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A New and Enhanced Version of Local Anesthetics in Dentistry

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1. Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Due to the fear of pain associated with dental injections, some people avoid, cancel, or fail to appear for dental appointments. Pain and anxiety control are among the most important aspects in local anesthetic administration in dental practice. Administration of local anesthetic produces pain and anxiety that may cause subsequent unfavorable behavior (1). As reliable management of pain is an important factor in reducing fear and anxiety in dental treatment, clinicians must have a thorough knowledge of local anesthetic solutions and techniques. When an agent and a technique are chosen, it is important for the clinician to understand the onset, depth, and duration of anesthesia in relation to the operative procedure to be performed (2). This chapter introduces new local anesthetic formulations, techniques, and postinjection complications in dentistry.

2. Pharmacologic properties of local anesthesia

The main working principle of local anesthetics is to inhibit the ion flow on nerve cell membranes to stabilize membrane potential and block stimulus conduction. Local anesthetics can be defined as compounds capable of reversibly suspending the ability of the nerve tissue to conduct stimuli (3).

Local anesthetics consist of a lipophilic aromatic part, which is responsible for the affinity of the compound to the nerve cells, joined by a connecting chain to a hydrophilic part that is responsible for solubility in water and diffusion among tissues. Decomposition of the compound is affected by the nature of the connecting chain, leading to changes in properties such as duration of action or toxicity. Local anesthetics can be divided into two groups according to the nature of the chemical bonding: esters (e.g., procaine) and amides (e.g., lidocaine) (3–4).

The therapeutic value of such compounds is determined by the typical pharmacological properties of local anesthetics. The compound with the longest history of clinical use,
procaine, is used as the basis for comparisons of novel agents. The minimum concentration at which the anesthetic can block stimulus conduction (potency), the therapeutic value of the compound in terms of the correlation between efficacy and tolerability (toxicity), ability of the anesthetic compound to reach tissues at some distance from the site of administration (diffusibility), duration of anesthesia (duration of action), and metabolism of the anesthetic compounds are commonly compared as general pharmacological properties of local anesthetics (3–6).

Vasoconstrictors are added to local anesthetic solutions to inhibit absorption and thus prolong the duration of action and reduce the toxicity of anesthetics as well as to achieve a suitable blood-free area for surgery. Therefore, it is necessary to take into consideration that reactive vasodilatation may occur after surgery with usage of local anesthetics with added vasoconstrictors (7–8).

Adrenaline is the most commonly used vasoconstrictor worldwide. Local anesthetic solutions generally contain adrenaline at a concentration of 1 part per 100000 or 1 part per 200000, resulting in a final content of 0.01–0.005 mg in 1 mL of anesthetic solution. Thus, anesthetic solutions contain adrenaline at very low concentrations compared to the levels required for general physiological effects in healthy individuals (0.3–0.5 mg by subcutaneous administration). There is a great deal of controversy regarding contraindications for the use of adrenaline-containing anesthetics. The mode of administration and quantity added must also be taken into consideration. The American Dental Association and American Heart Association recommend an upper limit of 0.2 mg of adrenaline to be administered in dental operations. On the other hand, the low potency of anesthetic solutions without adrenaline may lead to pain and elevated levels of stress during the operation, resulting in enhanced release of catecholamine (8).

Noradrenaline is another vasoconstrictor used in anesthetic solutions, which has a much weaker local vasoconstrictor effect than adrenaline. Noradrenaline is therefore applied at higher concentrations in anesthetic solutions. The most important advantage of noradrenaline is that it has no direct effect on the cardiovascular system (6–8).

3. Clinical properties of local anesthetics

This section discusses the characteristic clinical properties of the most commonly used local anesthetics.

**Procaine:** Procaine was synthesized by Einhorn in 1905 and is important in the history of the development of local anesthetics, as it was the first compound to be used in humans. Although it has been superceded in dental practice by more effective modern drugs, the clinical properties of such drugs are still compared with those of procaine as a baseline. Procaine is weaker than modern products currently in use in clinical practice. It is highly soluble in water, and its hydrochloride salt is used as a local anesthetic. It has a low toxicity level and a relatively short duration of action (3,7).

