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Review Article

Contemporary Trends in Dental Local Anaesthesia: A Review of Literature

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Abstract

Local anaesthesia is widely used to mitigate pain and discomfort in a variety of dental procedures. Dental local anaesthetics must be carefully used like any other drugs. Dentists should have basic knowledge and understanding of local anaesthetics before using these drugs. Despite their safety and effectiveness, local anaesthetics can produce unwanted adverse effects if used carelessly. Thus, there should be judicious use of local anaesthetic in dental procedures, especially in medically-compromised patients. This article aims to review the general characteristics of local anaesthetics, mechanism of action, physiologic properties, metabolism, and elimination mechanisms, the maximum recommended doses, and the roles of vasoconstrictors that are added to the dental local anaesthetics.

Keywords: Anaesthesia, Epinephrine, Local Anaesthetic, Mechanism, Pharmacology, Vasoconstrictor

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Introduction

Dental local anesthesia is commonly used in a variety of dental procedures to alleviate pain and discomfort. Good management of pain is a critical component of care for patients who undergo dental treatment. Local anesthesia causes the reversible loss of pain sensation in a specific area of the body.[1] It has been used and has been improving for more than a century.

Various local anaesthetic agent like lidocaine, articaine, and mepivacaine used in dentoalveolar surgery has shown effective pain management.[2-4] Haas & Gaffen reported that nowadays, the local anesthetic agents are generally considered safe to use in dentistry, and there is a minimal incidence of the adverse reactions associated with the drug administration.[5,6] Local anesthetics differ in their potency and pharmacological components and the selection of dental local anesthesia is usually guided by the type of dental remedy and the desired duration of anesthesia.[7,8]

There are a number of dental local anesthetics that provide a prompt onset and sufficient duration of

anesthesia.[5,9] Sisk reported that all the present-day local anesthetics have the vasodilation property.[10] Therefore, vasoconstrictors or vasopressors have been added into the dental local anesthetic solutions for several beneficial effects such as improving the quality and lengthening the duration of anesthesia.[10-12]

Even though the dental local anesthetic is regarded as safe and effective, this drug can provide some undesirable adverse reactions. A previous study revealed that the adverse reactions of anesthetic agents are not related to their actions but arise due to inappropriate drug administration.[4] Some local or systemic adverse reactions can occur from a large dose of local anesthetic.[5,6] This review article summarizes contemporary knowledge in dental local anesthesia.

General characteristics of local anesthetic

Local anesthetic has been long used in the dental patient remedy for more than 100 years. It can cause a reversible absence of pain sensation, with the ability to block the impulse conduction distal to the nerve axon.[1,11] Dental local anesthetics are generally classified according to their molecular structures, the anesthesia onset, the potency, and the anesthesia duration.[11] The local anesthetics commonly have specific elementary features.

The dental local anesthetics consist of the following three principal components: 1) lipophilic aromatic ring, 2) intermediate amide or ester linkage, and 3) terminal amine.[7,11,13-15] These three components provide different clinical properties to the dental local anesthetic.[7,13] Dental local anesthetic can be categorized into two major chemical classes based on the intermediate ester- or amide-based linkages.[15,16] Currently, all local anesthetics available in the dental cartridges are usually affiliated with the amide group, namely, articaine, lidocaine, bupivacaine, prilocaine, and mepivacaine. The ester group such as procaine is not currently available in the dental cartridge. However, benzocaine which is ester-based is still available as the topical anesthetic.[15]

Local anesthetic mechanism of action

Local anesthetics provide reversible blockage to the nerve impulse conduction.[11,14,16] Covino reported that the nerve impulse depends on the concentration of the electrolyte in the nerve cytoplasm and extracellular fluid, with the cell membrane permeability of sodium and potassium ions.[16]

Typical depolarization can produce the changes of nerve membrane to allow sodium ions crossing through the specified sodium channels that lead to the transmission of the action potential along the neuron.[11] The interruption of the nerve impulse conduction by local anesthetic occurs by inhibiting the sodium ions entry through the specified sodium channels or ionophores within the nerve membranes. This impedes the momentary surge of sodium ions that generate the action potential.[11,13,15]

