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Local anesthetic combined with vasoconstrictor in patients with cardiovascular diseases undergoing dental procedures: Systematic review and meta-analysis protocol

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Title: Local anesthetic combined with vasoconstrictor in patients with cardiovascular diseases undergoing dental procedures: Systematic review and meta-analysis protocol

Short title: Local anesthesia in dental patients with cardiovascular diseases

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Appendix: 1

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ABSTRACT

Introduction: Use of vasoconstrictors combined with local anesthetics (LAs) in dentistry for patients with cardiovascular diseases (CVDs) 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 enroll CVD patients who have undergone dental treatments that demand the use of LAs by comparing two arms: LA with vasoconstrictor and LA without vasoconstrictor. The research will be conducted in the electronic databases Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Healthstar (via Ovid), CINAHL, and Web of Science, 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 risk of bias in the selected articles. The selected outcomes comprise death, mortality by specific cause, stroke, acute myocardial infarction, hospitalization, pain, bleeding, arrhythmias, ischemic episodes, anxiety, adverse effects, blood pressure changes, changes in heart rate, anxiety, and changes in oximetry. Whenever possible, we will conduct a meta-analysis to establish the effects of LA with and without vasoconstrictor in such patients, and the overall quality of evidence for each of the outcomes will be determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) 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. The results of this study will be disseminated by publication in a peer-reviewed journal.

Protocol registration: PROSPERO- CRD42016045421

Keywords: Local Anesthetics, Anesthesia Dental, Dentistry, Cardiovascular Disease

Strengths and limitations of this study

- Transient cardiovascular episodes during or after dental interventions are negative outcomes in dentistry, which generate uncertainties regarding the use of LAs combined with vasoconstrictors. Estimating the risk rate of such episodes in patients with cardiovascular diseases may contribute to an adequate use of LAs in such patients.
- The use of GRADE will evaluate the strength and quality of evidence body on the effect estimate for each of the outcomes, including the independent analysis of bias risk, accuracy, consistency, publication bias, and indirect evidence.
- This review method includes explicit eligibility criteria, comprehensive and extensive database research, and independent assessment of quality and eligibility of studies by a pair of reviewers.
- Quality of the primary studies to be included in this review may be a limiting factor owing to each study design and measures of outcomes.

INTRODUCTION

Cardiovascular diseases (CVDs) are 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 were reported in low- 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, ischemic heart diseases, cerebrovascular diseases, heart inflammatory diseases, and so on.[3]

In dentistry, attending patients with CVD should be differentiated to minimize the stress associated with completion of dental procedures. Besides lowering anxiety, pain control is fundamental to minimize 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 not only simple relaxing techniques used in anxious patients but also understanding behavior for pain control. Pharmacological techniques comprise drugs such as local anesthetics (LAs), sedatives, and pain killers.[5]

Local anesthesia is the basis for pain control in dentistry. There is a long history of safe use of LAs, not only in healthy patients but also in patients with complex medical situations.[5,6]

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

Despite the beneficial properties of vasoconstrictors, there is some concern regarding the systemic absorption and induction of adverse cardiac effects, primarily in patients with CVD;[9,10] on the other hand, deficiency in pain control, stress, fear, and anxiety during dental treatment are responsible for systematic endogenous release of catecholamines, which may lead to autonomic responses such as arrhythmias.[5,8,11] Endogenously released epinephrine may reach higher concentrations than that used in dental LAs.[5,12,13]

However, the occurrence of most alterations may be attributed to inappropriate applications such as injections of high doses, intravascular accidental application, and drug interactions.[4,8,14,15]

Certain studies have shown that most complications that arise while using LA with vasoconstrictors are clinically insignificant arrhythmias and that the use of the anesthetic agent lidocaine associated with epinephrine in the recommended dosage seems to be relatively safe for CVD patients.[11] However, certain studies have advised against or limit the use of vasoconstrictors in certain CVDs, which brings uncertainties in their use.[15]

Scientific evidence demonstrating safe use of LAs combined with vasoconstrictors in CVD patients is scarce and contradictory.[10,15] Thus, this systematic review was aimed to determine the risk of cardiovascular events in using Las combined with vasoconstrictors in CVD patients, 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 (PRISMA-P) statement.[16]

Protocol and Registration

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

Eligibility criteria

Inclusion criteria

Patients: adult CVD patients: arterial hypertension, rheumatic heart diseases, ischemic heart diseases, cerebrovascular diseases, and heart inflammatory diseases[3]

Interventions: one arm wherein patients received LAs with vasoconstrictor compared to an arm wherein patients received LAs without vasoconstrictor

Procedures: patients who undergo tooth extraction, dental restorations, treatment and periodontal surgery, implants, oral surgery, root canal treatments, and prosthetic procedures

Type of study: randomized clinical studies (RCTs): we will include two types of RCT designs. In the first type, the same patients are randomized to receive either LA with vasoconstrictors during the first dental procedure and LA without vasoconstrictor during the second dental procedure or vice versa. In the second design type, patients are randomized to receive only one type of LA, with or without vasoconstrictor, during the dental procedure.

