Effect of 4% articaine and 2% lidocaine both with 1:100,000 epinephrine on hemodynamic changes in impacted mandibular third molar surgery: prospective, double-blinded, randomized clinical trial

Efecto de 4% de articaína y 2% de lidocaína, ambos con epinefrina 1: 100,000 sobre los cambios hemodinámicos en la cirugía del tercer molar mandibular impactada: ensayo clínico prospectivo, doble ciego, aleatorizado

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Abstract

Hemodynamic effect of local anesthetic should be investigated to prevent unwanted complications. The present study assessed the hemodynamic alterations after injecting two of the most commonly used local anesthetic formulations for impacted mandibular third molar surgery. A prospective, double-blinded, randomized clinical trial were designed, and patients that attended the oral and maxillofacial surgery department for surgical removal of impacted mandibular third molar were asked to participate. Patients were divided into two groups and randomly received one of the two interventions; 2% lidocaine with 1:100,000 epinephrine (LE) and group 2: 4% articaine with 1: 100,000 epinephrine (AE). Pulse rate, oxygen saturation, and systolic/diastolic blood pressure were assessed at three different times: before the procedure, five minutes after injecting local anesthetics, and after finishing the surgery. Eighty patients between the age of 18 to 45 years old participated in the study which 44 (55%) were female, and 36 (45%) male. The pulse rate significantly increased when comparing three different measurement intervals for each local anesthetic. Oxygen saturation in the LE group was statistically different comparing each interval, but there was no significant difference in the AE group. There were changes in systolic and diastolic blood pressure at each measurement point, but it was not statistically significant. There was no significant difference in hemodynamic changes between the two groups. Hemodynamic alteration after local anesthetic administration should be expected. The two formulations were safe and showed no statistically significant hemodynamic changes in healthy patients.

Keywords: Articaine, blood pressure, epinephrine, pulse rate, hemodynamic, lidocaine

Resumen

El efecto hemodinámico de la anestesia local debe investigarse para prevenir complicaciones no deseadas. El presente estudio evaluó las alteraciones hemodinámicas después de inyectar dos de las formulaciones anestésicas locales más utilizadas para la cirugía del tercer molar mandibular impactada. Se diseñó un ensayo clínico prospectivo, doble ciego, aleatorizado, y se solicitó la participación de los pacientes que acudieron al departamento de cirugía oral y maxilofacial para la extracción quirúrgica del tercer molar mandibular impactado. Los pacientes se dividieron en dos grupos y recibieron aleatoriamente una de las dos intervenciones; 2% de lidocaína con 1: 100,000 de epinefrina (LE) y grupo 2: 4% de articaína con 1: 100,000 de epinefrina (AE). La frecuencia del pulso, la saturación de oxígeno y la presión arterial sistólica / diastólica se evaluaron en tres momentos diferentes: antes del procedimiento, cinco minutos después de inyectar anestésicos locales y después de terminar la cirugía. Ochenta pacientes entre las edades de 18 a 45 años participaron en el estudio, de los cuales 44 (55%) eran mujeres y 36 (45%) hombres. La frecuencia del pulso aumentó significativamente al comparar tres intervalos de medición diferentes para cada anestésico local. La saturación de oxígeno en el grupo LE fue estadísticamente diferente comparando cada intervalo, pero no hubo diferencias significativas en el grupo AE. Hubo cambios en la presión arterial sistólica y diastólica en cada punto de medición, pero no fue estadísticamente significativa. No hubo diferencias significativas en los cambios hemodinámicos entre los dos grupos. Se debe esperar una alteración hemodinámica después de la administración anestésica local. Las dos formulaciones fueron seguras y no mostraron cambios hemodinámicos estadísticamente significativos en pacientes sanos.

Palabras clave: articaína, presión arterial, epinefrina, pulso, hemodinámica, lidocaína.

