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A comparative review of epinephrine and phenylephrine as vasoconstrictors in dental anesthesia: exploring the factors behind epinephrine's prevalence in the US

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This review paper delves into the comparative study of epinephrine and phenylephrine as vasoconstrictors in dental anesthesia, exploring their histories, pharmacological properties, and clinical applications. The study involved a comprehensive literature search, focusing on articles that directly compared the two agents in terms of efficacy, safety, and prevalence in dental anesthesia. Epinephrine, with its broad receptor profile, has been a predominant choice, slightly outperforming in the context of prolonging dental anesthesia and providing superior hemostasis, which is crucial for various dental procedures. However, the stimulation of beta-adrenergic receptors caused by epinephrine poses risks, especially to patients with cardiovascular conditions. Phenylephrine, a selective alpha-1 adrenergic agonist, emerges as a safer alternative for such patients, avoiding the cardiovascular risks associated with epinephrine. Moreover, its vasoconstrictive effect may not be as deleterious as that of epinephrine, due to its selective action. This review reveals that despite the potential benefits of phenylephrine, epinephrine continues to dominate in clinical settings, due to its historical familiarity, availability, and cost-effectiveness. The lack of commercially available pre-made phenylephrine dental carpules in most countries, except Brazil, and a knowledge gap within dental academia regarding phenylephrine, contribute to its limited use. This review concludes that while both agents are effective, the choice between them should be based on individual patient conditions, availability, and the practitioner's knowledge and familiarity with the agents. The underuse of other vasoconstrictors like levonordefrin and the unavailability of phenylephrine in pre-mixed dental cartridges in many countries highlights the need for further exploration and research in this field. Furthermore, we also delve into the role of levonordefrin and examine the rationale behind the exclusion of phenylephrine from commercially available pre-mixed local anesthetic carpules, suggesting a need for a responsive approach from pharmaceutical manufacturers to the distinct needs of the dental community.

Keywords: Dental Procedures; Epinephrine; Hemostasis; Local Anesthetics; Phenylephrine; Vasoconstrictors.

INTRODUCTION

The use of vasoconstrictors in combination with local anesthetics has been an integral aspect of dental practice for over a century [1]. Vasoconstrictors enhance the efficacy of local anesthetics by prolonging their duration, improving hemostasis, and providing better pain management during dental procedures. Among the available vasoconstrictors, epinephrine has maintained its predominant position. However, levonordefrin, while available to a limited extent, remains a distant second in popularity compared to epinephrine [2]. Levonordefrin primarily acts on alpha-1 adrenergic receptors, with

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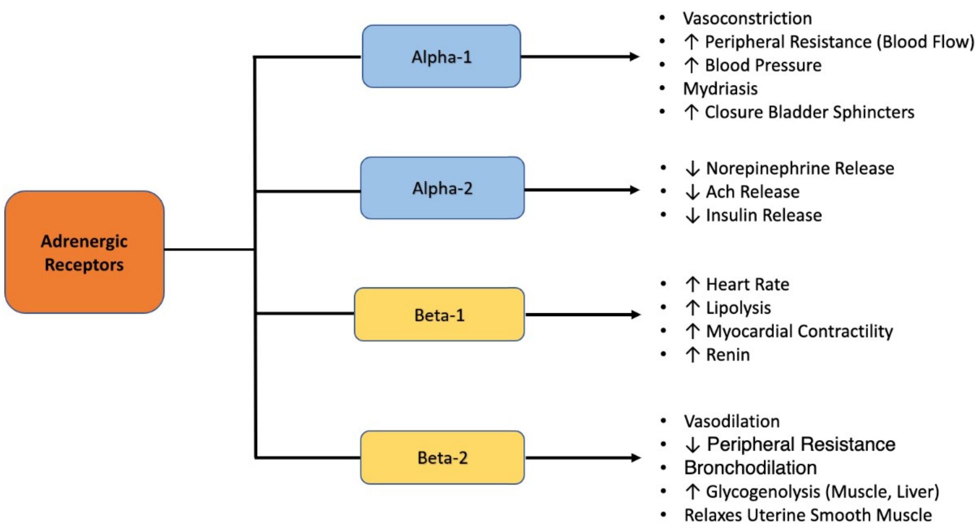

Fig. 1. Brief review of adrenergic receptors [5].

