Evaluation of Hypothermic and Analgesic Effects of Local Anesthetics Based on Non-Contact Thermography and Registration of Evoked Responses

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Abstract

Literature provides information that local hypothermia has a nonspecific anti-inflammatory effect. Aim: to assess the intensity of the hypothermic effect of application drugs with local anesthetic properties and determine the tropism of local anesthetics to the tissues of the maxillofacial region.

The study of temperature indicators from the oral mucosa was carried out using an infrared thermometer before, immediately, 1, 2 and 5 minutes after the application of a gel based on 10% lidocaine, 20% benzocaine and a gel based on a chelate complex organogermanium compounds with guanine. Skin temperature was determined using a thermal imager before and after injections of 4% articaine with an epinephrine 1:100000 and 1:200000. To evaluate the effectiveness of injectable forms of local anesthetics, a study of thermal evoked potentials was performed using a Contact heat evoked potential stimulator.

A study of the cooling effect of application of anesthesia showed that immediately after application in all groups, especially in nonanesthetic gel chelate organogermanium complex immediately after application 32.92 °C, 1 minute - 32.84 °C, 3 minutes - 33.67 °C, 5 minutes - 34.69 °C. The use of an increased content of the vasoconstrictor at the periphery of the injection site results in depression of the microvasculature, as indicated by a decrease in the temperature background. According to CHEPS registration 4% articaine is somewhat more effective for anesthetizing teeth and bones, as it often causes deeper anesthesia and 3% mepivacaine without epinephrine is physiologically more suitable for working with soft tissues.

In the presence of acute inflammatory diseases of the oral mucosa or chronic and / or recurrent processes, the drug of choice may be a chelate organogermanium gel. It is necessary to take into account not only its tropism to tissues, but also its hypothermic effect.

Keywords: Hypothermia, local anesthetic, oral mucosa, articaine, evoked potential.

Received date: 19 February 2021
Accept date: 18 April 2021

Introduction

Assessment of body temperature is basic in the diagnosis of most diseases, especially those accompanied by changes in thermoregulation and autonomic reactions.

For example, in the work, anatomical and constitutional data of thermally active zones of the face and neck are presented, indicating a different temperature gradient that can be taken into account in clinical practice¹. Was showed convincing evidence of greater efficiency in the diagnosis of sinusitis compared to X-ray diagnostic methods, determining not only the high sensitivity of the method to early and preclinical manifestations of diseases, but also focusing on the economic components of the method².

Since one of the components of the pain response is vegetative, its assessment and registration of the response intensity can be used in practical health care. The literature provides

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data on the successful use of thermal imagers in the diagnosis of vascular lesions, cardiovascular disorders, in sports medicine, with metabolic disorders\(^3\), \(^4\), \(^5\), \(^6\), \(^7\).

Of interest are data on the assessment of the effectiveness of pain relief and pain in general using infrared thermometry. It was presented as the results of the implementation of the assessment criterion “thermally related pain intensity” (TAPI) in patients undergoing local anesthesia\(^8\). It is noted that the use of non-contact infrared thermography in the postoperative care unit for monitoring respiratory rate disorders, as an important factor affecting mortality, has shown high efficiency and clarity on a par with electrocardiography\(^9\).

Measurement of skin temperature after a sciatic nerve block using ropivacaine has shown that nerve anesthesia will lead to an increase in temperature, and this will correlate with existing tests for sensory blockade\(^10\). Thus, the authors suggest that infrared thermal imaging can be used as an assessment test for local anesthesia at a time when sensory tests are not available.

Optimal diagnostic time to assess the effectiveness of local anesthesia. In their study of axillary nerve blockade, the authors argue that thermography provides an early and objective assessment of the success and failure of axillary regional blockade\(^11\).

The high visibility and effectiveness of the assessment of the performed anesthesia is also indicated in the study of paravertebral blockade\(^12\). Thus, according to the authors, additional monitoring of temperature changes performed by an infrared camera can confirm the appropriate range of pain relief required for the operation.

Modern studies of the characteristics of pain sensitivity of the trigeminal nerve system are focused mainly on diagnosing the effectiveness of treatment for various pathologies noting the difficulty of recording responses when studying the effectiveness of local anesthesia or ranking according to the types of local anesthetics\(^13\). These studies combine evidence of the clarity and specificity of the method in relation to pain sensitivity\(^14\), \(^15\).

