REVIEW

USE OF LOCAL ANESTHETICS WITH A VASOCONSTRICTOR AGENT DURING DENTAL TREATMENT IN HYPERTENSIVE AND CORONARY DISEASE PATIENTS. A SYSTEMATIC REVIEW

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ABSTRACT

Background
Coronary disease and Hypertension are highly prevalent health problems worldwide, with the latter being one of the most common diseases in patients visiting dental clinics. Local anesthetics (LAs) with vasoconstrictor agents (VC) are known to be commonly used in dental practice. For the above-mentioned reasons, dentists should know how to adapt and treat patients with these hazardous conditions.

Objective
The aim of this study was to find out if the use of local anesthetics (LAs) in combination with vasoconstrictor (VC) agents in dental treatment presents a risk in patient with a known history of Hypertension and/or Coronary disease.

Materials and methods
This systematic review was conducted in accordance with The PRISMA guidelines and registered on the PROSPERO database (CRD42020187369). The search strategy was based on Mesh terms, Boolean operator AND, and the PICO model. It was designed to identify all the randomized clinical trials (RCTs) published in the last 30 years, which assessed whether the use of LA with VC agents in dental treatment produces a significant increase/decrease in hemodynamics in patients with known history of Hypertension and/or Coronary disease. The Cochrane Collaboration's tool was used to assess risk of bias of the included RCTs.

Results
An initial electronic search resulted in 87 papers; however only 9 RCTs met the inclusion criteria. There was a total of 482 subjects ($N = 482$), of which 412 had a known history of Hypertension or Coronary disease.

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Hypertension, Coronary disease, Hemodynamics, Vasoconstrictor-agents, Dentistry

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Conclusions
According to the literature reviewed, the use of 1 to 2 cartridges of local anesthetics with 1:80,000, 1:100,000 or 1:200,000 epinephrine in patients with controlled Hypertension and/ or Coronary disease is safe. Randomized clinical trials are essential in determining the safety or risks associated with the use of LAs with VC agents in patients with poorly controlled Hypertension and Coronary disease.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death globally.[1-3] Hypertension, a subgroup of CVDs, is considered one of the leading causes of premature death worldwide.[2] This condition may increase the risk of heart attack, stroke, kidney failure and other diseases.[2] Hypertension is defined as a blood pressure equal to or greater than 140 mm Hg/90 mm Hg. Conversely, the ideal blood pressure, in which the individual has the lowest cardiovascular risk, is 120 mm Hg/ 80 mm Hg.[2-6] Coronary disease refers to the reduction of heart blood vessels lumen[7]. Coronary disease and Hypertension are highly prevalent health problems worldwide,[1-3] with the latter being one of the most common diseases in patients visiting dental clinics.[5,6] This means that every health professional should know how to treat patients with these conditions to avoid situations which may jeopardize their health, and consequently their life.[3-6]

Local anesthetics (LAs) with vasoconstrictor (VC) agents are widely used in dentistry, especially in oral surgery.[5-19] The most commonly used VC agent is Epinephrine,[5-12,14-19] because it provides many advantages such as reducing toxicity, increasing the anesthetic effect and improving hemostasis.[5-14,16] Nonetheless, Felypressin is also used.[5,13] Epinephrine is a catecholamine type vasoconstrictor[14] which has a non-selective adrenergic profile. It causes the reduction of peripheral blood-vessel diameter (α1 agonist), and stimulates β1 receptors, increasing heart rate (HR) and consequently, blood pressure (BP). In β2 receptors, Epinephrine stimulates vasodilation in muscles and internal organs.[5,16]

On the other hand, Felypressin is a synthetic analogue of the antidiuretic hormone, Vasopressin. It has been suggested as an alternative to epinephrine to decrease the systemic adverse reactions because it is considered to have no direct effect on the myocardium. In that sense, the blood pressure increase is attributed to peripheral resistance.[5,13,14]

For the above reasons, the association of a local anesthetic (LA) with a VC agent might result in adverse hemodynamic effects, thus making its use controversial in patients with a history of Hypertension (HTN) and/or Coronary disease.[4-19] Concerning patients, the psychological and emotional factors must be taken into account. Anxiety or a stressful experience may generate an exaggerated endogenous catecholamine production, which also may lead into hemodynamic and metabolic disturbance.[6,10,13,16]

The aim of this study was to review the published literature in order to find out whether the use of LAs in combination with a VC agent in dental treatment presents a risk in patient with a known history of Hypertension (HTN) and/or Coronary disease.

MATERIALS AND METHODS

This systematic review was conducted in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[20] and registered on the PROSPERO database (CRD42020187369). To select the RCTs included, we used the PICO strategy,[21] as follows: Participants (P) were "Patients with known history of Hypertension and/or Coronary disease"; the intervention (I) was "use of LAs with a VC agent"; the control (C) was "use of LAs without a VC agent" or "healthy patients"; and the outcome (O) was "hemodynamic changes occurred when using LA with and without a VC agent" (Figure 1).

