REVIEW

Effectiveness and safety of the use of room air compared to 100% oxygen in neonates under cardiac arrest at birth: systematic review protocol

Efetividade e segurança do uso do ar ambiente em comparação ao oxigênio a 100% nos neonatos em parada cardíaca: protócolo de revisão sistemática

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Abstract

Introduction: Cardiac arrest at birth represents a serious problem worldwide. The commonly recommended practice for resuscitation of asphyxiated newborns has been the use of 100% oxygen for assisted ventilation. However, there is increasing evidence that ambient air is as effective as 100% oxygen and that 100% oxygen can have adverse effects on respiratory physiology and cerebral circulation. Objective: To compare the effectiveness and safety of using room air versus 100% oxygen in the resuscitation of neonates with cardiac arrest at birth. *Methods*: For this purpose, we will perform a systematic review of randomized controlled trials (RCTs). We will register the study protocol in the Prospero Platform. We will include neonates of any gestational age,

diagnosed with cardiac arrest or neonatal asphyxia. We will perform searches 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 Literature and the Caribbean in Health Sciences (Lilacs) via the Virtual Health Library Portal, with no restrictions on language or year of publication. The selection of studies, data extraction, assessment of bias of included studies and assessment of certainty of evidence will be performed by two independent researchers. *Expected Results*: We expect to clarify the effectiveness and safety of using ambient air compared to 100% oxygen, to provide useful information for clinical decision-making, and to support future high-quality randomized clinical trials on the subject

Keywords: heart arrest; cardiopulmonary resuscitation; infant, newborn; oxygen.

Resumo

Introdução: A parada cardíaca ao nascimento representa um problema grave em todo o mundo. A prática comumente recomendada para reanimação de recém-nascidos asfixiados tem sido o uso de oxigênio a 100% para ventilação assistida. No entanto, há evidências crescentes de que o ar ambiente é tão eficaz quanto o oxigênio a 100% e que o oxigênio a 100% pode ter efeitos adversos na fisiologia respiratória e na circulação cerebral. *Objetivo*: Comparar a efetividade e segurança do uso do ar ambiente com o oxigênio a 100% na ressuscitação de neonatos em parada cardíaca ao nascimento. *Métodos*: Realizaremos uma revisão sistemática de ensaios clínicos randomizados (ECR) e registraremos o protocolo do estudo na Plataforma Prospero. Incluiremos neonatos a termo, diagnosticados com parada cardíaca ou asfixia neonatal. As buscas serão realizadas nas 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, Literatura Latino-Americana e do Caribe em Ciências da Saúde (Lilacs) via Portal da Biblioteca Virtual em Saúde, sem restrições de idioma ou ano de publicação. 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*: Esperamos esclarecer a efetividade e segurança do uso do ar ambiente em comparação com o oxigênio a 100%, fornecendo informações úteis para a tomada de decisão clínica e para embasar futuros ensaios clínicos randomizados de alta qualidade sobre o assunto

Palavras–chave: parada cardíaca; reanimação cardiopulmonar; recém-nascido; oxigênio.

Introduction

Cardiorespiratory arrest stands as a significant global clinical concern. Marked by the cessation of blood circulation due to the deficiency or inefficacy of cardiac mechanical functions [1], this condition results in an estimated fatality count of one million individuals, with a commensurate number enduring subsequent complications including encephalopathy, neurodevelopmental retardation, and epilepsy [2].

In the context of cardiorespiratory arrest, the absence of oxygenated blood perfusion to vital organ systems precipitates organ dysfunction culminating in death. Within this paradigm, the administration of supplemental oxygen amid cardiopulmonary resuscitation endeavors emerges as a logical and promising intervention. This approach, when coupled with resuscitative maneuvers, stands among the foremost advocated therapeutic measures within the Neonatal Intensive Care Unit for addressing such occurrences [3,4].

Notwithstanding its indispensability to sustenance of life, the administration of oxygen, if executed improperly, bears the potential for toxicity and the subsequent onset of severe repercussions. The extent of this toxicity, contingent upon variables encompassing the absolute pressure of dispensed oxygen, temporal span of exposure, and the inherent susceptibility of the individual, constitutes a primary constraint in its application [5]. Elevation of oxygen levels to toxic thresholds transpires with the emergence of hyperoxia, denoting the inhalation of elevated fractions of oxygen across protracted intervals or at heightened concentrations.

