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ORIGINAL ARTICLE

Efficacy and safety of intraseptal and periodontal ligament anesthesia achieved by computer-controlled articaine + epinephrine delivery: a dose-finding study

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Abstract
Objectives The main purpose of this study was to evaluate the dose-dependent anesthetic efficacy of the intraseptal anesthesia (ISA) and periodontal ligament anesthesia (PLA) obtained with different volumes of 4 % articaine and 1:100,000 epinephrine (Ar + Ep) in human mandibular premolars, using a computer-controlled local anesthetic delivery system (CCLADS). The safety profile of Ar + Ep was also studied by investigating the stability of cardiovascular parameters.
Material and methods One hundred and eighty randomly selected healthy volunteers (ASA I) entered the single-blinded study to receive 16 mg+4 μg, 24 mg+6 μg, and 32 mg+8 μg of Ar + Ep, obtained with different volumes (0.4, 0.6, and 0.8 ml, respectively), for the ISA and PLA. Success rate, onset, and duration of profound pulpal anesthesia were evaluated by the electrical pulp tester, while the width of the anesthetic field and duration of soft tissue anesthesia were recorded using the pinprick testing. A monitor was used for the measurement of cardiovascular parameters.
Results A dose-dependent duration of pulpal and soft tissue anesthesia was obtained only by the ISA. Success rate, duration of both pulpal and soft tissue anesthesia, and its width were significantly better in the ISA compared with the PLA. No significant cardiovascular changes were seen in both groups.
Conclusions It can be suggested that 0.6 and 0.8 ml of 4 % Ar + 1:100,000 Ep, delivered by CCLADS, offer high success rate and effective clinical parameters of ISA as a primary anesthesia.
Clinical relevance It seems that dental procedures requiring profound pulpal, bone, and soft tissue anesthesia could be effectively and safely obtained by mentioned anesthetic protocol.

Keywords Articaine with epinephrine · Efficacy and safety · Intraseptal anesthesia · Periodontal ligament anesthesia · CCLADS

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Introduction

Local anesthesia for posterior mandibular teeth is usually obtained by the inferior alveolar nerve block (IANB). However, this regional block, due to anatomical consideration, pathology, or anesthetic techniques and principles, is followed with different types of success [1]. When IANB fails in producing an effective pulpal, bone, and soft tissue anesthesia, there is a need for supplemental anesthesia, such as the periodontal ligament anesthesia (PLA) or intraseptal anesthesia (ISA) [2–4]. Both the PLA and ISA could be also used as primary anesthesia in different indications of restorative dentistry, periodontal treatments, and oral surgery [5–10]. Traditionally, these anesthetic techniques have been performed with a high-pressure syringe, which allows

placement of local anesthetic solution directly into the cancellous bone adjacent to the tooth to be anesthetized. Under the high-pressure condition, a fairly high success rate of pulpal anesthesia, ranging from 42 to 86 %, has been reported for the PLA and ISA (0.4 to 0.8 ml of 2 % lidocaine with epinephrine 1:100,000) when used as primary techniques for healthy mandibular teeth [8, 11, 12].

The new approach in the local application of drugs into oral tissue is the introduction of a controlled delivery system and, for local anesthetics, a computer-controlled local anesthetic delivery system (CCLADS) is an example. Benefits in using controlled delivery approaches include improved pharmacokinetic response, greater ability to localize the drug adjacent to the place of action, and more control of local concentration at a lower total dosage. Comparing reported studies concerning the high-pressure local anesthetic injection and CCLADS, there are data showing a lower pain level for needle insertion, less postoperative discomfort scores, and no changes in heart rate (HR) using the CCLADS [10, 13–16].

Having in mind that both of these local anesthetic techniques are intraosseous, their success primary depends on the penetration of local anesthetic through the alveolar bone. Concerning the ability of diffusion through bone among amide local anesthetics, articaine represents an exception. Namely, unlike other amide-type local anesthetics, articaine contains a thiophene ring as the aromatic moiety and aromatic methoxycarbonyl substituent. The presence of the methoxycarbonyl-substituted thiophene is generally accepted to contribute to a higher lipophilicity of articaine compared to other amino amide local anesthetics [17], which give articaine a better ability to penetrate bone and other tissues [18, 19]. A clinical consequence of the high lipophilicity of articaine is evidenced on its high anesthetic success rate compared to lidocaine in anesthetizing mandibular and maxillary posterior teeth by buccal infiltration [20–22].

It is interesting to note that only one prospective randomized, double-blind study of the anesthetic efficacy of 4 % articaine with 1:100,000 epinephrine for PLA administered with CCLADS for mandibular posterior teeth exists [12]. Due to deficiency of data concerning the dose dependency of the local anesthetic effect of articaine with epinephrine as a primary technique for PLA and ISA with CCLADS for posterior mandibular teeth, the following aims were formed for our study:

1. Evaluation of a dose dependency for clinical parameters of PLA and ISA, obtained with computer-controlled delivery of 16 mg+4 μg, 24 mg+6 μg, and 32 mg+8 μg articaine (4 %) + epinephrine (1:100,000), obtained with different volumes of 0.4, 0.6, and 0.8 ml, respectively;
2. Evaluation of a dose dependency for cardiovascular changes (systolic and diastolic blood pressure [SBP and DBP], mean arterial pressure [MAP], and HR) after PLA and ISA, obtained with computer-controlled delivery of 16 mg+4 μg, 24 mg+6 μg, and 32 mg+8 μg articaine (4 %) + epinephrine (1:100,000), obtained with different volumes of 0.4, 0.6, and 0.8 ml, respectively.