The sodium channels usually exist in a resting state. During this condition, sodium ions cannot enter the cell. When the nerve is excited, the channels open allowing the diffusion or entry of the sodium ions into the cell thereby instigating depolarization. Then the sodium channels become inactivated following a rapid change in the membrane potential, which inhibits the additional influx of the ions. The active transport mechanisms move sodium ions outside of the cell. The sodium channels change into the normal resting state following this repolarization.[13,17]

It should be noted that local anesthesia bind and inhibit the sodium channel from a site that is not directly accessible from outside the cell, preventing the transient of sodiumions influx that is associated with membrane depolarization (Modified from Becker *et al.*[13]).

The article by Becker and Reed publicized that local anesthetic molecules bind more to their receptors located in the sodium channels during their activation and inactivation than when they are in their resting stage.[13] The relation between inhibition of local anesthetic and a nerve fiber sensitivity is determined by axonal diameter, myelination, and anatomical and physiological factors. Among the same type of nerve fibers, the small fibers are generally more sensitive to local anesthetic than the large fibers due to the greater amount of sodium channels inhibited by the local anesthetic agent.[13,17] Consequently, the sensitivity of the small autonomic fibers is the highest followed by sensory fibers and motorfibers respectively.

The branches of trigeminal nerves that are commonly anesthetized for dental procedures consist exclusively of the small sensory fibers that differ in terms of their diameters and impulse conduction rates. The fibers that transmit pain impulses are more sensitive than those carrying pressure and proprioception. Therefore, the patient may interpret the sensation of pressure as pain during dental procedures.[13]

Physiological activity of local anesthetic

1. Lipid solubility and anesthetic potency

A direct relation exists between the potency of a local anesthetic and its lipid solubility as the nerve membrane is primarily made of lipids.[7,11,13,18A] previous study by Tetzlaff revealed that the hydrophobic nerve membrane can relate between lipid solubility and anesthetic potency.[19] Higher lipid solubility of the drug enables it to penetrate a nerve faster resulting in a blockade of more sodium channels. With a greater lipid solubility, the potency of local anesthetic is improved.[7,11,18,19] Becker and Reed in their review mentioned that the anesthetic potency depends on the concentrations of local anesthetics, which typically range from 0.5% to 4%.[13] Moreover, the lipid solubility is also determined from an aromatic ring and its aliphatic replacements, as well as an addition of the tertiary amine, such as bupivacaine with a higher lipid solubility has more potency than articaine. Consequently, this reason forms the basis for formulating bupivacaine at 0.5% concentration (5mg/mL).[7,11,13]

2. Ionization and onset time

All local anesthetics exist in the solution partly as the nonionized lipid-soluble form (B) and the ionized water-soluble form (BH+).[10,11,17,20] The nonionized form can diffuse through the neural membranes and occlude the sodium channels.[11,18,20] An article by Patel and Sadoughi[20] reported that the nonionized form also has a faster onset owing to its greater diffusion rate.

The pKa of the local anesthetic and the pH of the injection site influence the proportions of ionized and nonionized forms. pKa is defined as the pH at which the proportions of the ionized and the nonionized forms are the same.[17] The local anesthetic with a pKa closest to the physiological pH (7.4) will have a greater portion of the nonionized lipid-soluble form that diffuses more readily through the neural sheath (epineurium) and passes through the neuronal membrane promoting the rapid onset of action.[17,20]

The previous study by Patel and Sadoughi[20] also showed that the decrease in pH can shift an equilibrium toward the ionized form causing a delay in the onset of local anesthetic action. This can describe slower onset and decreased effectiveness of local anesthetics in the inflamed tissue, which has an acidic milieu due to a lower pH.[11,15,20] Only benzocaine among the local anesthetics has a pKa lower than the physiological pH (7.4). Previous reviews by Eappen & Datta and Tetzlaff reported that at any pH higher than pKa, the proportion of non-ionized form of the anesthetic will be lesser.[18,19]

