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Ventilatory weaning strategies for predicting extubation success in children following cardiac surgery for congenital heart disease: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Congenital heart disease (CHD) comprises the anatomic malformations that jeopardise the structure and function of the heart. It can be extremely complex and serious, corresponding to 30% of all deaths in the first month of life. The surgical approach for adequate treatment requires postoperative mechanical ventilation. The most critical decision related to the postoperative management of patients submitted to cardiac surgery is the right time for extubation, especially because not only abrupt or inadequate discontinuation of ventilatory support can lead to clinical decline and necessity of reintubation but also extended time of mechanical ventilation, which can lead to complications, such as pneumonia, atelectasis, diaphragm hypertrophy, and increasing morbidity and mortality.

Methods and analysis This systematic review plans to include individual parallel, cross-over and cluster randomised controlled trials regarding any breathing trial test to predict extubation success in children submitted to cardiac surgery due to CHD. Studies with paediatric patients submitted to cardiac surgery for congenital cardiopathy repair, attended at a critical care unit, and under mechanical ventilatory support will be included. The main outcomes analysed will be success of extubation, reduction of pulmonary complications and time reduction of mechanical ventilation.

Ethics and dissemination We will not treat patients directly; therefore, ethics committee approval was not necessary because it is not a primary study. We expect that this study may improve healthcare and medical assistance, helping healthcare professionals with routine daily decisions regarding the correct time for extubation.

PROSPERO registration number CRD42021223999.

Strengths and limitations of this study

- ► Well-accepted standards for the conduct and reporting of systematic reviews will be followed.
- ► The systematic approach (Cochrane handbook and Grading of Recommendations Assessment, Development and Evaluation approach) for summarising the current available evidence on the effects of ventilatory weaning strategies for predicting extubation success in children following cardiac surgery for congenital heart disease will strengthen the review.
- ► Since only randomised controlled trials (RCTs) or quasi-RCTs will be included, some comparisons of different extubation protocols may have little available evidence.
- ► We will not impose any language or date limit to our review to be more sensitive and follow the Cochrane standard.
- ► However, it can be challenging to access evidence from original reports in non-familiar languages such as Japanese or Russian.

INTRODUCTION

Congenital heart disease (CHD) comprises the anatomic malformations that jeopardise the structure and function of the heart. CHD can be classified as cyanotic or acyanotic and result from the deviation of blood flow, sometimes from left to right and sometimes in reverse, due to obstruction of the flow in the cardiac chambers or even by the mixture of the systemic and pulmonary circulation, leading to desaturation.[1 2]

The aetiology of CHD is complex and due to various causes, such as environmental factors during pregnancy, drug and alcohol use and genetic factors. This congenital abnormality can be diagnosed from the eighth gestational

week and represents the leading cause of mortality in the first year of life, accounting for 2%–5% of all neonatal deaths. In this population, serious hypoxemia or cardiac failure account for 30% of deaths in the first month of life.[1 3]

Several studies reveal that sundry factors influence the clinical outcomes, which are serious cardiopathy or bigger heart structure commitment (even systemic commitment as left heart hypoplasia syndrome), transposition of large arteries and others. This type of influence can reflect in intensive care or hospital length of stay, pulmonary commitment, increasing rates of morbidity and mortality.[2 4 5] Congenital cardiopathy should be repaired up until the first year of life due to the severity of the clinical presentation.[6]

The duration of surgical procedure, anaesthetic management, need for aortic cross-clamping and use of cardiopulmonary bypass feature the requirement for postoperative mechanical ventilation.[6 7] Mechanical ventilation is used to support critically ill patients, but it is associated with serious complications, such as pneumonia, atelectasis, diaphragm hypertrophy and increasing morbidity and mortality.[2 8]

Early extubation and fast-tracking protocols have been largely described in children following cardiac surgery.[4 6 7 9 10] Postoperative long-term mechanical ventilation is required for many cases, which is most related to complex surgical procedure, low age and weight or even critical illness prior to surgery.[4 9]

An abrupt or inadequate discontinuation of ventilatory support may result in clinical decline, necessity for reintubation, and longer duration of mechanical ventilation, with increased mortality.[2 9] The most critical decision related to the postoperative management of patients submitted to cardiac surgery is the right time for extubation.[10]

In the paediatric population with CHD, the evidence about delayed ventilator weaning is poor and not described as in the adult population.[5]

Currently, there is no consensus about the ideal timing and strategy of weaning ventilation. This systematic review aims to evaluate the effects of breathing trial tests for predicting the success of extubation in children following cardiac surgery for CHD.