Materials and methods

Study population

One hundred and eighty healthy volunteers (ASA I physical status) enrolled in this single-center, single-blinded, randomized clinical study. Before undergoing any study procedures, all subjects signed an informed consent, after they were informed of the details of the study protocol and the aim of the study. The study was approved by the Ethical Committee of the Faculty of Dentistry, University of Belgrade (No. 36/3).

Subjects had to be between 20 and 35 years of age and have no contraindications to the administration of local anesthetic and its associated vasoconstrictor. All patients passed through the screening visit which included a medical examination to confirm the health status of participants. In addition, medical examination excluded subjects who were smokers or who had known or suspected alcohol or drug dependence. For the subjects to continue participation in the study, a complete dental examination was done. Subjects who had any dental treatment or had taken any medication within the last 48 h were excluded from the study. Clinical examinations indicated that all the tested teeth were free of caries, large restorations, and acute periodontal disease and none had a history of tooth trauma or sensitivity. All elected volunteers underwent ultrasound and root scaling periodontal treatment and received oral hygiene instructions using 15 ml of 0.12 % chlorhexidine mouth rinse twice a day for 30 s during 5 days before the injection in order to reduce inflammation at the local anesthetic injection sites. The tested teeth were mandibular first premolars.

Local anesthesia

Volunteers were randomly allocated by drawing coded opaque envelops to receive 4 % articaine with 1:100,000 epinephrine (Ar + Ep) in three different doses for the ISA and PLA:

1. Ar (16 mg)+Ep (4 μg)—0.4 ml,
2. Ar (24 mg)+Ep (6 μg)—0.6 ml,
3. Ar (32 mg)+Ep (8 μg)—0.8 ml.

There was no premedication or additional medication given during the period of investigation. Anesthetic solution was injected with computer-controlled local anesthetic delivery system (CCLADS) (Anaeject®, Septodont,

Sallanches, France) with constant pressure, speed, and dose, approximately 0.005 ml/s. Periods of application were 40, 60, or 80 s for three doses of 0.4, 0.6, or 0.8 ml, respectively. Both mesial and distal sites of injection per tooth were used and the doses were divided into equal halves per site. Two minutes before the injection of the ISA and PLA, a topical anesthetic (2 % Lidocaine Chloride Gel®, Galenika a.d., Zemun, Serbia) was applied to that area.

The ISA requires the deposition of local anesthetic solution into the cancellous bone providing the local anesthesia of soft tissue and alveolar bone that supports teeth. The area of needle insertion for the ISA was determined with the center of the interdental papilla adjacent to the investigated tooth, 2–3 mm below the tip of interdental mesial and distal papilla, with 90 ° angulation of the needle to the surface of the papilla. Patients were in the supine or semisupine position to allow maximal access and visibility to the area of injection. When the needle entered the papilla, it was advanced until contact with the bone was made, without deposition of anesthetic throughout the papilla. After that, the needle was pressed a little deeper, 1 to 2 mm into the interdental bone where anesthetic solution was applied in the appropriate doses. No resistance to the depositions of anesthetic solution was noticeable since the CCLAD system was used. Blanching of the gingiva overlying bone with no leaking of the anesthetic was an indicator that the anesthetic solution had been properly deposited. The site of needle insertion for the PLA was the region of gingival sulcus at 30 ° to the tooth long axis at the bucomesial and bucodistal aspect of the root. A 30-G short needle (Septodont®, Dental Needle, Guyancourt, France), for both the ISA and PLA, was used. The anesthetic techniques were always performed by one of the participating dentists who were not involved in the analysis of anesthetic parameters.

Parameters of local anesthesia

The anesthetic efficacy (success rate), onset, and duration were assessed by the measurement of maximal changes in sensory threshold of the dental pulp after electric tooth stimulation using a commercially available electrical pulp tester (EPT) (Vitality Scanner Model 2006®, SybronEndo, Orange, CA, USA). Anesthesia was considered successful when 2 or more consecutive no response at 80 readings was obtained as a maximum. Before the injections were given, the experimental tooth and control contralateral premolar were tested three times by means of a Vitality Tester to record baseline vitality. The tip of the pulp tester probe was placed in the middle third of the buccal side of tested teeth, while fluoride gel (Fluorogal Forte®, Galenika, Belgrade, Serbia) was used as an electrolyte between the pulp tester probe and the tooth.

Onset time for anesthesia was defined as the time, in seconds, from completion of the injection to the time when profound anesthesia (EPT ≥ 80) was established. If profound anesthesia was not achieved in 10 min, as evidenced by 2 or more consecutive EPT ≥ 80, we considered it as an unsuccessful rate of anesthesia. Duration of complete pulpal anesthesia was a period between the first and the last 80 readings on EPT, defined as a profound anesthesia. We assessed the duration of anesthesia at 2-min intervals. Using the same intervals, duration of soft tissue anesthesia was recorded by negative response to pinprick testing until the moment when patient felt sharp pain during pinprick testing in the region of buccal-attached gingiva. We used a 27-gauge sterile needle (MonoJect®, Dental Needle, Mansfield, USA) for pinprick testing. Pinprick testing was done directly until contact with the periosteum and bone occurred. The width of the anesthetic field, expressed in millimeters, was measured in the region of buccal-attached gingiva, lingual-attached gingiva, and oral mucosa 10 min after successful anesthesia was obtained by flexible ruler and pinprick testing.

Evaluation of cardiovascular parameters and local side effects

At each treatment session, a responsible investigator recorded supine blood pressure, SBP, DBP, MAP, and HR by electrocardiogram monitor (Datex-Engstrom AS/3, Helsinki, Finland) at six times: prior to anesthesia, during anesthetic injection, and 5, 10, 15, and 30 min after administering anesthesia.

