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Literature review

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Deleterial effects of invasive mechanical ventilation in prematures: sistematic review

Efeitos deletérios da ventilação mecânica invasiva em prematuros: revisão sistemática

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RESUMO | INTRODUÇÃO: O recém-nascido é considerado pré-termo pela Organização Mundial da Saúde (OMS) quando nascido com menos de 37 semanas de gestação. A prematuridade acarreta consigo diversos problemas devido a imaturidade biológica, dentre as complicações mais graves relacionadas à prematuridade está o subdesenvolvimento do sistema respiratório. **OBJETIVOS:** reexaminar a literatura dos últimos 5 anos sobre os efeitos deletérios da VM em prematuros. **MATERIAIS E MÉTODOS:** Foi realizada uma revisão sistemática de estudos em bases de dados *Medical Literature Analysis and Retrieval System Online* (PubMed/Medline) e Literatura Latino-Americana e do Caribe em Ciências da Saúde (LILACS) e SciELO. Foram excluídos os artigos de revisão narrativa e os demais artigos que não correspondessem aos critérios de inclusão: Artigos que abordassem em seu desfecho primário ou secundário os efeitos deletérios da ventilação mecânica em prematuros, nos idiomas inglês, português ou espanhol. **RESULTADOS:** Foram selecionados 20 artigos, 12 de intervenção, 3 observacionais, 3 revisões sistemáticas e 2 meta-análise, que obtiveram pontuação entre 8 e 25 segundo critérios utilizados por Vieira e colaboradores e pontuação máxima na versão adaptada do instrumento AMSTAR, respectivamente, em sua qualificação metodológica. Foram encontrados 15 tipos de efeitos deletérios associados ao uso de ventilação mecânica invasiva. **CONCLUSÃO:** Demonstrou a ocorrência de 15 tipos diferentes de efeitos deletérios associados ao uso de ventilação mecânica em prematuros e dentre estes o efeito com maior incidência é a broncodisplasia pulmonar seguido pela lesão pulmonar induzida pela ventilação mecânica.

PALAVRAS-CHAVE: Respiração. Artificial. Recém-nascido. Prematuro. Efeitos.

ABSTRACT | INTRODUCTION: The newborn is considered preterm by the World Health Organization (WHO) when born with less than 37 weeks of gestation. Prematurity brings with it several problems due to biological immaturity, among the most serious complications related to prematurity is the underdevelopment of the respiratory system. **OBJECTIVES:** This study aims to review the literature of the last 5 years on the deleterious effects of MV in preterm infants. **MATERIALS AND METHODS:** A systematic review of the Medical Literature Analysis and Retrieval System Online (PubMed / Medline) and Latin American and Caribbean Literature in Health Sciences (Lilacs) and Scielo databases was carried out. Narrative review articles and other articles that did not correspond to the inclusion criteria were excluded: Articles that addressed the deleterious effects of mechanical ventilation in premature infants in the English, Portuguese or Spanish languages in their primary or secondary outcome. **RESULTS:** Twenty articles, 12 intervention, 3 observational, 3 systematic reviews and 2 meta-analysis were selected, which scored between 8 and 25 according to criteria used by Vieira and collaborators and maximum score in the adapted version of the AMSTAR instrument, respectively. methodological qualification. We found 15 types of deleterious effects associated with the use of invasive mechanical ventilation. **CONCLUSION:** It demonstrated the occurrence of 15 different types of deleterious effects associated with the use of mechanical ventilation in premature infants and among these the effect with a higher incidence is pulmonary bronchodysplasia followed by mechanical ventilation-induced lung injury.

KEYWORDS: Respiration. Artificial. Infant. Premature. Effects.

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Introduction

A newborn is considered preterm by the World Health Organization (WHO)[1] when born with a gestational age of less than 37 weeks. Preterm birth, low birth weight (weight below 2,500g), and problems during pregnancy and childbirth characterize the major risk factors related to early neonatal death[2,3]. According to DATASUS (2015)[4], 10.3% of live births in 2015 in Brazil were preterm births and almost 1000 deaths in the first year of life are related to perinatal complications.

