Efficiency of Long Acting Local Anaesthetics: Bupivacaine and Ropivacaine - A Review

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***Abstract*: Two long-acting local anesthetics, bupivacaine and ropivacaine, have been added to the dental armamentarium. The efficacies, onset times, durations, and hemostatic characteristics of these agents have been well described for a variety of clinical applications. Assessments of their usefulness in managing postoperative pain following oral surgery, endodontics, and periodontics have also been published. Bupivacaine, a long-acting amide local anesthetic, is a chemical analogue of mepivacaine with high lipid-solubility and protein-binding characteristics. These properties contribute to bupivacaine's greater potency and anesthetic duration as compared to other local anesthetics used in dentistry. The prolonged anesthesia it produces has been shown to limit postoperative pain following third molar extractions and endodontic procedures. Bupivacaine 0.5% with 1:200,000 epinephrine provides a safe and valuable alternative to the anesthetic agents presently available in dentistry. This aspect of bupivacaine is compared to ropivacaine, another long acting local anesthetic of propyl group. This article reviews the clinical utility of these agents and compares there properties.**

***Keywords*: long acting local anesthetics, Bupivacaine, Ropivacaine, Pain, mechanism of action**

INTRODUCTION

Dentistry and pain are often horrifying in the minds of patients, especially those with poor dentition like those who needs to undergo multiple extractions, those having periodontal disease requiring surgery, or symptomatic teeth requiring endodontic therapy. A good dentist according to the members of the public is a practitioner who causes little or no discomfort. In turn, dental practitioners search for and identify a good anesthetic agent as one that allows them to focus solely on operative procedures without distractions from pain induced patient movements. The everyday practice of dentistry is therefore based upon achieving adequate local ee and causing little or no discomfort to the patient.

Pain is a result of stimulation of nociceptors that are receptors preferentially sensitive to a noxious stimulus or a stimulus that will become noxious if prolonged. Pain gets perceived when nociception reaches the cerebral cortex. Interruption of the pathways that carry the information of the stimulus from the periphery of the body to the central nervous system abolishes the pain by blocking

the central nervous system, or by removing the stimulus. Local anesthetics block sensory neuronal conduction of noxious stimuli from reaching the central nervous system.
Pain control through truncates block of the inferior alveolar nerve is one of the locoregional anesthetic techniques most widely used in oral surgery, affording comfort and safety for both the patient and operator when correctly used.
The choice of anesthetic solution should be based on the three main clinical considerations, which are the anesthetic potency, latency and duration of the anesthetic effect along which the pharmacokinetics and toxicity of the drug also acts as a major clinical considerations for the selection of anesthetic.
IN ORAL SURGICAL practice, two long-acting anesthetics are used: bupivacaine (Marcaine) and etidocaine (Duranest). The application of long-acting anesthetic for infiltrative anesthesia enables painless stomatological and surgical work in the mandibular; on the other hand, it is not the case with the maxilla, and the data indicate that bupivacaine with adrenaline enables shorter anesthetic periods in comparison to lidocaine and adrenaline when they are used for the anesthesia of tooth pulp cavity.(1)
The current article helps in the comparison of bupivacaine and rupivacaine.

