Review Article

Dental Anesthesia in the Presence of Inflammation: Pharmacological Mechanisms for the Reduced Efficacy of Local Anesthetics

Hironori Tsuchiya*

Department of Dental Basic Education, Asahi University School of Dentistry, Japan

*Corresponding author

Hironori Tsuchiya, Department of Dental Basic Education, Asahi University School of Dentistry, 1851 Hozumi, Mizuho, Gifu 501-0296, Japan, Tel: 81-58 329 1266; Fax: 81-58 329 1266; Email: hiro@dent.asahi-u.ac.jp

Abstract

Profound analgesia or pain control with local anesthetics is essential for most dental procedures in endodontic and restorative treatments, tooth extraction and minor oral surgery. However, dental clinicians frequently experience that it is difficult for infiltration and nerve block injections to achieve clinically acceptable local anesthesia in the presence of pupil and periapical inflammation. Local anesthetic failures are well documented especially when treating mandibular posterior teeth with inflamed pulps. Successful local anesthesia of patients with irreversible pulpitis is continually challenging in dentistry. A variety of mechanisms have been hypothetically proposed for such reduced efficacy of local anesthetics. Among mechanistic hypotheses, technical injection errors, mandibular anatomical variations and psychological factors are not directly related to inflammation, whereas inflammation-relevant mechanisms include alterations in the peripheral vascular system, nociceptive neurons, drug targets and central nervous sensitivity. However, none of them explain all aspects of dental anesthetic failures. The reasons why inflammatory lesions affect local anesthetics to decrease their effects are not fully understood. This article reviews pharmacological mechanisms underlying the failures of dental local anesthesia by focusing on inflammatory acidosis, products and mediators which would modify the properties of anesthetic agents and their targets. From a pharmacological point of view, different strategies to enhance the efficacy of local anesthetics are discussed about the drug selection based on structural and physicochemical characteristics, the buffering of injection solutions, the promotion of peripheral vasoconstriction, the premedication with anti-inflammatory drugs, the use of drug delivery systems, the application of new dental anesthetics, and the supplementary anesthesia.

INTRODUCTION

Local anesthesia is clinically an essential part of dental practices to perform endodontic and restorative treatments, tooth extraction and minor oral surgery without pain preoperatively, intraoperatively and immediate postoperatively. There are basic techniques for dental anesthesia: infiltration, nerve block and topical application [1]. For infiltration anesthesia, local anesthetic solutions are administered close to teeth and periodontal tissues to be anesthetized, diffusing anesthetic molecules only to the terminal nerve endings. The induced anesthesia and analgesia are confined to the injection zone and the structures innervated by the network of fine nerve branches, not extending beyond the diffusion zone of drugs. Infiltration injection is employed when an individual tooth or a specific area is required to be anesthetized. This technique is commonly useful for anesthetizing maxillary teeth and soft tissues. For nerve block anesthesia, local anesthetic solutions are administered around the main trunk of a sensory nerve to block all sensory inputs from the all regions of tissues innervated by that nerve. The anesthetized area involves all of the nerve distribution distal to the injection site, so being wider than that in infiltration anesthesia. Topical anesthesia is used to block free nerve endings supplying the mucosal surfaces. Local

anesthetics applied as a liquid spray or a paste can minimize the discomfort or pain of needle insertion.

Maxillary teeth receive the sensory nerve supply from anterior, middle and posterior superior alveolar nerves, all of which are branches of the maxillary division of a trigeminal nerve. To affect these nerves, buccal and palatal infiltrations are employed as well as a posterior superior alveolar nerve block. Anesthetizing maxillary teeth is relatively easy because the cortical bone of a maxilla is so thin on its buccal aspect that administered anesthetic solutions can readily diffuse through it. The satisfactory anesthesia of dental pulps is achievable in most restorative treatments by a single buccal infiltration injection. Mandibular teeth receive the sensory nerve supply from an inferior alveolar nerve, which is a branch of the mandibular division of a trigeminal nerve. The cortical bone of a posterior mandible is too thick to permit the penetration of local anesthetics administered by the buccal infiltration. The inferior alveolar nerve is anesthetized by blocking the nerve trunk before it enters the bone at a mandibular foramen on the medial aspect of the ramus. Inferior alveolar nerve block is predominantly used to produce analgesia for the mandibular body and the pulps of mandibular teeth on the injection side of a mouth, except a central incisor where there may be the cross-over supply from an inferior alveolar nerve on the opposite side.

In addition to these characteristics in administration and affected peripheral nerves, dental local anesthesia has a distinctive feature that anesthetic agents are almost always administered to patients with pulpal, periapical, periodontal and alveolar inflammation. However, such cases are problematic for obtaining clinically satisfactory effects. Dental clinicians frequently experience poor analgesia in teeth having inflammatory lesions or fail to achieve profound anesthesia by infiltration and nerve block techniques in the situations of pulpitis and apical periodontitis [2,3]. Especially in teeth with irreversible pulpitis, the anesthetic effects of infiltration, nerve block and intraosseous injections are remarkably decreased [4-6]. Buccal infiltration anesthesia shows the success rates of 57-87 % for patients with irreversible pulpitis in maxillary teeth [7-9] and 65-69 %for patients with irreversible pulpitis in mandibular teeth [10]. For infiltration injections supplemented after an incomplete inferior alveolar nerve block, the anesthesia success ranges 29-71 % [11]. With respect to inferior alveolar nerve block anesthesia for mandibular posterior teeth, clinical studies have demonstrated high failure rates of 30-45% or low success rates of 19-56% in patients with irreversible pulpitis even when experienced clinicians perform and proper procedures are employed [2,12]. Inferior alveolar nerve block injections with different local anesthetics show the anesthesia success rates of 58–76 % for mandibular posterior teeth with irreversible pulpitis [10,13]. Neither buccal-plus-lingual infiltration nor nerve block alternative to conventional techniques gives profound anesthesia to mandibular molars with pulpal inflammation [14]. Achieving clinically satisfactory analgesia of inflamed pulps remains a challenging problem in dental anesthesia [15].

The reduced efficacy of dental anesthetics has been interpreted by a variety of hypothetical mechanisms. Besides inflammation-irrelevant causative factors such as technical injection errors, mandibular anatomical variations and psychological contributions, mechanistic hypotheses associated with inflammatory lesions have been proposed as follows: (1) the influence on the peripheral vascular system, (2) the alteration of nociceptors, (3) the sensitivity reduction of anesthetic targets and (4) the central sensitization [15,16]. In inflamed tissues, inflammatory mediators and pathological vasculature changes induce peripheral vasodilation, which decreases the concentrations of local anesthetics at the administered site by promoting their systemic absorption. Inflammatory mediator prostaglandin E_2 is a potent vasodilator to synergize with other vasoactive mediators: bradykinin and histamine [17]. Bradykinin activates nociceptors and prostaglandin E_2 sensitizes nociceptors to reduce the neuronal firing threshold. Such alterations lead to the resistance of peripheral nerves against local anesthetics [18]. As described below, local anesthetics primarily target Na^+ channels, which are classified into tetrodotoxin-sensitive and -resistant Na^+ channels. Among them, tetrodotoxin-resistant Na^+ channels expressed on nociceptors are much less sensitive to local anesthetics [19]. While Na^+ channels are increasingly expressed in inflamed dental pulps [20], one subtype of tetrodotoxin-resistant Na^+ increases in patients with neuropathic pain [21]. Since these pathological changes are localized near the injection site, not evident at areas distant from it, they are likely to be responsible for the failure of infiltration anesthesia rather than that of nerve block anesthesia. Inflammation may also induce central sensitization, the increased excitability of pain fibers in the central nervous system [22], contributing to local anesthetic failures. However, none of these hypotheses explain all aspects of unsuccessful dental anesthesia.

This article reviews pharmacological mechanisms underlying the reduced efficacy of dental anesthetics in the presence of inflammation. Based on them, possible strategies to improve the success rate of local anesthesia and produce clinically acceptable analgesia are also discussed.

Local anesthetics and dental formulations

Since the discovery of cocaine as a first local anesthetic in 1884, a variety of local anesthetics have been introduced to dentistry. However, ester local anesthetics like procaine were largely replaced by more effective, longer acting, but less allergic drugs of an amide type. Representative amide local anesthetics are shown in Figure (1).

Dental formulations of currently used local anesthetics are shown in Table (1), together with the clinical properties [23-25]. Because of lower effectiveness and higher incidence of allergic reactions, dental formulations containing ester agents are no longer marketed in the United States [26]. Lidocaine is the predominant local anesthetic in dentistry because of excellent efficacy and safety [27]. Articaine shows the onset time and profundity of anesthesia almost comparable to those of lidocaine, whereas it possesses the shortest metabolic half-life of dental anesthetics due to its characteristic structure containing an ester side-chain. Almost all of local anesthetics intrinsically exert vasodilatory effects, but with different potencies. Therefore, vasoconstrictors such as epinephrine and levonordefrin (only for dental mepivacaine cartridges) are concomitantly used to retain anesthetic molecules in the vicinity of neuronal tissues
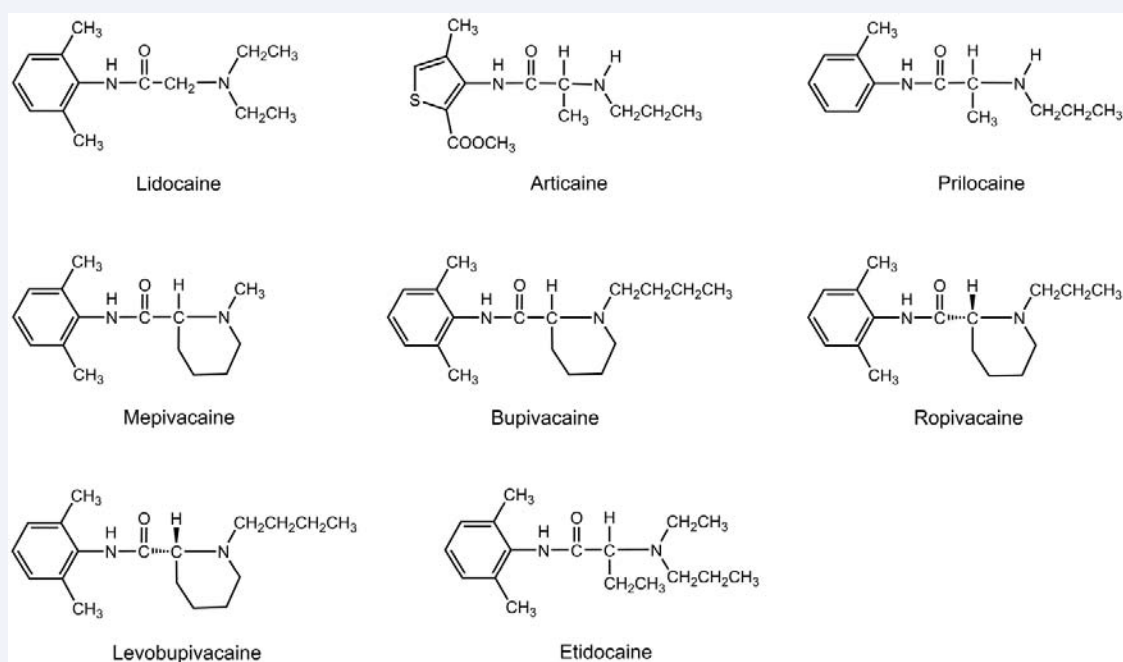
Figure 1 Representative amide local anesthetics.

Table 1: Local anesthetic formulations available in dental cartridges.

