INTRODUCTION

Achieving adequate depth of local anesthesia is an important parameter affecting the success of dental treatments [1,2]. Epinephrine is the main vasoconstrictor present in the composition of most local anesthetic agents and its concentration ranges from 1:50,000 (20 µg/mL) to 1:200,000 (5 µg/mL) in commercially available dental anesthetic cartridges [1,3,4]. Evidence shows that epinephrine, depending on its concentration, can cause biochemical changes in healthy individuals [5,6].

Effect of the inferior alveolar nerve block injection versus maxillary infiltration with two local anesthetic agents on cardiovascular parameters: A randomized comparative double-blind clinical trial

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ABSTRACT
This study aimed to assess the effect of inferior alveolar nerve (IAN) block of the mandible and infiltration anesthesia of the maxilla using lidocaine plus epinephrine or prilocaine with felypressin anesthetic agents on systolic and diastolic blood pressures, heart rate (HR) and peripheral oxygen saturation rate of patients. This randomized double-blind clinical trial evaluated 112 patients in four groups (n=28) based on the jaw (maxilla or mandible) and type of anesthetic agent (lidocaine with epinephrine or prilocaine with felypressin). Groups 1 and 2 received IAN block of the mandible or infiltration anesthesia of the maxilla, respectively, with 2% lidocaine plus 1:80.000 epinephrine. Groups 3 and 4 received IAN block of the mandible or infiltration anesthesia of the maxilla, respectively, using prilocaine with felypressin. Systolic and diastolic blood pressures and HR were measured by an automatic upper arm blood pressure monitor and the percentage of peripheral oxygen saturation rate was measured by a finger pulse oximeter 10 minutes before the injection, immediately after injection, 10 minutes after injection and 20 minutes after injection.

The mean diastolic blood pressure showed a greater reduction following the administration of lidocaine with epinephrine, as compared with prilocaine with felypressin (p<0.001). The mean HR showed a significantly greater increase following the administration of lidocaine with epinephrine, as compared with prilocaine with felypressin (p<0.001). The effect of type of anesthetic agent on diastolic blood pressure depended on the type of injection (p=0.033). Administration of 2% lidocaine with 1:80.000 epinephrine, in comparison to prilocaine with felypressin, can cause changes in cardiovascular parameters such as heart rate and diastolic blood pressure in patients undergoing restoration of a maxillary or mandibular molar tooth. Type of injection has no significant effect on cardiovascular parameters.
Use of a low-dose vasoconstrictor such as epinephrine is required in local anesthesia since it increases the depth and duration of anesthesia, decreases bleeding during the procedure and lowers the immediate uptake of local anesthetic agent and its subsequent entry into the blood stream and the cardiovascular system [7]. Thus, it reduces the level of anesthetic agent in the blood stream and minimizes the risk of toxicity, overdose and other side effects [8,9]. Despite these advantages, an adrenergic vasoconstrictor can increase the heart muscle contraction and resistance of peripheral blood vessels, as well as enhance systolic and diastolic blood pressure, and lead to dysrhythmia, ischemic changes and hypokalemia, which can cause problems for cardiovascular and hypertensive patients - and even result in their death [1,5,10]. These changes can be regulated by the balance between the activity of sympathetic and parasympathetic systems. However, stress and pain can further change the autonomous responses [1]. A previous study on cardiovascular effects of felypressin present in anesthetic agents on hypertensive patients reported no change in their hemodynamic status following the administration of felypressin at 0.03 IU/mL dosage [11].

Pain and anxiety during dental treatments can induce the release of catecholamines from the adrenal medulla. Moreover, injection of anesthetic agent and vasoconstrictor can change blood pressure levels and induce the release of catecholamines. Synergistic effects of these two conditions can, in turn, adversely affect the cardiovascular system [9,12]. Thus, injection of anesthetic agents containing vasoconstrictor and the anxiety related to dental procedures may induce the release of catecholamines, increase the oxygen demand of myocardium and cause arrhythmia [12].

A high number of dental patients have uncontrolled high blood pressure or cardiovascular problems [13]. Thus, blood pressure and HR are important and should be closely monitored during dental treatment of these patients [9,14,15]. Local anesthetic injection is a concern for these patients since it may have adverse effects on these patients and cause hypertension [14]. For this reason, most dental clinicians prefer to use anesthetic agents devoid of vasoconstrictor in these patients. However, evidence shows that anesthetic agents without a vasoconstrictor increase the risk of hypertensive crisis caused by pain, which occurs due to inadequate depth of anesthesia [14].