BUPIVACAINE

This long-acting agent plays a significant role in the overall management of postoperative pain associated with dental care. Because of its higher solubility in lipids and higher binding ability to proteins, bupivacaine has a longer duration of action than lidocaine, which is the gold standard all new local anaesthetics are compared with. (2) In addition, bupivacaine provides soft tissues, bones and pulp with relatively rapid and profound anaesthesia and therefore is widely used in dental treatments such as endodontic therapies, tooth extractions and dental surgery.
Until the beginning of the twentieth century, cocaine was the drug of choice for surgical and dental pain control despite its significant limitations such as its low therapeutic index, the risk of addiction and potentially lethal arrhythmias. In 1904, after its synthesis by Alfred Einhorn procaine became the main local anesthetic in medicine and dentistry. Because of the long latency period of procaine and allergies to ester anesthetics, lidocaine, the first amide anesthetic, quickly became the gold standard after its synthesis in 1943 by Nils Löfgren. Other amide anesthetics have subsequently been introduced (3,4). Bupivacaine was developed in 1957 by Ekenstam, Egner and Pettersson. Widman described its clinical uses in 1964, and in 1983 it became commercially available in dental cartridges. It is a powerful amide anesthetic, with intermediate onset of action and long duration, allowing a slow return to normal sensation, which has been associated with a corresponding gradual onset of pain.
It has been suggested that long-acting local anesthetics such as bupivacaine, could provide additional analgesia time known as "residual analgesia" and minimize the duration of postoperative pain, facilitating postoperative care and maintenance of proper oral hygiene. Its main indications are lengthy procedures and postoperative pain management. Levobupivacaine, the S-enantiomer of bupivacaine, is a new anaesthetic agent and is thought to have a better safety profile and equivalent efficacy compared with racemic bupivacaine. (5,6)

Mechanism of action

The inward flow of sodium ions are obstructed by these anesthetics through. The nerve membrane, thus preventing the generation of an action potential. Competitive binding to calcium sites is postulated to occur in the external lipid layer of the nerve membrane with resultant secondary interference of mobile phosphate groups. Reconfiguration of molecular membrane from sodium impermeable (resting state) to sodium permeable (active state) is prevented due to the blockage of passage of sodium ions. The increased duration of action of bupivacaine is ascribed to its affinity for nerve tissues (7).
Local anesthetics that are attracted more strongly to plasma protein tend to have longer durations of action than those that are less strongly attracted. Soft tissue anesthesia after bupivacaine with epinephrine varies from 5to9 hr, approximately 2to3 times longer than anesthesia after lidocaine with epinephrine (8).
Following oral surgical procedures, the period of time before the onset of pain is significantly longer for bupivacaine with epinephrine when compared to lidocaine with epinephrine. Onset of postoperative pain is usually noted before soft tissue sensation returns to normal. All reported clinical trials of bupivacaine in oral surgery for third molar extraction have confirmed the safety and efficacy of the drug (9,10) Clinical trials of bupivacaine in endodontic procedures have also reported the effectiveness of this local anesthetic agent. Bupivacaine provides a relatively rapid onset, profound soft tissue, bone, and pulpal anesthesia, and prolonged duration after mandibular or other nerve block anesthesia.

Clinical Effectiveness

Effectiveness of bupivacaine is evaluated by toxicity to potency ratio, latency of onset, degree of sympathetic, sensory, and motor block, duration of analgesia, and regression time. Statistical data and clinical results are inseparably related to the vascularity of the area of injection and the concentration and quantity of the agents used.
Sympathetic fibers are more easily blocked than sensory or motor fibers. Sympathetic blocks may manifest themselves in clinical phenomena as Horner's syndrome (11) or hypotension. Bupivacaine blocks sympathetic fibers more effectively than rupivacaine.

ROPIVACAINE

One of the lesser known anesthetic in dentistry but which is well known and used in other medical areas. Ropivacaine is structurally related to Bupivacaine and is a long-acting regional anaesthetic. Unlike Bupivacaine, which is a racemate, ropivacaine is a pure S(-) enantiomer, developed for the purpose of reducing potential toxicity and improving relative sensory and motor block profiles. Bupivacaine was noted to be associated with cardiac arrest, particularly in pregnant women after which ropivacaine was developed to compensate bupivacaine s contraindications. Ropivacaine has been introduced and used in surgery, gynecology and obstectics

due to its positive clinical profiles, such as long duration of action, low toxicity and selective ness for nerve fibers responsible for pain transmission rather than motor function.
It is one of a group of local anaesthetic drugs, the pipecoloxylidides (12,13), which were first synthesized in 1957. Mepivacaine and bupivacaine are both well known members of this group and have been in clinical use for more than 30 years.

