

Neurosensory complications associated with articaine use in dental procedures: a narrative literature review¹

Complicações neurosensoriais associadas ao uso da articaína em procedimentos odontológicos: uma revisão narrativa da literatura

Complicaciones neurosensoriales asociadas al uso de la articaína en procedimientos dentales: una revisión narrativa de la literatura

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ABSTRACT

Local anesthesia is essential for pain control in dentistry; however, neurosensory complications, particularly paresthesia affecting the lingual and inferior alveolar nerves, remain clinically significant adverse events. This narrative review critically evaluated the association between 4% articaine and neurosensory disturbances in dental practice. Methods: A comprehensive search of PubMed, SciELO, LILACS Plus (via BVS), and Google Scholar was conducted in May 2026. Controlled vocabulary and free-text terms were combined for articaine/carticaine, adverse drug effects, paresthesia, facial paralysis, formication, and dysesthesia. Of 320 records identified, 16 studies met predefined PICO-based eligibility criteria after deduplication and screening. Studies involving articaine combined with other anesthetics, animal models, or

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non-dental settings were excluded. Results: Included studies, published between 1995 and 2026, comprised pharmacovigilance analyses, randomized clinical trials, and case reports. Pharmacovigilance data suggested disproportionate reporting of paresthesia after 4% articaine compared with 2% lidocaine, with estimated incidences of approximately 1:609,000 and 1:1,100,000 injections, respectively, and relative risks up to 3.6 times higher than expected by market share. Conversely, prospective randomized trials did not identify statistically significant differences in neurotoxicity between articaine and lidocaine. The lingual nerve accounted for 70–79% of mandibular nerve injuries, possibly owing to its superficial location and predominantly unifascicular architecture. Most pharmacovigilance studies did not report anesthetic volume, symptom duration, or adequately control for surgical trauma, injection technique, and anatomical variation. Evidence from peripheral regional anesthesia in medicine has not demonstrated a reproducible articaine-specific neurotoxic signal. Conclusions: Current evidence does not support intrinsic, exclusive neurotoxicity of 4% articaine. Neurosensory complications are likely multifactorial, involving anatomical vulnerability, needle trauma, injection technique, anesthetic concentration, and administered volume. Disproportionate reporting may reflect reporting bias, preferential use in complex inflammatory cases, and procedure-related confounding. Prospective studies with standardized reporting of dose, volume, symptom duration, and permanent versus temporary injury are needed.

Keywords: Carticaine. Paresthesia. Dental anesthesia. Nerve injury. Neurotoxicity. Pharmacovigilance.

RESUMO

A anestesia local é essencial para o controle da dor na odontologia; no entanto, complicações neurossensoriais, especialmente a parestesia que afeta os nervos lingual e alveolares inferiores, permanecem eventos adversos clinicamente significativos. Esta revisão narrativa avaliou criticamente a associação entre 4% de articaína e distúrbios neurossensoriais na prática odontológica. Métodos: Uma busca abrangente no PubMed, SciELO, LILACS Plus (via BVS) e Google Scholar foi realizada em maio de 2026. Vocabulário controlado e termos em texto livre foram combinados para articaína/carticaína, efeitos adversos de medicamentos, parestesia, paralisia facial, formicação e disestesia. Dos 320 registros identificados, 16 estudos atenderam a critérios pré-definidos de elegibilidade baseados em PICO após deduplicação e triagem. Estudos envolvendo articaína combinada com outros anestésicos, modelos animais ou ambientes não odontológicos foram excluídos. Resultados: Os estudos incluídos, publicados entre 1995 e 2026, abrangeram ensaios clínicos randomizados e relatos de casos. Dados de farmacovigilância sugeriram relatos desproporcionais de parestesia após 4% de articaína em comparação com 2% de lidocaína, com incidências estimadas de aproximadamente 1:609.000 e 1:1.100.000 injeções, respectivamente, e riscos relativos até 3,6 vezes maiores do que o esperado em termos de participação de mercado. Por outro lado, ensaios randomizados prospectivos não identificaram diferenças estatisticamente significativas na neurotoxicidade entre articaína e lidocaína. O nervo lingual representava 70–79% das lesões do nervo mandibular, possivelmente devido à sua localização superficial e arquitetura predominantemente unifascicular. A maioria dos estudos de farmacovigilância não relatou volume anestésico, duração dos sintomas ou controle adequado para trauma cirúrgico, técnica de injeção e variação anatômica. Evidências da anestesia regional periférica na medicina não demonstraram um sinal neurotóxico específico da articaína reproduzível. Conclusões: As evidências atuais não apoiam neurotoxicidade intrínseca e exclusiva de 4% de articaína. As complicações neurossensoriais provavelmente são multifatoriais, envolvendo vulnerabilidade anatômica, trauma por agulha, técnica de injeção, concentração anestésica e volume administrado. A notificação desproporcional pode refletir viés de notificação, uso preferencial em casos inflamatórios complexos e confusão relacionada a procedimentos. São necessários estudos prospectivos com relato padronizado de dose, volume, duração dos sintomas e lesão permanente versus temporária.

