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REVIEW

Effects of high frequency non-invasive ventilation in premature newborn infants: systematic review protocol

Efeitos da ventilação não invasiva de alta frequência em recém-nascidos prematuros: protocolo de revisão sistemática

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Abstract

Introduction: Premature birth is a condition, which can be induced by several factors. High Frequency non-invasive ventilation is a promising new mode of non-invasive ventilation that aims to offer adequate ventilation and oxygenation, but much has yet been discussed about its effectiveness and safety. *Objective*: To evaluate the effectiveness and safety of high frequency non-invasive ventilation in premature infants. *Methods*: To this end, we will carry out a systematic review. The study protocol was recorded on the Prosperous Platform. We will include premature newborns who used high-frequency non-invasive ventilation requiring ventilation as an initial support, after extubation or as a rescue mode (after failure of initial non-invasive therapy). The

searches will be carried out in the databases: Medical Literature Analysis and Retrieval System Online (Medline) via Pubmed, Excerpta Medica dataBASE (Embase) via Elsevier, Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Library, Latin American and Caribbean Literature in Health Sciences (LILACS) via the Virtual Health Library Portal and Physiotherapy Evidence Database We will evaluate the methodological rigor of the included studies and the certainty of the evidence of the main outcomes of the systematic review using Cochrane's Risk of Bias 2.0 tool and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, respectively. The selection of studies, data extraction, evaluation of the bias of the included studies and evaluation of the certainty of the evidence will be carried out by two independent researchers. *Expected Results*: The results of this review are expected to present a critical and up-to-date summary of the topic and facilitate safer decision-making by physiotherapists regarding the best recommendation for ventilatory support in the NICU, based on the best scientific evidence currently available.
Keywords: premature birth; infant, premature; noninvasive ventilation, high-frequency ventilation.

Resumo

Introdução: A prematuridade tem sido a principal causa de mortalidade neonatal no mundo por pelo menos uma década, e é uma condição que pode ser induzida por vários fatores. A ventilação não invasiva de alta frequência (VAF) é um novo modo promissor de ventilação não invasiva que visa oferecer uma ventilação e oxigenação adequadas. Entretanto, muito ainda se tem discutido sobre sua efetividade e segurança. *Objetivo*: Avaliar a efetividade e segurança da ventilação não invasiva de alta frequência oscilatória, a jato e percussiva em recém-nascidos prematuros. *Métodos*: Para tanto, realizaremos uma revisão sistemática. O protocolo do estudo será registrado na Plataforma Prospero. Incluiremos recém-nascidos prematuros que utilizaram a ventilação não invasiva de alta frequência com necessidade de ventilação como suporte inicial, após a extubação ou como modo de resgate (após falha de terapia não invasiva inicial). As buscas serão realizadas nas bases de dados: Medical Literature Analysis and Retrieval System Online (Medline) via Pubmed, Excerpta Medica dataBASE (Embase) via Elsevier, Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Library, Literatura Latino Americana e do Caribe em Ciências da Saúde (Lilacs) via Portal da Biblioteca Virtual em Saúde e Physiotherapy Evidence Database (PEDro), sem restrições de idioma ou ano de publicação. Avaliaremos o rigor metodológico dos estudos incluídos e a certeza da evidência dos principais desfechos da revisão sistemática utilizando a ferramenta Risco de Viés 2.0 da Cochrane e a abordagem

Grading of Recommendations Assessment, Development and Evaluation (GRADE), respectivamente. A seleção dos estudos, extração de dados, avaliação do viés dos estudos incluídos e avaliação da certeza da evidência serão realizados por dois pesquisadores independentes. *Resultados Esperados*: Espera-se que os resultados desta revisão apresentem uma síntese crítica e atualizada do assunto e facilitem a tomada de decisão de fisioterapeutas de forma mais segura quanto a melhor recomendação de suporte ventilatório em UTIN, baseadas na melhor evidência científica disponível atualmente.

Palavras–chave: nascimento prematuro; recém-nascido prematuro; ventilação não invasiva; ventilação de alta frequência.

