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Prevention and Treatment of Bronchopulmonary Dysplasia (BPD) in Infants; Systematic Review

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Abstract: **Bronchopulmonary dysplasia (BPD) stays a major cause of mortality and morbidity in incredibly low birth weight (ELBW) babies and is associated with an increased danger for neurodevelopmental disability in later years. The purpose of this systematic review was to evaluate roles of prevention and determine the therapeutic approaches for Bronchopulmonary dysplasia among premature infants, we attended to overview the evidence based of most important studies about this topic. We conducted a search of the Cochrane database to evaluate the preventions medications and treatment for Bronchopulmonary dysplasia in newborn infants that were studied up to 2016. We used this list as MeSH terms or equivalent to compose searches of MEDLINE and EMBASE for all studies evaluating these medications and strategies for prevention *bronchopulmonary dysplasia* OR *respiratory distress syndrome, newborn*. We concluded The requirement for prolonged mechanical ventilation (more than 2 hours) may be an early marker for the advancement of BPD in preterm infants of more than 26 weeks GA. This association may assist to identify a target population with a high danger of BPD.**

Keywords: **MEDLINE and EMBASE, Bronchopulmonary dysplasia (BPD).**

1. INTRODUCTION

Bronchopulmonary dysplasia (BPD) stays a major cause of mortality and morbidity in incredibly low birth weight (ELBW) babies and is associated with an increased danger for neurodevelopmental disability in later years [(1)]. The pathogenesis of BPD is carefully connected to inflammatory processes within the immature lung [(2,3,4)]. Due to their anti-inflammatory properties, corticosteroids have actually been and are still extensively utilized for both the avoidance and treatment of BPD in preterm babies [(4)]. Infants with BPD are at increased risk for death, and survivors have life-long morbidities [(5,6,7)]. In spite of the increased survival of very premature babies, BPD remains a major morbidity [(5,6,7,9)]. Roughly 40% of infants born in between 22 and 28 weeks' pregnancy are identified with BPD, defined as oxygen supplements at 36 weeks' postmenstrual age (PMA) [(8,9)].

The National Institutes of Child Health-Neonatal Research Network likewise has actually provided info on 9575 babies of 22-28 weeks' pregnancy born from 2003-2007 [(10)]. The occurrence of BPD did not reduce over the 5 years in this population of well-studied babies. The BPD results are classified for each gestational age according to the 2000 category of BPD as mild (oxygen usage for 28 days), moderate (oxygen need at 36 weeks), or extreme (ventilatory assistance at 36 weeks) (**Fig. 1**). These curves are a beneficial visual tip of the very high danger for extreme BPD at the earliest gestational ages. Overall, the numbers of infants with serious consistent BPD have decreased [(10)].

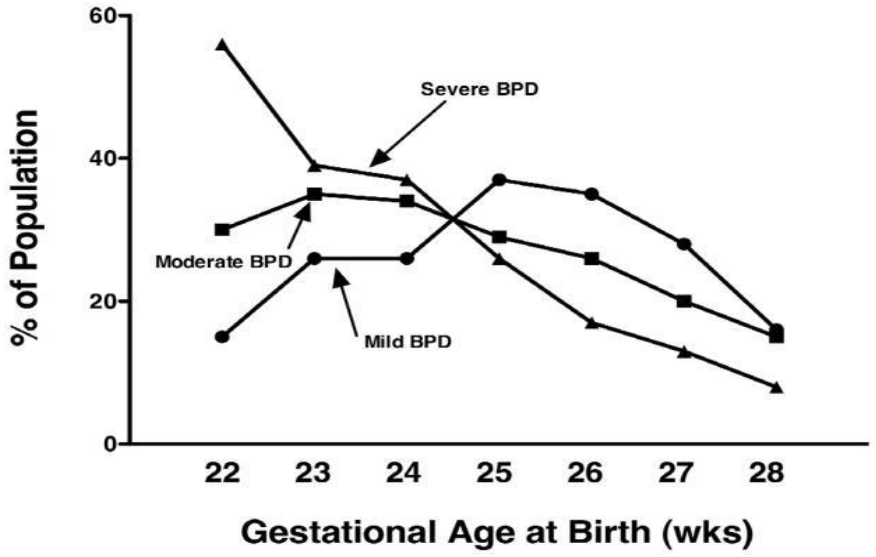

Fig.1: Percent of population of 9575 infants categorized as to severity of BPD based on the 2000 NIH conference definition. 68% of these infants had BPD. Severity of BPD decreased as gestational age increased. Data abstracted from [10]

The purpose of this systematic review was to evaluate roles of prevention and determine the therapeutic approaches for Bronchopulmonary dysplasia among premature infants, we attended to overview the evidence based of most important studies about this topic.

2. METHODS

Systematic study was conducted following the "Preferred reporting items for systematic reviews and meta-analyses" (PRISMA) statement for reporting of this systematic review [12].