**Lidocaine:** Lidocaine is currently the most widely used local anesthetic in clinical practice throughout the world. First synthesized by Löfgren and Lundquist in 1943, its potency is
fourfold greater than that of procaine, and its toxicity is double that of procaine. The duration of action of lidocaine is double that of procaine, and it shows good diffusibility (4).

**Articaine:** This preparation, introduced to medical practice by Muschavek and Rippel in 1974, has similar potency, toxicity, and duration of action to lidocaine. Articaine is used almost exclusively in dental practice (7).

**Bupivacaine:** The toxicity of bupivacaine is ten times that of procaine and has a longer duration of action than lidocaine (7).

**Mepivacaine:** The potency and toxicity of mepivacaine are similar to those of lidocaine. This agent has a mild vasoconstrictor effect, which leads to a prolonged duration of action (5,6).

**Prilocaine:** Prilocaine is used in dentistry as a 4% solution containing a vasoconstrictor. This agent has potency equivalent to that of procaine and a toxicity level slightly lower than that of lidocaine and 1.5 times that of procaine (7).

### 4. Methodology of local anesthesia

Local anesthesia can be classified into two groups according to the manner in which the clinician wants to reach the nerve elements to be anesthetized. The term terminal anesthesia, also called infiltration anesthesia, is used to explain the mode of anesthesia in which the nerve elements are reached at their organ endings, such as the tooth and the periodontal membrane. Practically, there are a number of variants, *i.e.*, topical anesthesia, submucosal infiltration, intramucosal infiltration, and block anesthesia. The term block anesthesia is used to explain blocking of peripheral nerve conduction along the nerve’s course. The anesthetic solution is administered at a site some distance from where the clinician wishes to apply the anesthesia (6,7,8,12).

#### 4.1 Anesthesia of upper teeth

In accordance with the maxillary bone structure, anesthesia of the upper teeth is generally performed terminally. The maxilla is covered by a thin cortical layer, and the internal structure of the bone is sponge-like, which facilitates diffusion of local anesthetic solution. The alternative possibility is the nerve-block method, which can be performed in some cases after careful consideration of the advantages and associated risks (7).

#### 4.2 Anesthesia of lower teeth

In contrast to the maxilla, the anatomic structural properties of the mandible force the practitioner to utilize nerve-block anesthesia methods instead of terminal anesthesia. The cortical bone layer that surrounds the mandible is thicker than the maxilla, and the nerve fibers lie in deeper bone structures, leading to poor performance of terminal anesthesia because of the lack of diffusion of the anesthetic solution into deeper parts of the mandible. Therefore, it is essential to be familiar with the anatomical structures and supply areas of the nerves to be affected when performing local anesthesia in the mandible. There is still
disagreement regarding whether terminal or nerve block anesthesia is the most appropriate method for the lower incisors (9–11).

4.3 Complications of local anesthesia

Although local anesthesia is commonly defined as a safe and noninvasive procedure, some complications have been reported that can be classified into two groups: general and local (7).

General complications are related to the nature and composition of the local anesthetic solution. The most important general complications are toxic and allergic in nature, both of which are capable of causing death in severe cases. Toxic reactions are rarely seen in dentistry, as the quantities of anesthetic agents applied in dentistry and oral surgery are generally within safe limits. If overdosing occurs, central nervous system effects predominate, and spasms, loss of consciousness, and respiratory depression may occur. It is important not to confuse the overdose reactions with those caused by vasoconstrictors. Allergic reactions are the other most important general complications of local anesthesia. Although allergic reactions caused by local anesthetic solutions with amide linkages are extremely rare, clinicians should always be aware of the symptoms of allergic reactions, especially in patients with a history of polysensitivity to other compounds (11–14).

The most common local complications of local anesthesia in dentistry and oral surgery practice are hematoma, nerve damage, trismus, facial paralysis, and tongue and lip injuries. These local complications may be due to the method of anesthesia used, injury to adjacent anatomical structures, or administration of local anesthetic to an inappropriate site (11–14).