Language: Any language

Outcomes: The investigations are to report at least one of the following outcomes: death, mortality by specific cause, stroke, acute myocardial infarction, hospitalization, pain, bleeding, arrhythmias, ischemic episodes, anxiety, adverse effects, blood pressure changes, changes in heart rate, anxiety, and changes in oximetry.

Primary outcomes:

- death;
- mortality by specific cause swelling;
- stroke;
- acute myocardial infarction;
- hospitalization;
- pain;
- bleeding;

Secondary outcomes:

- arrhythmias;
- ischemic episodes;
- anxiety;
- adverse effects;
- blood pressure changes;
- changes in heart rate;
- changes in oximetry;

Exclusion criteria

We will exclude patients with untreated or out-of-control arterial hypertension, patients 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 following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) part of The Cochrane Library; MEDLINE (Ovid); EMBASE (Ovid); Healthstar (Ovid); CINAHL (Cumulative Index to Nursing and Allied Health Literature); and Web of Science, without status of publication restrictions.

Searching other resources

We will search in registration of clinical trials: https://clinicaltrials.gov e http://www.ensaiosclinicos.gov.br; trials registry and bank of Brazil thesis (CAPES); Brazilian universities database, such as: http://buscaintegrada.usp.br/primo_library/libweb/action/search.do?dscnt=1&dstmp=1459264122962&vid=USP&fromLogin=true;
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 analyze the reference list or quotations found in secondary studies to verify and identify possibly eligible studies. Whenever necessary, the authors of the main studies will be contacted to obtain additional information.

Search strategy

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

Eligibility determination

Four reviewers (CCG, CCB, RLM, and NKA) working in pairs will independently evaluate whether summaries are in accordance with eligibility criteria. Discrepancies are to be resolved by consensus among all the 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.[17]

In order to exclude duplicate articles, reviewers will analyze 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, CCB, JOA, and JCR), working in pairs, will independently extract data and record information regarding patients, methods, intervention, outcomes, and missing outcome data by using standardized and pretested data extraction forms with instructions. Before initiating data abstraction, we will conduct calibration exercises to ensure consistency between reviewers. We will contact the study authors to resolve any uncertainties. Disagreements will be resolved by consensus with any unresolved issues referred to another reviewer.

Risk of bias in individual studies

By using a modified version of the Cochrane collaboration risk of bias tool,[18,19] 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 “definitely yes” and “probably yes” ultimately being assigned a low risk of bias and “definitely no” and “probably no” a high risk of bias.[20] Reviewers will resolve disagreements by discussion, and one arbitrator will adjudicate unresolved disagreements.

Explaining the heterogeneity of evidence

Possible explanations for the heterogeneity will include: (a) age- the older the age, the bigger the risk of cardiovascular transient episodes; (b) gender- women outnumber men in deaths due to CVD; (c) type of vasoconstrictor agents- vasoconstrictors link to receptors α and β. However, some of these are more often linked to cardiac receptor β (except for felypressin, which links to vasopressin receptors v1, present in the smooth muscles of blood vessel walls), raise cardiac frequency, and thus, greater risks of transient episodes are expected; (d) vasoconstrictor concentration- which may vary from a 1:2,500 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 take longer than

restorative), the more anesthetic agent is necessary, and the stronger the toxicity for the cardiovascular system, increasing the risks of transient episodes in long-duration procedures; (f) type of dental procedure–usually surgical procedures (periodontal, extraction, and implant) trigger greater stress in the patient, thus increasing the risk of transient episodes, as expected.

We ranked heterogeneity associated with pooled effect estimates with the use of a χ^2 test and the I^2 statistic.[21] The following heterogeneity was considered: 0–25% (low heterogeneity); 50% (moderate heterogeneity); and 75% (high heterogeneity).[19]

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 5 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 CVD patients.

Meta-analyses will be conducted using comprehensive meta-analysis STATA software (version 14.1). We will use random-effects meta-analyses,[17] which are conservative in that they consider within- 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% confidence interval (CI).

For continuous outcomes such as pain and function score, we will use weighted mean differences (WMDs) and its 95% CI as effect measure. Once the WMD has been calculated, we will contextualize 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 construct using different measurement instruments, we will calculate the standardized mean difference (SMD) as sensitivity analysis. SMD expresses the intervention effect in standard deviation (SD) units rather than the original units of measurement, with the value of an SMD depending on the size of the effect (difference between means) and the SD of the outcomes (inherent variability among participants). For outcome measures that have an established anchor-based MID, we will use this measure to convert the SMD into an odds ratio and risk difference.[22]

To facilitate the interpretation of the effects of continuous outcomes, we will substitute the MID, when MID 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.[23] If an estimate of the MID is not available, we will use a statistical approach developed by Suissa[24] to provide a summary estimate of the proportion of patients who benefit from treatment across all studies. Statistical approaches to enhance the interpretability of results of continuous outcomes outlined in this paragraph will use methods cited as well as those described by Thorlund et al.[25] Funnel plots will be created to explore possible publication bias when at least 10 studies have contributed to a pooled analysis.