Table 1. Length of anesthesia in minutes from onset of anesthesia until complete return of pain sensation to pin pick. (Range of values and mean* provided in table and graph form) [10].

Test Drugs	Range of Value (min.)	Mean (min.)
Carbocaine	36-151	103.5
Carbocaine with epinephrine	65-226	152
Carbocaine with phenylephrine	136-317	238.7
Procaine	35-92	61.5
Procaine with epinephrine	94-426	214.0
Procaine with phenylephrine	37-119	76.7
Lidocaine	33-179	102.6
Lidocaine with epinephrine	68-444	209.8
Lidocaine with phenylephrine	105-327	220.4
Normal saline	0-104	12.6

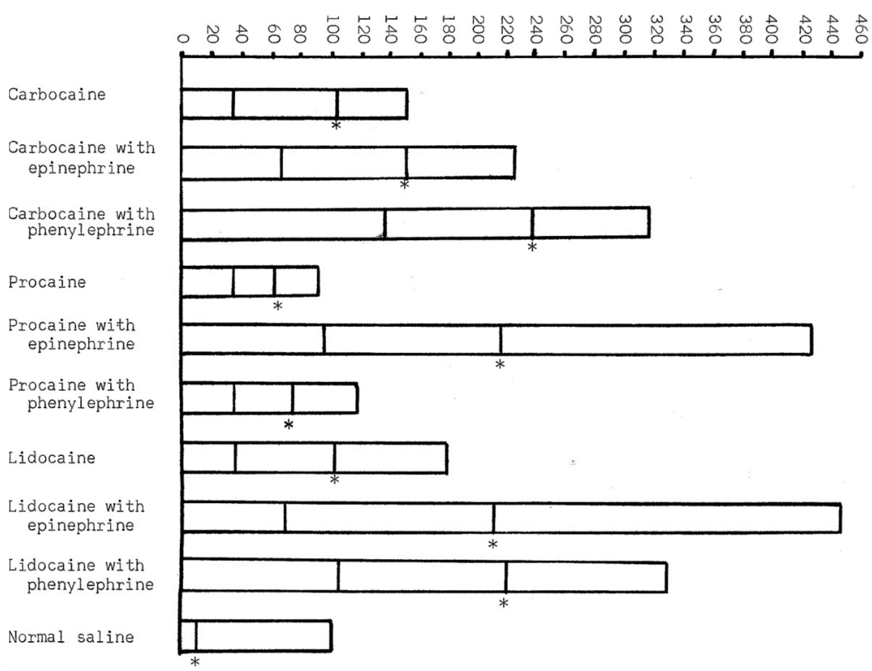

Table 2. Supplementary Statistical Data [10].

	Mean (min.)	Standard Deviation (min.)	Standard error of the mean (min.)	Standard error of the difference between means (min.)	Relative deviation
Procaine	61.5	20.5	6.5	31.3	4.8
Procaine with epinephrine	214.0	96.4	31.0	31.3	4.8
Lidocaine	102.6	58.4	18.7	46.0	2.3
Lidocaine with epinephrine	209.8	130.3	41.9	46.0	2.3
Carbocaine	103.5	37.1	12.0	17.4	2.76
Carbocaine with epinephrine	152.0	40.1	12.9	17.4	2.76
Procaine	61.5	20.5	6.5	11.0	1.36
Procaine with phenylephrine	76.7	27.4	8.7	11.0	1.36
Lidocaine	102.6	58.4	18.7	29.0	4.03
Lidocaine with phenylephrine	220.4	69.3	22.3	29.0	4.03
Carbocaine	103.5	37.1	12.0	21.3	6.5
Carbocaine with phenylephrine	238.7	56.0	18.1	21.3	6.5

moderate effects on beta-2 receptors [3]. Notably, phenylephrine in local anesthesia is available in the USA only if it is custom-prepared by the individual provider. Understanding the historical development of these two agents provides valuable insights into their distinct properties and applications in dental settings.

