with death, severe IVH, IP, Retinopathy Of Prematurity (ROP), Periventricular Leukomalakia (PVL).

Hitzert et al/ 2012/ Netherlands	To determine the effects of Hydrocortisone and Dexamethasone therapy in preterm infants on neurological functioning as assessed by the quality of GMs until 3 months after term.	Observational Retrospective Cohort Study	Subjects: N= 56 – 17 infants treated with Hydrocortisone, 17 with Dexamethasone and 22 control group. BW: mean for Hydrocortisone treated infants 800g – for Dexamethasone treated infants 970g – for controls 930g GA: mean for Hydrocortisone treated infants 27.1 – for Dexamethasone treated infants 27.9 – for controls 27.2 weeks Mechanical ventilator after 7 day of life.	Hydrocortisone: starting dose 5mg/kg/day – median 24 days. Dexamethasone:starting dose 0.5/kg/day – median 22 days.	No difference on the quality of General Movements between Hydrocortisone and Dexamethasone group. At 3 months Hydrocortisone group had higher median motor optimality score (MOS) than Dexamethasone infants (p=0.015) and lower compared to the control (p=0.010).
Ben Said et al./2013/ France	To compare the efficacy and tolerance of Betamethasone and Hydrocortisone in	Observational Retrospective Cohort Study	Subjects: N=67 – 35 infants trea`ted with Betamethasone and 32 treated with Hydrocortisone. BW: mean for	Betamethasone:0, 1 mg/kg/day for 3 days, then 0.05mg/kg/day for 3 days and	No significant differences on extubation: Hydrocortisone 72%, Betamethasone 83% (p=0.281). The need for insulin was similar (Betamethasone: 11% vs. Hydrocortisone: 15%,

	weaning in extremely low birth weight infants with bronchopulmonary dysplasia from the ventilator.		Betamethasone treated infants 740g – for Hydrocortisone treated infants 745g GA: mean for Betamethasone and Hydrocortisone treated infants 26 weeks Mechanical ventilator after 15 days of life.	then 0,16mg/kg/day for 3 days - total 9 days Hydrocortisone:5 mg/kg for 3 days, 3mg/kg for 2 days and 1mg/kg for 1 day - total 6 days	p=0.460), MAP was lower in infants treated by BTM 30 days after the end of treatment compared with Hydrocortisone group (46mmHg vs. 51mmHg, p=0.009). Differences in z-scores between the beginning and end of postnatal treatment were significantly greater in Betamethasone group than in the Hydrocortisone group for both body weight (-0.59 SD vs. -0.27 SD, p=0.003) and head circumference (-0.55 SD vs. -0.14 SD, p=0.004)
Kersbergen et al./ 2013/ Netherlands	To assess whether there was an adverse effect on brain growth after Hydrocortisone treatment for bronchopulmonary dysplasia in a large cohort of infants without dexamethasone exposure.	Observational Cohort Study	Subjects: N= 146 - 73 infants treated with Hydrocortisone and 73 control group after ≥7days of life and who had MRI. BW: mean for treated infants 863 – means for control group 948 Mechanical ventilator GA: mean for treated infants 26.6 – mean for control group 26.9	Hydrocortisone (HC):5mg/kg/day for 7 days, then a subsequent tapering course every 5 days, leading to a total treatment - 22 days.	No differences in total brain tissue volumes (p=0.08) and cerebral volumes (p=0.39) with or without HC.

Table 2. The effects of Dexamethasone, Hydrocortisone and Betamethasone on preterm infants according to the clinical findings of research studies. ✓ means that there is an effect and no means that there is no effect.

Researches / Effects	Huysman (2003)	Kristi L Watterberg (2004)	Huysman (2005)	Mataloun (2005)	Doyle (2006)	Parikh (2007)	Aucott (2008)	Hitzert (2012)	Ben Said (2013)	Kersbergen (2013)
Dexamethasone										
Lower Mortality rate					✓					
Lower incidence of BPD				✓						
Better extubation					✓					
Better ventilation score	✓									
Lower weight			✓	✓	✓					
Lower head circumference			✓	✓						
No gain in crown heal length, knee heal length			✓							
Blood glucose					No					
Blood pressure					No					
Intestinal perforation					No					
Decrease of growth hormone level	✓									
Cerebral palsy								✓		
General Movements								No		
Lower motor optimality score								✓		
Smaller cerebral and cortical tissue						✓				
Decrease of sub cortical gray						✓				
Hydrocortisone										
Lower mortality rate		✓					✓			

Increase of mortality (only with extremely high doses)							✓			
Morbidity rate							✓			
Better extubation									✓	
Intestinal perforation		✓								
Intestinal perforation (only with extremely high doses)							✓			
Periventricular leukomalacia (only with extremely high doses)							✓			
Intraventicular hemorrhage or severe intraventicular hemorrhage (only with high or extremely high doses)							✓			
Retinopathy (only with extremely high doses)							✓			
Weight		No							No	
Head Circumference		No							No	
Cerebral palsy								No		
General Movements								No		
Better motor optimality score								✓		
MAP									No	
Need for insulin									No	
Total brain tissue volumes and cerebral volumes										No
Betamethasone										
Better extubation									✓	
Lower weight									✓	
Lower head circumference									✓	
Lower MAP									✓	
Need for insulin									No	

