Int J Pharm Bio Sci 2014 April ; 5 (2) : (P) 457 - 465

Review Article **Pharmacology**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

EFFICACY OF LIGNOCAINE IN DENTAL EXTRACTIONS

PRATISHTA JAIN[1] AND NABEEL NAZAR*[2]

[1] Final Year BDS – Saveetha University, Chennai, India.
[2] Department of Oral & Maxillofacial Surgery, Saveetha University, Chennai, India

ABSTRACT

Dental extractions are associated with pain and therefore require potent local anesthetics that can keep the patient comfortable during the procedure. Lignocaine is available for more than half a century and is still being widely used in clinical practice even with the advent of newer anesthetic agents. It is also a standard of comparison for newer anesthetic agents. The systemic effects of the anesthetic agents also has to be considered when administering these drugs. The drug with the most potent anesthetic effect and least systemic toxicity is considered the most ideal. Inspite of extensive studies, the ideal agent is still debatable. The efficacy of lignocaine in dental extractions is reviewed here.

KEY WORDS: **Amides; Dental extraction; Epinephrine; Lignocaine; Local anesthetic;**

NABEEL NAZAR
Department of Oral & Maxillofacial Surgery, Saveetha University, Chennai, India

INTRODUCTION

Dental extraction is a commonly performed procedure and is associated with pain. It is therefore an issue of fear and anxiety for most of the patients. Pain control in dentistry reduces the fear and anxiety associated with dental procedures[1]. Local anesthetics form the backbone of pain control techniques in dentistry and there has been substantial research interest in finding safer and more effective local anesthetics. Lignocaine was first introduced in the market in 1948[2]. Local anesthetics can be broadly classified into two:esters and amides. The ester type agents have been used for over the past 50years but they have been associated with a higher incidence of allergic reactions due to the para-amino-benzoic acid (PABA) metabolite. Since then, amide local anesthetics such as lignocaine, have been providing safe and effective control of pain to facilitate the ever advancing surgical techniques[3].

Pharmacology of lignocaine

Local anesthetics have been defined as a loss of sensation in a circumscribed area of the body caused by a depression of excitation in nerve endings or an inhibition of the conduction process in peripheral nerves[4].

Mechanism of action

Local anesthetics act by blockade of sodium channels thus preventing action potential to occur. . When the propagation of these action potentials is prevented, the sensation cannot be transmitted from the source of stimulation, such as a tooth or the periodontium to the brain[4].

Structure of a local anesthetic molecule

A local anesthetic molecule is made up of three parts: a lipophilic (aromatic) end, a hydrophilic (amine) end and in between the two ends is a hydrocarbon chain containing either an ester or amide linkage[5]. For the past 20 years amides such as lignocaine have been used predominantly. Lignocaine synthesized by Nils Lofgren in 1943 and approved by the FDA in 1948, is one of the most commonly used amide local anesthetic.

Uptake

When injected into the soft tissues, lignocaine produces a certain degree of vasodilation. When injected rapidly in a dose of 1mg/0.1 ml of saline it produces a vasodilating activity of 1[6].

Absorption

When taken by the oral route, lignocaine undergoes a hepatic first pass effect. It gets absorbed into the gastrointestinal tract, and then enters enterohepatic circulation. A part of it also goes to the liver , where it is bio transformed[7].

Distribution

Once absorbed, lignocaine is distributed through blood to all the body tissues. The plasma concentration of a local anesthetic plays a significant role in the potential toxicity of the drug. The rate at which the local anesthetic is removed from the blood is known as its elimination half life. The half life of lignocaine has been calculated to be 1.8 hours[8].

Biotranformation

The primary site of its biotransformation is in the liver. In patients having normal liver function, about 70% of injected lignocaine is biotransformed.

Excretion

The excretion of lignocaine occurs through the kidneys. Less than 10% is unchanged and 80% occurs through various metabolites[7].

Physicochemical Properties of lignocaine

An anesthetic's dissociation constant (pKa) plays a major role in determining its rate of onset and diffusion properties. It is the pH at which a drug's ionised and non ionised forms are in equal concentrations. Lignocaine having a pKa of 7.9 has a rapid onset of action, around 2-3 minutes[4]. As lignocaine causes vasodilatation, which leads to rapid diffusion away from the site of action, it results in a very short duration of action.The protein binding characteristics are also an important determinant of the duration of

anaesthesia. Lignocaine is approximately 65% protein bound whereas bupivacaine is 95% protein bound. Hence 2% lignocaine has a short duration of action and bupivacaine has a comparatively longer duration of action[4,9]. The addition of a vasoconstrictor can effectively increase the duration of action. 2% lignocaine with epinephrine 1:50,000 and 2% lignocaine with epinephrine 1:100,000 have an intermediate duration of action[10].

