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Review article

Paresthesia in dentistry: The ignored neurotoxicity of local anesthetics

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ABSTRACT

Local anesthetics are frequently used by dentists to relieve localized discomfort of the patient and improve treatment conditions. The risk of paresthesia after local anesthesia is frequently encountered in dental clinics. The neurotoxicity of local anesthetics is a disregarded factor in paresthesia. The review summarizes the types of common local anesthetics, incidence and influencing factors of paresthesia after local anesthesia, and systematically describes the neurotoxicity mechanisms of dental local anesthetic. Innovative strategies may be developed to lessen the neurotoxicity and prevent paresthesia following local anesthesia with the support of a substantial understanding of paresthesia and neurotoxicity.

1. Introduction

Local anesthetics can assist in reducing patient discomfort, ensuring comfort for the patient, and creating ideal conditions for dental treatment by temporarily neutralizing pain stimuli by blocking the ion channels in the regional nerves [1]. Cocaine was the first local anesthetic successfully extracted from coca leaves in 1860 and used in 1864 for topical anesthesia in eye surgery; following this, more and more local anesthetics are being discovered and used clinically. However, owing to the use of local anesthetics, patients are reporting more neurological complications.

Bennett, in 1957, originally described the first case of lidocaine-induced psychic disturbance, while Goldman reported the second case in 1958 [2,3]. Since then, to describe the most common neurological complications associated with intraspinal anesthesia, the concept of temporary neurological syndromes was developed gradually [4]. Back pain or dysesthesia which began within the first 24 h after local anesthesia and can radiate to the thighs, calves, hips, or buttocks, constitutes transient neurological symptoms [5]. Researchers concluded that transient neurological symptoms are significantly influenced by the neurotoxicity of local anesthetics. Currently, based on the National Institute of Neurological Disorders and Stroke, a natural or manmade toxic substance is considered neurotoxic when it can disrupt or even kill neurons to alter the normal activity of the nervous system, such as local anesthetics [6]. The neurotoxicity of local anesthetics has been extensively discussed in clinical medicine, pharmacy, and other fields; however, limited

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data are available in dentistry.

According to the Food and Drug Administration's recommendation, the maximum dose of lidocaine and articaine in dental clinics that is considered safe for adult patients without any other underlying conditions is 7 mg/kg [7]. However, several local anesthetics are also potentially neurotoxic at clinical concentrations [8]. Paresthesia is the most common neurological complication induced by local anesthetics; it is an abnormal feeling that occurs in the absence of a specific physical stimulation or is not typical for that stimulus and can be caused by complications anywhere along the somatosensory pathways from the peripheral nerves to the thalamus or postcentral gyrus of the parietal lobe [9]. It generally occurs wing to surgical trauma in dentistry [10]. However, we generally tend to focus more on operational errors than the neurotoxicity of local anesthetics. Therefore, this review first introduces the incidence of paresthesia after local anesthesia in dentistry and the factors influencing this incidence to gather data regarding ways how to prevent paresthesia in clinics; furthermore, some mechanisms of neurotoxicity of local anesthetics have also been discussed. A better comprehension of the mechanisms of neurotoxicity of local anesthetics will preclude neurotoxicity and develop novel local anesthetics with lower neurotoxicity.

2. Local anesthetics in dentistry

Local anesthetics can interact with voltage-gated sodium (Na^+) channels to restrain Na^+ current and the production of an action potential, thus, inhibiting nerve impulse conduction and suppressing pain [11]. Na^+ channels comprise four homologous domains (DI–DIV), with each homologous domain being composed of six transmembrane-spanning segments (S1–S6) (Fig. 1) [12]. The different transmembrane segments have different functions. The cytoplasmic aspect of the pore is formed by the S6 transmembrane segments and is associated with rapid Na + permeation [11]. Local anesthetics have proven to can interact with well-defined residues of the S6 segments [13].

The structure of injectable local anesthetics can be divided into the following three parts: (a) aromatic or lipophilic, influencing drugs' lipophilicity; (b) amino-terminal, affecting drugs' hydrophilicity; and (c) an intermediate chain connecting aromatic and amino-terminal parts. According to the latter structure, common local anesthetics can be divided into the following two categories: ester and amid (Fig. 2) [14]. The ester class includes benzocaine, procaine, and tetracaine, while the amide class includes lidocaine, articaine, bupivacaine, and mepivacaine [15].

Ester local anesthetics all contain an ester group, which can be hydrolyzed in plasma by cholinesterase. They are metabolized to produce *p*-aminobenzoic acid, possibly causing allergic reactions, including dermatitis and tissue necrosis [16]. In contrast, ester local anesthetics are more effective vasodilators compared with amide local anesthetics. The absorption rate of local anesthetics is increased by vasodilation, thereby reducing their action time and increasing the possibility of systemic toxicity [17]. Because of this, ester local anesthetics have been gradually abandoned in dental treatment.