Local anesthetic	Concentration	Vasoconstrictor	Onset*	Pulpal anesthesia duration (expected duration)**
Lidocaine	2%	Plain	Fast	Very short (10 min)
	2%	1:100,000 Epinephrine	Fast	Medium (60 min)
	2%	1:50,000 Epinephrine	Fast	Medium (60 min)
Articaine	4%	1:200,000 Epinephrine	Very fast	Medium (60 min)
	4%	1:100,000 Epinephrine	Vary fast	Medium (60 min)
Mepivacaine	3%	Plain	Fast	Short (20-40 min)
	2%	1:20,000 Levonordefrin	Fast	Medium (60 min)
Prilocaine	4%	Plain	Fast	Short ~ Medium (5-60 min)
	4%	1:200,000 Epinephrine	Fast	Medium ~ Long (60-90 min)
Bupivacaine	0.5%	1:200,000 Epinephrine	Medium	Very long (90-180 min)

* Data from Jastak JT, Yagiela JA, Donaldson D [23].
** Data from Malamed SF [24].

after injection, prolong the duration of local anesthesia, reduce the adverse or toxic effects of anesthetics, and decrease localized bleeding at the administration site. Because mepivacaine and prilocaine have minimal or much less vasodilating activity compared with other local anesthetics, their formulations without a vasoconstrictor (plain agents) are also available. Although its cardiotoxicity is relatively high, long-acting bupivacaine provides not only adequate surgical anesthesia but also effective postoperative pain control.

Pharmacological mechanisms of local anesthetics

Local anesthetics are a class of drugs to prevent signals transferred from the periphery to the central nervous system by regional administration. They remain the most effective and safest drugs in dentistry to control intraoperative pain. In the currently accepted mode of action, local anesthetics are

considered to block voltage-gated (voltage-dependent, voltage-sensitive) Na⁺ channels (Nav channels) with a higher affinity to Na⁺ channels in an inactivated phase and inhibit sensory and motor functions reversibly [28].

Voltage-gated Na⁺ channels, integral membrane proteins composed of a core α-subunit associated with one or more regulatory β-subunits, are responsible for the initiation and propagation of action potentials in excitable cells in the peripheral nervous system and the cardiac system. The α-subunit not only forms the pore permeable for Na⁺ ions but also contains the binding or receptor site for local anesthetic and anti-arrhythmic drugs, and for several neurotoxins. Local anesthetics bind to such a site, causing occlusion of the pore to block Na⁺ channels. At least nine distinct Na⁺ channel α-subunits (Nav1.1 to Nav1.9) have been cloned from mammals. Nav1.7, Nav1.8 and Nav1.9 are the primary isoforms of nociceptive neurons in the peripheral nervous system and Nav1.1, Nav1.2, Nav1.3 and Nav1.6 are the primary isoforms in the central nervous system, whereas Nav1.4 and Nav1.5 are in skeletal muscle and heart, respectively [29]. Nav1.7 and Nav1.8 isoforms are especially crucial for the excitability of pain neurons (nociceptors), therefore both channels are implicated as the essential targets for anesthetic and analgesic drugs. Based on their affinity for a specific neurotoxin, Na⁺ channel subtypes are also divided into tetrodotoxin-sensitive voltage-gated Na⁺ channels (including Nav1.1, Nav1.2, Nav1.3, Nav1.4, Nav1.6 and Nav1.7) and tetrodotoxin-resistant voltage-gated Na⁺ channels (including Nav1.5, Nav1.8 and Nav1.9), in which Nav1.8 and Nav1.9 are predominantly found in dorsal root ganglion neurons.

Amide local anesthetics have the common amphiphilic structure that is composed of three portions: the hydrophobic moiety consisting of an aromatic ring, the intermediate chain of an amide bond and the hydrophilic moiety consisting of an amino terminus (Figure 1). The aromatic residue confers lipid-solubility on a drug molecule, whereas the positively chargeable amino group, water-solubility. Local anesthetics occur *in vivo* in uncharged and charged forms. According to the Henderson-Hasselbalch equation (Log_{10} [uncharged molecules] / [charged molecules] = pH – pKa), the relative fraction of uncharged to charged molecules depends on drug's pKa and medium pH. Because of the presence of substituted amino groups, amide local anesthetics are referred to as the bases with pKa values ranging from 7.7 to 8.1 at 37℃ [30]. Most solutions of local anesthetics are manufactured at pH 3-4 because their molecules in a charged form are more stable at acidic pH as is a concomitantly used vasoconstrictor. Once drug solutions are injected, the equilibrium between uncharged and charged molecules is established in extracellular fluids, where their relative proportion is determined by the regional tissue pH and drug pKa values (Figure 2). Only uncharged molecules are able to diffuse into or across the lipid bilayers of neuronal membranes to access Na⁺ channel binding sites or act on membrane lipids as well as penetrate tissues through the lipid barriers of nerve sheaths. After diffusing across cell membranes, the equilibrium between uncharged and charged molecules is re-established in intracellular fluids of cytoplasm.

In the drug-protein interaction mechanism (Figure 3), charged molecular species exclusively bind to the receptor sites of Na⁺ channels, with a resultant change of channel protein conformation and subsequent prevention of the influx
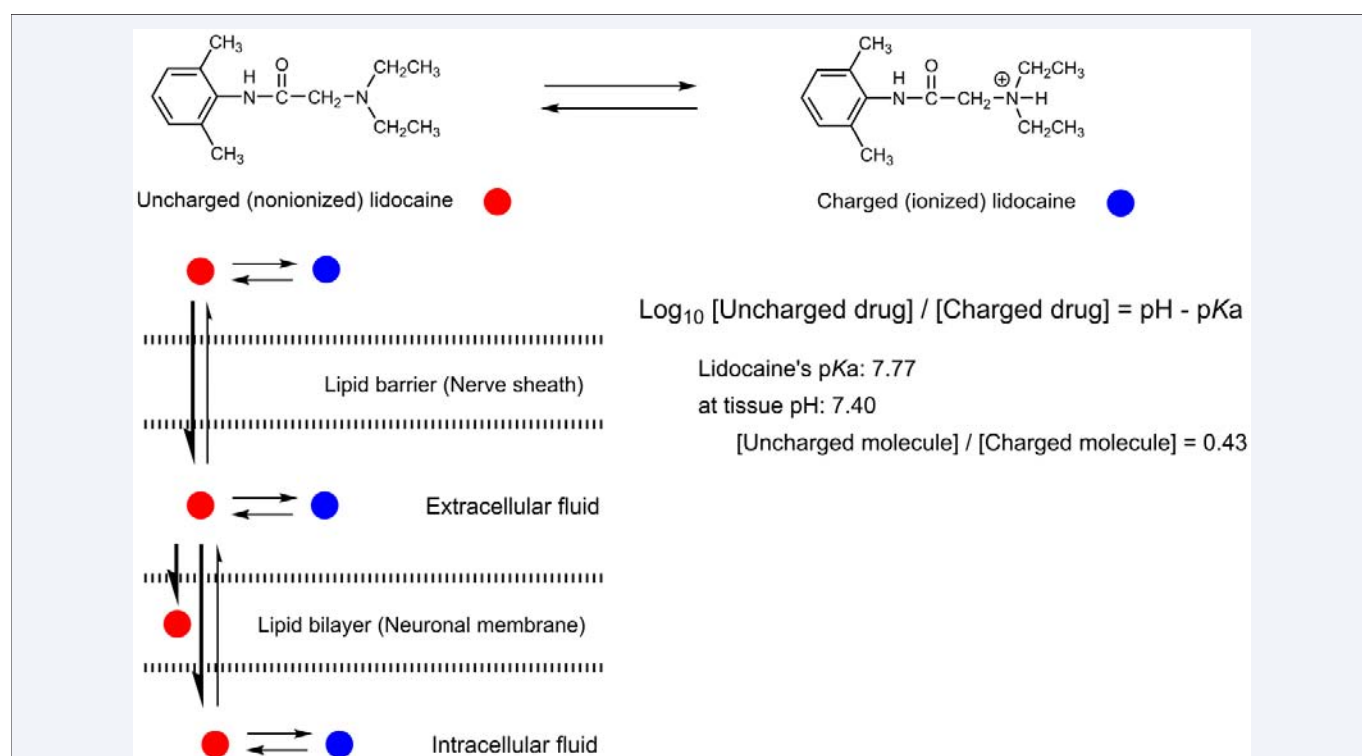

$$\mathrm{Log}_{10} \text{ [Uncharged drug] / [Charged drug]} = \mathrm{pH} - \mathrm{p}K\mathrm{a}$$

Lidocaine's pKa: 7.77
at tissue pH: 7.40
    [Uncharged molecule] / [Charged molecule] = 0.43

Figure 2 Equilibrium between uncharged and charged molecules of lidocaine, the *in vivo* relative fraction of which is determined according to the Henderson-Hasselbalch equation.
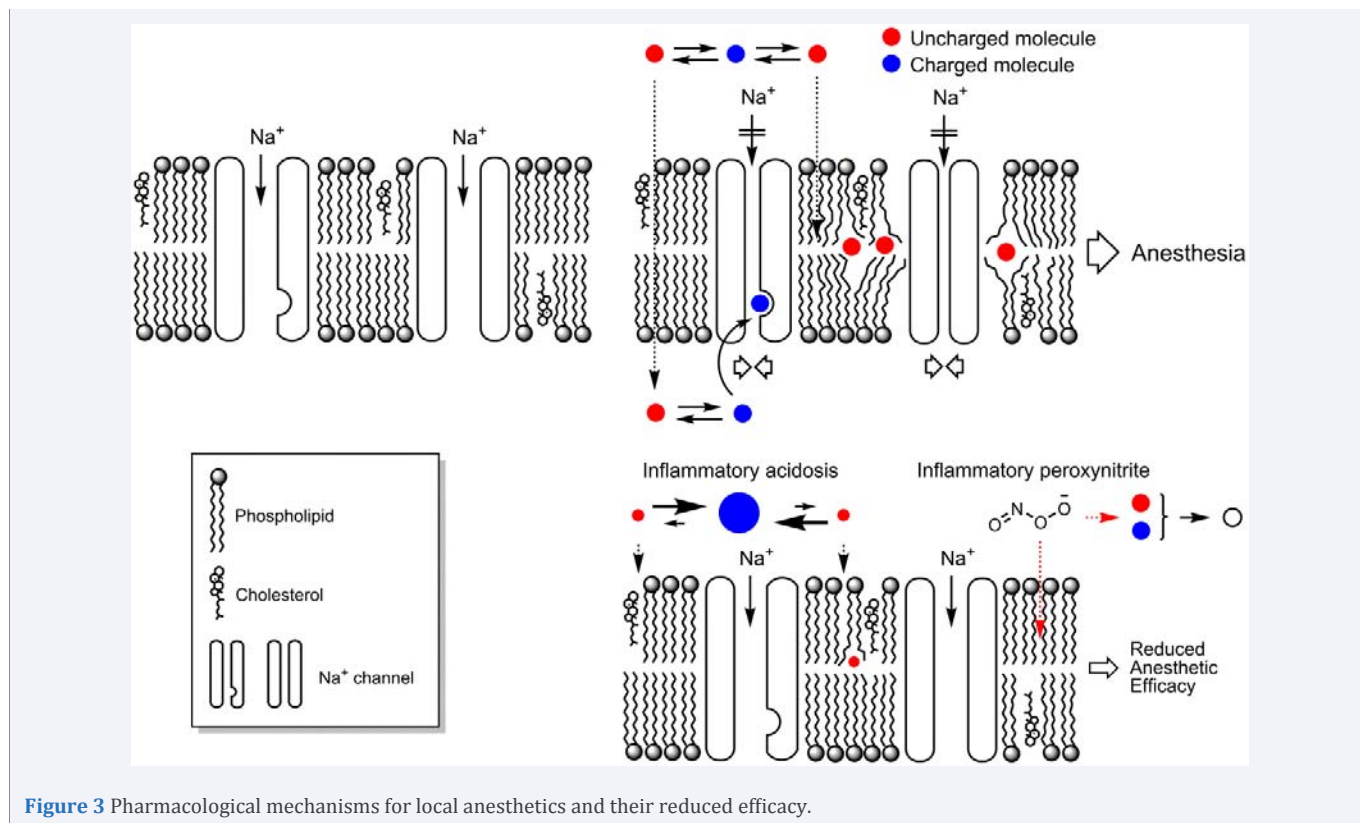
Figure 3 Pharmacological mechanisms for local anesthetics and their reduced efficacy.

