Local Anaesthetics Combined with Vasoconstrictors in Controlled Hypertensive Patients Undergoing Dental Procedures: Systematic Review and Meta-Analysis

Uso de Anestésicos Locales con Vasoconstrictor en Pacientes con Hipertensión Controlada Durante la Atención Odontológica: Una Revisión Sistemática y Metaanálisis

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ABSTRACT: The aim of this systematic review is to assess the safety of local anaesthetics (LA) combined with vasoconstrictors (VC) for patients with controlled hypertension undergoing dental procedures. A comprehensive search strategy were used to identify all relevant randomized controlled trials (RCTs) that evaluated the effect of LA combined with VC. All searches covered the period from 1990 to February 2021. We performed a meta-analysis using random-effect models and assessed overall certainty in evidence using GRADE approach. Our search strategy yielded 1262 references. Finally, seven randomised trials were included, but only three were included in the meta-analysis. The use of LA with VC may result in little to no difference in the heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP), but the certainty of the evidence was assessed as low. Death, stroke, acute myocardial infarction, need for hospitalization, pain and bleeding were not reported by the included studies. The hemodynamic changes using VC do not imply an increased risk of occurrence of adverse cardiovascular events. The use of VC could even be recommendable considering their multiple advantages.

KEY WORDS: hypertension, epinephrine, anaesthesia dental, vasoconstrictor agents, dentistry.

INTRODUCTION

Hypertension (HT) is a highly prevalent chronic cardiovascular disease characterised by permanent high vascular tone, higher cardiac output, and cumulative damage. This produces a constant increase in blood pressure over normal boundaries which may contribute to the development of other diseases diminishing life quality of the patients in the long term. Therefore, HT timely diagnosis is extremely important in order to reduce its impact on public health (World Health, 2013). Hypertension is defined as systolic blood pressure ≥ 130 mmHg or diastolic blood pressure is ≥ 80 mmHg. Isolated systolic hypertension is defined as a blood pressure ≥130 mmHg systolic and <80 mmHg diastolic, and isolated diastolic hypertension is defined as a blood pressure <130 mmHg systolic and ≥80 mmHg diastolic (Whelton Paul et al., 2018). As blood pressure can be extremely variable and can elevate substantially on certain occasions, usually in a clinical setting, a diagnosis of hypertension should be made on the basis of blood pressure measurements taken on two or more different occasions (Chobanian et al., 2003). Hypertensive emergencies during dental treatment can bring potentially fatal outcomes (Gungormus & Buyukkurt, 2003).

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Local anaesthetics (LA) have been utilised in dental clinical practise for decades in order to reduce pain during dental procedures (Godzieba et al., 2014). Overall, LA with vasoconstrictors using (VC) counteracts LA vasodilator effect, allowing lesser LA systemic absorption, extending its duration, increasing anaesthetic depth, lowering LA toxicity and achieving better haemostasis control (Haas, 2002; Hardeman, 2017; Moore, 2019).

Several dentists prefer LA without VC administration on patients with cardiovascular diseases in order to avoid potential complications and VC adverse effects. However, pain and anxiety generated during dental treatment may trigger endogenous catecholamine release which can increase blood pressure and heart rate (Chaudhry et al., 2011). Nevertheless, the current American dental association guidelines (ADA) highlights that LA with VC utilisation is not contraindicated in adult patients with controlled HT, because VC use should not have any stimulant effect on the cardiovascular system (Moore, 2019). Notwithstanding the advantageous effects of LA with VC, their utilisation is still controversial in patients with HT, considering possible appearance of hemodynamic events (Whelton Paul et al., 2018; Casey Jr et al., 2019). The objective of this systematic review is to provide a rigorous and updated summary of the evidence available on the cardiovascular effects of LA with VC in patients with controlled HT under dental procedures.

**MATERIAL AND METHOD**

This manuscript complies with the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” (PRISMA) guidelines for reporting systematic reviews and meta-analyses (Liberati et al., 2009). The protocol was registered in the International Prospective Register of Systematic Reviews.

**Inclusion criteria**

**Study design:** Randomized controlled trials (RCTs), both parallel and split-mouth designs, were included. Studies evaluating effects in animal models or in vitro conditions were excluded.

**Participants:** RCTs that considered patients diagnosed with controlled HT undergoing any dental procedure under LA were included. Studies that included patients with heart disease different than HT or patients with uncontrolled systemic diseases were excluded.