Amide local anesthetics all contain an amide group and can be metabolized in the liver by microsomal mixed functional oxidase dealkylation. However, amide local anesthetics cannot produce *p*-aminobenzoic acid, which greatly reduces the possibility of allergic reaction. Therefore, they seldom cause true allergic reactions, and most of the reports of adverse reactions are usually attributed to a reaction to epinephrine, vasovagal syncope, or overdose toxicity [18]. Even so, some patients continue to have allergies to amide local anesthetics. Researchers demonstrate that in a patient who is allergic to amide local anesthetics, 1% diphenhydramine with 1:100,000 epinephrine is an effective and safe alternative, though treating these patients under general anesthesia more is more commonly advised [19]. Articaine is the only amide local anesthetic containing an ester group; therefore it also has the properties of ester local

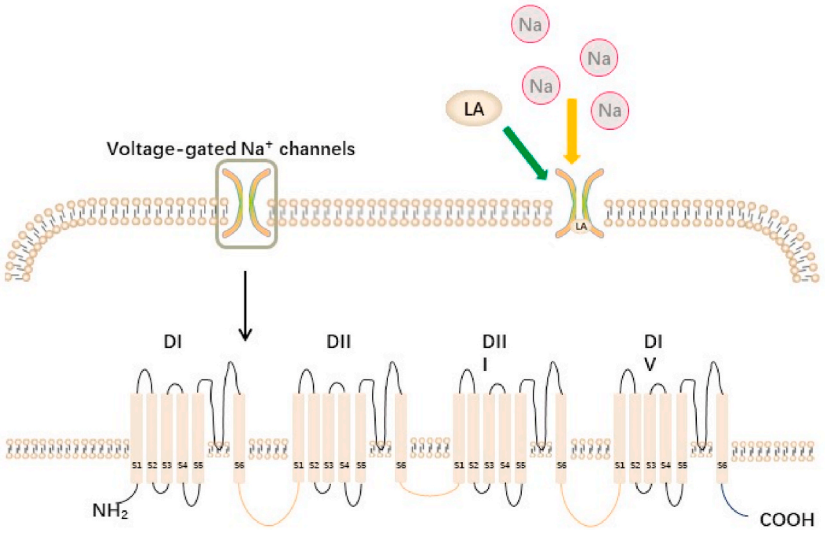

Fig. 1. The mechanism of action of local anesthetics and organization of voltage-gated Na^+ channels.

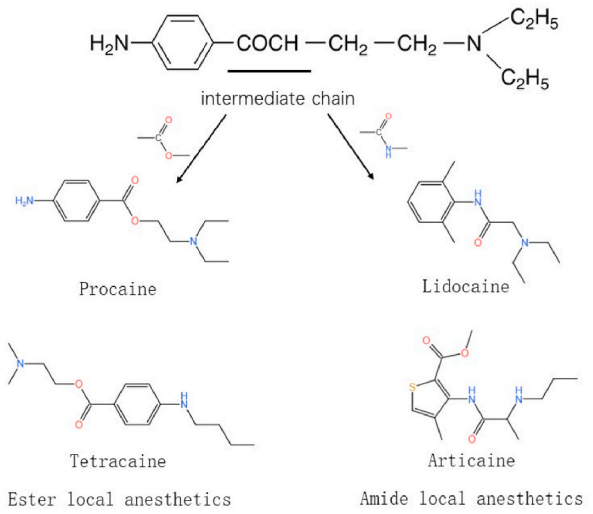

Fig. 2. Classification of local anesthetics.

anesthetics and can be hydrolyzed by cholinesterase in plasma. This increases its metabolic activity, shortens its half-life, and reduces the possibility of systemic toxicity [20].

Based on the duration of local anesthetics, which is relative to their pKa, they can also be classified into short, medium, and long-acting local anesthetics [21]. The medium-acting local anesthetics such as lidocaine and articaine have become a reasonable choice

Table 1
Overview of retrospective cohort studies regarding paresthesia after local anesthesia in dentistry.

Incidence of paresthesia	Number of patients with paresthesia	Involved techniques	Involved local anesthetics	Reference number	Authors, year
1:785,000	143 (14 in 1993)	not stated	articaine (10); prilocaine (4) in 1993	[26]	Haas et al., 1995
not stated	54	mandibular nerve block	4% articaine (29); 3% prilocaine (10); 2% lidocaine (10); 3% mepivacaine (8); multiple anesthetics (1)	[27]	Hillerup et al., 2006
1:20,000 to 850,000	57	inferior alveolar nerve block	lidocaine (20); articaine (17); prilocaine (17); bupivacaine (1); multiple anesthetics (2)	[22]	Pogrel, 2007
1:609,000	182	mandibular nerve block (172); mandibular nerve block combined with other techniques (8) incisive or mental nerve block (1); infiltration and intraligamentary injection (1)	articaine (109); prilocaine (29); lidocaine (23); mepivacaine (6); multiple anesthetics (15)	[25]	Gaffen et al., 2009
1:13,800,970	248	mandibular nerve block (207); infiltration (10); mental nerve block (2); not stated (29)	4% articaine (116); 4% prilocaine (97); 2% lidocaine (11); 0.5% bupivacaine (1); 3% mepivacaine (1); multiple anesthetics (22)	[23]	Garisto et al., 2010
not stated	not stated	not stated	prilocaine (34%); articaine (33%); lidocaine (25%)	[28]	Pogrel, 2012
1:9,698,358	44	not stated	articaine (34); lidocaine (7); prilocaine (1); mepivacaine (1)	[29]	Zahedi, 2012
not stated	573	not stated	lidocaine (247); bupivacaine (99); articaine (85); prilocaine (30); multiple anesthetics (45)	[24]	Piccinni et al., 2015

because dental clinical treatment generally requires local anesthetics to have characteristics such as fast-acting, moderate duration and low toxicity.

