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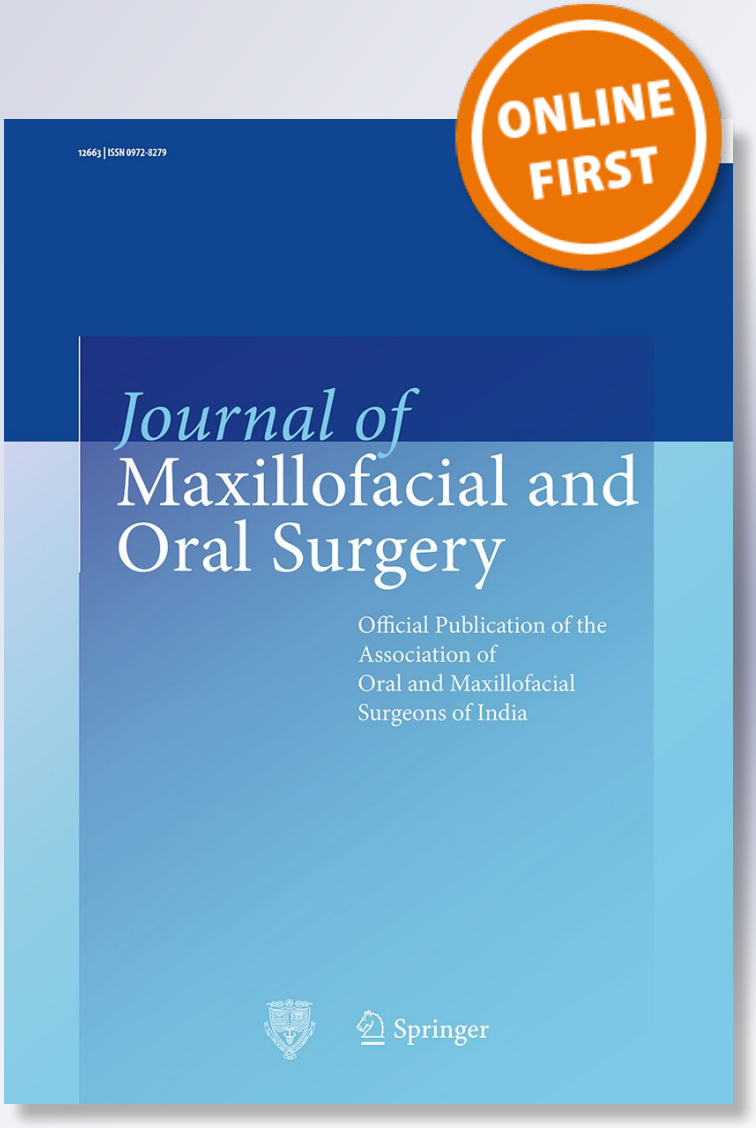

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ORIGINAL ARTICLE

4% Articaine and 2% Lignocaine for Surgical Removal of Third Molar by Mandibular Nerve Block: A Randomized Clinical Trial for Efficacy and Safety

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Abstract

Objective Articaine entered clinical use in 1976; however, evidence basis for articaine's reputation is not entirely clear. The aim of the study is to compare and analyze 4% articaine with 1:100,000 epinephrine and 2% lignocaine with 1:100,000 epinephrine in patients operated for mandibular third molar impaction with respect to efficacy and safety, time of onset and duration of anesthesia and duration of postoperative analgesia.

Methods The study was done on fifty patients requiring surgical extraction of mandibular third molar; randomly divided into two groups of 25 each, receiving 4% articaine hydrochloride with 1:100,000 epinephrine and 2% lignocaine hydrochloride with 1:100,000 epinephrine. Difficulty index for extraction, volume, onset and duration of anesthesia and duration of postoperative analgesia were recorded. Pain was assessed using Heft-Parker VAS. The data were analyzed using appropriate statistical analysis.

Results The mean onset time for articaine and lignocaine is 3.16 ± 0.55 and 3.2 ± 0.48 min, respectively. Articaine group experienced statistically significant longer period of analgesia and duration of action 289.04 ± 40 and 361.88 ± 40 min, respectively, as compared to lignocaine which is 144.2 ± 12 and 197.44 ± 25 min, respectively. No statistical difference between the two groups with regard to pain experience.

