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Review Article

The efficacy of hydrocortisone in preventing bronchopulmonary dysplasia: An integrative literature review.

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Abstract

Introduction: Bronchopulmonary dysplasia (BPD) is a chronic lung disease that affects mostly premature neonates, its pathophysiology is still uncertain, proliferative, apoptotic, and pro-inflammatory mechanisms are linked. The use of corticosteroids is an option in an attempt to prevent BPD. Objective: This literature review seeks to understand whether hydrocortisone has benefits in preventing BPD in preterm neonates. Methodology: An integrative review was carried out using Medline / Pubmed, Biblioteca Virtual da Saude (BVS), Cochrane, EMBASE, and Scielo as databases, searching for articles, between 2015 and 2021, that used only hydrocortisone for the prevention of BPD. To assess the methodological and evaluation quality, AMSTAR criteria, and GRADE system were used respectively. Results: From a total of 194 articles, 5 were included in the study, 2 studies observed a decrease in the need for mechanical ventilation, 3 had a decreased mortality rate and in 2 studies the cases of BPD were reduced with the use of hydrocortisone. One study did not show statistical significance for either mortality or BPD prevention with drug use compared with placebo. These studies showed a reduction in the need for invasive mechanical ventilation, as well as an increase in the extubation rate. The death rate for newborns who used hydrocortisone was also lower compared to the control group. Regarding the prevention of BPD, hydrocortisone showed a slight reduction in the number of cases compared to placebo, when started early (<24 hours) and with a low dose. Conclusion: The use of low-dose and early-onset of hydrocortisone was superior to placebo in preventing BPD, but hydrocortisone is still not an ideal drug for preventing BPD.

Keywords: Bronchopulmonary dysplasia, hydrocortisone, neonatology, BPD, corticosteroid.

Introduction

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that was first described in 1967, at the time being characterized in premature infants who required mechanical ventilation (1). It happens because birth occurs when the lungs are still developing in the canalicular phase (an increase of the bronchial lumen and consequently its vascularization) or in the saccular phase (appearance of the first terminal sacs, which increase in number and their wall thins, becoming more similar to the alveoli). Most of them affect preterm neonates (2), especially in the extremes and weighing less than 1500g, who are submitted to mechanical ventilation and non-physiological oxygen exposure, triggering the release of inflammatory factors that are part of the pathophysiology of BPD (3). It is also known that its incidence is higher in Caucasian males and that there is a hereditary issue involved. Some genes, such as SPOCK2 and the increased transmission of the A allele of rs4351 in the angiotensin-converting enzyme are present in patients with BPD (4).

The lack of knowledge about its pathophysiology makes its treatment difficult, it is known that proliferative, apoptotic, and pro-inflammatory mechanisms are involved (5, 6, 7). Therefore, there is no consensus on a specific treatment for BPD, and most of those that have been tested do not appear to be effective. Currently, there are preventive strategies, such as the use of minimal inspiratory fractions of oxygen and gentle mechanical ventilation, in addition to care with hydration, with pathologies such as patent ductus arteriosus and early use of surfactant, among others. (8, 9).

Given the morbidity and mortality resulting from BPD, strategies to prevent this disease are a constant search, knowing that inflammatory mediators are involved in its pathophysiology, the use of corticosteroids to minimize the risks of developing BPD becomes possible in some cases.

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However, these medications are not harmless to the neonate, especially the premature ones, so it is necessary to understand the role of these drugs in the prevention of BPD.

Hydrocortisone is one of the corticosteroids being studied for the prevention of BPD. It is an affordable medication and its prophylactic use in low doses seems to increase the survival rate in neonates (10). However, in preterm infants on mechanical ventilation, when administered between 7 and 14 days of life, no improvement in survival was found. The risk of side effects due to corticosteroid use should also be taken into account (17).

Due to the increase in the number of recent studies on hydrocortisone in the prevention of BPD, a review of the literature is necessary, to understand the role of this corticosteroid in the prevention of this pathology.

Hypotheses

Does the use of hydrocortisone bring benefits or not for the prevention of BPD in premature newborns?

Goals

To carry out an integrative review of the current literature to understand if there is benefit in the use of hydrocortisone for the prevention of bronchopulmonary dysplasia in premature newborns.

Specific objectives:

Classify publications by year, place of publication, type of study, and main results.