At the conclusion of the testing session, any adverse local reactions were recorded. Patients were followed up for 5 days to record any local postoperative side effects, such as sensitivity of tooth to biting, papillary hematoma, necrosis, or swelling.

Statistic

Statistical analysis was performed using the statistical software SPSS, version 18.0. The results were presented as the mean ± standard deviation (SD). The chi-square test was used to determine differences in gender and success rate among groups. Age and weight of patients, duration of pulpal anesthesia, and width of anesthetic field in the region of attached gingiva were analyzed using nonparametric Kruskal–Wallis and Mann–Whitney tests. Analysis of variance (ANOVA) and post hoc Bonferroni test were used to determine differences among groups in duration of soft tissue anesthesia and width of anesthetic field of oral mucosa and lingual-attached gingiva. Comparisons were considered significant at $p<0.05$. Power of the study was 97.3 %. We estimated that the difference in success rate between the best and worst groups would be between 20 and 26.7 %. Enrolment of 30 patients, in each group, will

achieve 97.3 % power to detect a significant difference in this outcome between the observed groups, at a two-tailed significance level of 0.05, using chi-square test.

Results

The relevant subject demographic data are listed in Table 1. There were no statistically significant differences between the two groups with respect to age, sex, and weight. The mean age ± SD of all subjects was 27.8 ± 9.9 years (range from 24 to 31 years). The study included 94 (52 %) female and 86 (48 %) male subjects. Before the anesthetic injection, all patients had normal sensory perception of lower premolars and all patients completed the study.

Parameters of local anesthesia

A total of 30 subjects in each investigated group were analyzed for the success rates of pulpal anesthesia. There was no dose-dependent relationship between the success rates of pulpal anesthesia and used doses of Ar + Ep in both the ISA and PLA. In all treated groups, 90 % success rate was obtained only with 0.6 and 0.8 ml of Ar + Ep for the ISA. There were statistically significant differences in the success rate between 0.6 ml of Ar + Ep in the ISA-treated group and 0.6 ml of Ar + Ep in the PLA-treated group (Table 2). Only data for subjects who achieved profound anesthesia (22 out of 30, 27 out of 30, and 27 out of 30 subjects in the ISA and 15 out of 30, 19 out of 30, and 21 out of 30 subjects in the PLA, respectively) were available to calculate onset, duration, and width of the anesthetic field. Pulpal and soft tissue anesthesia was achieved immediately after anesthetic injection in all patients (data not shown). Duration of the ISA increased in a dose-related manner, with a significant difference for both pulpal and soft tissue anesthesia. The significant difference in the pulpal and soft tissue anesthesia duration was recorded between ISA and PLA (0.6 and 0.8 ml for ISA against 0.6 and 0.8 ml for PLA) (Table 2).

The evaluation of the width of the anesthetic field in the region of the buccal- and lingual-attached gingiva and oral mucosa did not show a dose-related effect of Ar + Ep in the investigated groups. The width of the anesthetic field of the buccal-attached gingiva was significantly higher in the ISA than in the PLA using 0.4 and 0.8 ml of Ar + Ep. On the other hand, the width of the anesthetic field of the buccal oral mucosa and lingual-attached gingiva were significantly higher in the ISA than in the PLA regardless of the used doses (Table 3).

Parameters of cardiovascular function

Parameters of cardiovascular function were measured in 22 out of 30, 27 out of 30, and 27 out of 30 subjects in the ISA and 15 out of 30, 19 out of 30, and 21 out of 30 subjects in the PLA, respectively, with successful pulpal anesthesia. In the observed periods, before anesthetic injection, during anesthesia administration, and 5, 10, 15, and 30 min after the administration of Ar + Ep, there were no significant differences in the SBP, DBP, MAP, and HR in the ISA- and PLA-treated patients. All three doses of Ar + Ep, applied by the ISA and PLA, produced stable parameters of cardiovascular function (Figs. 1, 2, 3, and 4).

Local side effects

The sensitivity of tooth to biting was recorded only in patients who received the PLA—in five patients with 0.4 ml, three patients with 0.6 ml, and two patients with

Table 1 Subject demographic data

Subject characteristics	ISA			PLA		
	Doses of articaine + epinephrine					
	0.4 ml	0.6 ml	0.8 ml	0.4 ml	0.6 ml	0.8 ml
N	30	30	30	30	30	30
Age (years)[a]	24.4±6.6	28.3±9.9	25.2±5.3	29.0±12.0	31.0±13.0	28.9±12.8
(Median)	(23.50)	(26.00)	(25.00)	(25.00)	(26.50)	(25.00)
Male/female[b]	13/17	15/15	15/15	17/13	13/17	13/17
Weight (kg)[a]	78.6±3.8	69.9±6.8	70.4±9.8	73.2±5.7	82.1±12.8	78.3±14.2
(Median)	(77.00)	(67.50)	(70.00)	(70.00)	(81.50)	(75.50)

Values are presented as the mean ± SD

N number of anesthetized teeth, *ISA* intraseptal anesthesia, *PLA* periodontal ligament anesthesia

[a] Kruskal–Wallis test, Mann–Whitney test

[b] Chi-square test

Table 2 Success rate and duration of pulpal and soft tissue anesthesia for the ISA and PLA