Search strategy:

We conducted a search of the Cochrane database to evaluate the preventions medications and treatment for Bronchopulmonary dysplasia in newborn infants that were studied up to 2016. We used this list as MeSH terms or equivalent to compose searches of MEDLINE and EMBASE for all studies evaluating these medications and strategies for prevention *bronchopulmonary dysplasia* OR *respiratory distress syndrome, newborn*. We also included *chronic lung disease* as a title and abstract search term. We included search terms for age: *infant, newborn*; and *randomized controlled trial*s, reviews and meta-analysis studies as well. We performed an additional search to identify related references to our studies among the reviewed articles. References identified via the literature search will be screened by the authors, and disagreement will be resolved either by discussion or with the aid of an additional reviewer. our search was limited to English language studies.

3. RESULTS AND DISCUSSION

We have identified several studies concerning treatment and prevention strategies for Bronchopulmonary dysplasia. Previous meta-analyses have tried to separate studies of avoidance and treatment, in spite of significant overlap in ages at administration of the inhaled steroid [12,14]. Shah et al. [12] reported a meta-analysis of research studies of "early" postnatal inhaled steroids, defined as administration that was started prior to the age of 2 weeks. This analysis included 7 trials with 492 infants, although the secondary and main outcome variables were only reported in 5 of the 7 trials consisting of 429 infants [12]. The duration of the study intervention varied from 10 days to 4 weeks. Onland et al. carried out a meta-analysis of "late" research studies specified as treatment began after 7 days of age [15].

We consisted of a very important big systematic study [16] which included 13 RCTs for 5 drugs (N registered= 4,794) that demonstrated a decrease in BPD. There was an FDA label for 3 of the 5 drugs (vitamin A, caffeine citrate, and dexamethasone) for the neonatal population, although none for the prevention of BPD (**Table 1**).

Vitamin A is FDA-labeled for use in prevention of vitamin A shortage however is utilized off-label for prevention of BPD. Two RCTs examined the use of vitamin A for BPD prevention in 856 infants (17,18). One trial [17] discovered no

difference in between the incidence of BPD when infants were treated with 2000 IU intramuscular vitamin Each day for 2 weeks versus placebo [17]. The other trial discovered the relative danger (RR) of death or BPD specified either as oxygen requirement at 28 days or 36 weeks PMA after treatment with 5000 IU intramuscular vitamin A 3 times a week over four weeks was 0.89 (95% confidence interval; 0.80-- 0.99) (18); this study was preceded by a phase I dosing research study [19]. In a meta-analysis, intramuscular vitamin A significantly decreased the incidence of BPD [20].

Table1: Summary of RCTs (n=47) and early-phase studies (n=19) included in review, by drug studied [16]

	Total infants enrolled*	**Infants enrolled in RCTs**	**Preliminary data**	**Prevents BPD**	**Favorable RCTs, N/total (%)‡**	**# IND/ # RCTs**
Vitamin A	947	856	Y	Y	1/2 (50)	0/2
Caffeine	2006	2006	Y	Y	1/1 (100)	0/1
Dexamethasone	1671	1631	Y	Y	4/10 (40)	0/10
Inositol	233	233	Y	Y	1/1 (100)	0/1
Clarithromycin	68	68	Y	Y	1/1 (100)	0/1
Surfactant	10,128	1647†	Y	N	4/8 (50)	0/8
Inhaled nitric oxide	3092	2712	Y	N	2/7 (28)	0/7
Selenium	529	529	N	N	0/1 (0)	0/1
Hydrocortisone	451	411	Y	N	0/3 (0)	0/3
Allopurinol	400	400	N	N	0/1 (0)	0/1
N-acetylcysteine	391	391	Y	N	0/1 (0)	0/1
Inhaled beclomethasone	352	313	Y	N	0/2 (0)	0/2
Azithromycin	255	220	Y	N	0/1 (0)	0/1
Estrogen/progesterone	115	85	Y	N	0/1 (0)	0/1
Alpha-1-antitrypsin	106	106	N	N	0/1 (0)	0/1
Inhaled salbutamol	87	87	Y	N	0/1 (0)	0/1
Superoxide dismutase	59	33	Y	N	0/1 (0)	0/1
Cromolyn sodium	55	26	Y	N	0/1 (0)	0/1
Inhaled fluticasone	53	53	Y	N	0/1 (0)	0/1
Thyroxine	49	49	N	N	0/1 (0)	0/1
Zinc	97	97	Y	N	0/1 (0)	0/1
Total	**21,176**	**11,953**	**17**	**5**	**14/47 (30%)**	**0/47**

**Infants included in both RCTs and early-phase studies.*

†Of the 8481 infants included in preliminary surfactant studies, 8263 were included under a treatment IND protocol for safety assessment.

‡"Favorable" defined as statistically significant results indicating a reduction in the incidence of BPD as provided in meta-analyses.

Four RCTs [21,22,23,24] of surfactant lowered the occurrence of BPD. However, meta-analyses of surfactant have not regularly supported a decrease in BPD for survivors [25,26,27] While 1 trial showed reductions in both the combined result of death or BPD (RR= 0.73 [0.65-- 0.83] and BPD alone (RR= 0.75 [0.61-0.92] [25], the other trial [27] showed reductions in only the combined outcome (RR=0.89 [0.82-0.97]. Although initial data were referenced in the surfactant trials, these were not PK, efficacy, or safety information consistent with early-phase trials. 2 of 7 iNO trials showed a decrease in the incidence of BPD, however a meta-analysis did disappoint a reduction [28].