3. The incidence of paresthesia after local anesthesia in dentistry

In general, the probability of paresthesia following the local anesthetic is minimal. Persistent paresthesia induced by local anesthetics range from 1:20,000 [22] to 1:13,800,970 [23] according to existing literature. However, to identify paresthesia related to local anesthesia, different publications have different methods, and these methods will influence the estimation of the incidence of paresthesia after local anesthesia in dentistry [8].

Additionally, the reporting rate of paresthesia related to articaine is relatively high among all common local anesthetics in dentistry. According to a 2010 study, in the 248 reports of oral paresthesia caused by local anesthetics in the Food and Drug Administration Adverse Event Reporting System from November 1997 to August 2008, 4% articaine and 4% procaine were the most commonly used anesthetics [23]. A similar evaluation report pointed out in 2015 that among the 528 reported cases of local anesthesia-related complications from 2004 to 2011, 82 cases were involved in oral paresthesia [24]. Research on the market shares of various local anesthetics from 2006 to 2008 in Canada revealed that the market share of articaine during this period was 44% and it was responsible for 70% of paresthesia events after the administration of local anesthetic [25]. Many similar studies and reports reflect the high proportion of paresthesia after the use of articaine. Some retrospective cohort studies are presented in Table .1.

Different researchers have varied perspectives on this issue. Some researchers reviewed previous literature to determine whether 4% articaine had a greater risk of nerve injury when used for inferior alveolar nerve block than 2% lidocaine and concluded no conclusive evidence that 4% articaine caused more nerve injury than 2% lidocaine [30]. Similar views were expressed in a recent study [31]. After summarizing the relevant literature, another group of scholars concluded that the use of 4% articaine for mandibular third-molar extraction is a safe choice [32]. Hopman et al. put forward the following explanations for a higher risk of paresthesia using 4% articaine compared with other low-concentration anesthetics in some retrospective studies: (a) Articaine was used at 4% concentration, higher than most other anesthetics used during dental treatment. (b) After using the articaine, the lingual nerve was more easily damaged than the inferior alveolar nerve. The lingual nerve damage demonstrates more unpleasant symptoms and increases the likelihood of more frequent reporting than inferior alveolar nerve damage. (c) Other factors. There was a consensus that local anesthetic concentrations should not exceed 4% in dental clinical practice [33].

The reasons given by Hopman et al. to elucidate the problem are valid [33]. Procaine is commonly used in clinical practice at a concentration higher than 2%, and relatively high numbers of procaine-related paresthesia instances have been documented [34]. Moreover, the lingual nerve is the most frequently damaged statistically, and there are two possible reasons to explain [28]. In anatomical terms, the lingual nerve is stretched quite tightly in the standard, mouth-open position for a mandibular block and is less likely to deflect during an injection [35]. From histological aspects, the number of fascicles present within the lingual nerve ranges from 1 to 8 and an unifascicular nerve may be injured more easily than a multifascicular one [36]. However, the latter cannot completely elucidate the high rate of paresthesia associated with articaine because all local anesthetics are subject to the problem when used in block anesthesia. Perhaps dentists' preference for local anesthetics used in block anesthesia is a possible reason. Moreover, commercial articaine is routinely combined with epinephrine; thus, increasing the risk of neurotoxicity caused by articaine while epinephrine is generally not added to other common commercial local anesthetics in dentistry.

4. The influencing factors of paresthesia after local anesthesia in dentistry

Many factors can influence the possibility of paresthesia after local anesthesia in dentistry. In addition to local anesthetics

Table 2
Results of experiments *in vitro* comparing the neurotoxicity of different local anesthetics.

Material	Results	Reference number	Authors, year
chick embryos' dorsal root ganglion neurons	lidocaine > bupivacaine > mepivacaine > ropivacaine	[42]	Radwan et al., 2002
the freshwater snail *Lymnaea stagnalis*' cultured neurons	dibucaine > tetracaine > lidocaine > bupivacaine = ropivacaine > mepivacaine = procaine	[43]	Kasaba et al., 2003
human SH-SY5Y neuroblastoma cells	bupivacaine > ropivacaine > chloroprocaine > lidocaine > or = mepivacaine > procaine	[44]	Perez-Castro et al., 2009
neuroblastoma cells (SHEP)	tetracaine > bupivacaine > prilocaine = mepivacaine = ropivacaine > lidocaine > procaie = articaine	[37]	Werdehausen et al., 2009
human SH-SY5Y neuroblastoma cells	bupivacaine > lidocaine > prilocaine > mepivacaine > articaine > ropivacaine	[45]	Malet et al., 2015
human SH-SY5Y neuroblastoma cells	articaine is no more neurotoxic than lidocaine	[39]	Albalawi et al., 2018
rat developing motor neurons	lidocaine > bupivacaine > ropivacaine	[38]	Koo et al., 2021

themselves, clinical operations and patients' physical conditions can also have an impact. Thus, understanding them can give us some insights into how to avoid paresthesia after local anesthesia.