Introduction

Prematurity has consistently emerged as the primary contributor to neonatal mortality on a global scale for at least the past decade [1]. Annually, a staggering 15 million infants are born prematurely, accounting for an estimated 11% of all births worldwide [1]. This elevated incidence of preterm birth can be attributed to a multitude of risk factors associated with this condition, encompassing infections, cervical abnormalities, uterine hyperdistension, insufficient progesterone levels, vascular irregularities (including uteroplacental ischemia and decidual hemorrhage), maternal and fetal stress, graft-related responses, allergic phenomena, and conceivably, several other unidentified factors [2]. Consequently, preterm birth often precipitates challenges in sustaining spontaneous respiration without assistance among preterm neonates [2]. This complication can arise from various factors, including underdeveloped lung functionality, instability in the chest wall, obstruction of the upper airway, and compromised central respiratory control, collectively augmenting the likelihood of necessitating invasive ventilatory interventions and admission to Neonatal Intensive Care Units (NICUs) to reestablish optimal lung function [2-4].

Non-invasive ventilation techniques have gained traction as prospective avenues for mitigating the unfavorable repercussions associated with invasive ventilatory measures, specifically endotracheal intubation, such as the onset of bronchopulmonary dysplasia (BPD) [5]. Despite notable advancements in neonatal intensive care, BPD continues to engender elevated risks of morbidity and mortality in certain cases [6]. Infants who survive BPD face an increased susceptibility to respiratory infections, wheezy infant syndrome, pulmonary hypertension, heightened hospitalization rates within the initial two years of life, as well as heightened vulnerabilities pertaining to growth and neurodevelopmental deficits [7].

Several non-invasive ventilation modalities can be harnessed, including continuous positive nasal airway pressure (nCPAP) [8], nasal intermittent positive pressure ventilation (nIPPV) [9], high-flow nasal cannula (HFNC) [10], and high-frequency ventilation (HFV). Within this spectrum, high-frequency ventilation (HFV) represents a safeguarding mode of ventilation that can be executed through three distinct methods: jet HFV, oscillatory HFV, and percussive HFV. Among the array of protective ventilation strategies pertinent to pediatric and neonatal care, HFV has surfaced as a promising non-invasive approach aimed at furnishing optimal ventilation and oxygenation. A defining feature of this modality involves employing an exceptionally low tidal volume (ranging from 1 to 3 mL/kg, which is notably smaller than the anatomical dead space volume of the respiratory system), concurrently with inducing minimal pressure fluctuations within the airways. To achieve this, HFV leverages a frequency surpassing physiological norms (ranging from 3 to 50 Hz). Recent investigations indicate the potential of HFV in diminishing the imperative for mechanical ventilation, alongside a reduction in associated complications [11].

An earlier systematic assessment conducted by Li [12] corroborated the utility of oscillatory HFV as a ventilatory support mechanism in preterm infants, noting enhanced carbon dioxide elimination and a lowered intubation risk relative to monophasic or biphasic nasal CPAP. However, it is noteworthy that the study conducted by Li [12] encompassed publications up to four years ago, rendering it outdated. Furthermore, no extant systematic review has, to date, comprehensively evaluated the impact of jet HAV and percussive HAV.

Objective

To evaluate the effectiveness and safety of noninvasive oscillatory, jet, and percussive HFV in premature newborns.

Methods

Type of study

This systematic review protocol will be conducted in accordance with the methodological recommendations of the Cochrane Handbook [13] and will be reported following the recommendations of PRISMA [14].

Types of studies included

Parallel randomized controlled clinical trials (RCTs) published in full text or in abstract only will be included.

Types of participants

Premature neonates (defined as those born at less than 37 weeks of gestational age) who used non-invasive HFV requiring ventilation as initial support, after extubation or as a rescue mode (after failure of non-invasive therapy) initial invasive) will be eligible.

Types of interventions

Studies that evaluated the effects of non-invasive oscillatory, jet or percussive HF in premature infants in the hospital environment will be considered.

Types of comparisons

The following comparison groups will be considered: nCPAP, NIPPV, HFNC, other therapies or other comparisons in which the effect of non-invasive HFV can be evaluated exclusively.

Primary outcomes

For assessing the effectiveness of the intervention, the following will be assessed:
- Mortality from all causes (in- and out-of-hospital).
- Length of stay in the ICU.

To assess safety, the following will be taken into account:
- Serious adverse events (example: pneumothorax, emphysema or any other events related to the intervention that lead to prolonged hospitalization time or death).

Secondary outcomes

For evaluating the effectiveness of the intervention, the following will be assessed:
- Need for invasive mechanical ventilation.
- Incidence of chronic respiratory disease.

