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Short title: 4% articaine with epinephrine for AMSA nerve block with CCLADS
ABSTRACT

Introduction/Aim To investigate and compare parameters of pulpal anesthesia and cardiovascular parameters after anterior middle superior alveolar (AMSA) nerve block with 4% articaine with epinephrine administered by conventional cartridge-syringe and computer controlled local anesthetic delivery system (CCLADS).

Methods This controlled double-blind cross-over randomized clinical study included 38 healthy volunteers. Efficacy of pulpal anesthesia after AMSA nerve block was evaluated by measuring success rate, onset and duration of pulpal anesthesia, using electrical pulp tester. Parameters of cardiovascular function (systolic and diastolic blood pressure, heart rate) were monitored noninvasively.

Results Successful pulpal anesthesia of all tested teeth was obtained in 57.9% participants with CCLADS and in 44.7% participants with conventional syringe. The onset time was not significantly different between two investigated groups. Pulpal anesthesia duration was not significantly different neither within, nor between investigated groups. Systolic and diastolic blood pressures were significantly decreased in both investigated groups, in comparison with baseline values. Heart rate was significantly decreased within CCLADS from 10th to 30th minute when compared to baseline.

Conclusion The efficacy of pulpal anesthesia and safety of cardiovascular profile of 0.6 ml of articaine with epinephrine (1:100,000) delivered with CCLADS were improved in comparison to conventional syringe delivery. Significant changes of cardiovascular function were not observed.

Keywords articaine, anterior middle superior alveolar nerve block, computer controlled local anesthetic delivery
APSTRAKT

Uvod/ Cilj Ispitati i uporediti parametre anestezije zubne pulpe i kardiovaskularne parametre posle AMSA sprovodne anestezije postignute 4% artikainom sa epinefrinom, primenom standardne karpul-brizgalice i kompjuterski kontrolisanog sistema za primenu anestetickog rastvora (CCLADS).

Metod U ovom randomizovanom, prospektivnom, kontrolisanom, dvostruko slepom ukrstenom klinickom istraživanju učestvovalo je 38 ispitanika. Kvalitet anestezije zubne pulpe posle AMSA anestezije praćen je na osnovu uspešnosti, latentnog perioda i trajanja anestezije zubne pulpe, primenom električnog pulp-testera. Parametri kardiovaskularne funkcije (sistolni i dijastolni krvni pritisak, srčana frekvencija) praćeni su neinvazivno, primenom aparataza monitoring.

Rezultati Uspešna anestezija zubne pulpe svih ispitivanih zuba bila je prisutna kod 57,9% ispitanika posle primene CCLADS i kod 44,7% ispitanika posle primene standardne karpul-brizgalice. Latentni period i trajanje anestezije zubne pulpe nisu se značajno razlikovali između ispitivanih grupa. Sistolni i dijastolni pritisak bili su značajno sniženi u praćenim vremenskim intervalima u odnosu na početne vrednosti. Srčana frekvencija je bila značajno snižena unutar CCLADS grupe od 10. to 30. minuta u odnosu na početne vrednosti.

Zaključak Kontrolisanom kompjuterizovanom primenom (CCLADS) 0,6 ml 4% artikaina sa epinefrinom (1:100,000) za AMSA sprovodnu anesteziju, postignut je bolji kvalitet anestezije zubne pulpe u odnosu na primenu artikaina sa epinefrinom standardnom karpul brizgalicom. Nisu uočene bitnepromene funkcija kardiovaskularnog sistema.

Ključne reči artikain, blok anestezijaprednjih i srednje gornje zubne grane, kompjuterski kontrolisana primena anestetika
INTRODUCTION

The efficient dental anesthesia, which is related to clinically adequate depth, duration and the width of anesthetic field, is an important prerequisite for successful dental treatment. Most commonly, pulp of the maxillary teeth, surrounding bone and soft tissue are anesthetized by buccal supraperiosteal infiltration of local anesthetic in the projection of the tooth apex \(^1\). Recently, anterior middle superior alveolar (AMSA) nerve block has been introduced as a technique which provides pulpal anesthesia of multiple maxillary teeth with single site injection, without collateral anesthesia of lip, face and muscles of facial expression \(^2\). Local anesthetic solution for AMSA nerve block is deposited palatal, at the point which bisects maxillary premolars, and midway between mid-palatal raphe and premolar free gingival margin crest. The target area is the anatomical region where anterior superior alveolar (ASA) and medial superior alveolar (MSA) nerves’ branches converge and form dental neural plexus. Therefore, anesthetic effect of a single AMSA block injection extends to the pulpal tissue of maxillary teeth from central incisor through second premolar, innervated by ASA and MSA nerves, with additional anesthesia of soft palatal tissue in the same region.