Since its discovery, epinephrine's vasoconstrictive properties and compatibility have made it a common additive to local anesthetics [4]. As an alpha and beta agonist, it has diverse effects on the body due to its ability to bind to multiple adrenergic receptors. It acts on both alpha-1 and alpha-2 receptors, as well as beta-1, beta-2, and beta-3 receptors. The activation of alpha-1 receptors results in vasoconstriction, which reduces blood flow to the injection site and prolongs the duration of anesthesia (Fig. 1) [5]. This property is particularly useful in dental or oral surgery settings, as it aids in controlling bleeding and providing a clearer operative field. Epinephrine's stimulation of beta-1 receptors leads to increased heart rate and contractility, which may be beneficial when these effects are needed (sepsis, shock). Moreover, the activation of beta-2 receptors can cause bronchodilation and vasodilation in some vascular beds, which may have additional implications for patient management [6]. These beta-adrenergic effects, however, can also pose risks to patients with cardiovascular conditions such as hypertension, angina, and cardiac arrhythmias [7].

Phenylephrine, a synthetic selective alpha-1 adrenergic agonist, first received its patent in 1927 and was introduced for medical use in 1938 [8]. Despite its later introduction and more targeted vasoconstrictive action, phenylephrine has been less commonly employed in dental settings compared to epinephrine [9]. Due to its lack of stimulation of beta-adrenergic receptors, phenylephrine avoids inducing the broader spectrum of cardiovascular effects seen with epinephrine, making it. This quality makes phenylephrine a more suitable choice for patients with contraindications to the use of epinephrine, including individuals with hypertension, thyrotoxicosis, and tachyarrhythmias. In a study conducted by Godfrey, phenylephrine was found to be as effective as epinephrine in prolonging the duration of anesthesia when used with lidocaine or carbocaine [10] (Table 1 and 2). This suggests that phenylephrine could be a viable alternative to epinephrine for prolonging the duration of anesthesia in dental or oral surgery settings, particularly for patients with specific medical conditions that limit the use of epinephrine. However, it is important to note that, due to its selective action on alpha-1 receptors, phenylephrine's vasoconstrictive effect may not be as potent as that of epinephrine. Therefore, its effectiveness in controlling bleeding or local anesthetic duration may differ, thus warranting further investigation.

This review delves into the histories of epinephrine and phenylephrine as vasoconstrictors in dental practice, exploring their respective pharmacological properties, development, and clinical applications. By examining the historical context surrounding these two agents, we aim to provide a comprehensive understanding of their respective roles in dentistry and the factors influencing their current use among dental professionals.

METHODS

Literature search and selection: A comprehensive literature search was conducted using the following databases: PubMed, JSTOR, and ProQuest, to identify relevant articles for this comparative review. The search strategy included the use of the following keywords and their combinations: "epinephrine," "phenylephrine," "levonordefrin," "vasoconstrictors," "dental anesthesia," "local anesthesia," "duration," "efficacy," "safety," and "prevalence." The search was limited to articles published in English and those available in full-text.

Inclusion and exclusion criteria: Articles were included in the review if they met the following criteria: (a) original research studies comparing the efficacy, safety, or duration of anesthesia using epinephrine and phenylephrine as vasoconstrictors in dental anesthesia, (b) studies providing information on factors contributing to the prevalence of epinephrine in dental practice, and (c) review articles summarizing current knowledge on the use of these vasoconstrictors in dental anesthesia. Exclusion criteria were: (a) studies involving non-human subjects or in vitro studies, (b) studies that did not directly compare epinephrine and phenylephrine, and (c) studies with insufficient data or lacking methodological rigor.