Methodology

This is an Integrative Review (IR). Therefore, the construction of the IR was adopted from the steps proposed by Mendes, Silveira, Galvão (2008) called: 1) Formulation of the research question, 2) Sampling, 3) Data extraction, 4) Critical Analysis, 5) Summary of Results and 6) Synthesis of Knowledge, which will be detailed below, except for steps 5 and 6, which are included in the presentation of the results and conclusions of this IR, respectively:

Step 1: Formulation of the guiding question of the work:

From the research question: "Does the use of Hydrocortisone bring benefits or not in the prevention of Bronchopulmonary Dysplasia in premature newborns?" The PICO protocol was established as follows:

P (population): Premature newborns;

I (Intervention): Use of hydrocortisone in the prevention of bronchopulmonary dysplasia;

C (control): comparison of the use or not of hydrocortisone;

O (result): Absence of pulmonary bronchodysplasia.

Step 2: Sampling:

The following descriptors were used to carry out the research: "hydrocortisone", "glucocorticoid", "corticosteroid and bronchopulmonary dysplasia", "corticoid and bronchopulmonary dysplasia", all found in the Health Sciences Descriptors (DeCS) database of the Virtual Library in Health and Medical Subject Headings (MeSH) of the PUBMED/ MEDLINE database, medical science journals and online books. The search strategy was carried out by combining the descriptors and MeSH terms from the Boolean operators AND and OR, and to search for the articles, the electronic database PUBMED was consulted, in which articles available online and in full were selected.

Inclusion and exclusion criteria

Randomized controlled studies from the year 2015 to April 2021 were included, in which the use of hydrocortisone in preterm infants (less than 37 weeks) was analyzed as prevention for BPD, written in English or Portuguese. Those who used other drugs in association with hydrocortisone, or studies that made a comparison other than placebo, were excluded.

Qualitative research, case study, case report, systematic reviews, meta-analyses, articles with missing information that even after contacting the author could not obtain the necessary information, and duplicate articles found in different databases were excluded from the work.

In this research, the search was carried out by two researchers, and the inclusion of articles was discussed with the supervisor of the work.

Step 3: Data Extraction

From the initial survey, the selected articles were tabulated in an instrument organized by the researchers themselves. And, for the organization and categorization of the results, the articles were also submitted to analytical reading, whose purpose is to order and summarize the information contained in the sources, in a way that makes it possible

to obtain the research response and reach the proposed objectives.

Thus, the data obtained from the selected publications were: author's name, publication date, place, and country of the study; participants and objective, sample, results referring to the object of this research. Then, the articles were grouped and organized based on the results and conclusions.

Step 4: Critical Analysis

Initially, a total of 194 articles were selected through the presence of descriptors in titles and abstracts, as follows: 50 articles found in the Pubmed database; 19 articles in the VHL database, 29 articles in Cochrane; 93 articles in EMBASE; and 3 articles in Scielo. The articles found were comprised in the years 2015 to 2021 according to the methodology of the work.

A second selection was performed to exclude duplicate articles (39 articles), review articles, and those that were not in line with the guiding question (150 articles), and then 5 articles were selected.

A third selection was performed by reading the 5 articles in full and from these, prospective, observational, or analytical studies were selected, which resulted in 5 articles considered potentially relevant to constitute this integrative review.

Ethical Aspects

As it is a literature review and offers minimal risks, this project was not submitted to the Ethics and Research Committee. However, the ethical requirements regarding the data collected during the research were respected, preserving the ethical rigor that implies not infringing the CNS Resolution nº 466/12.

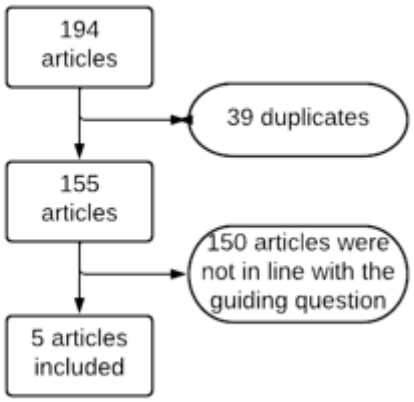

Figure 1: Presents the Flowchart for Selecting the Articles Included in the Analysis.

Results

Five articles were selected compatible with the objectives of this integrative review. As per the AMSTAR checklist, this study fits as a high-quality review. By the GRADE system, the quality of the articles selected for review varies in low, moderate, and high levels. The selected articles will be detailed below and compared in Table 1.