METHOD AND MATERIALS

Herein, we describe a protocol for a systematic review that will follow the recommendation guidelines from the Cochrane Handbook for Systematic Reviews of Interventions and will be reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol recommendations.[11 12] The protocol is registered with the International prospective register of systematic reviews (PROSPERO), and the published methodology has been made available for public comments.

Eligibility criteria

We plan to include individual parallel, cross-over and cluster randomised controlled trials (RCTs) that evaluate any breathing trial test to predict extubation in children submitted to cardiac surgery due to CHD. Quasi-RCTs or any non-randomised study will not be considered.

Types of participants

This systematic review (SR) will include studies with paediatric patients from newborns until 18 years of age who have been submitted to congenital cardiopathy repair, attended at a critical care unit, and under mechanical ventilatory support.

If we find studies with mixed populations, and only a subset of participants met our inclusion criteria, we will attempt to obtain data for the subgroup of interest from the trialists, so we can include the study. For studies with mixed populations for which we cannot get data for the subgroup of interest but at least 50% of the study population is of interest, we plan to include all participants in our analysis. Moreover, we plan to explore the effect of this decision in a sensitivity analysis. Studies in which less than 50% of the population is of interest and data for the subgroup of interest are not available will be excluded.

Types of interventions
Intervention

The intervention will consist of any type of breathing trial test performed to predict and sustain the decision to extubate paediatric participants submitted to cardiac surgery for congenital heart repair.

Comparators

We will include studies that compare one intervention (clinical decision or breathing test) versus another active comparator, or placebo or no treatment with any combination of interventions, provided that cotreatments were balanced between the treatment and control arms. We will pool studies that address the same comparisons.

The comparators may consist of:
1. Clinical decision versus any breathing test
2. One type of breathing test versus another type of breathing test

Types of outcome measures

We intended to present the outcomes at two different time points following the start of the intervention if data were available: short-term outcomes (at 30 days after surgery or before) and long-term outcomes (more than 30 days after surgery).

Our time point of primary interest is short term; we, therefore, intended to produce the related Summary of findings tables section only for this time point, and also planned to report the long-term outcomes at the longest possible time of follow-up.

Primary outcomes

1. Success of extubation rate (defined as the no need for reintubation for more than 48 hours after the extubation).[2 5 9]
2. Pulmonary complications (eg, atelectasis, pulmonary infiltrates, pleural effusion and diaphragmatic paralysis).

Secondary outcomes

1. Time of mechanical ventilation, in hours.
2. All-cause mortality.
3. Hospitalisation time, in days.

Search methods for identification of studies

Our goal is to identify all relevant RCTs, regardless of language, date or publication status (published, unpublished, in press or in progress). We will search the following databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library, Wiley.
2. Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed.gov;
3. Excerpta Medica dataBASE (Embase) via Elsevier.
4. Latin American and Caribbean Health Science Information (Lilacs, via Virtual Health Library) database.
5. Physiotherapy Evidence Database (PEDro);.
6. Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO.

For clinical trial protocols, we will search trial registries, such as:

1. The WHO International Clinical Trials Registry Platform (ictrptest.azurewebsites.net/Default.aspx).
2. ClinicalTrials.gov (clinicaltrials.gov).

The MEDLINE search strategy is provided in table 1, and it will be used as the basis for search strategies for the other databases listed. We will also check the reference lists of all included studies in order to look for other relevant studies. Furthermore, we will contact specialists in the field and the authors from included trials of any possible unpublished data.

Selection of studies and data extraction

We planned to use the Rayyan tool for the screening of the titles and abstracts and to select potentially relevant studies after merging the research results and removing duplicate records.[13] Two review authors (AAAG and AGdSV) will independently evaluate the access relevance of studies. Any disagreements will be solved based on a discussion among the authors or by a third author arbitration (LCUN). We will retrieve the full text of the relevant trials, and two review authors (AAAG and AGdSV) will independently examine and identify studies for inclusion. If a trial does not meet the eligibility criteria, we will identify and substantiate the reasons for exclusion. If there is disagreement about the relevance of a study, we will consult a third review author (LCUN) or solve it by discussion. The process of study selection will be illustrated in a Preferred Reporting Items for Systematic

Reviews and Meta-Analyses flowchart.[14] All excluded articles will be listed in the table entitled 'Characteristics of excluded studies' followed by the reasons for exclusion. Two independent reviewers (AAAG and AGdSV) will check in the included studies data related to study characteristics and outcomes as follows[15]:

1. Methods: study design, total duration of the study and period of carryout, number and location of study centres, research setting, exclusion and date of study.
2. Participants: amount, age parameters (ie, mean, range), gender, diagnosis of cardiopathy, type of cardiac surgery and inclusion/exclusion criteria.

