



## Comparison between cardiovascular effects of adrenaline and phenylephrine associated with lidocaine and the effects of felypressin with prilocaine during intrabuccal anesthesia in ASA I patients

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### ABSTRACT

**OBJECTIVE:** Evaluate the cardiovascular effects by infiltration of 1:100.000 epinephrine and 1:2.500 phenylephrine associated with 2% lidocaine compared with the effects by infiltration of 0.03 IU/ml felypressin with 3% prilocaine, during surgery of third molars in ASA I patients.

**METHODS:** Eighteen patients were divided into two groups. In group I (GI), the effects of epinephrine vs felypressin were evaluated and in group II (GII), the effects of phenylephrine vs felypressin. Cardiovascular parameters: systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and oxygen saturation (SatO<sub>2</sub>) were measured in pre, trans and post-operative periods.

**RESULTS:** Statistical analysis (T-TEST) on the cardiovascular parameters demonstrated with significance that, GI: felypressin presented HR average reduction in the postoperative period and SatO<sub>2</sub> average reduction in trans and postoperative periods. For GII: felypressin presented SatO<sub>2</sub> average reduction in the postoperative period; SBP averages for patients submitted to phenylephrine increased in trans and postoperative periods; and DBP averages for patients submitted to phenylephrine increased in pre and trans-operative periods.

**CONCLUSION:** We can conclude that phenylephrine may lead to increased SBP and DBP and felypressin generated a reduction in HR and SatO<sub>2</sub>. All these changes were well tolerated by ASA I patients.

**Keywords:** felypressin; epinephrine; vasoconstrictors agents; blood pressure; oral surgery.

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### Comparação entre os efeitos cardiovasculares da adrenalina e fenilefrina associadas à lidocaína e os efeitos da felipressina com a prilocaína durante a anestesia intrabucal em pacientes ASA I

#### RESUMO

**OBJETIVO:** Avaliar os efeitos cardiovasculares da infiltração de adrenalina 1:100.000 e fenilefrina 1:2.500 associadas à lidocaína a 2% comparados com os efeitos da felipressina 0,03 UI/ml associada à prilocaína a 3% durante a cirurgia de terceiros molares em pacientes ASA I.

**METODODOLOGIA:** Dezoito voluntários foram divididos em dois grupos. No grupo I (GI), adrenalina vs felipressina e, no grupo II (GII), fenilefrina vs felipressina. Os parâmetros de frequência cardíaca (FC), saturação de oxigênio (SatO<sub>2</sub>), pressão arterial sistólica (PAS) e pressão arterial diastólica (PAD) foram avaliados nos períodos pré, trans e pós-operatórios.

**RESULTADOS:** A análise estatística feita através do teste t pareado demonstrou que, no GI, a felipressina apresentou redução na FC no período pós-operatório e redução na SatO<sub>2</sub> nos períodos trans e pós-operatórios. No GII, a felipressina apresentou redução de SatO<sub>2</sub> no período pós-operatório. As PAS para os pacientes submetidos à fenilefrina apresentaram-se aumentadas nos períodos trans e pós-operatórios e as PAD para os pacientes submetidos à fenilefrina apresentaram-se aumentadas nos períodos pré e trans-operatórios.

**CONCLUSÃO:** A partir destes resultados podemos concluir que a fenilefrina pode acarretar aumento da PAS e PAD e a felipressina gerou uma redução na FC e SatO<sub>2</sub> alterações essas bem toleradas por estes pacientes

**Palavras-chave:** anestésicos locais; vasoconstritores; parâmetros cardiovasculares.

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**Received:** February 02, 2018  
**Accepted:** January 16, 2019

**Conflict of Interests:** The authors state that there are no financial and personal conflicts of interest that could have inappropriately influenced their work.

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## INTRODUCTION

Lidocaine is the local anesthetic most used in dentistry worldwide and is also taken as the reference standard in comparative studies with other drugs [1].

Vasoconstrictors are widely used in dentistry as adjuncts to local anesthetics for their recognized effect on increasing the quality and duration of anesthetic blockade, decreasing the vasodilatory action of the local anesthetic, delaying its absorption through the systemic circulation, reducing the systemic toxicity of local anesthesia and bleeding at the surgical site [2-5].