Roles of Chorioamnionitis in treatment of BPD:

The medical research study on relationships between antenatal infection (chorioamnionitis) and RDS or BPD remains uncertain. Chorioamnionitis induced in sheep by pro-inflammatory arbitrators such as E.coli LPS, IL-1, or live Ureaplasma cause both lung maturation and a phenotype of fetal lung inflammation [29]. Chorioamnionitis in fetal mice stimulates angiogenesis and an inflammatory profile similar to the swollen lungs of infants developing BPD [30]. The infants in the ELGANS research study had extensive evaluations for histologic chorioamnionitis; and simply over 50% were exposed to chorioamnionitis, however there was no correlation of chorioamnionitis with severity of early breathing disease or BPD [31] (**Table 2**). A multicenter research study from the Canadian Neonatal Network found that medical chorioamnionitis associated with increased dangers for intraventricular hemorrhage and early-onset sepsis, however not respiratory outcomes [32]. The basic associations of chorioamnionitis with RDS and BPD are confounded by the unknowns-- period of fetal direct exposure, degree of fetal responses, and the organisms prompting the reactions, factors that are essential based upon animal model literature [33]. Scientific examples of the intricacy of the relationships were offered by Been and associates [34,35]. Chorioamnionitis separated to the placenta and chorion was connected with decreased RDS while chorioamnionitis with fetal participation increased the danger of RDS in early gestational age infants (35). Infants exposed to serious chorioamnionitis had actually decreased medical responses to surfactant treatment and those less favorable responses associated with longer mechanical ventilation and more BPD [34].

Table 2: Clinical Characteristics of 1346 Infants Grouped by Patterns of Lung Disease to 14 Days of Age (31)

	Consistently Low FiO_2	**Pulmonary Deterioration**	**Persistent Lung Disease**
N	249	484	576
Percent of Population	20%	38%	43%
Any Chorioamnionitis	55%	54%	53%
Initial FiO_2	0.25	029	0.38
FiO_2 – 7d	0.22	0.28	0.42
FiO_2 – 14d	0.21	0.40	0.49
Surfactant treatment	78%	89%	97%
CPAP – 7d	50%	30%	10%*
Mechanical Ventilation – 7d	21%	57%	84%*
No PDA	52%	36%	28%*
BPD	17%	51%	67%*

Ventilation and CPAP: Similar to oxygen direct exposure alone, mechanical ventilation alone can hinder development of the saccular lung in animal models. Mokres, et al. [36] demonstrate that ventilation of newborn mice with space air for 24h induced apoptosis, disrupted alveolar septation, and hindered angiogenesis. Current clinical research has checked out methods to decrease ventilation-mediated injury or to avoid mechanical ventilation entirely. A meta-analysis of individual patient data from 10 randomized regulated trials demonstrates no benefit from high frequency ventilation relative to standard ventilation for BPD or other negative outcomes [37]. Either approach to ventilatory support works but avoidance of mechanical ventilation is the best technique in theory. A variety of studies provide the clinician guidance as to how that can be carried out in practice. The same 1316 infants that were randomized to oxygen saturation varies in the NICHD trial [35] were likewise randomized prior to birth to intubation at shipment and surfactant treatment within 1 hour of birth or to CPAP at delivery and surfactant as clinically indicated (38). The protocol specified early extubation when possible. Although there was no distinction in the main result of BPD or death, the majority of the breathing signs favored the CPAP group [31] (**Table 3**). The large decrease in use of postnatal corticosteroids with CPAP is particularly interesting with respect to the new policy statement from the American Academy of Pediatrics that recommends caution for the use of postnatal corticosteroids for BPD [39]. This trial randomized infants prior to birth such that it included both depressed and healthier infants. The current COIN trial randomized only infants requiring some ventilatory support at 5 min of age to CPAP or intubation, which omitted the depressed and "normal" infants [40].

Table 3: Outcomes for Early CPAP vs. Intubation and Surfactant [31]

	Early CPAP	Intubation and Surfactant	P
N	663	653	
Gestational age (weeks)	26.2±1.1	26.2±1.1	
Death or BPD	47.8%	51.0%	0.30
Death	14.2%	17.5%	0.09
BPD – O_2 use at 36 weeks	48.7%	54.1%	0.07
Mechanical Ventilation (median)	10 days	13 days	0.03
Survival without mechanical ventilation	55.3%	48.8%	0.01
Any air leak	6.8%	7.4%	0.56
Postnatal steroids for BPD	7.2%	13.2%	<0.01

4. CONCLUSION

The requirement for prolonged mechanical ventilation (more than 2 hours) may be an early marker for the advancement of BPD in preterm infants of more than 26 weeks GA. This association may assist to identify a target population with a high danger of BPD.

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