Prematurity entails several problems due to the biological immaturity resulting from the interruption of intrauterine development. Among the most serious complications related to prematurity is the underdevelopment of the respiratory system[5]. In the embryonic stage, the respiratory system begins to be formed in the fourth week and its development continues until birth. From the 26th week onwards, in the terminal phase of pregnancy, the differentiation of the alveolar epithelium into type I and type II pneumocytes takes place[6].

Type II pneumocytes are the cells responsible for secreting surfactant, a substance whose function is to reduce surface tension and prevent alveolar collapse[6]. Thus, preterm infants, especially in case of moderate to extreme prematurity, need a ventilatory support and often exogenous surfactant. The use of surfactant reduces the period of mechanical ventilation and prevents the risk of pulmonary complications[7].

Mechanical ventilation (MV) is an invasive method that uses a positive pressure through an endotracheal tube to conserve gas exchanges, aiming to reduce the use of inspiratory oxygen fraction (FiO2), and reduce the risk of mortality in newborns. It can lead to risks and trigger pulmonary pathologies such as bronchopulmonary dysplasia, barotraumas, oxidative stress caused by hyperoxia, nosocomial infections, traumas in the airways and prolonged hospitalization time, among others[8]. Criteria for indication of MV are: important dyspnea in continuous positive airway pressure (CPAP); frequent apneas in CPAP; PaO2 <50 with FiO2 > 60; untreatable metabolic acidosis and neuromuscular diseases[8].

As preterm infants require mechanical ventilation support, mainly the moderate to extreme preterm, and because their pulmonary underdevelopment predisposes them to complications, it is justified to perform the present study whose objective is to systematically reexamine the literature about the deleterious effects of invasive mechanical ventilation in preterm infants during the last 5 years.

Materials and methods

This is a systematic review of the literature and the guiding question of this study was: "What are the deleterious effects of invasive mechanical ventilation in preterm infants?" This research was directed through the formulation of the question, definition of inclusion and exclusion criteria, categorization of the studies and data to be extracted, data analysis, interpretation of result, and finally preparation of the article.

Data collection was performed in the databases Scielo, Pubmed and Virtual Health Library (VHL). The descriptors according to Health Sciences Descriptors (DeCS) used in the search were Respiration, Artificial, Infant, Preterm, and effects, and their correlates in Portuguese. The articles were selected according to the following inclusion criteria: articles found in databases that have the searched terms simultaneously, through the use of the Boolean indicators "and" and "and not", original researches that addressed the deleterious effects of mechanical ventilation in preterm infants as their primary or secondary outcome; studies carried out from January 2013 to September 2017 and published in English, Portuguese and Spanish. Intervention studies, observational studies, case studies and systematic reviews with meta-analyses or not were included; narrative review articles were excluded.

The information in the selected articles was ratified by two independent reviewers through a structured form including the names of the authors, associated with the journal and year of publication, title, place and period of study, study design and data analysis.

In cases of disagreement between the reviewers regarding the selection of articles to be analyzed, they were evaluated by a third reviewer. The research followed the items in the PRISMA protocol for systematic reviews.

Evidence quality

Intervention articles, observational studies and case reports that were selected according to the inclusion criteria were methodologically qualified, with scores according to criteria used by Vieira and collaborators9.

The score "zero" was attributed to the items when the information was not specified in the text, or when it did not meet the respective quality classification criteria. In the individual evaluation, the maximum possible score was 30 points. Qualification criteria and their respective scores are shown in Table 1.

Table 1. Qualification criteria and scores used to evaluate intervention and observational studies in the systematic review.

