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REVIEW ARTICLE

Treatment of pulmonary broncodysplasia: a systematic review

Tratamento da broncodisplasia pulmonar: uma revisão sistemática

Vitor Fernandes Alvim[1], Sarah Carvalho Ribeiro[1*], Larissa Cruvinel Leite[1], Ana Carla Ferreira Lana e Silva[1], Ana Luísa dos Santos Maciel[1], Lucas Bernardes Cerqueira Campos[1], Nathália Carvalho de Souza[1], Isabela Karina Silva Dias[1], Anna Beatriz Soares Dias[1], Lucas Fahel Vaz[1], Laura Mendes Ferreira Castelani[1], Yago Ricardo Pedrosa[1], Laís de Almeida Fraga Lopes[1], Larissa Fontes Cal Sperancini[1], Bruno Cassiano dos Santos[1]

ABSTRACT

Introduction: Bronchopulmonary dysplasia (BPD) is a complication among preterms, with an incidence inversely proportional to gestational age. It results from an inflammatory process that causes abnormal lung development, with severe consequences. Although therapeutic options are limited and do not substantially strike the course of the disease, they are important tools and need further elucidation. **Purpose**: Address the most recent aspects of the literature regarding the prevention and treatment of BPD. **Methods**: A literature review was carried out in the MEDLINE database, in 2021, in which only controlled and randomized clinical studies performed in humans in the last 5 years were included. Studies that were not directly related to the theme were excluded. **Results**: The incidence of BPD was lower in those cases exposed to inhaled budesonide, intravenous fish oil containing lipid emulsion (FO) and docosahexaenoic acid (DHA). There was improvement in survival with a low-dose use of hydrocortisone, dexamethasone with gradual dose reduction, and dexamethasone associated with postnatal corticosteroids (which generated reduction in neurodevelopmental impairments as well). Hydrocortisone, dexamethasone, inhaled hydrofluoalkane-beclomethasone dipropynate and FO reduced the time or need for ventilation and oxygen therapy. The main complications were sepsis, retinopathy, intraventricular hemorrhage and necrotizing enterocolitis in studies that addressed DHA, hydrocortisone, dexamethasone and inhaled nitric oxide. **Conclusion**: The therapeutic approaches that proved to be conclusive were the use of glucocorticoids associated with ventilatory therapy and an early approach. No benefits were found with the use of ventilation with sustained inflation, administration of inhaled hydrofluoralkane-beclomethasone dipropionate and DHA.

Keywords: Bronchopulmonary Dysplasia; Prematurity; Therapy.

[1] Faculdade de Ciências Médicas e da Saúde de Juiz de Fora - SUPREMA, Juiz de Fora, Minas Gerais, Brazil.

Associate Editor Responsible:
Marcia Rocha Parizzi
Secretaria Municipal de Saúde
Belo Horizonte/MG, Brazil

Corresponding Author:
Sarah Carvalho Ribeiro
E-mail: sarahcarvalhorr@gmail.com

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RESUMO

Introdução: Displasia broncopulmonar (DBP) é uma grave complicação entre pré-termos, com incidência inversamente proporcional à idade gestacional. Resulta de processo inflamatório com desenvolvimento pulmonar anormal, gerando graves consequências. Apesar de serem limitadas e não afetarem substancialmente a evolução da doença, as opções terapêuticas para prevenção e tratamento da DBP são importantes, porém carecem de melhor elucidação. **Objetivos:** Abordar aspectos recentes da literatura quanto à prevenção e tratamento da DBP. **Métodos:** Revisão de literatura na base de dados MEDLINE, em 2021, incluindo ensaios clínicos controlados e randomizados, realizados em humanos e nos últimos 5 anos, excluindo estudos não diretamente relacionados ao tema. **Resultados:** A incidência de DBP foi menor naqueles casos leves expostos à budesonida inalatória, óleo de peixe intravenoso contendo emulsão lipídica (OP) e ácido docosahexaenoico (DHA). Houve aumento da sobrevida com uso de hidrocortisona em baixas doses, dexametasona com redução gradual da dose, por 42 dias, e dexametasona associada a corticosteroides pós-natais (este ainda com redução dos prejuízos no neurodesenvolvimento). Hidrocortisona, dexametasona, dipropianato de hidrofluoalcano-beclometasona inalado e OP reduziram o tempo ou a necessidade de ventilação e oxigenoterapia. A mortalidade foi menor nos estudos envolvendo hidrocortisona e elevada no que avaliou budesonida. As principais complicações foram sepse, retinopatia, hemorragia intraventricular e enterocolite necrosante, nos estudos abordando DHA, hidrocortisona, dexametasona e óxido nítrico inalado. **Conclusão:** Abordagens terapêuticas satisfatórias foram os glicocorticoides associado à terapia ventilatória e à abordagem precoce. Não houve benefícios com uso de ventilação com insuflações sustentadas, administração de dipropionato de hidrofluoralcano-beclometasona inalada e DHA.

