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Efficacy of Local Anesthetic: A Narrative Literature Review and Clinical Update in Dentistry

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ABSTRACT

Achieving adequate anesthesia in patients is one of the most important aspects of the practice of dentistry to control or eliminate of pain. Pain is one of the most commonly experienced symptoms in dentistry and is a major concern to the dentist. The most essential skill of all dental practitioners is the ability to provide safe and effective local anesthesia. Several local anesthetics are used by the dentist, lidocaine has been considered as the golden standard for local anesthetic agents in dentistry for years. Articaine and mepivacaine both relatively new anesthetic agents are now widely used too. The purpose of this article is to provide a pharmacological profile of the various local anesthetic formulations in current use and their technical considerations.

1. INTRODUCTION

Pain control in dentistry is an important factor for reducing the fear and anxiety associated with dental procedures. An epidemiological study in America revealed that more than 50% of people avoid dental treatments because of fear of pain. Management of pain is influenced by the duration of the procedure, the patient's health conditions, and the type of local anesthetic (LA) used. Local anesthesia is a principal way of preventing pain and discomfort in dental treatment. As the backbone of pain control techniques in dentistry and there has been substantial research interest in finding safer and more effective LAs. Lidocaine, mepivacaine, and articaine are the most frequently used LA in dentistry. [1–4]

In the late 1940s a new group of LA compounds, the amides, was introduced. The initial amide LA, lidocaine (Xylocaine), revolutionized pain control in dentistry worldwide. it quickly became a favorite of the dental profession, replacing procaine as the “gold standard.” Lidocaine’s onset of action was measurably faster (three to five minutes); its duration of anesthesia (pulpal) was longer and more profound; and it provided more consistently reliable anesthesia than did the esters. [5] In 1960, the second amide, mepivacaine was introduced as a 2% solution with vasoconstrictor. it has a similar onset and anesthetic potency as lidocaine Lidocaine but a higher success rate. (2,5)

The 1970s saw an increase in the number of surgical procedures, along with an increase in the length of many other dental procedures. Bupivacaine and etidocaine, provide up to 12 hours of soft tissue anesthesia. these drugs have been extremely useful, in conjunction with orally administered nonsteroidal anti-inflammatory drugs, in the prevention or management of postoperative pain. In Indonesia, this LA is unpopular and rarely used by dentists. Bupivacaine has been the most widely used long-acting LA for several decades. However, after the report of several cases of almost simultaneous seizure and cardiac arrest, with prolonged resuscitation and a disproportionally high number of deaths after unintended intravascular injection of bupivacaine, it became evident that bupivacaine differs from other LAs in that it has a narrower margin of safety. [5,6]

In 1976, a new amide LA articaine was introduced. Articaine possesses clinical actions similar to lidocaine but has additional properties which make the drug quite attractive in dentistry. (7) Articaine, with epinephrine, provides a duration of pulpal and soft tissue anesthesia similar to that noted with lidocaine, mepivacaine, and prilocaine Introduced in Canada in 1983, and the United States in 2000, articaine has become a very popular LA. (5)

Amide LAs (mepivacaine, prilocaine, bupivacaine, and etidocaine) gave the dental practitioner a LA armamentarium with a vasopressor, approximately one-hour pulpal and three to five hours of soft tissue. This group proved to be more rapid-acting than the older ester-type drugs and, at least from the perspective of allergenicity, safer. (7) This study aims to investigate the evidence about the Efficacy of Local Anesthesia in dentistry.

2. METHOD

This research was conducted in April-May 2023. The inclusion criteria of studies included in this review were articles in English and published in the past 25 years.