**Interventions:** LA with VC administration. No restriction was made based on type of anaesthetic, type of VC or anaesthetic technique used. The comparison of interest was LA without VC administration.

**Outcomes:**

- Primary: Death, stroke, acute myocardial infarction, need for hospitalization, pain, bleeding, and adverse effects associated with the use of LA with and without VC.

- Secondary: arrhythmias, ischemic episodes, anxiety, changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP), changes in heart rate (HR), and changes in oxygen saturation.

**Electronic searches:** A comprehensive search in the following databases was performed: Cochrane Central Register of Controlled Trials (CENTRAL), PUBMED, Embase and Epistemonikos. The searches covered from 1990 to February 2021. The following strategy was used to search in databases and was adapted it to the syntax of other databases ((hypertens* OR "blood pressure") OR htn OR "pre-hypertension" OR prehypertensi* OR "high bp" OR "elevated bp") AND (exodontia* OR (dentist* OR dental* OR dentin* OR dentate* OR dentition* OR teeth* OR tooth* OR odonto* OR molar*)) AND ((local* AND (anesthe* OR anaesthe*)) OR vasoconstrictor* OR epinephrin*)).

To ensure saturation in the search, the relevant references of the reviewed studies were also included. An extended search was conducted to identify articles that may have been overlooked in the search for electronic databases, to identify "grey literature" and unpublished studies.

**Data screening:** Titles and abstracts were screened by three authors independently and yielded against the inclusion criteria. We obtained the full reports for all titles that met the inclusion criteria or required further analysis and then decided about their inclusion. We recorded the reasons for excluding trials in any stage of the search and outlined the study selection process in a PRISMA flow diagram which we adapted for the purpose of this review.

**Extraction and management of data:** Using standardised forms, three reviewers independently
extracted the following data from each included trial: study design, participant characteristics, details about the intervention and comparison; the outcomes assessed and the time they were measured; the risk of bias assessment for each individual study.

Disagreements were resolved by discussion with one arbiter adjudicating unresolved disagreements.

Risk of Bias: The risk of bias was carried out independently by five investigators to then make a consensus decision on each one of the trials. To determine the risk of bias, the guide of recommendations established by the Cochrane Collaboration for the elaboration of systematic review was followed.

The risk of bias for each randomised trial was assessed by using the 'risk of bias' tool (RoB). The analysis was based on the evaluation of the following domains: generation of random sequence, concealment of allocation, blinding of participants, staff and outcome assessors, management of incomplete data, selective notification of each primary outcome and other sources of bias. The studies were judged on bias by establishing three categories: "low risk", "high risk" and "unclear risk". Discrepancies between review authors were resolved by discussion to reach consensus. If necessary, a third review author was consulted to achieve a decision. Finally a "Risk of bias" table, a "Risk of bias chart" and a "Summary of risk of bias" table were elaborated through the RevMan 5.4 system (Higgins et al., 2021).

Measures of treatment effect: For dichotomous outcomes, the estimate of treatment effect of an intervention was expressed as risk ratios (RR) along with 95% confidence intervals (CI). For continuous outcomes, the mean difference and standard deviation were used to summarise the data along with 95% CI. For continuous outcomes reported using different scales, the treatment effect was expressed as a standardised mean difference with 95% CI.

Strategy for data synthesis: For those outcomes in which it was not possible to calculate an effect estimate, a narrative synthesis is presented, describing the studies in terms of the direction and the size of effects, and any available measure of precision. For any outcomes for which data was available from more than one trial, a formal quantitative synthesis (meta-analysis) was conducted for studies clinically homogeneous using RevMan 5, using the inverse variance method with the random-effects model. Inconsistency was assessed by visual inspection of the forest plots and using the I² index.

Assessment of certainty of evidence: The certainty of the evidence for all outcomes was judged using the Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE Working Group), across the domains of risk of bias, consistency, directness, precision and reporting bias. For the main comparisons and outcomes, a Summary of Findings (SoF) tables were prepared (Guyatt et al., 2013a,b).

RESULTS

Search results: The database search yielded 1259 records (Fig. 1). After screening by RCTs, 484 results were obtained, of which 469 were excluded due the elimination of duplicates, language, year of publication, and dose that did not meet with the inclusion criteria according to title and abstract. We finally included 7 randomised trials (Ogunlewe et al., 2011; Torres-Lagares et al., 2012; Abu-Mostafa et al., 2015; Hashemi et al., 2016; Muhammad et al., 2017; Siddiqui et al., 2017).

