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RESEARCH ARTICLE

ARTICAINE IN ENDODONTICS: A REVIEW.

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Abstract

Introduction:-

Achieving profound pulpal anesthesia is a corner stone in endodontic practice and dentistry. Profound pulpal anesthesia during the root canal procedure benefits not only the patient, for obvious reasons, but also the dentist who will be less stressed worrying about patient reactions or sudden movement during therapy. Achieving adequate anesthesia in patients can, at times, be a challenge Clinicians constantly have sought an anesthetic solution with a better success rate than that of available anesthetics which has been demonstrated to be well below 100 percent.[1]

Root canal treatment has been described as significantly more painful for teeth with irreversible pulpitis and symptomatic apical periodontitis compared with teeth with necrotic pulps and asymptomatic apical periodontitis [2]. In addition,achieving profound pulpal anesthesia can be challenging in these cases[3]. For example, anesthesia may be sufficiently profound to access the pulp chamber, but canal instrumentation can result in severe pain[4]. In a survey of Diplomates of the American Board of Endodontic, 84% of respondents reported experiencing difficulties in anesthetizing acutely painful mandibular molars.[5]

The inability to achieve pulpal anesthesia has been shown to increase a patient's fear and anxiety, exacerbate systemic medical issues, extend the appointment duration, and generate doubt in the operator;any of these factors can contribute to the impression that receiving root canal treatments a painful procedure.

In the search for less allergic compounds with a faster onset, the amide-type local anesthetic lignocaine was synthesized by Swedish chemist Nils Löfgren in 1943 and marketed as lidocaine in 1949. Since then, other amide local anesthetics have been introduced and used clinically for their favorable onset time and duration, e.g., mepivacaine, prilocaine, bupivacaine, etidocaine, and ropivacaine. Among this group, articaine, originally synthesized as carticaine, entered dentistry practice in 1973. Epidural administration and comparison with lidocaine started in 1974. In 1984, it was released in Canada, followed by the UK in 1998, the rest of Europe and the US in 2000, and Australia in 2005. Currently, articaine 4% with adrenaline 5 µg/mL is widely used in dentistry.[6]

Articaine:-

Articaine {4-methyl-3-[2-(propylamino)propionamido]-2-thiophenecarboxylate}, was synthesized in 1969 by Rushing, but not used clinically until the mid-1970s in Germany.

Unlike other amide local anesthetics articaine has a thiophene ring. This increases its lipid solubility to a value close to that of prilocaine and not surprisingly it is used in similar concentrations (2-4%). It has a low pKa and clinical

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studies have confirmed a rapid onset of action. Protein binding is high and a prolonged duration might be expected. However, unlike other amide local anesthetics articaine contains an additional ester group, so that metabolism occurs in the plasma by non-specific cholinesterase's as well as in the liver. The rapid onset of articaine has been demonstrated by Altman in ophthalmic blocks, where it may prove useful as ocular movement returns rapidly after the completion of surgery. In addition, the rapid fall in plasma levels will also reduce the risks of toxicity. However, in patients with known deficiency of plasma cholinesterase's an alternative choice would be appropriate.[6]

Articaine has been widely used in dental surgery. Dentists started to use articaine around 1977.In dentistry, articaine has been investigated extensively. Clinical trials comparing articaine mostly with lidocaine have varied in study design and site of action. The overwhelming majority of references in the literature describing the alleged neurotoxicity of articain concern par aesthesia and prolonged numbness after dental procedures.. Although there may be controversy regarding its safety and advantages in comparison to other local anesthetics, there is no conclusive evidence demonstrating neurotoxicity or significantly superior anesthetic properties of articaine for dental procedures The choice whether to use articaine or another local anesthetic is based on the personal preference and experiences of individual clinicians. Currently, articaine is available as a 4% solution containing 1:100,000 or 1:200,000 epinephrine. Clinical trials comparing 4% with 2% solutions show no clinical advantage of 4% over a 2% solution Recognizing the importance of providing profound anesthesia for patients undergoing invasive dental procedures, clinicians continually seek to identify an anesthetic solution that provides the highest success rate at an affordable cost.[6]

Articaine can diffuse through soft and hard tissues more reliably than other LA so that maxillary buccal infiltration of articaine provides palatal soft tissue anesthesia.[7] The basis for the prevalent use of articaine is due to the belief that it has better diffusion through soft tissue and bone, rapid onset, excellent quality of anesthesia, and lower degree of toxicity than lidocaine. Articaine provides complete anesthesia even by infiltration technique due to its superior tissue penetrationcapability.[8]Lidocaine is the most widely used local anesthetic in medicine as well as dentistry. It is evident that extraction of the permanent maxillary tooth is possible with single buccal infiltration of 2% lidocaine without the need for palatal injection.[9]

