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REVIEW PROTOCOL

Effectiveness and safety of the use of room air compared to 100% oxygen in premature children in cardiorespiratory arrest: systematic review protocol

Efetividade e segurança do uso do ar ambiente em comparação ao oxigênio a 100% em prematuros em parada cardiorrespiratória: protocolo de revisão sistemática

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Abstract

Introduction: Cardiorespiratory arrest is a clinical situation characterized by the interruption of blood circulation. It is estimated that 11.1% of all live births in the world are premature, generating short and long-term repercussions. One of the main challenges during cardiacarrest in premature infants is providing sufficient, but not excessive, oxygen during assisted ventilation. *Objective:* To compare the effectiveness and safety of using room air in relation to 100% oxygen in the resuscitation of premature infants in

cardiorespiratory arrest. *Methods:* To this end, we will carry out a systematic review of randomized clinical trials (RCTs). The study protocol was registered on the Prospero Platform (CRD42024519724). We will include preterm infants with gestational age <37 weeks with CA. The searches were carried out in the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) via Pubmed, Excerpta Médica dataBASE (Embase) via Elsevier, Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Library, Latin American Literature and the Caribbean Doctor in Health Sciences (LILACS) through the Virtual Health Library Portal, without restrictions on language or year of publication. The selection of studies, transmission of data, assessment of the bias of included studies and assessment of the certainty of the evidence will be carried out by two independent investigators. Expected results*:* Clarify the transit and safety of using room air compared to 100% oxygen, provide useful information for clinical decision-making, and support future high-quality randomized clinical trials on the topic. *Conclusion:* This study aims to compile existing research to analyze the effectiveness and safety of application of 100% oxygen in the resuscitation of premature infants.
Keywords: Heart arrest; infant premature; systematic review**.**

Resumo

Introdução: A parada cardiorrespiratória é uma situação clínica caracterizada pela interrupção da circulação sanguínea. Estima-se que 11,1% de todos os nascidos vivos no mundo sejam prematuros, gerando repercussões a curto e longo prazo. Um dos principais desafios durante a parada cardíaca em bebês prematuros é fornecer oxigênio suficiente, mas não excessivo, durante a ventilação assistida. *Objetivo:* Comparar a efetividade e segurança do uso de ar ambiente em relação ao oxigênio 100% na reanimação de prematuros em parada cardiorrespiratória. *Métodos:* Para tanto, realizaremos uma revisão sistemática de ensaios clínicos randomizados (ECR). O protocolo do estudo foi registrado na Plataforma Prospero (CRD42024519724). Incluiremos bebês randomizadosom idade gestacional <37 semanas com AC. As buscas foram realizadas nas seguintes bases de dados: *Medical Literature Analysis and Retrieval System Online* (MEDLINE) via *Pubmed, Excerpta Médica dataBASE* (Embase) via *Elsevier, Cochrane Central Register of Controlled Trials* (CENTRAL) via *Cochrane Library, Latin American Literature e the Doutor Caribenho em Ciências da Saúde* (LILACS) através do Portal da Biblioteca Virtual em Saúde, sem restrições de idioma ou ano de publicação. A seleção dos estudos, transmissão dos dados, avaliação do viés dos estudos incluídos e avaliação da certeza das evidências serão realizadas por dois investigadores independentes. *Resultados Esperados:* Esclarecer o trânsito e a segurança do uso do ar ambiente em comparação ao oxigênio 100%, fornecer informações úteis para a tomada de decisões clínicas e apoiar futuros ensaios clínicos randomizados de alta qualidade sobre o tema. *Conclusão:* Esta pesquisa buscará organizar os estudos publicados e analisar a efetividade e segurança da aplicação de oxigênio 100% na reanimação de prematuros em parada cardiorrespiratória.
Palavras-chave: Parada cardiorrespiratória; Prematuridade; Revisão Sistemática.