Palavras-chave: Displasia Broncopulmonar; Prematuridade; Terapêutica.

Introduction

Bronchopulmonary dysplasia (BPD) is a serious complication of preterm birth, affecting almost half of babies born with a gestational age (GA) less than 28 weeks[1] and approximately 40% of babies born with a GA less than 30 weeks[2]. Its incidence varies inversely with the GA and, depending on the definition, can exceed 50% among those with extremely low weight[3].

BPD is an inflammatory process that causes abnormal lung development, decreased vascular and alveolar development, requiring supplemental oxygen or assisted ventilation at 36 weeks of postmenstrual age, configuring the most common complication of preterm birth[4].This determines adverse consequences, short and long term, being patients more susceptible to chronic cough and asthma-like symptoms at school age[5]. It can also cause neurodevelopmental abnormalities, growth deficiency, greater need for hospitalization[4] respiratory and cardiovascular morbidity[1,6-9]. Besides, it is associated with impaired lung function consistent with airway obstruction, reduced airflow measurements and reduced gas transfer, especially between 5 and 10 years[3].

In addition, the disease increases mortality in early childhood[10], with premature deaths predominantly occurring in the smallest and most vulnerable children[11]. With the growth in survival of babies with a lower GA, the rates of BPD are increasing[12].

It is known that lung inflammation and genetic variation are risk factors for BPD, and there are speculations about such variability interfering with therapeutic responses[1,12]. In the same way, exposure to oxygen stimulates the appearance of lesions, since fetuses they develop in an environment with little oxygen and, as premature babies have reduced antioxidant systems, this makes them more susceptible to oxidative stress[13]. In contrast, optimal nutrition is essential to prevent this condition[10].

Currently, therapeutic options for the prevention and treatment of BPD are limited and do not substantially affect the occurrence of the disease[7]. Previous studies point to the controversial use of postpartum steroids, as despite some benefits, systemic use would increase the chance of

unsatisfactory neurocognitive outcomes[14]. However, the use of inhaled glucocorticoids has shown beneficial pulmonary effects, with lower risk of adverse effects[9]. Furthermore, the type of ventilation to which preterms are submitted has influenced the prognosis, with reduction in mortality, incidence of BPD, episodes of hypocarbia, pneumothorax and intracranial hemorrhages[15]. In view of the above, despite the few options for treatment[14], pharmacological therapies and neonatal ventilatory strategies are important tools and need further elucidation regarding their application in BPD. Therefore, the present study aims to address the most recent aspects of the literature regarding the prevention and treatment of BPD.

Methods

A literature review was carried out in the MEDLINE database in 2021, using the keywords in English "pulmonary broncodysplasia", "prematurity" and "treatment" with their unique characteristics through the Medical Subject Headings Section (MeSH). In order to select the studies with greater investigation, only controlled and randomized clinical studies (CRCE) performed in humans. As an inclusion criterion, there are studies published in the last 5 years and, as an exclusion criterion, studies that were not directly related to the proposed theme. Twenty-two articles involving the theme were identified and, of these, twenty articles participated in the scope of this review. The PRISMA scale was used in order to improve the report of this review, as a demonstration of the flowchart (Figure 1).