Mechanism of action
Ropivacaine blocks impulse conduction in nerve fibers by causing reversible inhibition of sodium ion influx. This action is potentiated by dose-dependent inhibition of potassium channels.[14] Ropivacaine less likely to penetrates large myelinated motor fibres as it is less lipophilic than bupivacaine; therefore, it has selective action on the pain-transmitting A β and C nerves rather than Aβ fibres, which are involved in motor function.

Stereoselective properties of ropivacaine,[15] contributes to having a significantly higher threshold for cardiotoxicity and CNS toxicity than bupivacaine in animals [16] and healthy volunteers but ropivacaine is less lipophic when compared to bupivacaine. Ropivacaine interferes with the metabolism of commonly available medications such as fluvoxamine, theophylline, cimetidine and imipramine, as it gets metabolized by the cytochrome oxidase liver enzymes subcategory 1A2.
The lower lipophilicity of ropivacaine versus bupivacaine correlated with the lesser cardio depressant effects of both ropivacaine isomers than of the bupivacaine isomers in animal studies.[17]
A strict correlation exists between the lipid solubility of the local anaesthetic and its potency and toxicity. According to minimum local anaesthetic concentration (MLAC) studies, which are based on effective analgesia in 50% of patients) ropivacaine is less potent than bupivacaine and levobupivacaine at lower doses, whereas ropivacaine has similar potency to bupivacaine at higher doses, such as those used for epidural or intrathecal analgesia. Providing anaesthesia or analgesia for the majority of patients is more clinically relevant than the MLAC and, at higher doses used in clinical practice, this potency difference is not always evident.(18,19)

Comparison
Ropivacaine is the first produced pure enantiomer and a long-acting amide local anaesthetic agent. Similar effects are produced by ropivacaine as to other local anaesthetics via reversible inhibition of sodium ion influx in nerve fibres. Ropivacaine is a propyl group and bupivacaine a butyl group on the piperidine nitrogen atom of the molecule. Ropivacaine is less lipophilic when compared to bupivacaine and so it is less likely to penetrate large myelinated motor fibres, resulting in a relatively reduced motor blockade (20). Ropivacaine, theoretically could be used without vasoconstrictors like adrenaline. It has approximately 70 to 75 percent greater safety margin than bupivacaine. 0.5% ropivacaine has a maximum dosage of 200mg for minor nerve blocks and infiltration, in contrast to bupivacaine, which has a maximum dose of 90mg. But ropivacaine is not available in dental cartridges. Thus, ropivacaine has a greater degree of motor sensory differentiation, which could be useful when motor blockade is undesirable. The decreased potential for central nervous system toxicity and cardiotoxicity is associated with the reduces lipophilicity property of ropivacaine. The drug displays linear and dose proportional pharmacokinetics when administered intravenously up to 80 mg. It is metabolised extensively in the liver and excreted in urine(21).

CONCLUSION
Long acting local anesthetics are very essential for the suppression of the intraoperative pain. Long acting local anesthetics delays the onset of post operative pain and also reduces the intensity of postoperative pain that does occur after some time. Bupivacaine has the most significanct depressant and dysrythmogenic effects on the cardiovascular system. Ropivacaine may be effective for prolonged anesthesia and postoperative analgesia without the need for added vasoconstrictor. According to the collected data, ropivacaine has a greater degree of motor sensory differentiation when compared to bupivacaine.