of Na⁺ ions, blocking Na⁺ channels to inhibit the propagation of action potentials in neuronal and cardiac cells. Local anesthesia is an interfacial phenomenon associated with the molecular interaction that occurs at the interface between lipid-bilayer biomembranes and aqueous environments [31]. In the drug-membrane interaction mechanism (Figure 3), local anesthetics act on membrane-constituting lipids, directly affecting the neurotransmission function of nerve cells and indirectly inhibiting the activity of Na⁺ channels by altering the membrane lipid environments surrounding channel proteins through the modification of membrane property (fluidity, order, microviscosity or permeability), with a subsequent change of protein conformation [32,33]. Both channel protein interaction and membrane lipid interaction inhibit the depolarization of cell membranes to prevent the transmission of nerve impulses from the peripheral nociceptors to the central nervous system. The structure-dependent effects of local anesthetics are derived from the specific stereostructure of Na⁺ channel proteins and from the specific lipid composition of biomembranes [34-36].

Inflammatory acidosis mechanism for anesthetic failure

A carious lesion extends into the dentine and bacteria enter the pulp chamber, causing pulpal inflammation. Pathological changes caused by bacterial metabolic by-products reduce the pH within affected tissues [16]. Inflammation-relevant acidic metabolites like lactic acid are increasingly produced and concentrated in inflamed tissues, resulting in inflammatory acidosis that decreases the tissue pH at least the order of 0.5–1.0 pH unit [37,38].

While local anesthetics act on Na⁺ channels much faster and produce greater conduction block at alkaline pH compared with neutral pH, the major effect of pH is on drug ionization, not on channel protein [30]. Local anesthetics diffuse into and across the lipid bilayers of neuronal membranes in an uncharged (nonionized) form, whereas reversibly act on the cell-interior receptor sites of Na⁺ channels in a charged (ionized) form. Because the pKa values of almost all of local anesthetics in dental use are larger than 7.6 at 37°C [30,39], the relationship between uncharged and charged molecular fractions as a function of pH (5.0–7.6) is shown in Figure (4), which was calculated according to the Henderson-Hasselbalch equation by using the pKa values of drugs [39,40]. Greater proportions of the administered drugs exist in a charged form under acidic conditions. Because the charged molecules lose both membrane permeability and membrane activity in inflammatory acidosis, local anesthetics can neither access the intracellular binding sites on Na⁺ channels nor interact with the lipid bilayers of neuronal membranes as shown in Figure (3). Therefore, the efficacy of local anesthetics would be remarkably reduced in the presence of inflammation. This acidosis hypothesis has been widely accepted because of its theoretical simplicity and understandability.

The potencies of drugs to penetrate through nerve sheath lipid barriers, diffuse into or across neuronal membranes and act on membrane lipids can be comparatively studied by using the interactions with lipid membrane preparations [33,41]. However, the interaction of drug molecules with biomembranes is not identical to that presumed from the organic/aqueous phase partition or the partition between bulk apolar hydrocarbons and water, although such partitions have been quoted for building up the acidosis theory. The membrane lipid composition also

significantly influences the membrane interactivity of amphiphilic drugs. Tsuchiya et al. [42] and Ueno et al. [43] experimentally verified the acidosis mechanism by subjecting local anesthetics to the reactions with different biomimetic membranes at varying pH. Lidocaine, prilocaine and bupivacaine interacted with the membranes consisting of phosphatidylcholine at pH 6.4 (comparable to the inflamed tissue conditions) much less potently than at pH 7.4. However, these local anesthetics were found to interact with neuro-mimetic membranes containing phosphatidylserine at pH 6.4 with almost the same potency as at pH 7.4. Unlike zwitterionic phosphatidylcholine, membrane-constituting phosphatidylserine is anionic. Positively charged (cationic) molecules of local anesthetics are speculated to interact electrostatically with such anionic phospholipid membranes even under acidic conditions. The speculative electrostatic membrane interaction is supported by greater interactivity of bupivacaine with the membranes containing anionic cardiolipin [35]. These membrane interactions in experimental acidosis do not agree with the inflammatory acidosis mechanism. Inflammation decreases only the order of 0.5 pH unit in tissues [37] and the ability to buffer excess acidity is more potent in inflamed tissues [44,45]. Such pathological features are additionally unfavorable for the mechanistic acidosis hypothesis.

Other possible mechanisms associated with inflammation

Mechanisms alternative to the inflammatory acidosis are proposed to explain the failure of dental anesthesia. Mechanistic hypotheses include the contribution of inflammation-relevant peroxynitrite and the inflammation-induced alteration of nociceptors.

(1) Contribution of peroxynitrite: Peroxynitrite is implicated in the pathogenesis of various diseases including inflammation [46]. Inflammatory cells produce peroxynitrite through the reaction between nitric oxide and superoxide anion, both of which are present in inflamed tissues. Ueno et al. [43] investigated whether inflammatory peroxynitrite may contribute to the local anesthetic failure by interacting with drug molecules and/or membrane lipids (Figure 3). They treated neuro-mimetic membranes with lidocaine, prilocaine and bupivacaine together with 50 μM peroxynitrite at pH 7.4 and 6.4 under conditions consistent with the peroxynitrite exposure by activated inflammatory cells [47]. Consequently, the membrane-interacting properties of local anesthetics were significantly suppressed by peroxynitrite. In their following study [48], peroxynitrite was proved to affect local anesthetic molecules directly. Lidocaine interacted with phospholipid membranes to modify their physicochemical property at clinically relevant concentrations, but this membrane effect was decreased by pretreating lidocaine with 50–250 μM peroxynitrite. Ueno et al. [49] also investigated the effect of peroxynitrite on membrane lipids and revealed that the interactions of lidocaine with neuro-mimetic membrane are inhibited when pretreating the membranes with 0.1–50 μM peroxynitrite.

Inflammatory peroxynitrite also has the ability to react with lidocaine and bupivacaine [50,51]. Takakura et al. [52] reported that peroxynitrite decreases the inhibitory effect of lidocaine on trigeminal nerve response.

Peroxynitrite possibly affects local anesthesia by acting on both drug molecules and neuronal membranes. Since local anesthetic solutions are injected relatively near to inflammatory lesions in dental anesthesia [23], inflammatory peroynitrite would mechanistically contribute to the reduced efficacy of infiltration anesthesia.

(2) Alteration of nociceptors: Inflammation may affect pain perception to produce hyper-excitability or hyperalgesia [53]. The acidic pH is one of factors to activate and sensitize nociceptive neurons [54,55]. Inflammatory mediators and tissue acidosis are hypothesized to promote nociceptive transmission synergistically.

Inflammation was suggested to enhance the excitability of sensory nerves and induce the orofacial hyperalgesia by Byers et al. [56] and by Morgan and Gebhart [57]. Inflammatory mediators such as bradykinin and prostaglandin E_2 activate or sensitize nociceptive neurons to reduce the depolarization threshold of relevant Na^+ channels [58]. The sensitization and activation of peripheral nerves could make the nociceptive neurons resistant to local anesthetics [59].

As described above, local anesthetic-targeting voltage-gated Na^+ channels are classified into tetrodotoxin-sensitive and -resistant channels expressed on nociceptors. Na^+ channels of the latter type, including Nav1.8 and Nav1.9, are less sensitive to or more resistant to local anesthetics [19,60].Therefore, one possible mechanism for anesthetic failures is presumed, that is, inflammation may evoke an increase in local anesthetic-resistant Na^+ channels. Inflammation in rat dorsal root ganglion causes a significant increase of tetrodotoxin-resistant Na^+ channel density and enhances the excitability of sensory neurons [61]. Nav1.8 and Nav1.9 channel isoforms belonging to a subfamily of tetrodotoxin-resistant Na^+ channels are up-regulated in inflamed pulp tissues of human teeth [62,63]. Nakamura and Jang [64] reported that weak acid (≥ pH 6.0) makes tetrodotoxin-resistant Na^+ channels in sensory neurons isolated from rat trigeminal ganglia to be suitable for the repetitive activation at depolarized membrane potentials.

Pharmacological strategies to improve the efficacy of local anesthetics

In order to improve the efficacy of local anesthetics, different strategies are presumable from a pharmacological point of view. They include the drug selection based on structural and physicochemical characteristics, the pH adjustment of injection solutions, the promotion of peripheral vasoconstriction, the premedication with anti-inflammatory drugs, the use of drug delivery systems, the application of new dental anesthetics and the supplementary anesthesia. These strategies are summarized in Table (2).

(1) Drug selection strategy: The inflammatory acidosis mechanism has clinical implications for pharmacological strategies to improve the efficacy of local anesthetics. The proportion of membrane-permeable and membrane-interactive molecular species depends on drug's pKa, suggesting that the order of relative anesthetic potency may inversely correlate

SciMedCentral

Table 2: Strategies to improve the efficacy of local anesthetics.

