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Local anaesthetics combined with vasoconstrictors in patients with cardiovascular disease undergoing dental procedures: systematic review and meta-analysis protocol

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ABSTRACT

Introduction The use of vasoconstrictors combined with local anaesthetics (LAs) in dentistry for patients with cardiovascular disease (CVD) is still controversial in the scientific literature. It raises concerns regarding the possibility of transient episodes, triggering negative cardiovascular outcomes.

Method/design Trials eligible for our systematic review will enrol patients with CVD who have undergone dental treatments carried out with the use of LAs by comparing two arms: LAs with vasoconstrictors and LAs without vasoconstrictors. The research will be conducted in the electronic databases, namely Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, Healthstar (via Ovid), Cumulative Index to Nursing and Allied Health Literature and Web of Science, from their inception to December 2017, without any restrictions in terms of language and status of publication. A team of reviewers will independently assess titles, abstracts and complete text to determine eligibility. For eligible studies, the same reviewers will perform data extraction and evaluate the risk of bias in the selected articles. The selected outcomes comprise death, mortality by a specific cause, stroke, acute myocardial infarction, hospitalisation, pain, bleeding, arrhythmias, ischaemic episodes, anxiety, adverse effects, changes in blood pressure, changes in heart rate, anxiety and results obtained via oximetry. Whenever possible, we will conduct a meta-analysis to establish the effects of LAs with and without vasoconstrictors in the patients with CVD, and the overall quality of evidence for each outcome will be determined using the Grading of Recommendations Assessment, Development and Evaluation classification system.

Ethics and dissemination Ethics committee approval was not necessary because this is a protocol of systematic review. This systematic review will be submitted for presentation at conferences and for publication in a peer-reviewed journal. Our review will assess the risks of cardiovascular events when using LAs with and without vasoconstrictors in patients with CVD, focusing on important clinical outcomes.

Strengths and limitations of this study

► This review method includes explicit eligibility criteria, a comprehensive and extensive database research and an independent assessment of the quality and eligibility of studies by a pair of reviewers.

► The use of Grading of Recommendations Assessment, Development and Evaluation will evaluate the strength and quality of evidence body on the effect estimate for each outcome, including the independent analysis of bias risk, accuracy, consistency, publication bias and indirect evidence.

► The quality of the primary studies to be included in this review may be a limiting factor owing to each study design and outcome measures.

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INTRODUCTION

Cardiovascular disease (CVD) is the primary cause of death worldwide. It is estimated that 17.5 million people died from CVD in 2012, representing 31% of all deaths worldwide. Over three-fourths of deaths from CVD have been reported in low-income or middle-income countries.[1] In Brazil, CVD mortality accounted for one-third of all causes of deaths in 2002.[2] CVD comprises arterial hypertension, rheumatic heart diseases, ischaemic heart diseases, cerebrovascular diseases, heart inflammatory diseases and so on.[3]

In dentistry, clinical procedures in patients with CVD should be carefully assessed to minimise the stress associated with the completion of dental procedures. Besides lowering anxiety, pain control is fundamental to minimise transient episodes that may

trigger negative cardiovascular outcomes, primarily in such patients.[4]

Anxiety and pain control techniques in dentistry may be psychological as well as pharmacological. Psychological techniques may involve simple relaxing techniques used in anxious patients and understanding the behaviour regarding pain control. Pharmacological techniques comprise drugs such as local anaesthetics (LAs), sedatives and pain killers.[5]

Local anaesthesia is the basis for pain control in dentistry. There is a long history of the safe use of LAs in healthy patients and in patients with complex medical situations.[5 6]

Clinical anaesthetic agents are combined with vasoconstrictors to increase the duration of the anaesthetic effect, reduce systemic toxicity and optimise soft tissue haemostasis.[7 8]