Sources of Information

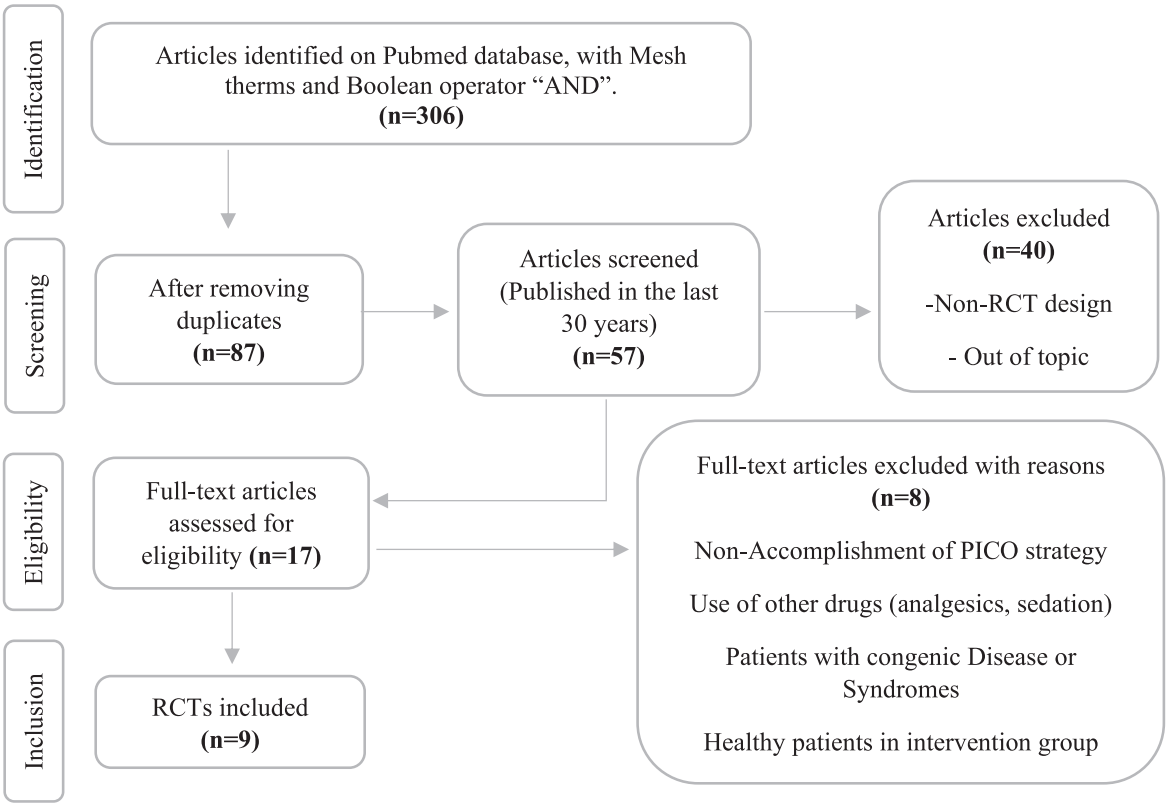
A thorough electronic literature review was conducted on PubMed, Cochrane Library and Scielo databases in May 2020. The identification of studies was based on the following search strategy and it was not limited by language.

Search Strategy

A detailed search based on Mesh terms was performed. It was structured with Boolean operator (AND) and designed to identify all randomized clinical trials (RCTs) published in the last 30 years, which assessed if the use of LAs with a VC agent in dental procedures represents a risk in patients with Hypertension and/or Coronary disease.

The Mesh terms used were: "hypertension AND anesthesia, local AND vasoconstrictor agents AND hemodynamics AND tooth extraction", "coronary disease AND anesthesia, local AND vasoconstrictor agents AND hemodynamics AND tooth extraction", "cardiovascular diseases AND anesthesia, local AND vasoconstrictor agents AND hemodynamics AND tooth extraction", "hypertension AND anesthesia, local AND vasoconstrictor agents AND tooth extraction", "coronary disease AND anesthesia, local AND vasoconstrictor agents AND tooth extraction", "cardiovascular diseases AND anesthesia, local AND vasoconstrictor agents AND tooth extraction", "hypertension AND anesthesia, local AND vasoconstrictor agents AND hemodynamics AND surgery, oral", "coronary disease AND anesthesia, local AND vasoconstrictor agents AND hemodynamics AND surgery, oral", "cardiovascular diseases AND anesthesia, local AND vasoconstrictor agents AND hemodynamics AND surgery, oral", "hypertension AND anesthesia, local AND hemodynamics AND dentistry", "coronary disease AND anesthesia,

Fig. 1. Article selection process and inclusion criteria used in this systematic review.



Selection criteria and Pico strategy.

Studies: RCT design
Patients: Coronary-disease or Hypertension
Intervention group: Use of LA with VC agent
Control group: Healthy patients /use of LA without VC agent
Outcomes: Changes in SBP, DBP; HR

RCT: Randomized clinical trial; LA: Local anesthetics; VC: Vasoconstrictor; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate.

Table 1. RCTs included. Demographic data and systemic condition of participants.

