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Review Article

Non-Injectable Eutectic Mixture of Local Anesthesia and Its Implementation in Dentistry – A Comprehensive Review.

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Abstract: Dental pain management is one of the most important components of contemporary dentistry that may impact a patient's quality of life. Before local anesthetic injection, oral cavity mucosa pain is frequently managed using topical anesthetics in oral and maxillofacial surgery**.** This review paper aims to learn about the Eutectic mixture of Local Anaesthetics as topical anesthesia and its implementation in dentistry, which is used to numb oral tissues. This paper aims to learn about the various mechanisms of action of the most common topical and local anesthetic agents, pharmacological action, therapeutic uses, and their side effects. Topical anesthetics work on peripheral nerves to lessen pain perception where they are applied. They are employed in dentistry to reduce localized discomfort brought on by needling, the implantation of orthodontic bands, the vomiting reflex, oral mucositis, and rubber dam clamps. The active chemicals in conventional topical anesthetics, which come in the shapes of solutions, creams, gels, and sprays, are lidocaine or benzocaine. These anesthetic agents come in various formulations created for various applications, to reduce unfavorable reactions, and for maximum anesthetic effectiveness. To give patients a pain-free environment, various strategies are offered. One of the most significant developments in dentistry to prevent patient phobia is the advancement of topical anesthetic drugs. Most are risk-free and cause little irritation or adverse reaction when administered to the oral mucosa. Currently, these medications come in a variety of potencies and indications. Topical anesthetics are helpful during dental procedures because they lessen dental fear, especially in kids, by easing pain and discomfort. A commercial anesthetic drug that has gained appeal among dental practitioners is the eutectic combination of local anesthetics (EMLA), which contains prilocaine and lidocaine. The effectiveness of EMLA as a topical anesthetic agent, which is applied while dental treatments are briefly reviewed in this article.

Keywords: Topical anesthesia, Lidocaine, Eutectic mixture of local anesthetics, local anesthetic, Prilocaine, Gel, Para-aminobenzoic acid (PABA), Sprays, Pain.

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1. INTRODUCTION

The Greek words an- (meaning "without"), as well as aesthesis (meaning "feeling") combine to get the English word anesthesia. General and local anesthetics are the two main categories of anesthesia. Local anesthetic describes a reduction effect brought on due to a temporary blockage of nerve conducting near the application area[1]. To relieve physical discomfort, local anesthetic is injected or applied topically. Local anesthetic injections are painful[2]. Additionally, it induces tissue inflammation, distorts the surgical site, and exacerbates needle phobia[3]. All these concerns can be avoided by using a topical anesthetic, which is increasingly used in clinical situations. Local anesthesia does not result in loss of consciousness, unlike general anesthesia. Topical anesthesia is the temporary lack of sensation caused by applying local anesthetic solutions, also available in creams and gels or sprayed directly to the skin, mucosa, or conjunctiva. Before surgery, it is used as an adjuvant to reduce discomfort and make patients more comfortable[2]; because of their potential efficacy in treating acute and chronic pain and their relative absence of systemic adverse effects, topical analgesic interest, and use have been rising. Topical anesthetics allow for pain-free intraoral procedures, symptomatic toothache alleviation, the treatment of superficial mucosal lesions, and the reduction of discomfort after tooth extraction[1]. A topical anesthetic is crucial for a wide range of dental operations, including treatment for various periodontal cases, gingival manipulation, anesthesia preparation, patients who need pediatric care, and oral tissues; a topical anesthetic is crucial[4-7]. The prime objective of administering topical anesthetic medications highlights reducing and curing painful stimuli by inserting the needle, effectively controlling the patient's pain and anxiety. EMLA (AstraZeneca do Brasil, Ltda., Cotia, SP, Brazil) is an anesthetic formula with a 2.5% prilocaine and a 2.5% lidocaine-based eutectic solution of local anesthetics. This formulation is suggested for managing pain during several superficial cutaneous operations[4,8,9]. This review paper aims to learn about the Eutectic mixture of Local Anaesthetics as topical anesthesia and its implementation in dentistry, which is used to numb oral tissues. This article aims to learn about the various mechanisms of action of the most common topical and local anesthetic agents, pharmacological action, therapeutic uses, and their side effects.