4. Results

In this systematic review included 10 articles from 2003 to 2013 which 4 of them took place in Netherlands, 3 in USA and the rest of them were in France, Australia and Brazil. The general aim was to evaluate the short–term effects of using corticosteroids on infants with Bronchopulmonary Dysplasia or with risk to develop this disease. Five of them were Randomized Control Trial, one Quasi–Experimental and four Cohort studies. The participants were preterm infants with a mean Gestational Age (GA) range of 24 to 29.6 weeks and with mean Birth Weight (BW) range 652 to 1092g. All premature infants were on mechanical ventilator. Corticosteroid regimens and duration days were different in each study. A note on Corticosteroid dosage: all regiments started with "High Dosage" (highest to lowest). Therefore the terms High Dosage and Low Dosage will refer to the highest and lowest values used by experimenters. Because of the variations in protocols, these dosages may not correspond to the same values between the studies. Five studies used Dexamethasone treatment with minimum starting dosage 0.15mg/kg/day and minimum duration two days. Three made use of Hydrocortisone, with minimum starting dosage 1mg/kg/day and minimum duration 15 days. One used both Hydrocortisone and Dexamethasone with minimum starting dosage 5mg/kg/day and 0.5mg/kg/day respectively and duration 24 and 22 days respectively. Lastly, one used both Hydrocortisone and Betamethasone with minimum starting dosage 5mg/kg/day and 0.1mg/kg/day respectively and duration 6 - 9 days respectively.

The tables 1 and 2 show the results of this literature review. Specifically in table one (1), author, year and country are mention in first column, followed by the aims, design of each study, sampling type, type of corticosteroid regimen, duration of days and finally the results. The second table (2) presents the findings according to the type of corticosteroid (Dexamethasone, Hydrocortisone and Betamethasone). The effects of each Corticosteroid will be examined below.

Dexamethasone

Dexamethasone treatment was used in six studies. Dosage and duration were different in each research (see table 1).

Starting with mortality rate, Doyle's study (2006) showed that there was a little reduction in premature infants (mean GA: 24 weeks, mean BW: 652g) from the experimental group (11%, 4 of 35) compared with the placebo group (mean GA: 25 weeks, mean BW: 700 g; 20%, 7 of 35). Incidence of BPD was lower in Dexamethasone (6.5%) group compared with placebo (30%) group (Doyle, Davis, Morley , McPhee, & Carlin, 2006).

As for the extubation, Doyle's study indicates a significant increase of successful treatment ($p<0.001$) in the most treated infants (60%, 21 of 35) than in control group (12%, 4 of 34). Better ventilation score ($p<0.05$) in treated group compared with the day before the start of Dexamethasone (Huysman, Hokken-Koelega, Hop, & Sauer, 2003).

Reduction of growth was the most common negative effect of Dexamethasone in preterm infants, as observed by the three aforementioned studies. Specifically in Huysmans' study (2003), ten preterm infants (mean GA: 29.6 weeks, mean BW: 1092g) treated with Dexamethasone showed a Growth Hormone (GH) reduction from a median 12.0μg/L to 4.4μg/L (mean $p<0.01$). In 2005, in a different study, Huysman (2005) treated thirty preterm infants with Dexamethasone but at the same time GH was given at half of them (mean GA: 27.2 weeks for GH treated and 27.3 weeks for placebo, mean BW: 889g for GH treated and 847g for placebo). High dose of GH treatment with Dexamethasone did not affect growth. Specifically, during high dose of Dexamethasone treatment (1mg/kg/day for 3 days) there was no measurable difference of Head Circumference (HC), weight, crown heel length or knee heel length between the GH and placebo groups. The growth during the six week period was not different between GH and placebo group with mean weight and HC in GH group 16.2g and 1.0cm respectively and mean weight and HC in placebo group 15.3g and 1.0cm respectively. During high dose of Dexamethasone there was stunting of head growth, whereas after the discontinuation, HC and weight were higher. Malaoun's study in 2005 involved the comparison of sixteen preterm infants treated with Dexamethasone (mean GA: 28.9 weeks and mean BW: 1082g) and twenty two where the control (mean GA: 29 weeks and mean BW: 970g). There was a reduction on growth of preterm infants with lower weight and HC in treated group with Dexamethasone (weight change: experimental group – 47g/week, control group – 85.5g/week, $p=0.06$; change in HC: experimental group – 0.75cm/week, control group – 1cm/week, $p=0.05$). In a similar study, Doyle (2006)supports that the weight change over ten

days of treatment which was lower in Dexamethasone group, but by the time of discharge weight, length and HC were not different.