4.4 Volume of local anesthesia

Local anesthesia is not always effective in dentistry. The success of inferior alveolar nerve block ranges from 53% to 100%. A higher degree of success would be expected with infiltration anesthesia. Nevertheless, infiltration injection is not always 100% successful. This can be explained by differences in the smoothness, density, porosity, and thickness of the bone surrounding the maxillary teeth, as well as by individual variations in response to the drug administered. When only the anterior maxilla teeth are considered for the anesthetic, the local anesthetic volume ranges from 0.5 to 1.8 mL (2). Brunetto et al. reported that 1.2 mL of 2% lidocaine + 1:100000 epinephrine induced faster onset of pulpal anesthesia, a higher success rate, and a longer duration of soft tissue/pulpal anesthesia of the maxilla (2). Cowan suggested that doses of less than 0.75 mL of 2% lidocaine + 1:80000 epinephrine were adequate for two adjacent teeth after maxillary infiltration. Noncontinuous anesthesia has been reported by other groups after inferior alveolar nerve block. This may be the result of the equilibrium between ionized and nonionized forms of the anesthetic, which results in periods of inadequate pulpal anesthesia (15).

5. Formulation

Inferior alveolar nerve (IAN) block is the most frequently used method for achieving local anesthesia for mandibular procedures. However, IAN block does not always result in
successful pulpal anesthesia. Local anesthetics are chemical compounds that cause reversible blockade of nerve impulses. They are weak bases with pKa values between 7.5 and 9.0, and their physicochemical properties largely determine their clinical anesthetic characteristics. Galindo et al. used pH-adjusted local anesthetic solutions (pH 7.4) in peripheral nerve block and regional anesthesia and reported better quality of anesthesia (16). Davies reviewed the relevant literature and concluded that buffering local anesthetics with sodium bicarbonate significantly reduced injection pain (17).

Whitcomb et al. reported that buffering 2% lidocaine + 1:100000 epinephrine with 0.17 mEq/mL sodium bicarbonate did not significantly increase the success of anesthesia, provide faster onset, or result in less pain at injection compared with unbuffered 2% lidocaine + 1:100000 epinephrine for inferior alveolar nerve block. They considered raising the pH of the anesthetic formulation to 7.9, which is the acid dissociation constant (pKa) of lidocaine, thereby producing equal amounts of the cation and the base form. However, a pilot study of various formulations demonstrated irritating effects (cellulitis and tissue injury). They found that a concentration of 0.17 mEq/mL of sodium bicarbonate raised the pH of the lidocaine formulation to 7.5 without causing an irritating effect. They used a total volume of 3.6 mL of the lidocaine/sodium bicarbonate formulation to allow more sodium bicarbonate to be used by volume than a volume of 1.8 mL would have allowed. Each subject received 72 mg of lidocaine by administration of unbuffered lidocaine, while use of buffered lidocaine resulted in administration of only 60 mg of lidocaine. Therefore, subjects in the buffered group received 17% less lidocaine. Although less lidocaine was administered to patients receiving the buffered formulation, the same success rate of anesthesia was achieved as with the unbuffered lidocaine formulation (18).

Maxillary and mandibular infiltration anesthesia is a common method of anesthetizing maxillary and mandibular teeth. Katz et al. reported that success of anesthesia and onset of pulpal anesthesia were not significantly different among 2% lidocaine + 1:100000 epinephrine, 4% prilocaine + 1:200000 epinephrine, and 4% prilocaine for the maxillary lateral incisor and first molar. For both the lateral incisor and first molar, 4% prilocaine + 1:200000 epinephrine and 2% lidocaine + 1:100000 epinephrine showed equivalent pulpal anesthesia. However, neither agent provided 1 hour of pulpal anesthesia. For both the lateral incisor and first molar, 4% prilocaine provided a significantly shorter duration of pulpal anesthesia compared with 2% lidocaine + 1:100000 epinephrine and 4% prilocaine + 1:200000 epinephrine. Katz et al. suggested that the infiltration injection of 1.8 mL of 2% lidocaine + 1:100000 epinephrine may not always be 100% successful because of individual variations in response to the drug administered, operator differences, and variations in anatomy and tooth position. The success rate of the infiltration of 4% prilocaine + 1:200000 epinephrine was 90% in the lateral incisor and 93% in the first molar. The success of the infiltration of 4% prilocaine was 83% in the lateral incisor and 80% in the first molar and provided a shorter duration of pulpal anesthesia (19).

