INPLASY PROTOCOL

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None declared.

Oxidative Stress in Patients with Congenital Heart Disease: A Systematic Review and Meta-Analysis

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Review question / Objective: **To conduct a systematic review and meta-analysis of clinical controlled studies comparing parameters measuring oxidative stress in blood of patients with congenital heart disease (CHD).**
Main objective: to review studies on the presence of oxidative stress in both children and adults with CHD.
Secondary objectives:
- to review methods to assess oxidative stress levels in peripheral blood of CHD
- to review factors with the potential to influence oxidative stress levels
- to study whether there are therapeutic options targeting oxidative stress in CHD.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 May 2023 and was last updated on 11 May 2023 (registration number INPLASY202350044).

INTRODUCTION

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Rationale: **To gain more insight into oxidative stress in blood of patients with CHD: in order to improve therapy and**

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preventive strategies, we need a better understanding of the underlying pathophysiological mechanisms.

Condition being studied: Congenital heart diseases (CHDs) compromise a wide range of cardiac malformations. Medical and surgical advances have dramatically increased the survival of patients with CHD leading to a continuously growing number of children, adolescents and adults CHD. Nevertheless, CHD patients have lower physical fitness, reduced quality-of-life and worse prognosis compared to healthy individuals of similar age. In addition to the left ventricle, life-long evaluation of the less studied right ventricle has proven to be a cornerstone in CHD prognosis. To improve therapy and preventive strategies, we need a better understanding of the underlying pathophysiological mechanisms.
Development and progression of heart failure (HF) is the main cause of morbidity and mortality in this population. Patients with heart failure induced by CHD and patients with heart failure induced by other etiologies share many characteristics. In patients with HF induced by other etiologies, increased oxidative stress is implicated in pathogenesis of cardiac injury and the disease progression.
The term oxidative stress refers to an imbalance between reactive oxygen species production and the body's antioxidant defenses. Oxidative stress may be of particular concern in CHD.

METHODS

Search strategy: Search terms: ("Congenital heart disease" OR "Heart Defects, Congenital"[Mesh]) AND ("Oxidative Stress" OR "Oxidative Stress" [Mesh]). Electronic database: Pubmed.

Participant or population: Patients (infants, children, adolescents or adults) with congenital heart disease.

Intervention: Measurement of oxidative stress levels in peripheral blood.

Comparator: Not applicable.

Study designs to be included: Clinical controlled studies.

Eligibility criteria: Exclusion criteria: (1) no full-text or abstract available in English, (2) comments on articles, editorial comments, (3) studies regarding oxidative stress during and shortly after surgery without baseline comparison of groups, (4) syndromic patients, (5) preterm infants with PDA, (6), research performed in animals, (7) assessment of oxidative stress in other tissues (e.g., urine, cardiac muscle, aortic tissue, ...), (8) only genetic analysis without oxidative stress maker in blood.

Information sources: Electronic database: Pubmed. If necessary, the corresponding authors are contacted for additional information (full text articles, additional data, ...)

Main outcome(s): Parameters measuring oxidative stress levels in peripheral blood of patients with CHD: (1) pro-oxidative stress markers, (2) anti-oxidative stress markers, (3) ratio of pro- to anti-oxidative stress markers.

Additional outcome(s): - factors with the potential to influence oxidative stress levels in CHD (e.g. patient characteristics, ...)
- therapeutic options targeting oxidative stress in CHD (e.g. medication, ...)

Data management: The literature was screened and data were extracted by two independent investigators. A consensus meeting was held. In case of discrepancy/ disagreement, a third person was involved.
The data were extracted in a data extraction sheet in a prepared Excel file. The extracted data were entered into the CMA-2 software (Comprehensive Meta-Analysis second version, Biostat, Englewood, USA).

Quality assessment / Risk of bias analysis: We used the STROBE checklist for case-control studies to assess the quality of the included studies.

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Strategy of data synthesis: Expecting an important degree of between studies heterogeneity (due to different measurement techniques and specific patient characteristics, e.g. age), a random-effects model was chosen to pool the individual study results and to examine the overall effect size of oxidative stress between groups. Effect sizes (levels of (anti-)oxidative markers in blood) were calculated as standardized mean differences and expressed as Hedges' g to correct for overestimating the true effect in small studies. The 95% confidence intervals (95% CI) were calculated for the individual studies and the overall estimate.
The Cochran's Q statistic and its corresponding p-value were calculated for heterogeneity testing and the I^2 statistic was assessed to express the degree of heterogeneity across studies. Publication bias was assessed per pro/anti/pro-anti through visual analysis of the funnel plot and formal testing for funnel plot asymmetry ('trim and fill' and 'fail 'n safe' algorithms). P-values less than 0.05 were considered significant.

Subgroup analysis: The main question we want to answer is whether there is more oxidative stress in the peripheral blood of patients with CHD compared to healthy controls. A subgroup analysis then investigates whether there is a difference in oxidative stress between patients born with a cyanotic or an acyanotic CHD.
The blood markers of oxidative stress are divided into 3 groups: (1) pro-oxidative stress markers, (2) anti-oxidative stress markers, (3) ratio of pro- to anti-oxidative stress markers.

Sensitivity analysis: Was carried out to investigate the effects of methodological heterogeneity.

Language restriction: English.

Country(ies) involved: Belgium.

Keywords: Oxidative stress; "oxidative stress" [Mesh]; reactive oxygen species (ROS); superoxide; "heart defects, congenital" [Mesh]; "congenital heart disease"

Dissemination plans: We aim to publish this study in a journal relative to oxidative stress or congenital heart disease in English.

Contributions of each author:
Author 1 - Inne Vanreusel - Author 1 performed the literature search, screening of articles, quality assessment of the articles, data extraction and statistical analysis and drafted and completed the writing of the manuscript.
Author 2 - Wendy Hens - Author 2 performed the literature search, screening of articles, quality assessment of the articles, data extraction and statistical analysis together with author 1, contributed to the development of the selection criteria, guided the writing of the article and approved the final manuscript.
Author 3 - Jan Taeymans - Author 3 provided statistical expertise and guided the writing of the article.
Author 4 - Emeline Van Craenenbroeck - Author 4 read, provided feedback and approved the final manuscript.
Author 5 - An Van Berendoncks - Author 5 read, provided feedback and approved the final manuscript.
Author 6 - Bernard Paelinck - Author 6 read, provided feedback and approved the final manuscript.
Author 7 - Vincent Segers - Author 7 read, provided feedback and approved the final manuscript.
Author 8 - Jacob J. Briedé - Author 8 contributed to the development of the selection criteria, guided the writing of the article and approved the final manuscript.

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