Formulation of a research question

The research question was identified using PICO (Patient/Population, Intervention, Comparison, Outcome):

- Population : Patient or participant in any region worldwide, any gender, and any race/ethnicity.
- Intervention : Administration of any injectable amide local analgesic with or without vasoconstrictor for dental procedures using any standard techniques of delivery (Maxillary and mandibular infiltration, intra-ligament injection, intra-pulpal injection, Inferior Alveolar Nerve Block)
- Comparison. : The use of the standard techniques and agents (as defined above) compared with the use of no LA.
- Outcomes : dental local anesthesia safety and efficacy

Source of databases and study selection

Research articles were searched using electronic databases such as Pubmed and Scopus. The combination of keywords used was (("local anesthetic" OR "regional anesthesia" OR "dental anesthesia"), AND ("dental" OR "dentistry"), AND ("lidocaine" OR "mepivacaine" OR " articaine")). The selection of studies was following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocols.

3. RESULTS AND DISCUSSION

Chemical Structure

The LA molecule consists of 3 components: (a) lipophilic aromatic ring, (b) intermediate ester or amide chain, and (c) terminal amine (Figure 1). [8]

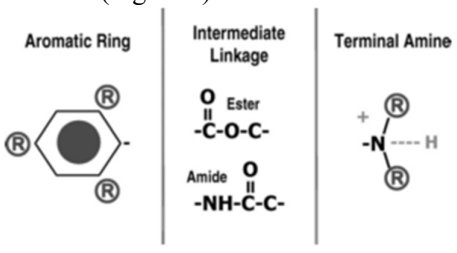

Figure 1. Structure of Local Anesthetics[8]

Local anesthetic molecules consist of an aromatic part linked by an ester or amide bond to a basic side chain. The presence of the ester or amide bond in LA molecules is important because of its susceptibility to metabolic hydrolysis. The ester LAs are hydrolyzed in the plasma by the enzyme pseudocholinesterase. A major metabolic product is a *p*-aminobenzoic acid (PABA) which is an allergic reaction that occurs (rarely) in the response to this molecule. Amide LAs are more stable. The primary

site is the liver. Articaine contains both ester and amide components metabolism in both blood and the liver. Amide LAs generally have longer plasma half-lives. [9–11] Because of these advantages, the majority used LAs in dentistry is the amide group (lidocaine, mepivacaine, articaine).[9,12]

Mechanism of action

Local anesthetics reversibly block the initiation and propagation of action potential by diffusing through the lipid-rich nerve membrane and then binding to sodium (Na+) channels and inhibiting the influx of sodium into the cell which prevents cell depolarization, such that sensation cannot be transmitted from the source of stimulation, such as a tooth or the periodontium, to the higher processing centers of the brain[9,12]

Onset

Local Anesthetics differ in potency and several pharmacokinetic parameters that lead to differences in the onset and duration of anesthesia. The selection of a particular agent must be adjusted to the duration of the procedure planned and issues regarding vasopressor concentrations. (8) The onset of local anesthesia depends on the lipid solubility and the pKa. The more lipid-soluble the greater its potency. The time for the onset of LAs is directly related to the proportion of molecules that convert to the lipid-soluble structure when exposed to physiologic pH (7.4). The higher the pKa, the fewer molecules are available in their lipid-soluble form and thus the further is in the delay in the onset of action. This implies to a patient with an infection is harder to anesthetize because the environment pH is much lower. (12)

Vasoconstrictors

Vasoconstrictors such as epinephrine or levonordefrin have vasoconstrictor activity so that the drug will be absorbed more slowly into the circulating bloodstream, increasing the (DOA) and decreasing bleeding at the sire of administration. (12,13) LAs with vasoconstrictors should be used carefully for patients with pre-existing hypertension or cardiac irritability as their presence in the body may further increase blood pressure or cause cardiac dysrhythmias. (12) Vasoconstrictor use in patients with heart disease is still controversial. Research by Ricardo et al[14] revealed that LA administration increases the blood pressure during the procedure. There are no differences in blood pressure and heart rate between coronary artery patients who receive 2% lidocaine with epinephrine and 2% lidocaine without epinephrine. The maximum epinephrine dose in local anesthesia is 0.2 mg per appointment for the healthy patient and 0.04 mg per appointment for patients with clinically significant cardiovascular disease. (2)