Introduction

The two most commonly used local anesthetic in dental surgeries are 2% lidocaine and 4% articaine. The addition of vasoconstrictor agents to these local anesthetics contributes to many beneficial effects such as depth and duration of anesthesia, decreasing systemic toxicity, and increasing hemostasis during surgery. These beneficial effects are achieved through counteracting the vasodilation effects of induced with local anesthetic agents[1,2]. Thus, the combination is widely justified and commonly used in dental practice[3]. The most common vasoconstrictor agent used in conjunction with lidocaine and articaine is epinephrine[4]. Epinephrine has a potent effect on beta receptors, although, both alpha and beta receptors are affected. Vasoconstrictor effect of epinephrine results from stimulating alpha one receptors in peripheral blood vessels[5]. While beta one receptors stimulation increases pulse rate and blood pressure[6]. Progressive administration of epinephrine at higher doses than those used in dentistry leads to an increase in cardiovascular activity and oxygen consumption[7]. The effect of epinephrine combined with fear and anxiety before surgery, pain, and discomfort during and after surgery can cause a further release of endogenous catecholamines with the consequential rise in blood pressure, pulse rate, and even arrhythmia[1,8,9].

Lidocaine is the most commonly used local anesthetic agent for pain control in dentistry, and it has satisfactory pharmacokinetics and low toxicity 4. Articaine, similar to lidocaine, is another local amide anesthetic and since its introduction into the market in 1976 many authors advocated superior efficacy to other moderate and short duration local anesthetics[10-13]. Articaine has benefited from an aromatic ring with a thiophene ring that enhances the lipid solubility and increases the potency of the solution up to 1.5 times more than that of lidocaine. Another advantage of incorporating an ester group in articaine molecular structure is dual metabolic routes of elimination both by liver microsomal enzymes and plasma esterases[14]. Longer duration and excellent distribution through bone popularized the articaine in the field of dentistry[15-19]. Although numerous studies appraised the efficacy of different articaine formulations, information on hemodynamic effects are still scarce. Thus, the present study aimed to compare the hemodynamic impact of two local anesthetic formulations in impacted mandibular third molar surgery.

Materials and methods

Before implementing the study, the protocol was approved by the institutional review board (IR.SUMS.REC.1398.516) and registered in a clinical trials registry (https://www.irct.ir/, Trial ID: 41125).

Sample size estimation

The sample size estimated using previous studies and using a power calculation of 0.9 with 1.2 estimated standard deviation. With the alpha level of significance of 0.05, the minimum number of samples in each group should be 38; thus, we needed at least 40 patients in each group.

Patients recruitment

Patients attended the Oral and Maxillofacial Surgery department with impacted mandibular third molars surgery participate in the study. The operating surgeon has clearly explained the entire procedure, including the advantages and disadvantages of their participation in the study in a quiet relaxing room. Patients were also asked to sign an informed consent.

Inclusion criteria were patients with impacted mandibular third molar in Level A and Class 1, according to the Pell and Gregory classification[20]. Exclusion criteria were: patients with known hypertension (BP<140/90 mmHg) or cardiovascular diseases, compromised immunity, systemic severe illness (ASA III,IV)[21], active infection or inflammation, renal disease, gastrointestinal bleeding or ulcerations, known allergic reaction to lidocaine or articaine or epinephrine, preoperative use of NSAIDs (known to increase blood pressure)[22], allergy to NSAIDs or identified asthmatic reaction that contraindicate postoperative prescription of NSAID, pregnancy or current lactation, sickle cell anemia, congenital methemoglobinemia, hyperthyroidism. We also excluded the patients who required more than two cartridges for adequate anesthesia before or during the surgery or if the operation was complicated and duration of surgery exceeded 40 minutes (due to any reason such as lack of patient cooperation or procedural difficulties).