Table 1 MEDLINE via Pubmed search strategy

1	"Thoracic Surgery"[Mesh] OR (Thoracic Surger*) OR (Heart Surger*) OR (Cardiac Surger*)
2	"Heart Defects, Congenital"[Mesh] OR (Congenital Heart Defect*) OR (Heart Abnormalit*) OR (Heart Malformation*) OR (Malformation* Heart*) OR (Congenital Heart Disease*)
3	"Cardiac Surgical Procedures"[Mesh] OR (Cardiac Surgical Procedure*) OR (Heart Surgical Procedure*) OR (Cardiac Surgical Procedure*)
4	"Breath Tests"[Mesh] OR (Automatic Tube Compensation) OR (Pressure Support Ventilation) OR (Extubation Readiness Test*) OR (Extubation Readiness Trial*) OR (Spontaneous Breathing Trial*) OR (Spontaneous Breathing Test*) OR (Pressure Support) OR (T Tube) OR (T-Tube) OR (T Piece) OR (T-Piece) OR (Breath Test*) OR (Breathalyzer Test*)
5	"Continuous Positive Airway Pressure"[Mesh] OR CPAP OR (Airway Pressure Release Ventilation) OR APRV OR (Biphasic Continuous Positive Airway Pressure) OR BIPAP OR (Biphasic Positive Airway Pressure) OR (Bilevel Positive Airway Pressure) OR (Bilevel Continuous Positive Airway Pressure) OR (CPAP Ventilation) OR (Nasal Continuous Positive Airway Pressure) OR (nCPAP Ventilation) OR (APRV Ventilation Mode*) OR (BiPAP Biphasic Positive Airway Pressure) OR (BiPAP Bilevel Positive Airway Pressure)
6	"Positive-Pressure Respiration"[Mesh] OR (Positive Pressure Respiration*) OR (Positive-Pressure Respiration*) OR (Positive-Pressure Ventilation*) OR (Positive Pressure Ventilation*) OR (Positive End-Expiratory Pressure*) OR (Positive End Expiratory Pressure*)
7	"Airway Extubation"[Mesh] OR (Airway Extubation*) OR (Tracheal Extubation*) OR (Intratracheal Extubation*) OR (Endotracheal Extubation*)
8	1 OR 2 OR 3
9	4 OR 5 OR 6 OR 7
10	8 AND 9
11	(Therapy/Broad[filter]) AND (#10)

MEDLINE, Medical Literature Analysis and Retrieval System Online; Mesh, medical subject headings.

3. Interventions: type of intervention, comparison and excluded interventions (ie, fast-track extubation or extubation in operation room).
4. Outcomes: primary and secondary outcomes (agreement between reported and planned).
5. Notes: conflicts of interest (declared or notable) related or not with funding.

For statistical analysis, one author (AAAG) will enter the data into Review Manager 5 software (RevMan 5, V.5.4.1, Nordic Cochrane Centre, Cochrane, Copenhagen).[16] In cases of insufficient results for meta-analysis, a descriptive analysis will be done.

Assessment of risk of bias in included studies

The critical evaluation of the included articles will be done in a double and independent way, regarding the risk of bias of the included studies. We will assess the risk of bias domains, using the 'Risk of Bias' V.1.0, as recommended by Cochrane.[17] Each of the following domains will be graded as high, low or unclear risk of bias. Blinding will be considered separately for different key outcomes when possible, according to the intervention as follows:
1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

Measures of treatment effect

The heterogeneity analysis will be performed to evaluate the ability of grouping data. When at least two studies are sufficiently homogeneous regarding participants, interventions and outcome measurements, we will pool their results into a meta-analysis. The meta-analysis will be performed using an inverse variance method and random effects model in Revman V.5.[16] For the dichotomous data, we will use relative risk, with 95% CIs; continuous data will be treated through the mean difference (MD) for equal scales or standardised MD for different scales, also with 95% CIs.

Unit of analysis issues

For all outcomes, the participant will be the unit of analysis based on intention-to-treat.