Although some studies have shown that there are no significant changes in the cardiovascular parameters of healthy individuals [2,6] or of patients with cardiovascular alterations [3,7,8], who received local anesthetic solutions containing adrenaline as vasoconstrictor, other studies have shown that changes occur and may be more significant, depending on the concentration of the vasoconstrictor used and the degree of impairment of the individual's health [9,10].

Felypressin, a derivative of vasopressin (antidiuretic hormone), is a option as a vasoconstrictor in dentistry, presenting a mechanism of action different from sympathomimetic vasoconstrictors. It acts on vasopressin V1 receptors present on the smooth muscle of the blood vessel wall [11]. The mechanism of action by which felypressin induces cardiovascular changes and its systemic effects have not yet been fully clarified [11]. It is therefore suggested that, because it is analogous to vasopressin, it promotes these effects through the same mechanisms [12], raising blood pressure through the activation of vascular V1 receptors and enhancing baroreflex through V1 receptors in the postrema area [12]. This regulation may play an important role in maintaining blood pressure, because through it vasopressin increases the baroreflex gain, thus preventing significant increases in blood pressure [12].

These facts show that, despite being a vasoconstrictor, when in direct contact with the vessel, this vasoconstriction is not completely translated into an increase in mean arterial pressure because it is minimized by reflex bradycardia induced by the action in the central nervous system [12]. However, studies have indicated possible effects of felypressin on the cardiovascular system, but there is still insufficient information on the clinical action of felypressin on possible cardiovascular changes within the safety anesthetic dose in normal patients.

Therefore, in view of the diversity of results found in literature regarding the cardiovascular dynamics of vasoconstrictors associated with local anesthetic bases and large-scale use of vasoconstrictors proposed in this study, it is important to evaluate the cardiovascular effects caused by different vasoconstrictors during third molar extraction.

## METHODS

This is an observational clinical study with 18 patients from the Oral Surgery Clinic of the Brazilian Association

of Dentistry (ABO-ES), totaling 36 monitored surgical procedures. This study was conducted in a period of one year. The research was performed with 01 modular vital signs cardioscope (DX-2010, DIXTAL Biomédica), from September 2007 to December 2008, according to the biweekly calendar of the corresponding course.

With approval of the research project by the ABO-ES Research Ethics Committee (20188.000-08) and signing the informed consent form, patients should meet the following inclusion criteria: patients without systemic alterations (ASA I), patients requiring extraction of the four third molars: 18, 28, 38 and 48. Exclusion criteria were: patients with history of systemic diseases, alcoholic patients, elderly patients or children and those with diseases that require continued medication.

Eighteen patients were randomly selected by screening performed in the ABO-ES oral surgery clinic with the need for extraction of four third molars: 18, 28, 38 and 48. Patients were random divided into two groups of 9 patients. In group I (GI), 9 patients were included to evaluate the cardiovascular effects of 2% lidocaine with adrenaline 1:100,000 compared to 3% prilocaine with felypressin 0.03 IU/ml. In group II (GII), another 9 patients were included, where the effects of 2% lidocaine with phenylephrine 1:2,500 were compared to 3% prilocaine with felypressin 0.03 IU/ml.

Each patient underwent two independent surgical procedures on different occasions on different sides (right and left). Each surgical procedure included the extraction of two third molars of the same mandibular quadrant. In one of the surgical procedures, 2% lidocaine associated with adrenaline or phenylephrine was used and in the other surgical procedure, 3% prilocaine hydrochloride with felypressin was used.

All information and guidelines were transmitted to volunteers, highlighting the non-requirement of permanence in the study and that no procedure that resulted in risk would be performed. For free consent, they signed the acceptance agreement.

Clinical interventions were performed by dental surgeons. The cardiac parameters were recorded pre-, trans- and post-surgery. A modular vital signs cardioscope (DX-2010, from DIXTAL Biomedical) was used. The sphygmomanometer was positioned in the proximal region of the left upper limb to obtain the values regarding systolic and diastolic pressures.