Local anesthetic usage in the USA is figured in Table 1. LAs available in dental cartridges in Indonesia today, namely lidocaine, mepivacaine, and articaine, belong to the amide class. (15)

Table 1. Local anesthetic usage in the USA, 2005 (Estimated)[(8)]

Local anesthetic	% of the U.S. market (estimated)
Lidocaine HCl	47
Articaine HCL	26
Mepivacaine HCL	15
Prilocaine HCL	6
Bupivacaine	1

Lidocaine

Lidocaine introduced first in 1943 has high efficacy, low allergenicity, and minimal toxicity proven through clinical use and research. (16) Onset of action is 3 to 5 min and the anesthetic half life 90 min. The duration of action (DOA) depends on the vasoconstrictor, for lidocaine without a vasoconstrictor duration for pulpal anesthetic is 5-10 min. This limited duration is caused by vasodilating properties of lidocaine. The duration of lidocaine with vasoconstrictor for pulpal anesthetic is 60 min, whereas for soft tissue is 180-300 min[9]. Sometimes lidocaine combines with bupivacaine which has a much longer (DOA); Bupivacaine had slow onset, so it is not an ideal sole agent for

procedural analgesia in most situations [15]. The slow onset also results in a more painful injection when used as a sole agent because one cannot practically 'freeze ahead of the needle'; the recipient, therefore, feels the needle tip traversing throughout the tissues being infiltrated, a painful experience. (17) Lidocaine is the most often used LA for oral surgical procedures and considered the gold standard in the United States is 2 percent lidocaine with 1:100,000 epinephrine. [5]

Mepivacaine

Mepivacaine is the third most widely used solution in dentistry only after articaine and lidocaine in some parts of the world. It's available as a 3% solution without any vasoconstrictors or as a 2% solution with vasoconstrictors such as 1:20,000 levonordefrin and 1:100,000 adrenaline. Naichuan et al[2] demonstrated 2% mepivacaine with 1:100,000 adrenaline has a higher success rate, a similar onset time of pulpal anesthesia, and superior pain control during the injection phase in comparison with 2% lidocaine with 1:100,000 adrenaline. Its superior effect is suspected because mepivacaine has a milder vasodilating ability than another LA, which leads to a long duration of anesthesia without a vasoconstrictor. (2,18) The research also revealed that 3% mepivacaine has a shorter onset time of pulpal anesthesia (2.6-4.0 min), and greater safety, although it's inferior in increasing the success rate and pain control during injection, in comparison with 2% lidocaine with 1:100,000 epinephrine. 3% mepivacaine is safer for patients with cardiac diseases because it didn't cause a heart rate increase. [2] Short duration of Mepivacaine 3% in soft tissue anesthesia, making it potentially useful in pediatric dentistry in which children are known to chew their lips after dental procedures. [11]

Mepivacaine DOA depends on the vasoconstrictor. 3% mepivacaine without vasoconstrictor has doa for pulpal 20-40 min and soft tissue 120-180 min. whereas 2% mepivacaine with vasoconstrictor has doa for pulpal 60 min and soft tissue 180-300 min.[9]

Articaine

Articaine entered clinical use in 1976 as a unique amide LA containing an ester and a thiophene group instead of a benzene ring. Which is increasing its liposolubility, facilitating better diffusion of the anesthetic solution to the nerve cell lipid membrane. This high lipid solubility increases LA potency, reducing patient anxiety and leading to improved treatment. [1,19]

The fact that the articaine chemical structure possesses both an amide and an ester linkage is of clinical significance in minimizing the risk of overdose (toxic reaction). The presence of the ester group made 90% articaine metabolized in plasma, resulting in a shorter half-life (20-30 min) than the other amide (90 min). The remaining 10% biotransforms within the liver.[1,7,19]