Lipid solubility is another factor that affects the onset of local anesthetic action. Though pKa appears to be the most important factor related to the onset time, local anesthetics such as lidocaine, mepivacaine, and prilocaine have rapid onset time despite having a low pKa.[17,18] A study by Eappen *et al.* reported that the higher concentrations or the greater total dose of the drug also speed the time of local anesthetic onset. Hence, at similar concentrations, chloroprocaine would have a slower onset than lidocaine, but increasing the concentration of chloroprocaine can offset this insufficiency.[18]

3. Protein binding property and anaesthesia duration

Many previous reviews showed that the protein binding property is related to the anaesthesia duration.[11,17-20] The local anesthetic agent can also reversibly bind to plasma proteins in blood circulation.[7,13] Previous works by Eappen *et al.* and Patel *et al.* reported that the greater number of local anesthetic molecules that bind to plasma proteins at the sodium channel, the longer the duration of anaesthesia of that anesthetic.[18,20] Previous research by Giovannitti mentioned that protein forms the major constituent of the sodium channels and their receptor sites and the protein-bound molecules attach

to the active site. Moreover, protein binding can produce a drug reservoir and become available as the unbound drug. This drug can also get removed from the active site by the vascular uptake.[11] So, greater protein binding can produce an extended anaesthesia duration. Poor protein-bound anesthetics such as procaine are weakly associated with the nerve membrane and have an extremely short anaesthesia duration. However, the tightly protein-bound ones (e.g. bupivacaine) are strongly attached with the nerve membrane and have a long anaesthesia duration.[19] The duration of anaesthesia is also determined by the lipid solubility of anaesthesia. Local anesthetics with greater lipid solubility have a long anaesthesia duration, due to a slower diffusion to the bloodstream.[17]

4. Vasodilatation property

Local anesthetics (except cocaine) exert a two-phased effect on the vascular smooth muscles. At lower concentrations, local anesthetics produce vasoconstriction, while at higher concentrations they create vasodilation. Vasodilation occurs through relaxation of the smooth muscle fibers at the peripheral arterioles.[20] Vasodilation property is also a factor affecting the anaesthesia duration. Because the drug is quickly diffused away from the anesthetic site, it will have a very short anaesthesia duration when used without a vasoconstrictor.[15,18] Patel and Sadoughi also reported that the greater vasodilation property of local anesthetic agents enables a faster absorption but imparts a shorter anaesthesia duration.[20] The local anesthetics are varying in their vasodilation ability. Some local anesthetics such as lidocaine, when used without any vasoconstrictors can provide greater vasodilation property and result in a short anaesthesia duration than others, such as mepivacaine and bupivacaine.[13,18] Many previous studies showed that vasopressors, such as epinephrine and levonordefrin, are added to the anesthetic solutions so that vasodilation can be compensated and the quality of anaesthesia can be improved.[13,15,20]

Local anesthetic metabolism and elimination

Becker and Reed reported that the intermediate linkage of local anaesthesia is useful for the classification of these drugs and also useful to determine their pattern of elimination.[13] An amide group of local anesthetics is biotransformed by enzymes in the liver, while an ester group is predominantly hydrolyzed by plasma pseudocholinesterase (plasma cholinesterase) in the bloodstream.[13,15-17]

Para-aminobenzoic acid (PABA), a byproduct with an allergic potential, is formed during the metabolism of the ester group of local anesthesia.[11,16,17] Genetic disorders such as pseudocholinesterase deficiency can slow the metabolism rate of ester-based anesthetics and increase the risk for a toxic overdose.[15,17] Nowadays no ester local anesthetics are available in the dental cartridges, except benzocaine that is used as a dental topical anesthesia.[13]

Amide-type local anesthetics are not metabolized by pseudocholinesterase. Thus, incidences of allergic reactions with these agents are seldom reported.[16] The metabolic rate of amides is consistently slower than the ester types. The rate of amides metabolism is determined by the hepatic circulation and function. Decreased liver function or hepatic circulation can prolong the metabolism of these amides leading to higher blood levels and predisposing to systemic toxicity.[11,17]

Giovannitti *et al.* mentioned that the intermediate chain of articaine qualifies it as an amide-type of local anaesthesia, but its aromatic ring possesses an ester side chain that can undergo partial metabolism by nonspecific plasma esterases.[11,13] The half-life of articaine is shorter than other amides local anesthetics, which reduces the risk of toxicity of this drug. Furthermore, as the lack of adequate pseudocholinesterase does not affect the metabolism of articaine, the risk of systemic toxicity in the patient is also reduced.[11]