Introduction

It is estimated that prematurity accounts for 11.1% of all live births worldwide, and its complications are responsible for one million deaths every year. Even if they survive, premature birth is the main reason for the significant increase in neonatal morbidity and complications, thus generating economic repercussions in terms of mechanical cardiac activity and represents a serious global health problem [3].

Cardiorespiratory arrest in the Neonatal Intensive Care Unit (NICU) predicts a high risk of mortality in premature infants and negative neurodevelopmental outcomes, with survival rates ranging from 35% to 61% until discharge. Previous studies have identified ventilation and oxygenation abnormalities, post-arrest hypotension, and hyperthermia as being associated with increased mortality and unfavorable neurological, cardiovascular, and pulmonary outcomes such as Cerebral Palsy, Patent Ductus Arteriosus, and Bronchopulmonary Dysplasia [4-7].

During cardiac arrest, due to the lack of pumping oxygenated blood to the systems, there is a period of ischemia that leads to reduced mitochondrial activity. The sudden influx of oxygen during reperfusion causes an increase in reactive oxygen species, which can overwhelm the cell's antioxidant defenses and thus worsen the injury (reperfusion injury). Therefore, oxygen supplementation during the attempt at cardiopulmonary resuscitation appears to be the most plausible intervention [8]. The main challenge in managing ischemic injury is to provide sufficient oxygen to facilitate cellular recovery without supplying excessive oxygen that may contribute to reperfusion injury. The standard recommended practice for resuscitating asphyxiated newborns has been the use of 100% oxygen for assisted ventilation [9,10].

However, evidence suggests that resuscitation with a high concentration of oxygen leads to the excessive release of oxygen free radicals during the post-hypoxemia period. These free radicals have the potential to cause cellular and organ damage [11]. Negative outcomes during resuscitation can be explained by previous studies that suggest hyperoxemia is associated with numerous side effects, including delayed onset of spontaneous breathing, increased oxygen consumption, and irregularities in cerebral circulation [9,11]. Thus, concerns about oxidative stress have led to the widespread use of lower levels (Fraction of Inspired Oxygen at 21%) to initiate ventilatory support, especially in preterm infants. However, recent studies by OEI et al. [12], observed that initiating resuscitation during cardiac arrest with low oxygen concentrations (FiO2 21%) was associated with an increased risk of death in premature infants. In contrast, THAMRIN et al. [13], demonstrated that initiating resuscitation with titration of oxygen at 21% had no significant effect on death or neurodevelopmental injury compared to 100% oxygen in premature infants. These studies suggest the investigation of titrating Fraction of Inspired Oxygen to reliably demonstrate reductions in mortality, morbidity, and/or disability [9,14] SORAISHAM *et al*. [15], They reviewed significant changes in recommendations, suggesting starting resuscitation with low oxygen (21% to 30%) for premature newborns <35 weeks. However, there is currently no detailed synthesis or high-quality evidence summary that summarizes these results into guidelines.

In light of the above, it is of great relevance for pediatric public health to explore current data and provide clinicians and researchers with evidence-based information for practice. Therefore, this study aims to evaluate the effectiveness and safety of using room air compared to 100% oxygen in resuscitating premature infants experiencing cardiac arrest.

Objective

To compare the effectiveness and safety of using room air versus 100% oxygen in the resuscitation of premature infants experiencing cardiac arrest.

Methods

Study Design

This is a systematic review protocol that will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The review will be conducted according to the methodological recommendations outlined in the Cochrane Handbook.

Ethical aspects and research location

The review protocol has been registered on the PROSPERO platform (CRD42024519724). This study will be conducted at the Federal University of Amapá (UNIFAP) Program of Post-Graduation in Health Science.

Eligibility criteria

Types of included studies

Randomized controlled trials (RCTs) published in full text or as abstracts will be included.

Types of Participants

Studies including preterm infants (<37 weeks of gestation) diagnosed with asphyxia or cardiac arrest in the neonatal period will be included.

Intervention

We will include studies that evaluated the use of room air in premature infants with cardiac arrest.

Comparison

We will consider studies comparing the use of 100% oxygen versus room air in neonates with cardiac arrest at birth.