Generally, palatal injections with conventional syringe have the potential to be unpleasant and painful. The new approach in dental anesthesia techniques develops systems of controlled anesthetic delivery is aimed to reduce not only patient’s discomfort during palatal soft tissue anesthesia, but also to increase quality of bone and dental pulp anesthesia. Some of the published studies using this computer-controlled local anesthetic delivery system (CCLADS) for AMSA nerve block, showed that continuous and controlled dosage of 2% lidocaine with epinephrine may achieve profound pulpal anesthesia from central incisor through second premolar, what was not seen after conventional delivery \(^2,3,4\). Although obtained clinical results were more favorable with CCLADS than with conventional delivery, the modest to low success rate, slow onset and rapid anesthesia duration declining observed after 2% lidocaine with epinephrine may decrease clinical utilization of AMSA nerve block due to anatomical properties of palatal injection site, as well as pharmacological properties of lidocaine with epinephrine solution \(^5,6\).
Since AMSA nerve block is obtained following diffusion of local anesthetic solution through palatal bone before reaching dental nerve plexus, the characteristics of local anesthetic could influence parameters of local anesthesia. Articaine is an amide local anesthetic with unique properties due to characteristics of thiophene ring in its structure, which ensures that diffusing property of articaine through soft and hard tissues is more pronounced than of other amide local anesthetics. There is evidence that palatal soft tissue anesthesia occasionally may be obtained by articaine diffusion after maxillary infiltration without additional palatal injection.

To our knowledge, there are no data concerning efficacy and safety of AMSA nerve block obtained with 4% articaine with epinephrine. Therefore, the aim of this study was to investigate and compare parameters of pulpal anesthesia and cardiovascular functions after AMSA nerve block with 4% articaine with epinephrine administered by conventional syringe and CCLADS.

METHODS

This prospective, double-blind cross-over randomized study included healthy volunteers (ASA I) who were admitted for regular dental examination at the Clinic of Oral Surgery, School of Dental Medicine, University of Belgrade, Serbia. After approval of the Ethical committee of the School of Dental Medicine (36/5-2015), study has been performed in accordance with ethical standards laid down in 1964 Declaration of Helsinki and its later amendments. United States National Institutes of Health clinical trial registration was performed (ClinicalTrials.gov: NCT02440347). All participants signed informed consent after they were informed in details, verbally and in written form, about study procedures and possible side effects.
Participants’ eligibility

Inclusion criteria were as follows: full maxillary dental arch with all maxillary teeth free of caries and restorations, without history of trauma, sensitivity or orthodontic treatment, with visible pulpal chamber on intraoral radiogram, responsive to electrical stimulation by pulp tester and clinically and radiographically healthy periodontium. Allergy to local anesthetics, presence of orofacial pain and/or use of any medicine within the previous 48 hours, pregnancy, lactation, drug and/or alcohol abuse, tobacco smoking and inhibition to give informed consent were exclusion criteria.

Study procedure

Patients served as their own control in cross-over design. The AMSA injection on one side of the maxillary arch was administered with CCLADS(Anaject®, Septodont, France) while conventional cartridge-syringe was used for the opposite side. The AMSA injection site was located at a point that bisects the maxillary first and second premolars, and midway between the crest of the free gingival margin and mid-palatine suture. The needle was orientated at a 45 degree angle with the bevel facing palatal tissue. All dental anesthesia glass cartridges were marked at the level of 0.6 ml of anesthetic solution. The 0.6 ml of 4% articaine with epinephrine 1:100 000 was administered in two minutes period, both with CCLADS or conventional cartridge-syringe. CCLADS enabled slow and constant administration of anesthetic, approximately 0.005 ml per second. The sound mode during administration of local anesthetic with CCLADS was switched off, in order to disable patient to distinguish the method of administration. Patients were instructed to rest prior to injection in supine position for 15 minutes in isolated dental office. In addition, patients were blindfolded with a commonly used sleeping mask so they would not distinguish which anesthetic delivery system was used. The same operator administered anesthesia of both sides and was excluded from measuring data and statistical analysis. The order of anesthesia techniques was blinded and randomly selected from sealed envelope for each patient, with washout period of 2 weeks between appointments.
Parameters of pulpal anesthesia

