Clonidine versus Adrenaline as an Adjunct to Lignocaine on Haemodynamic Parameters during Nerve Block for Third Molar Surgical Removal - A Systematic Review and Meta-Analysis

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Abstract

Background: Adrenaline or clonidine is used as adjuncts in conjunction with lignocaine to improve the depth of local anaesthesia in dental procedures. **Objectives:** This systematic review and meta-analysis intends to compare the haemodynamic parameters when clonidine or adrenaline is used in conjunction with lignocaine for third-molar surgical removal. **Data Sources:** Cochrane, PubMed and Ovid SP databases were searched using "MeSH" terms *(((nerve block) OR (IANB)) AND ((clonidine) OR (adrenaline))) AND (lignocaine).* **Study Eligibility Criteria:** Clinical studies where Clonidine + lignocaine and Adrenaline + lignocaine were compared directly during nerve block administration exclusively for third molar surgical removal were selected. **Participants, Study Appraisal:** This current systematic review is registered in Prospero database CRD42021279446. Two independent reviewers were involved in collection, segregation and analysis of electronic data. The data were compiled in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Search was conducted till June 2021. **Synthesis Methods:** Qualitative analysis of the selected articles was performed for systematic review. Meta-analysis is performed using RevMan 5 Software. Heterogeneity through the I^2 statistics. Change in the haemodynamic parameters was the primary outcome evaluated, and secondary outcomes evaluated were onset and duration of anaesthesia in both the groups. **Results:** In all databases, 1141 records were screened, out of which a total of 21 articles were included for the evaluation for full-text analysis. Out of these, 16 articles were excluded and 5 articles were included for the final systematic review. Meta-analysis was performed only for 4 studies. **Conclusion:** Amongst the evaluated haemodynamic parameters, there was a significant reduction in the heart rate (baseline to intraoperative period) in clonidine and lignocaine groups than in adrenaline and lignocaine groups during nerve block administration for third molar surgical removal. There was no significant difference between other primary and secondary outcomes evaluated. **Limitations:** Blinding was not performed in all the studies, randomisation was performed in only three studies. The volume of local anaesthesia deposited varied in the studies (2 mL in three studies and 2.5 mL in two studies). Most of the studies ($n = 4$) were evaluated on normal adults and only one study evaluated mild hypertensive patients.

Keywords: Adrenaline, clonidine, inferior alveolar nerve block, impaction, third molar

Introduction

In oral and maxillofacial surgery, local anaesthesia is the main prerequisite of dental treatment, especially for minor oral surgical procedures such as third molar extractions.[1-3] Local anaesthesia inherently acts as a mild vasodilator resulting in it getting quickly absorbed from the injection site. To prevent this, vasoconstrictor such as adrenaline is added to the local anaesthesia.[4] Adrenaline as a vasoconstrictor is used at varied concentrations according to the need i.e., 1:50,000, 1:80,000, 1:1,00,000 and 1:2,00,000.[5] Adrenaline increases cardiac stroke volume and hence is relatively contraindicated in heart diseases, uncontrolled hypertension and hyperthyroidism.[6-8] Clonidine is an alpha-2 adrenergic

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agonist used to treat hypertension and pain, amongst other conditions, and to treat withdrawal symptoms from various substances.[9,10] It has been used to prolong the anaesthesia effect of spinal and epidural anaesthesia.[11,12]

Many randomised control trials reported the improved efficacy of local anaesthesia when used in conjunction with clonidine. Due to the increased safety profile, clonidine has a better safety margin than adrenaline. This holds especially true in the case of patients with cardiac conditions.[13,14]

The aim of this present systematic review and meta-analysis was to compile and evaluate data regarding the haemodynamic parameters when clonidine or adrenaline is used as a vasoconstrictor for third molar surgical extraction under lignocaine local anaesthesia.

Methods

Protocol and registration

Registered under PROSPERO CRD42021279446. This study followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines during compilation. The search strategy was conducted using the population, intervention, comparison and outcome framework, based on the research question "*whether clonidine is a better alternative to adrenaline along with lignocaine on haemodynamic parameters during nerve block for third molar removal*." Search was performed electronically in PubMed, Cochrane and Ovid SP. The search was conducted till July 2021. Articles published in languages other than English were excluded. The search was based on the pre-set question using appropriate MeSH terms. *(((nerve block) OR (IANB)) AND ((clonidine) OR (adrenaline))) AND (lignocaine).*