The blood glucose and blood pressure there were no obvious effects of Dexamethasone ($p>0.23$) neither for Intestinal Perforation (IP) (Doyle, Davis, Morley , McPhee, & Carlin, 2006).

In Parikh's study (2007) eleven infants treated with Dexamethasone (mean GA: 25.1 and +mean BW: 740g) and thirty were the control group (mean GA: 26.2 and mean BW: 808g), all mechanical ventilator. Smaller Total Cerebral (10.2%, $p=0.03$) and Cortical Tissue (8.7%, $p=0.06$) volume found in Dexamethasone group. Also a decrease in sub-cortical gray matter (19.9%) and reduced Cerebellum (20.6%) in Dexamethasone group was measured.

Hydrocortisone

Hydrocortisone treatment was used in three studies. Dosage and duration were different in each research (see table 1).

One of the studies presented the relationship between Hydrocortisone usage and mortality rate as one of positive correlation. Specifically, in Watterberg's study (2004), one hundred eighty infants treated with Hydrocortisone (mean GA: 25.2 weeks and mean BW: 739g) and one hundred eighty with placebo (mean GA: 25.3 weeks and mean BW: 734g), all on mechanical ventilator. Infants exposed to choriamniotis had significantly improved survival without BPD (38%, 28 of 73) compared with placebo (24%, 18 of 76) and significantly lower mortality rate (12%, 9 of 73) than placebo treated infants (21%, 16 of 76). In the second study, Aucott (2008) observed three hundred and fifty infants with mean GA 25.3 weeks and mean BW 734g at postnatal age of 12 to 48 hours and at day 5 to 7 of 15 days of the treatment. As Hydrocortisone dosage increases there is higher risk for death. This effect is only observed when the dosage exceeds a specific threshold (varies for each individual). Below this threshold, Hydrocortisone dose is not associated with increase of and mortality.

Intestinal perforation (IP) was also investigated in Watterberg's study (2004). Infants who received Indomethacin with Hydrocortisone had more IP than the group that received only Hydrocortisone or placebo receiving Indomethacin or placebo alone ($p<0.01$). IP was

observed also in Aucott's study (2008) but only with extremely high concentrations of Hydrocortisone.

Periventricular leukomalacia (PVL), Intraventicular Hemorrhage or severe Intraventicular Hemorrhage (IVH) and Retinopathy Of Prematurity (ROP) were also observed only in high or extremely high concentrations with Hydrocortisone (Aucott, Watterberg, Shaffer, & Donohue, 2008).

Growth changes were inferred by measurements of weight and Head Circumference (HC). Neither weight (2014 +/- 318), nor HC (31.2 +/-1.5) were found to be decreased in the Hydrocortisone treated infants (Watterberg, et al., 2004).

In Kersebergen's study (2013), one hundred forty six infants were enrolled. Half of them were treated with Hydrocortisone (mean GA: 26.6 weeks and mean BW: 863g) and the other half with placebo (mean GA: 26.9 weeks and mean BW: 948g). No significant difference was observed in Total Brain Tissue Volume (p=0.08) and Cerebral Volume (p=0.39).

There are two studies mentioned neither in Dexamethasone, nor Hydrocortisone group because they treated infants with two different type of corticosteroids. In the first, lower Motor Optimality score (MOS) was observed (Hitzert , et al., 2012). In this study, there were three groups: Group one, comprised of seventeen infants treated with Dexamethasone (mean GA: 27.9 weeks and mean BW: 970g). Group two, seventeen with Hydrocortisone (mean GA: 27.1 weeks and mean BW: 800g) and Group three of twenty two were the control group (mean GA: 27.2 weeks and mean BW: 930g). At three months of age, infants were treated with Dexamethasone had a lower MOS than Hydrocortisone infants (p=0.015) and lower compared to the control (p=0.010). About the General Movements (GMs) there were no obvious differences on the quality between Dexamethasone and Hydrocortisone. In the second study the effects of Hydrocortisone on extubation period were also investigated, compared to those of Betamethasone. Specifically, thirty two infants treated with Hydrocortisone (mean GA: 26 weeks and mean BW: 745g) and thirty five with Betamethasone (mean GA: 26 weeks and mean BW: 740g). Most infants were extubated during treatment (Hydrocortisone: 72%, Betamethasone: 83%, p=0.281). The differences in scores between the beginning and end of

postnatal treatment were significantly greater in Betamethasone group than in the Hydrocortisone group for both body weight (-0.59 SD vs. -0.27 SD, p=0.003) and HC (-0.55 SD vs. -0.14 SD, p=0.004) (Ben Said, 2013). Variations of insulin levels as affected by the two corticosteroids were also measured in the same study. There was no significant difference between the two groups (Betamethasone: 11% vs. Hydrocortisone: 15%, p=0.460). The last variable under investigation with was Mean Arterial Pressure (MAP). MAP was lower in infants treated infants with Betamethasone compared with Hydrocortisone group (46mmHg vs. 51mmHg, p=0.009).