Contemporary evidence underscores the proposition that elevated oxygen administration during resuscitative efforts elicits an excessive release of oxygen-derived free radicals within the post-hypoxic phase. This phenomenon bears the potential to induce deleterious cellular and organ-level impairments. Such empirical insights have catalyzed a series of investigative endeavors, marked by experimental designs, aimed at elucidating the comparative efficacy of ambient air during neonatal resuscitation. Initial inquiries that juxtapose room air against pure oxygen for the resuscitation of asphyxiated neonates have yielded indications of parity in their effectiveness [6]. Nevertheless, amassed data highlight a discernible discrepancy: the cohort resuscitated with room air exhibited a notably abbreviated time frame for inaugural crying and a briefer duration of ventilation in achieving a sustained respiratory pattern, relative to the counterpart group resuscitated with 100% oxygen [7].

Adverse outcomes observed during the process of resuscitation find their rationale in prior investigations, which posit a correlation between hyperoxemia and a

spectrum of deleterious repercussions. These encompass a postponement in the initiation of autonomous respiratory activity, escalated oxygen utilization, and perturbations in cerebral blood flow dynamics [8]. Nonetheless, a comprehensive exploration into the primary complexities of hyperoxygenation-related complications in neonates experiencing cardiac arrest remains a sparsely traversed domain within the scientific literature.

In the present context, the assessment of extant empirical insights concerning the outcomes of neonatal resuscitation involving 100% oxygen in juxtaposition to ambient air assumes significant pertinence within the domain of pediatric public health. This evaluation serves a dual purpose: to furnish guidance for contemporary practices and to furnish a foundational scaffold for prospective inquiries in this realm. Accordingly, the principal objective of this study is to compare the effectiveness and safety of using ambient air with the use of 100% oxygen in cardiorespiratory resuscitation of neonates in cardiac arrest at birth.

Methods

Study design

This systematic review protocol will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) recommendations and will be conducted in accordance with the methodological recommendations of the Cochrane Handbook.

Type of studies

We will include randomized controlled clinical trials (RCTs) published in full text or only in abstract.

Participants

We will include studies with neonates at term (born > 37 weeks of gestational age) 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 neonates with cardiac arrest.

Comparison

We will consider as comparison groups the use of 100% oxygen in neonates with cardiac arrest at birth.

Primary outcomes

To evaluate the effectiveness of room air versus 100% oxygen, we will assess the following:
- Mortality: at hospital or up to 5 years of age.
- Hypoxic-ischemic encephalopathy (i. e. a clinical neonatal syndrome resulting from a severe and prolonged episode of ischemia or hypoxia that occurs before or during the time of delivery).

To evaluate the safety, we will analyze the following:
- Serious Adverse Events: defined as any untoward medical occurrence, that results in mortality, risk of death, situations that require hospitalization or extension of existing hospitalization, significant or persistent disability, congenital anomaly and clinically significant event.

Secondary outcomes

To evaluate the effectiveness of room air versus 100% oxygen, we will assess the following:
- Neonatal asphyxia (apgar 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 insufficient oxygen in the tissues.)
- Time to first spontaneous breath (minutes) (i. e. the time required to reach a breathing pattern without the intervention of the resuscitation team).
- Time to first cry (minutes)
- Duration of newborn resuscitation (minutes) (e. g. the time to establish heart rate > 100/min).
- Length of stay in Intensive Care Unit and in hospital
- Length of stay under invasive mechanical ventilation

- Neuropsychomotor development: Developmental milestones at 18 to 24 months of age including walking and talking

To evaluate the safety, we will analyze the following:
- Non-Serious Adverse Events (e. g. hyperemia, edema, nasal dryness, injuries related to the oxygen supply interface).

Search and selection of articles

We will carry out sensitive searches, using pre-specified relevant terms and descriptors, without limitation of year of publication or language, 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 the Cochrane Library;
- Latin American and Caribbean Literature in Health Sciences (Lilacs) and IBECS via the VHL Portal.

The selection of studies will be carried out by two completely independent reviewers, based on pre-specified eligibility criteria. Initially, studies that were indexed in more than one database (duplicate) will be excluded. After the analysis of potential duplicates, the evaluation will be carried out based on the titles and abstracts and, finally, we will read the full texts for further analysis. Disagreements between authors regarding the inclusion of studies will be discussed by them in a meeting held after the selection or through analysis by a third reviewer. To optimize the selection process, we will use the Rayyan application (https://www.rayyan.ai/). We will present the results related to the study selection process in a flowchart, as recommended by PRISMA.