Results

The selected studies analyzed a total sample of 4,722 patients, aged between 23 and 36 weeks of GA, with some children being reassessed later at 6, 12, 18, 24 months and/or at 5 and a half years of age. The forms of treatment or prophylaxis for BPD varied between articles, the main ones being: use of glucocorticoids (dexamethasone, hydrocortisone, budesonide or inhaled hydrofluoralkane-beclomethasone dipropionate), use of docosahexaenoic acid (DHA), use of inhaled nitric oxide (NIO), sustained insufflation, intermittent positive pressure ventilation, volume and work segmentation levels, proportional assisted ventilation (PAV), naturally adjusted assisted ventilation (NAAV), partial liquid ventilation, intravenous fish oil containing lipid emulsification (FO) and early intervention program, defined as preventive neurobehavioral interventions with the accompaniment of a physiotherapist and guided by the Child Behavior Assessment.

Although different approaches were taken between the studies, some points in common between them were listed. The data are detailed in Tables 1 and 2.

About the incidence of BPD, some articles showed a decrease in the occurrence of the disease in those who received some therapy. Among them, the studies by Bassler et al. (2018),[9] who performed prophylaxis of patients with inhaled budesonide, and from Hsiao et al. (2019),[16] whose intervention group was treated with FO, concluded in a lower rate of BPD in the intervention group when compared to placebo. Furthermore, in preterm babies submitted to NIO there was a lower rate of BPD, but statistical significance was not reported.[2]

Collins et al. (2017)[4] showed that the development of mild BPD was significantly lower in babies who received DHA up to the postmenstrual age of 36 weeks, but did not demonstrate a lower incidence of moderate or severe BPD in the group that received the same supplementation. Although the incidence of BPD has shown some satisfactory results, Marc et al. (2020)[10], found that the occurrence of BPD was higher in babies whose mothers were submitted to DHA.

In the study by Kirpalani et al. (2019)[11], there was no reduction in the risk of disease development in ventilation with 2 sustained inflations, when compared to standard intermittent positive pressure ventilation, as a measure of BPD prophylaxis. In the same aspect, the two articles that analyzed the effect of using hydrocortisone as a form of disease prevention did not show any statistical difference

