



## RESEARCH ARTICLE

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

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## Abstract

**Objectives:** 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.

**Materials and method:** A comprehensive search strategy was used to identify all relevant randomized controlled trials (RCTs) that evaluated the effect of LA combined with VC. All the 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.

**Results:** 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.

**Conclusion:** The hemodynamic changes using VC do not imply an increased risk of occurrence of adverse cardiovascular events. The use of VC could be even recommendable considering their multiple advantages.

## Keywords

Hypertension, Epinephrine, Anesthesia, 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 in 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 [1].

Hypertension is defined as systolic blood pressure  $\geq 130$  mmHg or diastolic blood pressure is  $\geq 80$  mmHg. Isolated systolic hypertension is defined as a blood pressure  $\geq 130$  mmHg systolic and  $< 80$  mmHg diastolic, and isolated diastolic hypertension is defined as a blood pressure  $< 130$  mmHg systolic and  $\geq 80$  mmHg diastolic [2]. 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 [3]. Hypertensive emergencies during dental treatment can bring potentially fatal outcomes [4].

Local anesthetics (LA) have been utilised in dental clinical practise for decades in order to reduce pain during

dental procedures [5]. Overall, LA with vasoconstrictors (VC) counteracts LA vasodilator effect allowing lesser LA systemic absorption, extending its duration, increasing anesthetic depth, lowering LA toxicity and achieving better haemostasis control [6-8].

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 [9]. Nevertheless, the current American Dental Association (ADA) guidelines highlights that the use of LA with VC is not contraindicated in adult patients with controlled HT, because VC use should not have any stimulant effect on the cardiovascular system [7].

Notwithstanding the advantageous effects of LA with VC, their use is still controversial in patients with HT, considering possible appearance of hemodynamic events [2,10].

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.

## Methods

This manuscript complies with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines for reporting systematic reviews and meta-analyses [11]. 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 anesthetic, type of VC or anesthetic 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 [12].

## 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 [14], using the inverse variance method with the random-effects model. Inconsistency was assessed by visual inspection of the forest plots and using the  $I^2$  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 (Table 1) [13,14].

## Results

### Search results

The database search yielded 1259 records, (Figure 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 [15-21].

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 [22,23]. Four studies did not compare the effect of VC [24-27]. One study compared the effect of VC under sedation [28]. One study performed the intervention in healthy subjects [29]. 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 [15,16,20].

## Included studies

The characteristics of the RCTs included in this review are summarized in the table Characteristics of included studies (Appendix Table 1).

## 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 [21].

## Countries

Two of the included trials were conducted in Pakistan [17,20], one in Spain [21], one in Saudi Arabia [15], one in Iran [16], one in Nigeria [19] and one in India [18].

## Participants

In all the selected trials, the participants had controlled HT as a baseline disease. In one of the trials [21], in addition to HT, three patients had concomitant hypercholesterolemia, two patients had hyperlipidemia, two had diabetes mellitus, one had alcoholic liver disease, and one patient had a degenerative aortic lesion.