Pulpal anesthesia parameters were tested in following teeth: upper central and lateral incisor, canine, first premolar and second premolar with contralateral canine as a control tooth.

The anesthetic success, onset and duration were registered with electrical pulp tester (EPT) (Vitality Scanner, Sybron Endo Model 2006®, Orange, CA, USA). The primary outcome was success of pulpal anesthesia. The anesthesia was considered successful when 2 consecutive no response at maximum (80) readings stimulation were obtained. Before the anesthesia was given, the experimental teeth and contralateral control canine were tested by means of Vitality Scanner to record baseline vitality. The fluoride gel (Fluorogal Forte®, Galenika, Belgrade, Serbia) was used as an electrolyte between tooth and pulp tester probe. The tip of pulp tester probe was placed in the middle third of the buccal side of tested teeth. The pulp response was tested immediately after the end of anesthetic application, in order from central incisor through second premolar, making repeated measurements for each tooth 4 minutes apart.

Secondary outcomes were onset and duration of pulpal anesthesia. Onset time for anesthesia was defined as the time from completion of the anesthetic injection to the time when profound anesthesia was achieved (EPT ≥80). Duration of pulpal anesthesia was period between the first and the last 80 readings on EPT, what was considered as a profound anesthesia.

Parameters of cardiovascular function

Cardiovascular parameters, such as systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) were recorded by electrocardiogram monitor (Datex-Engstrom AS/3, Helsinki, Finland) six times: 5 minutes prior anesthesia, during anesthetic injection, and 5, 10, 15 and 30 minutes after administering anesthesia. Also, participants were
monitored for potential changes in cardiac rhythm and possible signs of myocardial ischemia.

**Statistical analysis**

Data concerning demographic characteristics of participants were compared by $\chi^2$ test. Success of pulpal anesthesia was evaluated by descriptive statistical methods with $\chi^2$ test and Fisher’s test for within group analysis and McNemar test for between groups comparisons. Obtained differences in onset and duration of pulpal anesthesia between groups were tested for significance by Wilcoxon Sign Rank test, while Kruskall Wallis test was used for within group analysis, followed by Man-Whitney U test. Parameters of cardiovascular function (SBP, DBP and HR) were analyzed by two-way repeated measures ANOVA with group and time as main factors. Changes of cardiovascular parameters over time within investigated groups (baseline vs. observed time intervals), were compared by means of one-way repeated measures ANOVA with Bonferroni post hoc. Between group comparisons in cardiovascular function at observed time intervals were performed by paired samples t-test. Statistical analysis was carried out with SPSS 20.0 (Inc., Chicago, IL, USA) with level of significance set at 0.05. It was necessary to include at least 34 participants to obtain 20% difference in pulpal anesthesia duration between techniques with 80% statistical power at a two-tailed level of significance 0.05 using Man Whitney U test.

**RESULTS**

**Demographic data and participants flow**

Participants flow is presented in Figure 1. Sixty seven participants were assessed for eligibility and 40 of them were recruited to participate in this study. All participants received both treatments, but two of them had an unsuccessful anesthesia with both
delivery systems and were excluded from further analysis. The final number of analyzed participants with successful pulpal anesthesia of at least one tested tooth was 38.

Final study sample comprised of 20 females and 18 males, aging between 19 and 31 years (25.27±2.46), with mean body mass of 67.30±15.03 kg (data not presented).