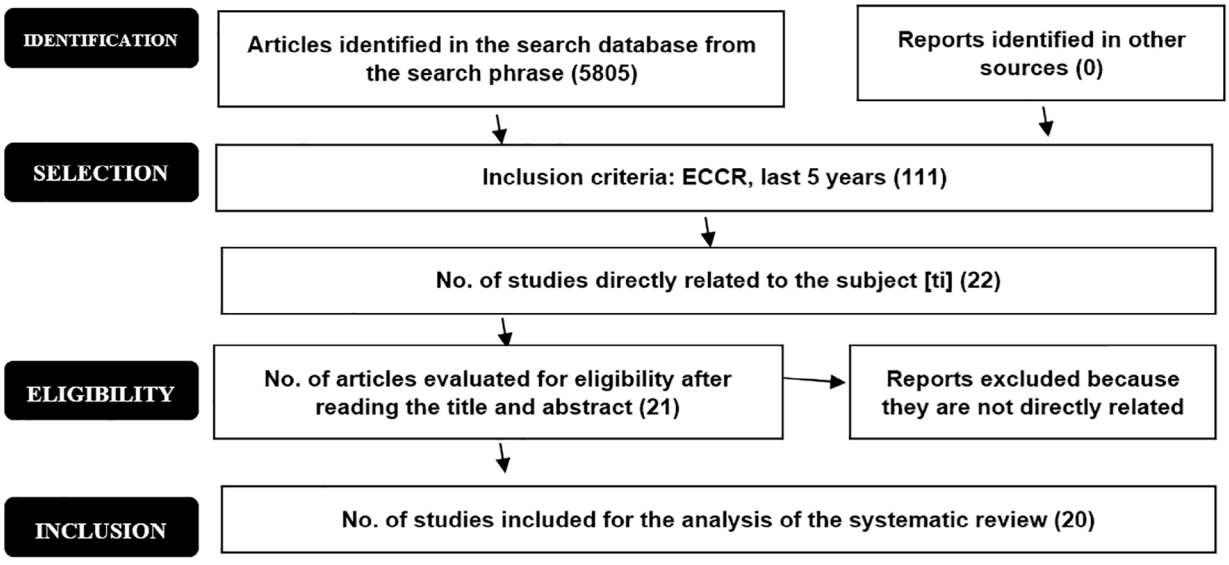

Figure 1. Research methodology used in the study.
Source: Author's own authory, 2021.

Table 1. Summary of studies and main results for the incidence of BPD and BPD-free survival.

Authors and year of publication	Sample	Intervention	Incidence of BPD in 36 weeks of postmenstrual	Survival free from DBP
Collins et al. (2017)[4]	1.205 babies with GA<29 weeks.	DHA enteral emulsion 60mg/kg/day (n=592) vs control emulsion (soybean) without DHA (n=613) up to week 36 of IPM.	Mild BPD: 13.5% DHA vs. 17.6% control; *p*=0.04. Moderate: 11.0% vs. 8.1%; *p*=0.10. Severe: 34.1% vs. 31.7%; *p*=0.36. Total physiological BPD: 49.1% vs. 43.9%; *p*=0.02. Clinical BPD: 53.2% vs. 49.7%; *p*=0.06.	Physiological BPD or death before 36-week MPI was higher in the DHA group (52.3% vs. 46.4%; *p*=0.045).
Marc et al. (2020)[10]	461 lactating women (≥16 years) and their 528 babies (GA<29 weeks). 375 mothers and 523 babies completed the study.	232 mothers (273 babies) taking oral capsules with 1.2g/d DHA vs. 229 mothers (255 babies) in the placebo group, until the child was 36 weeks of MPI.	41,7% grupo DHA vs. 31,4% grupo placebo; *p*=0,01.	There was no improvement in BPD-free survival at week 36 of PMA (54.9% DHA vs. 61.6% placebo survived without BPD; *p*=0.18).
Marr et al. (2019)[17]	59 babies with GA between 24 and 27 weeks.	Dexamethasone 0.5mg/kg/day 3 days, followed by a slow taper (42 days group, n=30) vs. dexamethasone 0.5mg/kg/day for the first 3 days followed by a rapid taper (group 9 days, n=29).	-	The 42-day group had a better disability-free survival rate compared to the 9-day protocol.
Onland et al. (2019)[1]	371 babies with GA<30 weeks.	Systemic hydrocortisone sodium succinate with a cumulative dose of 72.5 mg/kg (n = 181) vs placebo (n = 190), started 7 to 14 days after birth and lasting for 22 days.	55.2% hydrocortisone vs. 50.0% placebo; *p*=0.31.	Death or BPD at week 36 of PMA was 70.7% in the hydrocortisone group vs. 73.7% in the placebo group; *p*=0.54.
Baud et al. (2016)[14]	521 babies with GA<28 weeks.	Hydrocortisone emisuccinate 1mg/kg/day offered in 2 doses/day for the first 7 days of life, followed by 1 dose of 0.5mg/kg/day over the 3-day period (n=255) vs. placebo (n =266).	22% hydrocortisone vs. 26% placebo; *p*=0.25.	Survival without BPD was 60% hydrocortisone group vs. 51% placebo group; *p*=0.04.
Bassler et al. (2018)[9]	856 babies with GA between 23 and 27 weeks and 6 days.	2 inhalations of 200µg budesonide every 12 hours for the first 14 days of life and one inhalation of 12/12 hours from the 15th day onwards (n=437) vs. placebo (n=419).	28.2% budesonide group vs. 37.4% placebo; *p*NI.	-
Kugelman et al. (2017)[19]	38 babies with GA<32 weeks.	Hydrofluoalkane-beclomethasone (QVAR) inhaled 100µg per dose (n=18) vs. placebo (n=20) twice daily via Aerochamber with face mask.	-	-