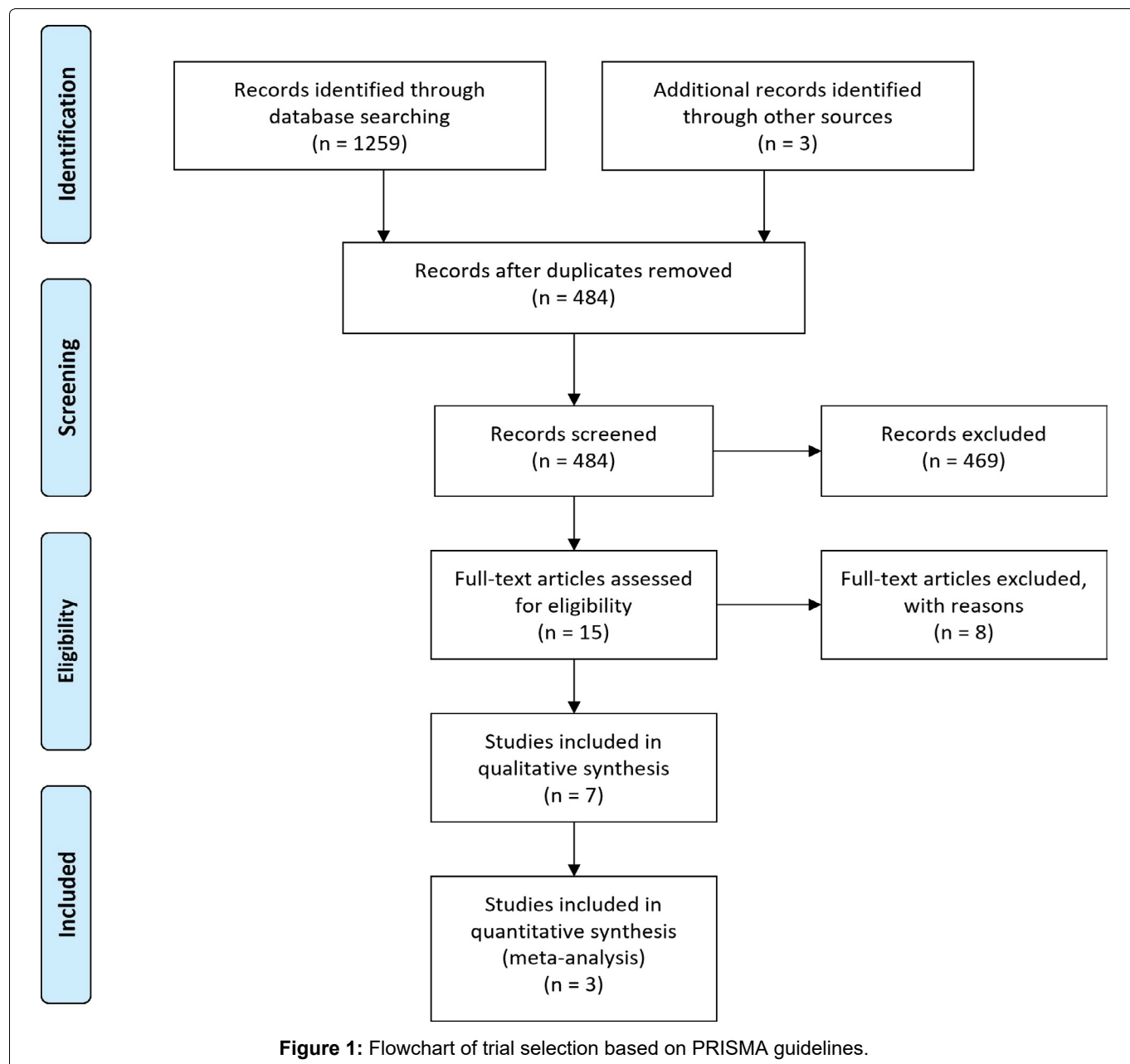
## Intervention

All trials administered LA with or without VC in dental procedures. The LA used were mepivacaine [15,16,18,21], Articaine [21], Lidocaine [15,17,19,20] and Prilocaine [15,16].

## 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 [15-21].

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 [16,21], one did so at 2 minutes after injection [20], three trials did so at 3 minutes [15,18,19] and two did so at 5 minutes [17,21].
- After the procedure: Two trials measured outcomes immediately after the end of the procedure [20,21], two trials measured outcomes at 3 minutes [15,18], and one trial measured outcomes at 15 minutes [19].

Four studies reported SBP and DBP during the procedure [15,16,19,21]. Only three trials reported HR during the procedure [15,19,21] and six trials reported HR after the procedure [15,16,18-21]. All trials measured SBP and DBP after the procedure.