Eligibility criteria

Clinical studies where clonidine + lignocaine and adrenaline + lignocaine were compared directly during nerve block administration exclusively for third molar surgical removal were selected. Studies evaluating infiltrations and inferior alveolar nerve block (IANB) for root canal treatments were excluded. Zotero was used to import the studies from three databases, later exclusion of duplicates was done, and relevant studies were then sent for full-text review. Two independent researchers were involved in collection, segregation and analysis of electronic data. The data compilation is carried out regarding author names and year of publication, study design, study and control drug, number of participants, haemodynamic parameters such as heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, onset, duration of anaesthesia and Visual Analogue Scale (VAS). The primary outcome sought was haemodynamic parameters for both the groups (clonidine group vs. adrenaline group) only during nerve block administration for third molar removal. The secondary outcome evaluated was onset and duration of anaesthesia in both groups. Means and standard deviations were collected from individual studies.

Data synthesis

A meta-analysis was undertaken to address the review question. Combined results were presented as a pooled mean difference, which was estimated using fixed and random-effect models. A statistical significance level of 5% was adopted. In the event of heterogeneity (Chi-square $P < 0.05$ or I^2 index >50%), the random-effect model was preferred.

Risk-of-bias assessment

Risk-of-bias (RoB) assessment was carried out independently by two reviewers using a seven-point criteria system by Cochrane Collaboration as having low, high or unclear bias risk.

Results

In all databases, 1141 records were found, out of which after removing irrelevant articles and duplicate articles, a total of 21 articles were included for the evaluation for full-text analysis. Out of these, 16 articles were excluded due to various reasons listed in Table 1.[13-33] Subsequently, five studies qualified for systematic review[14,18,20,27,28] out of which meta-analysis was performed in four studies.[14,18,20,27,28] A flowchart of the search results is presented in Figure 1.

Attributes of included studies

The attributes of the included studies are shown in Table 2. All these five studies were clinical studies published between 2005 and 2019. Amongst them, only two studies are double-blind studies[18,27] and the rest are clinical observational studies.[14,20,28] In total, 350 patients with ages ranging from 18 to 70 years received nerve block dental lignocaine injections with either clonidine or adrenaline as vasoconstrictors. Mandibular third molars were extracted under IANB in four studies.[14,20,27,28] One study evaluated the same in maxillary third molar removal under posterior superior alveolar nerve block and greater palatine nerve block.[18] All the five included studies evaluated

Table 1: Excluded studies with reasons

Excluded articles	Reasons for exclusion
MacDonald *et al*., 2021	For irreversible pulpitis
Sivaramakrishnan and Sridharan, 2018	Systematic review
Shadmehr *et al*., 2017	For irreversible pulpitis
Milic *et al*., 2016	Maxillary infiltrations
Jimson *et al*., 2015	Maxillary anaesthesia
Brovik *et al*., 2008	Maxillary anaesthesia
Melnikova, 2014	Paediatric patients and articaine are used
Melnikova, 2014	Paediatric patients and articaine are used
Ouchi *et al*., 2014	Dexmedetomidine used
Studer, 2012	Midazolam is used
Mutzbauer, 2005	Review
Yoshitomi, 2008	Dexmedetomidine used
Naja, 2007	Fentanyl used
Fanini, 1998	Oral clonidine, salivary reduction evaluated
Mishunin, 2002	Diazepine used
Urbanek, 2006	Review