Palavras-chave: Articaína. Parestesia. Anestesia odontológica. Lesão nervosa. Neurotoxicidade. Farmacovigilância.

RESUMEN

La anestesia local es esencial para el control del dolor en odontología; sin embargo, las complicaciones neurossensoriales, especialmente la parestesia que afecta a los nervios linguales e inferiores, siguen siendo eventos adversos clinicamente significativos. Esta revisión narrativa evaluó críticamente la asociación entre el 4% de la articaína y las alteraciones neurossensoriales en la práctica dental. Métodos: En mayo de 2026 se realizó una búsqueda exhaustiva en PubMed, SciELO, LILACS Plus (a través de BVS) y Google Scholar. Se

combinaron vocabulario controlado y términos de texto libre para articaína/carticaína, efectos adversos de medicamentos, parestesia, parálisis facial, formicación y disestesia. De los 320 registros identificados, 16 estudios cumplieron criterios de elegibilidad predefinidos basados en PICO tras la deduplicación y el cribado. Se excluyeron estudios que involucraban articaína combinada con otros anestésicos, modelos animales o entornos no dentales. Resultados: Los estudios incluidos, publicados entre 1995 y 2026, comprendieron análisis de farmacovigilancia, ensayos clínicos aleatorizados e informes de casos. Los datos de farmacovigilancia sugirieron una notificación desproporcionada de parestesia tras un 4% de la articaína frente al 2% de lidocaína, con incidencias estimadas de aproximadamente 1:609.000 y 1:1.100.000 inyecciones, respectivamente, y riesgos relativos hasta 3,6 veces superiores a los esperados por cuota de mercado. Por el contrario, los ensayos aleatorizados prospectivos no identificaron diferencias estadísticamente significativas en la neurotoxicidad entre la articaína y la lidocaína. El nervio lingual representaba entre el 70 y el 79% de las lesiones del nervio mandibular, posiblemente debido a su ubicación superficial y a su arquitectura predominantemente unifascicular. La mayoría de los estudios de farmacovigilancia no informaron volumen anestésico, duración de los síntomas ni un control adecuado para traumatismos quirúrgicos, técnicas de inyección y variaciones anatómicas. La evidencia de la anestesia regional periférica en medicina no ha demostrado una señal neurotóxica específica reproducible de la articaína. Conclusiones: La evidencia actual no apoya una neurotoxicidad intrínseca y exclusiva del 4% de articaína. Las complicaciones neurosensoriales probablemente sean multifactoriales, implicando vulnerabilidad anatómica, traumatismo por aguja, técnica de inyección, concentración anestésica y volumen administrado. La notificación desproporcionada puede reflejar sesgos de reporte, uso preferencial en casos inflamatorios complejos y confusión relacionada con el procedimiento. Se necesitan estudios prospectivos con informes estandarizados de dosis, volumen, duración de los síntomas y lesión permanente frente a temporal.

Palabras clave: Carticaine. Parestesia. Anestesia dental. Lesión nerviosa. Neurotoxicidad. Farmacovigilancia.

INTRODUCTION

Local anesthesia is recognized as the safest and most effective pharmacological technique for pain management in dentistry, making it indispensable for clinical and surgical interventions. However, although the overall incidence of serious complications is extremely low, nerve injuries remain one of the events with the greatest impact on patients' quality of life and one of the most feared by practitioners (Daubländer; Müller; Lipp, 1997). Such injuries manifest predominantly as paresthesia, dysesthesia, or hyperesthesia, primarily affecting branches of the trigeminal nerve, with particular involvement of the inferior alveolar and lingual nerves (Ghafoor *et al.*, 2023). The lingual nerve - and to a lesser extent, the inferior alveolar nerve - are the most susceptible structures due to their fascicular characteristics and anatomical location during conventional anesthetic block procedures (Ghafoor *et al.*, 2023; Renton *et al.*, 2010).

Historically, the etiology of these neurosensory alterations has been attributed to direct mechanical trauma during needle penetration, compression caused by edema or intraneural hemorrhage, and the chemical neurotoxicity of anesthetic agents (Pogrel, 2012). Classic studies suggest that any anesthetic solution possesses intrinsic neurotoxic potential if deposited in direct contact with the nerve bundle, especially within confined

anatomical spaces (Kim; Kim; Ahn, 2020; Neal *et al.*, 2015). However, the discussion regarding pharmacological safety intensified with the introduction of higher-concentration solutions, particularly 4% articaine (Aquilanti *et al.*, 2022; Haas; Lennon, 1995a). Synthesized in 1969 and widely used since the 1970s, articaine differs from other amides due to the presence of a thiophene ring in its molecular structure and an additional ester linkage (Aquilanti *et al.*, 2022; Haas; Lennon, 1995a; Snoeck, 2012; Hassan *et al.*, 2011; Singh; Koul, 2024). This configuration confers high lipid solubility, exceptional tissue diffusion capacity, and rapid systemic metabolism by plasma esterases - properties that ensure superior anesthetic efficacy and a favorable systemic toxicity profile (Snoeck, 2012; Tan *et al.*, 2023; Yapp; Hopcraft; Parashos, 2011). Epidemiological investigations and pharmacovigilance reports have suggested a disproportionate correlation between articaine use and the incidence of persistent paresthesia, fueling an ongoing debate regarding the drug's chemical toxicity versus physical trauma caused by the nerve block technique (Renton *et al.*, 2010; Neal *et al.*, 2015; Hillerup; Jensen; Ersbøll, 2011).