Authors	Mean age ± SD	"N"	Gender		Hypertensive or coronary-disease patients	Participants		Control group (Healthy patients)
			m	f		Medically controlled yes / no	Additional disease yes / no	
Abu-Mostafa N, et al. [5]	55.66 yrs	**45**	31	14	45	yes	ns	0
Santos-Paul MA, et al. [10]	63.4 ± 8.3 yrs	**70**	50	20	70	yes	yes, DM	0
Bronzo AL, et al. [13]	48±12 yrs	**71**	27	44	71	yes	no	0
Uzeda MJ, et al. [6]	20 to 60 yrs	**25**	ns	10	yes	ns	15	
Neves RS, et al. [7]	58.7 ± 8.8 yrs	**62**	51	11	62	yes	yes, DM	ns
Torres- Lagares D, et al. [12]	63±12.5 yrs	**10**	ns	10	yes	yes	0	
Ogunlewe MO, et al. [9]	50.1 ± 11.7 yrs	**33**	13	20	33	yes	no	0
Conrado VC, et al. [11]	58±7.98 55.3 ± 8.57 yrs	**54**	34	20	54	ns	yes	0
Zivotić-Vanović M, et al. [8]	65,5 ± 9,8 yrs	**112**	79	33	57	yes	no	55

DM, diabetes mellitus; ns, non-specified; SD, standard deviation; Yrs, years.

local AND hemodynamics AND dentistry", "cardiovascular diseases AND anesthesia, local AND hemodynamics AND dentistry".

Process of Data Collection

The search was conducted by two reviewers (MSA and BGN) to avoid bias. Disagreements were evaluated and resolved in consensus meetings with JLL, RAM and EJS.

Selection Criteria

Study eligibility was structured and based on the PICO strategy (Participants, Intervention, Control and Outcomes) .[21] Studies were selected according to the inclusion/exclusion criteria outlined in Figure 1.

Descriptive literature reviews, case reports, series of clinical reports, and studies that included congenital heart disease patients; as well as studies that evaluated the action of other drugs on patients' hemodynamics, were excluded (Figure 1).

Data Extraction

Data extracted from each study were analyzed and sorted by two independent examiners (MSA and BGN). The following characteristics were obtained: author, year of publication, number of patients in intervention group and control group, patient's sex, mean age, systemic condition, treatment performed, monitoring appliance and period, local anesthetics and vasoconstrictor agents used; as well as doses and number of cartridges. We also obtained data from the results of the papers, like significant differences on hemodynamic parameters between the intervention and control groups. Data were collected using a standardized form, considering only information available in the papers. The details of each study are presented in Tables 1-3. No meta-analysis was performed due to heterogeneity of data.

Analysis of the Quality of Included Studies

We used The Cochrane Collaboration's tool for assessing risk of bias in randomized clinical trials.[22] It covers six domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. MSA and RAM independently reviewed each RCT included and determined if there was a high, low or unclear risk of bias for each domain. Disagreements were arbitrated and resolved by discussion, with BGN, EJS and JLL.

The innovative approach of this systematic review, focused on patients with a known history of Hypertension and/or

Coronary disease, is that it may contribute to a scientific literature-based practice, and that it is based only in randomized clinical trials, representing a high level of scientific evidence.

RESULTS

Search and Selection Process

After removing the duplicate records, an electronic search resulted in 87 papers. However only 57 were published in the last 30 years. A total of 40 papers were discarded for being off topic or had a non-RCT design. Of the resulting 17 articles, only 9 met the inclusion criteria based on PICO strategy (Figure 1).

Analysis of the Quality of Studies

The Cochrane Collaboration's tool for assessing risk of bias of Randomized clinical trials was used.[22] As explained in Table 4, all the authors had a low risk of bias on "Attrition bias" and "Reporting bias" domains. In our point of view, we considered the "selection bias" and "reporting bias" domains as "very important domains". In that sense, only Abu Mostafa N, et al.[5] and Torres-Lagares D, et al.[12] had a low risk of bias in both. Conversely, the "Performance bias", "Detection bias" and "Other bias" were the domains with the worst profiles, which means a "high risk of bias". In this review, we determined "Other bias" when the authors performed "different kinds of treatments" or when "different persons performed the treatments" on subjects included in the study groups. These aspects may lead to different emotional responses, thus increasing risk of bias.

Sample Size and Characteristics

A total of 482 subjects ($N = 482$) were studied. Of those subjects, 412 had history of Hypertension and/or Coronary disease. The mean age's weighted average was $58{,}73 \pm 9{,}88$ years, without considering Abu-Mostafa N, et al.[5] and Uzeda MJ, et al.[6] which did not provide this data. The male/female ratio was 2.8:1.6. Eight studies included only medically-controlled Hypertensive and Coronary disease patients.[5-10,12,13] In the case of Conrado VC, et al.[11] it was not specified, but they focused on chronic coronary artery disease patients (confirmed by previous coronary angiograph), and with stable angina on exertion. Additionally, they reported the exclusion of patients with unstable angina; acute myocardial infarction (occurring < 3 months); imminent indication of cardiac surgery or angioplasty; heart diseases associated with coronary disease; heart failure; recent stroke (< 3 months); severe Hypertension (SBP >o = 180 mmHg and DBP >o = 110 mmHg) and uncontrolled Diabetes Mellitus. Regarding exclusion criteria, the most common reasons were: pregnancy and breastfeeding,[5,13] β-blockers medication, severe heart diseases[5,6,9,12] and uncontrolled systemic diseases or other medical disorders.[5-7,9,11-13] Nonetheless, Neves RS, et al.[7] and Santos- Paul MA, et al.[10] also included patients diagnosed with Diabetes Mellitus (DM). According to the treatment performed, most of the studies were related to oral surgery, especially tooth extraction.[5,6,8-11] However, Torres-Lagares D, et al.[12] and Bronzo AL, et al.[13] performed periodontal treatment, and Neves RS, et al.[7] single restorative procedures (Table 2).