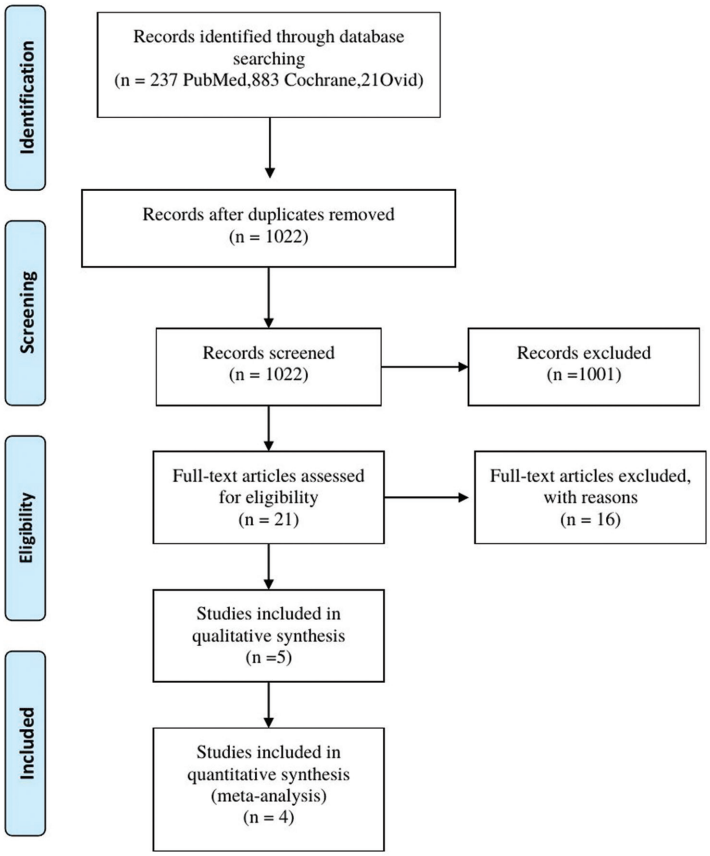

Figure 1: Flowchart showing PRISMA model for recruitment and selection of studies

haemodynamic parameters such as heart rate, systolic, diastolic blood pressure and mean arterial blood pressure at three intervals (baseline pre-operative, intraoperative and post-operative). The onset and duration of anaesthesia were also evaluated in all the five studies included. VAS was used to evaluate the pain measured in all the studies. A verbal rating scale for pain evaluation was used only in two studies.[14,27]

Risk of bias (RoB)

RoB [Figures 2 and 3] is evaluated according to Cochrane guidelines. Three studies mentioned randomisation ($n = 3$).[18,20,28] Type of randomisation was not mentioned in the study by Chowdhury, *et al*., in 2012, Patil and Patil in 2012.[18,20] Blinding was mentioned in only two studies.[18,27] Outcome blinding was not mentioned in any of the studies included. Attrition and selective reporting bias was not found in any of the studies.

Haemodynamic parameters during third molar removal

Heart rate

All the five studies evaluated heart rate (baseline pre-operative, intraoperative and post-operative), but numerical values are not mentioned in the study by Chowdhury *et al*. in 2012, hence were excluded from quantitative analysis. The heart rate of all the included studies was pooled and compared. *Heart rate preoperative versus intraoperative for clonidine and lignocaine group:* The pooled analysis showed lower heart rate for the clonidine group from pre-operative to intraoperative period, but the difference was not statistically significant (mean difference 1.63; 95% confidence interval [−1.23, 4.50]. $P = 0.26$) [Figure 4]. *Heart rate preoperative versus intraoperative for adrenaline and lignocaine group:* The pooled analysis showed increased heart rate for the adrenaline group from pre-operative to intraoperative period, and the difference was statistically significant (mean difference – 5.06; 95% confidence interval [−8.62, 1.51] $P = 0.005$) [Figure 4].

Systolic blood pressure

Systolic blood pressure was also evaluated in all the included studies (baseline pre-operative, intraoperative and post-operative); numerical values are not stated in the study by Chowdhury *et al.* in 2012,[20] hence were excluded from the quantitative analysis. *Systolic blood pressure preoperative versus intraoperative for clonidine and lignocaine group:* The pooled analysis showed lower systolic blood pressure for the clonidine group from pre-operative to intraoperative period, but the difference was not statistically significant (mean difference 2.34; 95% confidence interval [−2.02, 6.70] $P = 0.29$) [Figure 5]. *Systolic blood pressure preoperative versus intraoperative for adrenaline and lignocaine group:* The pooled analysis showed increased systolic blood pressure for the adrenaline group from pre-operative to intraoperative period, and the difference was not