Despite the beneficial properties of vasoconstrictors, there is some concern regarding systemic consequences due to inadvertent intravascular injection and the induction of adverse cardiovascular effects, primarily in patients with CVD.[9 10] In addition, pain, stress, fear and anxiety during dental treatment that are caused by lack of pain control and poor anaesthesia may be responsible for the systemic endogenous release of catecholamines, particularly norepinephrine,[11] which may lead to autonomic responses such as hypertension and arrhythmias.[5 8 12] A previous study reported that the stress-induced release of catecholamines could be more than 10 times greater than the basal level. In stressful situations, such as pain and anxiety, the release of endogenous catecholamines may reach concentrations higher than the low epinephrine concentrations used in dental LAs.[5 13 14]

Nevertheless, the occurrence of most alterations may be attributed to inappropriate applications such as high-dose injections, intravascular accidental injections and drug interactions.[4 8 15] Thereafter, endogenous or exogenous cathecolamines may cause or contribute to haemodynamic and cardiac changes.[16]

A systematic review has shown that most complications that arise while using LAs with vasoconstrictors are clinically insignificant arrhythmias and that the use of the anaesthetic agent lidocaine associated with epinephrine in the recommended dosage seems to be relatively safe for patients with CVD.[12] However, putative standards and guidelines continue to present and advise against or limit the use of vasoconstrictors in patients with CVD, which brings uncertainties in their use.[9]

Scientific evidence demonstrating the safe use of LAs combined with vasoconstrictors in patients with CVD is scarce and contradictory. Thus, this systematic review was aimed to determine the risk of cardiovascular events when using LAs combined with vasoconstrictors in patients with CVD, both during and immediately after dental procedures.

METHODS AND ANALYSES
The systematic review will be performed according to the recommendations specified in the *Cochrane Handbook for Interventional Reviews* and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[17]

Protocol and registration
Our review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO-CRD42016045421).

Eligibility criteria
Inclusion criteria
Patients
Adult patients with CVD: arterial hypertension, rheumatic heart diseases, ischaemic heart diseases, cerebrovascular diseases and heart inflammatory diseases.[3]

Interventions
One arm wherein patients received LAs with vasoconstrictors compared with another arm wherein patients received LAs without vasoconstrictors.

Procedures
Patients who undergo tooth extraction, dental restorations, treatment and periodontal surgery, implantation, oral surgery, root canal treatments and prosthetic procedures.

Type of study
Randomised controlled trials (RCTs): we will include two types of RCT designs. In the first type, patients are randomised to receive either LAs with vasoconstrictors during the first dental procedure and LAs without vasoconstrictors during the second dental procedure or vice versa. In the second type, patients are randomised to receive only one type of LA, with or without vasoconstrictors, during the dental procedure.

Language
Any language.

Outcomes
The investigations are to report at least one of the following outcomes:

Primary outcomes
► death
► mortality by a specific cause
► stroke
► acute myocardial infarction
► hospitalisation
► pain
► bleeding.

Secondary outcomes
► arrhythmias
► ischaemic episodes
► anxiety

- ► adverse effects
- ► changes in blood pressure
- ► changes in heart rate
- ► changes in results obtained via oximetry.

Exclusion criteria

We will exclude studies involving patients with untreated or out-of-control arterial hypertension, who are pregnant or breastfeeding, who are allergic to the LAs used in the studies, with out-of-control diabetes mellitus or who have had recent myocardial infarction, cancer and malignant hypertension.

Search methods for primary studies

Electronic searches

We will search the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) part of The Cochrane Library; MEDLINE (Ovid); Embase (Ovid); Healthstar (Ovid); Cumulative Index to Nursing and Allied Health Literature; and Web of Science, from their inception to December 2017, without restrictions on the status of publication or date. The searching will be running from each database beginning to the present.

Searching other resources

We will search in registration of clinical trials: https://clinicaltrials.gov, WHO clinical trials registry, http://www.ensaiosclinicos.gov.br; trials registry and bank of Brazil thesis (CAPES); conference proceedings of the Brazilian Congress of Cardiology, in the Brazilian Congress of Anesthesiology and in the International Congress of Dentistry (CIOSP).

We will also search the main LA production companies in Brazil.

Two reviewers will analyse the reference list or quotations found in secondary studies to verify and identify possible eligible studies. Whenever necessary, the authors of the main studies will be contacted to obtain additional information.