Local Anesthetics and Vasoconstrictor Agents

Two hundred and thirteen patients underwent dental treatment with the use of a LAs with epinephrine.[5-12] The concentrations administered were: 2%Lidocaine + 1:100,000 epinephrine.[6,7,10] 2%Lidocaine + 1:80,000 epinephrine.[5,9] 4%Articaine + 1:100,000 epinephrine and 4%Articaine + 1:200,000 epinephrine.[12] 2%Mepivacaine + 1:100,000 epinephrine.[11,12] 3% Lidocaine + 1:100,000 epinephrine.[8] Concerning Felypressin, 86 patients were treated with this VC agent. The concentration administered was: 3% Prilocaine + 0.03 IU Felypressin.[5,13] On the other hand, there were 264 patients treated without a VC agent. Thus, 3% Mepivacaine,[5,11,12] 2% Lidocaine,[9,10] 4% Prilocaine[13] and 3% Lidocaine[8] were used (Table 2). Doses of LAs (with or without VC agent) ranged from 1.8 ml to 5.4 ml, equaling to 1 to 3 cartridges.[5-13] It is important to highlight that Torres-Lagares D, et al.[12] and Bronzo AL, et al.[13] administered different LAs to the same patients. Of course, after wash-out periods of 1 week and 10 min, respectively.

Intervention and Control Groups

The studies included similar "intervention groups"; but different "control groups". Seven studies included only "Patients with history of Hypertension and/or Coronary disease" and compared the hemodynamic changes occurred when using LA with VC agents, with the hemodynamic changes occurred when using a LA plain.[5,7,9,10-13] In the case of Uzeda MJ, et al.[5] they compared the hemodynamic changes when using LAs with VC agents in Hypertensive and/or Coronary disease patients with the hemodynamic changes when used in healthy patients. While, Zivotić-Vanović M, et al.[8] separated the examined patients into two groups, "cardiovascular disease patients (CV)" and "healthy patients (H)"; then, those patients were randomly assigned to two subgroups: In the Group A ("CVa" and "Ha") the LA contained Epinephrine 1 :100,000; and in Group B ("CVb" and "Hb") the LA was plain Lidocaine. This allowed for two "control groups".

It should be highlighted that there were 2 studies which not only compared the use of a LA with a VC agent with the use of plain LA; but also, used another LA solution and/or another VC agent.[5,12] For example, Abu Mostafa N, et al.[5] had a total of $N = 45$ Hypertensive/ Coronary disease patients which were randomly allocated into 3 groups of 15 patients to compared the use of 2% Lidocaine + 1:80,000

Table 2. RCTS included. Groups allocation, dental treatment performed, Local anesthetics and vasoconstrictor doses assessed.

Authors	"N"	Groups allocation			Dental Treatment	Local anesthetics/ Doses		
		"N" with Epinephrine. IG	"N" with other LA or VC IG/CG	"N" without VC. CG		LA with Epinephrine	Other LA or VC agent	without VC agent
Abu-Mostafa N, et al. [5]	**45**	15	15	15	Tooth extraction	2% Lidocaine + 1:80,000 Epinephrine /3.6ml	3% Prilocaine + 0.03 IU Felypressin /3.6ml	3% Mepivacaine /3.6ml
Santos-Paul MA, et al. [10]	**70**	35	0	35	Tooth extraction	2% Lidocaine + 1:100,000 Epinephrine /5.4ml	no	2% Lidocaine /5.4ml
Bronzo AL, et al. [13]	**71**	0	71	71	Periodontal treatment	no	3% Prilocaine + 0.03 IU Felypressin /3.6ml	4% Prilocaine/ 3.6ml
Uzeda MJ, et al. [6]	**25**	25	0	0	Tooth extraction	2% Lidocaine + 1:100,000 Epinephrine /1.8–5.4ml	no	no
Neves RS, et al. [7]	**62**	30	0	32	Single restorative procedure	2% Lidocaine + 1:100,000 Epinephrine /1.8ml	no	2% Lidocaine /3.6ml
Torres- Lagares D, et al. [12]	**10**	10	10	10	Periodontal treatment	4% Articaine 1:100,000 /3.6 ml; 4% Articaine 1:200,000 /3.6ml	2% Mepiva-caine + Epinefrina 1:100,000 /3.6ml	3% Mepivacaine /3.6ml
Ogunlewe MO, et al. [9]	**33**	14	0	19	Tooth extraction	2% Lidocaine + 1:80,000 Epinephrine /3.6ml	no	2% Lidocaine /3.6ml
Conrado VC, et al. [11]	**54**	27	0	27	Tooth extraction	2% Mepiva-caine + 1:100,000 Epinephrine /3.6ml	no	3% Mepivacaine /3.6ml
Zivotić-Vanović M, et al. [8]	**112**	57	0	55	Tooth extraction	3% Lido-caine + Epinephrine 1:100,000/ ns	no	3% Lidocaine/ ns

CG, control group; IG, intervention group; LA, local anesthetics; ns, non-specified; VC, vasoconstrictor.

Epinephrine/3.6 ml, 3% Mepivacaine/3.6 ml, and 3% Prilocaine + 0.03 IU Felypressin/3.6 ml, respectively. As well as, Torres Lagares D, et al.[12] which had a total of $N = 10$ patients who underwent periodontal treatment of the 4 sessions using a different LA and VC agent in every session with a washout period of 1 week. The LAs and VC agents used were as follows: 4% Articaine 1:100,000/3.6 ml, 4% Articaine 1:200,000/3.6 ml, 3% Mepivacaine/3.6 ml, 2% Mepivacaine + Epinephrine1:100,000/3.6 ml.