- Incidence of non-respiratory comorbidities (example: peri-intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, retinopathy of prematurity).
- Neuropsychomotor development.

To evaluate the safety, the following will be analyzed:

- Non-serious adverse events (nasal or facial injury, hyperemia or local edema, or any event related to the intervention that does not lead to prolonged hospitalization time or death).

We will assess the outcomes separately considering the following time points:

- Short term: up to three incomplete months.
- Medium term: three months to one year.
- Long term: more than one year after the intervention.

Literature search strategy

Structured searches will be carried out, with pre-specified relevant descriptors and terms, without limitation of year of publication or language, in the following databases: Medical Literature Analysis and Retrieval System Online (Medline) via Pubmed, Excerpta Medica dataBASE (Embase) via Elsevier, Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library, Latin American and Caribbean Literature in Health Sciences (Lilacs) via the Virtual Health Library Portal and Physiotherapy Evidence Database (PEDro).

Selection of studies

The selection of studies will be performed by two totally independent authors (E.T.S.) and (L.L.O.), who, after excluding duplicates, will carry out the initial analysis of titles and abstracts, based on pre-specified eligibility criteria. Then, the full texts of references considered potentially eligible will be read for further analysis. Disagreements between authors regarding the inclusion of studies will be resolved by a third reviewer (A.C.P.N.P). The selection process will be carried out using the Rayyan application (https://www.rayyan.ai/) [15]. A flowchart will be used, as recommended by PRISMA, to present the results related to the study selection process.

Data extraction and management

Microsoft Excel 365 software will be used independently by two authors (E.T.S.) and (L.L.O.) to extract data from the included studies. The following data will be

extracted: 1) General characteristics of the study (title, authors, date and place of study), methods (study design, study setting (eg hospital), total duration of the study; 2) Participants: inclusion criteria and exclusion criteria, number of participants who were randomized, age, sex, period of ventilation, comorbidities; 3) Interventions: type of intervention (non-invasive HFV), ventilation details (equipment, parameters, duration, intensity and frequency), details of the comparator group intervention and concomitant interventions; 4) Outcomes: primary and secondary outcomes specified, collected, and actually reported, time points collected and reported, number of participants missed/not assessed for each outcome, and number of participants analyzed; 5) Notes: occurrence of funding for the study and potential conflicts of interest of the study authors. In case there are divergences or disagreements between the first two authors, a third reviewer (A.C.P.N.P.) will be consulted. In the absence of information or incomplete information, the authors of the studies will be contacted.

Evaluation of methodological rigor and certainty in the body of evidence

The risk of bias of the included studies will be assessed by two independent authors (E.T.S.) and (L.L.O.), using the tool developed by Cochrane, called risk of bias (ROB 2.0) [13]. The risk of the following biases will be assessed:

a) bias resulting from the randomization process. In this domain, it will be evaluated whether the method used to generate the sequence of allocation of participants was random, if the method used to allocate participants to the study groups was hidden and if there were imbalances between the characteristics of the participants that suggest a problem with the process of randomization.
b) bias due to deviations from intended interventions. For this evaluation, it will be taken into account whether the study team is unaware (it was “blind”) to which group the patient was allocated and whether there were deviations from the proposed intervention that could affect the outcome (for example: changing groups or the presence of co-interventions).
c) bias due to lack of outcome data. Losses to follow-up of study participants will be evaluated and, in the case of losses, the reason for their occurrence.
d) bias in measuring the outcome. It will be verified whether the outcome evaluators are unaware of which group the participants were allocated to and whether the possible lack of blinding could affect the effect estimate.
e) bias in the selection of the reported result. For this judgment, the possibility of the authors having evaluated the outcomes through multiple evaluations, but reporting only

the most convenient one, by checking the study protocol record and reporting the methodology used will be evaluated.

f) overall bias. It will be considered that the risk of general bias of the result corresponds to the most unfavorable evaluation carried out in at least one of the domains (for example: if in at least one of the domains it is judged that there is a high risk of bias, it will be considered that the result of the study has high risk of bias).

The Cochrane Collaboration algorithm will be used, which suggests judgments of high, some concerns and low risk of bias for each domain from the establishment of different degrees of importance given to each methodological limitation found in the evaluated domains and how much each limitation can influence the specific estimate of each outcome (e.g. lack of blinding of outcome assessors), to judge whether outcomes are of high, some concerns, or low risk of bias. If additional information is needed to judge the risk of bias, we will contact the authors of the studies. Disagreements regarding the assessment of bias will be resolved by consensus or, if necessary, by consulting a third reviewer (A.C.P.N.P).