Outcome Measures

Primary Outcomes

To assess the effectiveness of room air versus 100% oxygen, we will evaluate the following:

- Mortality: hospital or up to 5 years of age.
- Hypoxic-ischemic encephalopathy (i.e., a neonatal clinical syndrome resulting from severe and prolonged ischemia or hypoxia occurring before or during birth).
- To assess safety, we will analyze the following:
- Serious Adverse Events: defined as any unfavorable medical occurrence resulting in death, life-threatening situation, requirement for hospitalization or prolongation of existing hospitalization, significant or persistent disability, congenital anomaly, and clinically significant event.

Secondary Outcomes

To assess the effectiveness of room air versus 100% oxygen, we will evaluate the following:

- Neonatal asphyxia (Apgar score at 1, 5, and 10 minutes) (i.e., a clinical-neurological syndrome that develops when there is significant tissue hypoperfusion and decreased uteroplacental blood flow, or hypoxia, characterized by inadequate oxygen in tissues).
- Bronchopulmonary dysplasia: Response of immature lungs to acute lung injury caused by mechanical ventilation, oxygen, and various associated factors.

- Time to first spontaneous breath (minutes) (i.e., time required to achieve a respiratory pattern without intervention from the resuscitation team).
- Time to first cry (minutes).
- Duration of neonatal resuscitation (minutes) (e.g., time to establish heart rate > 100/min).
- Length of stay in the Neonatal Intensive Care Unit and hospital.
- Duration of invasive mechanical ventilation.
- Neuropsychomotor development: Developmental milestones at 18 to 24 months of age, including walking and talking.

To assess safety, we will analyze the following:

- Non-serious adverse events (e.g., erythema, edema, nasal dryness, oxygen supply interface-related injuries).

Collection procedure

Search and Selection of Articles

We will conduct sensitive searches using relevant pre-specified terms and descriptors without limitation on publication year 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 Cochrane Library;
- Latin American and Caribbean Health Sciences Literature (LILACS) and bero-American Science and Technology Education Consortium (IBECS) via the BVS Portal.

The complete search strategy for each database is presented in Appendix A.

Study selection will be performed by two reviewers (INLA) and (GCSA), who are completely independent, based on pre-specified eligibility criteria. Initially, studies indexed in more than one database will be excluded (duplicates). After potential duplicates are identified and removed, titles and abstracts will be screened, followed by full-text review for further analysis. Any disagreements between reviewers regarding study inclusion will be resolved through discussion or consultation with a third reviewer (ASAT). To streamline the selection process, we will use the Rayyan app (https://www.rayyan.ai/). Results related to the study selection process will be presented in a flow diagram following PRISMA guidelines (Figure 1).