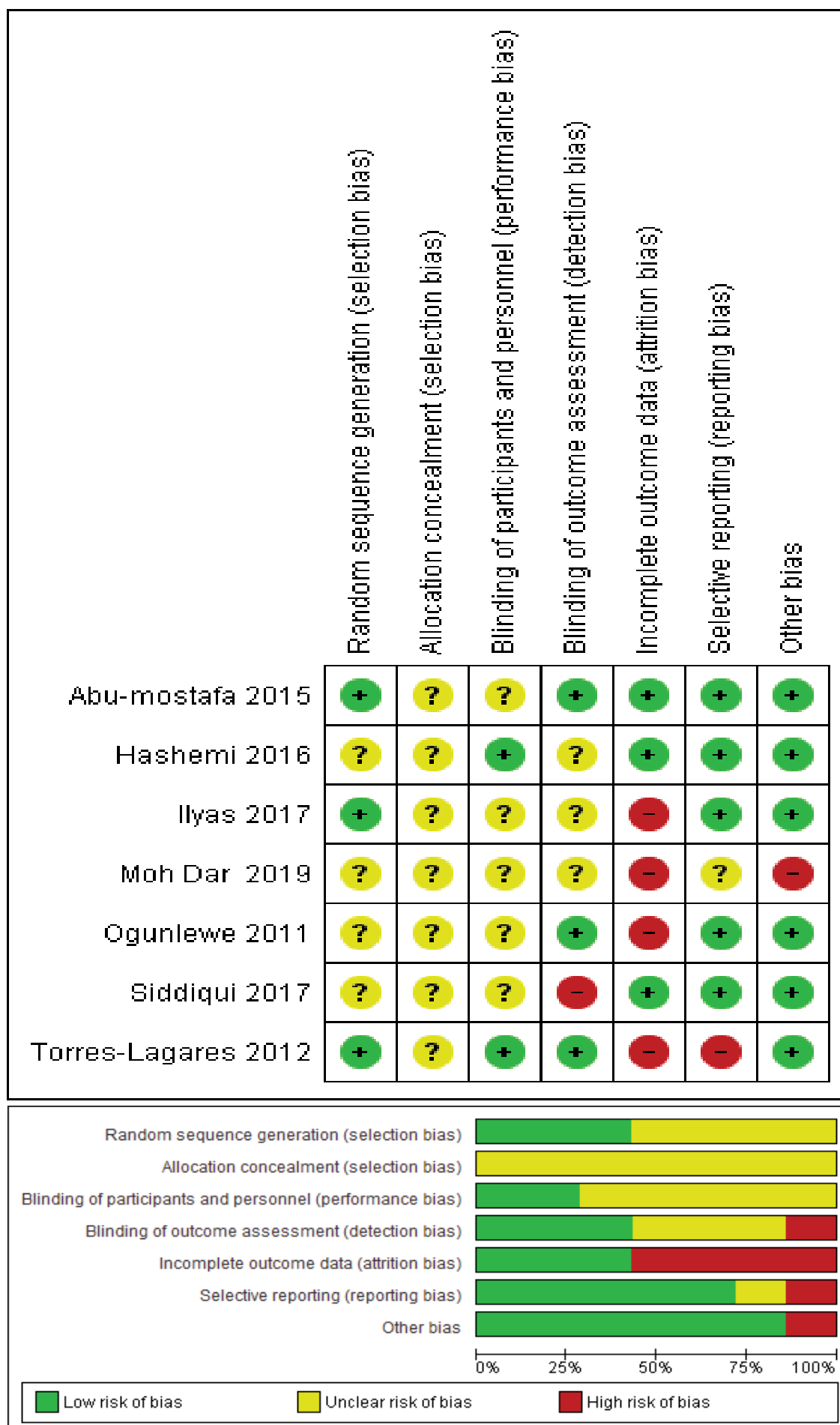
### Risk of bias

**Overall risk of bias:** None of the trials included in this review were categorized as low risk in all domains [15-

21]. One trial [15] 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 [16-21], were assessed as at high overall risk of bias because each of these had high risk of bias in one or more domains (Figure 2).