Hasan et al. (2017)[2]	451 babies with GA<30 weeks.	INO started 5 to 14 days after birth, lasting for 24 days. Initially applied at 20ppm, and later in decreasing doses until day 24 (n=229) vs. placebo using nitrogen (n=222).	61.9% INO group vs. 66.2% control group; *p*NI.	34.9% INO vs. 31.5% placebo; *p*NI. There was a slight increase in BPD-free survival in black babies treated with INO.
Kirpalani et al. (2019)[11]	426 babies with GA between 23 and 26 weeks.	Up to 2 sustained inflations at maximum peak pressure of 20cm HO using a T-piece and face mask (n=215) vs. standard with intermittent positive pressure ventilation (n=211).	Ventilation with 2 sustained breaths compared to standard intermittent positive pressure ventilation did not reduce the risk of BPD; *p*NI.	Rate of BPD or death in 36-week PMA was 63.7% vs. 59.2%; *p*=0.29.
Hunt et al. (2019)[15]	18 babies with GA<32 weeks.	Volume ventilation with targeting levels of 4, 5, 6 and 7ml/kg each for 20 minutes.	-	-
Hunt et al. (2020)[18]	18 babies with GA<32 weeks.	Basal ventilation for 1 hour followed by a two hour period of PAV (n=9) or NAAV (n=9).	-	-
Hsiao et al. (2019)[16]	60 babies with GA<32 weeks.	Infusion with fish oil containing lipid emulsion (n=30) vs. control (n=30)	13.3% intervention group vs. 36.7% control group; *p*=0.04. NOTE: evaluation performed out on the 8th day.	-
Van Hus et al. (2016)[20]	176 babies with GA<32 weeks.	Babies separated into early intervention (n=86) and control (n=90) groups.	-	-

Caption: GA: Gestational age; PMA: Post-menstrual age; *p*NI: *p*-value Not informed; n: Sample size; vs.: Versus. PAV: Proportional Assisted Ventilation; NAAV: Naturally Assisted Ventilation Adjusted.
Source: Author's own authory, 2021.

between the groups regarding the rate of BPD in the 36th week of postmenstrual age[1,14].

Concerning BPD-free survival, there was no significant difference in three studies that evaluated the use of hydrocortisone[1], DHA[10] and sustained insufflation[11]. The article evaluating prophylaxis with NIO showed a similar survival rate without BPD between groups, with a slight increase in BPD-free survival in black babies undergoing NIO[2]. On the other hand, there was an increase in BPD-free survival both in newborns up to 28 weeks who used low-dose hydrocortisone prophylactically[14], and in preterm babies with less than 27 weeks who underwent prophylactic use of dexamethasone with progressive dose reduction over 42 days[17]. In some cases, the intervention proved to be harmful in terms of BPD-free survival, as in cases of DHA use enteral route in a prophylactic manner[4].

Articles that addressed DHA, hydrocortisone, dexamethasone and NIO reported the occurrence of complications or adverse effects. The main ones were sepsis, retinopathy of prematurity, intraventricular hemorrhage and necrotizing enterocolitis. Persistence of the ductus arteriosus, pneumonia, gastrointestinal perforation and hyperglycemia requiring the use of insulin were also mentioned. In all these studies, the occurrence of complications or adverse effects was similar between the control and intervention groups[1,2,4,10,14,17]. One exception was the significantly higher occurrence of intraventricular hemorrhage grades 3 and 4 in the placebo group, when compared to the DHA group, in the study by Marc et al. (2020)[10].