It is appropriate to point out the use of the method for recording somatosensory evoked potentials in the clinic of traumatic trigeminal nerve lesions, where an increase in latency and a decrease in the amplitudes of early components indicate the severity of a structural defect\(^16\), \(^17\).

Normally, the so-called homeothermal core of the human body has a relatively constant temperature - about 37.5 \(^\circ\) C with daily fluctuations within 1 \(^\circ\) C\(^18\), \(^19\), \(^20\). These are the abdominal organs, the brain, the heart, the blood in the large arteries and the muscles located deep in the body. The temperature of peripheral tissues is much lower and varies widely\(^21\).

The literature describes the main causes of local hypothermia, including impaired arterial blood supply and decreased microcirculation\(^22\). In dentistry and, in particular, in assessing the functional effectiveness of local anesthesia by determining the degree of tissue ischemia against the background of the use of a vasoconstrictor, an assessment of a greater degree of microcirculation disturbance plays an important role. Thus, the literature provides data on the intensifying effect of low temperature on the effectiveness of local anesthesia\(^23\).

Research results show that local hypothermia has a nonspecific anti-inflammatory effect\(^24\). Experimental data indicate a vascular effect in the form of a process of vasoconstriction - vasodilation under the action of low temperatures due to vascular tone. The contraction of blood vessels by vasoconstrictors, which are part of the local anesthetic, leads to a decrease in oxygen supply and the development of hypoxia, which has a significant effect on the excitability of nerve fibers\(^25\), \(^26\). Myelinated nerve fibers are sensitive to a lack of oxygen, while unmyelinated fibers of group C practically do not change their excitability; the thicker the nerve fiber, the more its excitability decreases under the influence of hypoxia.

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage\(^27\). The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"\(^28\).

Various authors indicate the character of toothache intolerable for the patient\(^29\), \(^30\), \(^31\). Peculiarities of the pain reaction, depending on the type of stimulus (mechanical or inflammatory), can determine the level of damage, since a group of type A fibers, acutely reacting to stimuli, can signal reversible changes in the morphology of the human tooth pulp, and the occurrence of dull, pressing pain, prolonged during the period when
C fibers are activated, on the contrary, indicates irreversible processes. In this regard, the search for an optimal remedy to relieve pain associated with injury is urgent.

**AIM:** to assess the intensity of the hypothermic effect of application drugs with local anesthetic properties, the degree of external vasoconstriction and the tropism of local anesthetics to the tissues of the maxillofacial region according to the registration of thermal evoked potentials.

**Materials and methods**

The study involved 40 men and 60 women, the average age of men was 36.8 ± 5.02 years, the average age of women was 30.43 ± 2.14 years, who had local inflammatory complications in the oral cavity against the background of local anesthesia.

The study of temperature indicators from the oral mucosa was carried out using an infrared thermometer "CEM-Thermo Diagnostics" (Fig. 1) before, immediately, 1, 2 and 5 minutes after the application of a gel based on 10% lidocaine, 20% benzocaine and gel on based on the chelate complex of organogermanium compounds with guanine, and also recorded the usual value of blood pressure. To reduce the effect of background temperatures, the working part of the apparatus was shielded with a thermo-inert polymer ring, which creates a measuring corridor between the mucous membrane and the pyrometer.

The chelate complex of an organogermanium compound with guanine ensures the formation of local immunity of the oral mucosa, activates the production of cytokines (interferons and interleukins) and specific antibodies, thereby preventing the development and spread of infection and contributing to the speedy healing of skin and mucous membrane injuries. The complex can be used both individually and in combination with other therapeutic agents, including for the treatment of patients at risk: patients with diabetes mellitus, people with blood diseases, with immunodeficiency, patients after a course of hormonal therapy, antibiotic treatment, chemotherapy.

Xylitol stimulates the secretion of saliva, which contains specific antibodies IgA, IgM, IgG and nonspecific substances lactoferrin, lysozyme, lactoperoxidase, which maintain normal microflora and destroy foreign antigens. Alginic acid salts provide a prolonged antibacterial effect and are a sorbent for circulating immune complexes. Alginites obtained from the kelp kelp are widely used in medicine as a hemostatic, antiseptic and wound healing agent. Alginites have a regenerating and anti-inflammatory effect, improve blood circulation. Their immunomodulating effect is also known. Alginites stimulate phagocytosis and stabilize membrane structures.