5. Discussion

In this literature review all infants were very preterm with mean Gestational Age (GA) 24 – 29.6 weeks and with mean Birth Weight (BW) 652 – 1092 g and all on mechanical ventilator – dependent. Each clinical investigation employs different protocols, thus different treatment regiments for each participant, or experimental group. In reviewing the literature, caution is necessary when interpreting results from studies that adhere to different regiments, since their results may be incomparable with others. The effects of corticosteroids that observed in this study on premature infants were lower mortality and morbidity rate, lower incidence of Bronchopulmonary Dysplasia (BPD), facilitating extubation and better ventilation score. The short side-effects of the using corticosteroids vary, depending on the specific medication employed, dosage and time (before or after the first week of life). Short side effects include reduction of Growth, Intestinal Perforation, Metabolic Complications (Blood Pressure and Blood Glucose), Total Cerebral and Cortical Tissue, lower Motor Optimality Score (MOS), impaired General Movements (GMs), Periventricular Leykomalacia (PVL), Intraventicular Hemorrhage (IVH) & Retinopathy of Prematurity (ROP).

Mortality – Morbidity rate

In Doyle's study (2006) showed that there was a significant difference in mortality rate in premature infants who treated with Dexamethasone (11%) compared with placebo group (20%; $p = .33$). Two studies involving the administration of Hydrocortisone suggested a negative relationship between Hydrocortisone usage and mortality rate. Specifically, in Watterberg's study (2004) infants with choriamniotis had significantly lower mortality rate (12%) than placebo treated infants (21%). Improved survival without BPD also observed significantly improved survival without BPD (38%) compared with placebo (24%). In the second study, observed that low Hydrocortisone dose at baseline is not associated with increase of morbidity and mortality (Aucott, Watterberg, Shaffer, & Donohue, 2008). As Hydrocortisone dosage increases there is higher risk for death. This is not the case with Hydrocortisone alone. The same observations have been made for all corticosteroids, especially when they are administered after the end of the first week of life (Gien & Kinsella, 2011).

Incidence of BPD

Mataloun's study (2005) suggests that infants who received treatment with Dexamethasone had lower incidence of BPD (6.5%) compared with the control group (30%; P=0.07). Further observations supporting this notion can be found in another systematic review, in which the incidence of BPD was significantly lower in the infants who treated with Dexamethasone (Onland, Jaegere, Offringa, & Kaam, 2008). The incidence of BPD is a major issue in prematurity because BPD increases as birth weight decreases. Infants who weigh less than 1250 grams at birth constitute 97% of the infants with this condition (Walsh, et al., 2005).

Ventilation & Extubation

Corticosteroids, as anti-inflammatory drugs, produce a rapid improvement in pulmonary function and better gas exchange. These factors correspond to a reduction of extubation period (Tropea & Christou, 2012). Better Ventilation Score and Extubation were observed in three studies out of the ten that fit the criteria for this literature review: In Doyle's study (2006), there was a reduction of extubation period ($p < .001$) in the majority of treated infants with Dexamethasone (60%), compared to the control group (12%). Better ventilation score was found by Huysman (2003) in treated group compared with the day before the start of Dexamethasone ($p<0.05$). Similarly, in Ben Said's study (2013), most infants that were extubated during treatment with Hydrocortisone (72%) and with Betamethasone: (83%), ($p=0.281$). Many studies concluded that any type of corticosteroids can be useful for reducing the dependence on ventilator and oxygen (Doyle, Halliday, Ehrenkranz, Davis, & Sinclair,, 2005). Previous study suggests that infants who treated with Dexamethasone need less supplemental oxygen compared with placebo ($p=0.04$) group (Stark, et al., 2001). Remarkable fact is a pilot study which suggests that low dose of short course of Betamethasone has comparable efficacy with high dose of long course of Dexamethasone ($p<0.05$) in oxygen requirement (DeCastro, Khoury, Parton, Ballabh, & LaGamma, 2009). Also, a reduction in days of ventilator period has no significant difference in both groups (33 days in Dexamethasone group and 39 days in Betamethasone group). In addition, another study compares the effectiveness between Hydrocortisone with Placebo group and Dexamethasone with Placebo group (Heide-Jalving, et al., 2003). This review supports that Hydrocortisone

($p<0.01$) and Dexamethasone ($p<0.05$) can be equivalent in effectiveness on weaning from the ventilator and decreasing supplemental oxygen therapy overall compared with placebo groups.