4.1. Local anesthetics

Although neurotoxicity is present in all local anesthetics, the magnitude varies, which has been demonstrated by both *in vitro and vivo* experiments. According to the half-maximal neurotoxic effects (LD_{50}), in a 2009 study compared the neurotoxicity of different types of local anesthetics which resulted in the following order: tetracaine **>** bupivacaine **>** prilocaine = mepivacaine = ropivacaine **>** lidocaine **>** procaine **>** articaine [37]. In a recent study comparing the neurotoxicity of lidocaine, bupivacaine, and ropivacaine to rat developing motor neurons, another group of scholars concluded that lidocaine had the greatest neurotoxic effects, while ropivacaine had the least effects [38]. More results from studies *in vitro* that compare the neurotoxicity of different local anesthetics are presented in Table .2. Numerous studies did not find that articaine was more neurotoxic than lidocaine, which could elucidate the relatively high incidence of paresthesia associated with articaine. A more recent study also found that articaine does not disrupt neural cells any more than lidocaine does [39]. As for experiments *in vivo*, researchers got a result in an early study that lidocaine was more neurotoxic than mepivacaine and prilocaine in a rat intrathecal model [40]. An overview of some similar studies *in vivo* is presented in Table .3. Most studies used a rat intrathecal model to determine the neurotoxicity of local anesthetics to the spinal cord; however, a study used other models and focused on the neurotoxicity of local anesthetics to other nerves. In a 2013 study, 24 rats were divided into three groups and each group used different drugs to block the mental nerve. One group was administered 4% articaine with adrenaline, another 2% lidocaine with adrenaline, and one adrenaline. After 24h, researchers found that rats receiving 4% articaine with adrenaline showed more inflammatory infiltration than those that received 2% lidocaine with adrenaline or adrenaline only [41].

In clinical practice, adequate drug concentration and sufficient duration are necessary for a satisfactory anesthesia effect. The higher the concentration and dose, the quicker the local anesthetics act and the more effective they are. However, the concentration of local anesthetics also affects their neurotoxicity. Some experiments *in vitro* which were mentioned above found that local anesthetics induced developing motor neurons or neuroblastoma cell death in a concentration-dependent manner in rats [37,38,45]. A study *in vivo* used saline, 2% articaine, or 4% articaine injections that were administered intraneural into the rat sciatic nerve intraneural, and their effects were examined stereological, 4% articaine caused more neurotoxic injuries such as the reduction of the mean cross-sectional axon area and myelin sheath thickness than the other agents [51]. Therefore, the concentration of local anesthetics should be restricted during dental treatment to lower the danger of neurotoxicity on the premise of meeting clinical needs.

The dosage of local anesthetics and the length of time that the nerve is exposed to local anesthetics will influence the neurotoxicity of local anesthetics. A placebo-controlled study confirmed that the increases in the number of macrophages and transforming growth factor β-1 expression induced by local anesthetics which were assumed to be related to the neurotoxicity were connected to the length of time the nerve is exposed to local anesthetics [52]. Moreover, dentists sometimes readminister local anesthesia in some clinical condition, such as the mandibular third molar extraction or root canal treatment of a molar with irreversible pulpitis. Thus, this will increase local anesthetic dosage and length of time the nerve is exposed to local anesthetics. Some researchers administered ropivacaine at different concentrations to rats at 90-min intervals for 12 h to investigate the histological changes and behavioral effects and found that repeated intrathecal injection of 1% ropivacaine could induce neurotoxicity. Another study also demonstrated similar result [53,54].

Local anesthetics are commonly supplemented with adjuvants, such as epinephrine clinically. Epinephrine, as a vasoconstrictor,

Table 3
Results of experiments *in vivo* comparing the neurotoxicity of different local anesthetics.

Animal, injection technology	Results	Reference number	Authors, year
rat, intrathecal anesthesia	prilocaine caused more histologic injuries than lidocaine, but there wasn't a significant difference	[46]	Kishimoto et al., 2002
rat, intrathecal anesthesia	lidocaine was more neurotoxic than mepivacaine and prilocaine	[40]	Takenami et al., 2004
rat, intrathecal anesthesia	lidocaine was more neurotoxic than bupivacaine when administered intrathecally at equipotent concentrations	[47]	Sakura et al., 2005
rat, intrathecal anesthesia	lidocaine > bupivacaine	[48]	Takenami et al., 2005
rat, intrathecal anesthesia	procaine was less neurotoxic than mepivacaine, prilocaine and bupivacaine	[49]	Takenami et al., 2009
rat, intrathecal anesthesia	ropivacaine was less neurotoxic than procaine, bupivacaine, and levobupivacaine	[50]	Takenami et al., 2012
rat, mental nerve block	rats that received 4% articaine with adrenaline had more inflammatory infiltration than rats that received 2% lidocaine with adrenaline or adrenaline only	[41]	Baroni et al., 2013