To assess the degree of external vasoconstriction, the buccal region of the lower jaw was selected against the background of infiltration anesthesia in the molar region.

We used infiltration anesthesia with a 4% articaine local anesthetic with an epinephrine in a ratio of 1: 100000 and 1: 200000 at a dosage of 0.5-0.7 ml (Septanest with adrenaline) in same 100 patients. The temperature was determined using a Nec InfReC Thermo Gear G30 thermal imager according to the following parameters: minimum temperature; maximum temperature; average value. Analysis of infrared images was performed using the Thermography Studio software. The emissivity was 0.98.

Thermal images show temperature fluctuations in increments of 0.1 ° C. The device is equipped with a universal lens with a 28 × 21 capture. Focusing can be performed automatically or manually in 0.1 cm steps (Fig. 2). The Nec InfReC Thermo Gear G30 thermal imager is equipped with a matrix with a resolution of 160x120 pixels (Fig. 3). Thermograms are
distinguished by high detail and quality; they are highly informative, which ensures high efficiency of thermal diagnostics. The thermal imager also has a built-in video camera with a matrix of 752x480 pixels. Evaluation of infrared images and creation of research protocols were carried out using the professional software Thermography Studio.

Figure 2. Thermogram of patient G., 34 years old, before injection (1 - study area).

To evaluate the effectiveness of injectable forms of local anesthetics, a study of thermal evoked potentials was performed using a Contact heat evoked potential stimulator (CHEPS) device (Medoc Ltd, Ramat Yishai, Israel), which heats up the stimulating thermode by heating the outer layer (stanyol containing two thermoelements) with speed of 70 °C / sec and cooling it immediately after reaching the peak temperature at a rate of 40 °C / sec due to Peltier thermoelectric elements of the inner layer. The peak temperature was set at 54 °C, the base temperature at 33 °C. Through a contact thermode with a diameter of 27 mm, heat pulses of the same intensity were applied to the skin in the area of the lower jaw, alternately on the right and on the left with a variable time interval of about 8 seconds. The stimulus was subjectively perceived as slightly burning.

The first stimulus was always perceived more sharply, was often accompanied by a muscle artifact, so the response to the first 1-2 stimuli was not averaged. To reduce the habituation effect, the thermode was shifted after each impulse, the total stimulation area averaged 5 x 3 cm. The recording electrodes were placed in the vertex (active electrode) and ear lobe (reference electrode). 8-12 responses were averaged at an analysis epoch of 1000 ms (1 s) in the amplifier passband of 0.5-100 Hz. Received 2 responses, which were then also averaged to the final curve for analysis. The reproducibility of the answers served as a criterion for the reliability of the research results. The evoked responses were recorded twice: before local anesthesia and 5 min after anesthesia.

Using disposable carpool dental injectors manufactured in Russia, local anesthesia was performed near the chin foramen, the injection area was determined by palpation for the best identification of the target point. An aspiration test was performed before administration of the local anesthetic solution.

The distribution of 100 patients under study was as follows: 55 subjects were injected with a 4% solution of an 4% articaine local anesthetic with an epinephrine in a ratio of 1: 200000 (pH 4.8-5.4) and 45 subjects - a 3% solution of mepivacaine-containing local anesthetic without a vasoconstrictor (pH 5, 8-6.4). In different subjects, the sequence of the procedure after anesthesia was changed in a random order: first, the evoked responses to electrical stimulation were recorded, then to thermal stimulation, and vice versa, in order to avoid the influence of this factor on the result.

Recording of evoked responses and analysis of the resulting curves were performed by an investigator who was unaware of the anesthetic used. In thermally evoked responses the same parameters of the negatively positive N-P-N complex. In addition to digital data of absolute values of LP and amplitude, the changes in responses after anesthesia were also scaled according to the following scales:0 - the answer has not changed; 1 - slightly decreased; 2 -...
decreased by 50%; 3 - the answer disappeared.