Growth

Reduction of growth was the most common side-effect of Dexamethasone in preterm infants, which observed in three studies in this literature review. Specifically, in Huysman's study (2003), Growth Hormone (GH) reduction from a median 12.0μg/L to 4.4μg/L (mean $p<0.01$). In 2005, in a different study of Huysman high dose of Dexamethasone treatment with GH did not improve growth. Specifically, during high dose of Dexamethasone treatment (1mg/kg/day for 3 days), no gain in Head Circumference (HC), weight, crown heal length and knee heal length was observed in the experimental group (Dexamethasone and GH) or in the placebo group (Dexamethasone with inactive agent as placebo). There was no significant difference in Growth during the six week period between GH and placebo group. During high dose of Dexamethasone (1mg/kg/day for 3 days) there was stunting of head growth, whereas after the discontinuation, HC and weight where higher. In Malaoun's study (2005) there was a reduction on growth of preterm infants with lower weight and HC in treated group with Dexamethasone (change in weight: treated group – 47g/week, control group – 85.5g/week, $p=0.06$; change in HC: treated group – 0.75cm/week, control group – 1cm/week, $p=0.05$). Similarly Doyle (2006) suggests that the weight change over ten days of treatment was lower in Dexamethasone group, but by the time of discharge, the differences in weight, length and HC between the groups were diminished. Previous study supports that there is a reduction in Weight ($0=0.02$) and in HC ($p=0.04$) in Dexamethasone treated infants compared with placebo group (Stark et al., 2001). The American Academy of Pediatrics and Canadian Pediatric Society (2002) made a recommendation to revise the clinical guidelines regarding the use of Dexamethasone, encouraging practitioners to seek alternative treatment options.

The effects for Hydrocortisone on growth, however, reveal a different trend. There was no significant difference in reduction of weight (2014g/2034g) or HC (31.2cm/30.9cm) in the hydrocortisone treated infants and placebo group (Watterberg, et al., 2004). These observations are further supported by a retrospective study in which three groups (Dexamethasone, Hydrocortisone and Placebo) (Heide-Jalving, et al., 2003). The results indicate that Weight gain was halted in infants treated with Dexamethasone, while the Weight gain values of the Placebo and Hydrocortisone groups increased. Despite the differences

during the treatment, there were no significant differences in Weight gain after treatment regiments were completed between the Dexamethasone, Hydrocortisone and Placebo groups. In Ben Said's study (2013) the differences in scores between the beginning and end of postnatal treatment were significantly greater in Betamethasone group than in the Hydrocortisone group for both body weight (-0.59 SD vs. -0.27 SD, p=0.003) and HC (-0.55 SD vs. -0.14 SD, p=0.004). There are limited studies of comparing Betamethasone and Hydrocortisone treatment in preterm infants. However, a pilot study supports that low dose Betamethasone for short course is safety than high dose Dexamethasone for long course (DeCastro, Khoury, Parton, Ballabh, & LaGamma, 2009). There was a significant greater weight gain ($p<0.05$) in Betamethasone treated group.

Intestinal Perforation

Three studies measured the effects of corticosteroids on Intestinal Perforation (IP). One studied the relation between IP and Dexamethasone. Two of them investigated the possible relationship of IP and Hydrocortisone.

The study concerning Dexamethasone was a replication of a previous study, which found a significantly higher rate of IP during the first two weeks of life; but with the end-result of the study showing rates that were on par with the placebo group (Stark A.R., Carlo W.A., Tyson J.E. et. al, 2001 ; cited in Doyle, 2006). In the replicated study, Dexamethasone was not found to be related with IP (Doyle, Davis, Morley , McPhee, & Carlin, 2006). The difference between the two were attributed to the differences in the age of the infants that took part in the two studies: Stark et al. (2001; cited in Doyle, 2006), started measuring from the first day of birth, while Doyle (2006) used participants with a median age of 23 days. The possible relationship between Hydrocortisone and Intestinal Perforation was investigated in two studies that fit the criteria for the inclusion in the present literature review. Two experimental groups took part in the first study, as well as two placebo groups. The two experimental groups received Hydrocortisone, and Hydrocortisone combined with Indomethacin (HI). The first control group received Indomethacin with placebo, while the second received only placebo (Watterberg, et al., 2004). The patient enrollment was stopped at three hundred and sixty because of an increase in spontaneous IP in the HI group. Indomethacin was administered in forty four infants from placebo group and in forty one infants in the HI experimental group.

Infants who received Indomethacin with Hydrocortisone had more gastrointestinal perforations than the experimental group that received Hydrocortisone alone, or the two control groups (Placebo, Placebo with Indomethacin; $p<0.01$). In the second study, as Hydrocortisone dosage increases there is higher risk for IP. This effect is only observed when the dosage exceeds a specific threshold (varies for each individual). Below this threshold, Hydrocortisone dose is not associated with increase of IP.

Review of postnatal corticosteroids for preventing chronic lung disease in preterm infants (Halliday, Ehrenkranz, & Doyle, 2010) suggests that early corticosteroids increased the risks of IP (typical relative risk 1.81, 95% CI 1.33, 2.48, typical risk difference 0.04, 95% CI 0.02, 0.06; 15 studies and 2523 infants). However, another review supports that late corticosteroids administration (after one week of birth) is not associated with IP (typical relative risk 0.36, 95% CI 0.02, 8.05; number of studies 2 and number of infants 83) (Halliday, Ehrenkranz, & Doyle, Late (>7 days) postnatal corticosteroids for chronic lung disease in preterm infants (Review), 2009). In 2002 a study performed to determine whether early administration of high doses of Dexamethasone may cause IP (Stark, et al., 2001). There was a significant difference between Dexamethasone and placebo group ($p=0.02$) whereas 13% of treated infants had IP compared with 4% in Placebo group.