Hemodynamics

Hemodynamic parameters were recorded with conventional or digital sphygmomanometer and pulse-oximeter,[5,9,10,12,13] and with Holter ECG.[7,8] Conrado VC, et al.[11] also used biochemical markers to determine the ischemic risk. Uzeda MJ, et al.[6] did not specify which device they used. The RCTs included, reported whether a statistically significant increase or decrease in Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and Heart rate (HR) was found when comparing the intervention group with the control group. According to this, there were authors who did not find any statistically significant difference in SBP, DBP or HR between the groups,[7,9,10,11] and others who found it (Table 3) .[5,6,8,12,13] No adverse effects were reported in RCTs included in this review[5-13]; and surprisingly, all the authors defined the use of two[5,7-9,11-13] or three[6,10] cartridges of LAs with VC agent (1:80,000, 1:100,000 or 1:200,000 Epinephrine and 0.03 IU Felypressin) in controlled Hypertensive and Coronary disease patients as safe.[5-13]

DISCUSSION

The use of LAs with VC agents -mainly Epinephrine- in patients with a known history of Hypertension and/or Coronary disease patients, is controversial.[14,23] The mandatory reason is Epinephrine's adrenergic profile.[5,14,16,24] Even though a cartridge of LA with 1:100,000 epinephrine corresponds to a dose of 0.018 mg of epinephrine, which is very low in comparison with those administered for anaphylaxis or heart attacks (0.5 to 1 mg) ,[6,11] doubt remains when treating cardiovascular-risk patients. As mentioned in the introduction, Epinephrine offers many advantages such as reducing toxicity, increasing the anesthetic effect and improving hemostasis, thus being a useful tool for intra-operative bleeding control.[5-14,16,25] However, it must be taken into consideration that this hemostatic effect has been associated with delayed wound healing, an increase in the risk of infection, and determine harmful effects on soft tissue flaps, due to decreased blood flow.[25] Liu W, et al.[15] produced a systematic review which included 101 studies (RCTs, non-RCTs, case-control studies, case reports, case series, and cross-sectional studies published between 1967 and 2010) that focused on adverse drug reactions (ADRs) associated with the use of LAs. They found that ADRs related to LAs with epinephrine are 2.16 times higher than plain LAs (which suggests the need to be cautious when using a VC agent). They also explained that usually adrenergic reactions are misdiagnosed as allergic reactions, and how psychological stress due to the LA injection could be a contributory factor to develop a sympathetic activation that is correlated with stress hormones and metabolites blood levels increase. For this reason, many authors have studied whether the use of local anesthetics with a vasoconstrictor agent can significantly modify hemodynamic parameters.[5-13,16-19,26] In that sense, we conducted this systematic review. Among RCTs included, we found that 4 studies did not observe any statistically significant difference when comparing SBP, DBP and HR between the groups after the injection of 1 to 3 cartridges of LA with or without VC agent.[7,9,10,11] In the case of the authors who found them, they mentioned that those statistical differences had no clinical repercussion and attributed these differences to fear and anxiety experiences.[5,6,8,12,13] Despite the absence of clinical repercussions, it is important to discuss the results reported by Abu-Mostafa N, et al.[5] who found that the mean SBP increased after LA injection and decreased after extraction in the three groups of patients. They also highlighted that in the Mepivacaine plain group it was significantly higher than in the Lidocaine with Epinephrine group ($p = 0.037$ ANOVA). They also reported that the mean DBP of both Epinephrine and Felypressin groups decreased after injection and after extraction. In contrast, the mean DBP of the Mepivacaine plain group increased after injection and decreased after extraction but was still higher than pre-injection measurement. The mean HR also increased after injection and after extraction in all the groups; but the difference in HR and in DBP were not significant among the three groups. Uzeda MJ, et al.[6] reported a significant difference in BP between the groups in the waiting room (SBP and DBP) and at the moment of surgical drapes placement (SBP) with lower values in the normotensive group. They also found a statistically significant difference in HR at "10 minutes after LA injection", with lower values in the Hypertensive group.

Respecting VC agents, epinephrine is the most commonly used. There are, of course, other options like Felypressin[5,13,27,28] and Clonidine.[19,29] They are however not used routinely. Felypressin constricts venous outflow, so it is less vasoconstrictive than epinephrine. For that reason, it may cause less hemodynamic disturbance, and a smaller hemostatic effect. Kyosaka Y, et al.[28] conducted a RCT where 2 types of LA with VC agents were compared. They assessed the action of 2% lidocaine with 1:80,000 adrenaline (L + AD) and 3% prilocaine with 0.03 IU/mL felypressin (P + FP) on BP and HR in older adults with systemic diseases who underwent dental extraction ($n = 22$, aged over 65 years). Surprisingly, they found that (P + FP) administration increased the SBP and DBP. They also found that (L + AD) administration increased HR and decreased the DBP. They attributed

Table 3. RCTS included, monitoring periods and device used, hemodynamic changes and adverse effects reported.

