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RESEARCH ARTICLE

COMPARISON OF ANESTHETIC EFFICACY OF 4% ARTICAINE WITH 2% LIGNOCAINE IN SURGICAL EXTRACTION OF MANDIBULAR THIRD MOLARS: A DOUBLE BLINDED RANDOMISED CONTROLLED CLINICAL TRIAL

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ABSTRACT

Study Design: A prospective, randomized double-blind clinical trial was conducted (n=100)to compare the anesthetic efficacy of 4% articaine versus 2% lidocaine, with epinephrine 1:100,000, in truncal block of the inferior alveolar nerve during the surgical extraction of impacted lower third molars the Department of Oral and maxillofacial surgery at Government Dental College and Hospital, Nagpur, India. Single operator performed surgery on an extemporaneous basis. The study variables were: latency (time to action) and duration of anesthetic effect, the amount of anesthetic solution used, and the need of re-anesthetize the surgical zone. A visual analog scale was used to assess pain during surgery, and thus subjectively evaluate the anesthetic efficacy of the two solutions.

Results: The mean anesthetic latency period for Articaine was found to be short (64.05 ± 10.25secs) as compared to Lignocaine (84.2 ± 10.61 secs) ($p<0.0001$). The duration of anaesthesia was longer for Articaine (275±48.10 mins) as compared to Lignocaine (198.66±39.30 mins) with $p <0.0001$.Subjective intra-operative pain scoring by the patients indicating depth of anesthesia showed no significant differences between the two. There was no significant differences between the need for re-anesthesia with Articaine or Lignocaine ($p= 0.2919$). The duration of onset of post-operative pain was 223.33±29.44 mins and 166.67±32.93 mins for Articaine and Lignocaine respectively, indicating longer anesthetic duration with Articaine ($p<0.0001$). There was no significant difference in pain intensity at different point times between the two groups ($p=0.987$). The post-operative analgesic requirement between two groups at different point times showed a quantitative difference in number of analgesics used after surgery ($p<0.001$) at all period of time, considering both anesthetic solution.

Conclusion: Articaine was found to have longer duration of action than Lignocaine. Thus, adding to the patient comfort after extraction by increasing painless duration. Duration of analgesia was more with Articaine as compared to Lignocaine thus providing a larger pain-free post-operative period for patient after surgical extraction. Artcaine offers better post-operative analgesic effect clinically with a significant reduction in post-operative analgesic requirement as compared to Lignocaine thus increasing the patient comfort after surgical extraction and a faster recovery.

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INTRODUCTION

Nothing that is done by a dentist for a patient is of greater importance than the administration of drug that prevents pain during any dental treatment. Local anesthetics are the safest and the most effective drugs available for prevention and management of pain while performing any dental surgery. Surgical extraction of third molars is the most common surgery performed by an oral and maxillofacial surgeon.

Lignocaine is the time tested local anesthetic used since decades for prevention of pain because of its pharmacokinetic characteristics and low toxicity compared with ester type anesthetics which increases its value from safety point of view. Its potency is considered as a standard for comparison with other local anesthetics. Articaine hydrochloride (3-*N*-Propylamino-proprionylamino-2-carbomethoxy-4-methylthiophene hydrochloride) synthesized by H. Rusching *et al*., in 1969

is a unique amide local anesthetic which contains both amide and ester group. The drug is widely used in Germany, Europe, Canada and United States. Use of Articaine is still limited in developing countries like India. Unique pharmacological characterstics of this drug are responsible for its main clinical advantages like longer duration of action, greater potency, superior diffusion and dual metabolism. (Malamed *et al.,* 2000) Most studies comparing Articaine with Lignocaine are concerned with root canal surgery. There are limited number of blinded controlled clinical trial comparing Articaine with Lignocaine in third molar surgery. (Tortamano *et al.,* 2009; Bigby *et al.,* 2006) Present study compares the anesthetic efficacy of 4% Articaine versus 2% Lignocaine in surgical extraction of symmetrically impacted mandibular third molars.