Pharmacodynamic properties:-

Articaine blocks nerve conduction by reversibly binding to the α-subunit of the voltage-gated sodium channels within the inner cavity of the nerve, similar to other local anesthetics. Binding of articaine to the sodium channel reduces sodium influx so that the threshold potential will not be reached and impulse conduction stops. The blocking action of articaine on the sodium channel is state dependent: it has the highest affinity for the open state, an intermediate affinity for the inactivated state, and the lowest affinity for the resting state.[10]

The degree of neuronal block is affected by the diameter of the nerve. Larger-diameter fibers (touch/pressure/motor) require higher concentrations of local anesthetic compared with small myelinated fibers (pain afferents).6 Articaine is lipid soluble, highly protein-bound (94%), and has a dissociation constant (pKa) of 7.8. Articaine is an intermediate-potency, short-acting local anesthetic with a fast onset of action.[11]

Pharmacokinetic properties:-

Absorption and distribution:-

Local anesthetic drugs are administered to the areas around the nerves to be blocked, e.g., the skin, subcutaneous tissues, retro bulbar, intrathecal, and epidural spaces. Some of the drug will be absorbed into the systemic circulation; how much will depend on the vascularity of the area to which the drug has been applied and intrinsic effects of the drug or its additives on vessel diameter. Articaine, like most local anesthetics at concentrations that are used clinically, has a vasodilatory effect, increasing its systemic absorption. This is countered in preparations with epinephrine 1:60,000, 1:100,000, and 1:200,000 (5 μg/mL).[12]

The distribution of the drug is influenced by the degree of tissue and plasma protein binding of the drug. The more protein-bound the agent, the longer the duration of action, as free drug is more slowly made available for metabolism. Based on its physiochemical and stereochemical properties, protein binding of articaine is 94%.[13]

Metabolism and elimination:-

The molecular structure of articaine is characterized by having both lipophilic and hydrophilic ends connected by a hydrocarbon chain. The "CO linkage" between the hydrocarbon chain and the lipophilic aromatic ring classifies

articaine as being an ester local anesthetic, in which the link is metabolized in the serum by plasma cholinesterase. Articaine is quickly metabolized via hydrolysis into its inactive metabolite articainic acid, which is partly metabolized in the kidney into articainic acid glucuronide.[14]

The pharmacokinetics and metabolism of articaine have been studied in ten patients undergoing intravenous regional anesthesia using 40 mL articaine 0.5% (200 mg).[15]During tourniquet application and regional analgesia, 55% of the administered dose was already hydrolyzed by plasma (20%) and tissue (35%) esterase activity. After releasing the tourniquet, articaine and its metabolite articainic acid appeared in the blood; articaine was rapidly eliminated with a half-life of approximately 60 minutes . Low systemic concentrations and rapid metabolism of articaine also have been observed in a study during and after tumescent local anesthesia (infusion) for liposuction using dosages up to 38.2 mg/kg body weight.[16]Average maximum plasma concentrations Cmax) for articaine ranged from 136 (hips) to 264 ng/mL (abdomen); the average extent of absorption (AUC) ranged from 827 to 2203 ng· h/mL. The corresponding Cmaxand AUC values for articainic acid were substantially higher, ranging from 1719 to 7292 ng/mL and from 13,464 ng· h/mL (chin) to 74,962 ng· h/mL (abdomen), respectively. In liposuction, part of the applied drug is removed in the aspirate, and around 30% of the infused dose was recovered in the plasma is preserved in their erythrocytes.[17]

Toxicity and safety:-

All commonly used local anesthetics produce neurotoxicity in a concentration-dependent manner. Proposed causes for neurological deficits are neural ischemia (due to local vasoconstriction caused by the local anesthetic itself or by epinephrine) or inflammation.[18]

Clinical profiles of neurotoxicity of articaine have been based on the reported incidence of transient neurologic syndrome after spinal anesthesia and paresthesia in dentistry.[19-20]Articaine acquired from Sanofi Aventis (Paris, France) and other local anesthetics in relative experimentally effective anesthetic concentrations have been investigated for their potency to induce apoptosis in human tumor cells (SHEP neuroblastoma cells).[20]The observed neurotoxicity correlates with the lipophilicity and therefore with the potency of the local anesthetic. The concentrations of local anesthetics that induced apoptosis in their model are within the same range as those observed intrathecally after single-shot spinal anesthesia in primates and in sciatic nerves of rodents during nerve blockade.[21-22]