Author/ year	"N"	Monitoring		Statistically significant changes in Blood pressure and heart rate D / I / ND			Adverse effects reported
		Periods	Device	SBP	DBP	HR	
Abu-Mostafa N, et al. [5]	45	Dental chair (before injection), 3′ after LA injection, 3′ after extraction.	Electronic sphygmomanometer [OMRON® Automatic Blood Pressure Monitor] and Pulse oximeter	I	ND	ND	no
Santos-Paul MA, et al. [10]	70	1hr. before procedure; 5′ before procedure; after LA injection; 1hr. after procedure	Authomatic Sphygmomanometer (Microlife APA-P00001)	ND	ND	ND	no
Bronzo AL, et al. [13]	71	Rest (pre intervention); LA (la injection); Subgingival scaling (during technical procedure); Anesthetic peak (10′ after injection).	Automated oscillometric device (DIXTAL - model DX 2010, São Paulo, Brazil)	I	I	ND	no
Uzeda MJ, et al. [6]	25	waiting room; after surgical drapes placement; 10′ after injection; end of surgical procedure.	ns	I	I	I	no
Neves RS, et al. [7]	62	Baseline (1 hr. before anesthesia); Procedure (from the beginning of anesthesia until the patient left the dental chair); Post-procedure (until the 24 hrs. were completed).	24-hour electrocardiography (Holter) and ambulatory blood pressure monitoring (ABPM)	ND	ND	ND	no

(*continued on next page*)

Table 3 (*continued*)

Author/ year	"N"	Monitoring		Statistically significant changes in Blood pressure and heart rate D / I / ND			Adverse effects reported
		Periods	Device	SBP	DBP	HR	
Torres- Lagares D, et al. [12]	10	Baseline: beginning of monitoring; Baseline + 5′: end of stabilization period; LA: injection timing; LA + 5′: 5 min after injection; Treatment: onset of dental treatment; End: completion of treatment.	Avant 2020 pulseoximeter, Nonin Medical Inc. Minnesota, USA)	I	I	D	no
Ogunlewe MO, et al. [9]	33	Waiting room before surgery; 3′–6′after LA injection; during tooth extraction; and 15′ after tooth extraction.	Non-invasive electronic digital blood pressure monitor (Mark of Fitness® model MF-61, Mark of Fitness Inc, shrews bury, NJ077702, Japan)	ND	ND	ND	no
Conrado VC, et al. [11]	54	Prior to dental intervention; after pre-dental intervention; after 2′ of LA injection; during dental extraction; and after suturing. Also 24 hrs. after dental extraction.	Holter and ECG monitor and Biochemical markers (CKMB activity, CKMB mass, and troponin T)	ND	ND	ND	no
Zivotić-Vanović M, et al. [8]	112	Pre- procedure period; during LA injection; during dental extraction; and Relaxing period (R1: 3′ after extraction; R2: 3′after R1)	Datascope and ECG monitor	I	ND	ND	ns

BP, blood pressure; D, decrease; DBP, diastolic blood pressure; HR, heart rate; I, increase; ND, no differences; SBP, systolic blood pressure.

Table 4. Risk of bias evaluation using The Cochrane Collaboration tool.[22]

this variation to increased peripheral vascular resistance produced by (P + FP). On the other hand, Gazal G[27]. mentioned that prilocaine has a smaller vasodilator effect than lidocaine, thus overcoming the weakness of felypressin as vasoconstrictor and promoting a long-lasting anesthetic effect. In that sense, he recommended its use as an alternative for cardiovascular patients in dental treatment.

Clonidine is an α2-adrenoceptor agonist that is being increasingly used together with LA for spinal or epidural analgesia.[29] Clonidine might have hemodynamic advantages compared with epinephrine as a vasoconstrictor because of its central hypotensive effect.[19] Nevertheless, its main disadvantage is its shelf-life (6–8 hrs), and it must be mixed with the LA immediately before application.[19,29]

As mentioned before, dental treatments contribute to stress and anxiety due to pain and/or fear. This experience may generate an exaggerated endogenous catecholamine production (which has not been assessed nor demonstrated) [4,5,9,10,11,16,23] and consequently a hemodynamic disturbance.[3,6,11,16,23] This fact is also supported by Bronzo AL, et al.[13] who introduced an "anesthetic simulation" session as part of their study methodology and found that dur-

ing the simulation, both SBP and DBP increased significantly ($p<0.05$) compared to the other steps of the session (rest, assessment of oral health, and subgingival scaling). They also made a complementary analysis, and found that SBP increased significantly during anesthesia and subgingival scaling only in patients with highest trait anxiety. However, no significant difference was observed in DBP ($p>0.05$). We must emphasize that none of the authors who mention the possibility of endogenous catecholamines increase, assessed nor demonstrated it. For this reason, we consider it just a speculation.

Regarding the studies which also assessed ST-segment alteration (myocardial ischemia), Neves RS, et al.[7] reported no evidence of myocardial ischemia neither at the baseline period nor during the procedure. Although 10 patients experienced ischemic episodes, and 6 of them belonged to the non-epinephrine group, all of them occurred at least two hours after dental procedure had been completed, so they were attributed to the heart disease itself. Additionally, they did not find any statistically significant difference between the two groups, which agreed with Conrado VC, et al.[11] However, they reported three patients in the epinephrine group who had mild ST-segment ischemic depression (1.0 mm) in the initial period of anesthetic action, but the simultaneous occurrence of any other alteration considered as detectors of myocardial ischemia (left ventricular hypocontractility and elevation of myonecrosis markers) was not observed.