Strategy	Author	Local anesthetic	Study design and results*
Drug selection	Hinkley et al. [65]	2% Mepivacaine with 1:20,000 levonordefrin 2% Lidocaine with 1:100,000 epinephrine 4% Prilocaine with1:200,000 epinephrine	Inferior alveolar nerve blocks of molars, premolars and lateral incisors. U: Three preparations induced equivalent pulpal anesthesia.
	McLean et al. [66]	3% Mepivacaine 4% Prilocaine 2% Lidocaine with1:100,000 epinephrine	Inferior alveolar nerve blocks. U: Three preparations were not different in success and onset.
	Tortamano et al. [67]	4% Articaine with 1:100,000 epinephrine 2% Lidocaine with 1:100,000epinephrine	Inferior alveolar nerve blocks for patients with irreversible pulpitis in mandibular posterior teeth. U: Two preparations exerted the similar anesthetic effects.
	Sampaio et al. [68]	0.5% Bupivacaine with 1:200,000 epinephrine 2% Lidocaine with 1:100,000 epinephrine	Inferior alveolar nerve blocks for pulpectomy of mandibular posterior teeth with irreversible pulpitis. P: Two preparations showed different success rates.
	Barath et al. [69]	2% Mepivacaine with 1:80,000 epinephrine 2% Lidocaine with 1:80,000 epinephrine	Inferior alveolar nerve blocks for extraction of impacted molars. U: Not different between two preparations.
	Visconti et al. [70]	2% Mepivacaine with 1:100,000 epinephrine 2% Lidocaine with 1:100,000 epinephrine	Inferior alveolar nerve blocks for pulpectomy of posterior teeth with irreversible pulpitis. P: Mepivacaine was superior in analgesia to lidocaine.
	Nydegger et al. [71]	4% Articaine with 1:100,000 epinephrine 4% Lidocaine with 1:100,000 epinephrine 4% Prilocaine with 1:200,000 epinephrine	Buccal infiltration anesthesia of mandibular molars. P: Anesthesia success rates were articaine > lidocaine = prilocaine.
	Kanaa et al. [72]	4% Articaine with 1:100,000 epinephrine 2% Lidocaine with 1:100,000 epinephrine	Buccal infiltration anesthesia of mandibular teeth. P: Anesthesia success rates were articaine > lidocaine.
	Abdulwahab et al. [73]	Five marketed dental formulations	Mandibular buccal infiltrations for pulpal anesthesia. P: 4% Articaine with 1:100,000 epinephrine was more effective than others.
pH adjustment	Malamed et al. [79]	2% Lidocaine with 1:100,000 epinephrine alkalized to pH 7.31	Inferior alveolar nerve blocks for pulpal anesthesia. E: Alkalization decreased the onset time and injection pain.
	Kashyap et al. [80]	2% Lidocaine with 1:80,000 epinephrine buffered to pH 7.38	Inferior alveolar lingual and buccal nerve blocks. E: Buffering accelerated the onset of anesthesia.
	Saatchi et al. [81]	2% Lidocaine with 1:80,000 epinephrine after 8.4% sodium bicarbonate with 2% lidocaine containing 1:80,000 epinephrine	Inferior alveolar nerve block after buccal infiltration for mandibular molars with irreversible pulpitis. P: Anesthesia success rate was increased.
	Hobeich et al. [82]	2% Lidocaine with 1:100,000 epinephrine buffered with 5-10% sodium bicarbonate	Maxillary infiltration anesthesia. U: Onset and injection pain were not different from non-buffered lidocaine.
	Schellenberg et al. [83]	4% Lidocaine with 1:100,000 epinephrine buffered with 8.4% sodium bicarbonate	Inferior alveolar nerve block of posterior teeth with irreversible pulpitis. U: Buffering neither increased anesthesia success nor decreased injection pain.
	Saatch et al. [84]	2% Lidocaine with 1:80,000 epinephrine buffered with 8.4% sodium bicarbonate	Inferior alveolar nerve block. U: No beneficial effects were found.
	Shurtz et al. [85]	4% Articaine with 1:100,000 epinephrine buffered with 8.4% sodium bicarbonate	Mandibular buccal infiltration anesthesia. U: Buffering showed no effects on the success, onset and injection pain.
Vasoconstriction promotion	Dagher et al. [86]	2% Lidocaine with 1:50,000, 1:80,000 or 1:100,000 epinephrine	Inferior alveolar nerve blocks of molars, premolars and lateral incisors in healthy subjects. U: Not different in pulpal anesthesia.

|			
	Santos et al. [87]	4% Articaine with 1:100,000 or 1:200,000 epinephrine	Buccal, lingual and inferior alveolar nerve blocks for healthy volunteers. U: Epinephrine concentrations did not influence the clinical efficacy.
	Pereira et al. [88]	4% Articaine with 1:100,000 or 1:200,000 epinephrine	Intraosseous injections for the endodontic treatment of mandibular molars with irreversible pulpitis. U: Not different in anesthetic efficacy and success rate.
	Knoll-Köhler and Förtsch [89]	2% Lidocaine with 1:50,000, 1:100,000 or 1:200,000 epinephrine	Pulpal anesthesia by infiltration injections. E: The anesthetic duration was prolonged by changing 1:200,000 to 1:100,000 epinephrine.
Premedication with anti-inflammatory drugs	Parirokh et al. [92]	2% Lidocaine with 1:80,000 epinephrine	Patients with irreversible pulpitis were premedicated with ibuprofen or indomethacin. P: Both drugs increased the success rates of nerve block anesthesia.
	Aggarwal et al. [93]	2% Lidocaine with 1:200,000 epinephrine followed by 4% articaine plus 30 mg ketorolac	Patients with irreversible pulpitis received inferior alveolar nerve block, followed by buccal infiltration. P: Supplemented ketorolac increased the anesthetic success rate.
	Oleson et al. [95]	2% Lidocaine with 1:100,000 epinephrine	Patients with irreversible pulpitis received inferior alveolar nerve block after ibuprofen administration. U: The anesthetic success rate was not different from control.
	Aggarwal et al. [96]	2% Lidocaine with 1:200,000 epinephrine	Patients with irreversible pulpitis were premedicated with ibuprofen or ketorolac. U: Neither ibuprofen nor ketorolac increased the success rate of inferior alveolar nerve block anesthesia.
Drug delivery	Cereda et al. [100]	Liposome-encapsulated 2% prilocaine, lidocaine or mepivacaine	Infraorbital nerve blocks of rats. P: Both the intensity of anesthesia and the duration of analgesia increased.
	Wiziack Zago et al. [101]	Liposome-encapsulated 3% prilocaine	Buccal maxillary infiltration anesthesia for healthy volunteers. U: Encapsulation did not influence the anesthetic efficacy.
	Tofoli et al. [103]	Liposome-encapsulated 2-3% mepivacaine	Buccal maxillary infiltration anesthesia for healthy volunteers. U: The anesthetic efficacy did not change.
	Silva et al. [104]	Liposome-encapsulated 4% articaine	Infiltration anesthesia in rat inflamed tissues. U: Neither success rate nor duration increased.
	Ramos Campos et al. [105]	Nanosphere containing 0.5% lidocaine	Sciatic nerve blocks in mice. P: The intensity and duration of analgesia increased.
	Silva de Melo et al. [107]	Nanocapsule containing articaine	The cytotoxicity was assayed *in vitro*. E: Encapsulation reduced the toxicity.
	Serpe et al. [108]	Bupivacaine cyclodextrin inclusion complex	Inferior alveolar nerve blocks in rats. U: The efficacy of pulpal anesthesia did not increase.
New dental anesthetics	Krzemiński et al. [110]	0.5% Ropivacaine 4% Articaine with 1:100,000 epinephrine	Buccal infiltration anesthesia of volunteers' maxillary teeth. P: Ropivacaine induced more rapid and longer duration anesthesia of 100% efficacy compared with articaine.
	Bhargava et al. [111]	0.5 or 0.75% ropivacaine	Patients received inferior alveolar nerve block for extraction of impacted third molars. P: Ropivacaine was a good option for dental surgical procedures.
	Brajkovic et al. [112]	0.5% Levobupivacaine 0.5% Bupivacaine	Patients received inferior alveolar, lingual and buccal nerve blocks. P: Levobupivacaine was superior to bupivacaine intraoperatively and postoperatively.
Supplementary anesthesia	Kanaa et al. [113]	4% Articaine with 1:100,000 epinephrine 2% Lidocaine with 1:80,000 epinephrine	Patients with irreversible pulpitis in mandibular teeth received supplementary anesthesia. P: Supplementary buccal infiltration and intraosseous injection induced more successful pulpal anesthesia.
* Expected effects to improve the efficacy of local anesthetics: P: Promising; E: Equivocal; U: Unpromising.			
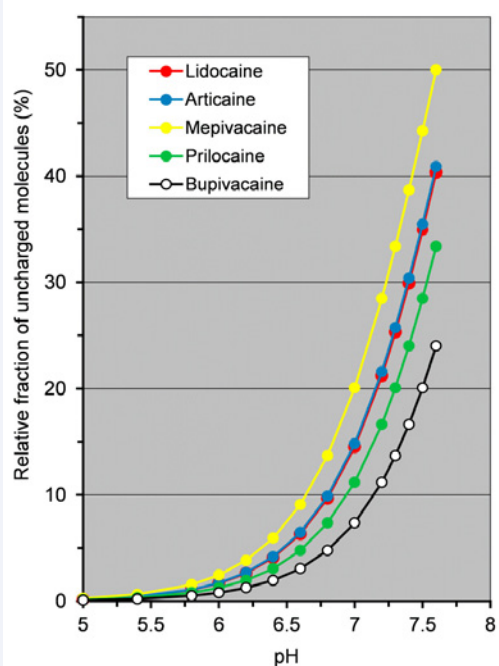
Figure 4 Relationship between uncharged and charged molecular fractions of local anesthetics with different p*K*a values as a function of pH (5.0–7.6). The relative fractions of uncharged to charged molecules were calculated according to the Henderson-Hasselbalch equation.

with the decreasing order of p*K*a being bupivacaine > prilocaine ≥ lidocaine ≥ articaine > mepivacaine [39,40]. Local anesthetics with smaller p*K*a values like mepivacaine are expected to be more effective at relatively low pH than ones with larger p*K*a values.

Hinkley et al. [65] compared the anesthesia degree of 2% mepivacaine with 1:20,000 levonordefrin, 2% lidocaine with 1:100,000 epinephrine and 4% prilocaine with 1:200,000 epinephrine by testing first molar, first premolar and lateral incisor with a pulp tester. They demonstrated that three anesthetic preparations are equivalent in inferior alveolar nerve block. McLean et al. [66] found no significant differences in onset and success of inferior alveolar nerve blocks when comparing 3% mepivacaine plain, 4% prilocaine plain and 2% lidocaine with 1:100,000 epinephrine. Tortamano et al. [67] investigated the comparative efficacy of conventional inferior alveolar nerve blocks with articaine and lidocaine. They revealed that 4% articaine with 1:100,000 epinephrine and 2% lidocaine with 1:100,000 epinephrine have similar effects on patients with irreversible pulpitis in mandibular posterior teeth. Sampaio et al. [68] also compared the anesthetic efficacy in pulpectomy of mandibular posterior teeth with irreversible pulpitis by performing conventional inferior alveolar nerve blocks of 0.5% bupivacaine with 1:200,000 epinephrine or 2% lidocaine with 1:100,000 epinephrine. According to patients' reports of none or mild pain during pulpectomy, the success rates of bupivacaine and lidocaine were 80% and 62.9%, respectively. However, these previous studies vary in the tested concentrations of local anesthetics and the presence of vasoconstrictors.

Barath et al. [69] conducted a double-blind, randomized,

clinical trial by using the same concentrations of local anesthetics and a vasoconstrictor. They used 2% mepivacaine and 2% lidocaine, both with 1:80,000 epinephrine, in inferior alveolar nerve blocks for the surgical extraction of mesioangular bilaterally impacted third molars, but found no significant differences between mepivacaine and lidocaine. In contrast, Visconti et al. [70] reported that mepivacaine is superior to lidocaine in pain control during pulpectomy of mandibular posterior teeth with irreversible pulpitis. In their study, patients received conventional inferior alveolar nerve blocks of either 2% mepivacaine with 1:100,000 epinephrine or 2% lidocaine with 1:100,000 epinephrine. The success rates of pulpal anesthesia determined by pulp tests were 86% for mepivacaine and 67% for lidocaine, and by patients' reports of no pain or mild pain, 55% for mepivacaine and 14% for lidocaine.