Despite the extensive literature, a gap in clinical consensus remains: while surveillance studies indicate warning signs, randomized clinical trials often fail to demonstrate significant differences in safety profiles between articaine and standard lidocaine (Renton *et al.*, 2010; Piccinni *et al.*, 2015; Martin; Nimmo; Jennings, 2021). This discrepancy highlights the need for a comprehensive critical analysis that weighs not only the drug's pharmacological aspects and the intrinsic neurotoxicity of local anesthetics but also anatomical variables, the precision of the operative technique, and the reporting bias (Weber effect) inherent in health surveillance systems.

The objective of this study is to conduct a narrative literature review on the various neurosensory complications associated with the use of articaine in dental procedures, investigating possible causes and explanations for their occurrence.

MATERIALS AND METHODS

To conduct this narrative literature review, a search was performed in the electronic databases PubMed, SciELO, LILACS Plus (via VHL), and Google Scholar on May 26, 2026. Search strategies were adapted to the specific requirements of each database, using combinations of controlled descriptors (MeSH terms) and free-text keywords.

The primary strategy used in PubMed was: Carticaine[MeSH Terms] OR Carticain*[Title/Abstract] OR Articain*[Title/Abstract] AND (((((Drug-Related Side

Effects and Adverse Reactions[MeSH Terms]) OR (“Drug-Related Side Effects and Adverse Reactions”[Title/Abstract])) OR ((“paresthesia”[MeSH Terms]) OR (paresthesia[Title/Abstract])) OR ((Facial Paralysis[MeSH Terms]) OR (Facial Paralysis[Title/Abstract])) OR ((Formication*[Title/Abstract]) OR (Dysesthesia*[Title/Abstract]))).

For the other databases, a simplified adaptation of these search combinations was used, focusing on the terms: Articaine, Carticaine, Drug-Related Side Effects and Adverse Reactions, Paresthesia, Facial Paralysis, Formication, and Dysesthesia. Table 1 presents the complete search strategy for each database.

Table 1 – Search strategy in the selected databases.

Database	Search Strategy
PubMed (www.ncbi.nlm.nih.gov/sites/pubmed)	(Carticaine[MeSH Terms] OR Carticain*[Title/Abstract] OR Articain*[Title/Abstract]) AND (((((Drug-Related Side Effects and Adverse Reactions[MeSH Terms]) OR (“Drug-Related Side Effects and Adverse Reactions”[Title/Abstract])) OR ((“paresthesia”[MeSH Terms]) OR (paresthesia[Title/Abstract])) OR ((Facial Paralysis[MeSH Terms]) OR (Facial Paralysis[Title/Abstract])) OR ((Formication*[Title/Abstract]) OR (Dysesthesia*[Title/Abstract]))
SciELO (search.scielo.org)	Articaine AND paresthesia OR Facial Paralysis OR Formication OR Dysesthesia
LILACS Plus (via BVS – bvsalud.org)	Carticaine OR Articaine AND Drug-Related Side Effects and Adverse Reactions OR paresthesia OR Facial Paralysis OR Formication OR Dysesthesia
Google Scholar (scholar.google.com.br)	Carticaine OR Articaine AND Drug-Related Side Effects and Adverse Reactions OR paresthesia OR Facial Paralysis OR Formication OR Dysesthesia

Source: Prepared by the authors (2026).

Eligibility criteria

Inclusion Criteria

To formulate the inclusion criteria, the PICO strategy was adopted, defined as follows:

- Population (P): Humans undergoing local anesthesia for dental procedures.
- Intervention (I): Dental local anesthesia using the anesthetic agent articaine.
- Control (C): Any other dental local anesthetic solution.
- Outcome (O): Occurrence of neurosensory complications (paresthesia, dysesthesia, paralysis, hyperesthesia, among others).

Exclusion Criteria

Studies presenting the following characteristics were excluded:

- Use of articaine in combination with general anesthesia, sedation, other local anesthetics, or medications;
- Studies involving non-traditional anesthesia methods (e.g., automated systems) or conducted in non-dental settings;
- Use of topical anesthetics or spray formulations;
- Studies conducted on animals (in vivo models) or in vitro studies;
- Articles that did not report neurosensory alterations in the full text; those in which the adverse effect appeared only in the abstract proceeded to full-text reading before exclusion;
- Inappropriate publication types (publications characterized as letters to the editor, editorials, or expert opinions lacking primary clinical data);
- Duplicate articles.