Vasoconstrictors

Vasoconstrictors decrease the blood flow to the site of injection by constricting the blood vessels. Hence, increased amounts of local anesthetics stay around the nerves for a longer time thereby, increasing the duration of anaesthesia[11,12]. Also it decrease the minimum concentration of local anesthetic agent needed for nerve block and reduces the peak plasma concentration of the local anesthetic minimizing the risk of local anesthetic toxicity[13,14,15]. Vasoconstrictors are also very effective in achieving bleeding control during a surgical procedure[16,17]. Epinephrine is one of the most commonly used vasoconstrictors in association with local anesthesia in dentistry and numerous studies have analysed its effects in local anesthetic solution for dental procedures[12,18,19]. The epinephrine vasoconstrictor that is added to local anesthetics in dentistry treatment provides excellent anesthesia and bleeding control[12,18,20,21]. In a study, it was observed that lignocaine without a vasoconstrictor did not offer a satisfactory pain relief whereas more intense anesthesia was achieved by adding epinephrine[20]. The possible reason for this could be blocking of large and small diameter nerve fibres[22,23].

Maximum recommended dosage: the maximum recommended dose of 2% lignocaine plain is 300mg (4.4mg/kg) for an adult and of 2%lignocaine with vasoconstrictor such as epinephrine is 500mg (6.6mg/kg) for an adult[24] and the maximum recommended dosage of epinephrine in healthy individuals is 0.2mg and those with cardiovascular diseases is 0.04mg[25].Clonidine, a central sympatholytic has been also used for the same purpose. It brings about haemodynamic changes by stimulation of alpha-2 receptors post-junctionally in medulla causing decrease in sympathetic outflow resulting in fall in blood pressure and bradycardia[26].Brkovic compared the effects of adding epinephrine and clonidine to lignocaine in maxillary infiltrations and inferior alveolar nerve blocks. It was concluded that clonidine could be a useful and safe alternative to epinephrine[27,28]. Clonidine is also proved to be a safe alternative to epinephrine in hypertensive patients[29].

Systemic effects of lignocaine

Lignocaine has a significant effect mainly on the central nervous system and cardiovascular system.

Effect on the Central Nervous System

Local anesthetics can readily cross the blood brain barrier. Hence ,one of their main pharmacological actions is CNS depression. At a blood level of 0.5-4 µg/ml lignocaine has some anticonvulsant properties[30,31]. There have been studies proving its efficacy in temporarily arresting status epilepticus when a dose of 2-3mg/kg is administered at a rate of 40-50mg/min[32]. At blood levels of 4.5-7 µg/ml it results in certain preconvulsive signs and symptoms. The preconvulsive signs include slurred speech, shivering, muscular twitching, tremor of muscles of face and distal extremities, dizziness, drowsiness, disorientation and visual and auditory disturbances. The preconvulsive symptoms that generally occur include numbness of the tongue and circumoral region, warm,flushed skin and the individual might experience a pleasant dreamlike state[33].At blood levels of greater than 7.5 µg/ml it brings about generalised tonic-clonic seizure.

Effects on the Cardiovascular System

Lignocaine significantly decreases the electrical excitability of the myocardium, decreases the conduction rate and decreases the force of contraction[34,35]. This has contributed to lignocaine being widely used for its anti-arrhythmic actions[36]. It is being used as a drug in advanced cardiovascular life support and also in the management of PVCs and ventricular tachycardia. It also has been used to manage cardiac arrest in ventricular defibrillation[37].Lignocaine also