To classify the certainty of the evidence, two independent authors (E.T.S) and (L.L.O) will use the GRADE profiler software (https://gdt.gradepro.org/app/), using the GRADE approach, to evaluate the following criteria that may decrease confidence in the evidence for each outcome: (i) overall risk of bias; (ii) inconsistency (iii) indirectness (iv) precision; and (v) risk of publication bias. Possible disagreements in these assessments will be resolved by a third reviewer (A.C.P.N.P.). A summary of main results table with the primary outcomes will be presented.

Statistical analysis

If at least two studies are homogeneous in terms of PICO (P – population = premature babies; I – intervention = HFV; C – comparison = other forms of non-invasive ventilation; O – outcome = death, intubation, morbidity, adverse effects - safety), the results will be pooled in meta-analyses. In the absence of homogeneity, the results of the study will be summarized only in a narrative synthesis.

We will evaluate in meta-analyses studies that included non-invasive oscillatory, jet and percussive HFV, separately. For each of the three types of HFV, we will also perform separate meta-analyses according to the objectives: (1) initial respiratory support; (2) for respiratory support after extubation; (3) after initial non-invasive therapy failure, totaling nine separate comparisons/meta-analyses. Meta-analyses will be performed using the inverse of variance method and random effects model in Review Manager 5.4 software. When possible, continuous variables will be summarized through

the difference in means (post and pre-intervention) with a 95% confidence interval (CI). If results are not reported as differences in means, we will use data reported after the intervention. If the studies use different measurement instruments to assess continuous outcomes, we will pool the data reporting them as differences in standardized means. Dichotomous variables will be summarized using relative risk (RR) with 95% CI. For dichotomous outcomes, the number of participants with one or more adverse events will be used, rather than the number of adverse events per participant. If the studies report adjusted data (ANCOVA or ANOVA), the use of these data will be prioritized. Wherever intention-to-treat data are available, these data will also be prioritized over data from per-protocol analyses.

To estimate the heterogeneity between the studies in each meta-analysis, the statistic 2 will be used and it will be considered that there is significant heterogeneity when the I2 is greater than 50%. We plan to perform subgroup analyzes to investigate possible causes of heterogeneity by performing additional meta-analyses, evaluating the effect estimates made with all studies, and then pulling out studies with the following characteristics: (1) with or without associated comorbidities ; (2) less than 28 weeks gestation versus 28 to 32 weeks gestation versus 32 weeks gestation or more; (3) ventilated with pressures lower or higher than 10cmH2O; (4) type of interface used to provide ventilation (prong or mask). Sensitivity analyzes will be performed as recommended by the Cochrane Manual for Systematic Reviews of Interventions, presenting results with and without studies at high risk of general bias. If there are at least 10 studies in a meta-analysis, we will assess the risks of publication bias through funnel plot analysis and Egger's test in R software (https://www.r-project.org/).

Expected results

The present study proposes to carry out a systematic review investigating the effectiveness and safety of HFV in preterm infants, and if possible, to pool data in meta-analyses to reduce the probability of type 2 error in comparisons. The results of this review will help provide a synthesis of the currently available evidence, clarifying the amount of published RCTs on the subject, in addition to showing whether HFV is indeed an effective and safe ventilatory mode for use in preterm infants.

It is possible that the synthesis of studies has limitations, such as the presence of studies with heterogeneous samples, with newborns with different comorbidities and with small samples or with biased analyses. In these cases, it is intended to perform additional sensitivity analyses, excluding studies with a high risk of bias and exploring their potential for bias in the final analysis. Some strengths of this review are the pre-

planned, transparent analyzes and the conduct following the rigor proposed by the Cochrane methodology. In addition, the use of extensive searches and contact with authors aims to reduce the risk of publication bias and reliably expose what are the real gaps in knowledge currently existing on the subject, supporting the planning of high-quality RCTs on the subject. The use of the GRADE approach, with the assessments of the certainty of the evidence for each outcome, may facilitate the interpretation of confidence in the data and the decision making of physiotherapists in a safer way regarding the best recommendation for ventilatory support in the NICU, based on the best currently available scientific evidence

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Não há.

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