Using the common 4% anesthetic formulations, Nydegger et al. [71] compared the efficacy of buccal infiltrations for mandibular first molars. They demonstrated that the anesthesia success rates were 55% for articaine with 1:100,000 epinephrine, 33% for lidocaine with 1:100,000 epinephrine and 32% for prilocaine with 1:200,000 epinephrine. Despite almost the same p*K*a values, Kanaa et al. [72] reported that articaine is more effective in infiltration anesthesia of mandibular teeth than lidocaine. In their randomized crossover double-blind trial, buccal infiltration of 4% articaine with 1:100,000 epinephrine showed 65% success of mandibular first molar pulp anesthesia, but 39% success for 2% lidocaine with 1:100,000 epinephrine. Abdulwahab et al. [73] comparatively studied five marketed dental formulations including lidocaine, articaine, prilocaine, mepivacaine and bupivacaine. They revealed that 4% articaine with 1:100,000 epinephrine induces profounder pulpal anesthesia in mandibular buccal infiltration compared with other formulations. A greater effect of articaine is interpretable by its characteristic molecular structure. Articaine exceptionally has a 2-carbomethoxy-4-methylthiophene ring (Figure 1), which forms the intramolecular hydrogen bond between amine nitrogen and ester carbonyl oxygen group [41]. The formed hydrogen bond could modify the hydrophobicity of articaine molecule, enhancing its diffusion through connective tissues and neuronal membranes. Molecular dynamics in membrane lipid bilayers are different between articaine and other local anesthetics [74].

The pharmacological features of bupivacaine are advantageous for the endodontic treatment of mandibular molars with irreversible pulpitis as well as for the control of postoperative pain. This long-acting local anesthetic is more effective on tetrodotoxin-resistant Na$^+$channels, including Nav1.8 and Nav1.9, compared with lidocaine [60]. Nav1.8 and Nav1.9 channel isoforms are up-regulated in inflamed pulp tissues [62,63] and the nerve fibers immunoreactive to Nav1.8 are significantly increased in human painful pulps [75]. Bupivacaine is expected to exert a more satisfactory effect. Sampaio et al. [68] compared the anesthetic efficacy during pulpectomy in patients with irreversible pulpitis of mandibular posterior teeth. The anesthesia success rates of inferior alveolar nerve blocks were 80% for 0.5% bupivacaine with 1:200,000 epinephrine and 63% for 2% lidocaine with 1:100,000 epinephrine. However, Parirokh et al. [76] found no differences between 0.5% bupivacaine with 1:200,000 epinephrine and 2% lidocaine with 1:80,000

epinephrine when comparing the efficacy of inferior alveolar nerve block injections for treating mandibular molars with irreversible pulpitis.

Considering the possibility that inflammatory peroxynitrite plays a causative role in the failure of dental local anesthesia, drugs with the antioxidant activity are beneficial to the anesthetic efficacy in the presence of inflammation. In addition to the intrinsic effects, membrane-acting drugs including anesthetics possess antioxidant properties to scavenge radicals and inhibit membrane lipid peroxidation [77]. Because bupivacaine and lidocaine are more effective in inhibiting the oxidative effect of peroxynitrite compared with other local anesthetics [78], these antioxidant local anesthetics may induce more satisfactory analgesia.

(2) pH adjustment strategy: Commercially available local anesthetic solutions have the pH ranging from 3.5 to 5.5, which are usually prepared by adding hydrochloric acid to increase drug's solubility and stability. Injecting such acidic preparations not only causes pain and burning sensation but also reduces the tissue pH of their administered sites. Once injected, the injection area temporarily exhibits acidosis, which increases the proportion of membrane-not-permeable and membrane-not-interactive molecular species of drugs, possibly affecting local anesthesia. Therefore, the speculative strategy is to adjust the pH of injection solutions and tissues to be administered. Buffering (alkalization to the physiological pH) of anesthetic solutions should enhance the lipid bilayer permeability and membrane interactivity of local anesthetics, and also suppress localized inflammatory acidosis. The buffering of local anesthetic solutions has been attempted to minimize the influence of pH changes [23]. Sodium bicarbonate, an alkalinizing agent for metabolic acidosis, is commonly used for the purpose of buffering.

Malamed et al. [79] compared the pulpal anesthetic effects of inferior alveolar nerve block between 2% lidocaine with 1:100,000 epinephrine alkalinized to pH 7.31 and 2% lidocaine with epinephrine 1:100,000 of pH 3.85. Alkalization of lidocaine solutions significantly reduced the onset time of local anesthesia and suppressed injection pain compared with non-alkalized solutions. Kashyap et al. [80] showed that 2% lidocaine with 1:80,000 epinephrine buffered to pH 7.38 accelerates the onset of anesthesia in standard inferior alveolar, lingual and buccal nerve blocks. In a prospective, randomized, double-blind study of Saatchi et al. [81], patients with irreversible pulpitis in mandibular first molars received a buccal infiltration injection of either 8.4% sodium bicarbonate with 2% lidocaine containing 1:80,000 epinephrine or sterile distilled water with 2% lidocaine containing 1:80,000 epinephrine in a double-blind manner. After 15 min, they received conventional inferior alveolar nerve blocks of 2% lidocaine with 1:80,000 epinephrine. Buccal infiltration of sodium bicarbonate increased the anesthesia success rate to 78%, compared with 44% for control.

In contrast, a prospective, randomized, double-blind comparative study of Hobeich et al. [82] is negative about buffering anesthetic solutions. Maxillary infiltrations of 2% lidocaine with 1:100,000 epinephrine buffered with 5% or 10% sodium bicarbonate did not differ in anesthetic onset and injection pain from those of non-buffered 2% lidocaine with

1:100,000 epinephrine. In a comparative study of Schellenberg et al. [83], patients with irreversible pulpitis in mandibular posterior teeth received inferior alveolar nerve blocks of 4% lidocaine with 1:100,000 epinephrine or 4% lidocaine with 1:100,000 epinephrine buffered with 8.4% sodium bicarbonate. The buffered lidocaine formulation provided neither an increase in success rate nor a decrease in injection pain. Saatchi et al. [84] reported the same negative results for a conventional inferior alveolar nerve block of 2% lidocaine with 1:80,000 epinephrine buffered with 8.4% sodium bicarbonate. In a prospective, randomized, double-blind study of Shurtz et al. [85], adult subjects received mandibular buccal infiltrations of 4% articaine with 1:100,000 epinephrine buffered with 8.4% sodium bicarbonate or 4% articaine with 1:100,000 epinephrine. When their molars were tested for pulpal anesthesia, buffered articaine did not exhibit any advantage over non-buffered articaine for anesthetic success, onset or injection pain.

(3) Vasoconstriction promotion strategy: The peripheral vasodilation hypothesis has pharmacological implications to provide dental anesthetics with profounder and longer effects. If inflammatory vasodilation increases the systemic absorption of administered local anesthetics and takes away their substantial amounts from the injection site, the promotion of vasoconstriction should lead to more satisfactory anesthesia. Contrary to expectations, however, usefulness of this strategy has been equivocal in previous clinical trials. Dagher et al. [86] compared standard inferior alveolar nerve blocks of 2% lidocaine with 1:50,000, 1:80,000 and 1:100,000 epinephrine. In pulpal anesthesia of the first molar, first premolar and lateral incisor, they found no significant differences among three concentrations of epinephrine, although their results were obtained from healthy subjects. In a double-blind, randomized, crossover study of Santoset al. [87], healthy volunteers received buccal, lingual and inferior alveolar nerve blocks of 4% articaine with 1:100,000 or 1:200,000 epinephrine. The concentration of epinephrine did not influence the clinical efficacy of articaine in mandibular third molar extraction. Pereira et al. [88] also failed to demonstrate a relation between vasoconstrictor concentration and local anesthesia in the endodontic treatment of mandibular molars with irreversible pulpitis. In their study, intraosseous injections of 4% articaine with 1:100,000 epinephrine and with 1:200,000 epinephrine showed no differences in anesthetic efficacy and success rate.

Knoll-Köhlerand Förtsch [89] exceptionally reported the vasoconstrictor's concentration-dependence in infiltration anesthesia. They compared the effects of 2% lidocaine with 1:200,000 epinephrine, 1:100,000 epinephrine and 1:50,000 epinephrine by injecting drug solutions into the mucobuccal aspect adjacent to the apex of a maxillary right incisor. The duration of effective pulpal anesthesia was prolonged by increasing the epinephrine concentration from 1:200,000 to 1:100,000, but not to 1:50,000.

(4) Premedication strategy with anti-inflammatory drugs: Inflammatory mediators like prostaglandin E_2 sensitize nociceptors and reduce the threshold to activate nociceptive neurons. Ketorolac, a non-steroidal anti-inflammatory drug usable for intramuscular injection, has a potent effect to inhibit

prostaglandin biosynthesis. Intraorally injected ketorolac was suggested as a useful adjunct for the management of endodontic pain [90]. Therefore, it is expected that the premedication with non-steroidal anti-inflammatory drugs may attenuate the pain-potentiating effects of inflammatory mediators.

Non-steroidal anti-inflammatory drugs, such as ketorolac, ibuprofen, indomethacin, diclofenac and lornoxicam, have been investigated as an oral premedication to increase the efficacy of lidocaine's nerve block anesthesia [91]. In a premedication study of Parirokh et al. [92], patients with irreversible pulpitis were given a capsule of 600 mg ibuprofen or 75mg indomethacin and after 60 min, they received inferior alveolar nerve blocks of 2% lidocaine with 1:80,000 epinephrine. Overall success rates were 78% for ibuprofen and 62% for indomethacin, compared with 32% for placebo, indicating that the premedication with ibuprofen and indomethacin is able to increase the efficacy of nerve block anesthesia. In a prospective, randomized, double-blind study of Aggarwal et al. [93], patients with irreversible pulpitis received standard inferior alveolar nerve blocks of 2% lidocaine with 1:200,000 epinephrine, followed by supplemental buccal infiltration with 4% articaine plus ketorolac of 30 mg. Consequently, supplemented ketorolac increased the success rate of nerve block anesthesia to 62%, being higher than 39% for control. However, Mellor et al. [94] reported that periapical infiltration with ketorolac (injected in the buccal sulcus adjacent to the tooth) causes severe injection pain, leading to the procedural discontinuation.

In a prospective, randomized, double-blind, placebo-controlled study of Oleson et al. [95], patients with irreversible pulpitis received standard inferior alveolar nerve blocks of 2% lidocaine with 1:100,000 epinephrine after the preoperative administration with capsules of 800 mg ibuprofen. The success rate for nerve block anesthesia was 41% for ibuprofen, but with no difference from controls. In a clinical trial of Aggarwal et al. [96], patients with irreversible pulpitis were given two capsules containing 300 mg ibuprofen or 10 mg ketorolac and after 60 min, they received standard inferior alveolar nerve blocks of 2% lidocaine with 1:200,000 epinephrine. Ibuprofen and ketorolac showed anesthesia success rate of 27% and 39%, respectively, both of which were not different from 29% for control. The preoperative administration of anti-inflammatory drugs does not necessarily improve the efficacy of nerve block anesthesia.

(5) Local anesthetic delivery strategy with drug carriers: The effects of local anesthetics could be increasingly influenced by drug delivery systems, in which drug carriers such as liposomes, nanoparticles and cyclodextrins are used. The effective drug delivery system is expected to modify or regulate the release, distribution, pharmacokinetics and toxicity of local anesthetic molecules [97].