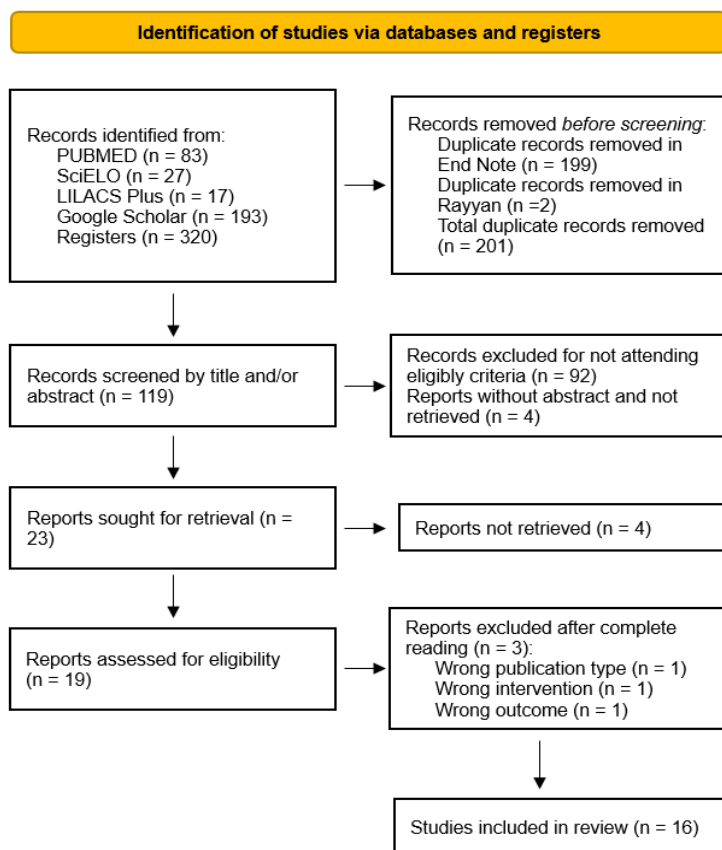
Study selection and data extraction

The initial search identified 320 records across the consulted databases (PubMed: 83; SciELO: 27; LILACS Plus: 17; Google Scholar: 193). References were exported to and managed using EndNote software (Clarivate), where initial duplicates were removed. Subsequently, the dataset was exported to the Rayyan web application, resulting in a total of 119 unique articles for initial screening.

The first selection phase involved reading titles and abstracts (Ti/Ab); 92 articles were excluded for failing to meet eligibility criteria, and 4 lacked abstracts and could not be retrieved in full text. The remaining 23 articles were selected for full-text reading. During the full-text reading phase, another 4 studies could not be retrieved, and 3 others were excluded due to various reasons of ineligibility: one article with an unsuitable publication format, one with a non-matching outcome, and a study by Papadopoulou and Anastasakis (2022) - which reported paralysis following lingual nerve supplementation with mepivacaine - thereby violating the exclusion criterion regarding the absence of association with other local anesthetics following the use of articaine. Ao final de todo o processo de triagem e da aplicação rigorosa dos critérios, 16 artigos foram mantidos e

incluídos na síntese qualitativa desta revisão narrativa. A Figura 1 apresenta o fluxograma de seleção dos estudos.

Figure 1 - Study selection flowchart.



Source: Prepared by the authors (2026). **Notes:** The initial search identified 320 records across four databases (PubMed: 83; SciELO: 27; LILACS Plus: 17; Google Scholar: 193). After removing duplicates using EndNote and Rayyan software, 119 unique articles remained for title and abstract screening. Of these, 92 articles were excluded for failing to meet eligibility criteria, and 4 articles lacked an abstract and could not be retrieved in full text. The remaining 23 articles were selected for full-text reading. During the full-text evaluation, 4 additional studies could not be retrieved, and 3 studies were excluded for the following reasons: unsuitable publication format (n = 1), outcome did not match (n = 1), and use of articaine in combination with another local anesthetic (mepivacaine supplementation for the lingual nerve) (n = 1). Finally, 16 studies were included in the qualitative synthesis of this narrative review.

RESULTS

Characteristics of the included studies

This narrative review synthesized evidence from 16 articles selected according to predefined criteria, published between 1995 and 2026. The methodological profile of the studies revealed a balanced distribution across different levels of scientific evidence. Large-scale retrospective studies based on pharmacovigilance databases - such as the FDA

Adverse Event Reporting System (FAERS) or regional registries - provided the epidemiological foundation necessary for analyzing incidence in large populations (Garisto *et al.*, 2010; Gaffen; Haas, 2009). In contrast, prospective controlled clinical trials offered data on the safety and efficacy of articaine under rigorous clinical conditions, while case reports allowed for the detailed documentation of rare complications and atypical anatomical variations (Papadopoulou; Anastasakis, 2022; Dascanio *et al.*, 2026).