Clinical signs are perioral and tongue parenthesis, a metallic taste, and dizziness, passing into slurred speech, diplopia, tinnitus, confusion, restlessness, and muscle twitching progressing to neuronal depression and leading to convulsions and coma. The severity of cardiovascular and central nervous system toxicity is directly related to the local anesthetic potency, dose, and rate of administration. In this context, one has to distinguish acute toxicity caused by accidental intravascular administration from toxicity caused by systemically absorbed local anesthetic.[23]maximum doses of local anesthetics lack scientific justification; as a consequence, the recommended highest dose of articaine, assumed to be around 4–7 mg/kg, has to be interpreted as an important guide number[24].In general, the site of local anesthetic injection in combination with patient-related factors and their expected influence on the pharmacodynamic or pharmacokinetic change are important reasons to reduce the dose, especially for repeated or continuous administration.

If administration of articaine or another local anesthetic is done expertly and cautiously, LAST can occur. Treatment options for LAST, particularly local anesthetic cardiotoxicity, have recently improved in the form of intravenous lipid emulsion therapy (an initial bolus of 1.5 mL/kg of a 20% solution followed by an infusion of 0.25 mL/kg/minute).[25-26]Lipid emulsion is a reasonably well-tolerated and effective treatment, especially when LAST is caused by a lipophilic local anesthetic like articaine. The effects of articaine and ropivacaine on the components of intracellular Ca2+ handling, the cause of negative isotropic actions, were studied and compared in canine ventricular myocardium.[27]Under conditions of normal application, both articaine and ropivacaine are free of cardio depressant effects.

Articaine is the center of heated discussions among dental surgeons as it has a faster onset and higher success rates than lidocaine as well as it has been demonstrated to increase the risk of paresthesia which could not be confirmed in a recent study[29-31] .Articaine has been shown to be a significantly better anesthetic agent as compared to lidocaine for infiltrations.[32-34].

The chemical composition of articaine contains a unique thiophene ring instead of the benzene ring found in lidocaine and other amide local anesthetics.This difference increases lipid solubility, thereby increasing diffusion through the lipid membrane of the epineurium, which purportedly explains its faster onset and higher success rate when compared with lidocaine.[35-36]

Teeth with irreversible pulpitis have shown greater difficulty in achieving anesthesia during endodontic treatment. In addition, achieving anesthesia in mandibular molar teeth with irreversible pulpitis is more difficult compared with other posterior teeth with the same condition.[37]

Articaine is an anesthetic solution that was approved by the Food and Drug Administration for use in dentistry in the United States in 2000.[38]Articaine is claimed to provide faster onset and longer duration of pulp anesthesia compared with lidocaine.[39] Several investigations have compared the anesthetic efficacy of articaine with other anesthetic agents.[40-45] The results of these studies have shown no significant difference between articaine and lidocaine when used for IANB injections.[40-45]

Available local anesthetic solutions.

DURATION OF ACTION	SOLUTION	INFILTRATION (PULPAL)	NERVE BLOCK (PULPAL)	DURATION OF EFFECT IN SOFT TISSUE
Short Duration, Plain	Lidocaine hydrochloride (HCl) 2 Percent	5 minutes	Not Indicated	2 hours
	Mepivacaine HCl 3 percent	20 to 30 Minutes	45 to 65 Minutes	2 to 3 hours
	PrilocaineHCl 4 percent	10 to 15 minutes	45 to 65 minutes	3 to 4 hours
Normal Duration, With Vasoconstrictor	ArticaineHCl 4 percent with epinephrine 1:100,000	60 to 75 Minutes	Up to 120 Minutes	3 to 5 hours
	ArticaineHCl 4 percent Withepinephrine 1:200,000	60 to 75 Minutes	Up to 120 Minutes	3 to 5 hours
	LidocaineHCl 2 percent Withepinephrine 1:50,000	55 to 65 Minutes	80 to 90 Minutes	3 to 5 hours
	LidocaineHCl 2 percent Withepinephrine 1:100,000	55 to 65 Minutes	80 to 90 Minutes	to 5 hours
	Mepivacaine HCl 2 percent Withlevonordefrin 1:20,000	40 to 60 Minutes	60 to 90 Minutes	3 to 5 hours
	PrilocaineHCl 4 percent Withepinephrine 1:200,000	35 to 45 minutes	50 to 70 minutes	3 to 6 hours
Long Duration	Bupivacaine HCl 0.5percent with Epinephrine1:200,000	Up to 7 hours	Up to 7hours	Up to 12 hours