The randomization process followed the guideline of the CONSORT statement[25]. Either 2% lidocaine with 1:100,000 epinephrine (LE) or 4% articaine with 1:100,000 epinephrine (AE) was distributed between two groups using a set of numbered sealed envelopes. Contents of the local anesthetic cartridges blinded to the surgeon and patients by using opaque adhesive coverage to ensure that each patient had an equal chance of receiving one of two local anesthetics.

Surgical Procedure

Patients were instructed to have light breakfast and avoid drinking alcohol or coffee at least 24 hours before

the surgery. All of the surgical procedure was executed in a quiet and friendly environment without any premedication. Each patient was operated by an experienced oral and maxillofacial surgeon with 15 years of experience. The same surgical technique used for all of the participants. Patients were asked to rinse with 0.12% chlorhexidine mouthwash for 60 seconds, and perioral skin prepared with povidone-iodine and draped with disposable surgical covering sheets. Each patient received a randomly numbered, sealed envelope containing two local anesthetic solution covered with an opaque adhesive. The anesthetic solution used for inferior alveolar nerve, lingual nerve, and buccal nerve regional nerve block after negative aspiration. Each cartridge contained 1.8ml of either local anesthetic, and patients with inadequate anesthesia received the additional anesthetic solution and were excluded from the study. The surgical procedure followed a standard surgical technique with similar instruments for all of the patients. The surgeon used Sulcular incision with distal releasing incision and raised a mucoperiosteal flap. Surgical bur is used for bony osteotomy and tooth sectioning under copious irrigation in sterile normal saline. Duration of surgery was measured from the first incision to the last suture. Procedures longer than 40 minutes due to lack of patients cooperation or instrument shortcomings or the need for other instruments were excluded from the study. After tooth removal, copious irrigation was done to remove any debris and flap repositioned and incision suture with silk 3-0.

Postoperative instruction was given verbally and reinforced in writing. Patients were instructed to use analgesics per needed and use a cold compress for 48 hours. Patients were reassured that moderate swelling is anticipated. The patients were advised to use a soft diet and avoid spitting, drinking with a straw, hot foods and drinks, and rinsing for 24 hours. Patients were asked for meticulous oral hygiene using 0.12% chlorhexidine with cotton swabs or ultra-soft surgical brushes twice daily until the removal of sutures. Patients were also asked to report any complications such as progressive pain, swelling, trismus, dysphagia, dyspnea, malaise, and malodor to the screening section of the department hospital for appropriate management.

Hemodynamic monitoring of the patients

Pulse rate, oxygen saturation, and systolic and diastolic blood pressure, evaluated preoperatively in a quiet relaxing room (T0). The second measurement acquired 3 minutes after local anesthetic injections (T1), and the third measurement was obtained after the last suture (T2), similar to Abu-Mosta fa et al[24] study. All the measurements were automated and non-invasive using the Microlife® BP A200 Plus (Microlife AG, Widnau, Switzerland) and Pulse oximeter OxyTrue A (Bluepoint Medical, Selmsdorf, Germany).

Statistical Analysis: Statistical package for the social sciences (ver. 19, Chicago, IL) was used for the analysis of the measurements. After testing for normality of the data, paired student t-test used to find any significant difference between the groups. P-value was 0.05.

Results

A total of 80 patients participated in the study (44 females and 36 males). There were 40 patients in each group, which in LE 24 patients were female, and 16 patients were male. In AE, 21 patients were female, and 19 patients were male. The mean age of participants in LE and AE were 33±7.09 and 32±7.25, respectively. There were no significant differences between LE and AE in age (p=0.85), gender (p=0.47), and weight (p=0.31).

Mean systolic, diastolic, pulse rate, and oxygen saturation at three different measurement times are presented in table 1.

Table 1. Hemodynamic parameters at different measurement times (n=40).