Quality Criteria	Score
Internal validity scale (type of study)	**0 a 5**
Randomized and controlled intervention	5
Cohort	4
Case-control	3
Cross section	2
Case report or case series	1
Not specified in the article	**0**
Structured summary*	**0 a 1**
Introduction with backgrpund and justification	**0 a 1**
Method of population recruitment	**0 a 3**
National	3
Local residents (city/neighborhood)	2
Clinical and service users	1
Not specified in the article	**0**
Sample selection	**0 a 6**
Census	6
Simple random	5
Systematic	4
Stratified	3
By clusters	2
Convenience	1
Not specified in article	**0**
Data collection instrument	**0 a 3**
Validated and standardized	3
Validated	2
Standardized	1
Not specified in the article	0
Non-informed response rate*	**0 a 1**
Training of interviewers*	**0 a 1**
Method of measuring results defined	**0 a 1**
Statiscal analysis performed*	**0 a 1**
Study hypothesis and biases considered*	**0 a 1**
Results interpreted according to evidence	**0 a 1**
Scale of generalization of results	**0 a 5**
Anywhere in the wolrd	5
Continents or a similar subcontinent	4
Same country	3
Same geographical region	2
Specific population	1
Not specified	**0**
Maximum score	**30**

*Score equal to zero when the information was not specified in the text or when it did not meet the criterion.

The systematic reviews and meta-analyses selected for the present systematic review were methodologically evaluated according to the criteria and scores of the AMSTAR instrument in the version adapted and validated by Costa and collaborators[10]. The instrument is divided into 14 yes/no questions. The response yes was scored 1, and no was scores 0, so that the maximum score is 14 points. Qualification criteria are shown in Box 1.

Box 1. Qualification criteria and scores used to evaluate Systematic reviews and meta-analysis in Systematic Review

The questions below refer to methodological criteria that are minimally necessary for a quality systematic review. The questions are accompanied by an explanatory text to aid their understanding. For each question, check yes or no, according to the presence or absence of the criterion in the review evaluated. In case of doubt and/or lack of clarity regarding the presence of any criterion, check no.	
1)Is the objective of the research clearly stated? The purpose of the research should be clearly described before the beginning of the review.	YES NO
2) Are the essential elements of the search strategy described? Key words and Boolean operators (and; or; not; etc.) should be indicated when used. Time cuts in the search should be clearly described if used in the study. The date when the search was performed should be described.	YES NO
3) Was the publication's nature used as a search criterion? The authors should mention if they did not include any publication due to their nature (thesis, dissertation, conference abstract) or language etc.	YES NO
4) Were the inclusion and exclusion criteria used in the selection of the studies described? Methodological criteria, such as design (e.g., experiments, surveys, case studies); type of instrument used (e.g. interviews, focus groups, testing, etc.); and analysis of data (e.g. content analysis, phenomenology, statistical tests, etc.) can be described as criteria for selection of studies, among others.	YES NO
5) Was a comprehensive search conducted? At least two electronic databases should be used (Psycinfo, Scielo, Medline, etc.) and described. Research can be complemented by other materials such as revisions, textbooks, technical texts, search in the references of the studies found and consultation of experts in the specific field of study.	YES NO
6) Did at least two judges carry out the search and selection of publications? At least two independent judges conducted the search and selected the studies based on inclusion and exclusion criteria. Consensus strategies in case of disagreement should be reported.	YES NO
7) Were the number of articles included and excluded at each stage of the search informed? It should be explicit whether in text, figure, list or chart, how many articles were included and excluded at each stage of the review.	YES NO
8) Did at least two judges perform the data extraction? At least two independent judges performed the extraction of data in the selected articles. Consensus strategies in case of disagreement should be reported.	YES NO
9) Were the characteristics of the included studies described? According to the objectives of the study, the characteristics of the reviewed studies should be described in an integrated manner, either in a table or verbatim. For example, age, race, gender, relevant socio-economic data, designs, sampling techniques, investigated outcomes, etc.	YES NO
10) Was the method of evaluation of the methodological quality of the studies described? The form of evaluation of the quality of the reviewed studies adopted should be reported. For example, different sample sizes, design types, statistical power of tests used, effect sizes, etc. can be considered. In the case of qualitative studies included in the selection, the authors should evaluate the data analysis performed and if this is theoretically supported, if there is a description of the coding procedure and or data analysis, including who coded and which were the units of analysis, etc.	YES NO
11) Were the methods used to integrate the results of the studies described? Methods for integrating results should be described and appropriate, both in reviews using quantitative and qualitative analyses. If the author wishes to integrate results from quantitative studies, tests should be performed to ensure the possibility of combining such results. In the case of reviews that use qualitative studies and/or that propose a qualitative analysis of the results, specific analysis methods for the integration should be reported (e.g. discourse analysis, content analysis, grounded theory, meta-synthesis). If the author chooses not to make the integration of the reviewed studies, in the case of a descriptive review, for example, this option should be described.	YES NO
12) Was the methodological quality of the included studies appropriately used in the formulation of conclusions? The conclusions of the review should take into account the different methodological qualities of the reviewed studies, discussing their limitations, especially in the formulation of future recommendations.	YES NO