Data extraction and synthesis: Two reviewers independently screened the titles and abstracts of the identified articles to assess their relevance to the review topic. Full-text articles were then obtained for further assessment, and any discrepancies were resolved through discussion and consensus. Data was then extracted from the selected articles, including study design, sample size, anesthetic agents used, vasoconstrictor concentrations, duration of anesthesia, efficacy, safety, and factors contributing to the prevalence of epinephrine in dental practice. The extracted data was synthesized and presented in a narrative format to compare the characteristics, efficacy, safety, and prevalence factors of epinephrine and phenylephrine as vasoconstrictors in local anesthesia.

RESULTS

Study characteristics: A total of 86,327 articles were identified through the search, and after applying the inclusion and exclusion criteria, twenty-five articles were included in the review as well as one reference to a product. Specifically, we included twenty references to peer-reviewed papers and five references from textbooks as well as one reference to the product page of pre-mixed phenylephrine carpules available outside North America. The studies were conducted in various countries and published between 1964 and January of 2023 (Table 3).

Efficacy and duration of anesthesia: The majority of the studies reported that both epinephrine and phenylephrine were effective in prolonging the duration of dental anesthesia. However, epinephrine was found to have a greater effect on anesthesia duration compared to phenylephrine [10]. This difference was attributed to epinephrine's action on both alpha and beta-adrenergic receptors, whereas phenylephrine acted predominantly on alpha receptors.

Safety: Epinephrine is associated with a higher incidence of adverse effects, mostly due to its action on beta-2-adrenergic receptors. In contrast, phenylephrine was found to be a safer alternative for patients with contraindications for the use of epinephrine, as it primarily acts on alpha-adrenergic receptors and has a lower risk of causing cardiovascular side effects [10]. However, it is important to note that alpha-1 constrictive adverse effects can be associated with both epinephrine and phenylephrine.

Factors contributing to the prevalence of epinephrine: Several factors were identified as contributing to the higher prevalence of epinephrine use in dental practice,