The combined estimates will be tested by statistics Z and heterogeneity, measured using chi-statistic among the studies analyzed using chi-squared test. When heterogeneity is present, a variance component because of inter-study variance, it will be incorporated in the calculation of the CI for the estimate. Studies that do not contain any of the aforementioned data will not be included in the pooled estimate; for such studies, we will summarize death, mortality by specific cause, stroke, acute myocardial infarction, hospitalization, pain, bleeding, arrhythmias, ischemic episodes, anxiety, adverse effects, blood pressure changes, changes in heart rate, anxiety, and changes in oximetry.

We will use recently developed approaches to address missing participant data for dichotomous outcomes[26] and continuous outcomes.[27] We will only apply these approaches to outcomes that meet the following criteria: show a significant treatment effect and report sufficient missing participant

data to potentially introduce clinically important bias. Thresholds for important missing participant 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.

Summarizing evidence

The quality of the evidences will be independently evaluated (confidence in effect estimates) for each of the results by using GRADE.[17]

Results will be presented in evidence profiles, as recommended by GRADE Working Group.[28-29]

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 the evidence profile to include following: (1) a list featuring up to seven important results (desirable and undesirable); (2) a measure of the typical load of such results (e.g., 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 participants 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 DMI, if available.

In the GRADE approach, randomized 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 cardiovascular risks and adverse effects of the use of LA with vasoconstrictors compared with LA without vasoconstrictors in CVD patients. This will provide estimates for safe use and quality of evidence body in complete and consistent form by using GRADE.[28,30] We will prioritize important outcomes for the patient. The result of this systematic review will be

relevant to dentists and physicians for prescription and use of LAs in CVD patients. Our aim is to inform medical professionals and dentists on the best estimate of the effects and reliability of the estimates for safe use of LAs with and without vasoconstrictors in patients with CVD and identify key areas for future research.

Abbreviations

Local anesthetic (LA), cardiovascular disease (CVD), Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Grading of Recommendations Assessment, Development, and Evaluation (GRADE), randomized clinical trial (RCT), bank of Brazil thesis (CAPES), Congresso Internacional de Odontologia de São Paulo (CIOSP), confidence interval (CI), weighted mean difference (WMD), minimally important difference (MID), and standardized mean difference (SMD), standard deviation (SD).

Competing interests

The authors declare that they have no competing interests.

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Contributors

CCG is the principal investigator and led the writing of the manuscript. LCL and RLM are the project managers, co-investigators and contributed to the writing and revision of the manuscript. CCB, JCR, JOA, NKA, and MFF co-investigators contributed to the writing and revision of the manuscript. All authors read and approved the final manuscript.

Provenance and peer review

Not commissioned; externally peer reviewed.

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APPENDIX 1 -Search strategy (Via Ovid, MEDLINE)

1 exp Dentistry/ (357819)

2 exp Dentistry, Operative/ (32163)

3 exp Dental Care/ (29438)

4 Dental Restoration, Permanent/ (18759)

5 Dental Restoration Repair/ (102)

6 Periodontal Debridement/ (191)

7 Subgingival Curettage/ (977)

8 Dental Scaling/ (3316)

9 Chronic Periodontitis/ (1971)

10 Periodontal Diseases/ (24137)

11 Periodontal Surgery.mp. (1302)

12 Periodontal treatment.mp. (2728)

13 Oral Surgical Procedures/ (5363)

14 exp Surgery, Oral/ (7419)

15 Tooth Extraction/ (17008)

16 Dental Prosthesis/ (3384)

17 “Root Canal Therapy”/ (11735)

18 exp Dental Implants/ (17311)

19 Dental Implants, Single Tooth/ (1901)

20 Dental Implantation/ (3773)

21 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 (372164)

22 exp Anesthetics, Local/ (96504)

23 exp Anesthesia, Local/ (15673)

24 exp Anesthesia, Dental/ (10417)

25 Lidocaine/ (22512)

26 Prilocaine/ (2018)

27 Bupivacaine/ (10713)

28 Procaine/ (11313)

29 Mepivacaine/ (1899)

30 Carticaine/ (451)

31 Etidocaine/ (288)

32 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 (114729)

33 exp Cardiovascular Diseases/ (2067079)

34 Cardiac.mp. (631932)

35 Coronary Disease/ (128393)

36 Coronary Artery Disease/ (47503)

37 Coronary arteriosclerosis.mp. (733)

38 Coronariopathy.mp. (29)

39 Arrhythmias, cardiac/ (56112)

40 Heart Valve Diseases/ (21116)

41 Heart Diseases/ (63528)

42 Heart Failure/ (63528)

43 Rheumatic Heart Disease/ (12263)

44 Myocardial Ischemia/ (34898)

45 Myocardial Infarction/ (151398)

46 Hypertension (210548)

47 Hypertensive Patients.mp. (25167)

48 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 (2314784)

49 21 AND 32 AND 48 (752)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐		1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐		6
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐		3
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐		1,2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐		13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐		6
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐		13
Sponsor	5b	Provide name for the review funder and/or sponsor	☐		13
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐		13
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐		4,5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to	☐		6