Table 2: Characteristics of included studies

Author-year	Study design	Sample characteristics	Study drug	Control drug	Heart rate	Systolic blood pressure	Diastolic blood pressure
Alam *et al.*, 2019	Clinical observational study	30 healthy patients aged 27-40 requiring 3rd molar extraction. Were divided into two groups of 15 each Inferior alveolar nerve block	2.5 mL of 2% lignocaine with clonidine (15 µg/mL)	2.5 mL of 2% lignocaine with adrenaline (12 µg/mL) 1:80,000 Concentration of adrenaline is used	Clonidine: Pre, intra and postoperative- 80.3±2.4, 83.1±3.5, 76.4±2.9 Adrenaline: Pre, intra and postoperative- 83.4±2.8, 85.6±2.8, 80.9±2.6 *P* value-not significant (0.4, 0.5, 0.2)	Clonidine: Pre, intra and postoperative- 129.7±2.3, 122.6±1.9, 119.8±1.7 Adrenaline: Pre, intra and postoperative- 122.2±3.7, 126.5±2.5, 124.2±2.4 *P* value- not significant (0.1, 0.2, 0.1)	Clonidine: Pre, intra and postoperative- 82.2±2.4, 75.6±1.9, 75.6±2.0 Adrenaline: Pre, intra and postoperative- 80.6±1.9, 81.3±2.5, 76.8±2.5 *P* value- not significant (0.6, 0.09, 0.7)
Chowdhury *et al.*, 2012	Clinical observational study	30 healthy patients aged 18-40 requiring 3rd molar extraction. Were divided into two groups of 15 each Inferior alveolar nerve block	2.5 mL of 2% lignocaine with clonidine (15 µg/mL)	2.5 mL of 2% lignocaine with adrenaline (12 µg/mL) 1:80,000 Concentration of adrenaline is used			
Brovik *et al.*, 2005	Double blind clinical study	40 healthy patients aged 18-70 requiring 3rd molar extraction. Were divided into two groups of 20 each	2 mL of 2% lignocaine with clonidine (15 µg/mL)	2 mL of 2% lignocaine with adrenaline (12 µg/ml) 1:80,000 Concentration of adrenaline	Clonidine: Pre, intra and postoperative- 85.4±2.7, 82.8±2.9, 77.3±2.4 Adrenaline: Pre, intra and postoperative- 93.6±3.2, 96.7±3.2, 86.6±2.8 *P* value- significant *P*<0.01	Clonidine: Pre, intra and postoperative- 128.0±3.6, 127.1±3.6, 118.7±3.4 Adrenaline: Pre, intra and postoperative- 130.3±4.1, 126.2±3.4, 121.7±2.8 *P* value- significant *P*<0.05	Clonidine: Pre, intra and postoperative- 79±2.1, 79.4±2.2, 72.9±2.6 Adrenaline: Pre, intra and postoperative- 77.4±1.9, 78.6±2.3, 74.4±2.1 *P* value- significant *P*<0.05
Dandriyal *et al.*, 2017	Clinical observational study	200 healthy patients aged 18-45 requiring 3rd molar extraction. Were divided into two groups of 100 each	2 mL of 2% lignocaine with clonidine (15 µg/mL)	2 mL of 2% lignocaine with adrenaline (12 µg/mL) 1:80,000 Concentration of adrenaline	Clonidine: Pre, intra and postoperative- 83±7, 78±7, 77±7 Adrenaline: pre, intra and postoperative- 79±8, 84±8, 86±8 Not significant	Clonidine: Pre, intra and postoperative- 135±7, 131±7, 131±8 Adrenaline: Pre, intra and postoperative- 133±10, 136±10, 136±10 Not significant	Clonidine: Pre, intra and postoperative- 79±4, 78±4, 78±4 Adrenaline: Pre, intra and postoperative- 78±6, 78±6, 79±8 Not significant
Patil and Patil, 2012	Double blind clinical study	A total of 50 patients with moderate hypertension divided into two groups	2 mL of 2% lignocaine with clonidine (15 µg/mL)	2 mL of 2% lignocaine with adrenaline (12 µg/mL) 1:80,000 Concentration of adrenaline	Clonidine: Pre, intra and postoperative- 92.4±2.7, 90.8±3.1, 92.3±2.5 Adrenaline: Pre, intra and postoperative- 93.6±3.2, 103.5±3.5, 93.8±2.1	Clonidine: Pre, intra and postoperative- 154±3.6, 156.8±3.9, 154.1±3.2 Adrenaline: Pre, intra and postoperative- 150.3±4.1, 162.7±3.4, 154.2±3.8	Clonidine: Pre, intra and postoperative- 92±2.1, 90.1±1.9, 92.2±1.7 Adrenaline: Pre, intra and postoperative- 92.1±1.9, 90.1±2.5, 92.1±2.3

Author-year	Mean arterial pressure	Onset of anaesthesia	Duration of anaesthesia	Pain score	VRS
Alam *et al.*, 2019	Clonidine: Pre, intra and postoperative- 98.0±2.2, 91.2±1.8, 90.4±1.7 Adrenaline: Pre, intra and Postoperative- 92.5±2.1, 93.1±2.6, 91.1±2.1 *P* value- not significant (0.08, 0.5, 0.8)	Clonidine: 120.0±8.2 Adrenaline: 106.0±8.2 *P* value- not significant (0.240)	Clonidine: 179.3±4.6 Adrenaline: 185.3±3.3 *P* value- not significant (0.305)	Pain score, using VAS with *P*=0.03 was statistically significant	In the clonidine group, 40% had just noticeable pain and 60% had weak pain. In the adrenaline group, 6.7% had no pain, 73.3% had just noticeable pain, and 20% had weak pain. The difference in mean VRS between the two groups was not statistically significant
Chowdhury *et al.*, 2012					

Contd...

Table 2: Contd...