As an interesting quote, one RCT excluded patients medicated with ß-blockers[5] and other studies also mentioned and endorsed this contraindication.[14,18,19] Bader, et al.[4] performed a systematic review that should be mentioned due to its contribution to understand the interaction between epinephrine (the most used vasoconstrictor agent) and non-selective ß-blockers (first-line antihypertensive medication). It is well known that beta receptors increase heart rate and contraction force (ß-1 receptors), but also produce vasodilation (ß-2 receptors). Thereby, when a non-selective ß-blocker interacts with epinephrine, the epinephrine-vasodilation action is eliminated, while the alfa-receptor activity (vasoconstriction) stays intact, thus contributing to a hypertensive crisis.

Another characteristic to be highlighted is the lack of studies focused on patients with severe cardiovascular diseases such as poorly-controlled hypertension, unstable angina, congestive heart failure, and acute myocardial infarction (occurring < 1 year). In fact, these conditions were also exclusion criteria in most of the studies.[5-7,9,11-13] That is why the use of LA with a VC agent could be contraindicated in these kinds of patients, until the literature demonstrates the opposite. Nevertheless, in imminent cases, motorization and postoperative follow-ups are necessary.[5,12,14] Another important aspect to consider is the correct administration of the local anesthetic, which must avoid intravascular injection to guarantee minimum systemic side effects.[5-13]

Limitations

The principal limitation was that the RCTs included in this Systematic review mentioned that they included patients diagnosed with Coronary disease and/ or Hypertension, but they did not clearly define nor specify what "Coronary disease" mean. Only Neves RS, et al.[7] described it as patients with clinical symptoms of stable angina and on drug therapy, positive exercise testing, and angiographically proven coronary stenosis > 70% in at least one major artery. Conrado VC, et al[11] also mentioned that they considered patients with stable angina on exertion. When talking about Hypertension, they all considered a blood pressure equal to or greater than 140 mm Hg/90 mm Hg.[5-13]

CONCLUSION

According to the literature reviewed, epinephrine is the most commonly used VC agent in dental treatment. The use of 1 to 2 cartridges of LA with 1:80,000, 1:100,000 or 1:200,000 of epinephrine in patients with controlled Hypertension and/or Coronary disease is safe. However, all the RCTs reviewed included only controlled patients, which makes not possible to apply this conclusion to patients with poorly-controlled Hypertension and/or Coronary disease or patients with severe cardiovascular diseases. Randomized clinical trials with low risk of bias are needed to determine the safety or risky profile of the use of LAs with VC agents in poorly-controlled Hypertensive and Coronary disease patients.

ETHICAL APPROVAL

Not required.

PATIENT CONSENT

Not required.

AUTHOR CONTRIBUTION

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jebdp.2021.101569.