MATERIALS AND METHODS

Present study was designed as a prospective double blinded randomized controlled clinical trial. The study was blind to both the patients and operator. Single operator enrolled for Masters course in Oral and maxillofacial surgery at Government Dental College and Hospital, Nagpur, India conducted the present study on 100 patients, having bilaterally symmetrical impacted mandibular third molars over a period of 24 months from December, 2011 to December, 2013 after obtaining approval from institutional ethical committee of Government Dental College and Hospital, Nagpur, India. Orthopantomograms were taken to ensure the similarity of tooth inclinations and angulations (Winter's Classification for angulation and Class A or B and Position 1 or 2 as per Pell and Gregory classification (Yuasa *et al.,* 2002).

***Inclusion criteria*:** The following inclusion criteria were considered:

- Healthy subjects without systemic disorders or allergy to local anesthetics,
- Above 18 years of age,
- Having bilaterally symmetrical impacted mandibular third molars.

***Exclusion criteria*:** The following exclusion criteria were considered:

- Existence of acute swelling or infection at the time of surgery,
- Subjects in which surgical procedure lasted for more than 60 minutes and
- Subjects who have taken NSAIDs or any other analgesic drug within 24 hrs before administration of study medication.

Written informed consents were obtained from all the selected subjects. All subjects were explained visual analogue scale for evaluating intra-operative and postoperative pain. The choice of first site to be operated and the group of anesthetic solutions to be used had been randomly distributed, after a random drawing using flip coin method. Departmental staff nurse prepared two syringes, 1.8ml each, of each local anesthetic solution and labeled them as solution 'A' or solution 'B' depending on the local anesthetic used. Two distinct local anesthetic solutions have been used i.e., 4% Articaine with 1:100000 adrenaline (Septodont company under the brand name Septanest SP) and 2% Lignocaine with 1:100000 adrenaline (Pharmcaine A Pharmax India Pvt Ltd). Third molar surgery was performed on day care basis, with a minimum washout period of one month between operations.

Injection site was prepared by painting the site with antimicrobial solution. Direct technique of inferior alveolar nerve block was performed following standard anatomical landmarks. 1.8 ml of anesthetic solution was administered to block inferior alveolar and lingual nerve using 1 $^{5/8}$ inch 25 gauge needle. Once the first signs of labial numbness appeared, long buccal nerve was anesthetized by administering 0.5ml from second syringe. After injecting anesthetic solution, time of onset of anesthesia was recorded (time elapsed from full needle withdrawal until the patient referred first evidence of Vincent's sign (Sierra Rebolledo *et al.,* 2007). Duration of anesthesia was calculated by recording the time of injection and patient reporting loss of numbness over lower lip or tip of tongue.

Same operator performed two extractions in same patient at different period of time to minimize the bias associated with surgical skill. When ostectomy and tooth sectioning were performed on one side, the other side received the same treatment in order to standardize the procedure. Subjects were also asked to rate the intra-operative pain on visual analogue scale of 0 to 100mm. According to Collin's *et al.,* (1997) if a patient records baseline VAS score in excess of 30mm they would probably have recorded atleast moderate pain on a 4 point categorical scale; in excess of 54mm then they would have recorded severe pain. Using the VAS and the correlation with a 4-point categorical scale, we determined four types of pain intensity: slight, moderate, intense and worst pain. Based on this we considered less than 30mm as a slight pain, ranging from 30mm to 45mm as a moderate pain, ranging from 45mm-54mm as intense pain and over 54mm as worst pain. Patients were asked to rate their pain intensity during ostectomy or odontectomy to subjectively assess the depth of anesthesia. Any necessity to re-anesthetize the surgical zone by infiltration was also recorded. At the end of each surgical procedure, patients received ten 50mg Diclofenac sodium tablets as supporting analgesic medication for use in case of pain, with instructions to write down the amount and the time when the medication was consumed. Time of onset of post-operative discomfort or pain was also recorded. All patients were given a chart containing visual analogue scale in their case report forms (CRF) and explained about the same, for evaluating postoperative pain in the intervals of 2,4,8,12 and 24 hours postoperatively. Statistically, overall descriptive results were expressed as mean values ± standard deviation. Statistical analysis of the results was carried out with unpaired T test, Chi-square test and two way repeated measure analysis of variance (ANOVA) test using STATA version 10.0 software.

RESULTS

Out of 100 subjects, 8 were excluded from the study due to the following reasons:

- 2 due to excess surgical time of more than 60 minutes,

- 2 due to development of paresthesia of inferior alveolar nerve,
- 1 because of development of severe post-operative pain and swelling requiring IV analgesic administration, and
- 3 due to voluntary dropout from the study.