Table 3. Findings of Selected Papers

Paper Title	Author(s)	Year Published	Main Purpose (Outcome)
Comparison of length of anesthesia using the vasoconstrictors: epinephrine and phenylephrine with procaine, carbocaine, and lidocaine	Godfrey, Merrill A	1964 [10]	Epinephrine significantly prolonged anesthesia, particularly with lidocaine and procaine. Phenylephrine, though less potent, extended carbocaine's anesthesia duration by about 50% compared to epinephrine. The study indicates phenylephrine as a potential alternative to epinephrine for certain patient groups.
The Components of an Effective Test Dose Prior to Epidural Block	Moore and Batra	1981 [20]	A test dose for epidural block must contain 0.015 mg of epinephrine to detect intravascular injections. Intravascularly injected epinephrine increases heart rate unless a beta-blocker is present. Proper test doses with epinephrine are essential for safe epidural procedures.
Alpha- and beta-adrenergic receptor subtypes properties, distribution and regulation	Molinoff	1984 [5]	Reviews adrenergic receptors: Catecholamines interact with α and β receptors in the nervous systems. α1-receptors are postsynaptic, while α2 regulate noradrenaline release. In the central system, both α types are postsynaptic. β1-receptors, in the heart and brain, respond to noradrenaline and adrenaline. β2-receptors affect vascular relaxation and catecholamine metabolism.
Epinephrine-containing test dose during beta-blockade	Mackie and Lam	1991 [22]	Epinephrine, used to detect intravascular injections during anesthesia, has unpredictable effects on patients on beta-blockers. In a study with 6 volunteers, epinephrine increased heart rate by 20±4% before beta-blockade but decreased it by 38±3% after using propranolol. In middle-aged men on beta-blockers, epinephrine can cause high blood pressure followed by a significant drop in heart rate.
Optimal Concentration of Epinephrine for Vasoconstriction in Neck Surgery	Dunlevy, et al.	1996 [13]	Adding epinephrine to local anesthetics reduces bleeding, minimizes systemic toxicity, and prolongs the effect. Yet, epinephrine comes with notable side effects. Four epinephrine levels were analyzed to identify the lowest concentration needed for optimal vasoconstriction.
Local Anaesthetics—Procaine (Novocaine, Ethocaine)	Ball and Westhrope	2004 [1]	This paper traces the evolution of local anesthetics, emphasizing the pivotal role of Novocaine in the early 20th century and the challenges and innovations associated with its use.
Analogue-based Drug Discovery	Fischer and Ganellin	2006 [8]	Delves into the history of phenylephrine, most importantly that phenylephrine was patented in 1927 and came into medical use in 1938.
Essential Clinical Procedures Chapter 22: Local Anesthesia	DiBaise, Michelle	2007 [12]	This chapter discusses local anesthesia, highlighting its mechanism, types, and factors influencing its effectiveness. It emphasizes the importance of understanding anatomy and potential complications to ensure patient safety during administration.
Clinical evaluation of the use of three anesthetics in endodontics	Maniglia-Ferreira, et al.	2009 [16]	The study assessed three anesthetics: 2% lidocaine with phenylephrine, 2% mepivacaine with adrenaline, and 4% articaine with epinephrine on 60 patients at Universidade de Fortaleza, Brazil. The evaluation focused on the number of cartridges for successful anesthesia, efficacy, duration, and cost-benefit. On average, 2.76 cartridges were needed across all groups. Lidocaine had the best cost-benefit, but all anesthetics were clinically effective with similar results for endodontic treatments.
Beta-adrenergic Blocking Agents and Dental Vasoconstrictors	Hersh and Giannakopoulos	2010 [3]	In dental settings, a rare but serious interaction can arise between epinephrine or levonordefrin and nonselective beta-blockers, causing notable hypertension and reflex bradycardia. The reaction's severity is dose-dependent. While typically milder with standard doses, some individuals are highly sensitive. Accidental intravascular injections or high doses can intensify the response, with cardiovascular patients being especially vulnerable.
Local Anesthesia Part 2: Technical Considerations	Reed, et al.	2012 [15]	Local anesthesia is essential in dentistry for pain prevention. It's most effective when applied close to the nerve. Patients value painless treatments, but the necessity of injections introduces the challenge of needle fear, leading to potential emergencies. In fact, over half of dental emergencies arise from local anesthetic administration. This paper focuses on the safe delivery of these drugs, discussing techniques, patient comfort, and the future of dental local anesthesia.
Contraindications of Vasoconstrictors in Dentistry	Balakrishnan and Ebenezer	2013 [19]	Discusses the advantages and risks of using vasoconstrictors, like epinephrine, in dental anesthesia. While they enhance anesthesia and reduce bleeding, they can be risky for patients with certain medical conditions. The study underscores the need for careful patient evaluation before their use.
Phenylephrine as a simulated intravascular epidural test dose in pediatrics: a pilot study	Pancaro, et al.	2013 [23]	Researchers examined phenylephrine's potential as an indicator for intravascular injections during neuraxial blocks. Children given phenylephrine showed a decreased heart rate, with 54% having increased blood pressure. The results suggest phenylephrine's potential use in this context, but more research is needed to determine the correct dosage and any age-related adjustments.
Comparative clinical evaluation of different epinephrine concentrations in 4 % articaine for dental local infiltration anesthesia	Kämmerer, et al.	2014 [4]	The study evaluated five 4% articaine solutions with different epinephrine levels. While anesthesia onset was consistent, duration and efficacy decreased with lower epinephrine. The epinephrine-free solution was least effective. The results underscore the role of vasoconstrictors in optimizing dental anesthesia.

including its long history of use in dental anesthesia, its availability, and its cost-effectiveness. However, pre-made phenylephrine dental carpules are not commercially available in most countries except Brazil,

Table 3. (continued)