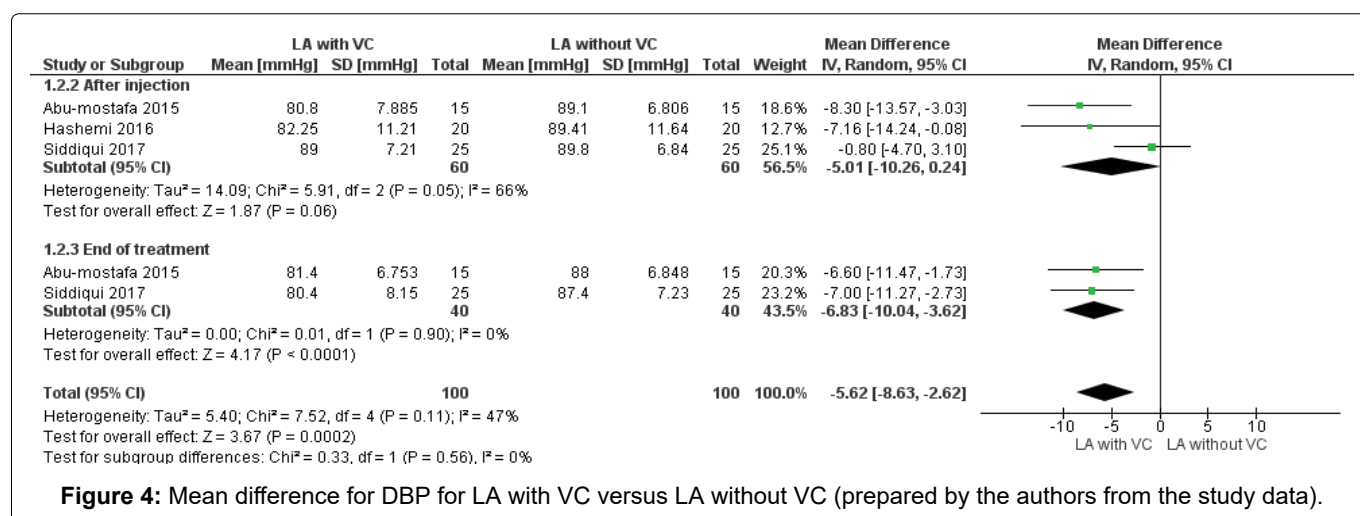
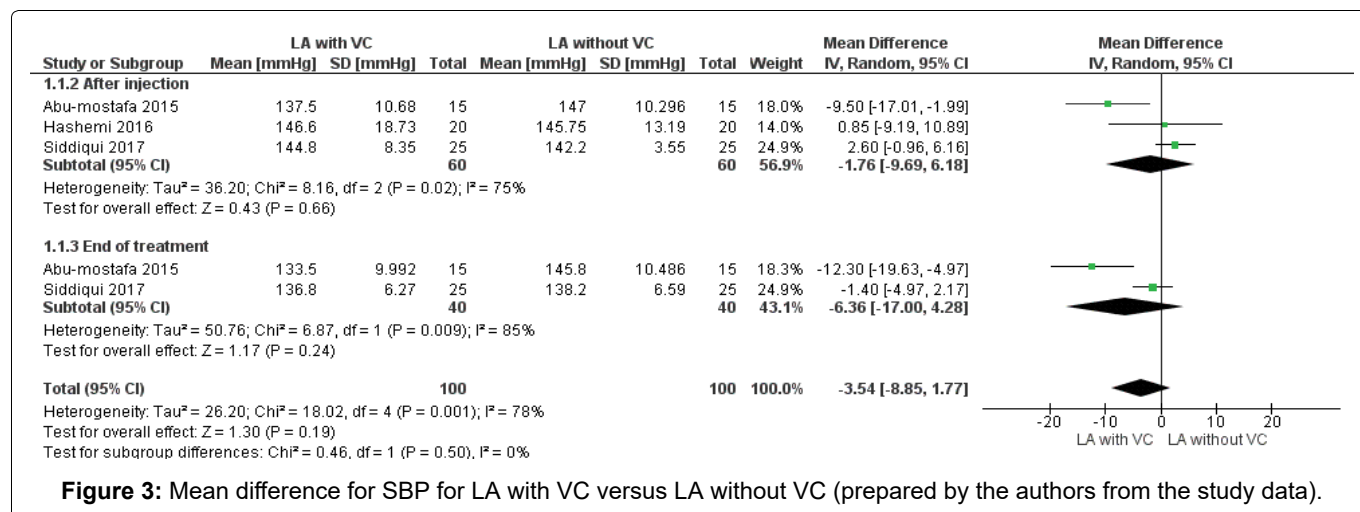
### Intervention effects

Four studies that met the inclusion criteria for this review did not report quantitative data adequately for inclusion in the meta-analysis [17-19,21]. Torres-Lagares, et al. [21] 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 [21] 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. [17] study reported its results subdividing the



**Figure 2:** Risk of Bias of Included Studies.





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 Moh Dar [18] and Ogunlewe [19], 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) (Figure 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 -5.642, 95% CI -8.63 to -2.62) the DBP (Figure 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 (Figure 5).