Participant demographics and the dental procedures performed covered a broad spectrum of clinical practice. Most investigations focused on adult patients, although safety in pediatric populations was addressed in specific efficacy studies (Malamed; Gagnon; Leblanc, 2001). Interventions ranged from routine restorative and endodontic procedures to more complex surgeries, such as third-molar extractions - the latter being frequently associated with reports of nerve injury due to anatomical proximity to neurovascular bundles (Dascanio *et al.*, 2026).

Incidence and spectrum of neurosensory complications

The incidence of neurosensory complications associated with articaine is classified in the literature as a rare event, although data vary depending on the collection methodology and the healthcare system analyzed. Retrospective studies suggest that 4% articaine carries a relative risk of paresthesia higher than expected based on its market share - up to 3.6 times greater than that of other anesthetic solutions (Garisto *et al.*, 2010). However, it is crucial to note that prospective clinical trials have not identified statistically significant differences in adverse event rates between articaine and lidocaine, suggesting that the safety profile remains acceptable for routine clinical use (Malamed; Gagnon; Leblanc, 2001).

The spectrum of injuries reported in the literature encompasses various sensory manifestations and, to a lesser extent, motor events. Regarding incidence metrics, retrospective studies indicate a rate of 1 case per 609,000 injections of 4% articaine, compared to a ratio of 1 per 1,100,000 injections observed for 2% lidocaine (Gaffen; Haas, 2009). Concerning injury types, there is an absolute predominance of paresthesia - characterized by partial or total loss of sensation - followed by cases of dysesthesia and hyperesthesia (Moore; Haas, 2010). Additionally, although occurring in isolation, atypical motor events such as facial nerve paralysis and glossopharyngeal nerve dysfunction have been documented (Papadopoulou; Anastasakis, 2022).

Regarding the duration of symptoms, the literature converges on the fact that most neurosensory alterations are transient, with complete recovery of sensation occurring within an average period of two to three months. However, the persistence of symptoms for more than one year characterizes the injury as permanent; this outcome, although infrequent, is more prevalent with inferior alveolar nerve blocks compared to infiltration techniques (Hillerup; Jensen; Ersbøll, 2011).

Clinical, anatomical, and pharmacological variables

Analysis of clinical variables reveals a marked anatomical predilection regarding the recorded complications. The lingual nerve emerges as the most susceptible structure, affected in approximately 70% to 79% of mandibular nerve injury cases (Garisto *et al.*, 2010; Kakroudi; Mehta; Millar, 2015). This vulnerability is attributed to its superficial anatomical location and fascicular structure, making it more prone to direct trauma during the administration of an inferior alveolar nerve block (IANB). At the level of the mandibular lingula, the lingual nerve is frequently characterized as unifascicular, whereas the inferior alveolar nerve exhibits a multifascicular conformation (Pogrel, 2012). This anatomical distinction implies that any trauma - whether mechanical (caused by the needle) or chemical (by the solution) - is more likely to compromise the entirety of the lingual nerve fibers, resulting in more extensive damage.

The anesthetic technique plays a decisive role, given that the vast majority of neurosensory complications are associated with regional blocks in the mandible. Maxillary infiltrations rarely result in persistent damage, reinforcing the hypothesis that the combination of an invasive block technique and the anesthetic's pharmacology heightens the risk of injury (Kakroudi; Mehta; Millar, 2015). Furthermore, the absence of significant reports of paresthesia in the maxilla or in medical contexts - where articaine is widely used for spinal and epidural anesthesia - supports the hypothesis that the risk is associated with the inferior alveolar nerve block (IANB) technique within a confined anatomical space, rather than exclusively with the anesthetic molecule itself (Piccinni *et al.*, 2015). The 4% concentration of articaine is frequently cited as a contributing factor to chemical neurotoxicity, given that exposing nerve tissue to higher concentrations of local anesthetic can induce axonal damage, independent of physical trauma caused by the needle (Hillerup; Jensen; Ersbøll, 2011; Piccinni *et al.*, 2015). Although articaine exhibits high lipid solubility and diffusibility - allowing for the use of smaller volumes - the literature debates

whether its 4% formulation is the primary etiological factor or if mechanical needle trauma and intraneural hemorrhages are the true causes of paresthesia (Malamed, 2006). To date, there is no definitive clinical evidence comparing 4% articaine with lower concentrations in a dental context, and the 4% concentration remains the standard for this anesthetic agent.

A critical point often overlooked in retrospective literature concerns the total volume of anesthetic administered. Most studies based on pharmacovigilance databases do not accurately report the number of cartridges used in cases that progressed to paresthesia (Garisto *et al.*, 2010). This omission is clinically relevant, given that 4% articaine delivers twice the mass of drug per volume (72 mg/1.8 mL) compared to 2% lidocaine (36 mg/1.8 mL). Thus, the administration of multiple articaine cartridges can result in an excessive molecular load at the injection site, suggesting that neurotoxicity may be a dose-dependent phenomenon exacerbated by the drug's high concentration.