produces peripheral vasodilation. At non toxic levels, it may result in a slight elevation or no change in blood pressure. At levels slightly below the toxic level, mild hypotension may result.At toxic levels there are significant hypotension, decreased cardiac output and bradycardia.At levels above the toxic level, cardiovascular collapse may occur.Abraham-Inpijn and others recorded changes in blood pressure, heart rate, and the electrocardiogram during and after tooth extraction under local anesthesia for both normotensive and hypertensive (preoperative systolic blood pressure -160 mm Hg, or diastolic blood pressure - 95 mm Hg) patients. Thirty eight of 40 patients received 2% lidocaine with 1: 80,000 epinephrine. Both groups showed a statistically significant increase in blood pressure, but the hypertensive patients experienced greater increases. Also noted was a 7.5%incidence of potentially dangerous cardiac dysrhythmiasin the hypertensive group[38].In a study of catecholamine effects on cardiovascular function Kiyomitsu et al found that the addition of 1: 80,000 epinephrine to 2% lidocaineresulted in increased cardiac output, heart rate, and stroke volume and decreased afterload and mean arterial pressure. These hemodynamic changes were more severe in older patients[39].

Effect of vasoconstrictors on the cardiovascular system

Pain has been shown to cause liberation of catecholamines which can bring about adverse hemodynamic effects including increase in blood pressure, heart rate and the frequency of arrhythmias in patients with heart valvular disease and therefore local anesthetics with epinephrine have to be effective to prevent these hemodynamic changes[40-45].In a study Niwa et al analysed the cardiovascular response to epinephrine and showed that the patients did not show any symptoms during treatment with a local anesthetic that contained epinephrine[19]. Also a study on cardiac patients by Laragnoit et al comparing plain lignocaine and lignocaine with epinephrine [1:100,000] showed that local anesthetic consisting of 2% lidocaine and epinephrine [1:100,000] did not alter arrhythmic conditions and did not have an impact on the heart rate or blood pressure thus warranting its safety for use on patients with cardiac valvular diseases[46].Blinder et al. showed that there was a high incidence of tachycardia when cardiac patients were but less arrhythmia or ST depression, as compared with a study that used anesthetic alone[41].Numerous studies have shown some degree of adrenergic activation in cardiac transplant recipients, when lignocaine with epinephrine was administered to them[47, 48].

Local tissue toxicity

An intramuscular or intravenous injection of lignocaine may produce reversible skeletal muscle damage.

Effect on hepatic system

Lignocaine metabolism is impaired in liver disease and its dose should be reduced to 50% in patients with liver. There is increased risk of overdose in patients with severe liver dysfunction, however such significant liver disease is rare in ambulatory patients who seek dental treatment.

Effect on the Respiratory system

At non overdose levels they act as bronchial smooth muscle relaxants and at toxic levels may produce respiratory arrest due to generalised CNS depression.

Effects on blood glucose

The effect of lignocaine with epinephrine on blood glucose levels have been studied. It is shown that lignocaine with adrenaline causes a slight increase in the blood glucose concentration, which is not found to be clinically significant and therefore safe to use on diabetic patients[49,50].