The research was approved by the Ethics Committee of the I.M. Sechenov First Moscow State Medical University (No. 06-17 of July 12, 2017).

The data were processed using the Medstatista software.

**Results**

Application of a gel based on 10% lidocaine is accompanied by the following temperature dynamics: the average temperature before application was 35.6 °C, immediately after application 34.56 °C, after 1 minute - 34.8 °C, after 3 minutes - 35.07 °C, after 5 minutes - 35.12 °C. The maximum hypothermic effect is achieved immediately after application of the drug. The high rate of recovery of the temperature of the oral mucosa in the area of application is associated with the vasodilating properties of the drug.

Application of a gel based on 20% benzocaine is accompanied by the following temperature dynamics: the average temperature before application was 35.2 °C, immediately after application 35.5 °C, after 1 minute - 34.59 °C, after 3 minutes - 35 °C, after 5 minutes - 35.15 °C. The maximum hypothermic effect is achieved immediately after application of the drug and lasts up to 1 minute, after which the restoration of the local temperature of the oral mucosa is determined.

Spearman's correlation coefficient (ρ) for local hypothermia using gels based on 10% lidocaine and 20% benzocaine is 0.700, which corresponds to a high Chaddock bond strength in the presence of a direct relationship with studies.

Application of a gel containing a chelate complex of organogermanium compounds with guanine was used. Summarized data of preparations based on germanium-containing gel is 0.900, which corresponds to a very high Chaddock binding strength in the presence of a direct relationship with studies.

At a significance level of p<0.05, we calculated the Mann Whitney U-test for drugs based on 10% lidocaine and germanium-containing gel. The obtained empirical value U (3) is in the zone of uncertainty, which indicates that the differences between the groups of subjects on this scale are significant at the significance level of p <0.05. Spearman's correlation coefficient (ρ) for local hypothermia using gels based on 20% benzocaine and a germanium-containing gel is 0.600, which corresponds to a noticeable Chaddock binding strength in the presence of a direct relationship with studies.

At a significance level of p≤0.05, we calculated the Mann Whitney U-test for preparations based on germanium-containing gel and 20% benzocaine. The obtained empirical value U (3) is in the zone of uncertainty, which indicates that the differences between the groups of subjects on this scale are significant at the significance level of p <0.05.

The hypothermic effect was greatest in the group where the gel based on the chelate complex of organogermanium compounds with guanine was used. Summarized data of temperature measurements are presented in table 1.

The average temperature before the thermographic study was 34.99 °C (Fig. 4). It has been shown that temperature asymmetry is observed when using different concentrations of the vasoconstrictor.

Thus, in 45 volunteers using a 4% articaine-containing local anesthetic with a vasoconstrictor in a ratio of 1: 200,000, an upward temperature asymmetry was noted at the 5th minute of the study, which was 38.5 ± 0.34 °C (Fig. 5). Further, there was a slight decrease
by 20 minutes and was 36.3 ± 0.39 °C. At the end of the study, at 40 minutes, the persisting temperature asymmetry was determined in comparison with the initial measurement up to 34.1 ± 0.37 °C.

The reduced content of the vasoconstrictor at the periphery of the injection site results in a compensatory activation of the microvasculature, which is subjectively indicated by a change in the temperature background.

When using a 4% articaine local anesthetic with an epinephrine 1: 100,000, 55 volunteers (Fig. 6) showed a downward temperature asymmetry at the 5th minute of the study was 30.7 ± 0.34 °C and slightly increased by 20 minutes and was 31.4 ± 0.39 °C (Fig. 7).

At the end of the study, at 40 minutes, the persisting temperature asymmetry was determined in comparison with the initial measurement up to 33.6 ± 0.37 °C.

The dynamics of the increased content of the vasoconstrictor at the periphery of the injection area gives a depression of the microvasculature, which is indicated by the change in the temperature background downward.

Student's t-test indicates the presence of a statistical difference at the 5th minute of the study using a 4% articaine local anesthetic with an epinephrine 1: 100,000 and 1: 200,000, because the obtained empirical value $t=40.2$ is in the zone of significance at $p≤0.05$. At a significance level of $p≤0.05$, the Mann-Whitney U-test shows that $U (0)$ is in the zone of significance. However, the estimate of Spearman's correlation coefficient ($\rho$) was 0.575, which corresponds to the noticeable strength of the Chaddock connection in the presence of a direct research connection.