1.1. History of Local Anaesthesia

The history of local anesthesia began in 1859 when Niemann isolated cocaine. Koller, an opthalmologist, was the first to use cocaine for topical anesthesia in 1884. The surgeon Halsted performed the first oral regional anesthesia in 1884. Einhorn reported the synthesis of procaine, the first ester-type local anesthetic agent, in 1905. For over four decades, procaine was the most commonly used local anesthetic. Löfgren synthesized lidocaine, the first modern local anesthetic agent, in 1943 because it is an amide-derivate of dimethylamino acetic acid. Lidocaine was first commercialized in 1948 and is now the most widely used local anesthetic in dentistry worldwide. In 1969, articaine was synthesized by the chemist Muschaweck and was approved in 1975 as a local anesthetic in Germany[55].

1.2. Mechanism of Action

Topical anesthetics, which focus on free nerve terminals within the mucosa, temporarily dull sensation in the targeted area by reversibly obstructing the transmission of a nerve close to the application area. Reduced sodium ion permeability of the nerve cell membrane prevents proper conduction for nerve impulses, potentially through competition with calcium-binding sites which regulate the permeability of sodium. As a result of the altered permeability, depolarization is reduced, and the excitability threshold is raised unless the function to generate action potentials gets obscured[2]. Topical anesthetics reduce pain by preventing the surface's little nerve endings from transmitting signals. Local anesthetics prevent neural supply done for preventing sodium ion influx through sodium ion channels within nerve terminals during their active and inhibited phases. The size of neural fibers affects anesthesia sensitivity. As a result, differential sensitivity influences the regeneration of nerve fibers in the following order: motor sensory and, after that, autonomic[3,10,11].

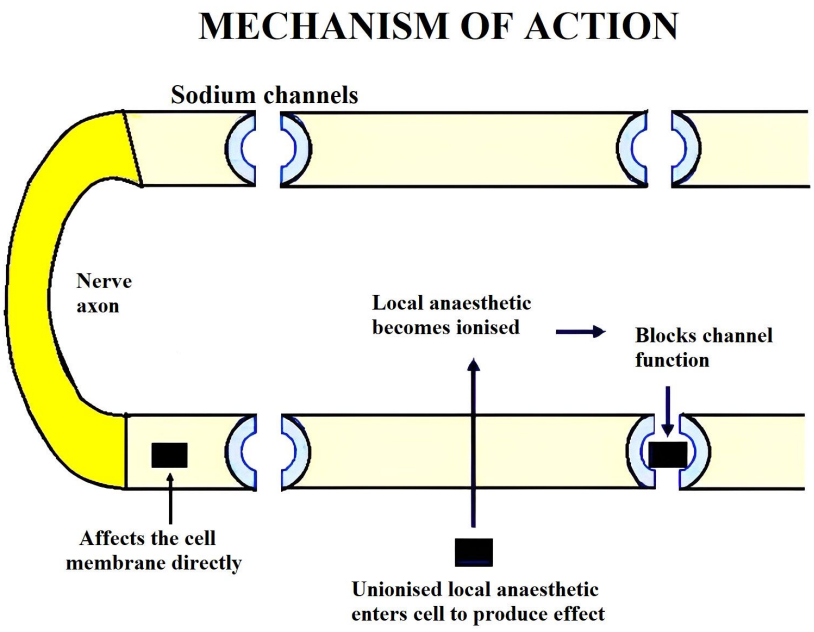

Fig 1: Diagrammatic representation of the mechanism of action of Local anesthesia.

1.3. Pharmacology

The bases of topical anesthetics are thin. The three crucial parts that make them up are:
1] An aromatic ring, 2] an intermediate length ester amide bond, and 3] tertiary amine. The intrinsic property of these drugs is determined by the aromatic ring, which also determines the capacity of lipids to dissolve, which permits diffusion through the cell membrane of the nerve. These agents can attach to proteins depending on their aromatic and amine components[2,12-15]. The individual local anesthetic's pKa level, pH level, oil-soluble lipid solvability protein binding, and vasodilatory actions all affect when anesthesia begins to take effect, how deep it goes, and how long it lasts. Area of application (acute onset at mucosa and locations along with thinner stratum corneum), the vascular capability of structures in the area applied, surface area, and length of treatment are other significant characteristics[2]. Topical anesthetics of the ester type are broken down by plasma cholinesterase and other esterases, which are not specific. In contrast, anesthetics of the amide type are predominantly broken down in the liver by microsomal enzymes[2,16]. While allergic reactions to amide anesthetics are believed to be extremely rare, allergic reactions to ester anesthetics are known to develop upon contact. It is also known that the ester hydrolysis metabolite para-aminobenzoic acid (PABA) is connected to allergy symptoms[2,17,18].