Box 1. Qualification criteria and scores used to evaluate Systematic reviews and meta-analysis in Systematic Review

The questions below refer to methodological criteria that are minimally necessary for a quality systematic review. The questions are accompanied by an explanatory text to aid their understanding. For each question, check yes or no, according to the presence or absence of the criterion in the review evaluated. In case of doubt and/or lack of clarity regarding the presence of any criterion, check no.	
13) Was the publication bias considered? The possibility that the data may be biased due to some limitation of the review itself should be considered. An analysis of publication bias may include a graphical combination (e.g., funnelplot or other available tests) and/or statistical tests (e.g., Egger regression test). The publication bias must be at least mentioned in the text as one of the limiters of the review.	YES NO
14) Was the conflict of interests described? Potential supporting sources should be clearly stated both in the systematic review and in the included studies. If there is no conflict of interest, the author must inform the reader of the absence of potential sources of conflict.	YES NO
TOTAL	

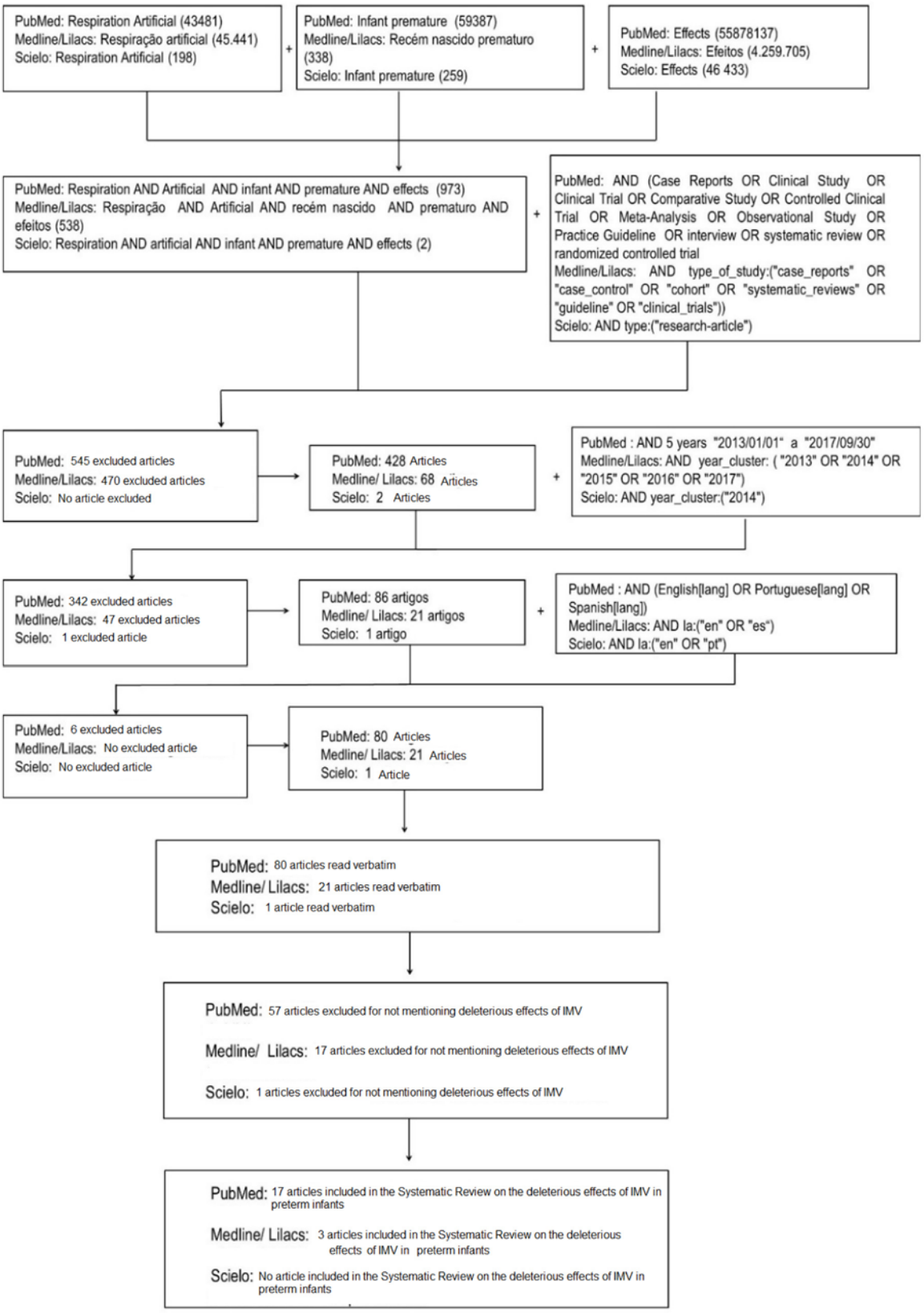
Results

The search using the terms Artificial Respiration and Respiração artificial separated found 43,481 articles in PubMed, 45,411 in Medline/Lilacs and 198 in Scielo. The search with the terms Infant premature and recém nascido prematuro found 59,387 articles in PubMed, 338 in MedLine/Lilacs and 259 in Scielo. And the search with the terms Effects and efeitos found 55,878,137 articles in PubMed, 4,259,705 in MedLine/Lilacs and 46,433 in Scielo. When we performed the advanced search using Boolean operators combining the terms Artificial Respiration and Infant premature and Effects and their correlates in Portuguese, we identified a total of 973 articles in PubMed, 538 in MedLine/Lilacs and 2 in Scielo.