Hemodynamic effects of lidocaine and prilocaine without a vasoconstrictor on hypertensive patients have been previously evaluated and it has been confirmed that they can be safely used in such patients [14]. With regard to 2% lidocaine, evidence shows that 2% lidocaine with 1:200,000 epinephrine should be preferably used in cardiovascular patients because 1:80,000 concentration of epinephrine can cause a significant increase in HR and blood pressure of these patients [10]. Indeed, research indicates that the epinephrine level of plasma increases by 27.5 folds 1 minute after the administration of 2% lidocaine plus 1:100,000 epinephrine, which results in 15% rise in systolic blood pressure and 33% increase in HR [3]. In addition, HR increases within 10 minutes and diastolic blood pressure decreases within 20 minutes following the administration of 2% lidocaine plus 1:80,000 epinephrine [11].

It has been well accepted that epinephrine has a wide safety range. However, its threshold for hypertensive and cardiovascular patients has not been clearly determined [1]. Moreover, no previous study has assessed the hemodynamic effects of inferior alveolar nerve (IAN) block and maxillary infiltration anesthesia with lidocaine plus epinephrine or prilocaine with felypressin on hemodynamic parameters of patients. Studies, therefore, are required to determine the safest type of injection and anesthetic agent with minimal effects on the HR, systolic and diastolic blood pressure and peripheral oxygen saturation rates [16]. Thus, this study aimed to compare the effects of infiltration anesthesia of the maxilla or IAN block of the mandible with lidocaine plus epinephrine or prilocaine with felypressin on cardiovascular parameters including the HR, systolic and diastolic blood pressure levels and peripheral oxygen saturation rate of patients.

**MATERIALS AND METHODS**

This randomized double-blind clinical trial used convenience sampling to evaluate patients who were selected among those presenting to dental clinics of Kermanshah City requiring restoration of their molar teeth. The study was approved by the ethics committee of Kermanshah University of Medical Sciences (ir.kums.rec.1396.389) and was registered in the Iranian Registry of Clinical Trials (IRCT20140527017880N6).

Sample size was calculated to be minimally 112 patients (n=28 in each group) assuming the standard deviation of diastolic blood pressure in the lidocaine plus epinephrine and prilocaine with felypressin groups to be 10.3 and 7.7, respectively, with mean values of 7.7 and 2.6, respectively.

The inclusion criteria were age between 20 to 50 years, good general health state, requiring restoration of a maxillary or mandibular molar tooth and signing informed consent forms. The exclusion criteria were history of cardiovascular diseases, hypertension, diabetes mellitus, renal disease, gastrointestinal ulcers or diseases, as well as taking anesthetic, analgesic or steroid medications, tranquilizers or antidepressants in the past 2 weeks prior to the experiment, allergy to anesthetic agent, or active oral lesion at the site of injection, pregnancy and nursing [9,10]. All patients signed informed consent forms prior to their participation in the study.

The closed envelope technique was used in order to randomly assign patients to the two groups of lidocaine with epinephrine and prilocaine with felypressin. Anesthetic cartridges were covered and coded 1 and 2 such that the operator, the statistician and the patients were all blinded to the group allocation of participants. Depending on the location of molar tooth to be treated (in the maxilla or mandible), 112 patients were placed into four groups (n=28) of IAN block of the mandible with 2% lidocaine and 1:80,000 epinephrine (Daroupaksh, Iran), infiltration anesthesia of the maxilla with 2% lidocaine and 1:80,000 epinephrine, IAN block of the mandible with prilocaine plus felypressin (Daroupaksh, Iran) and infiltration anesthesia of the maxilla with prilocaine plus felypressin. All cartridges were at room temperature and all injections were performed by the same operator in the morning before noon.
Buccal infiltration anesthesia of the maxilla was also performed by the same operator using a 1.8 mL anesthetic cartridge with a short 27-gauge needle (Nik Rahnama, Iran). The anesthetic agent was injected into the buccal vestibule above the apex of the respective tooth. The bevel of the needle faced the bone and the needle was inserted parallel to the longitudinal axis of the tooth for 2 to 4 mm. The anesthetic agent was injected within 1 minute.