Paper Title	Author(s)	Year Published	Main Purpose (Outcome)
Pharmacokinetics, Safety, and Cardiovascular Tolerability of Phenylephrine HCl 10, 20, and 30 mg After a Single Oral Administration in Healthy Volunteers	Gelotte and Zimmerman	2015 [18]	In a study with 28 adults, the pharmacokinetics and safety of phenylephrine HCl, a long-used nasal decongestant, were examined. Participants received varying doses or a placebo. Phenylephrine was rapidly absorbed, with its systemic concentration rising disproportionately with increased doses. Minimal amounts were found in urine, and only one mild side effect was attributed to the treatment. Overall, cardiovascular responses were consistent across doses, suggesting that phenylephrine HCl is safe and well-tolerated at the tested levels.
Cardiac Arrest and Seizures Caused by LAST After Peripheral Nerve Blocks: Should We Still Fear the Reaper?	Liu, et al.	2016 [25]	The study analyzed the safety of PNBs in relation to LAST. Major complications from LAST are rare, and ultrasound guidance may improve PNB safety. Despite using large anesthetic doses, few seizures linked to LAST were noted. However, the exact risk factors remain unclear due to the rarity of these events.
LAST: Not Gone, Hopefully Not Forgotten	Weinberg and Barron	2016 [26]	Liu et al.'s study suggests a decline in LAST in regional anesthesia, possibly due to improved practices like ultrasound guidance. However, despite the reduced frequency, the risk remains. The rarity of severe LAST cases can lead to practitioner complacency. It's crucial to maintain vigilance and prioritize continued education and prevention.
Pharmacology and Therapeutics for Dentistry Chapter 14: Local Anesthetics (Seventh Edition)	Haas and Quinn	2017 [2]	Local anesthetics are essential in dentistry, blocking nerve impulses by binding to sodium channels. Classified as esters or amides, their action duration is determined by redistribution. Most induce vasodilation, requiring a vasoconstrictor for dental applications. Adverse reactions are primarily psychogenic, with overdosing or intravascular injection leading to toxicity, especially in children. The chapter explores their chemistry, action mechanism, and pH influence.
Local anesthetic systemic toxicity: current perspectives	El-Boghdadly, et al.	2018 [21]	LAST is a severe side effect of local anesthetics, impacting the nervous and cardiovascular systems. Prevention, including ultrasound guidance, is crucial, with lipid emulsion therapy being a primary treatment. Awareness of LAST is vital for those administering local anesthetics.
Efficacy of epinephrine-free articaine compared to articaine with epinephrine (1:100 000) for maxillary infiltration, a randomised clinical trial	Paterakis, et al.	2018 [14]	In a study evaluating the efficacy of 4% articaine for dental treatments, it was found that articaine with epinephrine provided longer and more reliable anaesthesia than without epinephrine. While non-epinephrine articaine offers short-term relief without lasting numbness, the version with epinephrine is recommended for extended dental procedures.
Handbook of local anestheisa	Malamed	2020 [17]	A comprehensive guide on safe anesthesia practices in dentistry. The book covers the latest in science, equipment, and pain control techniques. It also delves into basic concepts, injection methods, dosage charts, and equipment care, highlighting potential hazards and errors that could lead to complications.
Local Anesthetic Usage Among Dentists: German and International Data	Halling, et al.	2021 [9]	The study analyzed dental anesthetic use in Germany from 2011-2017 and compared it internationally. Articaine was the dominant anesthetic in Germany with a 98% market share. While articaine was popular globally, the UK and US preferred lidocaine. Epinephrine was the favored vasoconstrictor, but there's a recommendation to shift towards lower concentrations due to the increasing number of medically compromised patients.
Use of Local Anesthetics with a Vasoconstrictor Agent during Dental Treatment in Hypertensive and Coronary Disease Patients. a Systematic Review	Seminario-Amez, et al.	2021 [7]	The study assessed the safety of local anesthetics with vasoconstrictors in dental treatments for patients with Hypertension or Coronary disease. From 87 papers, 9 were relevant, suggesting that specific epinephrine concentrations in anesthetics are safe for controlled conditions. Further research is needed for patients with uncontrolled conditions.
LAST, and Liposomal Bupivacaine	On'Gele, et al.	2022 [24]	Local anesthetics enhance patient care by reducing opioid use and related side effects, shortening hospital stays, and decreasing chronic post-surgery pain. Their use in nerve blocks and neuraxial analgesia has supported opioid-reduced anesthetic approaches. However, practitioners must be knowledgeable about the risks and management of LAST.
Epinephrine	Dalal and Grujic	Jan-23 [6]	Epinephrine is a critical medication used in emergencies like anaphylaxis and cardiac arrests. Healthcare professionals must be knowledgeable about its use and potential side effects. While it can boost survival in cardiac events, it may not improve long-term neurological outcomes. Effective team communication is essential for patient safety.