Author-year	Mean arterial pressure	Onset of anaesthesia	Duration of anaesthesia	Pain score	VRS
Brovik *et al*., 2005	Clonidine: Pre, intra and postoperative- 96.0±2.4, 95.1±2.4, 89.1±2.4 Adrenaline: Pre, intra and postoperative- 95.3±2.3, 94.9±2.5, 90.4±2.2	Adrenaline: 87±14 Clonidine: 54±7 *P* value- significant ($P<0.05$)	Adrenaline: 127±16 Clonidine: 136±13 *P* value- not significant	Adrenaline: 10.8±2.8 Clonidine: 6.3±1.9 *P* value- significant ($P<0.05$)	There was no significant statistical difference between the two groups VRS scale
Dandriyal *et al*., 2017	Clonidine: Pre, intra and postoperative- 97±5, 96±5, 96±5 Adrenaline: Pre, intra and postoperative- 96±8, 97±7, 98±6	Not evaluated in this study	Not evaluated in this study	Clonidine: 2±1 Adrenaline: 2±1 *P* value- not significant	
Patil and Patil, 2012	Clonidine: Pre, intra and postoperative- 104±2.4, 107.5±2.4, 104.3±2.1 Adrenaline: Pre, intra and postoperative- 105.3±2.3, 108.9±2.6, 105.5±1.9	Clonidine: subjective 82±8 and objective 289±17 Adrenaline: subjective 91±11 and objective 309±19	Clonidine: subjective 131±13 and objective 85±13 Adrenaline: subjective 123±17 and objective 92±11	Clonidine: 1.2±0.9 Adrenaline: 1.8±0.9	

VRS=Verbal Rating Scale; VAS=Visual Analog Scale

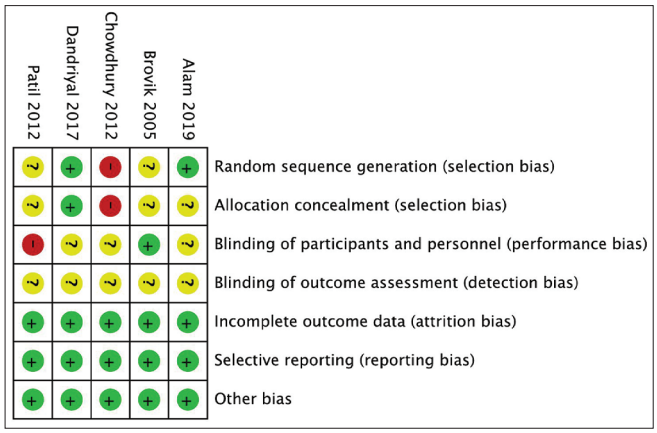

Figure 2: Risk of bias summary

statistically significant (mean difference - 3.91; 95% confidence interval [−10.95, 3.12] $P = 0.28$) [Figure 5].

Diastolic blood pressure

Diastolic blood pressure was also evaluated in all the included studies (baseline pre-operative, intraoperative and post-operative), numerical values are not mentioned in the study by Chowdhury *et al.* 2012,[20] hence was excluded from quantitative analysis. *Diastolic blood pressure preoperative versus intraoperative for clonidine and lignocaine group:* The pooled analysis showed lower diastolic blood pressure for the clonidine group from pre-operative to intraoperative period, but the difference was not statistically significant (mean difference 2.24; 95% confidence interval [−0.30, 4.79] $P = 0.08$) [Figure 5]. *Diastolic blood pressure preoperative versus intraoperative for adrenaline and lignocaine group:* The pooled analysis showed no significant difference in the diastolic blood pressure for the adrenaline group from pre-operative to intraoperative period (mean difference – 0.05; 95% confidence interval [−1.49, 1.59] $P = 0.95$) [Figure 5].

Mean arterial pressure

Mean arterial pressure was also evaluated in all the included studies (baseline preoperative, intraoperative and post-operative), Numerical values are not stated in the study by Chowdhury, *et al.*, 2012,[20] hence was excluded from quantitative analysis. *Mean arterial pressure preoperative versus intraoperative for clonidine and lignocaine group:* The pooled analysis showed lower mean arterial pressure for the clonidine group from pre-operative to intraoperative period, but the difference was not statistically significant (mean difference 1.29; 95% confidence interval [−2.90, 5.49] $P = 0.54$) [Figure 4]. *Mean arterial pressure preoperative versus intraoperative for adrenaline and lignocaine group:* The pooled analysis showed increased mean arterial pressure for adrenaline group from pre-operative to intraoperative period, and the difference was not statistically significant (mean difference 1.23; 95% confidence interval [−3.15, 0.69] $P = 0.21$) [Figure 4].