Data extraction

We will use a spreadsheet in Microsoft Excel 365 software to extract the data from the included studies. Independently, at least two authors (B.M.A.F), (E.C.S) and (I.L.) will extract the following data: 1) Details regarding the identification (title, authors, place and date of study); 2) Participants in the experimental and control groups: number of participants, gestational age, birth weight in grams, number of cesarean deliveries, general anesthesia, previous pregnancies, labor induction, aspiration of meconium and number of intubated; 3) Outcomes and estimates (mean, median, range, standard deviations, 95% confidence intervals, and number of events).

We will contact the authors of the studies to clarify any unclear or missing information regarding the evaluated domain. If the data are insufficient even after contacting the author, the results of the studies will be summarized only in narrative synthesis.

Chart 1 - *Complete search strategy for each database*

Database	Search Strategy
Pubmed	P: #1 "Child"[Mesh] OR child* OR infan* OR neonat* OR "Infant"[Mesh] OR newborn OR pre school OR pre-school OR baby OR babies OR pre-term OR prematur* OR low birth weight OR VLBW OR LBW AND #2 "Heart Arrest"[Mesh] OR Arrest, Heart OR Cardiac Arrest OR Arrest, Cardiac OR Asystole OR Asystoles OR Cardiopulmonary Arrest OR Arrest, Cardiopulmonary OR resuscitation OR asphyxi* AND I: #3 "Hyperoxia"[Mesh] OR O2 OR FiO2 OR hyperox* OR "Oxygen"[Mesh] OR oxygen*
Embase	#1 'child'/exp OR child* OR 'infant'/exp OR infan* OR neonat* OR newborn OR baby OR babies #2 'heart arrest'/exp OR 'heart arrest' OR 'arrest, heart' OR asystole OR asystolia OR asystoly OR 'cardiac arrest' OR 'circulation arrest' OR 'circulatory arrest' OR 'heart arrest, induced' OR 'heart asystole' OR 'heart standstill' OR 'induced heart arrest' OR 'cardiopulmonary arrest' OR 'arrest, cardiopulmonary' #3 'hyperoxia'/exp OR o2 OR fio2 OR hyperox* OR 'oxygen'/exp OR oxygen* #4 #1 AND #2 AND #3 #5 #4 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)
Cochrane	#1 MeSH descriptor: [Child] explode all trees #2 MeSH descriptor: [Infant] explode all trees #3 child* OR infant, newborn OR infan* OR neonat* OR newborn OR pre school OR pre-school OR baby OR babies #4 #1 OR #2 OR #3 #5 MeSH descriptor: [Heart Arrest] explode all trees #6 Arrest, Heart OR Cardiac Arrest OR Arrest, Cardiac OR Asystole OR Asystoles OR Cardiopulmonary Arrest OR Arrest, Cardiopulmonary #7 #5 OR #6 #8 MeSH descriptor: [Hyperoxia] explode all trees #9 MeSH descriptor: [Oxygen] explode all trees #10 FiO2 OR O2 OR hyperox* OR oxygen* #11 #8 OR #9 OR #10 #12 #4 AND #7 AND #11
Lilacs e IBECS	#1 mh:Criança OR mh:M01.060.406$ OR Crianças OR mh:Lactente OR mh:M01.060.703$ OR Lactentes OR recém-nascido OR infant* OR neonato* OR pré-escolar OR bebê OR bebês AND #2 mh:"Parada Cardíaca" OR mh:C14.280.383$ OR Assistolia OR (Parada Cardiopulmonar) OR (Parada Cardiorrespiratória) OR (Paralisia Cardíaca) AND #3 mh:Hiperóxia OR mh:C23.888.852.567$ OR O2 OR FiO2 OR hiperóx* OR oxigên* OR mh:D01.268.185.550$ OR mh:D01.362.670$ OR mh:SP4.097.063.949$ Filter: LILACS and IBECS

Risk of bias in each study and assessment of certainty of evidence

We will perform the assessment of the risk of bias of the included studies using the tool developed by Cochrane, called Risk of Bias 2.0 (Risk of bias - ROB 2.0), with the following domains: bias due to the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of outcome, bias in selection of reported result, and overall study bias.