After the association of the other Boolean indicators, narrative review articles and other articles that did not meet the inclusion criteria were excluded, resulting in 545 (PubMed), 470 (Medline/Lilacs), 0 (Scielo) exclusions; articles published before the last 5 years or published after September 30, 2017 were also excluded, resulting in 342 (PubMed), 47 (MedLine/Lilacs), 1 (Scielo) exclusions; and articles that were written in other languages werealso excluded, resulting in 6 (PubMed), 0 (Medline/Lilacs and Scielo) exclusions. The next step consisted in the complete reading of 80 articles from PubMed, 21 from MedLine/Lilacs and 1 article from Scielo.

In this review, the research revealed 20 articles that met the pre-specified eligibility criteria and 82 articles were excluded, as shown in the flow chart of selection of studies (Figure 1), but until the moment of realization of the present systematic review, there were no studies addressing the deleterious effects of invasive mechanical ventilation in preterm infants as main outcome. There may be other articles that were not published until the date of the survey or were published in a language not included in this systematic review.

Figure 1. Flowchart of selection of studies from the Medical Literature Analysis in Retrieval System Online (Pubmed/Medline), the Latin American and Caribbean literature on Health Sciences (Lilacs), and the Scientific Electronic Library Online (Scielo).



The study designs were: Multicenter clinical trial (4), Randomized controlled trial (4), Comparative study (1), Observational study (3), Secondary analysis of a cross-sectional study (1), Systematic review (3), Meta-analysis (2). Box 2 presents the description of the articles selected according to: author, year of publication and country of study, type of study, sample and deleterious effects of invasive mechanical ventilation.

Box 2. Studies included in the systematic review of the deleterious effects of IMV in preterm infants.