Hemodynamic parameters (units of measurement)	Groups	Measurement times		
		T0	T1	T2
Systolic blood pressure (mmHg)	LE	126.69±8.50	124.77±9.50	126.77±3.20
	AE	127.20±7.11	129.34±7.36	129.77±6.07
Diastolic blood pressure (mmHg)	LE	84.51±4.76	85.80±4.10	84.49±9.13
	AE	84.40±5.44	86.57±4.68	87.49±4.18
Pulse rate (pulse per minute)	LE	75.91±5.27[a,b]	77.20±5.43[a]	78.49±6.31[b]
	AE	77.40±6.23[c]	79.23±5.81[c,d]	77.49±5.97[d]
Oxygen saturation (SaO2)	LE	98.86±0.35[e,f]	98.66±0.48[e]	98.66±0.48[f]
	AE	98.80±0.40	98.77±0.42	98.91±0.28

*LE: 2%lidocaine with 1: 100,000 epinephrine, AE: 4%articaine with 1: 100,000 epinephrine, T0: before administering the local anesthetics, T1: three minutes after administering the local anesthetic, T2: after the last suture.

** Values with the same superscript letters were statistically different at P < .05.

There was no significant difference in systolic blood pressure at various time measurements in LE and AE (p=0.68) and between the two groups (p=0.24). **Figure 1** shows how systolic blood pressure changed at different measurement points.

Figure 1

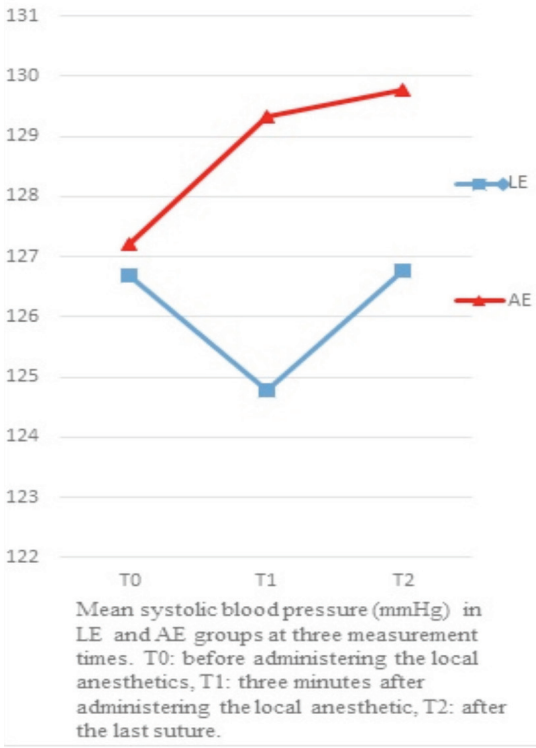

Figure 1. Changes in mean systolic blood pressure at different time measurements Mean diastolic blood pressure at different time measurements and between the two groups was no statistically significant (p=0.15, p=0.35, respectively). The changes in mean diastolic blood pressure demonstrated in figure 2.

There were significant differences in pulse rate in LE groups at different measurement points (p=0.001). The difference was between the mean pulse rate before and three minutes after injecting the local anesthetic (p=0.03), and before and the end of the procedure (p=0.00). There was no significant difference between three minutes after local anesthetic injection and the end of the procedure (p=0.10).

The pulse rate in AE groups also showed significant differences at different time measurements (p=0.01). The mean pulse rate before local anesthetic injection compared to three minutes after administering the AE (p=0.00), and three minutes after local anesthetic injection compared with the last suture (p=0.04) was significantly different. However, there were no differences when comparing local anesthetic injection compared to the end of the procedure measurement point (p=0.99). The change in pulse rate between the AE and LE was not significantly different (p=0.52).

The oxygen saturation in the LE group at a different time showed significant differences (p=0.04). The difference was between the time measurements before the local anesthetic injection compared to T1 (p=0.01), and T2 (p=0.03). The oxygen saturation at AE groups was not significantly different at different time measurements (p=0.17). Also, there were no statistically significant differences in oxygen saturation between the two groups (p=0.97).