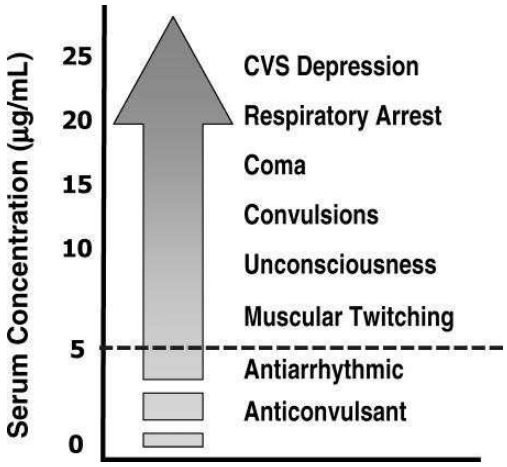

FIGURE 1
SYSTEMIC EFFECTS OF LIGNOCAINE

LIGNOCAINE: A LITERATURE REVIEW

The lipid solubility nature of articaine has been proposed for its improved local anesthetic action compared to lignocaine[51-53]. A meta-analysis by Katyal et al recommended 4% articaine (1:100,000 epinephrine) in routine dental practice over 2% lignocaine (1:100,000 epinephrine) showing that articaine is more effective than lignocaine in providing anesthetic success in the first molar region for routine dental[54]. There are also other studies which were in favour of articaine over lignocaine stating that articaine is better in terms of latency and duration[51,55]. However, In a randomized clinical study by Silva et al, the efficacy of articaine and lignocaine for third molar surgery was analysed and it was found that there was no difference between the two tested anesthetic solutions[56]. In a study evaluating the periods of latency and duration of 4% articaine and 2% lidocaine (with 1:100,000 epinephrine) it was seen that articaine had a prolonged duration only about 45 seconds more than lidocaine which was statistically insignificant, thus concluding that there was no difference between the two drugs in terms of latency and duration[54].Martinez Rodriguez also showed both articaine and lignocaine have similar properties for use in surgery and have good safety and tolerability[57].A randomised controlled trial evaluated lignocaine and mepivacaine for mandibular third molar surgery and found no difference between the two drugs[58]. In a randomised trial it was shown that centbucridine produced longer duration of anesthesia compared to lignocaine, however producing no clinical significance[59]. A study by Ebenezer et al[60] comparing lignocaine and bupivacaine in dentistry concluded that bupivacaine has a slower onset of anesthesia compared to lignocaine. They also concluded that lignocaine is the preferred local anesthetic agent in dentistry. Studies have shown that a buccal infiltration of 2ml lignocaine is sufficient for extraction of permanent maxillary tooth stating that lignocaine can diffuse through the porous maxillary bone and anesthetise the palatal mucosa[61,62].

METHODS OF IMPROVING THE EFFICACY OF LIGNOCAINE

Various methods have been employed to improve the efficacy of lignocaine such as warming the solution, adding a vasoconstrictor, buffering agent or steroids. In a double blind study, Gupta et al used sodium bicarbonate with lignocaine and 1:80,000 epinephrine and showed that sodium bicarbonate increases the pH of the solution and making it more effective in an acidic medium such as a peri-apical infection[63]. A mixture of 1.8 ml 2 % lignocaine with 1:200,000epinephrine and 1 ml of 4 mg dexamethasone called twin-mix was used in a randomised clinical trial and the results showed the addition of dexamethasone to the local anesthetic solution significantly improves the latency and duration of soft tissue anesthesia[64].Wolf et combined 0.5M mannitol with lignocaine and epinephrine in a clinical study and it was shown that adding

0.5 M mannitol significantly improved the effectiveness of anesthesia[65].

Safety level of lignocaine

Ezmek et al compared the hemodynamic effects of lignocaine without vasoconstrictor in hypertensive patients and showed it is a safe anesthetic solution[66]. Vasconcellos analysed the influence of local anesthetics with 1:100,000 adrenaline in basic vitals and showed lidocaine to be safe[67]. Anesthetics such as articaine and prilocaine have more reports of toxicity, the most common being the paresthesia of lip[68].

CONCLUSION

Even with the advent of newer anesthetic agents, lignocaine has a good margin of safety particularly in cardiovascular patients. Its efficacy in dental extractions is comparable with any potent local anesthetic and therefore an effective drug in dental extractions with higher safety margin.

CONFLICT OF INTEREST

Conflict of Interest: Conflict of interest declared none.

REFERENCES

1. Oliveira PC, Volpato MC, Ramacciato JC, Ranali J., Articaine and lignocaine efficiency in infiltration anaesthesia: a pilot study. Br Dent J,197 (1):45-6,(2004).
2. Ball C, Westhorpe R, Ball C, Westhorpe R., Local anesthetics—the introduction of xylocaine into clinical practice. Anaesth Intensive Care, 32(6):733, (2004).
3. Jeske AH., Xylocaine: 50 years of clinical service to dentistry. Tex Dent J, 115(5) 9-13,(1998).
4. Covino BG, Vassalo HG., Local anesthetics: mechanisms of action and clinical use, New York, Grune & Stratton,(1976)
5. Becker DE, Reed KL., Essentials of Local Anesthetic Pharmacology. Anesth Prog, 53(3): 98–109(2006)
6. Blair MR., Cardiovascular pharmacology of local anesthetics, Br J Anaesth, 47(suppl):247-252,(1975).
7. Arthur GR: Pharmacokinetics of local anesthetics. Local anesthetics: handbook of experimental pharmacology, vol 81, Berlin, Springer-Verlag,(1987).
8. Thomson PD, Melmon KL, Richardson JA, Cohn K, Steinbrunn W, Cudihee R, Rowland M., Lidocaine pharmacokinetics in advanced heart failure, liver disease, and renal failure in humans. Ann Intern Med 78(4):499-508,(1973).
9. Moore PA., Bupivacaine: a long lasting local anesthetic for dentistry. Oral Surg, 58(4):369-74(1984).
10. Sisk.,Vasoconstrictors in Local Anesthesia for Dentistry,Anesth Prog, 39(6):187-193(1992).
11. Gangarosa LP, Halik FJ., A clinical evaluation of local anesthetic solutions containing graded epinephrine concentrations. Arch Oral Biol,12(5):611-621(1967).
12. Jastak JT, Yagiela JA., Vasoconstrictors and local anesthesia: a review and rationale for use. J Am Dent Assoc,107(4):623-630,(1983).
13. Bulbring E, Wajda J., Biological comparison of local anesthetics. J Pharmacol Exp Ther,85:78-84,(1945).
14. Luduena FP., Effect of some vasoconstrictors on intradermal anesthesia. J Dent Res,39:947-954, (1960).
15. Aberg G., Studies on the duration of local anesthesia: apossible mechanism for the prolonging effect of "vasoconstrictors" on the duration of infiltration anesthesia. Int J Oral Surg,9(2):144-147, (1980).
16. Sveen K., Effect of the addition of a vasoconstrictor tolocal anesthetic solution on operative and postoperative bleeding, analgesia and wound healing. Int J Oral Surg, 8(4):301-306, (1979).
17. Meyer R, Allen GD., Blood volume studies in oral surgery: I. Operative and post-operative blood losses in relation to