Author/Year of Publication/Country of Study	Study type	Sample	Harmful effects of MV cited
Ancora G et al. [25], 2017, Italy	Multicenter Study	131 PTN in MV	Pain and distress during mechanical ventilation.
Onland W et al.[16], 2017, The Netherlands	Systematic review	21 studies	Pulmonary bronchopulmonary dysplasia.
Thome UH et al. [23],2017, Germany	A multicenter randomized trial	359 PTN	Pulmonary injury induced by ventilation and pulmonary bronchopulmonary dysplasia.
Viana CC et al.[24], 2016, Brazil	Cross-sectional randomized trial	28 PTN	Shearing injury related to the opening and closing of unstable pulmonary units.
Ozdemir SA et al.[13], 2016, Turkey,	Randomized, controlled, prospective study	34 PTN	Ventilator-induced injury, pulmonary bronchopulmonary dysplasia, volutrauma.
Manley BJ et al.[18], 2016, Australia	Secondary analysis after a randomized study	174 PTN	Pulmonary bronchopulmonary dysplasia, neurological impairment, death.
Ballard R et al.[17], 2016, USA	Multicenter randomized controlled blind study	511 PTN	Pulmonary bronchopulmonary dysplasia, volutrauma, oxidative stress.
Rojas-Reyes MX et al.[14], 2015, Colombia	Systematic review	6 articles	Ventilation-induced lung injury.
Dursun A et al.[12], 2015, Turkey	Comparative study	37 NBs	Ventilation-induced lung injury, barotraumas, oxidative stress.
Neumann RP et al.[21], 2015, Switzerland	Observational study	51 PTN	Pro-inflammatory response to the lung.
C. Grasso et al.[22], 2015, Italy	Observational, analytical, cross-sectional, case-control study	78 PTN	Volutrauma, barotraumas.
Lai M et al.[28], 2014, Australia	Systematic review	5 RANDOMIZED CLINICAL TRIALS	Airway damage, subglottic stenosis.
Erdemir A et al.[20], 2014, Turkey	Prospective, randomized, controlled study.	60 PTN	Atelectasis post intubation, inflammatory response to low vt.
Tan B et al.[29], 2014, China	Meta-analysis	8 STUDIES	Pneumonia associated with ventilation.
Cabral LA et al.[26], 2014, Brazil	Observational prospective exploratory study	40 PTN	Peripheral oxygen desaturation
Vendettuoli, V et al.[15], 2014, Italy	Multicenter cohort study	2465 PTN	Pulmonary bronchopulmonary dysplasia.
Fischer HS et al.[19], 2013, Germany	Meta-analysis	7 STUDIES	Pulmonary bronchopulmonary dysplasia.
Stefanescu BM et al.[30], 2013, USA	Experimental controlled randomized trial	41 infants	Pneumonia associated with ventilation.
Guven S et al.[11], 2013, Turkey	A randomized controlled trial	30 PTN in MV, 42 PTN in volume guaranteed	Ventilation-induced lung injury, volutrauma, barotrauma.
Vignaux L et al.[27], 2013, Switzerland	Prospective, randomized, and cross-sectional study	19 children	Patient asynchrony-ventilator.

Table 2. Qualification of the 15 intervention and observational studies according to criteria and scores.

Quality criteria	Dursun et al.	Cabral et al.	Guven et al.	Vendetuolli et al.	Manley et al.	Ballard et al.	Viana et al.	Stefanescu et al.	Ancora et al.	Thome et al.	Ozdemir et al.	Neumann et al.	Grasso et al.	Erdemir et al.	Vignaux et al.
Internal validity scale (type of study)	0	0	5	4	5	5	2	5	5	5	5	0	4	5	5
tructured abstract	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Introduction with background and justification	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Method of population recruitment	1	1	1	1	0	1	1	1	3	3	1	1	1	1	1
Sample selection	0	0	5	0	5	3	0	5	5	0	0	0	0	5	0
Data collection instrument	0	0	0	0	0	0	0	0	3	3	0	0	0	0	0
Non-informed response rate	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0
Training of interviewers	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Method of measuring results defined	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1
Statistical analysis performed	1	1	0	1	0	1	1	0	1	1	1	1	1	1	1
Study hypothesis and biases considered	0	1	1	0	0	1	1	0	0	1	0	1	0	0	0
Results interpreted according to evidence	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1
Scale of generalization of results	3	3	3	3	0	3	1	3	3	3	1	1	1	1	1
Maximum score	**9**	**10**	**18**	**13**	**8**	**18**	**10**	**18**	**25**	**20**	**12**	**8**	**11**	**17**	**12**

The results of the methodological qualification of the 15 articles (intervention and observational) that met the inclusion criteria of the current revision varied between 8 and 25 points (Table 2), and the systematic reviews and meta-analyses selected obtained the maximum score (Table 3).