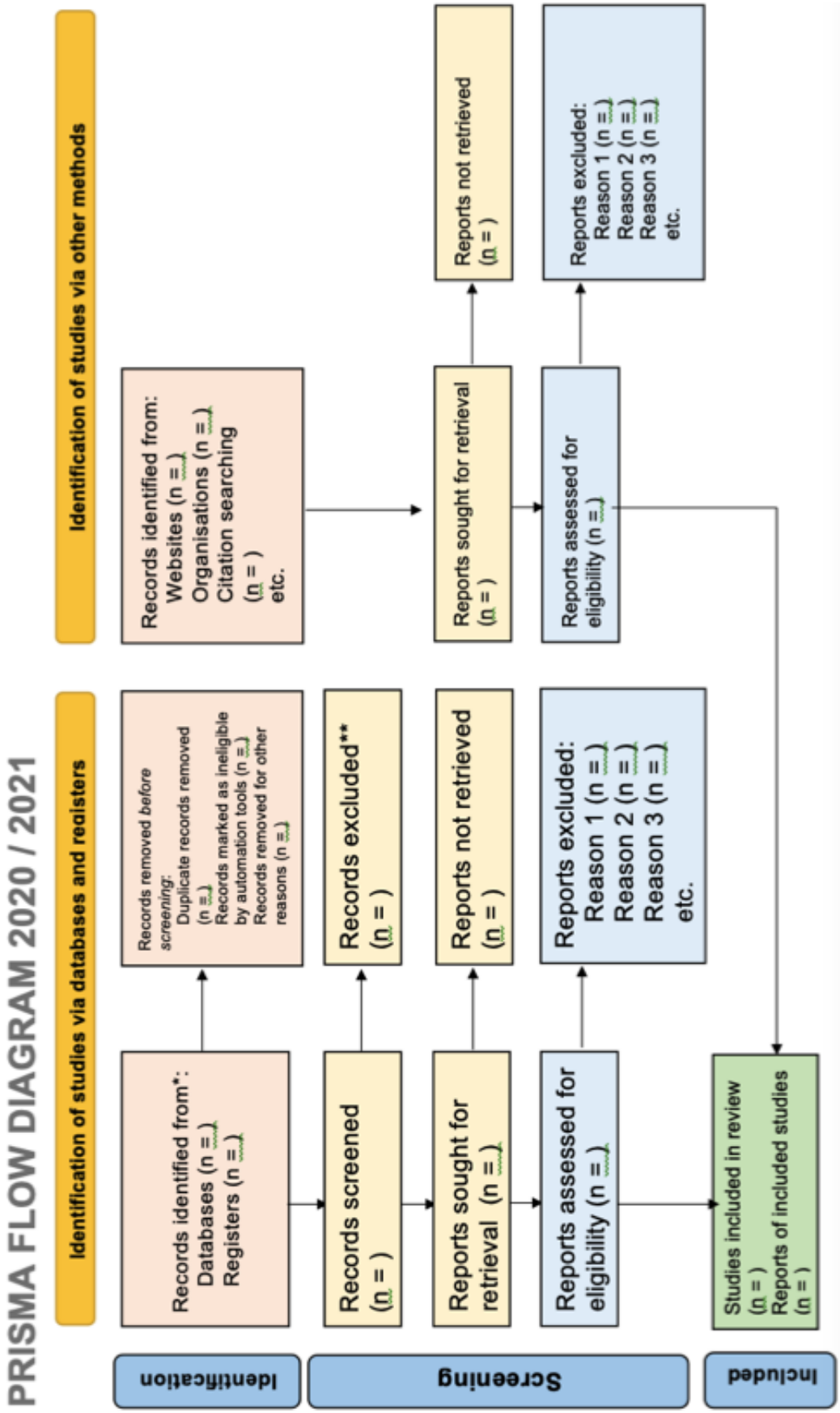

Figure 1 - *Systematic Review Flowchart*

Data Extraction and Management

Data from included studies will be extracted using a spreadsheet in Microsoft Excel 365. Independently, at least two authors will extract the following data:

1. Study Identification Details (title, authors, location, and study date).

2. Participants from experimental and control groups: number of participants, gestational age, birth weight in grams, birth weight below 2500g, number of cesarean deliveries, general anesthesia, previous pregnancies, labor induction, premature births, meconium aspiration, and number of intubated infants.

3. Outcomes: Death, hypoxic-ischemic encephalopathy, Apgar scores at 1, 5, and 10 minutes, time to first spontaneous breath, time to first cry, and duration of neonatal resuscitation.

We will contact study authors to clarify any unclear or missing information regarding the assessed domains. If data remain insufficient even after author contact, study results will be summarized in a narrative synthesis.

Bias Risks in Each Study and Assessment of Evidence Certainty

The risk of bias in included studies will be assessed using the Cochrane tool, ROB 2.0 (Risk of Bias 2.0) [16]. The following domains will be evaluated: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in outcome measurement, bias in selection of the reported result, and overall study bias.

Each domain will be judged as low risk of bias, high risk of bias, or some concerns regarding bias. We will use the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to classify the certainty of evidence [17]. To achieve this, we will consider factors that may decrease certainty in the evidence: (I) overall risk of bias in included studies; (II) indirectness of the evidence; (III) inconsistency of results; (IV) precision of estimates; and (V) risk of publication bias.