Articaine's efficacy and safety profile are supported by several studies in the literature. Articaine had 1.5 times higher anesthetic efficacy, superior ability in infiltration anesthesia, and more safety. Anesthetic onset is 1.5-1.8 min for maxillary infiltration and 1.5-3.6 min for mandibular block anesthesia. Several studies found that the mean time to onset of anesthesia with articaine was generally shorter for children than for adults. The DOA of articaine pulpal anesthesia is 30-120 min and soft tissue anesthesia is about 2.25 h for maxillary infiltration and 4 h for nerve block. (7,19)

Articaine as compared with lidocaine provides a higher rate of anesthetic success for infiltration or blocks for routine dental treatments. [1] For anesthesia buccal infiltration in upper and lower molar teeth, articaine 4% with epinephrine 1:100,000 has a rapid onset of action, earlier hard palate, longer duration, and teeth numbness than mepivacaine 2% with epinephrine 1:100,000. (20,21) Articaine provides a greater level of pulpal anesthesia after mandibular infiltration, as measured using EPT compared with 2% Lidocaine with 1:100.000 epinephrine. [12] Surprisingly, a higher than normal dose of articaine for buccal infiltration can anesthesia maxillary teeth for extraction without a need for palatal anesthesia effectively. (19)

Recent studies show no significant differences in anesthesia success comparing articaine buccal infiltration with mandibular block anesthesia in adults and children. Articaine may be used as a substitute for lidocaine mandibular block anesthesia. For anesthesia of mandibular teeth following failed mandibular block anesthesia, supplementary articaine buccal infiltration has a success rate of 42-73%. (19)

An open study of the anesthetic potential of articaine in 70 children under the age of 13 years was performed by Malamed. Fifty subjects received articaine 4% with epinephrine 1:100,000 and 20 subjects were treated with lidocaine (2% with epinephrine 1:100,000). Visual analog scale (VAS) scores indicate that articaine is an effective LA in children and that articaine is as effective as lidocaine when measured on this gross scale. Articaine 4% with epinephrine 1:100,000 is a safe and effective LA for use in pediatric dentistry.

Endodontists have become enamored with the drug as a more definitive means of achieving profound anesthesia to permit painless pulpal extirpation in "hot" mandibular molars. [5] Study by Martin et al[19] shows for mandibular block anesthesia in teeth with irreversible pulpitis undergoing endodontic treatment, articaine was superior to lidocaine which has a success rate 0f 87% compared to 60%. Following the research by Gao and Meng[4], articaine as a supplemental buccal infiltration following inferior alveolar nerve block is a more successful anesthetic agent in mandibular posterior teeth with irreversible pulpitis compared with lidocaine and mepivacaine. VAS ratings were significantly lower after buccal infiltration and during endodontic access.

Anesthetic dose related to articaine success rate. For anesthesia of the maxilla, a dose of 1.2 ml of articaine is more efficacious than a dose of 0.6-0.9 ml for buccal infiltration. For anesthesia mandibular first molars, 3.6 mls of articaine as a buccal infiltration provide more effective anesthesia than 1.8 ml. (19)

The advantages of articaine are tempered somewhat by reports of paresthesia after its use for inferior alveolar blocks. Haas and Lennon have demonstrated that articaine increased the risk of non-surgical postoperative paresthesia. In 1993 alone, 14 cases of paresthesia were reported, and all were attributed to articaine (see Table 2). [8]This finding, however, could not be confirmed in a recent study by Pogrel. [(1)]

At this time, there is no scientific evidence to demonstrate there is a greater risk of paresthesia associated with the administration of a 4 percent LA. All reports of paresthesia have been anecdotal. Evidence-based research does not exist. (5,19)

Articaine is administered frequently in nondental surgeries, such as in ophthalmology, orthopedic surgery, and spinal anesthesia. There are no reported cases of paresthesia in the medical literature (Medline search 1966-2006). So far, the reasons for these findings are speculative only [5,15]