Parameters of anesthesia	ISA			PLA		
	Doses of articaine + epinephrine					
	0.4 ml	0.6 ml	0.8 ml	0.4 ml	0.6 ml	0.8 ml
Success rate	73.0 %	90.0 %	90.0 %	50.0 %	63.3 %[c]	70.0 %
(*N*)	(22)	(27)	(27)	(15)	(19)	(21)
Duration of pulpal anesthesia/min	9.4±12.0[a]	14.7±10.7[a]	24.2±17.0	6.2±8.7	9.2±11.8[d]	10.4±9.3[d]
(Median)	(7.00)	(14.00)	(22.00)	(2.50)	(9.00)	(10.00)
(*N*)	(22)	(27)	(27)	(15)	(19)	(21)
Duration of soft tissue anesthesia/min	40.6±13.9[b]	54.4±10.2[b]	70.0±18.1	29.6±16.0	39.5±14.8[e]	40.4±19.2[e]
(*N*)	(22)	(27)	(27)	(15)	(19)	(21)

Significance within groups: [a] $p<0.05$: 0.4 vs. 0.6 ml, 0.4 vs. 0.8 ml, 0.6 vs. 0.8 ml (Kruskal–Wallis test, Mann–Whitney test); [b] $p<0.05$: 0.4 vs. 0.6 ml, 0.4 vs. 0.8 ml, 0.6 vs. 0.8 ml (ANOVA, post hoc Bonferroni test). Significance between groups: [c] $p<0.05$: ISA 0.6 ml vs. PLA 0.6 ml (chi-square test); [d] $p<0.05$: ISA 0.6 ml vs. PLA 0.6 ml, ISA 0.8 ml vs. PLA 0.8 ml (Kruskal–Wallis test, Mann–Whitney test); [e] $p<0.05$: ISA 0.6 ml vs. PLA 0.6 ml, ISA 0.8 ml vs. PLA 0.8 ml (ANOVA, post hoc Bonferroni test)

0.8 ml of Ar + Ep. After the ISA, three patients reported a slight hematoma of the papilla region: one patient with 0.6 ml and two patients with 0.8 ml Ar + Ep (data not shown).

Discussion

Although there is a possibility for delivery of more anesthetic solution, 1.4 ml (4 % articaine+1:100,000 epinephrine or 2 % lidocaine + 1:100,000 epinephrine), using CCLADS [12, 16, 23, 24], we investigated the efficacy of lower doses, 0.4, 0.6, and 0.8 ml of 4 % Ar+1:100,000 Ep for the ISA and PLA, especially concerning the safety profile of intraosseous local anesthetic injections.

Our results showed no significant dose-dependent relationship between the anesthetic success rates of pulpal anesthesia and used doses of Ar + Ep, 0.4, 0.6, and 0.8 ml, injected by controlled delivery system for both ISA and PLA, but there is such a tendency in the case of the PLA. Clinically acceptable success rate of pulpal anesthesia (90 %) was obtained with the ISA using 0.6 and 0.8 ml of Ar + Ep in contrast to the PLA. There is evidence that complete and profound pulpal anesthesia is necessary for achieving painless dental procedures on pulpal tissue, but not on alveolar bone and soft oral tissue [25, 26]. Our results

Table 3 Width of the anesthetic field for the soft tissue after the ISA and PLA

Parameters of anesthesia (mean ± SD)	ISA			PLA		
	Doses of articaine + epinephrine					
	0.4 ml	0.6 ml	0.8 ml	0.4 ml	0.6 ml	0.8 ml
Buccal-attached gingiva/mm	24.8±8.1[a]	31.9±5.1	32.9±4.4	14.5±8.3[a, d]	21.4±8.1	22.4±11.9[d]
(Median)	(24.50)	(32.00)	(33.00)	(16.00)	(21.00)	(21.50)
(*N*)	(22)	(27)	(27)	(15)	(19)	(21)
Buccal oral mucosa/mm	24.0±8.3[b]	30.7±5.4	32.5±4.8	11.2±9.0[b, e]	18.3±8.0[e]	18.3±13.6[e]
(*N*)	(22)	(27)	(27)	(15)	(19)	(21)
Lingual-attached gingiva/mm	18.6±10.0[c]	27.2±4.8	24.0±3.6	7.8±8.4[c, f]	16.3±8.6[f]	12.1±9.0[f]
(*N*)	(22)	(27)	(27)	(15)	(19)	(21)

Significance within groups: [a] $p<0.05$: ISA (0.4 vs. 0.6 ml, 0.4 vs. 0.8 ml), PLA (0.4 vs. 0.6 ml, 0.4 vs. 0.8 ml) (Kruskal–Wallis test, Mann–Whitney test); [b] $p<0.05$: ISA (0.4 vs. 0.6 ml, 0.4 vs. 0.8 ml), PLA (0.4 vs. 0.6 ml) (ANOVA, post hoc Bonferroni test); [c] $p<0.05$: ISA (0.4 vs. 0.6 ml), PLA (0.4 vs. 0.6 ml) (ANOVA, post hoc Bonferroni test). Significance between groups: [d] $p<0.05$: ISA 0.4 ml vs. PLA 0.4 ml, ISA 0.8 ml vs. PLA 0.8 ml (Kruskal–Wallis test, Mann–Whitney test); [e] $p<0.05$: ISA 0.4 ml vs. PLA 0.4 ml, ISA 0.6 ml vs. PLA 0.6 ml, ISA 0.8 ml vs. PLA 0.8 ml (ANOVA, post hoc Bonferroni test); [f] $p<0.05$: ISA 0.4 ml vs. PLA 0.4 ml, ISA 0.6 ml vs. PLA 0.6 ml, ISA 0.8 ml vs. PLA 0.8 ml (ANOVA, post hoc Bonferroni test)