Liposomes are microscopic vesicles composed of lipid bilayers that are biocompatible and biodegradable but not immunogenic. When amphiphilic phospholipids with a polar head and hydrophobic hydrocarbon tails are suspended in aqueous media, they spontaneously associate into bilayers with the hydrocarbon chains oriented toward one another and the polar head group in contact with the surrounding aqueous phase [98]. Liposomes are produced using glycerophospholipids with

or without cholesterol, and the resulting structures are classified by the size and the number of bilayers into small unilamellar vesicles, large unilamellar vesicles, multilamellar vesicles and multivesicular systems [99]. Because liposomes consist of an aqueous compartment surrounded by one or more lipid bilayers, they can entrap both hydrophilic and hydrophobic (lipophilic) drug molecules like local anesthetics. Cereda et al. [100] reported that liposome encapsulation modifies the efficacy of different local anesthetics. They prepared large unilamellar liposomes with egg phosphatidylcholine, cholesterol and α-tocopherol (4:3:0.07, molar ratio) by extrusion (400 nm) at pH 7.4, which encapsulated 2% prilocaine, lidocaine and mepivacaine. In rat infraorbital nerve blocks, liposomal formulations increased the intensity of anesthetic effects by 35.3%, 26.1% and 57.1% and the duration time of analgesia by 30%, 23.1% and 56% for prilocaine, lidocaine and mepivacaine, respectively, compared with the plain solutions. Despite the same liposomal formulations, however, randomized, double-blind, crossover studies of healthy volunteers showed the negative results that the efficacy of buccal maxillary infiltration anesthesia is not improved by liposome-encapsulated 3% prilocaine [101], liposome-encapsulated 0.5% ropivacaine [102] and liposome-encapsulated 2-3% mepivacaine [103], while being effective in increasing the duration of pulp and soft tissue anesthesia. Silva et al. [104] studied the anesthetic effects of liposomal formulations of articaine in inflamed tissues. They prepared multilamellar liposomes with egg phosphatidylcholine, cholesterol and α-tocopherol (4:3:0.07, molar ratio) at pH 7.4, and then prepared unilamellar liposomes by extrusion of the multilamellar vesicles using a 400 nm membrane. Articaine was added directly to the two liposome preparations to be a concentration of 4%. When comparing the anesthetic efficacy after infiltrations into rat inflamed tissues (induced by plantar incision into the hind paw), 4% articaine with 1:100,000 epinephrine provided higher success and longer duration of anesthesia rather than unilamellar and multilamellar liposome-encapsulated articaine.

Nanoparticles between 1 and 100 nm in size are composed of hydrophobic polymers such as poly(ε-caprolactone), polylactide, polylactide-co-glycolide, etc. There are different polymeric particles, including spheres and capsules. Nanospheres are the structures with a polymeric matrix, while nanocapsules are the reservoir systems consisting of a core normally with an oily medium surrounded by a polymeric wall [99]. Local anesthetic molecules can be retained or adsorbed by the matrix of nanospheres and be dissolved in the core or adsorbed onto the polymeric wall of nanocapsules. Ramos Campos et al. [105] prepared poly(ε-caprolactone) nanospheres to contain lidocaine and characterized their physicochemical properties and drug release mechanism. In sciatic nerve blocks of mice, they found that 0.5% lidocaine-containing nanospheres increase the intensity and duration of analgesia compared with 0.5% lidocaine plain solutions. Grillo et al. [106] reported the similar findings for 0.5% bupivacaine-containing polymeric alginate nanoparticles in mouse sciatic nerve block. Silva de Melo et al. [107] successfully encapsulated articaine in poly(ethylene glycol)-poly(ε-caprolactone) nanocapsules. They obtained the promising result that the nanocapsule encapsulation reduces the toxicity of articaine.

Cyclodextrins are cyclic oligosaccharides consisting of six or more α-1,4-linked D-glucopyranose units. Since this cyclical configuration produces a hydrophobic (lipophilic) central cavity and a hydrophilic outer surface, cyclodextrins form inclusion complexes with local anesthetics, allowing slow release of anesthetic molecules [99]. Serpe et al. [108] revealed that bupivacaine 2-hydroxypropyl-β-cyclodextrin inclusion complex prolongs the duration of local anesthesia in rats, but such a drug delivery system does not increase the efficacy of bupivacaine for pulpal anesthesia after inferior alveolar nerve block.

Although drug delivery systems are effective in prolonging the duration of nerve block to produce long-lasting anesthesia and analgesia, liposomes, nanoparticles and cyclodextrins do not necessarily increase the efficacy of dental local anesthetics. Nor they have been clinically used for infiltration and nerve block anesthesia of patients with irreversible pulpitis.

(6) Application strategy of new dental local anesthetics: Since the clinical use in the 1960s, bupivacaine had been commonly marketed as a racemic mixture of bupivacaine that consists of equimolar enantiomers: S(−)-bupivacaine of the *levo*-rotatory configuration and R(+)-bupivacaine of the *dextro*-rotatory configuration. In the 1990s, however, an urgent problem of its significant cardiotoxicity led to the first development of an S(−)-enantiomeric local anesthetic, ropivacaine, followed by levobupivacaine as a pure S(−)-enantiomer of bupivacaine [109]. Ropivacaine and levobupivacaine are less toxic to cardiovascular and central nervous systems than their counterpart enantiomer and racemate. Although neither ropivacaine nor levobupivacaine is available in dental cartridges, these enantiomeric drugs may meet the property as a long-acting anesthetic effective for pain control during the treatment of irreversible pulpitis and have clinical advantages over racemic bupivacaine. In particular, less cardiotoxic ropivacaine is expected to be a new dental local anesthetic because it needs no vasoconstrictors due to its vasoconstrictive activity at relatively low concentrations. In a randomized study of Krzemiński et al. [110], buccal infiltration with 0.5% ropivacaine plain achieved more rapid and longer duration anesthesia of pulp and soft tissue to show 100% efficacy for maxillary central and lateral incisors and canines. The comparative study on concentration and anesthetic efficacy of Bhargava et al. [111] suggested that 0.75% ropivacaine plain is suitable for inferior alveolar nerve block in the surgical extraction of mandibular molars. Levobupivacaine could be an alternative to bupivacaine in dental procedures requiring profound bone and soft tissue anesthesia. In inferior alveolar, lingual and buccal nerve blocks, 0.5% levobupivacaine plain is superior to 0.5% bupivacaine plain in intraoperative anesthesia and postoperative analgesia for the lower third molar surgery, although no differences were found in the success rate, onset and duration of mandibular nerve blocks [112].

(7) Supplementary anesthesia strategy: Inferior alveolar nerve block as the predominant choice for anesthetizing mandibular teeth does not always allow the pain-free treatment for patients with irreversible pulpitis. When failing in pain control by this technique, supplementary local anesthesia with intraosseous, intraligamentary and infiltration injections may provide clinically satisfactory results. Clinical trials of Kanaa et al. [113] indicated that supplementary anesthesia by buccal infiltration with 4% articaine plus 1:100,000 epinephrine and by intraosseous injection with 2% lidocaine plus 1:80,000 epinephrine are more successful for pulp anesthesia of patients with irreversible pulpitis in mandibular teeth than intraligamentary and repeat nerve block injections with 2% lidocaine plus 1:80,000 epinephrine. A supplementary intraosseous injection may be especially useful for increasing the anesthetic efficacy to a clinically acceptable level because this technique enables the deposit of local anesthetics directly into the cancellous bone adjacent to the root apex of a tooth to be anesthetized and the production of immediate anesthesia onset. While 2% lidocaine with 1:100,000 epinephrine and 4% articaine with 1:100,000 epinephrine are commonly used for supplementing incomplete anesthesia and analgesia, mepivacaine is recommended rather than these formulations because of its smaller pKa value and weaker vaso-activity. Although the intraosseous injection has one drawback to cause a transient increase of heart rate, 3% mepivacaine plain could increase the anesthetic efficacy without affecting the heart, so this formulation is usable for patients with contraindications to the use of vasoconstrictors. The relatively low risk of mepivacaine intraosseous injection has been suggested by recent studies [114,115].

CONCLUSION

Local anesthetics remain the most useful drugs in dentistry to control preoperative, intraoperative and postoperative pain. Although the detailed reasons are not yet fully understood, dental anesthesia frequently fails in the presence of inflammation. Such anesthetic failures cannot be accounted for by only one mechanism, but should be interpreted by a combination of different mechanisms on inflammatory acidosis, mediators and pathoses. Although various strategies are presumable in light of anesthetic pharmacology and inflammatory pathology, none of them satisfy all the clinical requirements for dental anesthesia. The detailed mechanisms for local anesthetic failures in patients with pulpal and periapical inflammation remain to be further studied together with the technical development for improving the efficacy of dental local anesthesia.

AKNOWLEDGEMENT

REFERENCES

1. Robinson PD, Pitt Ford TR, McDonald F. Local anesthesia in dentistry. Boston: Wright. 2000.

2. Potočnik I, Bajrović, F. Failure of inferior alveolar nerve block in endodontics. Endod Dent Traumatol.1999; 15: 247-251.

3. Boronat López, Peñarrocha Diago M. Failure of locoregional anesthesia in dental practice. Review of the literature. Med Oral Patol Oral Cir Bucal. 2006; 11: 510-513.

4. Reisman D, Reader A, Nist R, Beck M, Weaver J. Anesthetic efficacy of the supplemental intraosseous injection of 3% mepivacaine in irreversible pulpitis. Oral Surg Oral Med Oral Pathol Oral Radiol

Endod. 1997; 84: 676-682.

5. Claffey E, Reader A, Nusstein J, Beck M, Weaver J. Anesthetic efficacy of articaine for inferior alveolar nerve blocks in patients with irreversible pulpitis. J Endod. 2004; 30: 568-571.

6. Srinivasan N, Kavitha M, Loganathan CS, Padmini G. Comparison of anesthetic efficacy of 4% articaine and 2% lidocaine for maxillary buccal infiltration in patients with irreversible pulpitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009; 107: 133-136.

7. Kanaa MD, Whitworth JM, Meechan JG. A comparison of the efficacy of 4% articaine with 1:100,000 epinephrine and 2% lidocaine with 1:80,000 epinephrine in achieving pulpal anesthesia in maxillary teeth with irreversible pulpitis. J Endod. 2012; 38: 279-282.

8. Hosseini HR, Parirokh M, Nakhaee N, V Abbott P, Samani S. Efficacy of articaine and lidocaine for buccal infiltration of first maxillary molars with symptomatic irreversible pulpitis: a randomized double-blinded clinical trial. Iran Endod J. 2016; 11: 79-84.

9. Moradi Askari E, Parirokh M, Nakhaee N, Hosseini HR, Abbott PV. The effect of maxillary first molar root length on the success rate of buccal infiltration anesthesia. J Endod. 2016; 42: 1462-1466.

10. Poorni S, Veniashok B, Senthilkumar AD, Indira R, Ramachandran S. Anesthetic efficacy of four percent articaine for pulpal anesthesia by using inferior alveolar nerve block and buccal infiltration techniques in patients with irreversible pulpitis: a prospective randomized double-blind clinical trial. J Endod. 2011; 37: 1603-1607.

11. Ashraf H, Kazem M, Dianat O, Noghrehkar F. Efficacy of articaine versus lidocaine in block and infiltration anesthesia administered in teeth with irreversible pulpitis: a prospective, randomized, double-blind study. J Endod. 2013; 39: 6-10.

12. Fan S, Chen WL, Pan CB, Huang ZQ, Xian MQ, Yang ZH, et al. Anesthetic efficacy of inferior alveolar nerve block plus buccal infiltration or periodontal ligament injections with articaine in patients with irreversible pulpitis in the mandibular first molar. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009; 108: 89-93.

13. Sood R, Hans MK, Shetty S. Comparison of anesthetic efficacy of 4% articaine with 1:100,000 epinephrine and 2% lidocaine with 1:80,000 epinephrine for inferior alveolar nerve block in patients with irreversible pulpitis. J Clin Exp Dent. 2014; 6: 520-523.