The reasons for exclusion were the following: Two studies included patients with other cardiovascular diseases, without specifying the number of...
hypertensive patients in their population (Davenport 
et al., 1990; Kyosaka 
et al., 2019). Four studies did not compare the effect of VC (Ezmek 
et al., 2010; Miura 
et al., 2000; Niwa 
et al., 2000; Uzeda 
et al., 2014).

Table I. Summary of Findings (SoF) table.

<table>
<thead>
<tr>
<th>Local anaesthetics combined with VCs for controlled hypertensive adults undergoing dental procedures</th>
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<tbody>
<tr>
<td>Patients</td>
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<td>Local anaesthetics combined with VCs (as defined by the studies)</td>
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<td>Outcomes</td>
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<td>Any adverse effects</td>
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CI: confidence interval; RR: Risk ratio; MD: Mean difference; GRADE: Grading of Recommendations Assessment, Development and Evaluation.

*Other trial reported length of hospital stay, but data was not usable in meta-analysis

1 - The certainty of the evidence cannot be estimated since the studies did not report this outcome. It is highly likely that the outcome was measured in the studies.

2- The certainty of the evidence is based in the following judgments: Risk of bias: downgraded in one level since the overall risk of bias for studies was evaluated as 'high' and 'some concerns'; Inconsistency: no concerns; Indirectness: no concerns; Imprecision: no concerns; Publication bias: no concerns.

3- The certainty of the evidence is based in the following judgments: Risk of bias: downgraded in one level since the overall risk of bias for studies was evaluated as 'high' and 'some concerns'; Inconsistency: downgraded in one level for inconsistency since the studies show contradictory results; Indirectness: no concerns; Imprecision: no concerns; Publication bias: no concerns.
One study compared the effect of VC under sedation (Middlehurst et al., 1999). One study performed the intervention in healthy subjects (Replogle et al., 1999). Finally, to the four selected studies, three trials found in the gray literature that answered the question, and met the inclusion and exclusion criteria, were added. All of them were obtained searching from the references of the selected studies. All of the selected studies corresponded to randomized clinical trials, and three of them were used for the quantitative synthesis of this review (Abu-Mostafa et al., 2015; Hashemi et al., 2016; Siddiqui et al., 2017).

**Included studies**

The characteristics of the RCTs included in this review are summarized in the table Characteristics of included studies (Appendix Table I).

**Study design:** The seven studies included in this manuscript are RCT, six of them with parallel design and one of them with split-mouth cross-over design (Torres-Lagares et al., 2012).

**Countries:** Two of the included trials were conducted in Pakistan (Muhammad et al., 2017; Siddiqui et al., 2017), one in Spain (Torres-Lagares et al., 2012), one in Saudi Arabia (Abu-Mostafa et al., 2015), one in Iran (Hashemi et al., 2016), and one in Nigeria (Ogunlewe et al., 2011).

**Participants:** In all the selected trials, the participants had controlled HT as a baseline disease. In one of the trials (Torres-Lagares et al., 2012), in addition to HT, three patients had comitant hypercholesterolemia, two patients had hyperlipidemia, two had diabetes mellitus, one had alcoholic liver disease, and one patient had a degenerative aortic lesion.

**Intervention:** All trials administered LA with or without VC in dental procedures. The LA used were mepivacaine (Torres-Lagares et al., 2012; Abu-Mostafa et al., 2015; Hashemi et al., 2016), Articaine (Torres-Lagares et al., 2012), Lidocaine (Ogunlewe et al., 2011; Abu-Mostafa et al., 2015; Hashemi et al., 2016; Muhammad et al., 2017; Siddiqui et al., 2017) and Prilocaine (Abu-Mostafa et al., 2015; Hashemi et al., 2016).

**Outcomes:** Death, stroke, acute myocardial infarction, need for hospitalization, pain, bleeding, and adverse effects were not measured or reported by any of the included studies (Ogunlewe et al., 2011; Torres-Lagares et al., 2012; Abu-Mostafa et al., 2015; Hashemi et al., 2016; Muhammad et al., 2017; Siddiqui et al., 2017).