Overall 92 subjects with 184 interventions, 92 with 4% Articaine and 92 with 2% Lignocaine were included in the study. The reasons for extraction were: recurrent pericoronitis (mostly), prophylactic, prosthetic, periodontal and orthodontic reasons. The mean anesthetic latency for Articaine was 64.05 seconds (SD: 10.25 seconds) versus 84.2 seconds (SD: 10.61) for Lignocaine which showed a highly significant difference with p-value of <0.0001. The mean latency period for Articaine was found to be short as compared to Lignocaine. (Table 1). The mean and standard deviation of duration of anesthesia for Articaine and Lignocaine were 275 minutes (SD: 48.10) and 198.66 minutes (SD: 39.30) respectively, which indicated longer duration of anesthesia with 4% Articaine than 2% Lignocaine with a highly significant p-value of <0.0001. Subjective intra-operative pain scoring by the patients which indicated depth of anesthesia showed no significant differences between the two anesthetic solutions with 80.43 % patients reporting slight pain with Articaine as compared to 73.91% patients with Lignocaine, while 19.57% patients reported moderate pain with Articaine compared to 26.09% patients with Lignocaine with mean VAS scores of 24mm (SD: 8.90) for Articaine and 28mm (SD: 7.97) for lignocaine with p value of 0.2055 which is statistically not significant. Out of total 92 subjects with Articaine re-anesthesia of the surgical zone was necessary in 18 (19.52%) subjects as compared to 24(26.08%) subjects with Lignocaine. The non-parametric Chi-square test revealed no significant differences between the need for re-anesthesia with Articaine or Lignocaine (p value of 0.2919. The mean and standard deviation of duration of onset of post-operative pain for Articaine and Lignocaine were 223.33 minutes (SD: 29.44) and 166.67 minutes (SD: 32.93) respectively, which indicated longer anesthetic duration with 4% Articaine than 2% Lignocaine with a highly significant p-value of <0.0001. Two way repeated measure ANOVA was done to examine significant changes in pain at different time points between two groups. There was no significant difference in pain intensity at different point times between these two groups (p value- 0.987). Mean pain intensity score throughout 24 hrs investigation period is shown in Graph 1. To examine the changes in post-operative analgesic requirement between two groups at different point times, two way repeated measure ANOVA was done, which showed a quantitative difference in number of analgesics used after surgery (p value <0.001) at all period of time, considering both anesthetic solution (Graph 2).

DISCUSSION

Using local anesthetics to control a patient's pain is one of the most important factors for successful treatment. Articaine was originally synthesized as Carticaine in 1969 and entered the clinical practice in Germany in 1976. Articaine is unique among available amide local anesthetics because it is based on a thiophene moiety rather than a typical benzene group. Articaine unlike other amide local anesthetics undergoes biotransformation in both liver and plasma, thus cleared from the body quickly (Claffey *et al.,* 2004). Articaine has a reputation of providing an improved local anesthetic effect. The available literature indicates that Articaine is equally effective when statistically compared to other local anesthetics. Articaine is claimed to be superior to Lignocaine, owing to its better diffusion through soft tissue and bone, the rapid onset, the excellent quality of anesthesia and lower degree of the toxicity (Hassan *et al,* 2011). The present randomized, double blind study was done comparing 4% Articaine with 1:100000 epinephrine and 2% Lignocaine with 1:100000 epinephrine for the purpose of evaluating the efficacy of Articaine. Lignocaine was chosen as a reference local anesthetic , as its effect is well documented. Patients were selected randomly for the study. Due to within-subject split mouth study design, the patient constituted his/her own control, the influence of age, sex and weight, as well as other demographic factors, had a little effect on the treatment outcome. Onset and duration must be considered when comparing two or more local anesthetics. An ideal agent should have short onset and should last long enough to allow the completion of the procedure.