The IAN block of the mandible was performed by the same operator for all patients. A 1.8 mL anesthetic cartridge was used and the anesthetic agent was injected with a long 27-gauge needle (Nik Rahnama, Iran) using the indirect technique. For this purpose, the needle was inserted into the lingual side of the ramus at the intersection of a horizontal line (a hypothetical line from the coronoid notch to the deepest point of the pterygomandibular raphe, which is often 6 to 10 mm above the occlusal surface and determines the height of injection site) and a vertical line (the anterior ¼ of the distance between the coronoid notch and pterygomandibular raphe, which determines the anteroposterior position of the needle insertion site). The needle penetrated to 20 to 25 mm and the anesthetic agent was injected within 1 minute. In all patients, aspiration was performed by syringe (Anthogyr, France) before anesthetic injection. One anesthetic cartridge (1.8 mL) was only injected for each patient, and patients with unsuccessful anesthesia were excluded.

The systolic and diastolic blood pressure levels of patients were measured by an automatic upper arm blood pressure monitor (BO79; Emsig, Germany). The cuff was placed on the right upper arm of patients. The HR and peripheral oxygen saturation rate of patients were measured by a pulse oximeter (NK250B; Maxy, Italy) placed on the left index finger of patients. Measurements were made at four time points 10 minutes before the injection (T1), immediately after the injection (T2), 10 minutes after the injection (T3) and 20 minutes after the injection (T4). All measurements were double-checked by a second observer under standard conditions.

Tooth restoration was initiated 5 minutes after the infiltration anesthesia of the maxilla and 15 minutes after the IAN block of the mandible [11]. The patients’ hemodynamic status before the injection was considered as the resting position. The patients’ hemodynamic status immediately after the injection was considered as the hemodynamic reaction of patients to the anesthetic injection and the next assessments were considered as the patients’ reaction to both pharmacological effects of anesthetic agent and response to the dental procedure [11].

Normal distribution of data was evaluated using the Kolmogorov-Smirnov test. Chi-square test and independent sample t-test were applied to analyze the effect of type of anesthetic agent and type of injection on hemodynamic parameters based on age and gender of patients. Repeated measures ANOVA was applied to assess the effect of type of anesthetic agent and type of injection on the variables over time after controlling for age and sex of patients. All statistical analyses were performed using SPSS version 18 (SPSS Inc., IL, USA) at 0.05 level of significance.

RESULTS

Among 112 patients, 45 (40.2%) were males and 67 (59.8%) were females with a mean age of 30.75±7.99 years. The quantitative variables all had normal distribution (alpha=0.05 and study power of 90%). There was no significant difference in gender distribution of patients in different groups based on the type of injection (p=0.847) and type of anesthetic agent (p=0.335). There was no significant difference in the mean age of patients in different groups based on the type of injection (p=0.466) and type of anesthetic agent (p=0.573). Aspiration was performed prior to injection of anesthetic agent, which was positive in 10 cases (8.92%).

Table 1 shows the mean systolic blood pressure of patients in the four groups at different time points. Repeated measures ANOVA revealed no significant difference in the mean systolic blood pressure of patients at different time points (p=0.315). Type of anesthetic agent (p=0.635) and type of injection (p=0.551) had no significant effect on systolic blood pressure. The interaction effect of type of anesthetic agent and type of injection on systolic blood pressure was not significant either (p=0.095) (Figure 1).

Table 1. Mean systolic blood pressure of patients in the four groups at different time points

<table>
<thead>
<tr>
<th>Anesthetic Agent</th>
<th>Injection</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>1.8% Lidocaine</td>
<td>IAN block</td>
<td>122.93</td>
<td>9.12</td>
<td>120.18</td>
<td>9.20</td>
</tr>
<tr>
<td></td>
<td>Infiltration</td>
<td>119.29</td>
<td>7.99</td>
<td>117.96</td>
<td>7.28</td>
</tr>
<tr>
<td>Total</td>
<td>121.61</td>
<td>8.81</td>
<td>119.07</td>
<td>8.30</td>
<td>118.18</td>
</tr>
<tr>
<td>2% Prilocaine</td>
<td>IAN block</td>
<td>121.71</td>
<td>10.96</td>
<td>117.96</td>
<td>9.83</td>
</tr>
<tr>
<td></td>
<td>Infiltration</td>
<td>117.79</td>
<td>8.01</td>
<td>114.89</td>
<td>6.05</td>
</tr>
<tr>
<td>Total</td>
<td>119.75</td>
<td>9.71</td>
<td>116.43</td>
<td>8.23</td>
<td>115.79</td>
</tr>
<tr>
<td>2% Lidocaine Plus 1:80,000 Epinephrine</td>
<td>IAN block</td>
<td>122.82</td>
<td>10.05</td>
<td>119.07</td>
<td>9.50</td>
</tr>
<tr>
<td></td>
<td>Infiltration</td>
<td>118.54</td>
<td>7.96</td>
<td>116.43</td>
<td>6.81</td>
</tr>
<tr>
<td>Total</td>
<td>120.68</td>
<td>9.28</td>
<td>117.75</td>
<td>8.33</td>
<td>116.98</td>
</tr>
</tbody>
</table>