vasoconstrictors. J Oral Surg, 26(11):721-726,(1968).
18. Davenport RE, Porcelli RJ, Iacono VJ, Bonura CF, Mallis GI, Baer PN., Effects of anesthetics containing epinephrine on catecholamine levels during periodontal surgery. J Periodontol, 61(9):553-814,(1990).
19. Niwa H, Sugimura M, Satoh Y, Tanimoto A., Cardiovascular response to epinephrine-containing local anesthesia in patients with cardiovascular disease. Oral Surg Oral Med Oral Pathol Oral Radiol Endod,92(6): 610-6,(2001).
20. Cioffi GA, Chernow B, Glahn RP, Terezhalmy GT, Lake CR., The hemodynamic and plasma catecholamine responses to routine restorative dental care. J Am Dent Assoc, 11:67-70,(1985).
21. Laragnoit AB, Neves RS, Neves IL, Vieira JE., Locoregional anesthesia for dental treatment in cardiac patients: a comparative study of 2% plain lidocaine and 2% lidocaine with epinephrine(1:100,000). Clinics (Sao Paulo), 64(3):177-82,(2009).
22. Kabambe WM, Rood JP, Sowray JH., A comparison of plain 2 per cent lignocaine and 2 per cent lignocaine with adrenaline in local analgesia for minor oral surgery. J Dent,10(2):136-9,(1982).
23. Sakura S, Sumi M, Morimoto N, Saito Y., The addition of epinephrine increases intensity of sensory block during epidural anesthesia with lidocaine. Reg Anesth Pain Med,24(6):541-6,(1999).
24. Rosenberg PH,Veering BT, Urmey WF., Maximum Recommended Doses of Local Anesthetics: A Multifactorial Concept. Reg Anesth Pain Med,29(6):564-75,(2004).
25. Stanley F Malmed., Handbook of Local anesthesia, 6th edition, Elsevier, 2012
26. KD Tripathi., Essentials of medical pharmacology, 6th edition, Jaypee Brothers Medical Publishers, (2010)
27. Brkovic B, Gardasevic M, Roganovic J, Jovic N, Todorovic L, Stojic D., Lidocaine+clonidine for maxillary infiltration anaesthesia: parameters of anaesthesia and vascular effects.Int J Oral Maxillofac Surg, 37(2):149-55,(2008).
28. Brkovic B, Todorovic L, Stojic D., Comparison of clonidine and epinephrine in lidocaine anaesthesia for lower third molar surgery.Int J Oral Maxillofac Surg, 34(4):401-6, (2005).
29. Patil PM., Patil SP.,Is clonidine an adequate alternative to epinephrine as a vasoconstrictor in patients with hypertension?. J Oral Maxillofac Surg,70(2):257-62, (2012).
30. Bernhard CG, Bohm E, Wiesel T., On the evaluation of the anticonvulsant effect of different local anesthetics. Arch Int Pharmacodyn Ther, 108:392-407, (1956).
31. Julien RM.,Lidocaine in experimental epilepsy: correlation of anticonvulsant effect with blood concentrations. Electroencephalogr Clin Neurophysiol, 34(6):639-645, (1973).
32. Walker IA, Slovis CM., Lidocaine in the treatment of status epilepticus. Acad Emer Med, 4(9):918-922(1997).
33. Marsch SC, Schaefer HG, Castelli I., Unusual psychological manifestation of sysytemic local anesthetic toxicity. Anesthesiology, 88(2): 532-533, (1998).
34. Sugi K., Pharmacological restoration and maintenance of sinus rhythm by anti-arrhythmic agents. J cardiol, 39 suppl 01:59-64, (1999).
35. Alexander JH, Granger CB, Sadowski Z, Aylward PE, White HD, Thompson TD, Califf RM, Topol EJ., Prophylactic lidocaine use in acute myocardial infarction: incidence and outcomes from two international trials. The GUSTO-I and GUSTO-IIb Investigators, Am Heart J,137(5):599-805, (1999).
36. Collinsworth KA, Kalman SM, Harrison DC.,The Clinical Pharmacology of Lidocaine as an Antiarrhythymic Drug. Circulation, 50(6):1217-1230, (1974).
37. American Heart Association: Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation,102:8-149, (2000).
38. Abraham-Inpijn L, Borgmeijer-Hoelen A, Gortzak RA., Changes in blood pressure, heart rate, and electrocardiogram during dental