The lingual nerve's selective vulnerability compared to the inferior alveolar nerve (IAN) is supported by the fascicular architecture of these structures. The lingual nerve's unifascicular pattern - as opposed to the IAN's multifascicular conformation - means there is less connective tissue available to dissipate the mechanical energy of the injection or buffer against chemical insult.^{4,19} Furthermore, the lingual nerve's anatomical path - situated more superficially and potentially under tension during maximum mouth opening - increases the likelihood of direct contact with the needle (Pogrel, 2012; Malamed, 2006). In this context, shifting toward a paradigm focused on injection technique precision - prioritizing trajectories that minimize direct contact with nerve trunks - proves more critical for clinical success and patient safety than the choice of anesthetic agent alone (Dascanio *et al.*, 2026; Malamed, 2006).

In addition to sensory complications, the literature documents more severe - albeit atypical - motor neurological events, such as facial nerve paralysis and glossopharyngeal nerve dysfunction. These episodes generally occur due to anatomical variations or retrograde flow of the anesthetic agent (Papadopoulou; Anastasakis, 2022). The classic mechanism underlying temporary facial paralysis involves the inadvertent injection of the anesthetic solution into the parotid gland capsule, allowing the drug to diffuse through the cervical fasciae and reach branches of the seventh cranial nerve. Articaine's high diffusibility, a result of its molecular structure, can facilitate this unwanted spread if the regional block technique is not performed with strict adherence to anatomical landmarks.

Although these events are typically transient and self-limiting, they underscore the need for caution when administering an inferior alveolar nerve block and highlight the importance of negative aspiration to prevent intravascular or glandular deposition of the drug (Papadopoulou; Anastasakis, 2022; Malamed, 2006).

DISCUSSION

The primary etiology of neurosensory injuries associated with the use of articaine remains a central topic of debate in dental literature. A critical analysis of the evidence indicates that, although articaine demonstrates clinical efficacy comparable to that of other amide-type anesthetics, there is no consensus in the literature regarding its direct neurotoxicity, given that many reports of paresthesia stem from multifactorial causes, such as anesthetic technique and anatomical variability (Dascanio *et al.*, 2026). The discussion centers on the distinction between direct mechanical trauma caused by the needle - which can result in intraneural or extraneural hemorrhage and inflammatory processes arising from edema at the injection site - and the potential chemical neurotoxicity of the drug itself (Malamed, 2006).

Molecular properties and neurotoxic potential

The unique molecular properties of articaine are fundamental to understanding its neurotoxic potential. The presence of a thiophene ring in its structure - replacing the conventional benzene ring - confers high lipid solubility and a rapid rate of tissue diffusion (Malamed; Gagnon; Leblanc, 2001). Although these characteristics enhance the depth of anesthesia, research suggests that the increased risk of paresthesia may be correlated with the high concentration (4%) of articaine solutions, reinforcing the premise that clinical safety is intrinsically linked to dosage control (Gaffen; Haas, 2009). The hypothesis that the direct neurotoxicity of 4% articaine contributes to axonal alterations through prolonged contact lacks definitive mechanistic confirmation in the literature; however, the warning signal is more pronounced for this agent and for prilocaine compared to other anesthetics at lower concentrations (Piccinni *et al.*, 2015).

Comparative *in vitro* studies indicate that articaine does not exhibit inherently higher cytotoxicity than other local anesthetics when evaluated at equimolar concentrations. The clinical warning signal appears to be strictly linked to its commercial 4% formulation, which exposes neural tissue to a significantly higher solute concentration

(Malamed; Gagnon; Leblanc, 2001). It is also important to distinguish between temporary and permanent damage, as most reports do not specify the exact duration of symptoms, although the literature indicates that spontaneous recovery occurs in the vast majority of cases within a period of 8 to 12 weeks (Hillerup; Jensen; Ersbøll, 2011).

Evidence on regional anesthesia in medicine

Although articaine has historically been associated with reports of paresthesia in dentistry - particularly following inferior alveolar nerve block (IANB) - evidence from other medical specialties raises important questions regarding whether these events are attributable to the anesthetic itself or to procedure-specific factors. Articaine has been successfully used for peripheral nerve blocks in medicine, including axillary and interscalene brachial plexus blocks, digital nerve blocks, and ophthalmic regional anesthesia (Soeck, 2012; Lakhin *et al.*, 2025). Clinical studies comparing articaine with other local anesthetics have demonstrated favorable anesthetic efficacy, with no increase in the incidence of persistent neurological complications. For instance, in a prospective, randomized study on brachial plexus blocks, Lakhin *et al.* (2025) reported no permanent sensory deficits or neuropathies attributable to articaine, despite its direct administration around major peripheral nerves. Similarly, Ertikin *et al.* (2017) observed no neurological complications associated with articaine during axillary brachial plexus blocks for hand surgery.