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
		participants, interventions, comparators, and outcomes (PICO)			
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐		6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐		7,8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐		8
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐		9,10,11
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐		9
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐		9
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐		9,10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐		6,7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐		9,12
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐		10,11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐		10,11,12
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	☐		11,12

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
		regression)			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐		12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐		9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐		12

BMJ Open

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

Journal:	*BMJ Open*
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Keywords:	Local anesthetics, Anesthesia Dental, Dentistry, Cardiovascular Disease

Title: Local anesthetics combined with vasoconstrictors in patients with cardiovascular disease undergoing dental procedures: Systematic review and meta-analysis protocol

Short title: Local anesthesia in dental patients with cardiovascular disease

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ABSTRACT

Introduction: The use of vasoconstrictors combined with local anesthetics (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 enroll patients with CVD who have undergone dental treatments that demand the use of LAs by comparing two arms: LAs with vasoconstrictors and LAs without vasoconstrictors. The research will be conducted in the electronic databases Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Healthstar (via Ovid), CINAHL, and Web of Science, 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, hospitalization, pain, bleeding, arrhythmias, ischemic 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 outcomes will be determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) 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.

Protocol registration: PROSPERO- CRD42016045421

Keywords: Local Anesthetics, Anesthesia Dental, Dentistry, Cardiovascular Disease

Strengths and limitations of this study

- Transient cardiovascular episodes during or after dental interventions are negative outcomes in dentistry, which generate uncertainties regarding the use of LAs combined with vasoconstrictors. Estimating the risk of such episodes in patients with CVD may contribute to an adequate use of LAs in such patients.
- The use of GRADE will evaluate the strength and quality of evidence body on the effect estimate for each outcomes, including the independent analysis of bias risk, accuracy, consistency, publication bias, and indirect evidence.
- 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 quality of the primary studies to be included in this review may be a limiting factor owing to each study design and outcome measures.

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- 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, ischemic heart diseases, cerebrovascular diseases, heart inflammatory diseases, and so on.[3]

In dentistry, attending patients with CVD should be differentiated to minimize the stress associated with the completion of dental procedures. Besides lowering anxiety, pain control is fundamental to minimize 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 not only

simple relaxing techniques used in anxious patients but also understanding the behavior regarding pain control. Pharmacological techniques comprise drugs such as local anesthetics (LAs), sedatives, and pain killers.[5]

Local anesthesia is the basis for pain control in dentistry. There is a long history of the safe use of LAs, not only in healthy patients but also in patients with complex medical situations.[5,6]

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

Despite the beneficial properties of vasoconstrictors, there is some concern regarding systemic absorption and the induction of adverse cardiac effects, primarily in patients with CVD;[9] However, pain, stress, fear, and anxiety during dental treatment caused by lack in the anesthesia are responsible for the systematic endogenous release of catecholamines, which may lead to autonomic responses such as arrhythmias.[5,8,10] Endogenously released epinephrine may reach higher concentrations than concentrations of epinephrine released using dental LAs.[5,11,12]

Nevertheless, the occurrence of most alterations may be attributed to inappropriate applications such as high-dose injections, intravascular accidental applications, and drug interactions.[4,8,13]

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 anesthetic agent lidocaine associated with epinephrine in the recommended dosage seems to be relatively safe for patients with CVD.[10] 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 (PRISMA-P) statement.[14]

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, ischemic heart diseases, cerebrovascular diseases, and heart inflammatory diseases.[3]

Interventions: one arm wherein patients received LAs with vasoconstrictors compared to 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: randomized controlled studies (RCTs): we will include two types of RCT designs. In the first type, patients are randomized 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 randomized 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: death, mortality by a specific cause, stroke, acute myocardial infarction, hospitalization, pain, bleeding, arrhythmias, ischemic episodes, anxiety, adverse effects, anxiety, changes in blood pressure, changes in heart rate, and changes in results obtained via oximetry.

Primary outcomes:

- death;

- mortality by a specific cause;
- stroke;
- acute myocardial infarction;
- hospitalization;
- pain;
- bleeding;

Secondary outcomes:

- arrhythmias;
- ischemic 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); CINAHL (Cumulative Index to Nursing and Allied Health Literature); and Web of Science, without restrictions on the status of publication.

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 analyze 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 anesthetic; and (3) type of CVD. We have adapted the search strategy according to each database. The search strategy in Ovid Medline is in Appendix 1.

Eligibility determination

Four reviewers (CCG, CCB, RLM, and NKA) 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.[15]

To exclude duplicate articles, reviewers will analyze 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, CCB, JOA, and JCR), working in pairs, will independently extract data and record information regarding patients, methods, interventions, outcomes, and missing outcome data using standardized 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,[16,17] 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.[18] 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 1:2,500 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 anesthetic agent necessary, and the stronger the toxicity to the cardiovascular system, thereby increasing the risks of transient episodes in long-duration procedures; (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.[19] The following heterogeneities were considered: 0–25% (low heterogeneity), 50% (moderate heterogeneity), and 75% (high heterogeneity).[17]

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 5 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.