Observational cohort study performed with infants with a gestational age of 32 weeks or less, with a population of 48 patients receiving 5mg/kg/day of hydrocortisone, divided into 3 doses, for 5 days, with a total dose of 25mg/kg, in which 73% of patients received IV medication and 27% received the same oral dose. The study did not present the outcome according to the route of administration. Extubation was achieved in 50% of patients who were intubated at the start of hydrocortisone use, while 52.1% of patients had a reduction greater than or equal to 10% in inspiratory oxygen fraction (FiO2), in the placebo group in 34 .5% extubation was achieved by the tenth day, and in 38% there was a ≥ 10% reduction in FiO2. As a side effect, 10.4% of patients had an infection during treatment (13).

A randomized double-blind study, with a population of 64, carried out on children born weighing ≤ 1000g, between 10 and 21 days of life, who were dependent on mechanical ventilation. Treatment was made with hydrocortisone (sodium succinate) IV, 3 mg/kg/day for 4 days, 2 mg/kg for 2 days, and 1 mg/kg for 1 day, twice a day, for a total of 17 mg. /kg. The group that received hydrocortisone had a 10% lower mortality rate compared to the placebo group. Of the survivors, 3 (10%) of the study group had no BPD, while 5 (18%) of the placebo group had BPD (14).

In a randomized double-blind study carried out in 19 intensive care units in the Netherlands and Belgium, children born at less than 30 weeks and/or with birth weight less than 1250g, and who became ventilator-dependent between 7 and 14 days of life, with respiratory index greater than 3.5 for more than 12 h/day for at least 48 hours, with a population of 372. Treatment with hydrocortisone (sodium succinate) 5 mg/kg/day in 4 doses was introduced, for at least 7 days, followed by 3.75 mg/kg day in 3 doses daily for 5 days, then reducing the frequency to 1 dose every 5 days, for a cumulative total of 72.5

Article	13	14	15	16	17
GRADE	Low	Moderate	High	Low	High
Autors	Clauss C, et al	Parikh N A, et al	Onland W, et al	Peltoniemi.O M et al	Baud O, et al
Database	Medline (Pubmed)	Medline (Pubmed)	Medline (Pubmed)	Medline (Pubmed)	Cochrane
Kind of study	Observational cohort study	Double-blind randomized trial	Randomized double-blind study	Randomized double-blind study	Double-blind, placebo-controlled, multicenter, randomized study
Year of publication	2020	2015	2019	2015	2016
Country of origin	USA	USA	Netherlands and Belgium	Finland	France
Population	48	64	372	51	521
Inclusion criteria:	GA < 32 weeks	BW ≤ 1000g, between 10 and 21 days of life and dependent on IMV	GA < 30 weeks and/or BW< 1250g	GA between 23 and 30 weeks, BW between 501 and 1250g, on IMV in the first 24 hours of life	GA < 27 weeks
Dose	5mg/kg/day divided into 3 doses for 5 days	3 mg/kg per day for the first 4 days, 2mg/kg per day for 2 days, and 1 mg/kg for 1 day	5 mg/kg daily in 4 doses for 7 days, followed by 3.75 mg/kg daily in 3 doses for 5 days, reducing frequency by 1 dose every 5 days	2 mg/kg for 2 days, followed by 1.5 mg/kg for 2 days and 0.75 mg/kg for 6 days	1 mg/kg in 2 doses per day for 7 days, followed by a dose of 0.5 mg/kg for 3 days
	Total of 25 mg/kg	Total of 17 mg/kg	Total of 72.5 mg/kg	Total of 11.5 mg/kg	Total of 8.5 mg/kg
Start day	After birth	10 and 21 days of life	7 and 14 days of life	< 24 hours of life	< 24 hours of life
Duration	5 days	7 days	12 days	10 days	10 days
Route of administration	IV and OR	IV	IV	IV	IV
Side effects	Infection (10,4%)	not described	Hyperglycemia (18,2%)	Gastrointestinal perforation (11%) May have negative neurocognitive effects in preschoolers	NB between 24 and 25 weeks increase in the number of sepsis
Evaluated outcomes	Extubation index, FiO2 reduction	Mortality BPD	Mortality BPD	Mortality BPD	Permanence on IMV, mortality and BPD
Hydrocortisone group results	50% extubation rate in 10 days 52.1% reduction ≥ 10% in FiO2	31% death 10% without BPD	15.5% death 55.2% with BPD	8% death 33% with BPD	60% survived without BPD, 18% death, 22% BPD