Metabolic Complications (Blood Pressure & Blood Glucose)

Two studies investigated the relationship between blood pressure and glucose levels with Corticosteroids. Dexamethasone was the Corticosteroid investigated by the first, while the second studied the effects of both Hydrocortisone and Betamethasone. No significant alterations were observed ($p>0.23$) on Blood Glucose levels or in Blood Pressure from the Dexamethasone treatment, compared to the placebo group (Doyle, Davis, Morley , McPhee, & Carlin, 2006). This is a contradictory result because other studies suggest that there is a strong relationship between Dexamethasone, Hyperglycemia and Hypertension. Specifically, infants who received early administration of Dexamethasone (24 – 48 hours after delivery) were more likely to have Hypertension ($p<0.001$) and more likely to receive insulin treatment ($p=0.02$) for Hyperglycemia (Stark, et al., 2001). Another study of early administration observed increase of Mean Arterial Pressure (MAP) in Dexamethasone treated infants compared with

Placebo (p=0.015) and increase (p=0.25) of insulin therapy (Anttila et al., 2004). A systematic review in 2010 supports that late administration Dexamethasone after the first week of life is associated with Hypertension (p<0.001) and Hyperglycemia (p<0.001) (Doyle, Ehrenkranz, & Halliday , 2010). In addition, comparing the short term effects between Betamethasone and Dexamethasone, a pilot study found a significant difference (p<0.05). Dexamethasone treated infants were more likely to have Hyperglycemia compared with Betamethasone (DeCastro, Khoury, Parton, Ballabh, & LaGamma, 2009).

Ben Said's study (2013) supports that the need for insulin between Hydrocortisone group and Betamethasone group was almost the same (Betamethasone: 11% vs. Hydrocortisone: 15%, p=0.460), but the (MAP) was lower in infants treated infants by Betamethasone thirty days after the end of treatment compared with Hydrocortisone group (46mmHg vs. 51mmHg, p=0.009). Hydrocortisone tends to affect less Blood Pressure and Blood Glucose (Heide-Jalving, et al., 2003).

Total cerebral and cortical tissue volume

In Parikh's study (2007) smaller total cerebral (10.2%, p=0.03) and cortical tissue (8.7%, p=0.06) volume found in Dexamethasone group and also a decrease in sub cortical gray matter (19.9%) and smaller cerebellum (20.6%). By contrast, in Kersebergen's study (2013) total brain tissue (p=0.08) and cerebral volume (0.39) did not have differences with or without Hydrocortisone. Further study supported that cerebral cortical gray matter volume in preterm infants treated with Dexamethasone was reduced 35% (Murphy, et al., 2001). Premature infants treated with Dexamethasone had a reduction (30%) in total cerebral tissue volume compared with control group.

Motor Optimality Score (MOS) & General Movements (GMs)

In Hitzert's study (2012) lower Motor Optimality Score (MOS) was observed. In this research there were three groups: infants treated with Dexamethasone, with Hydrocortisone and two were the control group. At three months of age, infants were treated with Dexamethasone had a lower median MOS than Hydrocortisone treated infants (p=0.015) and lower compared to the control (p=0.010). About the General Movements (GMs) there were no obvious differences on the quality between Dexamethasone and Hydrocortisone. Previous

study supports that Dexamethasone administration associated with impaired GMs (Bos, et al., 1998). Specifically, after Dexamethasone treatment was started, a significant transient decrease of the quantity of most spontaneous movements ($p < 0.05$) and a reduction of speed and amplitude of GMs was found ($p < 0.05$).

Periventricular Leykomalacia, Intraventicular Hemorrhage & Retinopathy of Prematurity

Periventricular Leukomalacia (PVL), Intraventicular Hemorrhage (IVH) or severe IVH and Retinopathy Of Prematurity (ROP) were observed only in high or extremely high concentrations with Hydrocortisone (Aucott, Watterberg, Shaffer, & Donohue, 2008). In a systematic review Hydrocortisone treatment started in the first week of life of infants no significant effects on severe IVH ($p=0.62$), PVL ($p=0.83$) or ROP ($p=0.28$) were observed (Doyle, Ehrenkranz, & Halliday, 2010).

6. Conclusion

Corticosteroids, as anti – inflammatory drugs, can use for prevention or treatment of Bronchopulmonary dysplasia in prematurity, but perhaps this is the most controversial area of care. Lower incidence of BPD, lower mortality and morbidity rate, better ventilation score, extubation can observed in any corticosteroid regimen. However, the adverse effects on premature infants are changing with the type, the dosage and the time where given. Corticosteroids associated with numerous short – term effects, especially when is given early (less than 8 days after delivery) and in high dosages for long period (Tropea & Christou, 2012). Dexamethasone remains a drug with serious short – term effects compared with Betamethasone. Hydrocortisone tends to be safer. Very selective treatment for the highest risk infants with low dose of corticosteroid for as much short as possible duration is the best solution (Jobe, 2009). For further research recommended focus of study – specific medication instead of the broad category that is corticosteroids, so as to better investigate the effects of each drug, while avoiding the danger of over generalizing the effects of the category, without respects of variations between the medication.