Conclusion 4% Articaine is more potent and has longer duration of action with better postoperative analgesia and could be considered as an alternative to lignocaine in clinical practice. With management of postoperative pain being the critical component of patient care, clinical trials are required to develop long acting local anesthetic with increased postoperative analgesia effect.

Keywords 4% Articaine hydrochloride · 2% Lignocaine hydrochloride · Postoperative analgesia

Introduction

Local anesthetics use in dental practice started with discovery of cocaine followed by use of procaine as a safe substitute in 1904 by Alfred Einhorn & Associates [1]. With substantial research interest in finding safer and more effective local anesthetic, lignocaine was synthesized by Swedish chemist Nils Löfgren in 1943 and marketed in 1949 [2].

Their very low rate of allergenicity led to gradual and complete replacement of the ester-based anesthetics in dental use. Since then, other amide local anesthetics like mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine and articaine have been introduced clinically for their favorable onset time and duration [2]. Articaine hydrochloride, originally synthesized as carticaine introduced in 1969 by Rusching et al., has been in clinical use since 1976 [3, 4].

The clinical advantages of articaine include increased liposolubility allowing superior diffusion, increased potency and duration of anesthesia—only surpassed by

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ultra-long acting anesthetics like bupivacaine, etidocaine and ropivacaine which could have severe adverse effect on the central nervous system and cardiovascular system, giving articaine a reputation for providing an improved local anesthetic effect over lignocaine [4]. Comparison studies of articaine with lignocaine date back to 1974 with several studies reporting superiority of articaine. However, the evidence basis for articaine reputation is not entirely clear [1, 5, 6].

Theoretically, postoperative pain control is best achieved by local anesthetic with a more prolonged action. With management of postoperative pain and inflammation as a critical component of patient care, use of anesthetic with longer duration of action is justified. So this clinical trial aims to compare 4% articaine with 2% lignocaine for purpose of evaluating the efficacy and safety in patients operated for mandibular third molar impaction. Lignocaine was chosen as a reference substance, as its effects are well documented.

Materials and Methods

A total of fifty subjects fulfilling the inclusion and exclusion criteria who gave their consent were included in the single-center, randomized controlled, single-operator study design after IRB approval.

Inclusion Criteria Patients requiring surgical removal of impacted mandibular third molars aged 18–30

Exclusion Criteria Medical history suggestive of known or suspected allergies to amide, systemic disease, pregnancy/lactation, subjects who took analgesics 24 h prior and episode of pericoronitis in the past 6 months.

Procedure

Group A: 25 subjects received 4% articaine HCl with 1:100,000 epinephrine
Group B: 25 subjects received 2% lignocaine HCl with 1:100,000 epinephrine

Following intraoral antisepsis with 2% chlorhexidine gluconate, a regional anesthetic blockade (classical inferior alveolar nerve block, lingual nerve block, and long buccal nerve block) with 3 ml of the anesthetic solution and additional amounts as required. Vitals monitored throughout the procedure. Subjective and objective signs assessed and extraction carried out by a standard surgical technique. Patient instructed to take analgesic at the onset of pain and was asked to record the time, and the moment anesthetic effect had worn off.

Parameters Assessed Intra- and *Postoperatively*

Difficulty index assessment: using Pederson's scale [7].
Drug volume: (ml) and any additional injections were recorded.
Duration of the surgical procedure: (min) from time of incision to the last suture placed.
Intraoperative pain evaluation: based on Heft-Parker Visual Analog Scale [8].
Onset of anesthesia: (min) calculated by recording the time of injection, the time when patient first reports numbness of the lower lip and tongue and objectively checked on the attached gingiva with sharp dental probe. Time of soft tissue anesthesia − time of injection = time of onset.
Duration of anesthesia: (min) determined subjectively, patients recorded the time when anesthesia had worn off completely and telephonically informed the operator. Time of loss of numbness − time of injection = duration of anesthesia.
Duration of postoperative analgesia: (min) difference between the end of surgery and the ingestion of the first analgesic tablet for pain relief.

The data were analyzed using Shapiro–Wilk test to compare all the parameters of both the groups and independent *t* test for testing the significant difference between groups.

