The Role of Temperature in the Action of Mepivacaine

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The role of temperature in the action of local anesthetics was studied in 20 healthy young volunteers with plain 3% mepivacaine injected periapically twice in their maxillary first premolar, the first time with the solution at a temperature of 20°C and the second time at 4°C. The pulpal response was measured with a pulp tester every minute. The onset of pulp anesthesia was found to be of no statistical difference between 20°C and 4°C. On the other hand, mepivacaine at a temperature of 4°C was found to have a statistically significant longer duration of action. Our conclusion is that the drop in temperature of mepivacaine from 20°C to 4°C provides a longer duration of pulpal anesthesia.

Key Words: Temperature; Mepivacaine; Local anesthesia; Mechanism of action, onset, duration.

It is well known since ancient times that the placement of something cold (eg, ice) produces anesthesia at the specific site of its placement.[1] Moreover, the effect of lidocaine in blocking nerve impulses both in vitro and in vivo is potentiated by cooling.[2–4] The nerve-blocking effect of lidocaine is also reported as being potentiated by increasing the temperature above 37°C.[2] In other studies, the potency of various tertiary amine local anesthetics in impairing the excitability of frog skeletal muscle was markedly enhanced by an increase in temperature from 20°C to 30°C, and enhancement of the local anesthetic effects was also produced by a decrease in temperature to 5°C.[5] Temperature may thus be an interesting physical variable in the study of nerve-blocking mechanisms. Given the absence in the dental literature of studies about the implications of temperature in the action of local anesthetics, the purpose of this preliminary study is to investigate the effects on the onset and the duration of pulpal anesthesia caused by lowering the temperature of the injected plain 3% mepivacaine from 20°C to 4°C.

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METHODS

Twenty healthy young volunteers (12 women and 8 men, age 21–23 years) who were students in the Dental School of Aristotle University of Thessaloniki were included in this study. Before agreeing to participate in the study, each subject signed a relevant consent that included a brief description of the purpose and the therapeutic procedures involved. All the experimental procedures were conducted in accordance with the protocols outlined by Aristotle University of Thessaloniki regarding the recommended standard practices for Biological Investigations.

For each subject, 0.25 mL of 3% plain mepivacaine (Mepivastesin, 3M ESPE AG, ESPE Platz, D-82229 Seefeld, Germany) was slowly injected periapically with local infiltration in the maxillary first premolar (having no previous restorative treatment) in 2 appointments scheduled 1 week apart with the same tooth and by the same protocol. All injections were made with standard disposable 1-mL insulin syringes and 30-gauge needles. The quantity of 0.25 mL of mepivacaine was chosen after preliminary experiments as an appropriate dose because we did not want the total duration of the experiment to exceed 30–40 minutes.

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In the first appointment the anesthetic solution had a temperature of 20°C, whereas in the second appointment the temperature was 4°C. The temperature of 20°C was chosen because it is the common storage temperature for anesthetics in our department. The temperature of 4°C was chosen because it is used in similar in vitro studies and is easily achieved by keeping the syringes immersed in an ice water bath and making the injections right after removing the syringes from the bath. For each treatment, subjects were not informed about the temperature of the anesthetic, and the rate of injection was similar, with the application time lasting approximately 60 seconds. The first author (D.N.) performed all injections.

Because it can be administered without a vasoconstrictor additive, 3% plain mepivacaine was selected for this study. In the context of this preliminary study, epinephrine might have acted as an extra variable affecting duration and onset of anesthesia. The pulpal response was measured every minute with a digital pulp tester (Pulppen DP2000 Digital, Dental Electronic, Ballerup, Denmark) before the injection and after the application of the anesthetic.

We selected the first premolar because it allows an easy access of the pulp tester. The maxilla with its loose, spongy bone permits the uniform distribution of the drug and the possibility of making a qualitative analysis of our results. The tested tooth was first isolated with a cotton pad and dried, and then the tip of the pulp tester was applied at the buccal surface of the tooth. The tooth was considered anesthetized if the subject did not react under the maximum output of the pulp tester (32 on scale of 32). The onset of pulpal anesthesia was recorded as the time of the first no response to the pulp tester. The duration of pulp anesthesia was determined by the first recorded response to the pulp tester after the onset. One recording per minute was taken. The collected data were analyzed statistically by using the *t* test for paired samples.

Another parameter examined in this preliminary study was subjects' qualitative impressions after each injection. Thus, after the second appointment, subjects were asked to describe any differences they felt between the first and second anesthesia procedures.

RESULTS

The results of this study are summarized in the Table. Regarding the onset of complete pulpal anesthesia (no response at maximum reading on the pulp tester), there was no statistical difference between the use of anesthetic at 20°C and the use of anesthetic at 4°C. On the other hand, the duration of anesthesia with mepivacaine at a temperature of 4°C was found to be significantly longer by approximately 5 minutes as compared with the duration of mepivacaine at 20°C. It should be noted here that although there appears to be an extensive overlap in the summarized duration data as presented in the Table, the increase of anesthesia duration is statistically significant because the *t* test analysis was carried out with paired data for each subject.

The Clinical Onset and Duration of Anesthesia Related to the Temperature*

Anesthesia (N = 20)	*20°C*	*4°C*	*Significance*
Onset (min)	2.5 ± 0.9	2.3 ± 1.3	NS
Duration (min)	17.3 ± 6.8	22.3 ± 8.9	$P < .05$

* Data are presented as mean ± SD. NS indicates nonsignificant.

The majority of the subjects mentioned that in the second appointment (when the injected drug was at 4°C) the anesthesia seemed more concentrated at the site of injection than during the first appointment (20°C). The subjects also mentioned that in the second appointment the drug-injection phase was somewhat more painful than in the first appointment and that they sensed a faster onset of anesthesia. However, the subjects did not report any significant difference in pain experienced after the completion of the second anesthetic procedure.