REFERENCES

1. World Health Organization [web site]. The World Health Organization, 2017. Cardiovascular diseases (CVDs). Available at: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). Accessed May 20, 2020.
2. World Health Organization [web site]. The World Health Organization, 2019. Hypertension. Available at: https://www.who.int/news-room/fact-sheets/detail/hypertension. Accessed May 20, 2020.
3. Anderson L, Thompson DR, Oldridge N. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*. 2016;2016(1) CD001800. Published 2016 Jan 5. doi:10.1002/14651858.CD001800.pub3.
4. Bader J.D., Bonito A.J., Shugars D.A., A systematic review of cardiovascular effects of epinephrine on hypertensive dental patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2002;93(6):647–653. doi:10.1067/moe.2002.123866.
5. Abu-Mostafa N, Aldawssary A, Assari A, Alnujaidy S, Almutlaq A. A prospective randomized clinical trial compared the effect of various types of local anesthetics cartridges on hypertensive patients during dental extraction. *J Clin Exp Dent*. 2015;7(1) e84-e88Published 2015 Feb 1. doi:10.4317/jced.51534.
6. Uzeda MJ, Moura B, Louro RS, da Silva LE, Calasans-Maia MD. A randomized controlled clinical trial to evaluate blood pressure changes in patients undergoing extraction under local anesthesia with vasopressor use. *J Craniofac Surg*. 2014;25(3):1108–1110. doi:10.1097/SCS.0000000000000736.
7. Neves RS, Neves IL, Giorgi DM. Effects of epinephrine in local dental anesthesia in patients with coronary artery disease. *Arq Bras Cardiol*. 2007;88(5):545–551. doi:10.1590/s0066-782X2007000500008.
8. Zivotić-Vanović M, Marjanović M. Examination of cardiovascular function variables in tooth extraction under local anesthesia. *Vojnosanit Pregl*. 2006;63(1):43–47. doi:10.2298/vsp0601043z.
9. Ogunlewe MO, James O, Ajuluchukwu JN, Ladeinde AL, Adeyemo WL, Gbotolorun OM. Evaluation of haemodynamic changes in hypertensive patients during tooth extraction under local anaesthesia. *West Indian Med J*. 2011;60(1):91–95.
10. Santos-Paul MA, Neves IL, Neves RS, Ramires JA. Local anesthesia with epinephrine is safe and effective for oral surgery in patients with type 2 diabetes mellitus and coronary disease: a prospective randomized study. *Clinics (Sao Paulo)*. 2015;70(3):185–189. doi:10.6061/clinics/2015(03)06.
11. Conrado VC, de Andrade J, de Angelis GA. Cardiovascular effects of local anesthesia with vasoconstrictor during dental extraction in coronary patients. *Arq Bras Cardiol*. 2007;88(5):507–513. doi:10.1590/s0066-782X2007000500002.
12. Torres-Lagares D, Serrera-Figallo MÁ, Machuca-Portillo G. Cardiovascular effect of dental anesthesia with articaine (40 mg with epinefrine 0,5 mg% and 40 mg with epinefrine 1 mg%) versus mepivacaine (30 mg and 20 mg with epinefrine 1 mg%) in medically compromised cardiac patients: a cross-over, randomized, single blinded study. *Med Oral Patol Oral Cir Bucal*. 2012;17(4) e655-e660. Published 2012 Jul 1. doi:10.4317/medoral.17892.
13. Bronzo AL, Cardoso Jr CG, Ortega KC, Mion Jr D. Felypressin increases blood pressure during dental procedures in hypertensive patients. *Arq Bras Cardiol*. 2012;99(2):724–731. doi:10.1590/s0066-782X2012005000062.
14. Serrera Figallo MA, Velázquez Cayón RT, Torres Lagares D, Corcuera Flores JR, Machuca Portillo G. Use of anesthetics associated to vasoconstrictors for dentistry in patients with cardiopathies. Review of the literature published in the last decade. *J Clin Exp Dent*. 2012;4(2) e107-e111. Published 2012 Apr 1. doi:10.4317/jced.50590.
15. Liu W., Yang X., Li C., Mo A. Adverse drug reactions to local anesthetics: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;115(3):319–327. doi:10.1016/j.oooo.2012.04.024.
16. Silvestre F.J., Salvador-Martínez I., Bautista D., Silvestre-Rangil J., Clinical study of hemodynamic changes during extraction in controlled hypertensive patients. Med Oral Patol Oral Cir Bucal. 2011;16(3):e354-e358. Published 2011 May 1. doi:10.4317/medoral.16.e354.
17. Jané-Pallí E, Arranz-Obispo C, González-Navarro B. Analytical parameters and vital signs in patients subjected to dental extraction. *J Clin Exp Dent*. 2017;9(2) e223-e230Published 2017 Feb 1. doi:10.4317/jced.53474.
18. Chaudhry S, Iqbal HA, Izhar F. Effect on blood pressure and pulse rate after administration of an epinephrine containing dental local anaesthetic in hypertensive patients. *J Pak Med Assoc*. 2011;61(11):1088–1091.
19. Patil PM, Patil SP. Is clonidine an adequate alternative to epinephrine as a vasoconstrictor in patients with hypertension? *J Oral Maxillofac Surg*. 2012;70(2):257–262. doi:10.1016/j.joms.2011.07.011.
20. Urrútia G, Bonfill X. Declaración PRISMA: una propuesta para mejorar la publicación de revisiones sistemáticas y metaanálisis [PRISMA declaration: a proposal to improve the publication of systematic reviews and meta-analyses. *Med Clin (Barc)*. 2010;135(11):507–511. doi:10.1016/j.medcli.2010.01.015.

21. da Costa Santos CM, de Mattos Pimenta CA, Nobre MR. The PICO strategy for the research question construction and evidence search. *Rev Lat Am Enfermagem*. 2007;15(3):508–511. doi:10.1590/s0104-11692007000300023.

22. Higgins JP, Altman DG, Gøtzsche PC. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343 d5928Published 2011 Oct 18. doi:10.1136/bmj.d5928.

23. Guimaraes CC, Lopes Motta RH, Bergamaschi CC. Local anaesthetics combined with vasoconstrictors in patients with cardiovascular disease undergoing dental procedures: systematic review and meta-analysis protocol. *BMJ Open*. 2017;7(11) e014611Published 2017 Nov 22. doi:10.1136/bmjopen-2016-014611.

24. Callaway CW. Epinephrine for cardiac arrest. *Curr Opin Cardiol*. 2013;28(1):36–42. doi:10.1097/HCO.0b013e32835b0979.

25. Pippi R, Scorsolini MG, Luigetti L, Pietrantoni A, Cafolla A. Tooth extraction without discontinuation of oral antithrombotic treatment: a prospective study. [published online ahead of print, 2020 Sep 13]. *Oral Dis*. 2020;10. doi:10.1111/odi.13641.

26. Zeytinoğlu M, Tuncay Ü, Akay MC, Soydan İ. Holter ECG assessment of the effects of three different local anesthetic solutions on cardiovascular system in the sedated dental patients with coronary artery disease. *Anadolu Kardiyol Derg*. 2013;13(5):480–485. doi:10.5152/akd.2013.146.

27. Gazal G., Is prilocaine safe and potent enough for use in the oral surgery of medically compromised patients. Saudi Med J. 2019; 40(1), 97–100. doi.org/10.15537/smj.2019.01.23475

28. Kyosaka Y., Owatari T., Inokoshi M., Kubota K., Inoue M., Minakuchi S., Cardiovascular comparison of 2 types of local anesthesia with vasoconstrictor in older adults: a crossover study. Anesth Progress. 2019; 66(3), 133–140. doi.org/10.2344/anpr-66-02-04

29. Dandriyal R, Pachauri S, Giri KY, et al. Comparison of cardiovascular responses after injection of lidocaine with either clonidine or adrenaline: a two-year comparative analysis. *Br J Oral Maxillofac Surg*. 2017;55(1):67–70. doi:10.1016/j.bjoms.2016.09.011.