It is important to note that neurological complications following peripheral nerve blocks are well-recognized in anesthesiology, regardless of the local anesthetic used. Large prospective studies and systematic reviews (Neal *et al.*, 2015; Borgeat *et al.*, 2001; Brull *et al.*, 2007) have demonstrated that postoperative paresthesia, hypoesthesia, and transient motor deficits can occur following regional anesthesia with lidocaine, bupivacaine, mepivacaine, ropivacaine, and other agents. These complications are generally considered multifactorial, with the primary injury mechanisms being needle trauma, intraneural injection, high injection pressure, hematoma formation, ischemia, compression, postoperative inflammation, and patient-related anatomical factors (Neal *et al.*, 2015; Borgeat *et al.*, 2001). Consequently, contemporary anesthesiology literature does not attribute the majority of neurological complications to the intrinsic neurotoxicity of a specific anesthetic molecule.

This contrasts with dental literature, in which articaine - particularly at a 4% concentration - has been disproportionately associated with reports of lingual and inferior alveolar nerve paresthesia (Haas; Lennon, 1995a; Monteiro *et al.*, 2015). However, most of this evidence stems from spontaneous adverse event reports, retrospective case series, and pharmacovigilance databases, which are inherently incapable of establishing causality. Furthermore, a similar association has not been consistently demonstrated in randomized clinical trials or prospective comparative studies evaluating neurological outcomes.

Anatomical and technical considerations

The anatomical and technical characteristics of the inferior alveolar nerve block may partially explain this discrepancy. Unlike most peripheral nerve blocks performed in modern anesthesiology, the inferior alveolar nerve block is typically performed using anatomical landmarks, without direct visualization of the nerve. Consequently, inadvertent needle contact with the nerve, intrafascicular injection, high injection pressures, or localized hematoma formation may occur more frequently. Furthermore, the lingual nerve - identified by Pogrel (2007) as responsible for the majority of reported cases of post-anesthetic paresthesia in dentistry - appears particularly susceptible due to its superficial location, relatively limited connective tissue protection, and lower fascicular complexity compared to many peripheral nerves. These anatomical characteristics may increase its vulnerability to mechanical injury, regardless of the anesthetic solution administered.

Experimental evidence also challenges the hypothesis of articaine-specific neurotoxicity. In vitro and animal studies, such as those by Hillerup and Jensen (2006) and Radwan, Saito, and Goto (2002), have revealed that all amide-type local anesthetics exhibit concentration-dependent neurotoxic effects when neural tissue is exposed to sufficiently high concentrations. Although articaine has occasionally demonstrated cytotoxic effects comparable to those of other agents, there is no consistent evidence indicating that it is intrinsically more neurotoxic than lidocaine, mepivacaine, or bupivacaine when evaluated under equivalent experimental conditions. The observation that 4% prilocaine was also associated with paresthesia reinforces the hypothesis that the anesthetic concentration - rather than the specific molecule - may contribute to nerve injury when combined with unfavorable procedural circumstances (Haas; Lennon, 1995a; 2000).

Pharmacovigilance biases and the Weber Effect

Interpreting epidemiological data on articaine requires extreme caution due to the methodological limitations of the studies reviewed. Many investigations rely on retrospective case reports and pharmacovigilance systems that lack robust control groups, making it difficult to precisely distinguish between mechanical traumatic injuries and the chemical neurotoxicity inherent to the drug (Hillerup; Jensen; Ersbøll, 2011; Senes *et al.*, 2015). The voluntary nature of these reports often results in underreporting, limiting the accurate calculation of the true incidence of these complications (Gaffen; Haas, 2009).

Furthermore, the rarity of these events hinders the conduct of randomized clinical trials with sufficient statistical power to detect significant differences, rendering the direct association between articaine and persistent neurotoxicity inconclusive (Moore; Haas, 2010; Kakroudi; Mehta; Millar, 2015). Factors such as the “Weber effect” must also be considered, as articaine’s increased market visibility may have artificially inflated the incidence of reports compared to traditional anesthetics (Piccinni *et al.*, 2015). As it established itself as a new clinical standard, articaine underwent much more rigorous scrutiny than traditional agents, which may have introduced confirmation bias into voluntary reports (Gaffen; Haas, 2009).

Additionally, a clear selection bias is observed in clinical practice: articaine is frequently the drug of choice for highly complex procedures or cases involving acute inflammation (“hot teeth”) – situations where achieving anesthetic success is more challenging (Dascanio *et al.*, 2026). In these scenarios, surgical trauma, local edema, and instrumentation may be the actual causes of nerve compression, with paresthesia being erroneously attributed to the anesthetic agent used.

Synthesis of evidence and clinical implications

Taken together, the available evidence suggests that post-anesthetic paresthesia should be considered a multifactorial event resulting from the interaction of anatomical vulnerability, injection technique, mechanical trauma, local inflammatory responses, hematoma formation, injection pressure, anesthetic concentration, and, possibly, individual patient susceptibility. Therefore, although practitioners should remain alert to the rare occurrence of neurosensory complications following dental local anesthesia, current

evidence does not support the conclusion that articaine alone is responsible for these events.

In clinical practice, the safety of articaine depends primarily on the rigorous refinement of injection technique and dose control. Shifting to a paradigm focused on injection technique precision – prioritizing trajectories that minimize direct contact with nerve trunks, consistent use of negative aspiration, and limitation of the administered volume – proves more critical to clinical success and patient safety than the choice of anesthetic agent alone (Dascanio *et al.*, 2026; Kakroudi, Mehta; Millar, 2015).