Figure 1. Mean systolic blood pressure by type of anesthetic solution and type of injection over time
Table 2 shows the mean diastolic blood pressure of patients in the four groups at different time points. Repeated measures ANOVA revealed no significant difference in the mean diastolic blood pressure of patients at different time points (p=0.841). Type of anesthetic agent had a significant effect on diastolic blood pressure (p<0.001) such that the mean diastolic blood pressure experienced a greater reduction following the injection of lidocaine with epinephrine (type 1), compared with prilocaine with felypressin (type 2). Type of injection had no significant effect on diastolic blood pressure (p=0.073). The interaction effect of type of anesthetic agent and type of injection on diastolic blood pressure was significant (P=0.033) such that the effect of type of anesthetic agent on diastolic blood pressure depended on the type of injection (Figure 2).

No significant difference was noted in the mean change of diastolic blood pressure at T1 and T2 between the two anesthetic agents (p=0.179), but a significant difference existed in the mean change of diastolic blood pressure at T1 and T3 between the two anesthetic agents (p=0.002) such that the mean diastolic blood pressure following the use of lidocaine with epinephrine experienced a greater reduction, as compared with prilocaine with felypressin. A significant difference existed in the mean change of diastolic blood pressure at T1 and T4 between the two anesthetic agents (p<0.001) such that the mean diastolic blood pressure experienced a greater reduction following the use of lidocaine with epinephrine, as compared with prilocaine with felypressin (Figure 2).

Table 3 shows the HR of patients in the four groups. Repeated measures ANOVA found no significant difference in the mean HR of patients at different time points (Greenhouse-Geisser, p=0.257). Type of anesthetic agent had a significant effect on the HR (P<0.001) such that the mean HR following the use of lidocaine with epinephrine showed a greater increase, as compared with prilocaine with felypressin. Type of injection had no significant effect on the HR (p=0.513). The interaction effect of type of anesthetic agent and type of injection was not significant (p=0.251). The mean difference in HR at T1 and T2 was significant between the two anesthetic agents (p<0.001) such that the mean HR following the administration of lidocaine with epinephrine experienced a greater increase, as compared with prilocaine with felypressin.

A significant difference existed in the mean change of HR at T1 and T3 between the two anesthetic agents (p=0.001), and the mean HR experienced a greater increase following the administration of lidocaine with epinephrine. The difference in this respect was also significant at T1 and T4 (p=0.001) and the mean HR following the administration of lidocaine with epinephrine significantly increased, as compared with prilocaine with felypressin (Figure 3).

Table 4 shows the mean percentage of peripheral oxygen saturation in the four groups. Repeated measures ANOVA showed no significant difference in the mean percentage of peripheral oxygen saturation at different time points.
Type of anesthetic agent had no significant effect on the percentage of peripheral oxygen saturation (p=0.616). Type of injection also had no significant effect on the percentage of peripheral oxygen saturation (p=0.605). The interaction effect of type of injection and type of anesthetic agent on the percentage of peripheral oxygen saturation was not significant (p=0.992) (Figure 4).

Mean arterial pressure (MAP) of patients in the four groups at different time points are presented in Table 5. Data analysis showed a significant difference among the 4 times (groups) (p=0.001). Moreover, there was no significant difference between the two anesthesia techniques (p=0.505), but there was a significant difference between the two types of anesthesia solution (p=0.003).

DISCUSSION

This study assessed the effect of infiltration anesthesia of the maxilla and IAN block of the mandible using lidocaine plus epinephrine and prilocaine with felypressin anesthetic agents on systolic and diastolic blood pressure, HR and peripheral oxygen saturation rate. In our study, aspiration was performed prior to injection of anesthetic agent, which was positive in 10 cases (8.92%). Rate of positive aspiration in the literature varies from 3.6% to 22% [4]. Our results showed that the effect of type of anesthetic agent on diastolic blood pressure depended on the type of injection. However, the interaction effect of type of anesthetic agent and type of injection on systolic blood pressure, HR and percentage of oxygen saturation was not significant. The mean HR following administration of lidocaine with epinephrine experienced a greater increase immediately after injection and 10 and 20 minutes later compared with baseline, in comparison with prilocaine with felypressin. Also, the mean diastolic blood pressure experienced a greater reduction 10 and 20 min following administration of lidocaine with epinephrine, when compared with baseline, and in comparison with prilocaine with felypressin. Thus, type of anesthetic agent can affect the HR and diastolic blood pressure over time. Of note: the stress felt during the dental procedure can also play a role in this respect; however, these effects cannot be differentiated.