**Parameters of pulpal anesthesia**

Successful pulpal anesthesia of all tested teeth was achieved in 22 (57.9%) participants of the CCLADS group and in 17 (44.7%) participants of the conventional syringe group. Success rate with CCLADS was 68.4% for central incisor, 100% for lateral incisor and canine, 76.3% for first premolar and 86.8% for second premolar; with conventional syringe, successful anesthesia was achieved in 71% for central incisor, 94.7% for lateral incisor, 81.6% for canine, 71% for first premolar and 68.4% for second premolar. Within group analysis of pulpal anesthesia success rate in CCLADS group revealed: significantly higher success for lateral incisor in comparison with central incisor (p<0.001) as well as for lateral incisor in comparison with first premolar (p=0.012), and also for canine in comparison with central incisor (p<0.001) and for canine compared to first premolar (p=0.012). In the conventional injection group, pulpal anesthesia was significantly more successful for lateral incisor compared to central incisor (p=0.012), for lateral incisor compared to first premolar (p=0.012), as well as for lateral incisor compared to second premolar (p=0.006). Between groups comparison showed that for canine and second premolar significantly higher success rate of pulpal anesthesia was observed after CCLADS vs. conventional injection (Table 1).

Onset and duration of pulpal anesthesia with conventional syringe and CCLADS are presented in Table 2. The onset time was not significantly different between two investigated anesthetic techniques. Within group comparison revealed that there were no significant differences in onset time among teeth after CCLADS injection. However, onset of anesthesia was significantly longer in conventional injection group for central incisor in comparison with lateral incisor (p=0.024), for central incisor compared to first premolar (p=0.037) and also when central incisor was compared to second premolar (p=0.022); as
well as for canine in comparison with first premolar (p=0.044). Significant differences in pulpal anesthesia duration were not observed neither within, nor between investigated groups (Table 2).

**Parameters of cardiovascular function**

Two-way repeated measures ANOVA revealed significant effect of time factor for SBP (p<0.001), DBP (p<0.001) and HR (p=0.008), with significant interaction of main factors only for SBP (p=0.010) (data not presented).

Repeated measures one-way ANOVA with Bonferroni *post hoc* in CCLADS group showed significant decrease in SBP 5 minutes (p<0.001), 10 minutes (p=0.009) and 15 minutes (p=0.008) after injection in comparison with baseline values; after conventional injection, SBP was significantly lower after 10 minutes (p=0.001), 15 minutes (p=0.001) and 30 minutes (p=0.029) when compared to baseline values. Significantly lower SBP was observed at 5th minute (p=0.006) after conventional vs. CCLADS injection (Figure 2).

Statistical analysis revealed that there was significant decrease in DBP over time in CCLADS group at 5th minute (p=0.037) and 10th minute (p=0.036) when compared to baseline values, while after conventional injection, significant decrease in DBP was observed after 10 minutes (p=0.001) and 15 minutes (p=0.006) in comparison with baseline values (Figure 3).

Significant changes in HR were observed only in CCLADS group during observation time, with significantly decreased values at 10th (p=0.008), 15th (p=0.008) and 30th minute (p=0.003) when compared to baseline (Figure 4).

Changes in cardiac rhythm and signs of myocardial ischemia were not observed on electrocardiogram during the observation period.
DISCUSSION

This prospective, controlled-double-blind, cross-over randomized clinical study in healthy volunteers evaluated and compared anesthetic and cardiovascular effects of 0.6 ml 4% articaine with epinephrine (1:100,000) used for the AMSA nerve block delivered with computer-controlled delivery system and conventional syringe.