Placebo group results	There was no placebo group	41% death	23,7% death	11,5% death	51% survived without BPD
		18% without BPD	50,0% with BPD	36% with BPD	23% death, 26% BPD
Conclusion	Hydrocortisone is effective in reducing the need for ventilatory support	The use of late-onset hydrocortisone does not show statistical difference.	Newborns cannot tolerate high doses of hydrocortisone	Long-term use of hydrocortisone negatively affects neurocognition, and is not statistically significant for BPD	Hydrocortisone is beneficial at a low starting dose

Table 1: Comparison of studies and quality assessment according to the GRADE system.

GA = gestational age, BW = birth weight, IV = intravenous, OR = oral route, IVM = invasive mechanical ventilation, BPD = Bron cho-pulmonary dysplasia, FiO2 = Inspiratory oxygen fraction, NB = Newborn.

mg/kg. At the end of treatment, 70.7% of patients had BPD or died in the hydrocortisone group, and 73.7% in the placebo group. There was no statistical difference in the development of BPD (55.2% for the hydrocortisone group and 50% for the placebo group), however, mortality was reduced for the hydrocortisone group (15.5%) compared to the placebo group (23.7%) (15).

Another double-blind, randomized, multi-center study, with data collected between August 2002 and March 2004, was performed with low-dose hydrocortisone for the prevention of BPD, neonates weighing between 501 and 1250g, with gestational ages between 23 and weeks and 0 days to 30 weeks and zero-days, and who require mechanical ventilation before the first 24 hours of life. Hydrocortisone was administered IV to 25 infants at a dose of 2 mg/kg daily for two days, followed by 1.5 mg/kg for two days and 0.75 mg/kg for 6 days, with a total dose. of 11.5 mg/kg. The start of treatment was performed within the first 24 hours of life. The number of samples for the study was 16% of that intended due to the risk of gastrointestinal perforation becoming apparent. Of the 51 patients studied, 25 received hydrocortisone and 26 received placebo, with two deaths recorded in the hydrocortisone group and 3 in the placebo group. Patent ductus arteriosus was lower in the treatment group (22%), compared to 68% in the control group. Of the patients who received hydrocortisone, 11% had gastrointestinal perforation. As for BPD, 33% of the treated patients presented the condition, against 36% of the placebo group (16).

In a double-blind, randomized, multicenter, placebo-controlled study carried out in France and published in 2016, 521 neonates were included using the following criteria: GA from 24 weeks and 0 days to 27 weeks and 6 days, excluding newborns in which the membrane rupture occurred before 22 weeks, if BW was less than third percentile, severe perinatal asphyxia, if expected to die shortly after birth, or malformations. The beginning of the treatment started with less than 24 hours of life and was performed with hydrocortisone, intravenously, 1 mg/kg day for days, followed by 0.5 mg/kg day for 3 days, in a total dose of 8, 5 mg/kg for 10 days. Of the patients who received hydrocortisone, 153 (60%) survived without BPD at 36 weeks of postmenstrual age, while 136 (51%) in the placebo group. There were 47 (18%) deaths in the medicated group, while 60 (23%) died in the placebo group. In the corticosteroid group, 55 (22%) had BPD, while 70 (26%) in the placebo group. The increase in sepsis in newborns born between 24 and 25 weeks who received hydrocortisone was the only side effect with a statistical difference between the 2 groups (17).

Discussion

Among the pathologies that affect the premature neonate, bronchopulmonary dysplasia may have both short-term and long-term complications.

BPD prevention is one of the biggest challenges in neonatology today, and new drugs continue to be studied. Well-known medications such as macrolide antibiotics (18), vitamin D (19), and inhaled corticosteroids (20) are some examples.

Among the drugs that have been studied for the prevention of BPD, corticosteroids have a prominent place. They promote an anti-inflammatory and immunosuppressive response

through genomic mechanisms. They have the ability to diffuse through the cell membrane, binding to receptors, inducing a conformational change, forming a receptor-corticosteroid complex. This complex enters the nucleus and binds to DNA, thereby increasing the anti-inflammatory response and inhibiting pro-inflammatory mediators. Phospholipase 2 inhibition and inhibition of genes responsible for cyclooxygenase-2 expression are also part of the steroid response (20).