Maximum recommended doses of local anesthetic

The doses of local anesthetics are expressed in terms of milligrams per body weight, as mg/kg or as mg/lb.[1] The existing information about the dose of local anesthetics is usually not evidence-based; it is usually shown as the total maximum dose for preventing an excessive administration

and toxicity.[21,22] A study of Rosenberg *et al.* revealed that the recommended dose is individualized based on the characteristics of a patient, such as age, weight, the dental procedure to be performed, and the type of local anesthetics to be used.[21]

A review by Haas explained that the toxicity of a local anesthetic drug depends on various factors including the injection site, the injection speed, and the presence of vasopressor in the anesthetic solution.[15] Malamed and Haas mentioned that the calculation of maximum recommended doses of should always be decreased for children, medically compromised patients, debilitated patients, or elderly patients.[1,15] The liver function alteration, the plasma protein binding, the blood volume, and other important physiologic functions can influence the local anesthetics' distribution and biotransformation in the body.[1] The calculated dose of local anesthetics should be decreased for all at-risk persons. However, no formula can determine the total dose reduction for the patients at risk. Cox *et al.* stated that the maximum recommended dose of local anaesthesia should specifically define the type of local anesthetics, the type of injection, and the factor of body weight, age, and systemic diseases in the patient.[23]

Vasoconstrictors

Many previous studies reported that the local anesthetic provides several benefits by the addition of vasoconstrictor.[7,10,24] Vasopressor or vasoconstrictor produces blood vessel constriction by activating alpha-1(α1) adrenergic receptors thereby limiting the blood flow at the area of injection, retaining anesthesia for the dental operation, and delaying anesthetic absorption.[7,11,13] As a result, the vasoconstrictors can increase the safety of dental local anesthetics by decreasing the systemic toxicity of local anesthetic and reducing absorption into the systemic circulation.[24] Many studies have reported that the slower absorption of local anesthetic drug minimizes the chances of systemic toxicity but extends the anesthesia duration.[7,11,13,15] Furthermore, the vasoconstrictor addition can improve the quality of neural blockade and decrease bleeding at the operation.[4,7,10,24] Two vasoconstrictors (epinephrine and levonordefrin) are generally added in dental local anesthetics.[10,11]

There are approximately equal numbers of α and β receptors in the tissues, but due to greater sensitivity of the β receptors to epinephrine, the β-effects will normally predominate.[1] In submucosal vessels containing only β receptors, epinephrine can produce local vasoconstriction. While in systemic arteries containing much higher numbers of β2 receptors than α receptors, even a low concentration of epinephrine can produce vasodilation and influence the diastolic blood pressure.[7,13]

Low doses of epinephrine, such as in dental anesthetic, can increase heart rate, cardiac output, and peripheral vasodilation.[1] Various drugs like nonselective beta blockers, tricyclic antidepressants have potential interactions through common receptors as epinephrine.[15] Epinephrine with a half-life of 1 to 3 minutes is available in dental local anesthesia at the concentrations of 1: 50,000 (0.02 mg/mL), or 1: 100,000 (0.01 mg/mL), or 1: 200,000 (0.005 mg/mL). When administered intravenously, its action is terminated mainly through reuptake by adrenergic nerves. Escaped epinephrine is quickly inactivated by the enzymes in blood circulation. Therefore, only a minor proportion of approximately 1% epinephrine is unchanged and excreted in the urine.[1] From a previous article by Becker and Reed,[7] 0.3 mg or 300 µg of epinephrine can initiate allergic reactions.