April 2000. Articaine is available as a 4 percent solution, and lidocaine is available as a 2 percent solution. Both can be combined with various concentrations of vasoconstrictors. Articaine contains a thiophene ring, instead of the benzene ring found in lidocaine and other amide local anesthetics; this allows the molecule to diffuse more readily through the nerve membrane owing to increased lipid solubility.[46-47]A second molecular difference is the ester linkage incorporated into the articaine molecule, which results in hydrolysis of articaine by plasma esterase's. Ninety to 95 percent of articaine is metabolized in the blood by plasma esterase's, with the remainder being broken down in the liver,[46] whereas approximately 90 percent of lidocaine is metabolized by the liver. The articaine solution's plasma half-life has been reported to be as short as 20 minutes,

Although investigators have designed various clinical trials to compare articaine with a variety of other available anesthetic solutions, published data do not support a clear superiority of articaine in terms of anesthetic efficacy. Thus, clinicians still may wonder which anesthetic solution will afford them the best chance of success for a given procedure, particularly in cases of irreversible pulpits.

Clinical studies on articaine and lignocaine have focused on the time to onset of clinical anesthesia, dose, duration, depth of anesthesia along with the safety and efficacy profile, and mean time of onset in children versus adults, infiltrations and nerve blocks, conventional syringe versus computer controlled drug delivery system Single Tooth Anesthesia Wand (STA‑Wand) administered for restorative procedures and extractions.[47-48] The available literature on articaine confirms the effectiveness of conventional single buccal infiltrations in maxillary primary molar extractions replacing the need of painful palatal injections which is usually required whenever conventional infiltration anesthesia with lignocaine is preferred.[49] Interestingly, the literature available on the efficacy of articaineintraligamentary injections administered with Wand forpulpectomy procedures on primary molar teeth seems to be limited, and sometimes, the intraligamentary injections have also been considered to overcome the drawbacks of nerve block particularly when there is a need for treatment procedures in bilateral quadrants at the same appointment.[50-51]

Inferior alveolar nerve block and buccal infiltration or inferior alveolar nerve block and periodontal ligament injection using 4% articaine/HCl with 1:100,000 epinephrine could result in a high rate of anesthetic success in patients with irreversible pulpits in the mandibular first molar. Both offer effective strategies for practitioners and patients. Neither combination, however, provided total anesthetic success during irreversible pulpits treatments [52]

The use of 4% articaine is popular among dentists owing to its short plasma half-life. However, some researchers have suggested that this high concentration may be associated with nerve damage

No easy solution has been identified for successfully anesthetizing all patients with vital mandibular painful teeth diagnosed with symptomatic irreversible pulpitis patients clinical condition are more difficult to anesthetize for various reason, all of which are not fully understood.some of the reason described in the research literature are altered resting potentials and described excitability threshold of inflamed nerves, terodotoxin-resistant sodium channels increased expression of sodium channels in irreversibly inflamed pulps and apprehensive patients with lower pain thresholds. The reason most often cited but least likely to hold true is lowered pH of inflamed tissue. The theory hypothesizes that lowerd pH reduces the amount of base form of the anesthetic available to penetrate the membrane ther by preventing anesthesia. This is not best explanation for failure with inferior alveolar nerve block(IANB) when the injection is not given at the primary site of inflammation.likely, this is more complicated neuronal process.inflamation and bacterial insult can lead to sprouting of nerve fibers, increased expression of neuropeptides such as substance P and calcitonin gene related peptide, and the release of inflammatory mediators such as prostaglandins E2,prostaglandins F2a, interleukins 1 and 6, and tumor necrosis factor. This can also lead to excitability of nocieptor isoforms. This clinical condition may include neuronal plasticity allodynia,hyperalgesia peripherally and centrally, and central sensitization. These factors may help to explain why local anesthesia is not always effective when patients are in pain.[53]

In a study by Arrow et al, although the inferior alveolar nerve block with Articaine was more successful than that with Lidocaine, no significant differences were observed in the mandibular buccal infiltration technique between the two anesthetic agents.[54]