Digital pulse oximeter sensor was positioned on the right index finger for pulse and plasma oxygen saturation measurements.

The first data recording was performed 10 minutes before the beginning of the operative procedure. Subsequent records automatically followed 5-minute periods after the initial recording, which was performed during all operative intervention, and the patient was kept under observation and monitored for another 10 minutes after the end of the surgery. The total number of anesthetic cartridges used in each procedure was also recorded.

## Statistical Analysis

Descriptive analysis of data was performed through tables with mean and standard error of the mean. The comparison of parameters with study groups was performed through the paired t-test. The significance level adopted was 0.05 and the statistical package SPSS 15 (Social Package Statistical Science Version) was used for this analysis.

## RESULTS

From the applied methodology, the following results were obtained:

### Group I

**Table 1** below shows that in the pre and trans-operative periods, there were no significant variations between the mean heart rate in patients submitted to adrenaline in relation to those who received felypressin. However, in the postoperative period, felypressin presented a reduction ( $p < 0.05$ ) of 5.09% in mean heart rate in relation to adrenaline values. With respect to oxygen saturation, **Table 1** shows that, in the preoperative period, there was no significant variation between means of patients who received adrenaline in relation to those who received felypressin. However, felypressin presented a reduction ( $p < 0.05$ ) in the mean oxygen saturation of 1.24% in the trans-operative period and 2.5% ( $p < 0.05$ ) in the post-operative period in relation to adrenaline means.

**Table 2** below shows that in the pre-, trans- and post-operative periods, there were no significant variations between mean systolic blood pressure of patients submitted to adrenaline and those who received felypressin. Regarding diastolic blood pressure, data from **Table 2** shows that, in the pre-, trans- and post-operative periods, there were no significant variations between mean diastolic blood pressure

of patients submitted to adrenaline and those who received felypressin.

In group I, the mean number of cartridges used for adrenaline was lower by 30% ( $p < 0.05$ ) compared to the mean number of cartridges used for felypressin.

### Group II

Data in **Table 3** below show that, in the pre-, trans- and post-operative periods, there were no significant variations between the mean heart rate of patients undergoing phenylephrine compared to those receiving felypressin. In the pre- and trans-operative periods, there were no significant differences between mean oxygen saturation in patients submitted to phenylephrine in relation to those who received felypressin. However, in the post-operative period, felypressin presented a reduction ( $p < 0.05$ ) in the mean oxygen saturation of 2.83% in relation to phenylephrine values.

**Table 4** shows that the mean systolic blood pressure in patients submitted to phenylephrine was higher by 10.79% ( $p < 0.05$ ) in the trans-operative period and by 6.02% ( $p < 0.05$ ) in the post-operative period in relation to the mean systolic blood pressure of patients who received felypressin. In the pre-operative period, there was no significant variation between means of the corresponding values of phenylephrine and felypressin. Regarding diastolic blood pressure, data from xxx shows that the mean phenylephrine values were higher by 6.96% in the pre-operative period and 8.59% ( $p < 0.05$ ) in the post-operative period. However, in the post-operative period, there was no significant variation between means of phenylephrine and in relation to means of felypressin.

In group II, there was a small reduction of 2.17% in the amount of anesthetic used for phenylephrine compared to the amount used for felypressin. This variation was not significant.

**Table 1.** Mean heart rate (HR) and oxygen saturation (SatO<sub>2</sub>) values and number of cartridges used, comparing adrenaline to felypressin (group 1) and standard error of the mean (SEM), in pre- operative (pre), trans-operative (trans) and post-operative periods.

Group I	Cartridges	HR (bpm)			SatO <sub>2</sub> (%)			
		Pre	Trans	Post	Pre	Trans	Post	
Adrenaline (n=9)	Mean	4.2	84.6	85.3	84.6	97.7	97.9	97.8
	SEM	0.2	2.8	4.9	3.3	0.3	0.3	0.3
Felypressin (n=9)	Mean	6.0	84.8	82.7	80.5	97.7	96.7	95.4
	SEM	0.2	3.0	3.1	2.8	0.2	0.3	0.6

**Table 2.** Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) values and number of cartridges used, comparing adrenaline to felypressin (group I) and standard error of the mean (EPM) in pre- operative (pre), trans-operative (trans) and post-operative periods.