lengthens exposure of the nerve to local anesthetics and reduces blood flow, further leading to an increased ischemic nerve injury risk [55]. However, when the vasoconstrictive effect of epinephrine ceases, oxidative damage can occur owing to nerve ischemia-reperfusion, and apoptosis may be activated, leading to neuronal damage [8]. Moreover, local anesthetics with epinephrine can cause neurotoxicity by neuronal vacuolation though the phenomenon occurs when they are used for intraspinal anesthesia rather than infiltration or block anesthesia which is more relevant to dental clinical practice [56]. Besides epinephrine, the added preservative may sometimes increase the risk of neurotoxicity caused by local anesthetics. For example, a study found that when local anesthetics with benzethonium chloride were used in rabbits, they could cause neurotoxicity. Th researchers administered repeated doses of 1% ketamine with benzethonium chloride as a preservative into the epidural space of rabbits, and light and electron microscopy revealed that ketamine-treated rabbits showed significant histological changes compared with the control group [57].

In addition to the previously listed characteristics, several additional factors, such as the pH and even the methods used to store local anesthetics, can affect their neurotoxicity. By administering 2% lidocaine with epinephrine 1:100.000 solutions to rats in four different storage conditions (the original packaging and refrigeration, original packaging and room temperature, non-original packaging and room temperature, and brand new solution) and histologically analyzing their maxilla along with the soft tissue, a research group found how the ways to store local anesthetics could influence the pH and level of inflammatory reaction after the injection. Moreover, they also found that the non-original packaging and room temperature had the biggest influence [58].

4.2. Operation factor

An independent risk factor for peripheral nerve injury in dentistry is peripheral nerve block anesthesia, as concluded from a retrospective study of a large sample [59]. The possibility of paresthesia after local anesthesia in dentistry is affected by different nerve-block anesthesia methods. The conventional inferior alveolar nerve block is the anesthetic nerve block technique most frequently used in dentistry [60]. This technique can anesthetize inferior alveolar, buccal, and lingual nerves creating suitable conditions for dental treatments. However, the failure rate with this block anesthesia technology is greater than 20% [60]. This is partly owing to the doctors' technique level also affecting the risk of nerve injury. Moreover, the nerve injury risk caused by the techniques themselves is also different. The arched needle technique which is commonly used in clinics, increases the risk of needle breakage and tissue tear compared to a conventional inferior alveolar nerve block, though the success rate is also improved [61,62]. A nerve block anesthesia method was proposed by some dentists that positioned the needle anterior to the mandibular foramen when used for extracting the mandibular third molar and reduced the risk of nerve injury compared to other anesthesia methods [63]. A related radiographic provided experimental support for this anesthesia technique [64].

It is possible to pass a needle through a nerve during nerve block anesthesia and cause nerve injury. Some researchers assumed that this could cause hemorrhage into the neural sheath or direct trauma to the nerve with scar tissue formation [10,65]. Therefore, the location of injection can also affect the incidence of peripheral nerve injury caused by local anesthesia. Studies have demonstrated that peripheral nerve injury is more severe using intrafascicular injection than extrafascicular deposition. Considering this, passing a needle through a nerve should be avoided to reduce the possibility of paresthesia after local anesthesia [66,67].

In addition, the degree of nerve injury caused by the needles varies depending on the type of needle, with long-bevel needles more likely to cause nerve punctures; however, short-bevel needles cause more severe nerve injury. High pressure during the administration of local anesthesia also increases the risk of peripheral nerve injury [8].

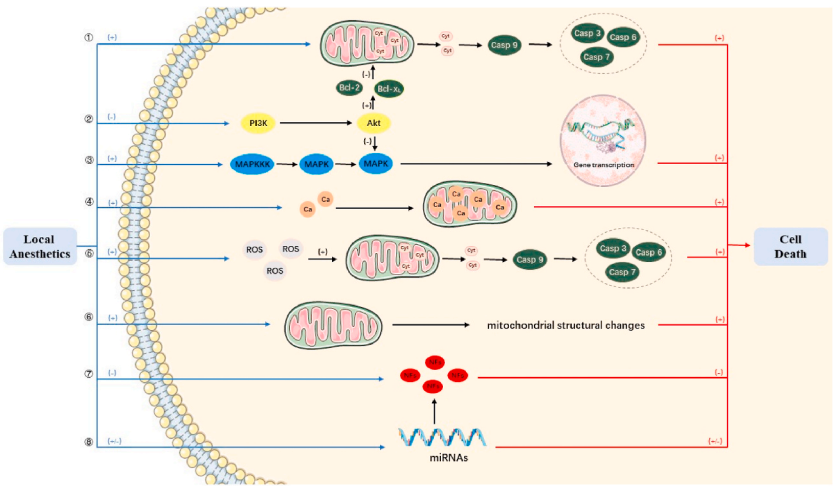

Fig. 3. Schematic diagram of neurotoxicity mechanism of local anesthetics.