Latency (Onset of action) of drug depend upon number of factors both under and not under operator control. Operator control factors are the concentration of drug and the pH of the local anesthetic solution. Factors not under the clinician's control are the diffusion constant (pKa) of the anesthetic drug and the anatomical diffusion barriers of the nerve. Smaller pKa values are associated with shorter latency period. Theoretically, Articaine with pKa value of 7.8 must have shorter latency period as compared to Lignocaine (pKa=7.9). In the present study, latency was measured from the time of full needle withdrawal to the time patient showed symptoms of anesthesia i.e., numbness of lower lip or tongue. The mean induction time for 4% Articaine was found to be 64.05 sec ± 10.25 seconds and for 2% Lignocaine was 84.2 sec ± 10.61 seconds, with the results being statistically significant. Latency of Articaine was 1.3 times shorter as compared to Lignocaine. Shorter latency period of Articaine was found, as compared to studies of (Cowan, 1997) and Malamed (Malamed, 2004), which may be due to differences in method of recording latency. (Cowan, 1997) found the latency of Articaine in application to mandibular block to be 1.48 minutes (Malamed, 2004). According to Malamed *et al*., 2000 (Cowan, 1997) the latency of 4% Articaine in mandibular block was 2-2.30 minutes. Mean latency period reported by Sierra-Rebolledo A. *et al*., 2007 (Claffey *et al.,* 2004) was 56.03 seconds for Articaine versus 75.04 seconds for Lignocaine. Martinez-Rodriguez *et al.,* reported latency period of 1.04 min and 3.75 min respectively for Articaine and Lignocaine. Though their results coincide with our results in establishing latency period between Artcaine and Lignocaine, statistically insignificant differences were found. Duration of action of local anesthetic drug depends upon the degree of protein binding of the drug, vasodilator activity and the presence of vasoconstrictor in the drug. Articaine presents one of the greatest protein binding percentages (95%) of all amide local anesthetics, comparable only to ultra-long acting local anesthetics such as bupivacaine, ropivacaine and etidocaine. This in turn applies a longer duration of anesthetic effect. The duration of action cited for each drug is an approximation. Factors exist that affect both

the depth and duration of anesthesia, either prolonging or decreasing it which includes: individual response to drug, accuracy in deposition of local anesthetic, status of tissue at the site of drug application, anatomical landmarks variation and volume of anesthetic solution used. Deposition of local anesthetic close to the nerve provides greater depth and duration of anesthesia compared with local anesthetic deposited at a greater distance from the nerve to be blocked (Malamed, 2004). The total duration of anesthesia recorded in present study was 275±48.10 minutes for 4% Articaine and 198.66±39.30 minutes for 2% Lignocaine which is statistically significant ($p<0.0001$), showing longer duration of anesthesia for 4% Articaine with 1:100000 epinephrine as compared to 2% Lignocaine with 1:100000 epinephrine. The values are comparable to those reported in literature (Tortamano *et al.,* 2009; Sierra Rebolledo *et al.,* 2005). In contrast to present study, Martinez-Rodriguez *et al*., 2012 found no statistically significant differences in the duration of action between 4% Articaine and 2% Lignocaine , 4hrs 6min ± 2hrs 28min for Articaine compared with 3hrs 33 min ± 2hrs 35min for Lignocaine, though greater duration times were seen for 4% Articaine. In present study, the efficacy of two anesthetic solutions was made by comparing the intra-operative pain on visual analogue scale and need to re-anesthetize the surgical zone during dental surgery, in view of the impossibility of performing an electric pulp stimulus test for the objective of assessment of anesthetic efficacy. Lipid solubility of a local anesthetic appears to be related to its intrinsic potency. Estimated lipid solubility of Articaine and Lignocaine are 17 and 4 respectively. Increased lipid solubility permits the anesthetic to penetrate the nerve membrane more easily and thus increases potency of drug and produces a more effective conduction blockade at lower concentrations (Malamed, 2004).