Overall success rate of pulpal anesthesia, as a primary outcome of the study, with CCLADS ranged from 68.4% to 100%, while with conventional syringe it was between 68.4% and 94.7%. Pulpal anesthesia in the present study was considered successful if two or more consecutive 80 readings were obtained by electrical pulp test without participant’s response. Regarding the fact that parameters of pulpal anesthesia after the AMSA nerve block obtained with articaine with epinephrine have not been investigated, available evidence concern the use of 2% lidocaine with epinephrine as a “gold standard”. Namely, in the study of Fukayama et al., lower success rates were observed (between 42% and 72%), based on one registered 80 reading without participant’s response during electrical stimulation, after AMSA nerve block obtained with 1.8 ml of 2% lidocaine with epinephrine 1:80,000 delivered by WAND computer controlled system. Similar low success rates, evaluated according to two consecutive 80 readings without participants response to electric pulp test, were also reported in comparative study by Lee et al. during 60 minutes observation period, after 1.4 ml of 2% lidocaine with 1:100,000 epinephrine delivered for AMSA nerve block, either with computer controlled system (success rate between 35% and 58%), or with conventional syringe (success rate between 20% and 42%). On the other hand, Corbett et al. reported higher anesthetic success of pulpal anesthesia (between 42% and 85%) during 47 minutes observation period, regarded as minimum two consecutive 80 readings without response to electrical stimuli, when 1 ml of 2% lidocaine with epinephrine 1:80,000 was delivered with WAND system for AMSA nerve block in comparison with infraorbital nerve block. Considering factors that influence success rate of pulpal anesthesia, as an important parameter of anesthesia quality, several of them, such as anesthetic pharmacological profile, regional anatomical specificity and local anesthesia technique, could contribute to higher success rate of local intraoral anesthesia. Since no difference was observed between delivery systems (CCLADS and
conventional cartridge-syringe), our results could be explained rather by pharmacological properties of local anesthetic applied than anesthetic technique used. Articaine is an amide local anesthetic with characteristic molecular structure that includes the presence of tiophene ring. The presence of tiophene ring increases the anesthetic liposolubility, and it is suggested that articaine diffuses more readily through soft and bone tissue than other local anesthetics. Increased lipid solubility of articaine (partition coefficient 17) in comparison with lidocaine (partition coefficient 4) permits more active anesthetic molecules to effectively penetrate the lipid nerve membrane, what is reflected in the increased anesthetic potency of articaine. Concerning that, it is clear that articaine provides higher rates of pulpal anesthesia success than lidocaine when used for infiltration and block anesthesia during routine dental treatments.\(^\text{11}\)

Further analysis of success rate in the present study compared the efficacy of CCLADS and conventional syringe delivery in obtaining successful pulpal anesthesia of specific teeth. Our results showed that pulpal anesthesia of canine and second premolar was significantly more successful after CCLADS injection in comparison with conventional injection. Significantly higher success rate of pulpal anesthesia with CCLADS compared to conventional injection was also observed in comparative study of Lee et al., but for all tested teeth from lateral incisor to second premolar after AMSA nerve block achieved with 1.4 ml of 2% lidocaine with epinephrine 1:100,000. Lower success rate obtained with conventional injection could be due to the difference in pressure gradient and flow rate between computer controlled and conventional delivery, since with computer controlled delivery system both factors are more precisely controlled and constant, providing better conditions for anesthetic solution diffusion through alveolar and palatal bone. Furthermore, within the groups, the most successful pulpal anesthesia was observed for lateral incisor and canine, while the lowest success rate was observed for central incisor and first premolar regardless the delivery system used. The obtained results could be explained by anatomical variability in innervation of the anesthetized area, since it is possible that buccal root of first premolar may be innervated by accessory branches of posterior superior alveolar nerve.\(^\text{12}\) Also, buccal position of the root defines greater distance and diffusion path of anesthetic solution which is deposited palatal. Similarly, the distance of central
incisor’s root from the deposition site could affect diffusion of anesthetic solution, leading to comparatively lower pulpal anesthesia success rate.

Onset of pulpal anesthesia was similar between the investigated groups in our study. Results of previous studies, after AMSA nerve block performed with 2% lidocaine with epinephrine, showed that onset time ranged between 5 and 11 minutes with CCLADS delivery system, and between 6 and 12 minutes with conventional injection delivery \(4,6\). Similar results are obtained in our study. Similarly as in previously mentioned studies, longer onset time was observed for central incisor and canine, with both delivery systems. It is possible that this delay in onset is due to greater diffusion distance of anesthetic solution through alveolar and palatal bone \(6\).