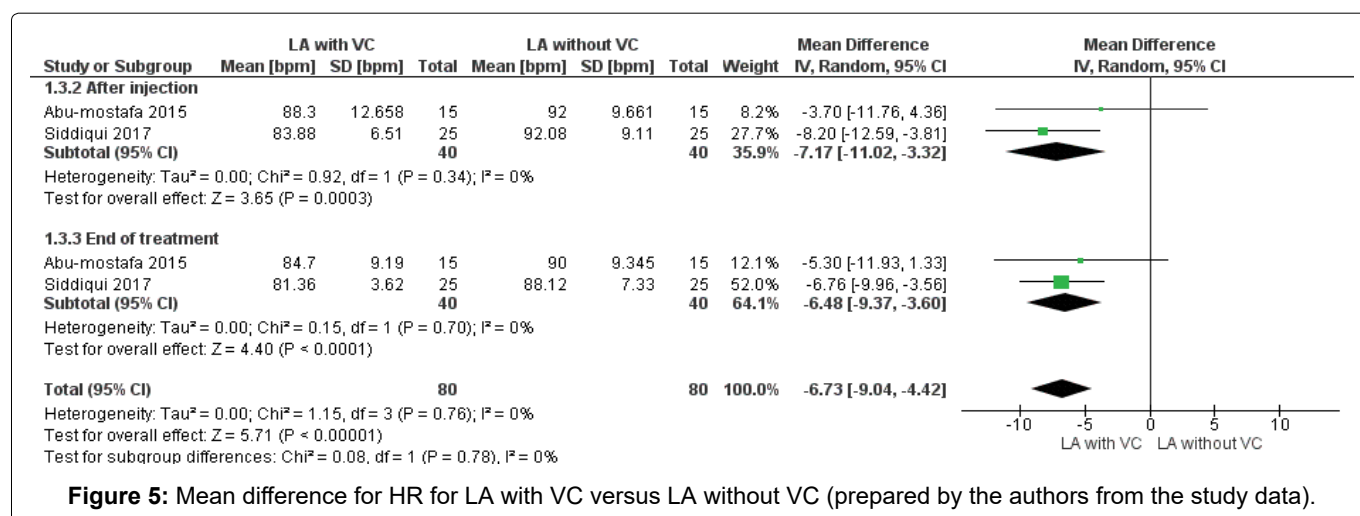
### Discussion

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 [30].

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 [30]. 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 [31] and concluded that the risk of adverse events among hypertensive patients



**Table 1:** Summary of Findings (SoF) Table.

Local anaesthetics combined with VCs for controlled hypertensive adults undergoing dental procedures						
Patients	Controlled hypertensive adults undergoing dental procedures					
Intervention	Local anaesthetics combined with VCs (as defined by the studies)					
Comparison	Local anaesthetics combined without VCs (as defined by the studies)					
Outcomes	Relative effect (95% CI)	Absolut effect*			Certainty of evidence (GRADE)	Key messages
	-- Patients/ studies	WITHOUT VCs	WITH VCs	Difference (CI 95%)		
All-cause mortality	--	Not reported			--(1)	This outcome was not measured or reported by the included studies
Cardiovascular complications	--	Not reported			--(1)	This outcome was not measured or reported by the included studies
Pain	--	Not reported			--(1)	This outcome was not measured or reported by the included studies
Heart rate	--  80 patients in 2 studies (17,22)	After injection			⊕⊕○○ Low (2)	Local anaesthetics with VC may result in little to no difference in the Heart rate
		92.08 bpm	83.88 bpm	MD: 7.17 bpm less (11.02 to 3.32 less)		
	--  80 patients in 2 study (17,22)	End of the treatment				
		88.12 bpm	81.36 bpm	MD: 6.48 bpm less (9.37 to 3.6 less)		
Systolic blood pressure	--  120 patients in 3 studies (17,18,22).	After injection			⊕⊕○○ Very low (3)	Local anaesthetics with VC may result in little to no difference in the Systolic blood pressure
		142.2 mmHg	144.8 mmHg	MD: 1.77 mmHg less (9.67 less to 6.18 more)		
	-  80 patients in 2 studies (17,22).	End of the treatment				
		138.2 mmHg	136.8 mmHg	MD: 6.36 mmHg less (17 less to 4.28 more)		

<b>Diastolic blood pressure</b>	120 patients in 3 studies (17,18,22).	<b>After injection</b>			⊕⊕○○ Low (2)	Local anaesthetics with VC may result in little to no difference in the Diastolic blood pressure
	80 patients in 2 study (17,22).	89.8 mmHg	89.0 mmHg	MD: 6.83 mmHg less (10.04 to 3.62 less)		
<b>Any adverse effects</b>	--	<b>End of the treatment</b>			--(1)	This outcome was not measured or reported by the included studies
		87.4 mmHg	80.4 mmHg	MD: 3.54 mmHg (8.85 less to 1.77 more)		

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.