The mandible is comprised of dense, thick cortical bone, and the efficacy of infiltration anesthesia for mandibular molars in dental procedures has therefore traditionally been considered inadequate. Abdulwahab et al. evaluated the efficacy of six local anesthetic formulations (2% lidocaine + 1:100000 epinephrine (L100), 4% articaine + 1:200000...
epinephrine (A200), 4% articaine + 1:100000 epinephrine (A100), 4% prilocaine + 1:200000 epinephrine (P200), 3% mepivacaine without vasoconstrictor (Mw/o), and 0.5% bupivacaine + 1:200000 epinephrine (B200) used for posterior mandibular buccal infiltration anesthesia. They showed that the maximum mean increases from baseline EPT measurements for the six formulations were 43.5% for L100, 44.8% for B200, 51.2% for P200, 66.9% for A200, 68.3% for Mw/o, and 77.3% for A100 (A100 vs. L100, \( P = 0.029 \)). They reported that the mean VAS pain ratings for injection pain were 32.2 for B200, 27.6 for L100, 26.2 for A100, 24.1 for A200, 22.9 for Mw/o, and 21.0 for P200 (20).

Inferior alveolar nerve block (IANB) is the most frequently used injection technique for achieving local anesthesia for mandibular restorative and surgical procedures. In asymptomatic patients, inferior alveolar nerve block fails 17–19% of the time in the first molar. Therefore, it would be advantageous to improve the success rate of the IANB technique. Additionally, slow onset of anesthesia occurs 12–19% of the time in the first molar with IANB and the use of articaine or lidocaine solutions. If supplemental buccal infiltration can reduce the failure rate and increase the speed of onset of pulpal anesthesia after IANB, the technique may be clinically useful. Haase et al. compared the anesthetic efficacy of articaine vs. lidocaine as supplemental buccal infiltration of the mandibular first molar after inferior alveolar nerve block. They found that with use of the 4% articaine + 1:100000 epinephrine formulation, successful pulpal anesthesia was achieved for the first molar in 88% of cases. With the 2% lidocaine + 1:100000 epinephrine formulation, successful pulpal anesthesia occurred in 71% of cases (21). Robertson and colleagues compared the degree of pulpal anesthesia achieved with mandibular first molar buccal infiltration of 4% articaine + 1:100000 epinephrine and 2% lidocaine + 1:100000 epinephrine. Using the lidocaine formulation, they achieved a success rate of 57% for the first molar. Using the articaine formulation, they achieved successful pulpal anesthesia in 87% of cases. The differences in rates achieved with 2% lidocaine and 4% articaine formulations were significant (\( P < 0.05 \)). Therefore, 4% articaine + 1:100000 epinephrine is superior to 2% lidocaine + 1:100000 epinephrine in mandibular buccal infiltration of the first molar. However, Robertson and colleagues found that pulpal anesthesia with both the 4% articaine and 2% lidocaine formulations declined slowly over 60 minutes (22). Foster et al. investigated the anesthetic efficacy of buccal and lingual infiltrations of lidocaine following inferior alveolar nerve block in mandibular posterior teeth. They found that adding buccal or lingual infiltration of 1.8 mL of 2% lidocaine + 1:100000 epinephrine to IANB did not significantly increase the success of anesthesia in mandibular posterior teeth (23).

Pabst et al. investigated the efficacy of repeated buccal infiltration of articaine in prolonging the duration of pulpal anesthesia in the mandibular first molar. The degree of pulpal anesthesia obtained with two sets of mandibular first molar buccal infiltrations given in two separate doses was examined in 86 adult subjects: an initial infiltration of a cartridge of 4% articaine + 1:100000 epinephrine plus a second infiltration of the same anesthetic and dose 25 minutes after the initial infiltration vs. an initial infiltration of a cartridge of 4% articaine + 1:100000 epinephrine plus mock repeat infiltration given 25 minutes following the initial infiltration. The authors used an electric pulp tester to test the first molar for anesthesia in 3-minute cycles for 112 minutes after the injections. The repeated infiltration significantly
improved pulpal anesthesia from 28 minutes to 109 minutes in the mandibular first molar. Repeated infiltration of a cartridge of 4\% articaine + 1:100000 epinephrine given 25 minutes after the initial infiltration of the same type and dose of anesthetic significantly improved the duration of pulpal anesthesia in the mandibular first molar compared with initial buccal infiltration alone (24).