Addressing missing data

Whenever we deem necessary, we will contact the authors or sponsors to request missing numerical outcome data and to verify details about methods and characteristics. We plan to estimate the MD using the method reported by Wan *et al*[18] to convert median and IQR into MD and CIs.[18] When it is not possible, we will narratively describe skewed data reported as medians and IQRs. If the missing data have different implications in the compared groups, the study will be considered to have a high risk of bias.[15]

Assessment of heterogeneity

The assessment of heterogeneity among studies will be performed by a visual inspection of forest plots and associated with the I^2 consistency test. The degree of heterogeneity should not be strict, but we will use I^2 according to the guide for interpretation in the Cochrane handbook for SRs of interventions[19] as follows:
1. 0%–40%: possibly not important.
2. 30%–60%: represents moderate heterogeneity.
3. 50%–90%: represents substantial heterogeneity.
4. 75%–100%: considerable heterogeneity.

When I^2 lay in an area of overlap between two categories (eg, nearly 50% and 60%), we will consider differences in participants and interventions among the trials contributing data to the analysis.[19]

Data will be analysed using the random effect model. We will investigate sources of heterogeneity by subgroup and/or sensitivity analysis. Subgroup analysis is foreseen considering the age of the children, type of cardiopathy, type of surgical procedure, type of breathing trial test as intervention and pulmonary complications. If more than 10 studies are included in a meta-analysis, we will perform a publication bias analysis. Data from all trials will be compiled and analysed using RevMan V.5 software.[16]

Assessment of reporting biases

If we can pool more than 10 trials, we will create and examine a funnel plot to explore possible small-study biases for all available outcomes investigating the funnel plot asymmetry. We plan to use R Studio software, V.1.4.1106, for additional tests if we suspect reporting bias.[20–22]

Subgroup analysis and investigation of heterogeneity

We will consider all types of breathing trial tests in this review. In the case of substantial heterogeneity and if sufficient data are available, we will do a subgroup analysis for the following characteristics:
1. Age (eg, infants 0–2 years old, children 3–12 years old and young people more than 13 and less than 18 years old).
2. Type of cardiopathy.
3. Type of surgical procedure.
4. According to risk scores such as Risk Adjustment for Congenital Heart Surgery-1 score or The Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery.

We will explore the data according to risk of bias, beyond the use formal testing for subgroup differences in RevMan V.5, and we will base our interpretation on it.[16 17]

Sensitivity analysis

A sensitivity analysis will be conducted to determine the impact of excluded studies with an overall high risk of bias, which are those studies with a high risk of bias in at least one of the main domains in the risk of bias tool, which analysed generation of a randomisation sequence, allocation concealment and blinding.[19] We also plan to

explore the decision to include all participants when at least 50% are of interest in a trial with a mixed population.

'Summary of findings' table

To generate a 'Summary of findings' table for each of the outcomes to be analysed in this review, we will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) software (GRADEpro).[23] Using the study limitations criteria, consistency of effect, imprecision, indirectness and publication bias, we will assess the certainty of the body of evidence that made up the data for the meta-analyses of the prespecified outcomes.[23 24] These criteria will be evaluated using the Cochrane recommendations, justifying any departures from the standard methods, will fill in the table.[15]

Patient and public involvement

The research question was developed from the authors' experience with treating paediatric patients who were critically ill, associated with methodological knowledge, in a way to look for the main patient-relevant outcomes. We intend to include patients or their family members in all steps of this research as advisors, besides maintaining a comprehensive language in the final text in order to be appropriate for consumers. The final version of this review, as results, conclusions and any changes in the protocol, will be published in an accessible international journal.

DISCUSSION

Our review will evaluate all evidences about the effects of breathing trial tests to predict the success of extubation in children submitted to surgical repair of CHD. The results of our SR will be of interest to managers and paediatric intensive care professionals worldwide. The information gathered in the implementation process will inform patients, families and health professionals about their effectiveness and safety, in a way to facilitate decision-making of its implementation into the practices of the ICU. This study will also identify gaps for future research. This systematic review will evaluate the effectiveness and safety of any breathing trial test as an extubation predictor in critical paediatric patients. The methodology of this review includes explicit eligibility criteria, extensive database searches and independent and paired evaluations for study selection. We will assess the risk of bias in the qualitative and quantitative included studies, and we will use the GRADE approach for the final evidence. The outcomes can guide patients, family members and intensive care professionals about the effectiveness and safety of breathing trial tests, improving decision-making on the complex heart disease unit.

Ethics and dissemination

We will not treat patients directly; therefore, ethics committee approval was not necessary because it is not a primary study. We intend to update the registry of this review, report any important protocol amendments and publish the results in a widely accessible journal.

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