The current study found no significant difference in systolic blood pressure between lidocaine with epinephrine and prilocaine with felypressin groups after injection, which was in line with the results of Meechan et al. [11], who found no significant difference between 2% lidocaine and 1:80.000 epinephrine and prilocaine with felypressin in this respect. It also agreed with the results of Santos et al. [17], who found no significant difference between articaine with 1:100.000 and 1:200.000 epinephrine. However, our findings in this respect were different from those of Abu-Mostafa et al. [4], Managutti et al. [10], Torres-Lagares et al. [1], and Troullos et al. [3], who reported that anesthetic agents with higher concentrations of epinephrine caused a greater increase in systolic blood pressure. The reason for such a difference in experiment outcome may be the use of different doses of anesthetic agents. We used in two groups, 1.8 mL of 2% lidocaine with 1:80.000 epinephrine, which contains 0.0225 mg epinephrine, and prilocaine without epinephrine in two other groups. In contrast, for instance, Abu-Mostafa et al. [4] administered 3.6 mL anesthetic agents containing 0.045 mg, 0.036 mg and 0.018 mg epinephrine and reported a significant increase in systolic blood pressure.
blood pressure after administration of 2% lidocaine with 1:80,000 epinephrine, compared with 4% articaine with 1:200,000 epinephrine [1,4,10,11,17].

The current results demonstrated a significant reduction in diastolic blood pressure following administration of lidocaine plus epinephrine, when compared with prilocaine with felypressin, which was in agreement with the findings of Abu-Mostafa et al. [4] and Meechan et al. [11], who reported a greater reduction in diastolic blood pressure following the use of solutions containing higher amounts of epinephrine. This comes about because reduction in diastolic blood pressure was found to occur following stimulation of B2 receptors by epinephrine - which results in vasodilation in skeletal muscles [4,11].

In contrast to our findings, Santos et al. [17] and Troullous et al. [3] found no significant difference among different anesthetic agents containing different concentrations of epinephrine at different time points. However, Managutti et al. [10] stated that 2% lidocaine plus 1:80,000 epinephrine caused a significant increase in diastolic blood pressure, as compared with 2% lidocaine plus 1:200,000 epinephrine. This effect can be due to the release of endogenic epinephrine into the systemic blood pressure as the result of emotional stress (and not the effect of epinephrine present in local anesthetic agent) [3,9,10,18].

What is more, our study showed a significant increase in HR following the administration of lidocaine plus epinephrine, when compared with prilocaine with felypressin, and, in this respect, our results were in line with those of Meechan et al. [11], Abu-Mostafa et al. [4], Managutti et al. [10], Santos et al. [17] and Troullous et al. [3], who reported a greater rise in HR following the administration of anesthetic agents containing epinephrine. This probably occurs because epinephrine mainly affects the beta receptors, and a beta-adrenergic agonist increases the speed of contraction of heart muscle, and, consequently the HR [3,4,10,11,17]. The current study found no significant difference in percentage of peripheral oxygen saturation between the two anesthetic agents, which was in line with the findings of Abu-Mostafa et al. [4], Torres-Lagares et al. [1] and Santos et al. [17].

There is a strong belief among the clinicians that anesthetic agents containing epinephrine result in more effective local anesthesia and decrease the release of endogenous catecholamines [11]. On the other hand, some others have reported that epinephrine can increase the cardiac muscle force, enhance resistance of peripheral vasculature and systolic and diastolic blood pressure, and cause dysrhythmia [1,5,10]. In the current study, lidocaine containing epinephrine induced a reduction in diastolic blood pressure and increased the HR.

CONCLUSION

Administration of 2% lidocaine with 1:80,000 epinephrine, even in a small volume, can cause changes in cardiovascular parameters such as HR and diastolic blood pressure of patients. Cardiovascular parameters are not affected by the IAN block of the mandible or infiltration anesthesia of the maxilla, given that the instructions for injection are precisely followed. The effect of epinephrine in the anesthetic solution on the cardiovascular system should be considered along with the type of injection.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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