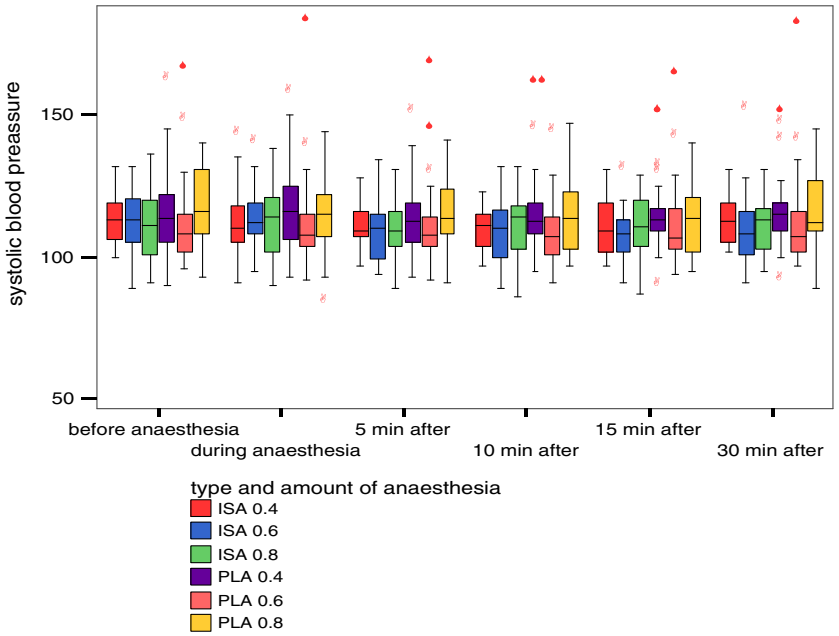

Fig. 1 Box plot of changes in SBP during ISA and PLA with 0.4, 0.6, and 0.8 ml of 4 % Ar + 1:100,000 Ep. Data were presented as the median (*horizontal line*), with the *box* representing the 75th centiles, *whiskers* representing the statistical range, and *points* and *asterisk* representing the outliers

have also shown that only the duration of the ISA increases in a dose-dependent manner for both pulpal and soft tissue anesthesia and that a significant difference in duration between the ISA and PLA existed in 0.6 and 0.8 ml of Ar + Ep. It is interesting to note that, to date, there have been no data concerning the quality of the ISA and PLA with such small doses of Ar + Ep using CCLADS. Only Berlin et al. [12], using a higher dose, 1.4 ml, of 4 % Ar+1:100,000 Ep, delivered by the CCLADS, reported 74 % success rate and 28.1±18.4 min duration of pulpal anesthesia after the PLA. Concerning our results, obtained with 0.8 ml of 4 % Ar+ 1:100,000 Ep, it is evident that a higher dose (1.4 ml) of this anesthetic mixture increased only the duration but not the success rate of the PLA.

Since EPT provides a precise assessment of complete and profound anesthesia, clinical implications of our results could be that the ISA, as a primary anesthesia, can be used not only for tooth extractions and periodontal surgery, but also for endodontic procedures, while PLA is only sufficient for procedures which may not require complete pulpal anesthesia. The higher success rate and duration of the ISA obtained in our study is most probable related, firstly, to the fact that, using the ISA, the whole amount of the local anesthetic is applied within the alveolar bone and, secondly,

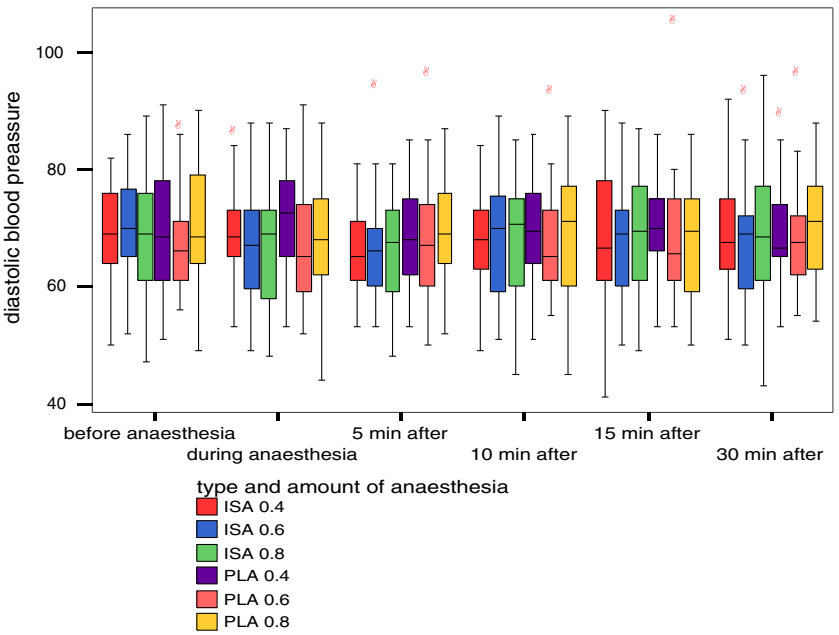

Fig. 2 Box plot of changes in DBP during ISA and PLA with 0.4, 0.6, and 0.8 ml of 4 % Ar + 1:100,000 Ep. Data were presented as the median (*horizontal line*), with the *box* representing the 75th centiles, *whiskers* representing the statistical range, and *points* and *asterisk* representing the outliers