Only two studies reported duration of pulpal anesthesia after AMSA nerve block achieved with 2% lidocaine with epinephrine. In the study of Fukayama et al., authors reported duration of pulpal anesthesia up to 40 minutes, including all tested teeth from central incisor to first molar, after the AMSA nerve block obtained with 2% lidocaine with epinephrine 1:80.000 with CCLADS delivery system \(3\). Similarly, Velasco and Soto observed duration of pulpal anesthesia of tested teeth between 23 and 40 minutes when 2% lidocaine with epinephrine 1:100.000 was applied with conventional cartridge-syringe \(4\). However, in the mentioned studies, statistical analysis of pulpal anesthesia duration was not performed due to low number of participants with successful pulpal anesthesia. In the present controlled clinical study, with confirmed statistical power, duration of pulpal anesthesia comparing two delivery systems was similar and ranged from 24 to 32 minutes for conventional syringe delivery, and between 26 to 29 minutes for CCLADS. Regarding the pharmacological profile of articaine, the degree of articaine protein binding (95%), which is higher than that of lidocaine (65%), is expected to ensure more firmly attachment of articaine molecules to protein receptors sites, responsible for longer duration of clinical activity. However, further comparative study of articaine and lidocaine might confirm anesthetic superiority concerning anesthesia duration after articaine delivery for the AMSA nerve block.

It still remains unclear whether AMSA nerve block truly acts as a nerve block, since anesthetic solution is not deposited directly in the vicinity of any main nerve trunk. Furthermore, success as well as duration of pulpal anesthesia varied with the distance and
bone thickness between tooth apex and deposition site, which favors more tissue infiltration as a type of anesthesia, over nerve block conduction. Taking all together, there could be a possibility that the AMSA nerve block acts as an intraosseous injection, which directly reflects to significance of articaine + epinephrine safety profile. This route of administration, due to the deposition of local anesthetic in highly vascularized bone area, allows rapid resorption of both, local anesthetic and vasoconstrictor. Therefore, the safety profile of AMSA nerve block in the present study was evaluated by monitoring of cardiovascular parameters. Systolic blood pressure was significantly decreased within CCLADS group from 5th to 15th minutes in comparison with baseline values, and in conventional group from 10th to 30th minute when compared to baseline. At the 5th minute, systolic blood pressure was significantly increased after conventional injection in comparison with CCLADS. Decreased systolic blood pressure within both groups in our study implies good safety of AMSA technique with regard to cardiovascular stability, which is supported also by decreased values of diastolic blood pressure from 5th to 10th minute for CCLADS injection and from 10th to 15th minute for conventional injection, in comparison with baseline values. Heart rate was significantly decreased only in CCLADS group from 10th to 30th minutes, which suggests more preferable cardiovascular profile after CCLADS injection, since heart rate is cardiovascular parameter that is the most sensitive to exogenous epinephrine effects.

In conclusion, in conditions of the present double-blind randomized controlled cross-over clinical study, the efficacy of pulpal anesthesia, especially for lateral incisor and canine, as well as safety of cardiovascular profile of 0.6 ml of articaine with epinephrine (1:100,000) delivered with CCLADS overcome conventional syringe delivery.

Acknowledgement This study was supported by Ministry of Education, Science and Technological Development of Republic of Serbia, Grant No. 175021.
REFERENCES


Enrollment

Assessed for eligibility (n=67)

Excluded (n=37)
- Not meeting inclusion criteria (n=21)
- Declined to participate (n=6)
- Other reasons (n=0)

Allocation

Randomized (n=40)

Received AMSA with conventional syringe (n=40)
Did not receive AMSA (n=0)

Did not receive AMSA (n=0)

Follow-Up

Lost to follow-up (n=0)
Excluded (n=2) (failed anesthesia)

Excluded (n=2) (failed anesthesia)

Analysis

Analyzed (n=38)
- Excluded from analysis (n=0)

Analyzed (n=38)
- Excluded from analysis (n=0)
Fig. 1 Flow diagram of randomization to either conventional injection or computer-controlled local anesthetic delivery system (CCLADS) for anterior and middle superior alveolar nerve block (AMSA) (CONSORT Statement 2010 Flow Diagram from Schulz KF, Altman DG, Moher D, for the CONSORT Group (2010) CONSORT 2010 statement: Updated guidelines for parallel group randomized trials. J Pharmacol Pharmacother. doi: 10.4103/0976-500X.72352)
Fig. 2 Changes in systolic blood pressure

a within group comparison, One-way repeated measures ANOVA (baseline vs. observed time interval, Bonferroni post hoc); for CCLADS 5th min (p<0.001), 10th min (p=0.009), 15th min (p=0.008); for conventional 10th min (p=0.001), 15th min (p<0.001), 30th min (p=0.029)

b between groups comparison, Paired samples t-test, 5th min (p=0.006)
Fig. 3 Changes in diastolic blood pressure