Group I	Cartridges	SBP (mmHg)			DBP (mmHg)			
		Pre	Trans	Post	Pre	Trans	Post	
Adrenaline (n=9)	Mean	4.2	122.5	126.7	121.3	77.5	77.0	75.6
	SEM	0.2	3.8	3.7	1.8	2.9	3.0	2.3
Felypressin (n=9)	Mean	6.0	123.5	122.7	117.7	76.3	79.8	78.4
	SEM	0.2	5.7	3.7	4.0	3.1	3.5	2.7

**Table 3.** Mean heart rate (HR) and oxygen saturation (SatO<sub>2</sub>) values and number of cartridges comparing phenylephrine to felypressin (group II) and standard error of the mean (SEM) in pre-operative (pre), trans-operative (trans) and post-operative periods.

Group II	Cartridges	HR (bpm)			SatO <sub>2</sub> (%)			
		Pre	Trans	Post	Pre	Trans	Post	
Phenylephrine (n=9)	Mean	4.5	82.0	75.3	81.1	98.5	98.0	98.0
	SEM	0.4	5.0	4.2	5.1	0.2	0.1	0.4
Felypressin (n=9)	Mean	4.6	79.4	78.4	80.1	98.1	97.5	95.3
	SEM	0.3	5.2	4.5	5.6	0.3	0.4	0.6

**Table 4.** Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) values and number of cartridges comparing phenylephrine to felypressin (group II) and standard error of the mean (SEM) in pre-operative (pre), trans-operative (trans) and post-operative periods.

Group II	Cartridges	SBP (mmHg)			DBP (mmHg)			
		Pre	Trans	Post	Pre	Trans	Post	
Phenylephrine (n=9)	Mean	4.5	119.4	127.3	117.9	69.1	75.8	74.6
	SEM	0.4	3.7	1.6	2.5	2.4	2.8	3.2
Felypressin (n=9)	Mean	4.6	117.1	114.9	111.2	64.6	69.8	69.9
	SEM	0.3	2.2	1.4	1.7	2.9	2.4	3.6

## DISCUSSION

In group I (adrenaline vs felypressin), felypressin presented a reduction ( $p < 0.05$ ) in the mean heart rate of 5.09% in the post-operative period in relation to adrenaline. This decrease in HR after administration of felypressin may be explained by the fact that this vasoconstrictor does not act on adrenergic receptors and has a modulating effect by potentiating the baroreflex and inhibiting sympathetic activity, thus promoting bradycardia and vasodilation. Similar results have been reported by [13].

With regard to oxygen saturation, felypressin presented a reduction ( $p < 0.05$ ) in mean oxygen saturation of 1.24% in the trans-operative period and 2.5% ( $p < 0.05$ ) in the post-operative period in relation to adrenaline. This reduction in oxygen saturation values can be explained by the use of prilocaine as the anesthetic salt associated with felypressin. Thus, although the risks of methemoglobinemia are associated with high doses of prilocaine, we believe that at lower doses, prilocaine metabolites would also reduce the blood's ability to carry oxygen, but in small proportions, inducing a slight decrease in the oxygen saturation values, as presented in our results.

Adrenaline, despite being a sympathomimetic amine, in this study it did not promote expressive systemic cardiovascular responses in normal patients, which confirms the reports of [2, 6, 14, 15, 16, 17] and even if in literature, felypressin is indicated as the anesthetic of choice and safer for patients with cardiovascular alterations, because it causes lower cardiovascular effects [18], the use of adrenaline is justified for most dental procedures and seems to be especially important in patients suffering from cardiovascular diseases [3, 5, 7, 19] because, in appropriate concentrations, the combination of adrenaline and local

anesthesia is a guarantee of adequate levels of anesthesia and hemostasis, thus avoiding pain and consequent stress to the patient [3, 8], since pain experienced during procedure may result in physiological changes that are much more significant than those caused by the addition of adrenaline to the anesthetic solution.