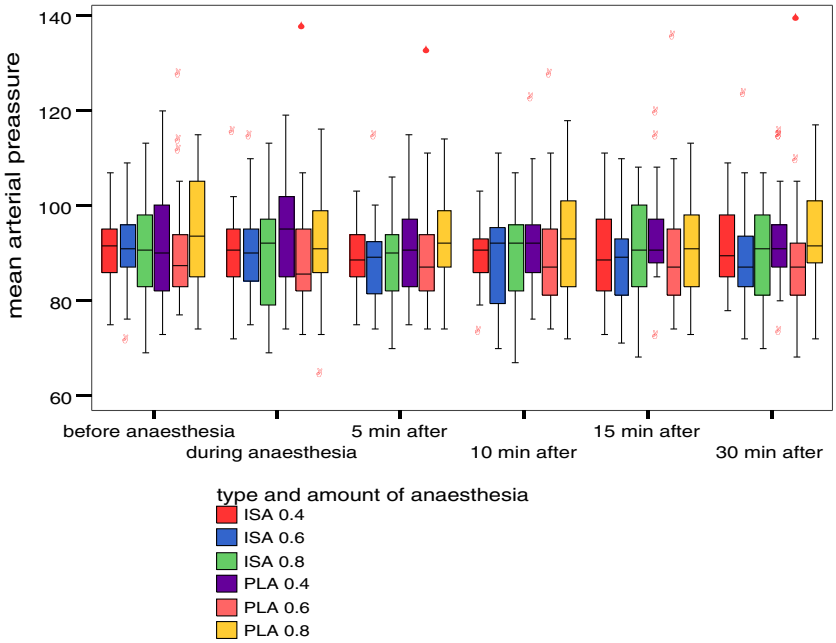

Fig. 3 Box plot of changes in MAP during ISA and PLA with 0.4, 0.6, and 0.8 ml of 4 % Ar + 1:100,000 Ep. Data were presented as the median (*horizontal line*), with the *box* representing the 75th centiles, *whiskers* representing the statistical range, and *points* and *asterisk* representing the outliers

to the unique pharmacokinetic characteristics of articaine—fast and complete penetration through the alveolar bone [19]. On the other hand, since the injection site of the PLA is usually inflamed, regardless of the one-visit periodontal tissue treatment that we did, it seems that the observed decreased success rate could be a result of decreased efficacy of articaine due to dissociation of local anesthetic in such tissue [27–29]. Finally, since Ar + Ep is applied by the PLA directly into the periodontal tissue, which blood supply is frequently localized in the gingival part of periodontium [30, 31], it is reasonable to assume that the vasoconstriction of this area could reduce the delivery of anesthetic inside the alveolar bone.

In all treated subjects, onset of ISA and PLA was immediate after the completion of the CCLADS application. This result is most probably related directly to the technique of anesthetic application. Namely, the CCLADS, due to continuous time-related anesthetic application, ensures simultaneous effect of the applied anesthetic concentrations until the end of controlled anesthetic delivery injection. The width of anesthesia in the region of attached gingiva and oral mucosa increased significantly greater in the ISA in comparison to the PLA. This finding can be explained with better spreading of anesthetic solution with the ISA regarding the characteristics of tissue at the site of injection [32]. Namely, when deposited directly into the interdental

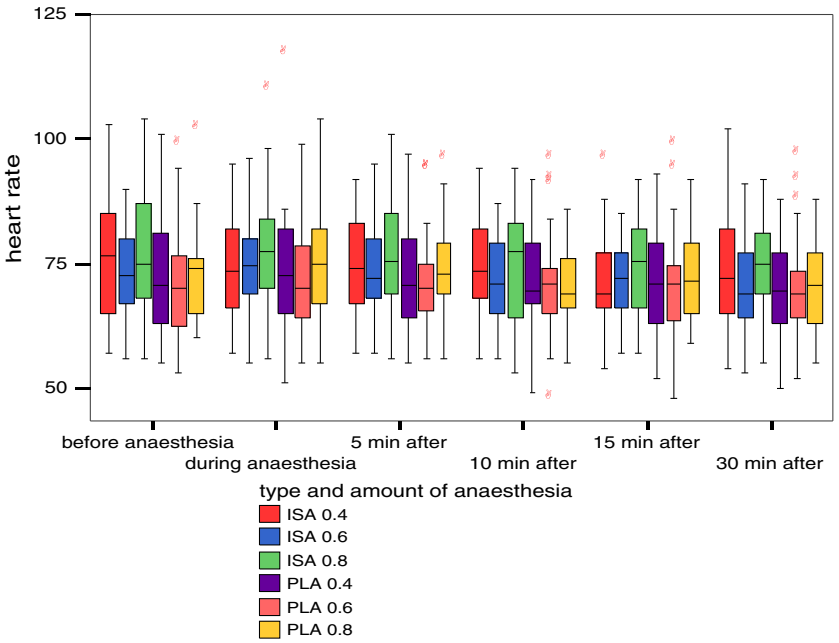

Fig. 4 Box plot of changes in HR during ISA and PLA with 0.4, 0.6, and 0.8 ml of 4 % Ar + 1:100,000 Ep. Data were presented as the median (*horizontal line*), with the *box* representing the 75th centiles, *whiskers* representing the statistical range and *points* and *asterisk* representing the outliers

septum, local anesthetic solution diffused through the very porous region of the alveolar bone and occupied the wider bone area [33]. The structure of alveolar bone and cortical perforations allows access of the anesthetic solution to more alveolar crest and, passing through buccal plate nutrition canal foramina, anesthesia of supraperiosteal soft tissue [31, 32]. The restricted area of anesthesia around lower premolars, obtained with the ISA and PLA, can be of considerable clinical benefit concerning the reduction of unwanted soft tissue distension which results in the elimination of the self-inflicted trauma of the lower lip or tongue which can occur after mandibular block anesthesia [7].