14. Aggarwal V, Singla M, Kabi D. Comparative evaluation of anesthetic efficacy of Gow-Gates mandibular conduction anesthesia, Vazirani-Akinosi technique, buccal-plus-lingual infiltrations, and conventional inferior alveolar nerve anesthesia in patients with irreversible pulpitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010; 109: 303-308.

15. Hargreaves KM, Keiser K. Local anesthetic failure in endodontics: mechanisms and management. Endod Topics. 2002; 1: 26-39.

16. Virdee SS, Seymour D, Bhakta S. Effective anaesthesia of the acutely inflamed pulp: part 1. The acutely inflamed pulp. Br Dent J. 2015; 219: 385-390.

17. Hohjoh H, Inazumi T, Tsuchiya S, Sugimoto Y. Prostanoid receptors and acute inflammation in skin. Biochimie. 2014; 107: 78-81.

18. Rood JP, Pateromichelakis S. Inflammation and peripheral nerve sensitisation. Br J Oral Surg. 1981; 19: 67-72.

19. Roy ML, Narahashi T. Differential properties of tetrodotoxin-sensitive and tetrodotoxin-resistant sodium channels in rat dorsal root ganglion neurons. J Neurosci. 1992; 12: 2104-2111.

20. Sorenson H, Skidmore L, Rzasa R, Kleier S, Levinson S, Hendry M. Comparison of pulpal sodium channel density in normal teeth to diseased teeth with severe spontaneous pain. J Endod. 2004; 30: 287.

21. Coward K, Plumpton C, Facer P, Birch R, Carlstedt T, Tate S, et al. Immunolocalization of SNS/PN3 and NaN/SNS2 sodium channels in human pain states. Pain. 2000; 85: 41-50.

22. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011; 152: 2-15.

23. Jastak JT, Yagiela JA, Donaldson D. Local anesthesia of the oral cavity. Philadelphia: WB Saunders. 1995.

24. Malamed SF. Local anesthetics: dentistry's most important drugs, clinical update 2006. J Calif Dent Assoc. 2006; 34: 971-976.

25. Giovannitti JA Jr, Rosenberg MB, Phero JC. Pharmacology of local anesthetics used in oral surgery. Oral Maxillofac Surg Clin North Am. 2013; 25: 453-465.

26. Moore PA, Hersh EV. Local anesthetics: pharmacology and toxicity. Dent Clin North Am. 2010; 54: 587-599.

27. Moore PA, Nahouraii HS, Zovko JG, Wisniewski SR. Dental therapeutic practice patterns in the U.S. I. Anesthesia and sedation. Gen Dent. 2006; 54: 92-98.

28. Fozzard HA, Lee PJ, Lipkind GM. Mechanism of local anesthetic drug action on voltage-gated sodium channels. Curr Pharm Des. 2005; 11: 2671-2686.

29. Catterall WA. Voltage-gated sodium channels at 60: structure, function and pathophysiology. J Physiol. 2012; 590: 2577-2589.

30. Butterworth JF 4th, Strichartz GR. Molecular mechanisms of local anesthesia: a review. Anesthesiology. 1990; 72: 711-734.

31. Frangopol PT, Mihăilescu D. Interactions of some local anesthetics and alcohols with membranes. Colloids Surf B Biointerfaces. 2001; 22: 3-22.

32. Yun I, Cho ES, Jang HO, Kim UK, Choi CH, Chung IK, et al. Amphiphilic effects of local anesthetics on rotational mobility in neuronal and model membranes. Biochim Biophys Acta. 2002; 1564: 123-132.

33. Tsuchiya H, Mizogami M. Interaction of local anesthetics with biomembranes consisting of phospholipids and cholesterol: mechanistic and clinical implications for anesthetic and cardiotoxic effects. Anesthesiol Res Pract. 2013; 2013: 297141.

34. Tsuchiya H, Mizogami M. Membrane interactivity of charged local anesthetic derivative and stereoselectivity in membrane interaction of local anesthetic enantiomers. Local Reg Anesth. 2008; 1: 1-9.

35. Tsuchiya H, Ueno T, Mizogami M, Takakura K. Local anesthetics structure-dependently interact with anionic phospholipid membranes to modify the fluidity. Chem Biol Interact. 2010; 183: 19-24.

36. Tsuchiya H, Mizogami M. R(+)-, Rac-, and S(−)-bupivacaine stereostructure-specifically interact with membrane lipids at cardiotoxically relevant concentrations. Anesth Analg. 2012; 114: 310-312.

37. Punnia-Moorthy A. Evaluation of pH changes in inflammation of the subcutaneous air pouch lining in the rat, induced by carrageenan, dextran and *Staphylococcus aureus*. J Oral Pathol. 1987; 16: 36-44.

38. De Backer D. Lactic acidosis. Minerva Anestesiol. 2003; 69: 281-284.

39. Strichartz GR, Sanchez V, Arthur GR, Chafetz R, Martin D. Fundamental properties of local anesthetics. II. Measured octanol:buffer partition coefficients and pKa values of clinically used drugs. Anesth Analg. 1990; 71: 158-170.

40. Malamed SF, Gagnon S, Leblanc D. Efficacy of articaine: a new amide local anesthetic. J Am Dent Assoc. 2000; 131: 635-642.

41. Skjevik AA, Haug BE, Lygre H, Teigen K. Intramolecular hydrogen bonding in articaine can be related to superior bone tissue penetration:

SciMedCentral

a molecular dynamics study. Biophys Chem. 2011; 154: 18-25.

42. Tsuchiya H, Mizogami M, Ueno T, Takakura K. Interaction of local anaesthetics with lipid membranes under inflammatory acidic conditions. Inflammopharmacology. 2007; 15: 164-170.

43. Ueno T, Tsuchiya H, Mizogami M, Takakura K. Local anesthetic failure associated with inflammation: verification of the acidosis mechanism and the hypothetic participation of inflammatory peroxynitrite. J Inflamm Res. 2008; 1: 41-48.

44. Wennberg E, Haljamäe H, Edwall G, Dhuner KG. Effects of commercial (pH ~3.5) and freshly prepared (pH ~6.5) lidocaine-adrenaline solutions on tissue pH. Acta Anaesthesiol Scand. 1982; 26: 524-527.

45. Punnia-Moorthy A. Buffering capacity of normal and inflamed tissues following the injection of local anaesthetic solutions. Br J Anaesth. 1988; 61: 154-159.

46. Demiryürek AT, Cakici I, Kanzik I. Peroxynitrite: a putative cytotoxin. Pharmacol Toxicol. 1998; 82: 113-117.

47. Ischiropoulos H, Zhu L, Beckman JS. Peroxynitrite formation from macrophage-derived nitric oxide. Arch Biochem Biophys. 1992; 298: 446-451.

48. Ueno T, Mizogami M, Takakura K, Tsuchiya H. Membrane effect of lidocaine is inhibited by interaction with peroxynitrite. J Anesth. 2008; 22: 96-99.

49. Ueno T, Mizogami M, Takakura K, Tsuchiya H. Peroxynitrite affects lidocaine by acting on membrane-constituting lipids. J Anesth. 2008; 22: 475-478.

50. Gunaydin B, Demiryurek AT. Interaction of lidocaine with reactive oxygen and nitrogen species. Eur J Anaesthesiol. 2001; 18: 816-822.

51. Tsuchiya H, Ueno T, Mizogami M, Takakura K. Antioxidant activity analysis by liposomal membrane system and application to anesthetics. Anal Sci. 2008; 24: 1557-1562.

52. Takakura K, Mizogami M, Ono Y, Ooshima K, Muramatsu I. Decrease of the inhibitory effect of lidocaine on trigeminal nerve response by the inflammatory oxidant peroxynitrite. Can J Anaesth. 2005; 52: 439-440.

53. Flake NM, Gold MS. Inflammation alters sodium currents and excitability of temporomandibular joint afferents. Neurosci Lett. 2005; 384: 294-299.

54. Steen KH, Steen AE, Reeh PW. A dominant role of acid pH in inflammatory excitation and sensitization of nociceptors in rat skin, in vitro. J Neurosci. 1995; 15: 3982-3989.

55. Deval E, Lingueglia E. Acid-sensing ion channels and nociception in the peripheral and central nervous systems. Neuropharmacology. 2015; 94: 49-57.

56. Byers MR, Taylor PE, Khayat BG, Kimberly CL. Effects of injury and inflammation on pulpal and periapical nerves. J Endod. 1990; 16: 78-84.

57. Morgan JR, Gebhart GF. Characterization of a model of chronic orofacial hyperalgesia in the rat: contribution of NA_V 1.8. J Pain. 2008; 9: 522-531.

58. Gold MS, Reichling DB, Shuster MJ, Levine JD. Hyperalgesic agents increase a tetrodotoxin-resistant Na^+ current in nociceptors. Proc Natl Acad Sci USA. 1996; 93: 1108-1112.

59. Rood JP, Pateromichelakis S. Local anaesthetic failures due to an increase in sensory nerve impulses from inflammatory sensitization. J Dent. 1982; 10: 201-206.

60. Scholz A, Kuboyama N, Hempelmann G, Vogel W. Complex blockade of TTX-resistant Na^+ currents by lidocaine and bupivacaine reduce firing

61. Wang JG, Strong JA, Xie W, Zhang JM. Local inflammation in rat dorsal root ganglion alters excitability and ion currents in small-diameter sensory neurons. Anesthesiology. 2007; 107: 322-332.

62. Wells JE, Bingham V, Rowland KC, Hatton J. Expression of Nav1.9 channels in human dental pulp and trigeminal ganglion. J Endod. 2007; 33: 1172-1176.

63. Suwanchai A, Theerapiboon U, Chattipakorn N, Chattipakorn SC. Na$_V$ 1.8, but not Na$_V$ 1.9, is upregulated in the inflamed dental pulp tissue of human primary teeth. Int Endod J. 2012; 45: 372-378.

64. Nakamura M, Jang IS. Acid modulation of tetrodotoxin-resistant Na^+ channels in rat nociceptive neurons. Neuropharmacology. 2015; 90: 82-89.

65. Hinkley SA, Reader A, Beck M, Meyers WJ. An evaluation of 4% prilocaine with 1:200,000 epinephrine and 2% mepivacaine with 1:20,000 levonordefrin compared with 2% lidocaine with 1:100,000 epinephrine for inferior alveolar nerve block. Anesth Prog. 1991; 38: 84-89.

66. McLean C, Reader A, Beck M, Meryers WJ. An evaluation of 4% prilocaine and 3% mepivacaine compared with 2% lidocaine (1:100,000 epinephrine) for inferior alveolar nerve block. J Endod. 1993; 19: 146-150.

67. Tortamano IP, Siviero M, Costa CG, Buscariolo IA, Armonia PL. A comparison of the anesthetic efficacy of articaine and lidocaine in patients with irreversible pulpitis. J Endod. 2009; 35: 165-168.

68. Sampaio RM, Carnaval TG, Lanfredi CB, Horliana AC, Rocha RG, Tortamano IP. Comparison of the anesthetic efficacy between bupivacaine and lidocaine in patients with irreversible pulpitis of mandibular molar. J Endod. 2012; 38: 594-597.

69. Barath S, Triveni VS, Sai Sujai GV, Harikishan G. Efficacy of 2% mepivacaine and 2% lignocaine in the surgical extraction of mesioangular angulated bilaterally impacted third molars: a double-blind, randomized, clinical trial. J Pharm Bioallied Sci. 2015; 7: 600-606.

70. Visconti RP, Tortamano IP, Buscariolo IA. Comparison of the anesthetic efficacy of mepivacaine and lidocaine in patients with irreversible pulpitis: a double-blind randomized clinical trial. J Endod. 2016; 42: 1314-1319.