In our study we observed VAS score between 10-45 for Articaine and 20-45 for Lignocaine. Out of 92 surgical extractions sites injected with 4% Articaine, 74 sites reported slight pain and 18 sites reported moderate pain, whereas 68 sites reported slight pain and 24 sites reported moderate pain with 2% Lignocaine, result being statistically non-significant with ($p =0.2055$). These results are comparable to those obtained in other studies by Malamed *et al*., 2000, Cowan *et al.,* 1977 and Sierra-Rebolledo *et al*., 2007 contrasting the performance of these two local anesthetics. The number of repeated anesthetic procedures was greater when using 2% Lignocaine. With Lignocaine 24 of 92 patients needed re-anesthesia compared to 18 of 92 patients with Articaine. However the difference in the mean frequency for re-anesthesia of surgical zone failed to reach statistical significance. These results are comparable to those obtained by Malamed, 2000 and Sierra-Rebolledo *et al.,* 2007. In theory, pain in the perioperative period represents an operation of multiple mechanisms, including nociceptive transduction, sensitization of peripheral somatic and visceral nociceptive nerve terminals and central neurons, and loss of local and descending inhibition of neurons in the brain stem and spinal cord. In particular, it has been suggested that central neuronal sensitization plays an important role in post-operative pain (Dirks *et al.,* 2002). Gordan *et al*., 1997 in their study showed that administration of long acting local anesthetics block the nociceptive input and decrease the development of central hyperexcitability, resulting in delayed onset of post-operative pain. In present study we found that onset of post-operative pain with 4% Articaine was after 223.33 minutes ± 29.44 min whereas with that of 2% Lignocaine was 166.67 minutes ± 32.93 min, with the results being highly significant ($p<0.0001$). Till now, none of the studies have compared the onset of post-operative pain between Articaine and Lignocaine. Trullenque-Eriksson *et al*., 2011 in their study compared the duration of residual analgesia between Bupivacaine and Articaine and found that duration of residual analgesia was higher for Bupivacaine, although the difference was not statistically significant. Noxious intra-operative inputs that arise from cutting of mucosa, muscle, nerve and bone and post-operative noxious inputs, including those that arise from the inflammatory response and ectopic neural activity in case of post-surgical nerve injury contribute to peripheral and central sensitization. Peripheral afferent neuronal barrage from the tissue injury produces central nervous system hyperexcitability which may contribute to increased post-operative pain. Blockade of afferent neuronal barrage has been reported to reduce pain following some, but not all, types of surgery. Clinical studies suggest that analgesia given before the nociceptive stimuli as more effective than same dose given later and that the effect of pre-emptive analgesia was to prevent or reduce the development of any "memory" of the pain stimuli in the nervous system.

Blockade of sensory input with a long acting local anesthetic reduces post-operative pain after the anesthetic effects have dissipated (Gordon *et al.,* 1997). The lower analgesic requirement is the result of this prevention or reduction in pain memory. In present study, a gradual reduction in pain intensity was identified, as well as in the percentage of patients with post-operative pain. This reduction is justified by the peaks of post-operative pain that generally occur in first 8 hrs which is the period of maximum pain after third molar surgery (Nayyar and Yates, 2006). Clinically, at all periods of time, pain intensity with Articaine was comparatively lower than Lignocaine. Pain intensity after 8 hours was considerably less with Articaine as compared to Lignocaine, however this could not reach to a level of static significance. Our results confirm previous study conducted by Silva *et al*., (2012) that also shows no significant reduction in post-operative pain between 4% Articaine and 2% Lignocaine in surgical extraction of third molars. In general evaluation, the similarity of effectiveness of the anesthetics used in post-operative pain control is well established, being based on the patient's analgesic consumption that presented a significantly different ratio. Mean analgesic consumption for Articaine at 8 hrs was only 1.33 ± 0.48 tablets as compared to 2.13 ± 0.51tablets for Lignocaine group. After 12 hrs the mean analgesic consumption for Articaine was same as that of 8 hrs while that of Lignocaine group increased to 2.40 ± 0.63 tablets and 2.53 ± 0.74 tablets at 12 hrs and 24 hrs respectively. When considering that pain manifests more intensely in first 12 hours with peak generally being observed around 8 hours this affirmation was found valid in this study, since these were the periods of evaluation when higher number of tablets used by the patients, thus coinciding our results with that of Silva LCF *et al*., (19) in terms of peaks in analgesic requirement. However our result contradicts their result, in terms of

quantitative consumption of analgesics, which showed an equivalent ratio in both the tested anesthetic solutions. As per the study, Articaine offers better post-operative analgesic effect clinically with a significant reduction in post-operative analgesic requirement. The reason for this finding is unknown, although it could be due to pharmacodynamic factors specific to the anesthetic (Trullenque-Eriksson *et al.,* 2011). Drug trials of pain controlling drugs are difficult to standardize due to difference in pain threshold of different patients and compliance of patient with visual analogue scale. Further development and refinement of pain measurement techniques will lead to increasingly accurate results.

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