Results

On compilation of the results, it was seen that out of the 50 patients selected for the study 21 were male and 29 were female with rest of the baseline characteristics as mentioned in (Table 1). The mean operating time in the articaine group was 34.72 ± 7.3 min and lignocaine group was 28.56 ± 5.2 min and with $p = 0.186$ the difference was not statistically significant.

Table 1 Baseline characteristics

Sl no	Parameters	Group	Value
1	Number of patients	Articaine	25
		Lignocaine	25
2	Sex: female/male	Articaine	15/10
		Lignocaine	14/11
3	Age (years)	Articaine	25.12
		Lignocaine	26.08
4	Side: right/left	Articaine	11/14
		Lignocaine	12/13
5	Mean operating time (min)	Articaine	34.72 ± 7.3
		Lignocaine	28.56 ± 5.2

Difficulty Index Assessment Distribution according to difficulty level given by Pederson scale is slightly difficult 34% articaine and 28% in lignocaine, moderately difficult 8% articaine and 16% in lignocaine and very difficult 8% articaine and 6% lignocaine (Fig. 1).

Drug Volume The mean volume of articaine administered was 3.12 ± 0.6 ml, and lignocaine was 3.4 ± 0.37 ml. Though the volume used in articaine group is slightly less, it is not statistically significant. 4% cases of the articaine group required re-injection which was lower than the 16% observed in the lignocaine group.

Time of Onset and Duration of Anesthesia: (Table 2) Though the articaine group has early onset of 3.16 ± 0.55 min as compared to lignocaine 3.2 ± 0.48 min, the data are statistically insignificant with $p = 0.9027$ (Fig. 2). Articaine group experienced statistically significant longer period of duration of action of 361.88 ± 40 min as compared to lignocaine which is 197.44 ± 25 min as $p = 0.00001$ (Fig. 3).

Intraoperative Pain Evaluation: (Table 3) We found VAS scores ranging 0–114, and the overall success rate of treatment is considered 50% with 28% in articaine group and 22% in lignocaine group. Although articaine group found to be superior, it is not statistically significant as $p = 0.994$.

Duration of Postoperative Analgesia Patients who had received articaine experienced a significantly longer period of analgesia about 289.04 ± 40 min as compared to lignocaine which is 144.2 ± 12 min with $p = 0.00001$ (Table 2). The duration of analgesia in the different difficulty index group was noted as mentioned in (Table 4). In slightly difficult and moderately difficult index subgroup, articaine experienced statistically significant longer period of analgesia about 312.88 ± 52 and 236.25 ± 80 min, respectively, as compared to lignocaine which is 138.21 ± 18 and 152.86 ± 20 min. In very difficult subgroup, articaine experienced a longer period analgesia of 240.5 ± 56 min as compared lignocaine which is 149 ± 30 min although statistically insignificant (Fig. 4).

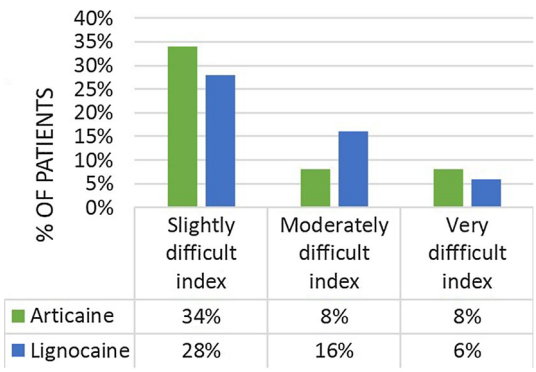

Fig. 1 Distribution of patients in different difficult index group

Adverse Reactions No adverse reactions were reported during the surgery and the first postoperative hour. The most common local complication was trismus in five subjects, three cases of articaine and two in lignocaine group, during the first postoperative week which subsided on its own.

Discussion

Pain is a protective mechanism of the body toward tissue injury by various stimulations, and dental pain is usually originated from acute inflammatory reaction. With varying range of intensity and duration of pain, pain control and reduction techniques have its usefulness justified and are been the subject of continuous research in the field of oral and maxillofacial surgery. The concept of local anesthetic action is based on aborting the generation or conduction of nerve impulses from reaching the brain and hence not interpreted as pain by the patient [9].