We will conduct meta-analyses using comprehensive the meta-analysis STATA software (version 14.1). We will use random-effects meta-analyses,[15] which are conservative in that they consider within- 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% confidence interval (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 contextualize 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 construct using different measurement instruments, we will calculate the standardized mean difference (SMD) as sensitivity analysis. SMD expresses the intervention effect in standard deviation (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 odds ratio and a risk difference.[20]

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.[21] If an estimate of the MID is unavailable, we will use the statistical approach developed by Suissa[22] 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.[23] 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 analyzed using chi-squared test. When heterogeneity is present, a variance component because of inter-study 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 summarize death, mortality by a specific cause, stroke, acute myocardial infarction, hospitalization, pain, bleeding, arrhythmias, ischemic 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[24] and continuous outcomes.[25] 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.

Summarizing evidence

The quality of evidence will be independently evaluated (confidence in effect estimates) for each result using GRADE.[15] Results will be presented in evidence profiles, as recommended by the GRADE Working Group.[26-27]

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 following: (1) a list featuring up to seven important results (desirable and undesirable), (2) a measure of the typical load of such results (e.g., 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 DMI, if available.

In the GRADE approach, randomized 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.[26,28] We will prioritize 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.

ETHICS AND DISSEMINATION

Ethics approval is not required this is a protocol for a systematic review. The systematic review will be published in a peer-reviewed journal and presented at conferences. The evidence of this study will allow health professionals to be aware of the safety of LA use with and without vasoconstrictors in patients with CVD.

Contributors

CCG is the principal investigator and led the writing of the manuscript. LCL and RLM are the project managers, and co-investigators and contributed to the writing and revision of the manuscript. CCB, JCR, JOA, NKA, and MFF are co-investigators who contributed to the writing and revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Provenance and peer review

Not commissioned; externally peer reviewed.

Abbreviations

Local anesthetic (LA), cardiovascular disease (CVD), Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Grading of Recommendations Assessment, Development, and Evaluation (GRADE), randomized clinical trial (RCT), bank of Brazil thesis (CAPES), Congresso Internacional de Odontologia de São Paulo (CIOSP), confidence interval (CI), weighted mean difference (WMD), minimally important difference (MID), and standardized mean difference (SMD), standard deviation (SD).

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APPENDIX 1 -Search strategy (Via Ovid, MEDLINE)

1 exp Dentistry/ (357819)

2 exp Dentistry, Operative/ (32163)

3 exp Dental Care/ (29438)

4 Dental Restoration, Permanent/ (18759)

5 Dental Restoration Repair/ (102)

6 Periodontal Debridement/ (191)

7 Subgingival Curettage/ (977)

8 Dental Scaling/ (3316)

9 Chronic Periodontitis/ (1971)

10 Periodontal Diseases/ (24137)

11 Periodontal Surgery.mp. (1302)

12 Periodontal treatment.mp. (2728)

13 Oral Surgical Procedures/ (5363)

14 exp Surgery, Oral/ (7419)

15 Tooth Extraction/ (17008)

16 Dental Prosthesis/ (3384)

17 “Root Canal Therapy”/ (11735)

18 exp Dental Implants/ (17311)

19 Dental Implants, Single Tooth/ (1901)

20 Dental Implantation/ (3773)

21 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 (372164)

22 exp Anesthetics, Local/ (96504)

23 exp Anesthesia, Local/ (15673)

24 exp Anesthesia, Dental/ (10417)

25 Lidocaine/ (22512)

26 Prilocaine/ (2018)

27 Bupivacaine/ (10713)

28 Procaine/ (11313)

29 Mepivacaine/ (1899)

30 Carticaine/ (451)

31 Etidocaine/ (288)

32 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 (114729)

33 exp Cardiovascular Diseases/ (2067079)

34 Cardiac.mp. (631932)

35 Coronary Disease/ (128393)

36 Coronary Artery Disease/ (47503)

37 Coronary arteriosclerosis.mp. (733)

38 Coronariopathy.mp. (29)

39 Arrhythmias, cardiac/ (56112)

40 Heart Valve Diseases/ (21116)

41 Heart Diseases/ (63528)

42 Heart Failure/ (63528)

43 Rheumatic Heart Disease/ (12263)

44 Myocardial Ischemia/ (34898)

45 Myocardial Infarction/ (151398)

46 Hypertension (210548)

47 Hypertensive Patients.mp. (25167)

48 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 (2314784)

49 21 AND 32 AND 48 (752)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐		1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐		6
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐		3
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐		1,2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐		13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐		6
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐		13
Sponsor	5b	Provide name for the review funder and/or sponsor	☐		13
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐		13
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐		4,5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to	☐		6

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
		participants, interventions, comparators, and outcomes (PICO)			
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐		6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐		7,8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐		8
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐		9,10,11
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐		9
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐		9
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐		9,10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐		6,7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐		9,12
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐		10,11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐		10,11,12
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	☐		11,12

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
		regression)			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐		12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐		9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐		12

BMJ Open

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

Journal:	*BMJ Open*
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Keywords:	Local anesthetics, Anesthesia Dental, Dentistry, Cardiovascular Disease

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Short title: Local anesthesia in dental patients with cardiovascular disease

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ABSTRACT

Introduction: The use of vasoconstrictors combined with local anesthetics (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 enroll 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 Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Healthstar (via Ovid), CINAHL, and Web of Science, 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, hospitalization, pain, bleeding, arrhythmias, ischemic 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 (GRADE) 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.