Table 2. Incidence of Paresthesia in Canada During 1994[(7)]

Anesthetic (No. of Cartridges Administered)	*Cases of Paresthesia*
Articaine (4,398,970)	10
Prilocaine (2,353,615)	4
Lidocaine (3,062,613)	0
Mepivacaine (1,569,037)	0
Bupivacaine (241,679)	0

Although the overall incidence of paresthesia is low, one cannot discount the increased risk that is associated with higher concentrations of LAs when used for nerve blocks. (8) It might be wise to limit the use of these agents for infiltration and reserve their use in nerve blocks for failed attempts with other agents.

A study investigating the safety of articaine by Malamed et al[7] which is involving the comparison of 2% lidocaine with 4% articaine, found that articaine is well tolerated and safe for use in dentistry at any age. There is no difference between articaine and lidocaine adverse events in children. Patients with liver or cardiovascular impairment need caution due to amide biotransformation occurring in the liver and the anesthetic can decrease myocardial function for patients with advanced cardiovascular disease. (7)

Pregnant and Lactating Women

Local anesthetics may be safely used when treating pregnant and postpartum patients if careful guidelines are followed. Because teratogenic risks are highest in the first trimester, the second trimester

is usually the period chosen for nonemergent and routine dental care. Dental care is generally deferred during the late third trimester and immediately after giving birth. Awareness of the potential maternal and fetal effects of any drug used during dental care is of prime importance.

Strict adherence to good LA techniques is required. Aspiration to avoid intravascular injection, needle placement accuracy, and limiting to safe dosages is advised. (15)

Lidocaine and prilocaine have the best Food and Drug Administration ranking (Table 3) as the safest LA for pregnant patients (category B). Lidocaine may be preferable because it has a lower concentration, which makes it easier to minimize the total dose and least associated with medical complications. [12,13,15] Mepivacaine and articaine have FDA category C which makes them less favorable for pregnant patients. (12,13)

Vasoconstrictors may be a concern for pregnant patients associated with their ability to increase blood pressure. Vasoconstrictors are considered safe during pregnancy, the doses of epinephrine used in LA formulations for dentistry are so low that they are unlikely to significantly affect uterine blood flow. The benefits of epinephrine or levonordefrin at the concentrations found in dental anesthetic cartridges justify their use. (13,15) Vasoconstrictors decrease the toxicity of anesthetics and can be used safely if intra-vascular injection is avoided. The American Academy of Pediatrics considers lidocaine to be safe for the breastfeeding mother. (23)

Table 3. Use of local anesthetics during pregnancy[15]

Drug	FDA category
Local anesthetics (injectable)	
Articaine	C
Bupivacaine	C
Lidocaine	B
Mepivacaine	C
Prilocaine	B
Vasoconstrictors	
Epinephrine 1:200,000 or 1:100,000	C (higher doses)
Levonordefrin 1:20,000	Not ranked

During the first trimester of pregnancy, only emergency dental procedures can be taken, because of the highest threat for teratogenicity. The second trimester is the lowest risk of fetal harm and LA should be safe to administer. While during the third trimester, there is a higher risk of aortocaval compression and increase conduction blockade. Lower doses of LA should be used if its needs to be administered. (12)

Local anesthetics represent dentistry's most important drugs. Their introduction revolutionized the practices of both dentistry and medicine. LAs are the safest and the most effective drugs in all of medicine for the prevention and management of pain in the perioperative period. The amide LAs available today provide the doctor with a broad range of durations of action, from short: (mepivacaine 3 percent) to long (bupivacaine 0.5 percent + epinephrine 1:200,000), as well as several formulations providing approximately one hour of pulpal anesthesia.