1.4. Pharmacokinetic evaluation

The observed plasma concentration data were used to calculate the maximum plasma concentrations (Cmax) of lidocaine and prilocaine and the time to reach Cmax (t_{max}). Areas under the plasma concentration curve (AUC) were calculated with observed plasma concentrations up to the last sampling point (AUC0-t). In patients where the 120-minute plasma sample was above the limit of quantification, the remaining area up to infinity (AUCt-inf) was extrapolated from the last observed value. Each patient's total AUC up to infinity (AUC0-inf) was compared to the mean AUC after IV administration (AUCIV) of a mixture of 10 mg lidocaine hydrochloride and 10 mg prilocaine hydrochloride to estimate the bioavailability (F) from topical application of 5 g EMLA cream (containing 125 mg lidocaine base and 125 mg prilocaine base). The mean AUCIV values for lidocaine and prilocaine were 183.56 and 68.25 ng h/mL, respectively. In each patient, the bioavailability was calculated as (AUC0-inf/AUCIV) x (Dose base form IV/Dose base form topical), i.e., for lidocaine: F= (AUC0-inf/183.56) (8.65/125) for prilocaine: F= (AUC0-inf/68.25) (8.58/125) 1 mg lidocaine HCl equals 0.865 mg lidocaine base, and 1 mg prilocaine HCl equals 0.858 mg prilocaine base[56]. EMLA is an efficient anesthetic agent which can be used for oral application. It represents the good local anesthetic duration for scaling and root planing (SRP) before needle injection during local anesthesia infiltration and various dental procedures[57].

Table 1: Classification of Topical Anaesthetics

Name	Type Of Anesthetics	Form	Concentration	Onset	Duration	Site Affected	Uses
Benzocaine	**Ester**	gel, gel patch, spray, ointment, or solution.	range from 6% to 20%	30 seconds	2-3 minutes	effectively operates on the tongue and alveolar mucosa but only marginally impacts the palatal mucosa.	
Tetracaine	**Ester**	spray and ointment	range from 0.2% to 2.0%	10 - 20 seconds	10 - 15 minute	quickly absorbed into the mucous membrane	Use of intranasal local anesthesia for dental pain control
Lidocaine	**Amide**	A 20% lidocaine patch, 5% ointment, 10% spray, and 5% gel and solution.	range 2%to 5%	3 -5 min	2-10 min	The palatal mucous membrane, but less effective on alveolar mucous.	Utilized as an analgesic in mouthwash and other products for patients getting radiation and chemotherapy who have oral mucositis.
Prilocaine	**Amide**	Cream and injection	range from 4% to 8%	2 min	4 hours	Tingling sensations at lip and mouth, numbness.	
Emla	**Amide**	Cream	range dosage of 2.5–5%.	5-10 min	2-3 hour		

Table number 1: shows the classification of topical anesthetics and their onset, duration, and action with the concentration and form in which it is used[2,3,9,21].