Fluctuations in cardiovascular parameters are common during block and infiltrative administration of local anesthetic with a vasoconstrictor. On the other hand, increased HR is a common side effect when anesthetics with vasoconstrictors are injected intraosseously [34]. This is because the intraosseous site of injection, as a highly vascularized area, allows rapid entry of the local anesthetic and vasoconstrictor. Thiophene ring and its methoxycarbonyl substituent make articaine as a suitable for plasma cholinesterase, with the consequence being a short half-life. This characteristic accounts for a possible increase of articaine systemic safety profile, compared with that of other dental local anesthetic solutions [19]. Systemic toxicity of articaine is rare and, for example, an unintentional intravascular injection of articaine 80 mg did not cause any toxic symptoms in healthy individuals [35]. Since the maximal amount of injected articaine in our study was only 32 mg, it is reasonable that any significant changes in blood pressure and HR were not observed after the Ar + Ep application with ISA and PLA. For a vasoconstrictor perspective, it was recommended that, for intraosseous PLA injection, the volume of epinephrine containing local anesthetic solutions should be kept to a minimum (2 to 4 μg in healthy individuals) to avoid possible cardiovascular changes [8, 26]. Amounts of epinephrine in our study are closely related to this recommendation. It is noteworthy that Nusstein et al. [16] reported nonsignificant cardiovascular changes after the computer-controlled delivery of a larger concentration of 1.4 ml Ar (4 %) + Ep (1:100,000) for the PLA in human volunteers. It seems that, besides the low toxicity of articaine and minimal amounts of epinephrine, the mode of their application—CCLADS—is also important for the safety profile of anesthesia since high-pressure injections of lidocaine + epinephrine for the PLA and ISA significantly increased HR in dogs, as well as in healthy volunteers [10, 15, 36]. It must be stressed that the subject population in our study consisted of young healthy adults who did not have cardiovascular diseases or diabetes mellitus, disorders associated with possible risk of cardiovascular effects of epinephrine-containing local anesthetic solutions [37–40]. Having in mind minimal amounts of epinephrine (4, 6, and 8 μg), observed immediate onset of anesthesia, successful pulpal anesthesia, and limited localization of anesthetic effect (approximately 24 to 32 mm of soft tissue anesthesia), it could be proposed that the CCLADS for the ISA with 0.6 ml of 4 % Ar + 1:100,000 Ep would be efficient and well-tolerated by many of these patients.

Conclusion

To summarize, since there are no data of a dose-dependent effect of the ISA in the literature, the results of this study indicated that the computer-controlled 4 % Ar + 1:100,000 Ep delivery, in volumes 0.4, 0.6, and 0.8 ml, produced a dose-related increase in duration of pulpal and soft tissue ISA, which were significantly longer then in the PLA using 0.6 and 0.8 ml. High success rate (90 %) and restricted anesthetic field were also obtained with 0.6 and 0.8 ml of Ar + Ep for the ISA. Both the ISA and PLA resulted in similar nonsignificant cardiovascular changes regarding the use of increased doses of Ar + Ep. Based on these data, it can be suggested that doses of 0.6 and 0.8 ml of 4 % Ar+ 1:100,00 Ep (24 mg+6 μg and 32 mg+8 μg) offer adequate, effective, and safe ISA obtained in healthy individuals by the CCLADS. Further studies are needed to distinguish the proposed doses of 4 % Ar+1:100,000 Ep delivered by the CCLADS for the ISA in their efficacy and safety in the risk group of cardiovascular and diabetic patients. Namely, of particular importance for cardiovascular patients is the safety profile of epinephrine, while for diabetic patients with vasculopathy and neuropathy resulting in impaired peripheral blood flow and nerve conduction, the safety profiles of both epinephrine and articaine are of special relevance.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. Bangerter C, Mines P, Sweet M (2009) The use of intraosseous anesthesia among endodontists: results of a questionnaire. J Endod 35:15–18. doi:10.1016/j.oen.2008.10.003
2. Nusstein J, Claffey E, Reader A, Beck M, Weaver J (2005) Anesthetic effectiveness of the supplemental intraligamentary injection, administered with a computer-controlled local anesthetic delivery system, in patients with irreversible pulpitis. J Endod 31:354–358
3. Fan S, Chen W, Pan C, Huang Z, Xian M, Yang Z et al (2009) Anesthetic efficacy of inferior alveolar nerve block plus buccal infiltration or periodontal ligament injection with articaine in patients with irreversible pulpitis in the mandibular first molar.