treatment with use of local anesthesia. J Am Dent Assoc 1988; 116(4):531-536, (1988).
39. Kiyomitsu Y, Sugiyama K, Joh S., The effects of catecholamines added to lidocaine on cardiac function. Anesth Prog, 36(4-5),198-200, (1989).
40. Brand HS, Abraham-Inpijn L., Cardiovascular responses induced by dental treatment. Eur J Oral Sci, 104(3), 245-52, (1996).
41. Chernow B, Balestrieri F, Ferguson CD, Terezhalmy GT, Fletcher JR, Lake CR., Local dental anesthesia with epinephrine. Minimal effects on the sympathetic nervous system or on hemodynamic variables. Arch Intern Med, 143(11),2141-3, (1983).
42. Salonen M, Forssell H, Scheinin M., Local dental anaesthesia with lidocaine and adrenaline. Effects of plasma catecholamines, heart rate and blood pressure. Int J Oral Maxillofac Surg, 17(6),392-4, (1988).
43. Meechan JG, Perry G, Rattray DT, Thomason JM., Effects of dental local anesthetics in cardiac transplant recipients. Br Dent J, 192(3):161-3, (2002).
44. Vanderheyden PJ, Williams RA, Sims TN., Assessment of ST segment depression in patients with cardiac disease after local anesthesia. J Am Dent Assoc,119(3):407-12, (1989).
45. Laragnoit AB, Neves RS, Neves ILI, Vieira JE., Locoregional anesthesia for dental treatment in cardiac patients: a comparative study of 2% plain lidocaine and 2% lidocaine with epinephrine (1:100,000). Clinics, 64(3):177-82, (2009).
46. Blinder D, Manor Y, Shemesh J, Taicher S., Electrocardiographic changes in cardiac patients having dental extractions under a local anesthetic containing a vasopressor. J Oral Maxillofac Surg, 56(12):1399-402, (1998).
47. Salonen M, Forssell H, Scheinin M., Local dental anaesthesia with lidocaine and adrenaline. Effects of plasma catecholamines, heart rate and blood pressure. Int J Oral Maxillofac Surg, 17(6):392-4, (1988).
48. Meechan JG, Perry G, Rattray DT, Thomason JM., Effects of dental local anesthetics in cardiac transplant recipients. Br Dent J, 192(3):161-3, (2002).
49. Kalra P, Rana AS, Peravali RK, Gupta D, Jain G., Comparative evaluation of local anaesthesia with adrenaline and without adrenaline on blood glucoseconcentration in patientsundergoingtoothextractions. J Oral Maxillofac Surg,10(3):230-5, (2011).
50. Haji IU, Siddiq M, Rao S, Rai G, Hiregoudar JS, Pitale U., Study on blood glucoseconcentration in patients with diabetes undergoingdentalextraction under local anesthesia with and without adrenaline.J Basic Clin Physiol Pharmacol., 23(4):169-71, (2012).
51. Sierra Rebolledo A, Delgado Molina E, Berini Aytis L, Gay Escoda C., Comparative study of the anesthetic efficacy of 4% articaine versus 2% lidocaine in inferior alveolar nerve block during surgical extraction of impacted lower third molars.Med Oral Patol Oral Cir Bucal, 12(2):E139-44, (2007).
52. Malamed SF, Gagnon S, Leblanc D., Articaine hydrochloride: a study of the safety of a new amide local anesthetic. J Am Dent Assoc., 2001:132(2), (2001).
53. Vahatalo K, Antila H, Lehtinen R., Articaine and lidocaine for maxillary infiltration anesthesia. Anesth Prog, 40(4):114-6, (1993).
54. Katyal V., The efficacy and safety of articaine versus lignocaine indental treatments: A meta-analysis. J Dent, 38(4): 307 – 17, (2010).
55. Ruprecht S, Knoll-Köhler E., A comparative study of equimolar solutions of lidocaine and articaine for anesthesia. A randomized, double-blind, cross-over study. Schweiz Monatsschr Zahnmed, 101(10):1286-90, (1991).
56. Silva LC, Santos TD, Santos JA, Maia MC, Mendonça CG., Articaine versus lidocaine for third molar surgery:A randomized clinical study. Med Oral Patol Oral Cir Bucal., 17 (1):e140-5, (2012).
57. Martínez-Rodríguez N, Barona-Dorado C, Martín-Arés M, Cortés-Bretón-