Regarding neurodevelopment, the study by Marr et al. (2019)[17], who prophylactically administered dexamethasone and followed up until school age, showed that there was no impairment in development according to the Wechsler Intelligence Scale (5th edition) and neurological examinations. Besides, in the study by Hus et al. (2016)[20], early longitudinal intervention for babies with BPD had significant positive effects on neural and cognitive outcomes, also using the aforementioned scale. According to Bassler et al. (2018)[9], the administration of budesonide for the prevention of BPD did not cause significant differences in relation to neural development. In the case of prophylaxis with NIO, although it did not reach significant differences in relation to neurodevelopment, Hasan et al. (2017)[2] found in some cases the occurrence of visual or hearing impairment and cerebral palsy. As for volume segmentation levels, it is noteworthy that according to Hunt et al. (2019)[15]

Table 2. Variables analyzed by the studies.

Authors and publication year	Ventilatory support and oxygen therapy	Mortality	Complications	Evaluation of neurodevelopment	Use of postnatal corticosteroid
Collins et al. (2017)[4]	Duration of ventilatory support 41.5±28.7 days in the DHA group vs. 40.4±27.7 days in the control group; p=0.63.	6.2% DHA vs. 4.5% control; p=0.23 before 36 weeks of PMA.	Sepsis, necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity; p>0.05.	-	21.2% DHA vs. 21.2% control; p=0.81.
Marc et al. (2020)[10]	Need for oxygen supplementation at week 36 of IPM: 35.7% vs. 31.4%; p=0.20. need for oxygen therapy: 25,2% vs 25,8; p=0,85).	6.0% DHA vs. 10.2% placebo; p=0.12.	p>0.05, except for the rate of intraventricular hemorrhage grades 3 and 4 (7.7% intervention vs. 16.1% placebo; p=0,005).	-	-
Marr et al. (2019)[17]	Babies in the 42-day group had shorter duration of ventilation (p<0.005).	Increased intact survival at school age in the 42 day group (75% vs. 34%; p=0.005)	Nosocomial sepsis, retinopathy of prematurity, periventricular leukomalacia.	Intact survival (normal neurological examination, IQ>70 and receiving school education without further educational support) at 7 years of age.	Reducing exposure to steroids increased the risk of neurodevelopmental sequelae and was negative for survival
Onland et al. (2019)[1]	The hydrocortisone group showed greater success in extubation of babies from the 3rd day (p=0.01)	15.5% hydrocortisone vs 23.7% placebo; p=0.048 at 36 weeks of PMA.	Sepsis, patent ductus arteriosus, pneumonia, retinopathy of prematurity above grade 2.	-	-
Baud et al. (2016)[14]	More babies undergoing hydrocortisone were extubated on the 10th day (p=0.0002) and did not need ventilatory support (p=0.22) or supplemental oxygen (p=0.04) in the 36th week of IPM.	8% hydrocortisone vs 15% placebo in babies 26 to 27 weeks GA; p=0.03.	Gastrointestinal perforation, sepsis, insulin requirement, necrotizing enterocolitis.	-	-
Bassler et al. (2018)[9]	-	19,9% budesonide vs. 14,5% placebo; p=0,04.	-	There was no significant difference between groups regarding the occurrence of neurodevelopmental impairment (48.1% vs. 51.4%; p=0.40).	In all, inhaled glucocorticoids were used in 24.2% of babies after hospital discharge. 42.6% had BPD at 36 weeks MPA.
Kugelman et al. (2017)[19]	Oxygen use tended to be lower in the QVAR group, but these findings did not reach statistical significance. Babies who required oxygen at discharge (5/17 vs 6/19) or at the end of the study (0/17 vs 2/19) were comparable.	-	-	-	They were most used in the placebo group