Search strategy

The search strategy will be individually conducted by: (1) type of dental intervention; (2) type of anaesthetic; and (3) type of CVD. We have adapted the search strategy according to each database. The search strategy in Ovid MEDLINE is in online supplementary appendix 1.

Eligibility determination

Four reviewers (CCG, CdCB, RHLM and NKdA) working in pairs will independently evaluate whether summaries are in accordance with eligibility criteria. Discrepancies are to be resolved by a consensus reached among all reviewers. Kappa test will be used to assess selection agreement, given that Kappa values between 0.40 and 0.59 are to be regarded as a weak agreement, values between 0.60 and 0.70 as intermediary agreement and 0.75 or larger as excellent agreement.[18]

To exclude duplicate articles, reviewers will analyse all eligible articles and identify those with one or more authors in common. In case of duplicate publications, we will use the article with more complete data.

Data extraction

Four reviewers (CCG, CdCB, JdOA and JCR), working in pairs, will independently extract data and record information regarding patients, methods, interventions, outcomes and missing outcome data using standardised and pretested data extraction forms with instructions. Before initiating data abstraction, we will conduct calibration exercises to ensure consistency among the reviewers. We will contact the study authors to resolve any uncertainties. Disagreements will be resolved by a consensus with any unresolved issues referred to another reviewer.

Risk of bias in individual studies

Using a modified version of the Cochrane collaboration risk of bias tool,[19 20] the same pairs of reviewers will independently assess the risk of bias for each RCT according to the following criteria: random sequence; allocation concealment; blinding of the patient, healthcare professionals, outcome assessors, data collectors and data analysts; incomplete outcome data; selective outcome reporting; and major baseline imbalance. Reviewers will assign response options of 'definitely yes,' 'probably yes,' 'probably no' and 'definitely no' for each of the domains, with the options 'definitely yes' and 'probably yes' ultimately being assigned a low risk of bias and 'definitely no' and 'probably no' as having a high risk of bias.[21] Reviewers will resolve disagreements by discussion, and one arbitrator will adjudicate unresolved disagreements.

Explaining the heterogeneity of evidence

Possible explanations for heterogeneity will include: (A) age: the older the age, the higher the risk of cardiovascular transient episodes; (B) gender: women outnumber men in deaths due to CVD; (C) vasoconstrictor type: vasoconstrictors are linked to receptors α and β. However, some of these are more often linked to cardiac receptor β (except for felypressin, which links to the vasopressin receptor v1, present in the smooth muscles of blood vessel walls), raise cardiac frequency, and thus, higher risks of transient episodes are expected. (D) Vasoconstrictor concentration, which may vary from a 1:2500 to a 1:200 000 greater risk, is expected with higher vasoconstrictor concentration; (E) dental procedure duration: the longer the duration to perform the procedure (surgical or periodontal procedures take longer than restorative procedures), the higher the concentration of anaesthetic agent necessary, and the stronger the toxicity to the cardiovascular system, thereby increasing the risks of transient episodes in long-duration procedures; and (F) dental procedure type: usually surgical procedures (periodontal, extraction and implantation) trigger great stress in the patient, thus increasing the risk of transient episodes.

We ranked heterogeneity associated with pooled effect estimates with the use of the χ^2 test and the I^2 statistic.[22] The following heterogeneities were considered: 0%–25% (low heterogeneity), 50% (moderate heterogeneity) and 75% (high heterogeneity).[20]

Data synthesis

We will conduct analyses for each LA intervention and pool these for each outcome of interest. We will determine the confidence in estimates for each body of evidence and conduct an analysis for the body of evidence that warrants greater confidence. Hypotheses, information for which has been documented in at least 10 studies for independent continuous variables or in at least five studies for independent categorical variables, will be examined.

The combined analyses will estimate risks of negative cardiovascular outcomes as well as adverse effects in the use of LAs with and without vasoconstrictors in patients with CVD.

Meta-analyses will be conducted using comprehensive the meta-analysis STATA software (V.14.1. We will use random-effects meta-analyses,[18] which are conservative in that they consider within-study and between-study differences in calculating the error term used in the analysis. For trials that report dichotomous outcomes, we will calculate the pooled relative risk with associated 95% CI.