Protocol registration: PROSPERO- CRD42016045421

Keywords: Local Anesthetics, Anesthesia Dental, Dentistry, Cardiovascular Disease

Strengths and limitations of this study

- Transient cardiovascular episodes during or after dental interventions are negative outcomes in dentistry, which generate uncertainties regarding the use of LAs combined with vasoconstrictors. Estimation of the risk of such episodes in patients with CVD allows clinicians to determine which drug will minimize the risk of an adverse event.
- The use of GRADE 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.
- 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 quality of the primary studies to be included in this review may be a limiting factor owing to each study design and outcome measures.

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- 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, ischemic heart diseases, cerebrovascular diseases, heart inflammatory diseases, and so on.[3]

In dentistry, clinical procedures in patients with CVD should be carefully assessed to minimize the stress associated with the completion of dental procedures. Besides lowering anxiety, pain control is fundamental to minimize 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 not only

simple relaxing techniques used in anxious patients but also understanding the behavior regarding pain control. Pharmacological techniques comprise drugs such as local anesthetics (LAs), sedatives, and pain killers.[5]

Local anesthesia is the basis for pain control in dentistry. There is a long history of the safe use of LAs, not only in healthy patients but also in patients with complex medical situations.[5,6]

Clinical anesthetic agents are combined with vasoconstrictors to increase the duration of the anesthetic effect, reduce systemic toxicity, and optimize soft tissue hemostasis.[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 anesthesia 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 released 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 hemodynamic 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 anesthetic 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 (PRISMA-P) 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, ischemic heart diseases, cerebrovascular diseases, and heart inflammatory diseases.[3]

Interventions: one arm wherein patients received LAs with vasoconstrictors compared to 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: randomized controlled studies (RCTs): we will include two types of RCT designs. In the first type, patients are randomized 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 randomized 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;
- hospitalization;
- pain;
- bleeding;

Secondary outcomes:

- arrhythmias;
- ischemic 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); CINAHL (Cumulative Index to Nursing and Allied Health Literature); and Web of Science, without restrictions on the status of publication.

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 analyze 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 anesthetic; and (3) type of CVD. We have adapted the search strategy according to each database. The search strategy in Ovid Medline is in Appendix 1.

Eligibility determination

Four reviewers (CCG, CCB, RLM, and NKA) 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 analyze 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, CCB, JOA and JCR), working in pairs, will independently extract data and record information regarding patients,

methods, interventions, outcomes, and missing outcome data using standardized 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 1:2,500 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 anesthetic agent

necessary, and the stronger the toxicity to the cardiovascular system, thereby increasing the risks of transient episodes in long-duration procedures; (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 5 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.

We will conduct meta-analyses using comprehensive the meta-analysis STATA software (version 14.1). We will use random-effects meta-analyses,[18] which are conservative in that they consider within- 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% confidence interval (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 contextualize 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 standardized mean difference (SMD) as

sensitivity analysis. SMD expresses the intervention effect in standard deviation (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 odds ratio 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[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 analyzed using chi-squared test. When heterogeneity is present, a variance component because of inter-study 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 summarize death, mortality by a specific cause, stroke, acute myocardial infarction, hospitalization, pain, bleeding, arrhythmias, ischemic 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.

Summarizing evidence

The quality of evidence will be independently evaluated (confidence in effect estimates) for each result using 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 following: (1) a list featuring up to seven important results (desirable and undesirable), (2) a measure of the typical load of such results (e.g., 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 DMI, if available.

In the GRADE approach, randomized 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 prioritize 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.

ETHICS AND DISSEMINATION

Ethics approval is not required this is a protocol for a systematic review. The systematic review will be published in a peer-reviewed journal and presented at conferences. The evidence of this study will allow health professionals to be aware of the safety of LA use with and without vasoconstrictors in patients with CVD.

Contributors

CCG is the principal investigator and led the writing of the manuscript. LCL and RLM are the project managers and co-investigators and contributed to the writing and revision of the manuscript. CCB, JCR, JOA, NKA, and MFF are co-investigators who contributed to the writing and revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Provenance and peer review

Not commissioned, externally peer reviewed.

Abbreviations

Local anesthetic (LA), cardiovascular disease (CVD), Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Grading of Recommendations Assessment, Development, and Evaluation (GRADE), randomized clinical trial (RCT), bank of Brazil thesis (CAPES), Congresso Internacional de Odontologia de São Paulo (CIOSP), confidence interval (CI), weighted mean difference (WMD),

minimally important difference (MID), and standardized mean difference (SMD), standard deviation (SD).