DISCUSSION

On the basis of studies suggesting that local anesthetic potency is increased at low temperatures,[2,6] we anticipated that by cooling a local anesthetic we might see an increase in the onset or the duration of the induced block. Our data indicate that the duration of action of mepivacaine was significantly increased by its cooling from 20°C to 4°C by approximately 5 minutes, representing a mean 29% increase in anesthesia action duration.

In local anesthesia, the agent must first enter through the connective tissue that surrounds the nerve trunk and then pass through the superficial nerve bundles to be able to block the axons that are placed along the nerve trunk.[7] Cooling-induced alterations in the vascular distribution of local anesthetic might delay or prevent the arrival of the anesthetic at the site of action,[8] affecting the uptake of local anesthetic from the nerve membrane.

It is also possible that cooling alters the efficiency and potency with which local anesthetics block the conduction of a stimulus. It is known that cooling decreases the amplitude and increases the duration and the latency of

the compound action potential.[2] Local anesthetics are known to shift the voltage dependence for sodium channel inactivation in the negative direction, hasten the onset of inactivation after depolarization, and retard recovery from inactivation upon repolarization.[9] The rate of recovery of sodium channels from inactivation during repolarization of skeletal muscle is slowed at low temperature.[10] It is possible that these effects of low temperature and local anesthetics on the kinetics of sodium channel inactivation are independent and merely additive as suggested by Harper et al.[11]

It is also known that cooling produces local anesthesia by itself. Moreover, Goto and Itano[12] and other researchers[13,14] have shown that the pK_a of lidocaine increases as the temperature decreases. Thus, when lidocaine is injected at low temperature, a higher percentage of the local anesthetic will be present in the ionized form once the non-ionizing form of the anesthetic penetrates the neuron. Protonated anesthetics are more potent inhibitors of the Na^+ channel, and this form leads to an apparent increase in lidocaine potency.

Supporting the above physicochemical studies is that cooling has been shown to potentiate anesthesia, general and regional in vitro. Cherkin and Catchpool[15] demonstrated that higher concentrations of diethyl ether, chloroform, halothane, or methoxyflurane were required to anesthetize goldfish as the temperature increased from 5°C to 30°C. Other researchers[2] have shown that when the temperature of the sciatic nerve of the rat was increased from 17°C to 24°C the required nerve-blocking concentration of lidocaine was increased fourfold. Cooling potentiated the dose-dependent blocking action of lidocaine. Total block of conduction occurred at 17°C with 100 μM lidocaine, at 20°C with 200 μM lidocaine, and at 24°C with 400 μM lidocaine.[2] Bradley and Richards[6] measured a 50% increase in benzocaine potency when frog sciatic nerves were cooled from 18°C to 2°C.

The increase in the potency of various anesthetics with the fall of temperature may also be the result of a change in the properties of the nerve.[11] It is also possible that cooling of the anesthetic enhances its binding to the proteins of the nerve membrane and thus increases the affinity of the charged anesthetic molecule to the receptors of the nerve membrane that produce anesthesia. The result is that the removal of the anesthetic from the receptors is taking place at a slower rate, and therefore the duration of anesthesia is enhanced in a cooler environment. Both the presence of local anesthetics and the alterations in temperature can influence changes in the conformation of membrane proteins that control the permeability of sodium channels that affect anesthesia. The paradoxical enhancement of local anesthesia appearing in the literature by both increase and decrease in temperature may be explained by the influence of altered fluidity on the kinetics of different steps in the sequence of conformational changes in the sodium channel, which is produced by changes in membrane potential. The most parsimonious explanation for the different results is that local anesthetics have at least 2 distinct effects: They may act to hasten the onset of inactivation upon depolarization as well as to shift the voltage dependence for steady-state inactivation. This effect can be enhanced by increased temperature and opposed by reduced temperature. Local anesthetics also may interfere with the conformational changes in sodium channel proteins, which are necessary for repolarization-induced reversal of inactivation leading to frequency dependence. This effect can be simulated or enhanced by reduced temperature. Thus, low temperature can oppose tonic block by local anesthetics while augmenting frequency-dependent block.[5]

In our study, there was no statistically significant difference between 20°C and 4°C regarding the onset of complete pulpal anesthesia. The subjects mentioned that anesthesia with the cool drug (4°C) seemed more concentrated at the site of injection than the room-temperature drug (20°C). This subjective feeling could be explained by cold-induced vasoconstriction.

Although the subjects mentioned that they sensed a faster onset of anesthesia in the second appointment (for the cold anesthetic), this was not expressed in our data and subsequent analysis. The reason for that difference between subjective sense and objective findings can be explained by the low rate of measurements (1 per minute), which did not allow for a more detailed qualitative analysis of the behavior of the anesthetics regarding the onset of anesthesia.

The majority of our subjects mentioned experiencing more pain during the cold injection. Many authors[16] suggest that warming the local anesthetic reduces the pain of injection, whereas others[17] conclude that there is no advantage. Our preliminary study suggests that the drop in temperature of a small quantity (0.25 mL) of plain mepivacaine 3% from 20°C to 4°C seemed to prolong the duration of pulpal anesthesia by an average of 5 minutes. However, we believe that more research is needed to investigate the onset and duration of various anesthetics at various concentrations and volumes in a range of temperatures before any useful clinical recommendations can be drawn. In addition, the drug-warming effect should also be investigated, for it is expected that a small quantity of cold anesthetic solution when injected in subcutaneous tissue environment at body temperature will warm up at a yet-unknown rate, thus possibly affecting anesthesia parameters.

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