It is important to note that, although they did not show significant changes, the mean effects of adrenaline on systolic blood pressure were slightly higher in the trans- and post-operative periods compared to the mean effects of felypressin, but adrenaline induced a reduction in diastolic blood pressure in trans- and post-operative periods, which corroborates the results of [2, 13]. This decrease in diastolic blood pressure can be explained by the  $\beta_2$ -adrenergic effects of adrenalin, leading to dilation of blood vessels of the skeletal muscle, which contributes to the reduction of peripheral vascular resistance. This parallel decrease in peripheral vascular resistance, reflecting the systemic activation of  $\beta_2$  receptors, helps preventing dramatic hypertensive responses. Therefore, when used in therapeutic doses and avoiding intravascular administration, the pressure changes that may occur, such as elevated systolic pressure, are compensated by a reduction in peripheral vascular resistance and, consequently, a decrease in diastolic pressure [19].

In group II (phenylephrine vs felypressin), it was observed that felypressin presented a reduction in mean post-operative oxygen saturation ( $p < 0.05$ ) in relation to phenylephrine values. This result can be explained, as previously described for group I.

The mean systolic and diastolic blood pressure values were higher for vasoconstrictor phenylephrine in trans- and post-operative periods in relation to the mean felypressin values. These higher blood pressure levels may be justified by phenylephrine being a vasoconstrictor that essentially acts on

$\alpha$ -adrenergic receptors, allowing peripheral vasoconstriction with increased blood pressure, that is, phenylephrine, for not interacting with  $\beta_2$ -adrenergic receptors, which in turn, are vasodilators, has no modulatory effect on this increase in blood pressure.

Felypressin demonstrated lower blood pressure averages compared to phenylephrine. This can be explained by the fact that felypressin has a modulating effect on the increase in blood pressure, that is, despite being a vasoconstricting agent, it has a modulating effect by increasing the baroreflex gain through its action on V1 receptors in the postrema area [12]. Thus, whenever there is an increase in blood pressure, the baroreflex inhibits sympathetic activity, modulating this increase. Another factor that could explain the lower pressure response would be the fact that this substance undergoes immediate metabolism in plasma, once it has a polypeptide structure and undergoes plasma hydrolysis.

Thus, by analyzing the results of group II, it could be concluded that the non-adrenergic vasoconstrictor, felypressin, has been shown to be safer in relation to changes in blood pressure when compared to adrenergic vasoconstrictor, phenylephrine. This low-risk behavior of felypressin has also been reported by [4, 12, 18, 20], so felypressin is often recommended for patients with cardiovascular diseases. However, studies have pointed out possible effects of felypressin on the cardiovascular system of patients with cardiovascular disorders due to their tendency to contract coronary blood vessels causing an imbalance between oxygen supply and the demand of the myocardial tissues in these patients [11], which would be of high risk for angina patients.

Regarding the number of cartridges used during surgeries, it was observed that in group I, the mean number of cartridges used for adrenaline was lower by 30% ( $p < 0.05$ ) compared to the average number of cartridges used for felypressin. This variation was statistically significant, indicating that the anesthetic lidocaine with adrenaline required a lower anesthetic volume to achieve the required anesthesia compared to anesthetic prilocaine with felypressin during dental surgeries, confirming an increased anesthetic potency for the anesthetic lidocaine with adrenaline, even taking into account the highest Prilocaine concentration of 3% compared to 2% lidocaine. In group II, the mean number of cartridges used for lidocaine with phenylephrine was slightly lower than the mean number of cartridges used for prilocaine with felypressin, but this variation was not significant. Thus, for these two anesthetic combinations evaluated in group II, the volume of anesthetic required for adequate anesthesia during the surgeries was similar.

## CONCLUSION

From these results we can conclude that felephrine may lead to increased SBP and DBP and felipressin generated a reduction in HR and  $\text{SatO}_2$  all these changes well tolerated by ASA I patients but these parameters should be evaluated with caution in patients with systemic alterations.

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