Limitations

The fact that included studies only in English language is one of the basic limitations of this literature review. Also worth noting is the finding in Watterberg's study (2004) because infants who received Indomethacin with Hydrocortisone had more gastroinetsinal perforations than group who received only Hydrocortisone or placebo receiving Indomethacin or placebo alone ($p<0.01$).The combination of corticosteroids and indomethacin together should be avoided. In addition, many studies were rejected as a result of inclusion of short and long term effects. Few studies have been conducted with betamethasone in the postnatal period (Jarreau PH, 2010).

Bibliography

AMERICAN ACADEMY OF PEDIATRICS, CANADIAN PAEDIATRIC SOCIETY. (2002). Postnatal Corticosteroids to Treat or Prevent Chronic Lung Disease in Preterm Infants. *Pediatrics*, 330-338.

Anttila, E., Peltoniemi, O., Haumont, D., Herting, E., Horst, H. t., Heinonen, K., . . . Group, S. (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), 472–481.

Aucott, S. W., Watterberg, K. L., Shaffer, M. L., & Donohue, P. K. (2008). Do Cortisol Consentrations Predict Short - Term Outcomes In Extremely Low Birth Weight Infants? *American Academy Of Pediatrics*(43), 775-781.

Beck, S., Wojdyla, D., Say, L., Merialdi, M., Rubens, C., Menonf, R., . . . Betran, A. P. (2010). The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ*(88), 31–38.

Ben Said, M., Hays , S., Loys , C. M., Coletto, L., Godbert, I., & Picaud, J. C. (2013). Postnatal steroids in extremely low birth weight infants: betamethasone or hydrocortisone? *Acta Paediatrica*(102), 689-694.

Bos, A., Martijin, A., Asperen , R. v., Hadders, M. A., Okken, A., & Prechtl, H. (1998). Qualitative assessment of general movements in high risk preterm infants with chronic lung disease requiring dexamethasone therapy. *Journal Of Pediatrics*(2), 300-306.

Canadian Pediatric Society: Joint statement with the American Academy of Pediatrics. (2002). *Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants.* Ottawa: Canadian Pediatric Society.

Carraro, S., Filippone, M., Da Dalt, L., Ferraro, V., Maretti, M., Bressan, S., . . . Baraldi, E. (2013). Bronchopulmonary dysplasia: The earliest and perhaps the longest lasting obstructive lung disease in humans. *Early Human Development*(31), S3–S5.

Chinese Society of Parenteral and Enteral Nutrition. (2013). Guidelines for nutrition support in neonates. *Asia Pacific Journal of Clinical Nutrition*(22), 655-663.

Committe On Fetus And Newborn. (2010). Policy Statement - Postnatal Corticosteroids to Prevent Or Treat Bronhopulmonary Dysplasia. *American Academy Of Pediatrics* , 800-809.

DeCastro, M., El-Khoury, N., Parton, L., Ballabh, P., & LaGamma, E. (2009). Postnatal betamethasone vs dexamethasone in premature infants with bronchopulmonary dysplasia: a pilot study. *Journal of Perinatology*(29), 297–304.

Doyle, L. W., Davis, P. G., Morley , C. J., McPhee, A., & Carlin, J. B. (2006). Low - Dose Dexamethasone Facilitates Extubation Among Chronically Ventilator - Dependent Infants: A Multicenter, International, Randomized, Control Trial. *American Academy Of Pediatrics, 43*, 75-84.

Doyle, L. W., Ehrenkranz, R. A., & Halliday , H. H. (2010). Dexamethasone Treatment after the First Week of Life for Bronchopulmonary Dysplasia in Preterm Infants: A Systimatic Review. *Neonatology*(98), 289-296.

Doyle, L. W., Ehrenkranz, R. A., & Halliday, H. L. (2010). Postnatal Hydrocortisone for Preventing or Treating Bronchopulmonary Dysplasia in Preterm Infants: A Systimatic Review. *Neonatology*(98), 111-117.

Fawke, J., Lum, S., Kirkby, J., Hennessy, E., Marlow, N., Rowell, V., . . . Stocks, J. (2010). Lung Function and Respiratory Symptoms at 11 Years. *American Journal Of Respiratory and Critical Care Medicine*(48), 237–245.

Gien, J., & Kinsella, J. P. (2011). Pathogenesis and Treatment of Bronchopulmonary Dysplasia. *Current Opinion Pediatrics*(51), 305–313.

Groothuis, J. R., & Makari, D. (2012). Definition and Outpatient Management of the Very Low-Birth-Weight Infant with Bronchopulmonary Dysplasia. *Advances Therapy*(75), 297-311.