Adverse effects of epinephrine include tachycardia, tremor, palpitations, arrhythmia, anxiety, headache, and hypertension.[1] Consequently, patients with cardiovascular disease should consider a minimal dosage of epinephrine. In cardiovascular disease patients or patients under medications that interact with epinephrine, the doses of epinephrine should be kept below 0.04 mg.[15] Epinephrine has a short duration of action (approximately ten minutes), thus the supplemental anesthesia containing epinephrine can be provided by the dentist when required. If multiple operations are required, the injection time should be extended. For lessening the systemic effects of vasoconstrictors in the

dental field, the dentist should aspirate before every dental-injection.[15]

2. Levonordefrin or Neo-Cobefrin is commonly available in a concentration of 1:20,000. This concentration should be considered analogous with 1:100,000 epinephrine.[15] The structure of levonordefrin resembles norepinephrine than epinephrine and also lacks the affinity for β2 receptors. Epinephrine causes tachycardia, increases systolic blood pressure but decreases diastolic blood pressure. However, norepinephrine increases systolic, diastolic, and mean arterial pressures producing reflex bradycardia.[7]

Levonordefrin is advised as a substitute for cardiovascular patients since it does not increase heart rate. Nevertheless, the previous article by Becker and Reed advocated failing in the consideration of undesirable influence on blood pressure.[7] After local anesthetic with 1:20000 levonordefrin infiltration injection, they have equivalent efficacy for constriction of submucosal vessels.[7,13]

The amount of vasoconstrictor in local anesthetics is important especially in excessively anxious or cardiovascular disease patients. Minimum amount of vasoconstrictor should be used in patients who are on medications that interact with these vasoconstrictors.[11] Epinephrine is most effective among the vasoconstrictors and the most commonly used sympathomimetic amine for dental local anesthesia.[24]

Allergic Reactions

Although local anesthetics show rare allergic reactions, it has been known to be associated with the contents of the dental cartridge. Local anaesthetic cartridges consist of chemical agents like sodium metabisulphite as antioxidants for preventing vasopressor deterioration and methyl paraben preservative.

Contact dermatitis, generalized urticaria and/or anaphylaxis, angioedema are common allergic drug reactions. Allergies to bisulfites may develop a severe response like bronchospasm particularly in patients with asthma. Therefore, the history of a patient with a known previous allergic reaction during dental or medical treatment related to local anesthesia is very important. Consultation and allergy testing should be considered if any uncertainty remains about the history.

If there is uncertainty regarding the history of allergic reactions, these drugs should not be used. Elective dental treatment should be delayed if possible to rule out the cause. In case of severe pain and infection, oral analgesics and antibiotics respectively can be given as temporary measures. A histamine blocker like diphenhydramine hydrochloride can be used with anaesthetic solution considering its burning sensation during injection as an undesirable side effect. If the documented history of a sulfite allergy is present then, local anesthetic solution without a vasopressor should be used. If the allergy is limited to ester anesthetics, an amide group of drugs should be used. It should not contain a paraben preservative, which is closely related to the esters. Various manufacturers have started developing local anesthetic cartridges without methylparaben. In case of immediate anaphylaxis reaction, emergency administration of epinephrine with 0.01 mg/kg (maximum dose of 0.5 mg) IM or IV followed by positioning of patient, supplemental oxygen, and volume resuscitation with IV fluids should be done.[25] Adverse reaction to local anaesthesia are often related to epinephrine, psychogenic factors, and other drugs. The toxic effect of LA may occasionally be misdiagnosed as an LA allergy.

Discussion

The dental local anesthetics currently offered in cartridges mostly belong to the amide group (articaine, lidocaine, and mepivacaine), and are selected based on their potency, onset, and duration.[26] The maximum recommended dosage and the medical history of the patient should be considered when using a local anesthetic. The physiologic activity of local anesthetic represents differences in the rate of onset and the duration of anesthesia. Thus, the selection of local anesthetics should depend on the anticipated duration of the dental procedure and the duration of the anesthesia required.

All local anesthetics are different in terms of anesthetic efficacy. Among the different anesthetics, the most widely used is lidocaine, which is the standard agent for comparison with other local anesthetics.[13,26,27] Many previous studies[28,29] showed mepivacaine has the same anesthetic efficacy as lidocaine. The study of Cohen *et al.*[26] mentioned that 3 % mepivacaine is as effective as 2 % lidocaine in achieving pulpal anesthesia in the inflamed mandibular molars after inferior alveolar nerve block. Porto *et al.*[29] compared 2 % lidocaine and 2 % mepivacaine with equal concentration of epinephrine for mandibular third molar surgery. The results were that both anesthetics had similar anesthesia time and produced profound anesthesia for procedures that lasted up to one hour. There were also no significant differences between these two local anesthetics in the postsurgical pain.