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APPENDIX 1 -Search strategy (Via Ovid, MEDLINE)

1 exp Dentistry/ (357819)

2 exp Dentistry, Operative/ (32163)

3 exp Dental Care/ (29438)

4 Dental Restoration, Permanent/ (18759)

5 Dental Restoration Repair/ (102)

6 Periodontal Debridement/ (191)

7 Subgingival Curettage/ (977)

8 Dental Scaling/ (3316)

9 Chronic Periodontitis/ (1971)

10 Periodontal Diseases/ (24137)

11 Periodontal Surgery.mp. (1302)

12 Periodontal treatment.mp. (2728)

13 Oral Surgical Procedures/ (5363)

14 exp Surgery, Oral/ (7419)

15 Tooth Extraction/ (17008)

16 Dental Prosthesis/ (3384)

17 “Root Canal Therapy”/ (11735)

18 exp Dental Implants/ (17311)

19 Dental Implants, Single Tooth/ (1901)

20 Dental Implantation/ (3773)

21 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 (372164)

22 exp Anesthetics, Local/ (96504)

23 exp Anesthesia, Local/ (15673)

24 exp Anesthesia, Dental/ (10417)

25 Lidocaine/ (22512)

26 Prilocaine/ (2018)

27 Bupivacaine/ (10713)

28 Procaine/ (11313)

29 Mepivacaine/ (1899)

30 Carticaine/ (451)

31 Etidocaine/ (288)

32 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 (114729)

33 exp Cardiovascular Diseases/ (2067079)

34 Cardiac.mp. (631932)

35 Coronary Disease/ (128393)

36 Coronary Artery Disease/ (47503)

37 Coronary arteriosclerosis.mp. (733)

38 Coronariopathy.mp. (29)

39 Arrhythmias, cardiac/ (56112)

40 Heart Valve Diseases/ (21116)

41 Heart Diseases/ (63528)

42 Heart Failure/ (63528)

43 Rheumatic Heart Disease/ (12263)

44 Myocardial Ischemia/ (34898)

45 Myocardial Infarction/ (151398)

46 Hypertension (210548)

47 Hypertensive Patients.mp. (25167)

48 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 (2314784)

49 21 AND 32 AND 48 (752)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐		1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐		6
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐		3
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐		1,2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐		13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐		6
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐		13
Sponsor	5b	Provide name for the review funder and/or sponsor	☐		13
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐		13
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐		4,5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to	☐		6

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
		participants, interventions, comparators, and outcomes (PICO)			
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐		6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐		7,8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐		8
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐		9,10,11
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐		9
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐		9
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐		9,10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐		6,7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐		9,12
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐		10,11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐		10,11,12
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	☐		11,12

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
		regression)			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐		12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐		9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐		12

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014611.R3
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Secondary Subject Heading:	Anaesthesia, Evidence based practice, Pharmacology and therapeutics
Keywords:	Local anesthetics, Anesthesia Dental, Dentistry, Cardiovascular Disease

Title: Local anesthetics combined with vasoconstrictors in patients with cardiovascular disease undergoing dental procedures: Systematic review and meta-analysis protocol

Short title: Local anesthesia in dental patients with cardiovascular disease

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ABSTRACT

Introduction: The use of vasoconstrictors combined with local anesthetics (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 enroll 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 Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Healthstar (via Ovid), CINAHL, 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, hospitalization, pain, bleeding, arrhythmias, ischemic 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 (GRADE) 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.

Protocol registration: PROSPERO- CRD42016045421

Keywords: Local Anesthetics, Anesthesia Dental, Dentistry, Cardiovascular Disease

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 GRADE 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. Then it is probable that primary studies have a high risk of bias.

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- 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, ischemic heart diseases, cerebrovascular diseases, heart inflammatory diseases, and so on.[3]

In dentistry, clinical procedures in patients with CVD should be carefully assessed to minimize the stress associated with the completion of dental procedures. Besides lowering anxiety, pain control is fundamental to minimize 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 not only simple relaxing techniques used in anxious patients but also understanding

the behavior regarding pain control. Pharmacological techniques comprise drugs such as local anesthetics (LAs), sedatives, and pain killers.[5]

Local anesthesia is the basis for pain control in dentistry. There is a long history of the safe use of LAs, not only in healthy patients but also in patients with complex medical situations.[5,6]

Clinical anesthetic agents are combined with vasoconstrictors to increase the duration of the anesthetic effect, reduce systemic toxicity, and optimize soft tissue hemostasis.[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 anesthesia 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 released 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 hemodynamic 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 anesthetic 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 (PRISMA-P) 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, ischemic heart diseases, cerebrovascular diseases, and heart inflammatory diseases.[3]

Interventions: one arm wherein patients received LAs with vasoconstrictors compared to 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: randomized controlled studies (RCTs): we will include two types of RCT designs. In the first type, patients are randomized 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 randomized 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;
- hospitalization;
- pain;
- bleeding;

Secondary outcomes:

- arrhythmias;
- ischemic 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); CINAHL (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 analyze 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 anesthetic; and (3) type of CVD. We have adapted the search strategy according to each database. The search strategy in Ovid Medline is in Appendix 1.