2. EUTECTIC MIXTURE OF LOCAL ANAESTHETICS

Eutectic mixtures of local anesthesia are combinations of topical anesthetic drugs used for local anesthesia (EMLA). To manufacture commercial medicine, mixing means mixing drugs or substituting a compound. The ultimate goal is to create effective local anesthetic formulations for treatments or surgeries with little to moderate pain. The first time EMLA cream was tried in the mouth was by Holst and Evers. In the attached gingiva, their findings demonstrated significant efficacy[19,20]. Although since the publication of this paper, several studies have confirmed the effect of EMLA cream on mucosal surfaces. Additionally, that is mentioned in numerous publications that using EMLA cream lessened pain throughout procedures like probing, hand scaling, ultrasonic Scaling, placing rubber-dam clamps, and palatine nerve blocks[18-25]. According to Nayak and Sudha, the high volatility of EMLA cream renders it difficult to manipulate and deliver regionally as a topical anesthetic at the area of the needle administration[19-21]. Svensson and Peterson overcame this obstacle by applying an Orahesive bandage that enhanced the topical anesthetic's benefits on pain alleviation[19,22]. However, the company does not advise using EMLA cream on mucous membranes, despite several discoveries suggesting its possibilities for use in dental. Furthermore, more research is required to determine the right intake level and the time frame for kids to avoid overexposure or negative impacts. Eutectic mixture of local anesthetics (EMLA), a recent development in dental operations, is a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine. It comprises a solution of both crystalline powders (2.5% lidocaine and 2.5% prilocaine) that transforms into liquid oil when it melts lower than room temperature. That would allow it to penetrate healthy tissue or mucosa to a deep layer of 5 mm. In a range of unpleasant superficial treatments, such as laser surgery and superficial surgery, EMLA provides adequate local anaesthesia[19,23,24]. The tolerability profile of EMLA was very good, with only brief and mild skin blanching. The most common unfavorable adverse effect of applying EMLA to the skin is erythema, but this side effect is easy to ignore. EMLA has been utilized to lessen discomfort during restorative operations, pocket scaling, small gingival surgeries, and dental injections[19,23-25]. The dosage for EMLA ranges from 2.5 to 5%. According to reports, 5% of EMLA has an effective duration of between 2 and 10 minutes, comparable to longer intraoral application times[19,28,29]. Materials known as eutectic mixtures melt at room temperature more than any of their parts. It allows for the use of larger anesthetic doses. It is a 5% oil-in-water emulsion cream with a melting point of 18°C that contains 25 mg/mL of lignocaine and 25 mg/mL of prilocaine and a thickener, emulsifier, and distilled water that has been pH-adjusted to 9.4. A thick layer of EMLA is applied to intact skin (1-2 g/10 cm2, up to a maximum dose of 20 g/200 cm2). The length of time in contact with EMLA affects the depth of anesthesia. The maximum depth of the anesthetic effect is 3 mm after a 60-min application and 5 mm after a 120-minute application [19,30].

2.1. Therapeutic Features

a. For local analgesia on intact skin: S-Caine PatchTM, 4% tetracaine, EMLA.
b. Use EMLA and 4% tetracaine to reduce pain before injecting or intravenous and arterial line access[2,31].
c. Heated lidocaine/tetracaine patches may be useful for treating myofascial trigger points and symptomatic alleviating chronic pain[2,32]. Additional reports of the topical anesthetics oxybuprocaine or proxymetacaine being successfully injected into the eye of a side affected to treat trigeminal neuralgia[33,34].
d. To ease itching and discomfort from burns, skin exanthem (such as herpes, sunburn, bug bites), stings, poison ivy, and small cuts and scratches. -ELA-max, bupivanor, lidocaine, epinephrine, and tetracaine (LET)
e. Topical treatment, "spray as you go" approach, employing a magic device, etc., to aid awake fiberoptic intubation. 2% lignocaine aqueous gel and drops, 0.5% tetracaine, 0.4% oxybuprocaine, and 0.5% proparacaine are used in ophthalmology and optometry, respectively.
f. EMLA has minimized discomfort during restorative operations, Scaling, small gingival surgeries, and dental injections.
g. In the oral mucosa and oral tissue—to help with rising fiberoptic canulation or laryngoscopy, local inspection,[2,35] laceration closure, slit and exudate in a peritonsillar abscess, and therapy of patients who have suffered acute dentoalveolar trauma, such as a maxillomandibular fix for mandible fractures. The pain brought on by the infiltration of local anesthetics, which can be a major source of anxiety for many patients, can be effectively relieved by topical anesthetics given to the mucous cavity in the mouth cavity.
h. At acute insertion is required, similarly electively or urgently, topical anesthetic in the larynx aids with diagnostic laryngoscopy and bronchoscopy, transnasal esophagogastroduodenoscopy, and endotracheal tube installation.
i. In the oral cavity and oropharynx—to support awake fiberoptic intubation or laryngoscopy, local examination,[35] laceration closure, incision and drainage of peritonsillar abscesses, and curing who have suffered an acute dentoalveolar injury, such as maxillomandibular fixation for mandible fractures. The pain and infiltration of local anesthetics, a source of significant worry for cases, can be helpfully reduced by topical anesthetics given to the mucosal membranes in the mouth cavity.