Brinkman J, Martínez-González JM., Evaluation of the anesthetic properties and tolerance of 1:100,000 articaine versus 1:100,000 lidocaine. A comparative study in surgery of the lower third molar.Med Oral Patol Oral Cir Bucal, 17(2):e345-51, (2012).
58. Porto GG, Vasconcelos BC, Gomes AC, Albert D., Evaluation of lidocaine and mepivacaine for inferior third molar surgery. Med Oral Patol Oral Cir Bucal., 12(1):E60-4, (2007).
59. Mansuri S, Bhayat A, Omar E, Jarab F, Ahmed MS., A randomized controlled trail comparing the efficacy of 0.5% centbucridine to 2% lignocaine as local anesthetics in dental extractions. Int J Dent., 2011:795047, (2011).
60. Ebenezer V, Balakrishnan R, Rajarajan C, Elumalai M., A comparative study of two local anesthetic agents- bupivacaine and lignocaine in dentistry. Int J Pharm Bio Sci, 4(1):955-959, (2013).
61. Badcock ME, Gordon I, McCullough MJ., A blinded randomized controlled trial comparing lignocaine and placebo administration to the palate for removal of maxillary third molars. Int J Oral Maxillofac Surg., 36(12):1177-82, (2007).
62. Sekhar GR, Nagaraju T, KolliGiri, Nandagopal V, Sudheer R, Sravan., Is palatal injection mandatory prior to extraction of permanent maxillary tooth: a preliminary study. Indian J Dent Res., 22(1):100-2, (2011).
63. Gupta S, Mandlik G, Padhye MN, Kini YK, Kakkar S, Hire AV., Combating inadequate anesthesia in periapical infection with sodium bicarbonate: a clinical double blind study. Oral Maxillofac Surg, Jun 6 (epub ahead of print), (2013).
64. Bhargava D, Sreekumar K, Rastogi S, Deshpande A, Chakravorty N., A prospective randomized double-blind study to assess the latency and efficacy of Twin-mix and 2 % lignocaine with 1:200,000 epinephrine in surgical removal of impacted mandibular third molars: a pilot study. Oral Maxillofac Surg., 17(4):275-80, (2013).
65. Wolf R, Reader A, Drum M, Nusstein J, Beck M., Anesthetic efficacy of combinations of 0.5m mannitol and lidocaine with epinephrine in inferior alveolar nerve blocks: a prospective randomised, single-blind study. Anesth Prog., 58(4):157-65, (2011).
66. Ezmek B, Arslan A, Delilbasi C, Sencift K., Comparison of hemodynamic effects of lidocaine, prilocaine and mepivacaine solutions without vasoconstrictor in hypertensive patients. J Appl Oral Sci., 18(4):354-9, (2010).
67. Vasconcellos RJ, Vasconcelos BC, Genú PR., Influence of local anesthethics with adrenalina 1:100.000 in basic vital constants during thirdu molar surgery. Med Oral Patol Oral Cir Bucal., 13(7):E431-7, (2008).
68. Haas DA, Lennon D., A 21 year retrospective study of reports of paresthesia following local anesthetic administration. J Can Dent Assoc 1995; 61(4):319-20, 323-6, 329-30, (1995).