LAST, local anesthetic systemic toxicity; PNB, peripheral nerve block.

where it is manufactured by a company named SSWhite [11].

In summary, the results of this review suggest that both epinephrine and phenylephrine are effective vasoconstrictors for dental anesthesia, with epinephrine providing a slightly longer duration of anesthesia. However, phenylephrine may be a safer alternative for patients with contraindications for epinephrine use. The higher prevalence of epinephrine in dental practice is likely due to a combination of historical factors, availability, and cost.

DISCUSSION

Epinephrine is a vasoconstrictor that is commercially available in North America. It has a proven efficacy, as numerous studies have demonstrated its effectiveness in extending the anesthetic effect when combined with local anesthetics [12,13]. By inducing vasoconstriction at the injection site, epinephrine reduces blood flow and slows the systemic absorption of the anesthetic agent, thereby allowing the anesthetic to remain in the targeted area for a longer period. This results in more effective and longer-lasting local anesthesia, which is crucial for the success of various dental procedures.

In contrast, although phenylephrine has vasoconstrictive properties and can also prolong local anesthesia, its use in dental settings is rare, mostly due to the lack of its availability as dental carpules. Dental professionals are more familiar with epinephrine, and its efficacy in extending the duration of anesthesia has been extensively documented [14]. Moreover, in clinical trials, peak blood levels of lidocaine were significantly higher when phenylephrine was used at 1:20,000 (lidocaine blood level = 2.4 μg/mL) when compared with lidocaine levels when epinephrine was used at 1:200,000 (1.4 μg/mL) [15]. However, epinephrine and phenylephrine appeared to be equally efficient and were found to demonstrate similar results in an endodontic study [16]. Ultimately, the fact that premixed dental cartridges of local anesthesia with phenylephrine are unavailable in North America most likely plays the biggest role in its lack of use. Although pre-mixed cartridges are available in Brazil [11], in the US, a practitioner would have to make their mixture using plain lidocaine and calculate the addition of phenylephrine at a 1:20,000 ratio [17].

Epinephrine plays a crucial role in hemostasis during dental procedures, particularly in those involving soft tissue manipulation or tooth extractions. Its vasoconstrictive effects constrict the blood vessels at the treatment site, reducing blood flow and minimizing bleeding. This controlled bleeding provides several benefits, including improved visualization of the surgical site, reduced bleeding, enhanced patient comfort, and faster healing. Furthermore, reduced bleeding during and after the procedure contributes to a smoother recovery process for the patient.

Phenylephrine, as an alternative vasoconstrictor, should possess a similar ability to provide hemostasis during dental procedures. Its efficacy and widespread use remain to be seen. It does, however, have an excellent safety profile despite the aforementioned potential adverse effects [18]. While phenylephrine may be a viable option in certain cases, particularly for patients with specific contraindications to epinephrine use (uncontrolled severe hypertension, uncontrolled hyperthyroidism, uncontrolled diabetes, etc.) [19], availability remains a significant challenge.

Epinephrine, boasting a lengthy history of use, proven efficacy, and an extensively documented safety profile, has ingrained itself deeply into the curriculum of dental education. It has thereby armed dentists with a thorough understanding of its effects, precise dosing, and potential side effects. This comprehensive familiarity breeds confidence in its use among dental professionals.