Onset of local anaesthesia

Three studies compared the effects of clonidine or adrenaline with lignocaine on the onset of local anaesthesia.[14,18,27]

All the three studies used objective measures (pinprick) to evaluate the onset of anaesthesia. Two studies evaluated subjective measures (numbness) to evaluate the onset of anaesthesia.[18,27] Clonidine was found to shorten the onset of local anaesthesia, but the difference was not statistically significant. Subjectively: (mean difference – 10.70; 95% confidence interval [−38.60, 17.19] P = 0.45) [Figure 6]. Objectively: (mean difference – 20.90; 95% confidence interval [−44.42, 2.62] P = 0.08) [Figure 6].

Duration of local anaesthesia

Three studies compared the effects of clonidine or adrenaline with lignocaine on the duration of local anaesthesia.[14,18,27]

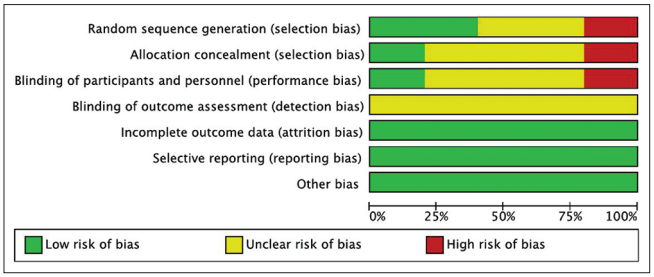

Figure 3: Risk of bias

All the three studies used objective measures (pinprick) to evaluate the duration of anaesthesia. Two studies evaluated subjective measures (numbness) to evaluate the same.[18,27] When measured subjectively, clonidine had increased duration of anaesthesia in comparison to epinephrine (mean difference 8.46; 95% confidence interval [2.32, 14.61] P = 0.007) [Figure 6]. When measured objectively (pinprick), epinephrine had increased duration of anaesthesia (mean difference 5.85; 95% confidence interval [−8.29, −3.41] P = 0.0001) [Figure 6].

Discussion

Five studies were included for the final qualitative assessment, amongst them, four studies were considered for meta-analysis.[14,20,27,28] Four studies evaluated mandibular third molar extractions and one study evaluated maxillary third molar extractions and hence was excluded from the meta-analysis.[18] All the subjects in the studies received lignocaine nerve block injections with vasoconstrictor either being adrenaline or clonidine. The primary outcome i.e., haemodynamic parameters and secondary outcome i.e., onset and duration of anaesthesia in both groups.