Adverse event

Allergy

Allergy of amide LA is extremely rare. Recent data of incidence is about 0.1 to 1 %. (12) Although rare, allergic reactions to lidocaine have been reported by Arya et al[10], the patient presented with erythema, edema, and itching 1.5 to 3 hours after tooth extraction. An allergic reaction might occur on exposure to other antigens such as bisulfate (an antioxidant), methyl-p-hydroxybenzoate (a preservative), methylparaben (a preservative), and latex. In patients suspected of allergy to LA or constituents, skin testing must be performed to determine the exact causative agent. [10]

Systemic toxicity

The high systemic concentration of circulating LA has severe consequences in neuralgia and cardiac. First, they will inhibit neurons in the nervous system, causing excitatory symptoms such as visual and sensory disturbance, seizures, and muscle toxicity. Furthermore, if plasma concentration continues to rise, depressive clinical manifestation occurs such as decreased level of consciousness that can be leading to coma and respiratory arrest. Following, the high plasma concentration of LA, sodium channels in areas of the heart are blocked causing tachyarrhythmias, bradyarrhythmias, and cardiac arrest. (12)

Systemic toxicity can be avoided with careful calculation of the maximum dose (table 4)

Table 4 – Recommended maximum doses of local anesthetics (12)

Drug	Maximum dose
Articaine WITH vasoconstrictor	7 mg/kg (up to 500 mg) 5 mg/kg in children
Lidocaine WITH vasoconstrictor	7 mg/kg (up to 500 mg)
Mepivacaine WITHOUT vasoconstrictor	6.6 mg/kg (up to 400 mg)
Mepivacaine WITH vasoconstrictor	6.6 mg/kg (up to 400 mg)

Intravascular injection

Local anesthetic which is deposited directly into the bloodstream may cause immediate symptoms such as palpitation, headaches, visual disturbance, and vertigo. One cartridge of lidocaine can produce seizures. (12)

4. CONCLUSION

There is difficulty in demonstrating one LA's alleged superiority over the other drugs. overall, dentists were quite satisfied with the rapid onset, depth (profoundness), duration, and consistency (reliability) of anesthesia produced by the entire class of amide LAs. (5) Lidocaine is the most often used LA for oral surgical procedures and is considered the gold standard. 3% plain mepivacaine is better for patients with cardiac diseases and useful in pediatric dentistry. Articaine/epinephrine has a rapid onset of action, and a greater level of pulpal anesthesia than mepivacaine/epinephrine. LAs may be safely used when treating pregnant and postpartum patients if careful guidelines are followed. Lidocaine is the best Drug Administration ranking in pregnant and lactation women. Because teratogenic risks are highest in the first trimester, the second trimester is usually the period chosen for nonemergent and routine dental care. Dental care is generally deferred during the late third trimester and immediately after giving birth. Awareness of the potential maternal and fetal effects of any drug used during dental care is of prime importance. However, as in all dental treatments and therapies, it is ultimately the doctor who must decide to use a type of LA drugs.

REFERENCES

[1] Katyal V. The efficacy and safety of articaine versus lignocaine in dental treatments: A meta-analysis. J Dent. 2010;38(4):307–17.

[2] Su N, Liu Y, Yang X, Shi Z, Huang Y. Efficacy and safety of mepivacaine compared with lidocaine in local anaesthesia in dentistry: A meta-analysis of randomised controlled trials. Int Dent J. 2014;64(2):96–107.

[3] Almeida PC De, Raldi FV, Ricardo F, Sato L, Dias R. Volume and effectiveness assessment of articain 4 % versus mepivacaine 2 % used in third molar surgery : randomized , double-blind , split-mouth controlled clinical trial. 2020;25(6).

[4] Gao X, Meng K. Comparison of articaine , lidocaine and mepivacaine for buccal infiltration after inferior alveolar nerve block in mandibular posterior teeth with irreversible pulpitis. 2020;228(8):605–8.

[5] Malamed SF. Local anesthetics: dentistry's most important drugs, clinical update 2006. J Calif Dent Assoc. 2006;34(12):971–6.