It is a mistake if a dentist assumes that soft tissue anesthesia is a sign of successful pulp anesthesia. Soft tissue anesthesia after the administration of an IANB only indicates that the injection has been administered at the correct

site, but it does not guarantee pulp anesthesia. Successful pulp anesthesia success is only achieved if no or minimal pain is reported by the patient during access cavity preparation and root canal instrumentation.[55] One of the suggested methods to overcome the failure of anesthesia after the administration of an IANB is to increase the volume of the anesthetic solution.[56-61] Most of the previous investigations have reported that increasing the volume has no significant effect on anesthesia success. However, these studies have only used lidocaine as the anesthetic solution.[56-68,61]

Irreversible pulpits , which is a severe damage to the pulp via bacteria in the vital dental pulp, would cause necrosis or death to pulp tissues, and thus leads to very intolerable severe spontaneous pain and forces patients to seek immediate treatment[62]articaine was the second most used dental local anesthetic in the US, only after lidocaine.[63]Articaine is generally effective in providing patients with pain-free treatment because of its high liposolubility which facilitates the diffusion of the anesthetic solution to the teeth, but local anesthetic failure is still a concern in treatment of irreversible pulpitis.[64]

The 4% articaine with 1:100 000 epinephrine resulted in shorter onset time in pulpal anesthesia than 2% lidocaine with 1:100 000 epinephrine. The onset time of anesthesia is directly related to the rate of epineural diffusion, which is correlated with the percentage of drug in the base form, which is proportional to the pKa of that agent. pKa was 7.8 in the articaine group, and was 7.9 in the lidocaine group.[63]

The intraosseous injection seems to raise the success rate to a reliable extent as shown in some previous studies.[65]It is not a preferable technique because it requires special equipment, drilling of the cortical bone, and preparing a site for administration of the anesthetic solution.[66] The intraligamentary injections have a short duration of action and may increase postoperative pain. [67]The intraosseous and intraligamentary techniques are effective in raising anesthesia levels in difficult anesthetic situations; however, it would be beneficial if similar results could be achieved by simpler options such as the infiltration technique. This technique has been studied extensively in asymptomatic teeth.[68-74]Some of these studies performed a comparison between lidocaine and articaine. [68-71]The results of some revealed no significant differences between the 2 anesthetics,[68-69] whereas the findings of others suggested that articaine was superior to lidocaine in raising pulpal anesthesia in mandibular teeth.[70-71]In a study by Kanna et al[75], lidocaine and articaine were compared in maxillary teeth with irreversible pulpits. The results of their study showed no significant differences between these anesthetics.

In a study by McEntire et al,[76]the anesthetic efficacy of 4% articaine with 1:200,000 epinephrine was shown to be comparable to 4% articaine with 1:100,000 epinephrine in a primary mandibular buccal infiltration of asymptomatic mandibular first molars.

In a study by Poorni et al [77]on mandibular molars with irreversible pulpits, the efficacy of an IANB with articaine or lidocaine showed similar success rates compared with a buccal infiltration with articaine that had not been supplemented with an IANB. This may bring up the point that the infiltration technique could be a reliable choice of anesthesia.

In a study by Matthews et al.[78] supplemental articaine infiltration injections were administered after failure of lidocaine IANB in posterior mandibular teeth with irreversible pulpits. They found that the articaine infiltration injection was successful 58% of the time. Aggarwal et al [79]compared lidocaine and articaine infiltration injections that were applied on both buccal and lingual sides of posterior mandibular teeth with irreversible pulpits after lidocaine IANB. They found the success rates of lidocaine and articaine to be 47% and 67%, respectively. Even though these studies investigated mandibular teeth with irreversible pulpits, they had performed the IAN blocks by using lidocaine, and the obtained results would not predict pulpal anesthesia in all patients.

Conclusion:-

Articaine seems to raise anesthetic success more effectively compared with other local anesthetics used in dentistry. In cases of persistent pulpal pain despite successful mandibular block anesthesia, supplementary infiltration with articaine instead of lidocaine has 3.5 times greater likelihood of achieving successful anesthesia. The clinical evidence concludes that 4%articaine with 1:100 000 epinephrine is superior in increasing the success rate of local anesthesia and pain control at the injection phase and treatment phase. This solution also results in shorter onset time of pulpal anesthesia and is superior in decreasing the percentage of patients undergoing adverse events compared

with 2% lidocaine with 1:100 000 epinephrine Achieving profound pulpal anesthesia in all patients remains a future goal requiring further investigation.

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