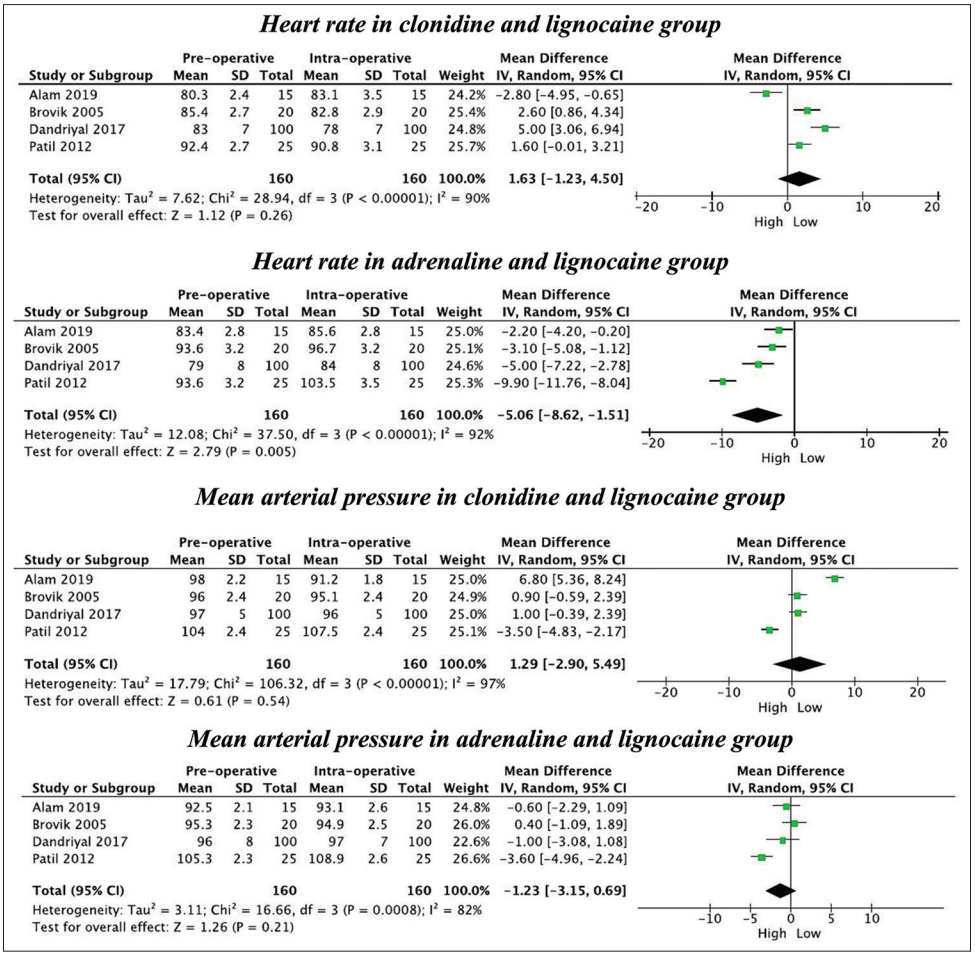

Figure 4: Heart rate and Mean arterial pressure in clonidine + lignocaine and adrenaline + lignocaine groups

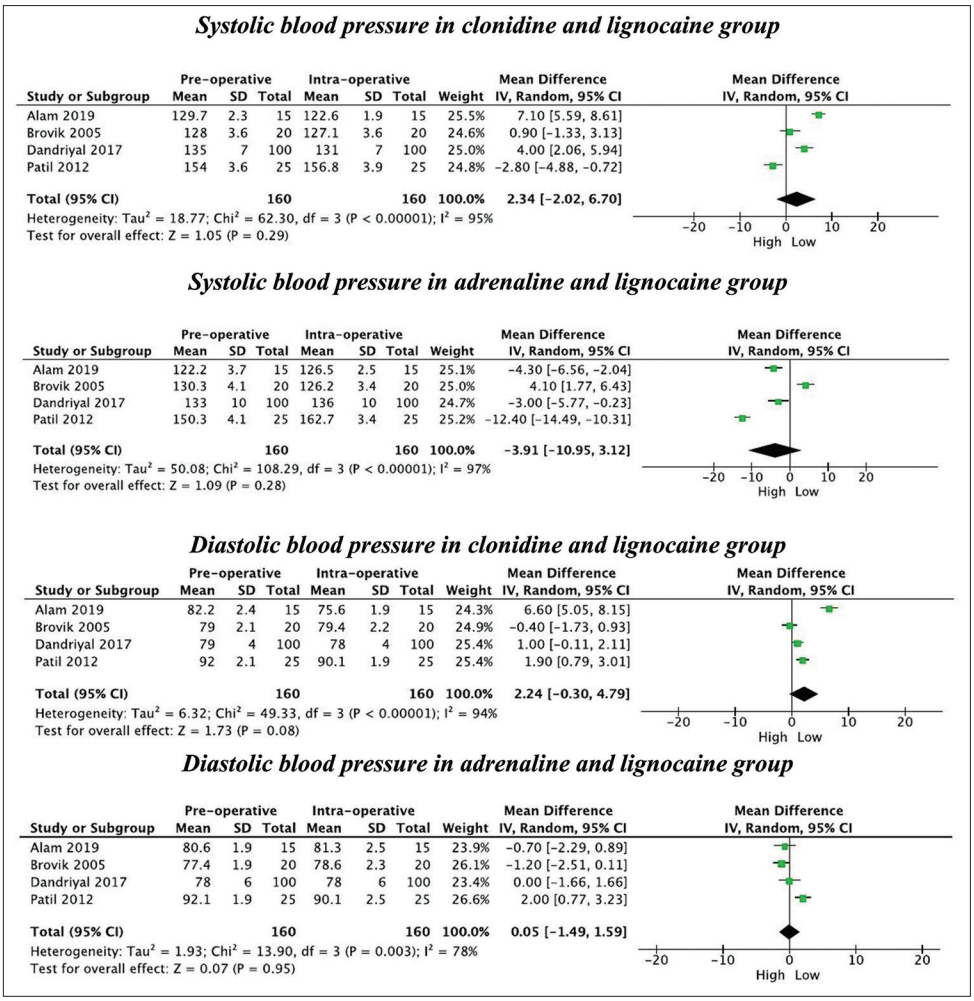

Figure 5: Systolic and Diastolic blood pressure in clonidine + lignocaine and adrenaline + lignocaine groups

The mean change of heart rate from pre-operative to intraoperative period was significantly higher in the lignocaine adrenaline group (mean difference- 5.06; 95% confidence interval [−8.62, −1.51] $P = 0.005$). In the lignocaine and clonidine groups, the heart rate dropped from pre-operative to intraoperative period but the difference was not significant statistically (mean difference 1.63; 95% confidence interval [−1.23, 4.50] $P = 0.26$). Hence, overall heart rate was relatively lower when lignocaine was used as a vasoconstrictor.