All included trials measured SBP, DBP and HR at some time period. Most studies recorded outcomes at two-time points:

- **After injection:** All trials measured their outcomes after LA injection. Two trials did so immediately after injection (H Torres-Lagares et al., 2012; ashemi et al., 2016), one did so at 2 minutes after injection (Siddiqui et al., 2017), three trials did so at 3 minutes (Ogunlewe et al., 2011; Abu-Mostafa et al., 2015) and two did so at 5 minutes (Torres-Lagares et al., 2012; Muhammad et al., 2017).

- **After the procedure:** Two trials measured outcomes immediately after the end of the procedure (Torres-Lagares et al., 2012; Siddiqui et al., 2017), two trials measured outcomes at 3 minutes (Abu-Mostafa et al., 2015), and one trial measured outcomes at 15 minutes (Ogunlewe et al., 2011).

Four studies reported SBP and DBP during the procedure (Ogunlewe et al., 2011; Torres-Lagares et al., 2012; Abu-Mostafa et al., 2015; Hashemi et al., 2016). Only three trials reported HR during the procedure (Ogunlewe et al., 2011; Torres-Lagares et al., 2012; Abu-Mostafa et al., 2015) and six trials reported HR after the procedure (Ogunlewe et al., 2011; Torres-Lagares et al., 2012; Abu-Mostafa et al., 2015; Hashemi et al., 2016; Siddiqui et al., 2017). All trials measured SBP and DBP after the procedure.

**Risk of bias**

**Overall risk of bias:** None of the trials included in this review were categorized as low risk in all domains (Ogunlewe et al., 2011; Torres-Lagares et al., 2012; Abu-Mostafa et al., 2015; Hashemi et al., 2016; Muhammad et al., 2017; Siddiqui et al., 2017). One trial (Abu-Mostafa et al., 2015) was assessed as at unclear risk of bias because there was insufficient information in the trial report available from the authors to determine the risk of bias in at least one domain. The remaining six trials (Ogunlewe et al., 2011; Torres-Lagares et al., 2012; Hashemi et al., 2016; Muhammad et al., 2017; Siddiqui et al., 2017), were assessed as at high overall risk of bias because each of these had high risk of bias in one or more domains (Fig. 2).
**Intervention effects:** Four studies that met the inclusion criteria for this review did not report quantitative data adequately for inclusion in the meta-analysis (Ogunlewe et al., 2011; Torres-Lagares et al., 2012; Muhammad et al., 2017). Torres-Lagares et al. (2012) describes in its methodology six times to measure its outcomes, however, it only reports four times in its result and in an unclear way. On the other hand, the same trial (Torres-Lagares et al., 2012) was the only one that used a dental procedure different from extractions, subjecting its participants to periodontal treatment by a split mouth methodology. Furthermore, Muhammad et al. (2017) study reported its results subdividing the participants according to the stage of HT, so it was not possible to extract their data adequately for inclusion in the quantitative synthesis of this review. The studies by Ogunlewe et al. (2011), although they randomized hypertensive patients and compared the use of LA with and without VC in dental extractions, reported the results using graphs, so it was not possible to reuse their data for the quantitative analysis. The results of the remaining studies are described in the following section in subgroups by outcome.

**Systolic blood pressure:** All trials included in the quantitative synthesis reported SBP before injection, after injection, and at the end of treatment.

Quantitative synthesis showed LA with VC resulted in little to no difference in the SBP after injection (MD -1.75, 95% CI, -9.69 to 6.18) and at the end of the treatment (MD -6.36, 95% CI -17.00 to 4.28). Overall, LA with VC compared to LA without VC resulted in little to no difference (MD -3.54, 95% CI -8.85 to 1.77) (Fig. 3).
Diastolic blood pressure. Quantitative synthesis showed that LA with VC slightly reduced the DBP after injection (MD -5.01, 95% CI, -10.26 to 0.24) and at the end of the treatment (MD -6.83, 95% CI -10.04 to -3.62). Overall, LA with VC compared to LA without VC slightly reduced (MD -5.64, 95% CI -8.63 to -2.62) the DBP. (Fig. 4).

Heart Rate. Quantitative synthesis showed that LA with VC slightly reduced the HR after injection (MD -7.17, 95% CI, -11.02 to -3.32) and at the end of the treatment (MD -6.48, 95% CI -9.37 to -3.60). Overall, LA with VC compared to LA without VC slightly reduced (MD -6.73, 95% CI -9.04 to -3.60) the HR (Fig. 5) (Table I).