The GRADE profiler software, available online (https://gdt.gradepro.org/app/), will be used to summarize judgments on the certainty of evidence for each primary outcome. These assessments will be presented in a table containing key findings for nine of the evaluated outcomes at the longest available time point.

1. Mortality

2. Hypoxic-ischemic encephalopathy

3. Neonatal asphyxia: Apgar at 1, 5, and 10 minutes

4. Bronchopulmonary dysplasia

5. Time to first spontaneous breath

6. Time to first cry

7. Duration of neonatal resuscitation

8. Length of stay in the Neonatal Intensive Care Unit and hospital

9. Duration of invasive mechanical ventilation

10. Neuropsychomotor development

Bias risk assessment and certainty of evidence will be conducted independently by two assessors (I.N.L.A) and (N.C.R.I), with any disagreements resolved through consultation with a third reviewer (A.C.N.P).

Statistical Analysis

If at least two studies exhibit sufficient homogeneity regarding participants, interventions, and assessed outcomes, their results will be pooled in meta-analyses. Meta-analyses will be conducted

using the inverse variance method and random-effects model in Review Manager 5.4 software.

Continuous variables will be summarized using mean differences (post- vs. pre-intervention) with 95% confidence intervals (CIs) where possible. In the absence of reported mean differences or when there is poor correlation between individual measures, post-intervention data will be utilized.

If studies use different measurement instruments for continuous outcomes, data will be pooled and reported as standardized mean differences. Dichotomous variables will be summarized using relative risks (RRs) with 95% CIs. For dichotomous outcomes, participants rather than events will be selected as the unit of analysis (i.e., number of participants with one or more adverse events, rather than number of adverse events per participant).

Adjusted data (ANCOVA or ANOVA) will be preferred if available. Whenever possible, intention-to-treat data will be prioritized over per-protocol analysis data.

To estimate heterogeneity among studies in each meta-analysis, we will use the I2 statistic [16]. If heterogeneity is significant (I2 > 50%), sources of heterogeneity will be explored through subgroup analyses or sensitivity analyses as recommended by the Cochrane Handbook for Systematic Reviews of Interventions. If there is slight clinical or methodological heterogeneity, sources of heterogeneity will also be investigated through subgroup or sensitivity analyses. Subgroup analysis will consider gestational age.

Sensitivity analyses will be conducted by excluding studies with high overall risk of bias from meta-analyses. If at least 10 studies are included in a meta-analysis, risk of publication bias will be assessed using funnel plot analysis and Egger's test in R software (https://www.r-project.org/). If a study has more than two groups, only relevant arms will be included.

Expected outcomes

This systematic review will use the Cochrane methodology, considered the best currently available methodology for evaluating health intervention studies. Possible limitations may include biased studies or small sample sizes that may not accurately estimate the effects of the intervention. However, transparency, methodological rigor, assessment of evidence certainty for each outcome, and extensive and careful searches will enable a safer and more reliable clinical response. The aim is to clarify the effectiveness and safety of using room air compared to 100% oxygen, providing useful information for clinical decision-making based on the best currently available evidence. Additionally, it is believed that the results of this study may highlight knowledge gaps and support future high-quality randomized clinical trials on the subject. This research may also assist professionals dealing with cardiopulmonary arrest in premature infants and contribute to updating resuscitation guidelines.

Conflicts of interest

We declare no conflicts of interest.

Funding sources

No funding sources was received.

Authors contribution

Conception and design of the research: Iosimuta NCR, Alves INL, Pinto ACPN; Data collection: Alves INL, Anjos GCS, Távora ASA; Data analysis and interpretation: Alves INL; Anjos GCS, Távora ASA; Statistical analysis: Alves INL; Iosimuta NCR, Pinto ACPN; Manuscript writing: Alves INL, Iosimuta NCR, Pinto ACPN; Critical revision of the manuscript for important intellectual content: Alves INL, Iosimuta NCR, Pinto ACPN.

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