On the contrary, phenylephrine has not received the same level of exposure within dental academia, resulting in a comparative dearth of knowledge regarding its clinical implications, dosing guidelines, and potential side effects. This knowledge gap can create hesitancy among dentists when considering phenylephrine as an alternative vasoconstrictor, thereby perpetuating the preference for the more established and familiar choice - epinephrine. However, availability does still seem to be the leading factor responsible for epinephrine’s predominance.

Furthermore, another factor to consider is the routine usage of epinephrine as a marker for intravascular injection during regional anesthesia [20]. This is primarily because, when an anesthetic is combined with epinephrine, any unintentional vascular injection can be identified swiftly due to the ensuing tachycardia induced by epinephrine, enabling the needle to be adjusted before proceeding with the rest of the injection [21]. Conversely, this reaction would not occur with phenylephrine, as tachycardia arises from the beta-1-adrenergic effects of epinephrine, while phenylephrine is solely an alpha agonist. However, it is crucial to acknowledge that we may not always be aware of the medications that patients are taking, or that such information might be inadvertently omitted from medical records. If patients are on beta blockers, the unopposed alpha-agonism could result in severe hypertension accompanied by significant bradycardia [22]. Consequently, the practice of supplementing a test dose of local anesthetic with 15 µg of epinephrine, serving as a marker for intravascular injection, has gained widespread acceptance since its efficacy was proven by Moore and Batra [20]. However, there have been notably fewer studies conducted to assess the effectiveness of phenylephrine as a test dose. Theoretically, the response should be uniform, given that the root cause is unopposed alpha-agonism, and phenylephrine acts as a pure alpha agonist. Furthermore, a solitary study explored the potential uses of phenylephrine as a test dose in pediatric patients undergoing general anesthesia, yielding promising results that warrant further investigations [23].

Finally, one last consideration could be Local Anesthetic Systemic Toxicity (LAST). LAST occurs when local anesthetics enter the systemic circulation in significant amounts, leading to adverse effects on the central nervous system (CNS) and the cardiovascular system [24]. Vasoconstrictors are frequently incorporated into local anesthetic solutions to hinder the systemic uptake of the anesthetic compound. Epinephrine, in concentrations ranging from 5 µg/mL to 20 µg/mL (1:200,000 to 1:50,000), is predominantly utilized for this objective. However, other sympathomimetic amines such as levonordefrin, norepinephrine, and phenylephrine are also or have previously been, employed. In North America, dental cartridges only contain epinephrine and levonordefrin as available options [2]. Interestingly, some authors are taking the stance that the incidence of LAST has decreased to such an extent that we may have effectively overcome the problem [25]. However, this is an area of intense debate, with some strongly advocating that LAST is still a pertinent concern, underscoring the requirement for further investigations into the specific effects of these various vasoconstrictors on LAST [26].

Furthermore, a review of epinephrine's superiority in the US would be incomplete without addressing the role of levonordefrin. Epinephrine's popularity dwarfs that of levonordefrin, despite the latter's presence in the landscape. This is largely due to levonordefrin's potency, which measures a mere one-sixth of epinephrine's, and its limited availability in 2% mepivacaine with 1:20,000 levonordefrin. Compounding this issue is levonordefrin's inadequate hemostasis, particularly when juxtaposed with epinephrine's superior hemostatic properties. Further, an absolute contraindication exists for levonordefrin in patients on tricyclic antidepressants, adding another layer of complexity to its usage [15].

In summary, the literature offers no explicit reason for the exclusion of phenylephrine, a pure alpha-agonist devoid of beta effects, from the formulary in commercially available pre-mixed local anesthetic carpules. It is a conundrum that beckons investigation. Is it a matter of cost-efficiency? Could it be due to concerns regarding shelf-life? Or does the perceived market size, or a complex network of other factors, play a role in this omission? It is pertinent to note that pharmaceutical manufacturers are responsive entities, poised to react if the dental community vocalizes a distinct need and fosters a commensurate demand.

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DATA AVAILABILITY: All data generated or analyzed during this study are included in this published article.

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