**DISCUSSION**

The use of LA with VCs in hypertensive patients has been a controversial issue in dental clinical practice. On the one hand, multiple benefits of the use of VC have been demonstrated, such as: a) reduction of blood flow at the site of administration b) delayed absorption of the LA into the cardiovascular system c) decreased plasma concentration and risk of bleeding, d) lower risk of toxicity, e) increased duration of anesthetic effect (Malamed, 2014).

However, there is still controversy about the use of LA with VC in hypertensive patients, because of possible adverse effects that might cause hemodynamic alterations (Malamed, 2014). In recent decades, research has been published that attempts to answer some of the questions on this subject, but there is still uncertainty due to the low quality of the evidence and the small number of studies available. The last systematic review on this topic was published...
in 2002 (Bader et al., 2002) and concluded that the risk of adverse events among hypertensive patients undergoing LA with VC was low and the probability of occurrence of these events was minimal. Therefore, the aim of this systematic review is to provide an updated and rigorous summary of the possible effects of the use of LA with VC in controlled hypertensive patients undergoing dental procedures.

Even if the result shows statistically significant changes in DBP and HR in favor of the use of LA with VC, we did not find any clinically significant meaning of these changes. These findings can be explained by the effects of the proper dental procedure. Some authors suggest that anxiety associated with dental attention can be used as a predictor of pain before, during, and after treatment (Lin et al., 2017). Dental anxiety corresponds to the exaggerated response of the patient to a specific stressor in dental attention, which is mostly associated with previous or unknown stimuli or experiences. Both dental anxiety and the pain associated with dental treatment produce deregulation of the body’s physiological responses through nociceptive stimulation of the brain and the liberation of adrenocorticotropic hormone (ACTH), with the consequent liberation of adrenal hormones such as cortisol and other glucocorticoids, which cause stimulation of the sympathetic nervous system, unleashing a reaction in the cardiovascular system that increases BP (Ewart et al., 2017). Other authors report that patients who undergo oral surgery produce large amounts of corticosteroids compared to those who do not undergo dental surgery (Agani et al., 2015).

In the present review, only studies with hypertensive patients without other cardiovascular diseases were included. However, there are similar reviews on hemodynamic effects in patients with cardiovascular disease undergoing dental procedures with LA and VC, whose results are similar to this review (Serrera Figallo et al., 2012; Godzieba et al., 2014; Guimaraes et al., 2017). Although statistically significant differences were reported between the studied groups in relation to DBP and HR, the clinical significance of these findings might not be relevant. The hemodynamic changes recorded did not exceed \([-4.43 \, [-6.61, -2.08]]\) mmHg for DBP and \([-6.73 \, [-9.04, -4.42]]\) bpm for heart rate, which is generally not sufficient to trigger cardiovascular adverse events such as hypertensive crisis or emergency.

Although this review does not present statistically significant differences in SBP, three studies did show a statistically significant increase in SBP with the use of LA without VC. This may be attributed to an increase in stress during dental procedures or an increase in endogenous catecholamines (Ogunlewe et al., 2011; Abu-Mostafa et al., 2015; Hashemi et al., 2016).

Finally, among the limitations of this review we would like to highlight a) the small sample size and b) the difficulty in determining the safety of the intervention, since none of the studies reported events of death, stroke, acute myocardial infarction, need for hospitalization, pain and bleeding outcomes. It should be noted that the conclusions of the studies used for this review are based on substitute results, so they should be analysed with caution, taking into account that they do not necessarily correlate with a clinical endpoint. It is suggested that in future research, studies should include a more heterogeneous sample, because most of the studies included in this review considered Asian populations. On the other hand, studies should be performed more specifically in relation to the type of dental procedure performed, for the studies included in this review were different in the type of procedure performed. In addition, for news RCT studies, we suggest implementing measuring instruments for anxiety, pain and heart rhythm and other cardiovascular parameters during the perioperative period.

**CONCLUSIONS**

In conclusion, the use of LA with VC in controlled hypertensive patients could be beneficial in dental care but the evidence is of poor quality, and solid conclusions cannot be drawn. On one hand, the hemodynamic changes before, during and after the dental procedure do not imply an increased risk of occurrence of adverse cardiovascular events. On the other hand, the use of VC could even be recommendable, considering their multiple advantages. However, standardized studies regarding other variables such as the type and concentration of VC or the type of dental procedure performed are still lacking.

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PALABRAS CLAVE: hipertensión, epinefrina, anestesia, agentes vasoconstrictores, odontología.

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