Hasan et al. (2017)[2]	There was no significant difference between the groups regarding the duration of the need for oxygen therapy and positive pressure ventilatory support.	-	Retinopathy of prematurity, patent ductus arteriosus, sepsis, intraventricular hemorrhage, necrotizing enterocolitis. $p>0.05$.	It was similar between groups at 18 to 24 months of IPM, with a total of 17.8% of the 360 babies evaluated with some damage.	It was equivalent between groups (18.9% NIO vs. 22.8% placebo; pNI).
Kirpalani et al. (2019)[11]	-	Ventilation involving 2 sustained insufflations did not reduce the risk of death at 36 weeks of MPA.	-	-	-
Hunt et al. (2019)[15]	From the use of ventilation at a tidal volume of 7ml/kg, there is a decrease in the work of breathing below the baseline.	-	-	An increase in the work of breathing can be detrimental in terms of proper development.	-
Hunt et al. (2020)[18]	There was no significant difference in mean oxygenation index (OI) between PAV and NAAV (p=0.7), but both showed a decrease in OI compared to traditional baseline ventilation.	-	-	-	-
Hsiao et al. (2019)[16]	The duration of ventilatory support and oxygen use was shorter in the intervention group (p<0.05).	-	-	-	-
Van Hus et al. (2016)[20]	-	-	-	For babies with BPD, there were positive effects in the longitudinal intervention for cognitive (0.7 SD; p=0.019) and motor (0.9 SD; p=0.026) outcomes.	-

Legenda: IGA: Gestational age; MPI: Post-menstrual age; pNI: p-value not informed; $p>0.05$: There was no significant difference between groups; $p<0.05$: There was significant difference between groups; vs.: Versus.
Source: Author's own authory, 2021.

the increased work of breathing can be disadvantageous to development.

In the case of the use of postnatal corticosteroids, two studies showed similarity between the DHA or NIO groups in relation to the control groups[2,4]. In the assessment made by Bassler et al. (2018)[9] of the prevention of BPD with budesonide[2,4] a total of 24.2% of the babies used inhaled glucocorticoids after hospital discharge, and of these, 42.6% had BPD at the 36-week postmenstrual age. In the study by Kugelman et al. (2017)[19] there was a trend towards greater use of additional steroids after discharge in the placebo group, which could mask the possible benefits of QVAR when both groups completed the study with comparable exposure to inhaled steroids. Furthermore, it is important to highlight that according to Marr et al. (2019)[17], which evaluated the use of dexamethasone, the attempt to minimize exposure to steroids had a negative impact on survival and increased the risk of neurodevelopmental sequelae.

Discussion

BPD is a serious complication that usually affects preterm newborns and may be associated with increased mortality rates. In addition, those who survive are more predisposed to respiratory and cardiovascular impairment, growth failure, and neurodevelopmental delay[4]. The selected studies evaluated different ways of performing treatment for BPD, nevertheless, exploratory analysis showed that at some point in the most evaluation obtained results that were not significant between the placebo group and the intervention group, whether in the rate of BPD, in the short or long-term efficacy, in the occurrence of adverse effects or in the rate of death.

In the therapeutic approach with glucocorticoids, the study presented by Marr et al. (2019)[17], demonstrated that the use of a higher dose of dexamethasone (7.56mg/kg) had higher intact survival of all patients, precocious extubation, lower reintubation rate, less time on ventilation and transfusions, compared to the control group. However, in the long term, one patient had brain paralysis and another had systemic arterial hypertension, requiring a reduction in the dose of dexamethasone.

Onland et al. (2019)[1] and Baud et al. (2016)[14], proposed to prevent the development of BPD through hydrocortisone therapy, which is an alternative to the use of dexamethasone. The first study showed a significant reduction in the mortality rate and the occurrence of pneumonia, as well as easier extubation in the intervention group, but it did not change the incidence of BPD and reported a greater chance of using insulin to control hyperglycemic episodes. While the second study was associated with early extubations, increased survival without BPD and reduced frequency of ligatures in patients with patent ductus arteriosus and mortality in babies 26 to 27 weeks of GA when treated with low doses of hydrocortisone. Adverse effects found included gastrointestinal perforation and sepsis, although they did not show statistical difference between groups.

Budesonide and inhaled hydrofluoalkane-beclomethasone dipropionate are alternatives in the treatment of BPD. According to Bassler et al. (2018)[9] the effects of budesonide were significant in reducing the incidence of BPD in the first 24 hours of use, but did not change the indices of cognitive delay and severe cerebral palsy. On the other hand, in the long term, the mortality rate was higher in the budesonide group. Furthermore, Kugelman et al. (2017)[19] evaluated the therapeutic outcome with the intervention of inhaled hydrofluoalkane-beclomethasone dipropionate and was not able to detect an effect on the respiratory course of BPD. In the primary outcome, readmission rate and oxygen use tended to decrease in the QVAR group, but without statistical significance. At the same time, there was a greater propensity to use additional post-discharge steroids in the placebo group, a condition that could mask the possible benefits of QVAR when both groups ended the study with comparable exposure to inhaled steroids.