2.2. Other Topical Agents

Various topical anesthetic agents other than a eutectic mixture of local anesthetics are
ELA-max
epinephrine
Proparacaine
4% tetracaine
Benzocaine
S-Caine patch
Tropicana
Lidocaine

2.3. Lidocaine

Lidocaine is the only amide-based local oral, topical anesthetic that can also be administered intravenously. A 2% or 5% gel, a 4% or 5% solution, a 5% lotion, or a 10% lidocaine spray are all utilized in dentistry. The activity lasts roughly 15 minutes, with the highest efficacy happening 5 minutes after the game begins. Despite having a strength comparable to 20% benzocaine, 5% ointments take longer to start working and at least 3 minutes to provide sufficient anesthesia. Upon alveolar mucus, it works, but not on the palate mucous membrane. Magic Mouth Wash treatment contains lidocaine liquid, which patients with oral mucositis brought on by radiotherapies[35-39].

2.4. Prilocaine

Prilocaine is the commonly utilized amide-based local anesthetic for infusion anesthesia in dental operations. Different topical anesthetics are employed in conjunction with this as well[14]. In contrast to the single agent and lidocaine, prilocaine is a secondary amide. Two different formulas of prilocaine are used 4% prilocaine or 4% prilocaine with 1:200,000 epinephrine. The total dose of prilocaine for humans, regardless of the presence of epinephrine, is 2.7 mg/lb or 6 mg/kg. Therefore, people must receive at most 400 mg overall. A pregnancy Category B rating for prilocaine indicates it is generally safe during pregnancy [35-38].

2.5. Side Effects

EMLA is employed to get you ready for such types of minor surgeries or treatments. However, if too excess numbness medication is taken via your skin, an excess might result in catastrophic symptoms. Irregular heart rates, seizures, unconsciousness, delayed breathing, or respiratory failure are some signs of excess.

2.6. Applications in dentistry

When administering local anesthesia, fear and anxiety about needles are unavoidable4[40,41]. EMLA, identical to lidocaine patches, showed reduced pain and discomfort after therapy for moderate chronic periodontitis compared to a placebo [38,39]. Antoniazzi et al. compared the effects of EMLA 25 mg/g in lidocaine, topical 2% benzocaine, and a placebo drug to lower pain during SRP. They concluded that EMLA was more effective than the other two groups and comparable to injectable lidocaine[41,38]. Due to shorter periods of pain, discomfort, and numbness, the topical anesthetic was preferred by 70% of the participants in that research. In research, Chung et al. compared the pain levels elicited by hand and ultrasonic tools [39,41]. They claimed that employing EMLA with ultrasonic equipment considerably increases patients' comfort. For EMLA to be most helpful on the skin, it must be left on for at least one hour[46-49]. The local anesthetic was kept in contact with the subjects during the current investigation. Materials are only considered beneficial in the oral cavity for a maximum of five minutes[46]. Shortness is helpful since the overall dosage and the application duration determine how much of a topical anesthetic is absorbed into the circulation from the mouth mucosa. Just after the administration of 4 g of EMLA, Haasio et al. found also the maximal plasma lidocaine level was 0.47 jig/mL at 5 min.

2.7. EMLA as a Topical Agent Before Needle Injection

Particularly in the anterior region of the palate mucosa, which has a thicker layer that is keratinized that prevents the actions of topical anesthetics and needle insertion, while local anesthesia infiltration may cause a triggered painful stimulation**.** The mucoperiosteum disturbance rather than the puncture is the main cause of the palatal injection's pain[41-43]. The palatal mucosa has evolved into a test for determining the effectiveness of any topical anesthetic drug because it is a severely painful site where the penetration of the needle occurs[44,45]. Before palatal injection, Franz-Montan et al. designed research to contrast the effectiveness of EMLA, liposome-encapsulated 2% ropivacaine and liposome-encapsulated 1% ropivacaine (liposomes are phospholipid vesicles performing the function of loading drugs and bring better cutaneous and percutaneous penetration, also takes time in release of the local anesthetic)[41,44].

2.8. Uses

It is now feasible to reduce, even completely remove, the discomfort associated with syringe penetration thanks to the development of EMLA. This topical anesthetic effectively induces skin analgesia in grownups. EMLA has indeed been demonstrated to greatly lessen the discomfort with epidermis and dermis procedures and cutaneous pierce in adults and teenagers. This straightforward procedure for combining local with general anesthesia relieves the workload and lowers health expenses for those greater cases while improving patient safety. The greatest advantages among both medications—the extremely quick beginning with lidocaine and the long durability of bupivacaine—can be obtained by mixing these two amides LA agents in a single needle, which benefits the doctor and the client[41-46].