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 didn't 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 [32]. 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 adrenocorticotrophic 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 [33,34]. Other authors report that patients who undergo oral surgery produce large amounts of corticosteroids compared to those who do not undergo dental surgery [35].

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 [5,36,37].

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 [15,16,19].

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, due none of the studies reported any death, stroke, acute myocardial infarction, need for hospitalization, pain and bleeding outcome. 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, we suggest for news RCT studies to implement measuring instruments for anxiety, pain and heart rhythm and other cardiovascular parameters during 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 be even 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.

## Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

## References

- Word Health O (2013) Global Brief on Hypertension: Silent Killer, Global Public Health Crisis. *Indian Journal of Physical Medicine and Rehabilitation* 24: 2.
- Whelton Paul K, Carey Robert M, Aronow Wilbert S, Casey Donald E, Collins Karen J, et al. (2018) ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice. *Hypertension* 71: e127-e248.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, et al. (2003) Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 42: 1206-1252.
- Gungormus M, Buyukkurt MC (2003) The evaluation of the changes in blood pressure and pulse rate of hypertensive patients during tooth extraction. *Acta Med Austriaca* 30: 127-129.
- Godzieba A, Smektała T, Jedrzejewski M, Sporniak-Tutak K (2014) Clinical assessment of the safe use local anaesthesia with vasoconstrictor agents in cardiovascular compromised patients: A systematic review. *Medical Science Monitor* 20: 393-398.
- Hardeman JH (2017) Hypertension and the Dental Patient. *Dent Toda* 36: 126-128.
- Moore PAHEV (2019) Local Anesthetics for Dentistry. In: *ADA Dental Drug Handbook: A Quick Reference*, Chapter 7, American Dental Association, Chicago, IL, USA.
- Haas D (2002) An update on local anesthetics in dentistry. *J Can Dent Assoc* 68: 546-551.
- Chaudhry S, Iqbal HA, Izhar F, Mirza KM, Khan NF, et al. (2011) Effect on blood pressure and pulse rate after administration of an epinephrine containing dental local anaesthetic in hypertensive patients. *J Pak Med Assoc* 61: 1088-1091.
- Casey DE Jr, Thomas RJ, Bhalla V, Commodore-Mensah Y, Heidenreich PA, Kolte D, et al. (2019) AHA/ACC Clinical Performance and Quality Measures for Adults With High Blood Pressure: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *J Am Coll Cardiol* 74: 2661-2706.
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 339: e1-e34.
- Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, et al. (2021) *Cochrane Handbook for Systematic Reviews of Interventions*. The Cochrane Collaboration: 1-639.
- Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, et al. (2013) GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *J Clin Epidemiol* 66: 158-172.
- Guyatt GH, Thorlund K, Oxman AD, Walter SD, Patrick D, et al. (2013) GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. *J Clin Epidemiol* 66: 173-183.
- Abu-Mostafa N, Aldawssary A, Assari A, Alnujaidy S, Almutlaq A (2015) 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* 7: e84-e88.
- Hashemi SHJ, Ladez SR, Moghadam SA (2016) Comparative Assessment of the Effects of Three Local Anesthetics: Lidocaine, Prilocaine, and Mepivacaine on Blood Pressure Changes in Patients with Controlled Hypertension. *Glob J Health Sci* 8: 227-232.
- Muhammad I, Zupash AK, Ibrahim K, Akif Z, Kainat I, et al. (2017) The Effect of Local Anesthesia (Lidocaine 2%) with Epinephrine (1:100,000) On Blood Pressure Level of Hypertensive Patients Reported To a Tertiary Care Hospital, Peshawar, Pakistan. *Biomedical Journal of Scientific & Technical Research* 1: 1687-1691.
- Mohd Dar M, Irfan dar J, Ahad H, Sadaf I (2019) Assessment of hemodynamic changes during extraction in controlled hypertensive patients. *J Adv Med Dent Scie Res* 7: 19-21.
- Ogunlewe MO, James O, Ajuluchukwu JN, Ladeinde AL, Adeyemo WL, et al. (2011) Evaluation of haemodynamic changes in hypertensive patients during tooth extraction under local anaesthesia. *West Indian Med J* 60: 91-95.
- Siddiqui H, Hussain A, Khan FNA (2017) Systemic Effects of Local Anaesthesia in Hypertensive Patients. *Pakistan Oral & Dental Journal* 37: 538-542.
- Torres-Lagares D, Serrera-Figallo MÁ, Machuca-Portillo G, Cor-cuera-Flores JR, Machuca-Portillo C, et al. (2012) Cardiovascular effect of dental anesthesia with articaine (40 mg with epinephrine 0.5 mg % and 40 mg with epinephrine 1 mg %) versus mepivacaine (30mg and 20 mg with epinephrine 1 mg%) in medically compromised cardiac patients: A cross-over, randomized, sing. *Medicina Oral, Patologia Oral y Cirugia Bucal* 17: e655-e660.
- Kyosaka Y, Owatari T, Inokoshi M, Kubota K, Inoue M, Minakuchi S (2019) Cardiovascular comparison of 2 types of local anesthesia with vasoconstrictor in older adults: A crossover study. *Anesthesia Progress* 66: 133-40.
- Davenport RE, Porcelli RJ, Iacono VJ, Bonura CF, Mallis GI, et al. (1990) Effects of Anesthetics Containing Epinephrine on Catecholamine Levels During Periodontal Surgery. *J Periodontol* 61: 553-558.