71. Nydegger B, Nusstein J, Reader A, Drum M, Beck M. Anesthetic comparisons of 4% concentrations of articaine, lidocaine, and prilocaine as primary buccal infiltrations of the mandibular first molar: a prospective randomized, double-blind study. J Endod. 2014; 40: 1912-1916.

72. Kanaa MD, Whitworth JM, Corbett IP, Meechan JG. Articaine and lidocaine mandibular buccal infiltration anesthesia: a prospective randomized double-blind cross-over study. J Endod. 2006; 32: 296-298.

73. Abdulwahab M, Boynes S, Moore P, Seifikar S, Al-Jazzaf A, Alshuraidah A, et al. The efficacy of six local anesthetic formulations used for posterior mandibular buccal infiltration anesthesia. J Am Dent Assoc. 2009; 140: 1018-1024.

74. Mojumdar EH, Lyubartsev AP. Molecular dynamics simulations of local anesthetic articaine in a lipid bilayer. Biophys Chem. 2010; 153: 27-35.

75. Renton T, Yiangou Y, Plumpton C, Tate S, Bountra C, Anand P. Sodium channel Nav1.8 immunoreactivity in painful human dental pulp. BMC Oral Health. 2005; 5: 5.

76. Parirokh M, Yosefi MH, Nakhaee N, Abbott PV, Manochehrifar H.

The success rate of bupivacaine and lidocaine as anesthetic agents in inferior alveolar nerve block in teeth with irreversible pulpitis without spontaneous pain. Restor Dent Endod. 2015; 40: 155-160.

77. Tsuchiya H, Ueno T, Tanaka T, Matsuura N, Mizogami M. Comparative study on determination of antioxidant and membrane activities of propofol and its related compounds. Eur J Pharm Sci. 2010; 39: 97-102.

78. Tsuchiya H. Lipid-peroxidation-inhibitory effects of perioperatively used drugs associated with their membrane interactions. Oxid Antioxid Med Sci. 2014; 3: 91-98.

79. Malamed SF, Tavana S, Falkel M. Faster onset and more comfortable injection with alkalinized 2% lidocaine with epinephrine 1:100,000. Compend Contin Educ Dent. 2013; 34: 10-20.

80. Kashyap VM, Desai R, Reddy PB, Menon S. Effect of alkalinisation of lignocaine for intraoral nerve block on pain during injection, and speed of onset of anaesthesia. Br J Oral Maxillofac Surg. 2011; 49: 72-75.

81. Saatchi M, Farhad AR, Shenasa N, Haghighi SK. Effect of sodium bicarbonate buccal infiltration on the success of inferior alveolar nerve block in mandibular first molars with symptomatic irreversible pulpitis: a prospective, randomized double-blind study. J Endod. 2016; 42: 1458-1461.

82. Hobeich P, Simon S, Schneiderman E, He J. A prospective, randomized, double-blind comparison of the injection pain and anesthetic onset of 2% lidocaine with 1:100,000 epinephrine buffered with 5% and 10% sodium bicarbonate in maxillary infiltrations. J Endod. 2013; 39: 597-599.

83. Schellenberg J, Drum M, Reader A, Nusstein J, Fowler S, Beck M. Effect of buffered 4% lidocaine on the success of the inferior alveolar nerve block in patients with symptomatic irreversible pulpitis: a prospective, randomized, double-blind study. J Endod. 2015; 41: 791-796.

84. Saatchi M, Khademi A, Baghaei B, Noormohammadi H. Effect of sodium bicarbonate-buffered lidocaine on the success of inferior alveolar nerve block for teeth with symptomatic irreversible pulpitis: a prospective, randomized double-blind study. J Endod. 2015; 41: 33-35.

85. Shurtz R, Nusstein J, Reader A, Drum M, Fowler S, Beck M. Buffered 4% articaine as a primary buccal infiltration of the mandibular first molar: a prospective, double-blind, randomized study. J Endod. 2015; 41: 1403-1407.

86. Dagher FB, Yared GM, Machtou P. An evaluation of 2% lidocaine with different concentrations of epinephrine for inferior alveolar nerve block. J Endod. 1997; 23: 178-180.

87. Santos CF, Modena KC, Giglio FP, Sakai VT, Calvo AM, Colombini BL, et al. Epinephrine concentration (1:100,000 or 1:200,000) does not affect the clinical efficacy of 4% articaine for lower third molar removal: a double-blind, randomized, crossover study. J Oral Maxillofac Surg. 2007; 65: 2445-2452.

88. Pereira LA, Groppo FC, Bergamaschi Cde C, Meechan JG, Ramacciato JC, Motta RH, et al. Articaine (4%) with epinephrine (1:100,000 or 1:200,000) in intraosseous injections in symptomatic irreversible pulpitis of mandibular molars: anesthetic efficacy and cardiovascular effects. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013; 116: 85-91.

89. Knoll-Köhler E, Förtsch G. Pulpal anesthesia dependent on epinephrine dose in 2% lidocaine. A randomized controlled double-blind crossover study. Oral Surg Oral Med Oral Pathol. 1992; 73: 537-540.

90. Penniston SG, Hargreaves KM. Evaluation of periapical injection of ketorolac for management of endodontic pain. J Endod.1996; 22: 55-59.

91. Lapidus D, Goldberg J, Hobbs EH, Ram S, Clark GT, Enciso R. Effect of premedication to provide analgesia as a supplement to inferior alveolar nerve block in patients with irreversible pulpitis. J Am Dent Assoc. 2016; 147: 427-437.

92. Parirokh M, Ashouri R, Rekabi AR, Nakhaee N, Pardakhti A, Askarifard S, et al. The effect of premedication with ibuprofen and indomethacin on the success of inferior alveolar nerve block for teeth with irreversible pulpitis. J Endod. 2010; 36: 1450-1454.

93. Aggarwal V, Singla M, Rizvi A, Miglani S. Comparative evaluation of local infiltration of articaine, articaine plus ketorolac, and dexamethasone on anesthetic efficacy of inferior alveolar nerve block with lidocaine in patients with irreversible pulpitis. J Endod. 2011; 37: 445-449.

94. Mellor AC, Dorman ML, Girdler NM. The use of an intra-oral injection of ketorolac in the treatment of irreversible pulpitis. Int Endod J. 2005; 38: 789-792.

95. Oleson M, Drum M, Reader A, Nusstein J, Beck M. Effect of preoperative ibuprofen on the success of the inferior alveolar nerve block in patients with irreversible pulpitis. J Endod. 2010; 36: 379-382.

96. Aggarwal V, Singla M, Kabi D. Comparative evaluation of effect of preoperative oral medication of ibuprofen and ketorolac on anesthetic efficacy of inferior alveolar nerve block with lidocaine in patients with irreversible pulpitis: a prospective, double-blind, randomized clinical trial. J Endod. 2010; 36: 375-378.

97. Hung O. Drug transformation: advances in drug delivery systems. Can J Anaesth. 2006; 53: 1074-1077.

98. Grant GJ, Bansinath M. Liposomal delivery systems for local anesthetics. Reg Anesth Pain Med. 2001; 26: 61-63.

99. de Paula E, Cereda CM, Fraceto LF, de Araújo DR, Franz-Montan M, Tofoli GR, et al. Micro and nanosystems for delivering local anesthetics. Expert Opin Drug Deliv. 2012; 9: 1505-1524.

100. Cereda CM, Brunetto GB, de Araújo DR, de Paula E. Liposomal formulations of prilocaine, lidocaine and mepivacaine prolong analgesic duration. Can J Anaesth. 2006; 53: 1092-1097.

101. Wiziack Zago PM, Baroni DB, Groppo FC, de Paula E, Ranali J, Volpato MC. Anesthetic efficacy of liposomal prilocaine in maxillary infiltration anesthesia. J Liposome Res. 2011; 21: 81-87.

102. Franz-Montan M, de Paula E, Groppo FC, Ranali J, Volpato MC. Efficacy of liposome-encapsulated 0.5% ropivacaine in maxillary dental anesthesia. Br J Oral Maxillofac Surg. 2012; 50: 454-458.

103. Tofoli GR, Cereda CM, Groppo FC, Volpato MC, Franz-Montan M, Ranali J, et al. Efficacy of liposome-encapsulated mepivacaine for infiltrative anesthesia in volunteers. J Liposome Res. 2011; 21: 88-94.

104. Silva CB, Groppo FC, Santos CP, Serpe L, Franz-Montan M, de Paula E, et al. Anaesthetic efficacy of unilamellar and multilamellar liposomal formulations of articaine in inflamed and uninflamed tissue. Br J Oral Maxillofac Surg. 2016; 54: 295-300.

105. Ramos Campos EV, Silva de Melo NF, Guilherme VA, de Paula E, Rosa AH, de Araújo DR, et al. Preparation and characterization of poly(ε-caprolactone) nanospheres containing the local anesthetic lidocaine. J Pharm Sci. 2013; 102: 215-226.

106. Grillo R, de Melo NF, de Araújo DR, de Paula E, Rosa AH, Fraceto LF. Polymeric alginate nanoparticles containing the local anesthetic bupivacaine. J Drug Target. 2010; 18: 688-699.

107. Silva de Melo NF, Campos EV, Gonçalves CM, de Paula E, Pasquoto T, de Lima R, et al. Development of hydrophilic nanocarriers for the charged form of the local anesthetic articaine. Colloids Surf B Biointerfaces. 2014; 121: 66-73.

SciMedCentral

108. Serpe L, Franz-Montan M, Santos CP, Silva CB, Nolasco FP, Caldas CS, et al. Anaesthetic efficacy of bupivacaine 2-hydroxypropyl-β-cyclodextrin for dental anaesthesia after inferior alveolar nerve block in rats. Br J Oral Maxillofac Surg. 2014; 52: 452-457.

109. Nau C, Strichartz GR. Drug chirality in anesthesia. Anesthesiology. 2002; 97: 497-502.

110. Krzemiński TF, Gilowski L, Wiench R, Płocica I, Kondzielnik P, Sielańczyk A. Comparison of ropivacaine and articaine with epinephrine for infiltration anaesthesia in dentistry - a randomized study. Int Endod J. 2011; 44: 746-751.

111. Bhargava D, Chakravorty N, Rethish E, Deshpande A. Comparative analysis of the anesthetic efficacy of 0.5 and 0.75 % ropivacaine for inferior alveolar nerve block in surgical removal of impacted mandibular third molars. J Maxillofac Oral Surg. 2014; 13: 431-434.

112. Brajkovic D, Brkovic B, Milic M, Biocanin V, Krsljak E, Stojic D.

Levobupivacaine vs. bupivacaine for third molar surgery: quality of anaesthesia, postoperative analgesia and local vascular effects. Clin Oral Investig. 2014; 18: 1481-1488.

113. Kanaa MD, Whitworth JM, Meechan JG. A prospective randomized trial of different supplementary local anesthetic techniques after failure of inferior alveolar nerve block in patients with irreversible pulpitis in mandibular teeth. J Endod. 2012; 38: 421-425.

114. Gallatin E, Stabile P, Reader A, Nist R, Beck M. Anesthetic efficacy and heart rate effects of the intraosseous injection of 3% mepivacaine after an inferior alveolar nerve block. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000; 89: 83-87.

115. Idris M, Sakkir N, Naik KG, Jayaram NK. Intraosseous injection as an adjunct to conventional local anesthetic techniques: A clinical study. J Conserv Dent. 2014; 17: 432-435.