2.9. Limitation

There are no significant adverse effects or contraindications for EMLA, but there are a few things to consider. Following cutaneous application of EMLA, the most prevalent adverse reactions include edema, erythema, and temporary pallor[41,52]. Furthermore, an EMLA overdose may result in methemoglobinemia and convulsions. Regarding oral administration, one paper documented cases where gingival desquamation and ulceration appeared one day after topical EMLA use[41,53].

2.10. Genetic Factor in Patient

Serum cholinesterase is a liver-produced enzyme required for the biotransformation of ester local anesthetics. An overdose can result from increased blood levels if it is genetically absent[54].

3. DISCUSSION

EMLA continues to be the most popular topical anesthetic due to its efficacy and safety, having been established in much clinical research. There are new advances in many recent topical anesthetic agents that show working in a 30-minute application time. An additional anesthetic effect is provided thanks to a supply of anesthetic that was found and held in the higher tissues of the skin during application 30 minutes after removal. The requirement for quicker onset, comparative efficacy, and safety trials will remain relevant as the practitioner's options expand [3-5,21-25]. Before palatal injection, Franz-Montan et al. designed a study to compare the efficacy of EMLA, liposome-encapsulated 2% ropivacaine, and liposome-encapsulated 1% ropivacaine. Their findings indicated that EMLA was a more effective pain reliever than the other agents studied[58,59]. Before palatal injection, the topical anesthetic efficacy of Liposome-encapsulated 5% lidocaine, Liposome-encapsulated 2.5% lidocaine, 5% xylocaine, and 2.5% EMLA agents was evaluated in another recent study. Liposome-encapsulated 5% lidocaine and EMLA produced better anesthetic results than other agents[59]. Topical anesthetics containing 20 mg of 1% ropivacaine gel, 60 mg of 1% ropivacaine gel, 20 mg of EMLA, 60 mg of EMLA, 20 mg of 20% benzocaine gel, and 60 mg of 20% benzocaine gel were evaluated when applied to the buccal fold of a maxillary canine tooth before local anesthesia infiltration. The results showed

that while all the topical anesthetics reduced the pain of needle penetration, EMLA 60 mg promoted a longer soft tissue anaesthesia[60]. Al-Melh and Andersson compared the anesthetic efficacy of 20% benzocaine gel with EMLA on the palatal anesthetic infiltration. They claimed that the EMLA group had significantly lower pain scores than the other groups [61]. McMillan et al. also compared EMLA to lignocaine gel and found that EMLA had better anesthetic efficacy[62]. EMLA, similar to lidocaine patches, demonstrated less pain and discomfort during treatment for mild chronic periodontitis compared to a placebo[63,64]. Antoniazzi et al. compared the pain-relieving effects of EMLA 25 mg/g, injectable lidocaine, topical 2% benzocaine, and a placebo substance during Scaling and root planing. They concluded that EMLA was as effective as injectable lidocaine and was superior to the other two groups. Derman et al. investigated the efficacy of intra-pocket EMLA application for Scaling and root planing. Their findings revealed that 72% of participants preferred using EMLA for Scaling and root planing, demonstrating its efficacy even in deep periodontal pockets[65].

4. CONCLUSION

Many individuals avoid dental treatments out of anxiety of having their anesthesia punctured, making dental anesthesia one of the procedures most frequently linked to patient phobia in dentist offices. However, people who have anxiety because of fear of having dental work done typically experience more pain during anesthesia than those who do not. Before anesthetic infusion, the primary goal of topical anesthesia is to eliminate pain. This technique optimizes infiltrative local anesthesia by lowering patient anxiety before needle penetration, reducing the chances of perforations necessary, and minimizing the quantity of anesthetic supplied. "Except for the needle penetration sensitivity test, the other evaluation tools were not sensitive enough to demonstrate a statistically significant difference between EMLA and benzocaine, in contrast to other reports that gave clearer conclusions on the superiority of EMLA.

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6. AUTHORS CONTRIBUTION STATEMENT

Author M Baheti conceptualized and gathered the data about this work. Dr. Pavan, Dr. Amit, and Dr. Unnati provided the necessary input toward the manuscript's design. All authors discussed and finalized the final manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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