24. Uzeda MJ, Moura B, Louro RS, Da Silva LE, Calasans-Maia MD (2014) A randomized controlled clinical trial to evaluate blood pressure changes in patients undergoing extraction under local anesthesia with vasopressor use. *Journal of Craniofacial Surgery* 25: 1108-1110.
25. Miura K, Matsumura K, Nakamura Y, Kurokawa H, Kajiyama M, et al. (2000) Suppression of cardiac sympathetic nervous system during dental surgery in hypertensive patients. *Hypertens Res* 23: 207-212.
26. Niwa H, Satoh Y, Matsuura H. Cardiovascular responses to epinephrine-containing local anesthetics for dental use: A comparison of hemodynamic responses to infiltration anesthesia and ergometer-stress testing. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 90: 171-181.
27. Ezmek B, Arslan A, Delilbasi C, Sencift K (2010) Comparison of hemodynamic effects of lidocaine, prilocaine and mepivacaine solutions without vasoconstrictor in hypertensive patients. *J Appl Oral Sci* 18: 354-359.
28. Middlehurst RJ, Gibbs A, Walton G (1999) Cardiovascular risk: The safety of local anesthesia, vasoconstrictors, and sedation in heart disease. *Anesthesia Progress* 46: 118-123.
29. Replogle K, Reader A, Nist R, Beck M, Weaver J, et al. (1999) Cardiovascular effects of intraosseous injections of 2 percent lidocaine with 1:100,000 epinephrine and 3 percent mepivacaine. *Journal of the American Dental Association* 130: 649-657.
30. Malamed S (2014) Handbook of local anesthesia. In: Elsevier H ed. St. Louis, Mo: Elsevier/Mosby.
31. Bader JD, Bonito AJ, Shugars DA (2002) A systematic review of cardiovascular effects of epinephrine on hypertensive dental patients. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 93: 647-653.
32. Lin CS, Wu SY, Yi CA (2017) Association between Anxiety and Pain in Dental Treatment. *J Dent Res* 96: 153-162.
33. Ewart CK, Elder GJ, Jorgensen RS, Fitzgerald ST (2017) The Role of Agonistic Striving in the Association Between Cortisol and High Blood Pressure. *Psychosom Med* 79: 416-425.
34. Hmud R, Walsh LJ. Dental anxiety: Causes, complications and management methods. *Journal of Minimum Intervention in Dentistry* 2: 237-248.
35. Agani ZB, Benedetti A, Krasniqi VH, Ahmed J, Sejfi Z, et al. (2015) Cortisol level and hemodynamic changes during tooth extraction at hypertensive and normotensive patients. *Medical archives (Sarajevo, Bosnia and Herzegovina)* 69: 117-122.
36. Serrera Figallo MÁ, Velázquez Cayón RT, Lagares DT, Corcuera Flores JR, Portillo GM (2012) Use of anesthetics associated to vasoconstrictors for dentistry in patients with cardiopathies. Review of the literature published in the last decade. *Journal of Clinical and Experimental Dentistry* 4: 107-111.
37. Guimaraes CC, Lopes Motta RH, Bergamaschi CDC, Araújo JDO, Andrade NKD, et al. (2021) Local anaesthetics combined with vasoconstrictors in patients with cardiovascular disease undergoing dental procedures: Systematic review and meta-Analysis protocol. *BMJ Open* 11: e044357.