4.3. Patient factor

As aforementioned, the blood flow reduction can make the nerve more vulnerable to damage. Some diseases, such as peripheral vascular diseases, vasculitis, and hypertension, will affect the microvascular system, leading to patients' nervous systems being more susceptible to ischemia than that in normal individual, thus indirectly improving the neurotoxicity of local anesthetics [67]. Similarly, illnesses, such as diabetic peripheral neuropathy and multiple sclerosis that affect the nervous system, also make patients more susceptible to nerve damage and develop paresthesia after using local anesthetics [68]. Caution should be administered when local anesthesia is used for patients with these systemic diseases.

5. The mechanisms of neurotoxicity of local anesthetics in dentistry

Currently, the cellular mechanism of neurotoxicity of local anesthetics in dentistry has not been fully elucidated. The major consensus is regarding cell apoptosis playing a significant part in the mechanisms underlying the neurotoxicity of local anesthetics. This is also one of the main research areas in the investigation of the mechanisms underlying the neurotoxicity of local anesthetics. And some mechanisms of neurotoxicity of local anesthetics have been put forward (Fig. 3).

①Intrinsic caspase pathway; ②PI3K/AKT pathway; ③MAPK pathway; ④Calcium overload; ⑤Oxidative stress; ⑥Mitochondrial structural changes; ⑦Lack of neurotrophic factors; ⑧MicroRNAs.

Cytochrome C (Cyt) Caspase (Casp) reactive oxygen species (ROS) neurotrophic factors (NFs) MicroRNAs (miRNAs)

Parts of the figure were drawn using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

5.1. Intrinsic caspase pathway

The spontaneous and orderly death of cells controlled by genes to maintain internal environment stability is cell apoptosis [69]. The extrinsic and intrinsic apoptosis pathways require caspase [70]. Some researchers found that T-lymphoma cells could be promoted by lidocaine by activating caspase-3 and releasing cytochrome C, which was accompanied by T-lymphoma cells viability reduction and a loss of the mitochondrial membrane potential, while in cells deficient in caspase-9, cell apoptosis induced by lidocaine was strongly reduced and lidocaine induced cell apoptosis was demonstrated through intrinsic caspase pathway [71]. *In vivo*, over-weight neonatal rats were administered ropivacaine and bupivacaine using intrathecal injection and both ropivacaine and bupivacaine could induce cell apoptosis and activate caspase-3 [72]. Ropivacaine promoted apoptosis of hepatocellular carcinoma cells through activating caspase-3 activity [73]. One of the mechanisms of the cytotoxicity of local anesthetics is the intrinsic caspase pathway, though hepatocellular carcinoma cells are not related to the nerve.

B-cell lymphoma (BCL) −2 family proteins demonstrate anti-apoptotic activities and can reduce the release of cytochrome C which can activate caspase-3 [74,75]. Cells overexpressing BCL-2 are less affected by lidocaine [71]. Many drugs, such as epigallocatechin gallate, which have a neuroprotective effect are proven to promote BCL-2 expression [76]. Neuroblastoma cells incubated in bupivacaine with epigallocatechin gallate were found with more viability, and their apoptosis was inhibited compared to those incubated in bupivacaine only. This was associated with a multi-fold decrease in the caspases-3, -8, and -9 expression in neuroblastoma cells and an increase in the Bcl-xL and Bcl-2 expression [77].

5.2. Phosphatidylinositol 3-kinase (PI3K)/AKT pathway

PI3K/AKT pathway, a classical intracellular signal transduction pathway, demonstrates a response to extracellular signals; promotes metabolism, proliferation, cell survival, growth, and angiogenesis; and inhibits apoptosis [78,79]. PI3K/AKT pathway is a key factor in neuronal survival and activated Akt can promote Bcl-2 expression to suppress the neurotoxicity of local anesthetics in different cell types, including hippocampal neurons and PC12 cells [80–83]. Moreover, bupivacaine can also suppress the Akt and *p*-Akt expression and induce neurotoxicity [77]. Therefore, whether drugs which can protect neurons work through the PI3K/AKT pathway was determined. The neuroprotective effects of plumbagin were assessed by detecting neuronal apoptosis in the hippocampal tissues and reduced apoptosis was detected along with raised PI3K/Akt pathway proteins in the hippocampal tissues. This indicated that plumbagin exerts its neuroprotective effects by regulating PI3K/AKT pathway [84]. Local anesthetic-induced neuron injury can be attenuated by pretreating using dexamethasone by preventing the decline in mitochondrial membrane potential and increasing Akt phosphorylation [85]. Lithium, epigallocatechin gallate, and genistein ddemonstrate neuroprotective effects through PI3K/AKT pathway [77,86–88].