REFERENCES
1. Maki Mizogamia*, Hironori Tsuchiyab, Jun Haradaa. Membrane effects of ropivacaine compared with those of bupivacaine and mepivacaine. Fundamental & Clinical Pharmacology 16 (2002) 325–330.
2. Anna Trullenque-Eriksson 1, Blanca Guisado-Moya. Comparative study of two local anesthetics in the extraction of mandibular third molars: Bupivacaine and articaine. Med oral Pathol med buccal, 2011. May 16 (3). e390-6.
3. Jastak J.T., Yagiela J.A., Donaldson D. Local Anesthesia for the Oral Cavity. W.B. Saunders, Philadelphia, USA. 1995. 3 Polley L.S., Columb M.O., Naughton N.N. et al. Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: implications for therapeutic indexes. Anesthesiology (1999) 90 944–950.
4. RituBahl. Local anesthesia in dentistry.American Dental Society of Anesthesiology. 51:138-142 2004.
5. Rosenberg ES.A computer-controlled anesthetic delivery system in a periodontal practice: patient satisfaction and acceptance. J Esthet Restor Dent. 2002;14:39-46.
6. Kraft TC, Hickel R. Clinical investigation into the incidence of direct damage to the lingual nerve caused by local anesthesia. J Craniomaxillofac Surg. 1994;22:294-296.
7. Pertl C, Heinemann A, Pertl B, et al. The pregnant patient in dental care. Survey results and therapeutic guidelines.SchweizMonatsschrZahnmed. 2000;110:37-46.
Owen M D, Dean L S. Ropivacaine. Exp Opin Pharmacother 2000; 1(2):325-336.
8. Kennedy M, Reader A, Beck M, Weaver J. Anesthetic efficiacy of ropivacaine in maxillary anterior infiltration. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001:91:406-412.

9. Meechan J G. A comparison of ropivacaine and lidocaine with epineprine for intraligamentary anesthesia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;93:469-473.
10. M. Pooja Umaiyal, Dhanaraj. Long acting local anesthetics in dentistry- a review. International Journal of Current Advanced Research 6(3):2783-2785. 11. Buric N. Ropivacaine as local anesthetic in the surgery of maxillary sinus. Acta Stomatologica Naissi 2003;19:167-172.
12. Markham A., Faulds D. Ropivacaine: a review of its pharmacology and therapeutic use in regional anesthesia. Drugs (1996) 52 429–449.
13. Malamed SF. Local anesthetics: dentistry's most important drugs, clinical update 2006. J Calif Dent Assoc. 2006;34:971-6.
14. Kumar R, Rao SN. Local anaesthetic for minor oral surgical procedures. Review. Indian J Dent Res. 2000;11:163-6.
15.Volpato MC, Ranali J, Ramacciato JC, de Oliveira PC, Ambrosano GM, Groppo FC. Anesthetic efficacy of bupivacaine solutions in inferior alveolar nerve block. Anesth Prog. 2005;52:132-5.
16. Moore PA, Nahouraii HS, Zovko JG, Wisniewski SR. Dental the- rapeutic practice patterns in the U.S. I. Anesthesia and sedation. Gen Dent. 2006; 54:92-8.
17. Malamed SF, Gagnon S, Leblanc D. Efficacy of articaine: a new amide local anesthetic. J Am Dent Assoc. 2000;131:635-42.
18. Malamed SF, Gagnon S, Leblanc D. Articaine hydrochloride: a study of the safety of a new amide local anesthetic. J Am Dent Assoc. 2001;132:177-85.
19. Fernandez C, Reader A, Beck M, Nusstein J. A prospective, ran- domized, double-blind comparison of bupivacaine and lidocaine for inferior alveolar nerve blocks. J Endod. 2005;31:499-503.
20. Nayyar MS, Yates C. Bupivacaine as pre-emptive analgesia in third molar surgery: Randomised controlled trial. Br J Oral Maxillo- fac Surg. 2006;44:501-3.
21. Gregorio LV, Giglio FP, Sakai VT, Modena KC, Colombini BL, Calvo AM, et al. A comparison of the clinical anesthetic efficacy of 4% articaine and 0.5% bupivacaine (both with 1:200,000 epinephrine) for lower third molar removal. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;106:19-28.