Critical issues and evidence gaps

Several critical issues emerge from this analysis and warrant explicit consideration. First, regarding the volume of anesthetic injected: most studies do not report the number of cartridges administered to patients who developed paresthesia or paralysis. Given that articaine requires fewer cartridges than lidocaine for an effective inferior alveolar nerve block (IANB), the question arises as to whether an excessive number of articaine cartridges - rather than the drug itself - might be the cause of the paresthesia. The potential involvement of the vasoconstrictor in neurosensory alterations, potential cartridge contamination, or the influence of anesthesia duration (the time required for the patient's body to eliminate the anesthetic) also remain underexplored.

Second, the selective vulnerability of the lingual nerve compared to the inferior alveolar nerve, along with the absence of reports regarding neurosensory alterations in the maxilla, argues against the hypothesis of primary chemical neurotoxicity. If the anesthetic itself were the primary cause, one would expect neurosensory complications to be distributed more evenly across injection sites, which is not the case. Similarly, the lack of consistent reports of paresthesia associated with articaine use in medical regional anesthesia undermines the hypothesis that this drug possesses a unique neurotoxic profile.

Third, the temporal classification of the injuries remains problematic. How many of the reported cases of paresthesia/paralysis were permanent (persisting for more than 8 weeks), and how many were transient? The lack of specificity in reports regarding whether the neurosensory damage is temporary or permanent represents a significant limitation of the current evidence base. The absence of reports must also be taken into account in any balanced risk assessment. Fourth, when evaluating the total amount of articaine administered worldwide compared to other anesthetics, it remains unclear whether the

incidence of paresthesia is genuinely higher than that observed with other agents. The potential role of campaigns encouraging the reporting of adverse events - and the “Weber effect”- in generating “fear” of articaine raises the possibility that reporting bias has been progressively accepted as fact within certain segments of the dental community.

Finally, a possible confounding factor is the preferential use of articaine in more complex procedures: those involving pre-existing inflammation or causing local inflammation; those requiring longer operating times - leading to local edema and nerve compression; or those involving nerve manipulation or potential local hemorrhage resulting in nerve trauma. These procedure-related factors, rather than the anesthetic agent itself, may represent the true underlying etiology in a significant proportion of reported cases.

Limitations of this review

This narrative review has limitations that should be acknowledged. As it is a narrative rather than a systematic review, the selection of studies – while guided by predefined criteria – did not follow a fully systematic protocol involving independent, duplicate screening of all records. Restricting the scope to publications in English and Portuguese may have excluded relevant studies published in other languages. Furthermore, the heterogeneity of study designs, outcome definitions, and reporting standards among the included studies precluded a quantitative synthesis. Finally, the review is limited by the quality of the primary evidence base, which is predominantly retrospective and observational.

Current literature does not support the hypothesis of intrinsic and exclusive neurotoxicity associated with 4% articaine. Evidence - supported by the drug’s safe use in medical regional anesthesia - indicates that neurosensory complications in dentistry (predominantly lingual nerve paresthesia) have a multifactorial etiology.

Such events stem primarily from the anatomical vulnerability of the lingual nerve (particularly its unifascicular architecture within the pterygomandibular space), the mechanical trauma inherent to the inferior alveolar nerve block (IANB) technique, and the confined anatomical space where the injection is administered. These factors may be exacerbated by the drug’s high concentration (4%) and the volume administered, but they are not caused exclusively by the articaine molecule itself.

The disproportionate reporting of paresthesia associated with articaine in pharmacovigilance systems may be partially explained by: (1) the Weber effect, whereby newly introduced drugs or those gaining academic prominence generate an increase in adverse event reports; (2) selection bias, given that articaine is preferentially used in complex surgical cases involving pre-existing inflammation; (3) confounding by procedure-related factors, such as surgical trauma, edema, and instrumentation; and (4) the lack of standardized documentation regarding the administered volume and the temporal classification of the injuries (temporary versus permanent).

The absence of a reproducible signal of neurosensory complications associated with the use of articaine in medical regional anesthesia - a setting in which the drug is administered near major peripheral nerves under ultrasound guidance - further weakens the hypothesis of a neurotoxic profile unique to articaine and reinforces the role of technique-related factors in dental complications.

CONCLUSION

In summary, clinical safety with articaine depends primarily on the rigorous refinement of injection technique (including precise identification of anatomical landmarks, performance of negative aspiration, slow injection, and minimization of the administered volume) and on dose control. Well-designed prospective randomized studies with standardized outcome reporting - including clear documentation of the number of cartridges administered, a distinction between temporary and permanent injuries, and systematic assessment of confounding variables - are needed to definitively distinguish traumatic from chemical nerve injuries in dental practice. Until such evidence is available, the clinical approach should prioritize injection precision and dose limitation over the choice of a specific anesthetic agent.

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