5.3. Mitogen-activated protein kinase (MAPK) pathway

MAPK can be divided into the following four subfamilies: extracellular regulated protein kinases (ERK), c-Jun N-terminal kinase (JNK), p38 MAPK, and ERK5. These regulate many important physiological and pathological effects, such as cell growth, differentiation, stress, and inflammatory responses [89,90]. The neuronal differentiation in PC12 cells requires MAPK-dependent activation of c-Jun and c-Fos suggesting that the MAPK pathway may have a relationship with the neurotoxicity of local anesthetics [91]. The rat dorsal root ganglia cells in culture mediums were incubated using with lidocaine alone or with SB203580, a p38 MAPK inhibitor, and detected a more significant reduction in the number of cells in the culture medium without SB20358. They thought that neuron

apoptosis might be induced by lidocaine through the p38 MAPK pathway in the rat dorsal root ganglia cells because the death of rat dorsal root ganglia, was partly mediated by apoptosis [92]. Lidocaine also could induce neurotoxicity by activating of p38 MAPK pathway specifically in a time-dependent manner in pheochromocytoma cell line cultures [93]. In addition to lidocaine, the relevance of the p38 MAPK pathway for bupivacaine- and ropivacaine-induced neurotoxicity had also been demonstrated while the JNK pathway also contributed to the neurotoxicity of bupivacaine [94].

Additionally, some drugs demonstrate neuroprotective behavior through this pathway. Lithium could protect cells against the neurotoxicity induced by bupivacaine by the suppression of activation of the ERK pathway [86]. Moreover, plumbagin also has neuroprotective effects through this pathway [84].

5.4. Calcium overload

The depolarization of mitochondria which is one of the most important calcium pools in cells, is caused by the increase of calcium ion concentration, leading to its overload, inhibiting mitochondrial function, and promoting nerve injury [95]. Local anesthetics have been demonstrated to cause the rise of intracellular calcium ion concentration in rat dorsal root ganglion, which was associated with the neurotoxicity of local anesthetics. After adding a calcium-selective chelating agent into the extracellular fluid, calcium ions decreased significantly along with the reduction of the degree of spinal dorsal root ganglion injury induced by local anesthesia. This indicated that the neurotoxicity caused by local anesthesia is owing to intracellular calcium overload [96]. Now, as researchers get closer, Cav3.1, Cav3.2, and Cav3.3 T-type calcium channels are considered to be closely related to local anesthetics neurotoxicity. Previous studies have confirmed that p38 MAPK phosphorylation was reduced, the calcium ion concentration in rat dorsal root ganglion cells increased, and neuronal injury induced by lidocaine improved upon Cav3.1 gene silencing. Moreover, lidocaine could up-regulate Cav3.1mRNA and protein expression to induce neuroblastoma cell toxicity [97,98]. Calmodulin-dependent protein kinase II (CaMKII) β, Cav3.2, and Cav3.3 expression were up-regulated in injured dorsal root ganglion induced by ropivacaine, while inhibition of CaMKIIβ and Cav3.3 expression could improve the cell damages and decrease cell apoptosis rate [99,100]. However, lidocaine can directly act on microglia and inhibit the increase of intracellular calcium concentration [101]. This indicated that calcium overload may be not the only mechanism of the neurotoxicity of local anesthetic.

5.5. Oxidative stress

Oxidative stress eliminates excessive free radicals produced by harmful stimuli. It refers to a state of imbalance between oxidation and antioxidant effects [102,103]. However, excessive accumulation of the product of oxidative stress, reactive oxygen species (ROS) will lead to cell senescence and death [104]. Oxidative stress is one of the common phenomena of neurotoxicity. In 2005, bupivacaine was found to induce ROS generation before the activation of caspase-3. Moreover, poly ADP-ribose polymerase degradation and anti-oxidants could block the generation of ROS and significantly inhibit bupivacaine-induced apoptosis [105]. Recently, researchers also found that ropivacaine could cause excessive accumulation of ROS, decrease in ATP production, and p38 phosphorylation in human neurons *in vitro*, resulting in neuron death [106]. As a tea polyphenol, it was determined whether epigallo catechin gallate demonstrated its neuroprotective effect by protecting the cells against oxidative stress. H_2O_2 was added in PC12 cells to induce oxidative stress with or without epigallo catechin gallate and cell death was assessed. This verified the above assumption and led to the result that epigallo catechin gallate treatment attenuated cell death [107]. By inhibiting oxidative stress via the ROS-mediated PI3K/PKB pathway, capillaries could protect neuroblastoma cells against bupivacaine-induced apoptosis [108].

5.6. Mitochondrial structural changes

The homeostasis of mitochondria, which is an energy-producing structure in cells and a major site for aerobic respiration involves both functional and structural aspects; thus, changes in either aspect will cause homeostasis imbalance [109,110]. Mitochondria is directly or indirectly involved in some of the mechanisms of neurotoxicity of local anesthetics, such as intrinsic caspase pathway, calcium overload, and oxidative stress, primarily through functional changes. The structure of mitochondria is also important for homeostasis and cell function, and modifications may also lead to neuron apoptosis. The mitochondrial membrane potential could be depolarized by intracellular alkalization to cause morphological changes and early apoptosis of rat dorsal root ganglion neurons at clinical concentrations [111,112]. A recent study found that the expression of the major mitochondrial regulator peroxisome proliferator-activated receptor-gamma coactivato -1α and its downstream transcription factors reduced in neuronal cells when exposed to ropivacaine, indicating that mitochondrial impairment is a key event in neurotoxicity induced by ropivacaine [113]. Another study confirmed that ropivacaine could cause mitochondrial morphological changes and dysfunction, associated with the rise of mitochondrial fission protein dynamin-related protein 1 (DRP1). Moreover, silencing of DRP1 in neuronal cells decreased ropivacaine-induced apoptosis and mitochondrial dysfunction, indicating that DRP1 has an important impact on mitochondrial homeostasis imbalance [114]. Additionally, mitofusin also plays an important role in mitochondrial homeostasis. At present, literature regarding how mitofusin is involved in apoptosis regulation, is limited, the studies about mitofusin and the neurotoxicity of local anesthetics in dentistry are fewer [115].