Student's t-test shows the presence of a statistical difference at 20 minutes of the study using 4% articaine local anesthetic with an epinephrine 1:100000 and 1:200000, because
the obtained empirical value $t = 4.8$ is in the zone of significance at $p \leq 0.05$. With a significance level of $p \leq 0.05$, the Mann-Whitney U-test at 20 minutes of the study using 4% articaine local anesthetic with a epinephrine 1: 100000 and 1: 200000 shows that $U (0)$ is in the zone of significance. However, the estimate of Spearman's correlation coefficient ($\rho$) was 0.243, which corresponds to a weak connection strength according to Chaddock in the presence of a direct research connection.

At the end of the study (40 minutes), there is also a statistical difference according to Student's $t$-test in the study of 4% articaine-containing local anesthetic with a vasoconstrictor 1: 100000 and 1: 200000, because the obtained empirical value $t = 4.1$ is in the zone of significance at $p \leq 0.05$. At a significance level of $p \leq 0.05$, the Mann-Whitney U-test at 20 minutes of the study using 4% articaine local anesthetic with an epinephrine 1: 100000 and 1: 200000 shows that $U = 0.5$ is in the zone of significance. However, the estimate of Spearman's correlation coefficient ($\rho$) was 0, which corresponds to a weak Chaddock relationship in the presence of research feedback. In this case, the number of degrees of freedom ($f$) is 2; which indicates the statistical significance of the dependence of the features ($p < 0.05$).

The evoked potentials to thermal stimulation demonstrated a significant decrease in the amplitude of all components and a lengthening of the latency period of the main negative-positive complex N2-P2 after anesthesia as compared to the initial thermal evoked responses (Table 2, Fig. 8). It was difficult to estimate the latency period of the last N3 component after anesthesia, since in some cases it apparently extended beyond the analysis epoch. The complete disappearance of thermal responses was observed in 87 out of 100 subjects (87%), insignificant changes in only 13 (13%).

### Table 1. Dynamics of temperature indicators when using various application preparations with local anesthetic activity according to infrared thermometry data.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Thermal evoked potential components ($M \pm \sigma$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N2</td>
</tr>
<tr>
<td>Latency period in ms before anesthesia</td>
<td>404±51</td>
</tr>
<tr>
<td>after anesthesia</td>
<td>474±66**</td>
</tr>
<tr>
<td>Amplitude in $\mu V$ before anesthesia</td>
<td>47.0±17.3</td>
</tr>
<tr>
<td>after anesthesia</td>
<td>8.4±7.4**</td>
</tr>
</tbody>
</table>

* reliability of differences at $p < 0.05$  ** reliability of the shift at $p < 0.01$.  

### Table 2. Parameters of long-latency evoked potentials for thermal stimulation before and after anesthesia in the healthy group as a whole.

* reliability of differences at $p < 0.05$  ** reliability of the shift at $p < 0.01$.  

![Figure 8. Average thermal evoked potentials before anesthesia (curve 1) and after anesthesia (curve 2). The main components are indicated.](image)

![Figure 9. Average thermal evoked potentials before anesthesia (curve 1) and after anesthesia by 4% articaine (curve 2) and anesthesia (curve](image)
3) and after anesthesia by 3% mepivacaine (curve 4). The main components are indicated.

<table>
<thead>
<tr>
<th>Components</th>
<th>4% articaine injection</th>
<th>3% mepivacaine injection</th>
</tr>
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<tbody>
<tr>
<td>Latency period in ms</td>
<td>Amplitude in µV</td>
<td>Latency period in ms</td>
</tr>
<tr>
<td>N1 before anesthesia</td>
<td>414±17</td>
<td>231±7,8</td>
</tr>
<tr>
<td>after anesthesia</td>
<td>451±42 *</td>
<td>8,2±9,1 **</td>
</tr>
<tr>
<td>P2 before anesthesia</td>
<td>546±12</td>
<td>56,3±13,7</td>
</tr>
<tr>
<td>after anesthesia</td>
<td>575±71 *</td>
<td>15,2±18,2 **</td>
</tr>
<tr>
<td>N3 before anesthesia</td>
<td>742±58</td>
<td>29,8±11,9</td>
</tr>
<tr>
<td>after anesthesia</td>
<td>725±88 *</td>
<td>6,7±10,1 **</td>
</tr>
</tbody>
</table>

Table 3. Parameters of thermal evoked potentials before and after anesthesia by 4% articaine and 3% mepivacaine.