The use of DHA is another possibility for the treatment of BPD. The studies by Collins et al. (2017)[4] and Marc et al. (2020)[10] reached the common outcome that the use of DHA did not lead to improvements or decrease in the incidence of such pathology. Additionally, an increased risk of developing BPD was observed in patients who received this supplementation. Regarding the therapeutic approach through respiratory support, the study by Hasan et al. (2017)[2], found that the use of NIO did not increase survival and did not demonstrate significant secondary results with regard to adverse effects, respiratory outcomes and neurodevelopment. However, the study showed a small but non-significant increase in BPD-free survival in black patients who were treated with ONI.

Two studies carried out by Hunt et al. (2019, 2020)[15,18]. The first addressed the relationship of volume segmentation levels in babies with evolving or established BPD, demonstrating that only with ventilation at a tidal volume of 7ml/kg the pressure-time product of mid-diaphragm was significantly reduced compared with pressure-limited ventilation. So, the use of volume-directed ventilation at certain levels, when compared to pressure-limited ventilation, is responsible for reducing the work of breathing in babies with BPD. The second evaluated PAV versus NAAV, noting that there was no significant result, but when compared to conventional ventilation, they obtained a reduction in the oxygenation index. PAV, when compared to NAAV, presented significantly lower mean airway pressure and SpO_2/FiO_2, greater need for FiO_2 and worse alveolar-arterial oxygen gradient; compared to conventional ventilation, there was a reduction in the oxygenation index in patients with respiratory distress syndrome. On the other hand, NAAV, when compared to pressure-controlled ventilation and pressure-synchronized intermittent mandatory ventilation, exhibited favorable results, with a reduction in the work of breathing and lower peak inspiratory pressures, in addition to a reduction in the need for FiO_2.

Still regarding the ventilatory mode, Kirpalani et al. (2019)[11] compared sustained inflation ventilation with standard intermittent positive pressure ventilation, concluding that extremely preterm babies who required resuscitation at birth had no reduction in the risk of BPD or death. From another perspective, a study by Hsiao et al. (2019)[16] containing very low birth weight babies who received a lipid emulsion containing fish oil parenterally had lower levels of IL-1B and IL-6 in serum and bronchoalveolar lavage fluid from the eighth day of treatment, culminating in a decrease in the incidence of BPD.

Finally, Hus et al. (2016)[20] investigated the effects of the Child Behavioral Assessment and Intervention Program on the cognitive and motor development of very preterm babies and found that the program led to long-term developmental improvements in the intervention group, especially in babies with BPD.

Through the present study, it was possible to conclude that there are different approaches to the treatment of BPD. Regarding the use of glucocorticoids, we concluded that dexamethasone, hydrocortisone and budesonide are effective in the treatment of BPD, reducing the risk of hospital morbidity and promoting increased survival. The use of ventilation with sustained inflation and the administration of inhaled hydrofluoalkane-beclomethasone dipropionate and DHA did not show favorable results to justify its use in BPD. In addition, the use of ventilation with a guaranteed volume of 7ml/kg was more advantageous than positive pressure ventilation. PAV and NAAV were also more effective compared to conventional ventilation. However, further studies are needed to compare PAV and NAAV with volume-guaranteed pressure ventilation and also to certify the preventive use of early administration of FO. In addition, the approach of the assessment and early intervention program in preterm babies with BPD has, over time, shown benefits in both cognitive and motor domains. In summary, it was conclusive that the use of glucocorticoids associated with ventilatory therapy (PAV, NAAV or guaranteed volume) and early intervention, contributed to reducing morbidity and mortality associated with BPD.

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