5.7. Lack of neurotrophic factors

Neurotrophic factors have the potential to treat nerve injury because of their importance in the growth, survival, and function of

neurons in both the central and peripheral nervous systems, including neurotrophins and growth factors that regulate the survival of neurons [116,117]. Neurotrophic factors can reverse the growth cone collapse induced by lidocaine, mepivacaine, and bupivacaine in the primary cultured sensory neurons [118,119]. Researchers also found the upregulation of brain-derived neurotrophic factor antisense RNA (BDNF-AS) and suppression of the BNDF transcription during bupivacaine-induced neurotoxicity in the dorsal root ganglion neurons [120]. Therefore, supplementing neurotrophic factors may be a way to reduce the neurotoxicity of local anesthetics. Pretreatment using monosialoganglioside, a pleiotropic neurotrophin that can promote central nervous system regeneration and prevent it damage can protect against bupivacaine-induced neurotoxicity [121].

5.8. MicroRNAs (miRNAs)

The miRNAs, the small endogenous RNAs, are important in the posttranscriptional regulaton of gene expression and have gained attention in both basic biological and clinical studies [122]. The miRNAs have been found to play a dual role in the neurotoxicity of local anesthetics. The miR-34a-5p and miR-132 were significantly up-regulated with the decrease in cell viability and increase of apoptosis level in neuroblastoma cells treated with bupivacaine compared to the control group [123,124]. However, miR-183-5p could protect neuroblastoma cells against mepivacaine-induced neurotoxicity [125]. The regulatory effects of miRNAs on local anesthetic neurotoxicity are also related to the above mechanisms. Many miRNAs, such as miR-132, miR-375, and miR-33-5p, have been found to influence the neurotoxicity by regulating the expression of neurotrophic factors [123,126,127]. The miR-22 and miR-429 are related to the intrinsic caspase pathway by targeting BAG5 which can influence the expression of Bcl-2 [128,129]. The role of miRNAs, including other noncoding RNAs, in local anesthetic neurotoxicity will persist as a point of discussion.

Additionally, the adenosine phosphate activated protein kinas route, nuclear factor kappa-B pathway, and other pathways may also be involved in the neurotoxicity of local anesthetics. All the mechanisms are associated with each other. For example, oxidative stress usually will activate the intrinsic apoptosis pathway. Though many mechanisms have been detected, the neurotoxicity of local anesthetics in dental clinics persists as a challenge. Local anesthetics have different neurotoxic mechanisms for different types of cells, indicating that more basic research related to dental clinic is needed.

6. Conclusions

Dentists should learn proper ways, safe dosages, and any potential safety concerns while using local anesthetics, such as their neurotoxicity, which is critical to understanding paresthesia following local anesthesia in dentistry. Even if the incidence is low based on the existing literature, other researchers think that the true incidence may be up to five times higher. Thus, the risk cannot be disregarded [130]. It is recommended that the concentration of local anesthetics used in clinical practice should not exceed 4%, and intrafascicular injection and high-pressure injection should be avoided to prevent paresthesia after local anesthesia in dental clinics. Additionally, people with peripheral vascular or nervous system diseases require greater attention.

Several mechanisms have been attempted to elucidate the neurotoxicity of local anesthetics. Based on these, some drugs, such as lithium and epigallo catechin gallate, are found that can protect neurons against neurotoxicity of local anesthetics [76,77,86,87,107]. Recent research has concentrated on decreasing the neurotoxicity of local anesthetics by creating novel drug delivery technologies, such as nanoparticles, liposomes, hydrophobic-based polymers, poly microspheres, injectable paste, and solid polymer [131,132]. These drug delivery systems can extend the duration of local anesthetic effects and lessen neurotoxicity and cardiotoxicity, according to numerous animal studies and clinical trials [133–135]. In addition, local anesthetics are cytotoxic to many different cell types, including T lymphoma cells, human melanoma cell lines, and oral squamous cell carcinoma cell lines [136–139]. Moreover, by reducing neurite development and cancer cell signaling *in vivo*, local anesthetics can prevent the spread and metastasis of breast cancer [140]. Therefore, using local anesthetics as a cancer therapy is feasible [141,142]. As we assess the neurotoxicity of local anesthetics further, it will become a tool for us rather than something which we try to avoid.

Author contribution statement

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no competing interests.

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