Table 3. Qualification of the 5 systematic reviews and meta-analyses according to criteria and scores.

Quality criteria	Onland et al.	Rojas-reyes et al.	Lai et al.	Tan B et al.	Fischer et al.
Item 1	Y	Y	Y	Y	Y
Item 2	Y	Y	Y	Y	Y
Item 3	Y	Y	Y	Y	Y
Item 4	Y	Y	Y	Y	Y
Item 5	Y	Y	Y	Y	Y
Item 6	Y	Y	Y	Y	Y
Item 7	Y	Y	Y	Y	Y
Item 8	Y	Y	Y	Y	Y
Item 9	Y	Y	Y	Y	Y
Item 10	Y	Y	Y	Y	Y
Item 11	Y	Y	Y	Y	Y
Item 12	Y	Y	Y	Y	Y
Item 13	Y	Y	Y	Y	Y
Item 14	Y	Y	Y	Y	Y
TOTAL	**14**	**14**	**14**	**14**	**14**

Among the selected studies, 15 types of deleterious effects were identified due to invasive mechanical ventilation in preterm infants. Bronchopulmonary dysplasia was reported in 7 articles, followed by pulmonary injury induced by ventilation (5), oxidative stress (2), volutrauma (4), barotrauma (3), ventilation-associated pneumonia (2), atelectasis (1), pain during ventilation (1), shear injury (1), peripheral oxygen desaturation (1), patient-ventilator asynchrony (1), airway injury (1), pro-inflammatory response to tidal volume (2), neurological development (1) and death (1).

Discussion

The current systematic review of the literature sought to identify the deleterious effects associated with the use of invasive mechanical ventilation in preterm infants. Although this tool is an important ally of survival rates[7], the findings showed that there are several complications associated with its use. However, no studies were found in the Brazilian literature or in the international literature covered in this review addressing these effects as the main outcome.

Among the studies evaluated, the most frequent deleterious effect was bronchopulmonary dysplasia. Dursun et al.[12] say that the pathogenesis of

ventilation-induced lung injury includes barotraumas, alveolar hyper distension, oxidative stress and/or repetitive opening and closing of the alveoli. However, Ozdemir et al.[13] and Rojas-Reyes et al.[14] associate ventilation-induced lung injury as an important contributory factor for the development of bronchopulmonary dysplasia and chronic lung disease.

Vendetuolli et al.[15] conceptualize bronchopulmonary dysplasia as a multifactorial disease that includes in its pathogenesis immature lung tissue, barotraumas, volutraumas, oxygen toxicity and prolonged use of mechanical ventilation. In addition, volutrauma is reported to be more significant in the development of bronchopulmonary dysplasia than barotrauma8.

Bronchopulmonary dysplasia is also defined as the dependence of oxygen at 36 weeks post menstrual age according to Onland et al[16]. And Barllard et al.[17] point out the occurrence of bronchopulmonary dysplasia in almost 70% of cases in which mechanical ventilation lasted longer than in the first 7 days of life.

In addition to bronchopulmonary dysplasia, Manley et al.[18] point to neurological impairment and death as a consequence of prolonged mechanical ventilation. Guven et al.[11] further mention that pulmonary pressure damage, barotrauma, and damage caused by the use of high tidal volume, volutrauma, are common complications in the use of MV to treat preterm neonates.