Hack, M., & Fanaroff, A. A. (1999). Outcomes of children of extremely low birthweight and gestational age in the 1990's. *Early Human Development*, 193-218.

Halliday ,, H. L., Ehrenkranz RA, R. A., & Doyle, L. W. (2010). Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. (89).

Halliday, H., Ehrenkranz, R., & Doyle, L. (2009). Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants (Review). *John Wiley & Sons*(89), 1-44.

Halliday, H., Ehrenkranz, R., & Doyle, L. (2009). Late (>7 days) postnatal corticosteroids for chronic lung disease in preterm infants (Review). *John Wiley & Sons*(89), 1-37.

Hitzert , M. M., Benders, M. J., Roescher, A. M., Bel, F. v., Vries, L. S., & Bos, A. F. (2012). Hydrocortisone vs. dexamethasone treatment for Bronchopulmonary Dysplasia and their effects on general movements in preterm infants. *Clinical Investigation*(67), 99-106.

Huysman , M. W., Hop, W. C., Cromme-Dijkhuis, A. H., Sauer , P. J., & Hokken-Koelega, A. C. (2005). A Randomized, Placebo - Controlled GH Trial in Very Preterm Infants Who Were at Risk for Bronchopulmonary Dysplasia and Were Treated with Dexamethasone. *Pediatric Research*(05), 705-712.

Huysman, M. W., Hokken-Koelega, A. C., Hop, W. C., & Sauer, P. J. (2003). Effect of Dexamethasone Treatment on Serum GH, IGF-1, and the Blinding Proteins IGFBP-1 and -3 in Ventilated Very Preterm Infants. *Pediatric Research*(03), 37-43.

Jarreau, P., Fayon, M., Baud, O., Autret-Leca, E., Danan , M., Verdelhan, A. D., & Castot, A. (2010). The use of postnatal corticosteroid therapy in premature infants to prevent or treate Bronchopulmonary Dysplasia: current situation and recommendations. *Archives Of Pediatrics*(24), 1480-1487.

Jobe, A. H. (2009). Postnatal Corticosteroids for BPD. *National Institute Of Health*(36), 177-188.

Johnson, T. J., Patel, A. L., Jegier, B., Engstrom, J. L., & Meier, P. (2013). The Cost of Morbidities in Very Low Birth Weight Infants. *J. Pediatr.*(2), 243 - 249.

Kersbergen, K. J., Vries , L. S., Kooij, B. J., Isgum, I., Rademaker, K. J., Bel, F. v., . . . Benders, M. J. (2013). Hydrocortisone Treatment for Bronchopulmonary Dysplasia and Brain Volumes in Preterm Infants. *The Journal Of Pediatrics*(6), 666-671.

Martin,, J. A., & Osterman, M. J. (2013). *Preterm Births — United States, 2006 and 2010.* 136-138: Morbidity and Mortality Weekly Report.

Mataloun, M. M., Leone, C. R., Gibelli, M. A., & C.Vaz, F. A. (2005). Effects of corticosteroids in very very low birth weight newborns dependent on mechanical ventilation. *Clinics*(2), 113-120.

Parikh, N. A., Lasky, R. E., Kennedy , K. A., Moya, F. R., Hochlauser, L., Romo, S., & Tyson, J. E. (2007). Postnatal Dexamethasone Therapy and Cerebral Tissue Volumes in Extremely Low Birth Weight Infants. *American Academy Of Pediatrics*(10), 265-272.

Russell, R. B., Green, N. S., Steiner, C. A., Meikle, S., Howse, J. L., Poschman, K., . . . Petrini, J. R. (2007). Cost of Hospitalization for Preterm and Low Birth Weight Infants in the United States. *Pediatrics*(34), 2006 - 2386.

Stark, A. R., Carlo, W. A., Tyson, J. E., Paple, L. A., Wright, L. L., Shankaran, S., . . . Stoll, B. J. (2001). Adverse Effects Of Early Dexamethasone Treatment In Extremely - Low - Birth - Weight Infants. *The New England Journal Medicine*(344), 95-101.

Tropea, K., & Christou, H. (2012). Current Pharmacologic Approaches for Prevention and Treatment of Bronchopulmonary Dysplasia. *International Journal of Pediatrics*(48), 1-9.

Walsh, M. C., Szefler, S., Davis, J., Allen, M., Marter, L. V., Abman, S., . . . Jobe, A. (2005). Summary Proceedings From the Bronchopulmonary Dysplasia Group. *Pediatrics*(24), 1098 - 4275.

Watterberg, K. L., Gerdes , J. S., Cole, C. H., Aucott, S. W., Thilo, E. H., Mammel, M. C., . . . Shaffer, M. L. (2004). Prophylaxis of Early Adrenal Insufficiency to Prevent Bronchopulmonary Dysplasia: A Multicentre Trial. *American Academy Of Pediatrics*(6), 1649-1658.