The changes in the pulse rate and oxygen saturation at different time measurements are shown in table 1.

Discussion

This study investigated the effect of two different local anesthetic formulation on the hemodynamic status of the patients undergone impacted third molar surgeries. The hemodynamic monitoring was performed before, three minutes after injection, and at the end of the procedure. The hemodynamic effect of epinephrine is known to occur three minutes after the injection. The intravascular injection must be avoided to prevent irregular variations in the hemodynamic status of the patients. Thus, aspiration before local anesthetic administration was performed, and if sufficient stream of blood was mixed with the anesthetic solution, the needle was withdrawn until negative aspiration was achieved. The percentage of blood to be considered positive aspiration varies in literature and range between 8.6% to 22%[26]. Positive aspiration is more likely to occur in nerve block compared to infiltration technique[24]. In the present study, positive aspiration encountered in 13 patients (16.25%) of inferior alveolar nerve block injections, and no positive aspiration was observed in local infiltrations around the impacted third molars.

Previous studies evaluated the effect of epinephrine concentration on hemodynamic alterations with variable results. Cardiovascular impact of 4% articaine with 1:100,000 epinephrine compared to 4% articaine with 1:200,000 when used at its maximum recommended dosage (seven cartridges or 476 mg of articaine) resulted in significant systolic blood pressure elevation after 10 minutes of administration. In the present study, there were no significant differences in systolic blood pressure at each time intervals and between the two groups. There was a reduction in systolic blood pressure after AE injection, but it was not significant. The diastolic blood pressure has also decreased after injection in the AE group and at the end of the procedure, but it was not significant at different measurement intervals and with the LE group.

The result is consistent with Abu-Mustafa et al 24 and Hersh et al 27 study that found a decrease in diastolic blood pressure even after 30 minutes of injection. The beta-2 receptors stimulation by epinephrine could be the cause of the vasodilation of blood vessels in the skeletal muscle[24].

Similar to the present study, Santos et al 29 demonstrated no significant changes in systolic or diastolic blood pressure with different amounts of epinephrine in combination with articaine in third molar surgery. A series of studies by de Morias et al[1,2,30].comparing multiple formulations of local anesthetics and their effects on hemodynamic changes showed no significant differences in hemodynamic status in healthy patients.

Kämmerer et al 31.examined five different amounts of epinephrine concentration and articaine plain by using infiltration technique and found no significant alterations in pulse rate, blood pressure, or oxygen saturation.

The controversies between different studies in the literature might be due to the different amounts of local anesthetic used. Abu-Mustafa et al. used 3.6 ml of three different local anesthetics containing 0.027 mg, 0.036 mg, and 0.018 mg of epinephrine and found a significant difference in systolic blood pressure[24]. Others used 2.7 ml of a local anesthetic containing 0.027 mg, or 0.0135 mg of epinephrine[1,2,30,31], and Kämmerer et al. used the only 1.7ml of local anesthetic[31]. It seems that a small volume of epinephrine has relatively transient cardiovascular effects in healthy people[28]. When more substantial amounts of epinephrine are used by Hersh et al.[26] (0.119 mg or 0.0595 mg), and Abu-Mustafa et al[24] (0.027 mg, 0.036 mg, 0.018 mg) stimulation of alpha and beta-1 adrenergic receptors has contributed to changes in hemodynamic parameters.

Hersh et al and de Morais et a[1], reported an increase in pulse rate after local anesthesia administration of 4% articaine with 1:100,000 epinephrine cause significant rise as compared to 4% articaine with 1:200,000 epinephrine. Similarly, LE was associated with a more considerable increase in pulse rate than 4% articaine with 1:200,000 epinephrine[1,24].

In our study, a significant increase in pulse rate observed after injecting both AE and LE at each measurement interval. The current result might be because both groups had 1:100,000 epinephrine. On the other hand, Santos et al. found no significant increase in pulse rate, and the type of local anesthetic use d29 did not affect the differences[29].