For continuous outcomes such as pain and function score, we will use the weighted mean differences (WMD) and its 95% CI as an effect measure. Once the WMD has been calculated, we will contextualise this value by noting, when available, the corresponding anchor-based minimally important difference (MID). The smallest change in instrument score that patients perceive is important.

If studies report the same framework using different measurement instruments, we will calculate the standardised mean difference (SMD) as sensitivity analysis. SMD expresses the intervention effect in SD units rather than the original units of measurement, with the value of an SMD depends on the size of the effect (difference between means) and the SD of the outcomes (inherent variability among patients). For outcome measures that have an established anchor-based MID, we will use this measure to convert the SMD into an OR and a risk difference.[23]

To facilitate the interpretation of the effects of continuous outcomes, we will substitute the MID, when it is available for different scales, with the SD (denominator) in the SMD equation, which will result in more readily interpretable MID units instead of SD units.[24] If an estimate of the MID is unavailable, we will use the statistical approach developed by Suissa and Shuster[25] to provide a summary estimate of the proportion of patients who benefit from treatment across all studies. Statistical approaches to enhance the interpretability of the results of continuous outcomes outlined in this paragraph will use methods cited as well as those described by Thorlund et al.[26] Funnel plots will be created to explore a possible publication bias when at least 10 studies have contributed to the pooled analysis.

The combined estimates will be tested by statistics Z and heterogeneity, measured using chi-statistic among the studies analysed using χ^2 test. When there is heterogeneity, a variance component because of interstudy variance, it will be incorporated in the calculation of the CI for the estimate. Studies that do not contain the aforementioned data will not be included in the pooled estimate; for such studies, we will summarise death, mortality by a specific cause, stroke, acute myocardial infarction, hospitalisation, pain, bleeding, arrhythmias, ischaemic episodes, anxiety, adverse effects, changes in blood pressure, changes in heart rate, anxiety and changes in results obtained via oximetry.

We will use recently developed approaches to address missing patient data for dichotomous[27] and continuous outcomes.[28] We will only apply these approaches to outcomes that meet the following criteria: show a significant treatment effect and report sufficient missing patient data to potentially introduce clinically important bias. Thresholds for important missing patient data will be determined on an outcome-by-outcome basis.

If the meta-analysis is not appropriate owing to excessive heterogeneity of the study population, intervention, comparator, outcome or methodology, we will construct summary tables and provide a narrative synthesis.

Summarising evidence

The quality of evidence will be independently evaluated (confidence in effect estimates) for each result using Grading of Recommendations Assessment, Development and Evaluation (GRADE).[18] Results will be presented in evidence profiles, as recommended by the GRADE Working Group.[29 30]

Evidence profiles will provide brief presentations of evidence quality and effect magnitude. With the help of the software program GRADEpro (http://ims.cochrane.org/gradepro), we will construct an evidence profile to include the following: (1) a list featuring up to seven important results (desirable and undesirable), (2) a measure of the typical load of such results (eg, control group or estimated risk), (3) a measure of the difference between risks with and without intervention, (4) the relative magnitude of the effect, (5) number of patient and studies that address these outcomes as well as the follow-up time, (6) an overall assessment of confidence in the effect estimate for each outcome and (7) comments, which will include the MID, if available.

In the GRADE approach, randomised studies start with high-quality evidence, but they may be assessed as low-quality evidence by one or more of the five restriction categories: independent assessment of risk of bias, precision, consistency, directness, and publication bias.

DISCUSSION

Our review will evaluate the cardiovascular risks and adverse effects of the use of LAs with vasoconstrictors compared with those of LAs without vasoconstrictors in patients with CVD. This will provide estimates for the safe

use of LAs and quality of evidence in complete and consistent form using GRADE.[29 31] We will prioritise important outcomes for the patients. The result of this systematic review will be relevant to dentists and physicians for the prescription and use of LAs in patients with CVD. Our aim is to inform medical professionals and dentists on the best estimate of the effects and reliability of the estimates for the safe use of LAs with and without vasoconstrictors in patients with CVD and identify key areas for future research.

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