Increasing attention has been focused on the clinical application of $\alpha$-2 adrenoceptor agonists for anesthetic management. Furthermore, various methods of administration, such as epidural, intrathecal, and peripheral injections, have been examined alone or in combination with another drug to prolong and intensify the anesthesia. The $\alpha$-2 adrenoceptor agonist, clonidine, combined with a local anesthetic, has been found to extend the duration of peripheral nerve block. The action of clonidine was suggested to be due to local vasoconstriction and/or direct inhibition of impulse conduction in peripheral nerves. However, the mechanism of action has not been fully elucidated. Clonidine is not particularly specific to $\alpha$-2 adrenoceptors and also acts via $\alpha$-1 adrenoceptors at comparatively high concentrations. Clonidine has the ability to induce vasoconstriction, and it is therefore unclear whether it acts via $\alpha$-2 adrenoceptors. On the other hand, another $\alpha$-2 adrenoceptor agonist, dexmedetomidine, acts more specifically against $\alpha$-2 adrenoceptors and has more than eight times greater affinity for $\alpha$-2 adrenoceptors of clonidine(25). It has sedative, analgesic, and sympatholytic effects that blunt many of the cardiovascular responses (hypertension, tachycardia) seen during the perioperative period (26). Dexmedetomidine has also been reported to enhance central and peripheral neural blockade by local anesthetics; however, the peripheral effects have not been fully clarified. Yoshitomi et al. reported that dexmedetomidine and other $\alpha$-2 adrenoceptor agonists (oxymetazoline hydrochloride, yohimbine hydrochloride, prazosin hydrochloride) enhanced the local anesthetic action of lidocaine in the periphery (25).

Ketamine is a well-known general anesthetic and short-acting intraoperative analgesic. Ketamine has multiple effects throughout the central nervous system, including blocking polysynaptic reflexes in the spinal cord and inhibiting excitatory neurotransmitter effects in selected areas of the brain. It dissociates the thalamus (which relays sensory impulses from the reticular activating system to the cerebral cortex) from the limbic cortex (which is involved with the awareness of sedation). While some brain neurons are inhibited, others are tonically excited. Clinically, this state of dissociative anesthesia causes the patient to appear conscious (eg, eye opening, swallowing, muscle contracture) but unable to process or respond to sensory input (26). This agent is a nonselective antagonist of supraspinal N-methyl-D-aspartate (NMDA) receptors, which are activated by the excitatory neurotransmitter glutamate. Inhibition of NMDA receptors decreases neuronal signaling and is likely responsible for some of the analgesic effects of ketamine. Satilmis et al. demonstrated that the combination of a local anesthetic and subanesthetic doses of ketamine during surgical extraction of third molars can produce good local anesthesia while affording a comfortable procedure for both surgeon and patient, providing good postoperative analgesia with reduced swelling and significantly less trismus than local anesthesia alone (27).
Failure to achieve anesthesia can be a significant problem in dental practice. Studies have shown that more than 50% of adults in the USA miss dentistry services because of a fear of pain. Controlling patients’ anxiety and distress, good treatment of root canals, effective use of local anesthetics, and drug therapy cover the main factors in the management of dental pain. Amitriptyline is one of the most common tricyclic antidepressants (TCAs) and binds to pain sensory nerve fibers close to the sodium channels; hence, it may interact to some degree with receptors of local anesthetics. Although TCAs have been successfully used in the treatment of some types of neuropathic pain and they have been shown to have efficacy in blocking Na channels in the nervous system, they have not been used systemically for the completion of anesthesia in dental pain because of the potential risks of adverse drug reactions. However, topical use of a lipid-soluble TCA, e.g., amitriptyline, administered directly into the pulp cavity of a painful tooth in addition to routine local anesthetic injection may synergistically complete analgesia through coinhibition of Na channels on pain sensory fibers. Moghadamnia et al. reported that inter-pulp-space administration of 2% amitriptyline gel for completing analgesia in irreversible pulpitis pain was effective and useful as a conjunctive therapy to injection of local anesthetics (28).

6. References


Local anesthetics are being increasingly applied in different surgeries. Lower side effects of neuroaxial anesthesia, regional anesthesia, and field block, in comparison to general anesthesia (volatile and intravenous agents), are the main reasons why physicians prefer to conduct surgeries under local anesthesia, especially in outpatient and day care surgeries. It is important to emphasize the presence of an anesthesiologist, and vigilant monitoring of the homodynamic parameters, in decreasing a patient's anxiety, exerting other modalities for analgesia and increasing the safety margin in many procedures.

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