[6] Cuvillon P, Nouvellon E, Ripart J, Boyer JC, Dehour L, Mahamat A, et al. A comparison of the

pharmacodynamics and pharmacokinetics of bupivacaine, ropivacaine (with epinephrine) and their equal volume mixtures with lidocaine used for femoral and sciatic nerve blocks: A double-blind randomized study. Anesth Analg. 2009;108(2):641–9.
[7] Malamed SF, Gagnon S, Leblanc D. A comparison between articaine HCl and lidocaine HCl in pediatric dental patients. Pediatr Dent. 2000;22:307–11.
[8] Becker DE, Reed KL. Essentials of local anesthetic pharmacology. Anesth Prog. 2006;53(3):98–108; quiz 109–10.
[9] Malamed SF. Handbook of Local Anesthesia. 7th. Louis S, editor. Mosby; 2020.
[10] Arya V, Arora G, Kumar S, Kaur A, Mishra S. Management of patients with allergy to local anesthetics: two case reports. J Dent Anesth Pain Med. 2021;21(6):583.
[11] Rang HP, Ritter JM, Flower RJ, Henderson G. Rang and Dale's Pharmacology. eight edit. China: Elsevier Churcill Livingstone; 2016.
[12] Decloux D, Ouanounou A. Local Anaesthesia in Dentistry: A Review. Int Dent J [Internet]. 2021;71(2):87–95. Available from: https://doi.org/10.1111/idj.12615
[13] Ouanounou A, Haas DA. Drug therapy during pregnancy: Implications for dental practice. Br Dent J [Internet]. 2016;220(8):413–7. Available from: http://dx.doi.org/10.1038/sj.bdj.2016.299
[14] Neves RS, Neves ILI, Giorgi DMA, Grupi CJ, César LAM, Hueb W, et al. Effects of epinephrine in local dental anesthesia in patients with coronary artery disease. Arq Bras Cardiol. 2007;88(5):545–51.
[15] Haas DA. An Update on Local Anesthetics in Dentistry (Mise à jour sur les anesthésiques locaux utilisés en dentisterie). J Can Dent Assoc (Tor). 2002;68(9):546–51.
[16] Vinycomb TI, Sahhar LJ. Comparison of Local Anesthetics for Digital Nerve Blocks: A Systematic Review. J Hand Surg Am. 2014;39(4):744-751.e5.
[17] Best CA, Best AA, Best TJ, Hamilton DA. Buffered lidocaine and bupivacaine mixture - the ideal local anesthetic solution? Plast Surg (Oakville, Ont). 2015;23(2):87–90.
[18] Moore PA, Hersh E V. Local Anesthetics: Pharmacology and Toxicity. Dent Clin North Am. 2010;54(4):587–99.
[19] Martin E. Articaine in dentistry : an overview of the evidence and meta-analysis of the latest randomised controlled trials on articaine safety and ef fi cacy compared to lidocaine for routine dental treatment. BDJ Open [Internet]. 2021;(June):1–13. Available from: http://dx.doi.org/10.1038/s41405-021-00082-5
[20] Gazal G, Alharbi AM, Al-Samadani KH, Kanaa MD. Articaine and mepivacaine buccal infiltration in securing mandibular first molar pulp anesthesia following mepivacaine inferior alveolar nerve block: A randomized, double-blind crossover study. Saudi J Anaesth. 2015;9(4):397–403.
[21] Gazal G, Alharbi R, Fareed W, Omar E, Alolayan A, Al-Zoubi H, et al. Comparison of onset anesthesia time and injection discomfort of 4% articaine and 2% mepivacaine during teeth extractions. Saudi J Anaesth. 2017;11(2):152.
[22] Fayans EP, Stuart HR, Carsten D, Ly Q, Kim H. Local Anesthetic Use in the Pregnant and Postpartum Patient. Dent Clin North Am. 2010;54(4):697–713.