Besides associating invasive mechanical ventilation as one of the factors that predispose to the development of bronchopulmonary dysplasia, Fischer et al19 explains that mechanical ventilation in extremely preterm newborn triggers an inflammatory cascade involving chemokines and other pro-inflammatory cytokines, the migration of inflammatory cells into airspaces, pulmonary lesions secondary to proteases which cause lung fibrosis and abnormal lung development. Erdemir et al[20] and Neumann et al[21] argue that mechanical ventilation causes lung lesions that may progress to bronchopulmonary dysplasia.

Thus, according to Grasso et al.[22], the reduction of intubation and invasive mechanical ventilation may contribute to the reduction of volutraumas, barotraumas and bronchopulmonary dysplasia, and Thome et al[23] suggest that using low tidal volume and accepting high values of PcO2 (permissive hypercapnia) contribute to the prevention of the development of injury induced by ventilation and bronchopulmonary dysplasia.

Dursun et al[12] report that mechanical ventilation can damage lungs through the oxidant-antioxidant system, so that ventilation increases systemic oxidative stress and decreases antioxidative capacity in neonates and this oxidative stress is also a predisposing factor for the development of bronchopulmonary dysplasia[20].

According to Viana et al.[24], patients who use invasive mechanical ventilation present alterations in mucociliary function due to the presence of the orotracheal tube, which may function as an airway irritant[22], high oxygen concentrations and aspiration lesions. Associated with this process and the excessive production of mucus, there is the risk of mucus retention and thus the development of lung infection and atelectasis.

Cabral et al.[25] correlate mechanical ventilation time with surfactant therapy as impacting factors in the reduction of peripheral oxygen saturation and triggering other effects such as: bradycardia, pulmonary hemorrhage and systemic hypotension, and changes in blood flow may occur. Vignaux et al.[26] also report that mechanical ventilation time causes asynchrony between patient and ventilator causing inefficient commitment in preterm infants. In turn, according to Lai et al.[27], the prolonged period of mechanical ventilation causes damage to the airways and subglottic stenosis.

Ancora et al.[28] characterize invasive mechanical ventilation as a process involving pain, stress and distress in the newborn, and in addition, processes such as extubation cause more pain[17] and uncontrolled prolonged pain negatively impacts neurological development[28].

Mechanical ventilation associated to pneumonia was described by Tan et al.[29] and by Stefanescu et al.[30] as an important short-term complication resulting in high rates of morbidity and mortality in newborns. The retention of mucus in the airways makes the environment conducive to the colonization

of microorganisms resulting in pneumonia and consequently in the reduction of lung compliance[21].

Methodological considerations

The evaluation of the intervention and observational studies demonstrated a quality of evidence that presented a score between 8 and 25 points, so that this qualification aimed to evaluate questions such as structure, presentation of the article and basic principles that ensure the research validation.

A low score indicates the absence of requirements in the article's structure that may involve the risk of bias. However, there is no cut-off point that defines articles evaluated as good or bad.

In addition to these, it is necessary to emphasize that there is the risk of bias induced by the search tools, such as terms used and articles that were not indexed to the databases used.

However, despite the risks of bias described, the present study had as a positive point the use of methods to qualify the selected studies, in addition to a comprehensive survey that included different types of studies, in different languages and countries.

Conclusion

Invasive mechanical ventilation increases NB survival, but may have deleterious effects. The present review demonstrated the occurrence of 15 different types of deleterious effects associated with the use of mechanical ventilation in preterm infants, and among these the effect with the highest incidence is bronchopulmonary dysplasia followed by lung injury induced by mechanical ventilation. In addition to these, 13 (thirteen) episodes were already mentioned.

Recognizing the importance and impact of these deleterious effects is crucial for the analysis of the strategies used and an incentive to studies for the development of new ventilatory methods aiming at minimal side effects. Moreover, knowledge about these effects guides neonatal care so that preventive and curative techniques can be more effective.

This study primarily shows the scarcity of studies on the proposed theme because there were no studies until the date of collection of articles that addressed the deleterious effects of invasive mechanical ventilation in preterm infants as main outcome, but only secondary outcomes were found, which indicates the need for further research.

Author contributions

Guedes JM and Conceição SL participated in the data collection and article writing. Albergaria TFS reviewed and coordinated the study.

Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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