\^a within group comparison, One-way repeated measures ANOVA (baseline vs. observed time interval, Bonferroni post hoc); for CCLADS 5\textsuperscript{th} min (p=0.037), 10\textsuperscript{th} min (p=0.036); for conventional injection 10\textsuperscript{th} min (p=0.001), 15\textsuperscript{th} min (p=0.006)
Fig. 4 Changes in heart rate

*within group comparison, One-way repeated measures ANOVA (baseline vs. observed time interval, Bonferroni post hoc); for CCLADS 10\(^{th}\) min (p=0.008), 15\(^{th}\) min (p=0.003), 30\(^{th}\) min (p=0.003)

<table>
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<td>CCLADS (p^a)</td>
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<td></td>
<td>n/N n/N N</td>
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<td>29/38</td>
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<tr>
<td>Second premolar</td>
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<td>33/38</td>
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\(p^b\) \(0.020<0.001\)
Table 1

Success of pulpal anesthesia after AMSA injection of 4% articaine with conventional syringe and CCLADS

\[ \text{N number of participants, } n \text{ number of successfully anesthetized teeth} \]
\[ \text{\textsuperscript{a} between groups comparison (McNemar test)} \]
\[ \text{\textsuperscript{b} within group comparisons (} \chi^2 \text{ test, Fisher’s test post hoc), } *p<0.05: \text{ conventional injection for lateral incisor vs. central incisor (p=0.012), lateral incisor vs. first premolar (p=0.012), lateral incisor vs. second premolar (p=0.006); CCLADS injection for lateral incisor vs. central incisor (p<0.001), lateral incisor vs. first premolar (p=0.012), canine vs. central incisor (p<0.001), canine vs. first premolar (p=0.012)} \]
Table 2
Onset and duration of successful pulpal anesthesia after AMSA injection of 4% articaine with conventional syringe and CCLADS

<table>
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<tr>
<th>Tooth</th>
<th>Onset (n)(n)(n)(n)</th>
<th>Duration</th>
<th>Conventional</th>
<th>CCLADS p&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CCLADS p&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CCLADS p&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central incisor</td>
<td>10.61±5.31*10.31±5.45</td>
<td>24.62±18.92</td>
<td>28.31±15.79</td>
<td>0.411</td>
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<tr>
<td>Lateral incisor</td>
<td>8.01±4.17 8.00±4.68</td>
<td>33.14±19.95</td>
<td>28.11±17.51</td>
<td>0.168</td>
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<tr>
<td>Canine</td>
<td>9.45±4.58*</td>
<td>8.68±5.03</td>
<td>32.19±17.04</td>
<td>29.58±19.38</td>
<td>0.710</td>
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</tr>
</tbody>
</table>
Values given in minutes as mean±SD, n number of successfully anesthetized teeth

<table>
<thead>
<tr>
<th></th>
<th>First premolar</th>
<th>Second premolar</th>
<th>p</th>
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<tbody>
<tr>
<td></td>
<td>7.07±5.45</td>
<td>7.08±5.50</td>
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<tr>
<td></td>
<td>7.74±6.59</td>
<td>8.45±5.02</td>
<td>0.172</td>
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<td>(27)</td>
<td>(26)</td>
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<td>0.057</td>
</tr>
<tr>
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<td>32.55±14.30</td>
<td>31.62±16.11</td>
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</tr>
<tr>
<td></td>
<td>26.34±9.26</td>
<td>29.46±17.94</td>
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<tr>
<td></td>
<td>(27)</td>
<td>(26)</td>
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<td>0.407</td>
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<td>0.896</td>
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<td>(27)</td>
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</tr>
</tbody>
</table>

Values given in minutes as mean±SD, n number of successfully anesthetized teeth

*a* between groups comparison (Wilcoxon Sign Rank test)

*b* within group comparison (Kruskal Wallis test, Mann Whitney U test *post hoc*), *p*<0.05: conventional injection for central incisor vs. lateral incisor (p=0.024), central incisor vs. first premolar (p=0.037), central incisor vs. second premolar (p=0.022), canine vs. first premolar (p=0.044)