A well-studied corticosteroid is dexamethasone, a long-acting steroid 25 times more potent than hydrocortisone. It is a drug that has already shown improvement in BPD patients, but there are still controversies in the literature about the best time and dose for its use. According to a meta-analysis performed, cumulative doses between 4 and 6 mg/kg implied a reduction in mortality. It is known that the long-term use of dexamethasone can have consequences for neurological development, and like all corticosteroids, it has an increased chance of hypertension, hyperglycemia, and infections (21).

Another drug that has been showing good results is budesonide. The association of intratracheal budesonide with surfactant showed a decrease in the probability of developing bronchopulmonary dysplasia and mortality. However, there is still doubt whether there may be impacts on the neurological development of neonates and therefore more studies need to be carried out for it to be implemented on a large scale (22).

Hydrocortisone has fewer side effects compared to dexamethasone, mainly in neurodevelopment; in animal models, the hydrocortisone doesn't have apoptotic effects on the hippocampus. There are currently few studies strengthening the use of glucocorticoids to prevent BPD, maybe because the physiopathology of this disease is multifactorial (11).

An analysis of the 5 selected studies, comparing the groups that used hydrocortisone with the placebo group, resulted in: 2 studies observed a decrease in the need for mechanical ventilation (13, 17), 3 had a decreased mortality rate (14, 16, 17) and in 2 studies the cases of BPD were reduced with the use of hydrocortisone (16, 17). One study did not show statistical significance for either mortality or BPD prevention with drug use compared with placebo (15).

In general, the groups that used hydrocortisone had a greater benefit, compared to the placebo group, because in the analyzed outcomes (extubation time, mortality, and BPD) all those that used hydrocortisone had lower rates, even if not as significant, except for the result found by the PREMILOC group, which had an evident benefit when used with an early and low dose (17).

Regarding the side effects found by the 5 studies, one of them had an intestinal perforation rate of 11%, and the sample number had to be reduced due to this finding. The final dose of hydrocortisone used in this study was one of the lowest (11.5 mg/kg) compared to the others, but the onset was early (<24 hours of life) and lasted 10 days (16). A similar study, with the same duration and start of the drug, however with a larger population, did not have this side effect and obtained a favorable result, in relation to BPD and mortality, with the use of hydrocortisone (17). This may be due to the use of a lower dose, both total (8.5 mg/kg) and daily (1mg/kg/day), especially in the first 4 days of life, compared to 2-1.5 mg/kg/day of the study that had the side effect of intestinal perforation.

The study that used a higher final dose (72.5 mg/kg) and for a longer period of 12 days, but started at 7 days of age, did not report any side effects other than hyperglycemia in 18.2% (15), therefore, not confirming the relationship between the intestinal perforation finding and the dose or duration of corticosteroid use, but perhaps with an association of early-onset (< 24 hours of life) and high initial dose, so more studies should be performed to have a better understanding of these data. One of the studies looked at how hydrocortisone use can have negative neurocognitive effects in preschoolers (16). Another concern when using corticosteroids is the possibility of increased infection in preterm infants, and this was a side effect observed in 10.4% of the population in the study by Clauss et al., as seen in other studies on the use of corticosteroids. hydrocortisone (13, 17, 23).

All selected studies have a high quality according to the AMSTAR system and the quality of evidence was based on the GRADE system, with only two studies considered of high quality of evidence because they had a representative sample and adequate design that the others did not have, and they have divergent results, but one started hydrocortisone with less than 7 days of life, with a favorable result in relation to BPD (17) and the other with a late start (> 7 days of life), with an unsatisfactory result, not encouraging the use of the drug (15).

The review has limitations due to the small number of studies published with the characteristics analyzed in the last 5 years. Among those selected, there is no methodological uniformity, especially regarding the dose and start time of the

medication. Studies like these are laborious and involve several scientific aspects that make execution difficult, but they are necessary. Regarding the prevention of BPD, just one study, with high quality of evidence, with neonates who received the hydrocortisone showed a slight reduction in the number of cases compared to placebo with statistical significance, it was observed when started early and with a low dose (17), it is evident the need for further studies in the area.

Conclusion

The use of low-dose and early-onset of hydrocortisone was superior to placebo in preventing BPD, but hydrocortisone is still not an ideal drug for preventing BPD. More long-term studies are needed to analyze the risks and benefits.

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