Eligibility determination

Four reviewers (CCG, CCB, RLM, and NKA) 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 analyze 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, CCB, JOA and JCR), working in pairs, will independently extract data and record information regarding patients,

methods, interventions, outcomes, and missing outcome data using standardized 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 1:2,500 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 anesthetic agent

necessary, and the stronger the toxicity to the cardiovascular system, thereby increasing the risks of transient episodes in long-duration procedures; (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 5 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.

We will conduct meta-analyses using comprehensive the meta-analysis STATA software (version 14.1). We will use random-effects meta-analyses,[18] which are conservative in that they consider within- 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% confidence interval (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 contextualize 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 standardized mean difference (SMD) as

sensitivity analysis. SMD expresses the intervention effect in standard deviation (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 odds ratio 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[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 analyzed using chi-squared test. When heterogeneity is present, a variance component because of inter-study 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 summarize death, mortality by a specific cause, stroke, acute myocardial infarction, hospitalization, pain, bleeding, arrhythmias, ischemic 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.

Summarizing evidence

The quality of evidence will be independently evaluated (confidence in effect estimates) for each result using 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 following: (1) a list featuring up to seven important results (desirable and undesirable), (2) a measure of the typical load of such results (e.g., 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 DMI, if available.

In the GRADE approach, randomized 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 prioritize 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.

ETHICS AND DISSEMINATION

Ethics approval is not required this is a protocol for a systematic review. The systematic review will be published in a peer-reviewed journal and presented at conferences. The evidence of this study will allow health professionals to be aware of the safety of LA use with and without vasoconstrictors in patients with CVD.

Contributors

CCG is the principal investigator and led the writing of the manuscript. LCL and RLM are the project managers and co-investigators and contributed to the writing and revision of the manuscript. CCB, JCR, JOA, NKA, and MFF are co-investigators who contributed to the writing and revision of the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Provenance and peer review

Not commissioned, externally peer reviewed.

Abbreviations

Local anesthetic (LA), cardiovascular disease (CVD), Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Grading of Recommendations Assessment, Development, and Evaluation (GRADE), randomized clinical trial (RCT), bank of Brazil thesis (CAPES), Congresso Internacional de Odontologia de São Paulo (CIOSP), confidence interval (CI), weighted mean difference (WMD),

minimally important difference (MID), and standardized mean difference (SMD), standard deviation (SD).

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31. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. BMJ 2008;**336**(7652):1049-51.

APPENDIX 1 -Search strategy (Via Ovid, MEDLINE)

1 exp Dentistry/ (357819)

2 exp Dentistry, Operative/ (32163)

3 exp Dental Care/ (29438)

4 Dental Restoration, Permanent/ (18759)

5 Dental Restoration Repair/ (102)

6 Periodontal Debridement/ (191)

7 Subgingival Curettage/ (977)

8 Dental Scaling/ (3316)

9 Chronic Periodontitis/ (1971)

10 Periodontal Diseases/ (24137)

11 Periodontal Surgery.mp. (1302)

12 Periodontal treatment.mp. (2728)

13 Oral Surgical Procedures/ (5363)

14 exp Surgery, Oral/ (7419)

15 Tooth Extraction/ (17008)

16 Dental Prosthesis/ (3384)

17 “Root Canal Therapy”/ (11735)

18 exp Dental Implants/ (17311)

19 Dental Implants, Single Tooth/ (1901)

20 Dental Implantation/ (3773)

21 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 (372164)

22 exp Anesthetics, Local/ (96504)

23 exp Anesthesia, Local/ (15673)

24 exp Anesthesia, Dental/ (10417)

25 Lidocaine/ (22512)

26 Prilocaine/ (2018)

27 Bupivacaine/ (10713)

28 Procaine/ (11313)

29 Mepivacaine/ (1899)

30 Carticaine/ (451)

31 Etidocaine/ (288)

32 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 (114729)

33 exp Cardiovascular Diseases/ (2067079)

34 Cardiac.mp. (631932)

35 Coronary Disease/ (128393)

36 Coronary Artery Disease/ (47503)

37 Coronary arteriosclerosis.mp. (733)

38 Coronariopathy.mp. (29)

39 Arrhythmias, cardiac/ (56112)

40 Heart Valve Diseases/ (21116)

41 Heart Diseases/ (63528)

42 Heart Failure/ (63528)

43 Rheumatic Heart Disease/ (12263)

44 Myocardial Ischemia/ (34898)

45 Myocardial Infarction/ (151398)

46 Hypertension (210548)

47 Hypertensive Patients.mp. (25167)

48 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 (2314784)

49 21 AND 32 AND 48 (752)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☐		1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐		6
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐		3
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐		1,2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐		13
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐		6
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐		13
Sponsor	5b	Provide name for the review funder and/or sponsor	☐		13
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐		13
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☐		4,5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to	☐		6

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
		participants, interventions, comparators, and outcomes (PICO)			
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☐		6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☐		7,8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☐		8
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☐		9,10,11
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☐		9
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☐		9
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☐		9,10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☐		6,7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☐		9,12
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐		10,11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐		10,11,12
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	☐		11,12

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
		regression)			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐		12
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐		9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐		12