* reliability of differences at p < 0.05  ** reliability of the shift at p < 0.01.

In thermal EPs, a decrease in the amplitude and elongation of the LA was observed both after anesthesia with articaine and mepivacaine (Table 3, Fig. 9). The total disappearance of the response was in 40 of 55 healthy (90%) after the use of 4% articaine and only in 34 of 45 (75.56%) after the use of 3% mepivacaine (p < 0.05). Weak changes - in 10 (10%) in the 4% articaine group and in 11 (24.4%) in the 3% mepivacaine group.

Therefore, it can be stated that a 4% solution of articaine is somewhat more effective for anesthetizing teeth and bones, as it often causes deeper anesthesia.

In this regard, we can say that a 3% solution of mepivacaine without a vasoconstrictor is physiologically more suitable for working with soft tissues, incl. due to the pH value being closer to the neutral position.

Discussion

Topical anesthesia is an important stage in the formation of the patient's psychological comfort during injection anesthesia. Due to the absence of a statistical difference between the data on the use of these drugs, gels based on 20% benzocaine should be preferred, since low concentrations of lidocaine increase the risk of polymorphic arrhythmias 33. Of particular interest are the results of a study of a gel based on a chelate complex of an organogermainium compound with guanine, immediately after application of which severe hypothermia is observed, which, together with the anti-inflammatory activity of the drug, can be recommended for patients at risk.

There is an opinion that with a local decrease in temperature in the tissues, biochemical changes in homeostasis occur, which actively affect interstitial metabolism. In this case, the accumulation of tissue preservation products or stimulants of biological origin occurs, and endogenous interferon is released, which actively diffuses into cells, preventing the activation of the virus.

With the development of recurrence of herpes in the area of the injection site, an increase in the expression of mRNA of IFN-α, IL-1β, IL-8, IL-4, a decrease in the synthesis of IL-12 mRNA was revealed 34. Preservatives and epinephrine quite dynamically change the concentration of local immunity indicators 35. The authors point out that of all anesthetics, mepivacaine to a greater extent blocks the synthesis, which protects the oral mucosa from pathogenic microorganisms, potential allergens and antigens, activates phagocytosis and a number of complement factors.

The study of the temperature asymmetry over the area of the local anesthetic depot showed that an increased content of the vasoconstrictor (1: 100000) at the periphery of the injection area gives a depression of the microvasculature and, as a consequence, a decrease in the temperature background, and when using a lower concentration of a vasoconstrictor (1: 200000), an increase the temperature of the skin over the area of the anesthesia depot, which indirectly indicates the compensatory activation of the microvasculature. A special novelty of the study was the study of the results of the application of thermal evoked potentials (CHEPS method), which allows registering selective activation. The most pronounced reduction was more often observed in thermal EPs; in 58% of cases, their complete disappearance was noted after anesthesia. Thermal EPs are associated with the selective activation of fine nerve fibers of the Aδ and C types, which are responsible for pain and temperature sensitivity 36,37,38.

Thus, the decrease in these responses was quite consistent with the desired effect of anesthesia and objectified it. Nevertheless, not all subjects showed a decrease in thermal EP, in 12.5% of cases there were no noticeable changes.
Conclusions

1. When choosing an application drug with local anesthetic activity, preference should be given to 20% benzocaine with a neutral pH.

2. In the presence of acute inflammatory diseases of the oral mucosa or chronic and / or recurrent processes, the drug of choice may be a chelate gel based on a chelate complex of an organogermanium compound with guanaine.

3. Analysis of the dynamics of evoked responses depending on the type of anesthetic showed that 4% articaine solution and 3% mepivacaine solution cause a significant reduction in evoked brain responses, with the only difference that articaine is somewhat more effective than mepivacaine, since it more often causes deeper anesthesia.

Declaration of Interest

The authors report no conflict of interest.

References