Several clinical studies[27,30-32] have compared articaine with other local anesthetics and shown similar or better anesthetic efficiency of articaine. The previous study of Arrow[30] showed no significant difference in the success of the local analgesia when 4 % articaine with 1: 100,000 epinephrine and 2 % lignocaine with 1: 80,000 epinephrine, administered either as an inferior alveolar nerve block or buccal infiltration for restorative treatments in mandibular posterior teeth in pediatric population were compared.

In the study of the inferior alveolar nerve anesthesia for the surgical removal of impacted mandibular third molars, the previous studies by Rebolledo *et al.* and Kambalimath *et al.* compared 4 % articaine and 2 % lidocaine with 1: 100,000 epinephrine for their anesthetic efficacies. These articles reported that 4 % articaine had better anesthetic potential and anesthesia duration than 2 % lidocaine. However, the anesthetic efficacy of the solutions was similar.[26,31] Also, a previous study by Boonsiriseth *et al.*[32] showed that the 4 % articaine attains anesthesia onset earlier than 4 % lidocaine (higher concentration than conventional lidocaine). However, there were also no clinically significant differences between these two local anesthetics. Anaesthetic delivery technique has also been found to be an important factor in terms of effectiveness and pain perception. Computer controlled Intraosseous anaesthetic technique when compared to convention inferior alveolar nerve block has resulted in less pain during anesthesia induction with enough depth of anaesthesia in impacted tooth surgery.[33]

Even though local anesthetics are very safe and effective for pain management during dental procedures, every local anesthetic can create undesirable adverse effects. The adverse effects of local anesthetic can manifest as systemic or local reactions. The symptoms of systemic reactions from local anesthetics include dizziness, tremors, convulsions, tachycardia, seizures, hypotension, drowsiness, respiratory depression, and loss of consciousness.[11,13,26] These symptoms are the consequences of toxicity due to intravascular injection or overdoses of the local anesthetics.[4] Additionally, paresthesia from the toxic effect of high concentration local anesthetic may also occur.

In distinction, a previous study of Baroni *et al.*[34] assessed the toxic effects of articaine and lidocaine in the mental nerve of rats. Damages to the nerve that could elicit paresthesia were not noticed. Although we have many types of anesthetics for dental usage, more research focusing on the efficacy and safety of the local anesthetics is required.

A vasoconstrictor (epinephrine) has been added into the local anesthetic for increasing the quality of local anesthesia. On the other hand, the dental local anesthetics without a vasoconstrictor (3 % mepivacaine) may be selected for short dental procedures. Epinephrine is most commonly used in dental local anesthesia.[1,10,13] Many previous studies support the safety and efficacy of the addition of vasoconstrictors within the local anesthesia.[7,10,24,35]

Bader *et al.*[35] in their review reported that the use of epinephrine in local anesthetic caused minimal but not significant increase in systolic and diastolic blood pressure without any adverse outcomes in patients with uncontrolled hypertension. This concept was supported by the study of Niwa *et al.*[36] which reported that a low dose of epinephrine present in local dental anesthetic is safe for use in patients with mild cardiovascular disease. Vasoconstrictors, especially epinephrine can be used with the local anesthetic agent

for dental remedy, but the dose should be minimized for the medically compromised patients, especially patients with cardiovascular disease.

In conclusion, local anesthetics commonly used in dental science are very safe and are effective drugs for intraoperative and postoperative pain control. Dentists should have knowledge and a comprehensive understanding of local anesthetic to enhance the care of patients. While the local anesthetics are safe and have established usage, all local anesthetics have undesirable adverse reactions or side effects. Hence, the selection of these drugs should be based on the required duration of anesthesia, the assessment of the patient's general health, and the properties of the local anesthetics. The most reasonable practice could be administering the optimal doses rather than the maximum doses of local anesthetics after assessing the health of the patient. If the systemic health status of the patient is a concern, a reassessment of vital signs after the administration of local anesthetics should be done.

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