We will judge each domain as: low risk of bias, high risk of bias, or some concern about risk of bias. To classify the certainty of evidence, we will use the Grading of Recommendations Assessment, Development and Evaluation System. We will consider factors that may decrease the certainty in the evidence: (I) the overall risk of bias of the included studies; (II) the indirectness of the evidence; (III) the inconsistency of the results; (IV) the precision of the estimates; and (V) the risk of publication bias.

To summarize judgments about the certainty of evidence for each main outcome, we will use the GRADE profiler software, available online (https://gdt.gradepro.org/app/), and will present the findings in a table with the seven main outcomes, at the longest available time point:

1. Mortality
2. Hypoxic-ischemic encephalopathy
3. Neonatal asphyxia: apgar 1, 5 and 10 minutes
4. Time of the first spontaneous breath
5. Time to first cry
6. Duration of newborn resuscitation
7. Neuropsychomotor development

The assessment of the risk of bias and the certainty of the evidence will be carried out independently by two evaluators and any disagreements will be resolved through the analysis of a third examiner.

Statistical analysis

If at least two studies present sufficient homogeneity in terms of participants, interventions and evaluated outcomes, we will pool their results in meta-analyses. When it is possible to carry out meta-analyses, the data will be grouped using the inverse variance method and the random effects model in the Review Manager 5.4 software.

When possible, we will synthesize the continuous variables through the difference in means (post and pre-intervention) with a 95% confidence interval (CI). In the absence of results reported as differences in means, or in the absence of good correlation between individual measurements, the reported data will be used after the intervention.

We will summarize the dichotomous variables using relative risk (RR) with a 95% confidence interval (CI). Regarding dichotomous outcomes, we will consider participants as the unit of analysis, rather than events (i.e., the number of participants experiencing one or more adverse events, rather than the number of adverse events per participant). To assess the variability among studies in each meta-analysis, we will employ the I2 statistic. In cases of significant heterogeneity (I2 > 50%), we will explore potential sources of heterogeneity through subgroup or sensitivity analyses, following the recommendations outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Additionally, if there is minor clinical or methodological heterogeneity, we will investigate the sources of heterogeneity through similar subgroup or sensitivity analyses. Subgroup analysis will encompass factors such as weight at birth and presence of comorbidities.

We will conduct sensitivity analyzes, removing studies with a high risk of general bias from the meta-analyses. If at least 10 studies are included in a meta-analysis, we will assess the risk of publication bias by analyzing the funnel plot and Egger's test in the R software (https://www.rproject.org/). When there is a study with more than two groups, we will only include the relevant arms.

Expected results

Through conducting a thorough systematic review, our objective is to furnish informative foundations for clinical practice concerning oxygen administration to full-term neonates experiencing cardiac arrest. Aligned with the Cochrane methodology, recognized as the gold standard in the analysis of health intervention studies, this protocol was rigorously elaborated. We recognize the potential for limitations, encompassing potential biases in investigations and studies characterized by restricted sample sizes, which may hinder precise estimations of intervention outcomes. Nevertheless, this study endeavors to mitigate such constraints by rigorous methodological, systematic assessment of the certainty of evidence across diverse outcomes, and comprehensive, judicious literature exploration. These collective efforts converge to yield a more robust clinical insight, with a specific aim to elucidate the comparative efficacy and safety of ambient air versus 100% oxygen in newborns under

cardiac arrest at birth. This effort to clarify things is based on the strongest evidence we have, providing important insights to support informed clinical decision-making.

Furthermore, the anticipated outcomes of this protocol possess the potential to expose gaps in existing knowledge and furnish impetus for future high-quality RCTs within this domain. Such revelations hold the promise of furnishing indispensable support to practitioners tasked with the management of neonatal cardiorespiratory arrest, alongside the endeavor of refining resuscitation guidelines and substantially enrich and elevate the standards of clinical practice.

Contribuição dos autores
Concepção e desenho da pesquisa: Pinto ACPN, Freires BMA, Santos EC; *Coleta de dados*: Pinto ACPN, Freires BMA, Santos EC, Nogueira FGSB, Alves INL; *Análise e interpretação dos dados*: Pinto ACPN, Santos ET, Oliveira LL; *Análise estatística*: Pinto ACPN, Freires BMA, Santos EC, Nogueira FGSB; *Redação do manuscrito*: Pinto ACPN, Freires BMA, Santos EC; *Revisão crítica do manuscrito quanto ao conteúdo intelectual importante*: Pinto ACPN, Freires BMA, Santos EC, Nogueira FGSB, Amaral JAR, Iosimuta NCR.

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