We found a significant decrease in oxygen saturation in the LE group at different measurement points. While Abu-Mustafa et al. found a similar decline in oxygen saturation, Santos et al. and de Morais et al. found an increase in oxygen saturation after injection of 4% articaine with epinephrine concentration of 1:100,000 or 1:200,000[2,24,29].

Literature shows the insignificant effect of various epinephrine concentrations on local anesthetic efficacy. Similar success in inferior alveolar nerve block observed when 2% lidocaine either with 1:100,000 or 1:200,000 epinephrine has been compared[30], Even the pulpal anesthesia was insignificant when 2% lidocaine with either 1:80,000 or 1:100,000 is used by infiltration injections[31]. Likewise, 4% articaine with either 1:100,000 or 1:200,000 showed the similar success on pulpal anesthesia following infiltration, nerve block, and intraosseous injections[32]. Also, the two formulations 4% articaine with either 1:100,000 or 1:200,000 produced comparable anesthesia for periodontal surgery[36], as well as anesthesia required for lower third molar extraction regarding anesthesia properties, intraoperative hemostasis, and lack of influence on hemodynamic parameters[26,27].

Despite that every attempt should be made to avoid intravascular injections of local anesthetic by performing an aspiration, false-negative results are unavoidable[36]. The needle bevel could be in direct contact against the vascular endothelium, which blocks the needle lumen on aspiration. Also, the extreme intense aspiration can cause the collapse of a minor vessel and results in false-negative aspiration[25]. logically, the less vasoconstrictor in anesthetic solution could be safer, especially for patients at risk of cardiovascular problems[37]. Therefore, it is suggested to use 4% articaine with 1:200,000 epinephrine instead of 4% articaine with 1:100,000 epinephrine for lower third molar surgeries, as well as pulpal anesthesia[24,29,33,34,36,37]. Epinephrine concentration seems to be the most influential factor in hemodynamic changes. The same concentration of epinephrine with 2% lidocaine and 4% articaine has no significant difference in hemodynamic parameters.

Conclusions

In summary, changes in hemodynamic parameters such as pulse rate and oxygen saturation are expected at different measurements time with either of these two formulations, but there is no difference between the two local anesthetics.

Clinical significance: The two formulations were safe and showed no statistically significant hemodynamic changes in healthy patients.

References

1. De Morais HHA, Holanda Vasconcellos RJ, De Santana Santos T, et al. Clinical study of hemodynamic changes comparing 4% articaine hydrochloride with 1:100,000 and 1:200,000 epinephrine. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;**116**(1):e14–22.
2. De Morais HHA, De Santana Santos T, Da Costa Araújo FA, et al. Hemodynamic changes comparing 2% lidocaine and 4% articaine with epinephrine 1: 100,000 in lower third molar surgery. J Craniofac Surg. 2012;**23**(4):1204–11.
3. Haas DA. An update on local anesthetics in dentistry. J Can Dent Assoc. 2002;**68**(9):546–51.
4. Daubländer M, Müller R, Lipp MD. The incidence of complications associated with local anesthesia in dentistry. Anesth Prog. 1997;**44**(4):132–41.

5. Brown RS, Rhodus NL. Epinephrine and local anesthesia revisited. Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology. 2005;**100**(4):401–8.

6. Cecanho R, De Luca LA, Ranali J, et al. Cardiovascular effects of felypressin. Anesth Prog. 2006;**53**(4):119–25.

7. Sung BH, Robinson C, Thadani U, et al. Effects of 1-epinephrine on hemodynamics and cardiac fiinction in coronary disease: Dose-response studies. Clin Pharmacol Ther. 1988;**43**(3):308–16.

8. Silvestre FJ, Verdú MJ, Sanchís JM, et al. Effects of vasoconstrictors in dentistry upon systolic and diastolic arterial pressure. Med Oral. n.d.;**6**(1):57–63.