Slightly lower values of systolic blood pressure, diastolic blood pressure and mean arterial pressure was observed from pre-operative to intraoperative period when clonidine was used as a vasoconstrictor but the difference was not statistically significant *(P* = 0.29, 0.08, 0.54, respectively). A slight increase in the values of systolic blood pressure, diastolic blood pressure and mean arterial pressure was observed from pre-operative to intraoperative period when the adrenaline was used as a vasoconstrictor but the difference was not statistically significant *(P* = 0.28, 0.95, 0.21, respectively).

Clonidine when used as a vasoconstrictor has lowered the onset of anaesthesia (subjectively and objectively) but the difference is not statistically significant *(P* = 0.08).

Conflicting results were reported for the duration of anaesthesia. When measured subjectively, clonidine had increased duration of anaesthesia in comparison to epinephrine (mean difference 8.46; 95% confidence interval [2.32, 14.61] $P = 0.007$). When measured objectively (pinprick), epinephrine had increased duration of anaesthesia: Mean difference 5.85; 95% confidence interval (−8.29, −3.41) $P = 0.0001$. This might be due to the difference in the number of studies that evaluated subjective and objective parameters (three studies used objective measures [pinprick] and only two studies evaluated subjective measures [numbness]). Pooling and comparing both subjective and objective measures will not be accurate.

Summary of the evidence

The present systematic review and meta-analysis compared and evaluated the usage of clonidine as a vasoconstrictor in comparison to adrenaline in nerve block injections on haemodynamic parameters and on onset and duration of local

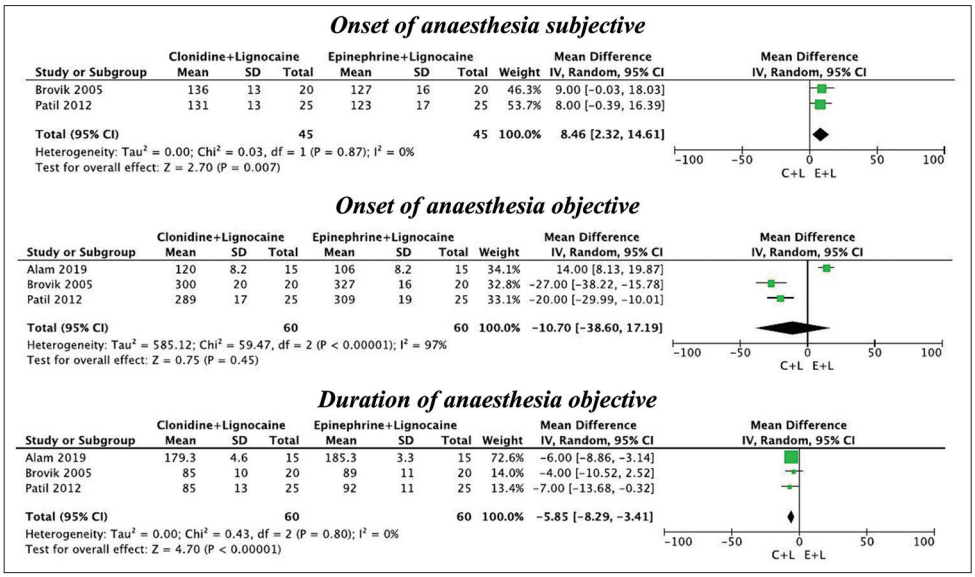

Figure 6: Subjective and Objective onset of anaesthesia and duration of anaesthesia

anaesthesia. Heart rate was significantly lower when clonidine was used as a vasoconstrictor with lignocaine for nerve blocks for third molar extractions.

Limitations

Blinding was not performed in all the studies, randomisation was performed in only three studies. The volume of local anaesthesia deposited varied in the studies (2 mL in three studies and 2.5 mL in two studies). Most of the studies ($n = 4$) were evaluated on normal adults, only one study evaluated in mild hypertensive patients.

Directions for future research

The usage of clonidine as a vasoconstrictor in conjunction with lignocaine for nerve blocks in hypertensive patients requiring third molar extraction can be an excellent topic for future research.

Conclusion

Based on the above results following conclusions can be made:

1. Clonidine can be used as an alternative to epinephrine as a vasoconstrictor along with lignocaine for nerve block injections in third molar removal, especially in hypertensive patients
2. RoB is high, so the quality of available evidence is low.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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