Oral Surg Oral Med Oral Pathol Oral Radiol Endod 108:e89–e93. doi:10.1016/j.tripleo.2009.06.012
4. Childers M, Reader A, Nist R, Beck M, Meyers WJ (1996) Anesthetic efficacy of the periodontal ligament injection after an inferior alveolar nerve block. J Endod 22:317–320
5. Edwards RW, Head TW (1989) A clinical trial of intraligamentary anesthesia. J Dent Res 68:1210–1213
6. Walton RE (1990) The periodontal ligament injection as a primary technique. J Endod 16:62–66
7. Meechan JG (1992) Intraligamentary anaesthesia. J Dent 20:325–332, Review
8. Meechan JG, Ledvinka JI (2002) Pulpal anaesthesia for mandibular central incisor teeth: a comparison of infiltration and intraligamentary injections. Int Endod J 35:629–634
9. Woodmansey K (2005) Intraseptal anesthesia: a review of a relevant injection technique. Gen Dent 53:418–420
10. Brkovic BM, Savic M, Andric M, Jurisic M, Todorovic LJ (2010) Intraseptal vs. periodontal ligament anaesthesia for maxillary tooth extraction: quality of local anaesthesia and haemodynamic response. Clin Oral Investig 14:675–681. doi:10.1007/s00784-009-0352-7
11. White JJ, Reader A, Beck M, Meyers WJ (1988) The periodontal ligament injection: a comparison of the efficacy in human maxillary and mandibular teeth. J Endod 14:508–514
12. Berlin J, Nusstein J, Reader A, Beck M, Weaver J (2005) Efficacy of articaine and lidocaine in a primary intraligamentary injection administered with computer-controlled local anesthetic delivery system. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 99:361–366. doi:10.1016/j.tripleo.2004.11.009
13. Yeniseu M (2009) Comparison of the pain levels of computer-controlled and conventional anesthesia techniques in prosthodontic treatment. J Appl Oral Sci 17:414–420
14. Nicholson JW, Berry TG, Summitt JB, Yuan CH, Witten TM (2001) Pain perception and utility: a comparison of the syringe and computerized local injection techniques. Gen Dent 49:167–173
15. Pashley DH (1986) Systemic effects of intraligamental injections. J Endod 12:501–504
16. Nusstein J, Berlin J, Reader A, Beck M, Weaver JM (2004) Comparison of injection pain, heart rate increase, and postinjection pain of articaine and lidocaine in a primary intraligamentary injection administered with a computer-controlled local anesthetic delivery system. Anesth Prog 51:126–133
17. Skjevik AA, Haung BE, Lygre H, Teigen K (2011) Intramolecular hydrogen bonding in articaine can be related to superior bone tissue penetration: a molecular dynamics study. Biophys Chem 154:18–25
18. Malamed S (2009) What's new in local anaesthesia? SAAD Dig 25:4–14
19. Vree TB, Gielen MJ (2005) Clinical pharmacology and the use of articaine for local and regional anaesthesia. Best Pract Res Clin Anaesthesiol 19:293–308. doi:10.1016/bpa.2004.12.006
20. Kanaa MD, Whitworth JM, Corbett IP, Meechan JG (2006) Articaine and lidocaine mandibular buccal infiltration anesthesia: a prospective randomized double-blind cross-over study. J Endod 32:296–298
21. Robertson D, Nusstein J, Reader A, Beck M, McCartney M (2007) The anesthetic efficacy of articaine in buccal infiltration of mandibular posterior teeth. JADA 138:1104–1112
22. Lima-Júnior JL, Dias-Ribeiro E, de Araújo TN, Ferreira-Rocha J, Honfi-Júnior ES, de Moraes Sarmento CF, Seabra FRG, de Sousa M (2009) Evaluation of the buccal vestibule-palatal diffusion of 4 % articaine hydrochloride in impacted maxillary third molar extractions. Med Oral Patol Oral Cir Bucal 14:E129–E132
23. Nusstein J, Lee S, Reader A, Beck M, Weaver J (2004) Injection pain and postinjection pain of the anterior middle superior alveolar injection administered with the wand or conventional syringe. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 98:124–131
24. Goodell GG, Gallagher FJ, Nicoll BK (2000) Comparison of a controlled injection pressure system with a conventional technique. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90:88–94. doi:10.1067/moe.2000.107365
25. Moore PA, Boynes SG, Hersh EV, DeRossi SS, Sollecito TP, Goodson JM, Leonel JS, Floros C, Peterson C, Hutcheson M (2006) The anesthetic efficacy of 4 percent articaine 1:200,000 epinephrine: two controlled clinical trials. JADA 137:1572–1581
26. Malamed SF (2004) Supplemental injection techniques. In: Malamed SF (ed) Handbook of local anesthesia, 5th edn. Mosby, St. Louis, pp 255–261
27. Walton RE, Garnick JJ (1982) The periodontal ligament injection: histologic effects on the periodontium in monkeys. J Endod 8:22–26
28. Roberts GJ, Simmons NB, Longhurst P (1992) Odontogenic bacteraemia and intraligamental analgesia. Br Dent J 173:195
29. Bender IB (1995) Post-treatment bacteriemia. JADA 126:1474–1476
30. Birn H (1966) The vascular supply of the periodontal membrane. An investigation of the number and size of perforations in the alveolar wall. J Periodontal Res 1:51–68. doi:10.1111/j.1600-0765.1966.tb01846.x
31. Garfunkel A, Sciaky I (1971) Vascularization of the periodontal tissues in the adult laboratory rat. J Dent Res 50:880–887
32. Saadoun AP, Malamed SF (1985) Intraseptal anesthesia in periodontal surgery. JADA 111:249–256
33. Taheritalesh K, Yazdani J, Ghavimi M, Khashabi E (2009) Crestal anesthesia: an efficient, fast and reliable technique in posterior mandible exodontias; a case–control clinical and CT scan assessment. Res J Biol Sci 4:369–374
34. Replogle K, Reader A, Nist R, Beck M, Weaver J, Meyers WJ (1999) Cardiovascular effects of intraosseous injections of 2 percent lidocaine with 1:100,000 epinephrine and 3 percent mepivacaine. JADA 130:649–657
35. Oertel R, Rahn R, Kirch W (1997) Clinical pharmacokinetics of articaine. Clin Pharmacokinet 33:417–425
36. Smith GN, Pashley DH (1983) Periodontal ligament injection: evaluation of systemic effects. Oral Surg Oral Med Oral Pathol 56:571–574
37. Meechan JG, Parry G, Rattray DT, Thomason JM (2002) Effects of dental local anaesthetics in cardiac transplant recipients. Br Dent J 192:161–163
38. Niwa H, Sugimura M, Satoh Y, Tanimoto A (2001) Cardiovascular response to epinephrine-containing local anesthesia in patients with cardiovascular disease. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 92:610–616. doi:10.1067/moe.2001.118903
39. Partridge BL (1991) The effects of local anesthetics and epinephrine on rat sciatic nerve blood flow. Anesthesiology 75:243–250
40. Kalichman MW, Calcutt NA (1992) Local anesthetic-induced conduction block and nerve fiber injury in streptozotocin-diabetic rats. Anesthesiology 77:941–947