9. Silvestre F, Salvador-Martínez I, Bautista D, et al. Clinical study of hemodynamic changes during extraction in controlled hypertensive patients. Med Oral Patol Oral y Cir Bucal. 2011;**16**(3):e354–8.

10. Daubländer M, Müller R, Lipp MD. The incidence of complications associated with local anesthesia in dentistry. Anesth Prog. 1997;**44**(4):132–41.

11. Kambalimath DH, Dolas RS, Kambalimath H V, et al. Efficacy of 4 % Articaine and 2 % Lidocaine: A clinical study. J Maxillofac Oral Surg. 2013;**12**(1):3–10.

12. Sancho-Puchades M, Vílchez-Pérez ÁM, Valmaseda-Castellón E, et al. Bupivacaine 0.5 % versus articaine 4 % for the removal of lower third molars. A crossover randomized controlled trial. Med Oral Patol Oral Cir Bucal. 2012;**17**(3).

13. Pellicer-Chover H, Cervera-Ballester J, Sanchis-Bielsa JM, et al. Comparative split-mouth study of the anesthetic efficacy of 4% articaine versus 0.5% bupivacaine in impacted mandibular third molar extraction. J Clin Exp Dent. 2013;**5**(2):66–71.

14. Gregorio LVL, Giglio FPM, Sakai VT, et al. A comparison of the clinical anesthetic efficacy of 4% articaine and 0.5% bupivacaine (both with 1:200,000 epinephrine) for lower third molar removal. Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology. 2008;**106**(1):19–28.

15. Malamed SF, Gagnon S, Leblanc D. Efficacy of articaine: A new amide local anesthetic. J Am Dent Assoc. 2000;**131**(5):635–42.

16. Senes AM, Calvo AM, Colombini-Ishikiriama BL, et al. Efficacy and Safety of 2% and 4% Articaine for Lower Third Molar Surgery. J Dent Res. 2015;**94**(September):166S-173S.

17. Beena S, Bhargava D, Gurjar P, et al. Comparison of latency and efficacy of twin mix and modified twin mix in impacted mandibular third molar surgery – A Preliminary Randomized Triple Blind Split Mouth Clinical Study. J Stomatol Oral Maxillofac Surg. 2019. [Epub ahead of print]

18. Saralaya S, Adirajaiah SB, Anehosur V. 4% Articaine and 2% Lignocaine for Surgical Removal of Third Molar by Mandibular Nerve Block: A Randomized Clinical Trial for Efficacy and Safety. J Maxillofac Oral Surg. 2019 Sep;18(3):405-411.

19. Zhang A, Tang H, Liu S, et al. Anesthetic Efficiency of Articaine Versus Lidocaine in the Extraction of Lower Third Molars: A Meta-Analysis and Systematic Review. J Oral Maxillofac Surg. 2019;**77**(1):18–28.

20. Jayasuriya NSS, Jayasundara JH, Pallegama RW. Efficacy of buccal infiltration anaesthesia with articaine for extraction of mandibular molars: a clinical trial. Br J Oral Maxillofac Surg. 2019;**57**(3):296–7.

21. Pell GJ GB. Impacted mandibular third molars classification and modified technique for removal. Dent Dig. 1993;**39**:330–8.

22. Doyle DJ, Garmon EH. American Society of Anesthesiologists Classification (ASA Class). StatPearls Publishing; 2019.

23. Snowden S, Nelson R. The Effects of Nonsteroidal Anti-Inflammatory Drugs on Blood Pressure in Hypertensive Patients. Cardiol Rev. 2011;**19**(4):184–91.

24. Abu-Mostafa N., Al-Showaikhat F., Al-Shubbar F., Al-Zawad K., Al-Banawi F. Hemodynamic changes following injection of local anesthetics with different concentrations of epinephrine during simple tooth extraction: A prospective randomized clinical trial. *J Clin Exp Dent* 2015;**7**(4):e471–6. Doi: 10.4317/jced.52321.

25. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;**10**(1):28–55.

26. Delgado-Molina E, Tamarit-Borrás M, Berini-Aytés L, et al. Evaluation and comparison of 2 needle models in terms of blood aspiration during truncal block of the inferior alveolar nerve. J Oral Maxillofac Surg. 2003;**61**(9):1011–5.

27. Abu-Mostafa N, Al-Showaikhat F, Al-Shubbar F, et al. Hemodynamic changes following injection of local anesthetics with different concentrations of epinephrine during simple tooth extraction: A prospective randomized clinical trial. J Clin Exp Dent. 2015;**7**(4):e471–6.

28. Hersh E V, Giannakopoulos H, Levin LM, et al. The pharmacokinetics and cardiovascular effects of high-dose articaine with 1:100,000 and 1:200,000 epinephrine. J Am Dent Assoc. 2006;**137**(11):1562–71.

29. Haas DA. An Update on Local Anesthetics in Dentistry (Mise à jour sur les anesthésiques locaux utilisés en dentisterie). J Can Dent Assoc. 2002;**68**(9):546–51.

30. Santos CF, Modena KCS, Giglio FPM, et al. Epinephrine Concentration (1:100,000 or 1:200,000) Does Not Affect the Clinical Efficacy of 4% Articaine for Lower Third Molar Removal: A Double-Blind, Randomized, Crossover Study. J Oral Maxillofac Surg. 2007;**65**(12):2445–52.

31. De Morais HHA, De Santana Santos T, Da Costa Araújo FA, et al. Hemodynamic changes comparing lidocaine HCl with epinephrine and articaine hcl with epinephrine. J Craniofac Surg. 2012;**23**(6):1703–8.

32. Kämmerer PW, Seeling J, Alshihri A, et al. Comparative clinical evaluation of different epinephrine concentrations in 4 % articaine for dental local infiltration anesthesia. Clin Oral Investig. 2014;**18**(2):415–21.

33. Aggarwal V, Singla M, Miglani S, et al. Comparison of the anaesthetic efficacy of epinephrine concentrations (1 : 80 000 and 1 : 200 000) in 2% lidocaine for inferior alveolar nerve block in patients with symptomatic irreversible pulpitis: a randomized, double-blind clinical trial. Int Endod J. 2014;**47**(4):373–9.

34. Kanaa MD, Whitworth JM, Meechan JG. A Comparison of the Efficacy of 4% Articaine with 1:100,000 Epinephrine and 2% Lidocaine with 1:80,000 Epinephrine in Achieving Pulpal Anesthesia in Maxillary Teeth with Irreversible Pulpitis. J Endod. 2012;**38**(3):279–82.

35. Moore PA, Boynes SG, Hersh E V, et al. The anesthetic efficacy of 4 percent articaine 1:200,000 epinephrine. J Am Dent Assoc. 2006;**137**(11):1572–81.

36. McEntire M, Nusstein J, Drum M, et al. Anesthetic Efficacy of 4% Articaine with 1:100,000 Epinephrine versus 4% Articaine with 1:200,000 Epinephrine as a Primary Buccal Infiltration in the Mandibular First Molar. J Endod. 2011;**37**(4):450–4.

37. Pereira LAP, Groppo FC, Bergamaschi C de C, et al. Articaine (4%) with epinephrine (1:100,000 or 1:200,000) in intraosseous injections in symptomatic irreversible pulpitis of mandibular molars: anesthetic efficacy and cardiovascular effects. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;**116**(2):e85–91.

38. Moore PA, Doll B, Delie RA, et al. Hemostatic and Anesthetic Efficacy of 4% Articaine HCl With 1:200,000 Epinephrine and 4% Articaine HCl With 1:100,000 Epinephrine When Administered Intraorally for Periodontal Surgery. J Periodontol. 2007;**78**(2):247–53.