The diversity of anesthetic substances currently available in the market requires the need for assessment, from basic properties to clinical characteristics. Among the local anesthetics, lidocaine is the "gold standard," compared to articaine which is recently been considered as an outstanding local anesthetic for dental procedures and control of postoperative pain. Its chemical structure is different from the rest due to substitution of aromatic ring with a thiophene ring making articaine more lipid soluble with potency 1.5 times that of lidocaine which has benzene ring [3]. The reason for instant popularity of articaine is its excellent efficacy reported from dentists worldwide in extraction of molars following infiltration.

In our study, the patient's age, gender were not significantly different among the groups with mean age ranging 25–26 years which can be verified in the majority of comparative studies related to anesthetics and third molar surgery. One major consideration in our study is that efficacy of anesthetic is evaluated using equal volumes rather than equal doses and by the need for re-anesthesia during surgery, in view of impossibility of performing an electric pulp stimulus test for the objective assessment of anesthetic efficacy. Mean volume used in our study correlates with the study of Malamed et al. [10], where he mentioned the dose required to achieve adequate anesthesia was 2–4.2 ml for articaine and 2.6–4.5 ml for lignocaine. We also observed a comparatively low rate of re-injection in articaine although not statistically significant.

Intraoperative profoundness of anesthesia was determined by means of VAS but no statistically significant

Table 2 Comparison of onset, duration of anesthesia and duration of postoperative analgesia of articaine and lignocaine

Parameter	Grps	*N*	Mean (95% confidence interval)	SD	Std. error mean	*df*	*t*	Sig. (2-tailed) *p* value at 0.05
Onset (min)	A[£]	25	3.16 ± 0.55	1.4046	0.2800	24	− 0.124	0.9027
	B[€]	25	3.2 ± 0.48	1.2247	0.244	24		
Duration of anesthesia (min)	A[£]	25	361.88 ± 40	102.05	20.413	24	6.816	0.00001*
	B[€]	25	197.44 ± 25	64.28	12.85	24		
Duration of postoperative analgesia (min)	A[£]	25	289.04 ± 40	102.12	20.42	24	6.771	0.00001*
	B[€]	25	144.2 ± 12	31.75	6.35	24		

*There is significant difference between two groups in case of duration of anesthesia and postoperative analgesia since $p < 0.00001$, $p < 0.00001$, respectively, which is $p < 0.05$

[£]Articaine group

[€]Lignocaine group

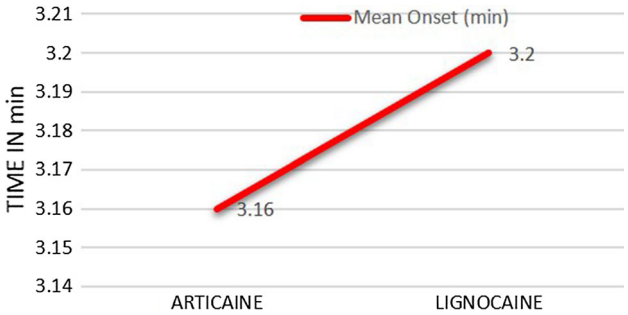

Fig. 2 Graph showing time of onset for the two groups

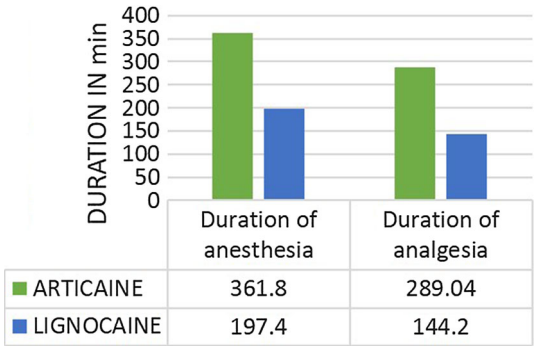

Fig. 3 Graph showing duration of anesthesia and duration of analgesia in the two groups

difference between the scores of the two groups observed [8]. Although the mode of depth of anesthesia analyzed in our study is subjective based, overall success rate of 28 and 22%, respectively, was seen in articaine and lignocaine group which is in accordance with studies performed by other authors like Malamed et al., Kambalimath et al., Rebolledo et al. [4, 10, 11]. On the contrary, an objective-based study performed by Berlin et al. to monitor depth of anesthesia following intraligamentary injections by electric pulp tester, demonstrated equal anesthetic effect for

Table 3 Mean pain ratings for articaine and lidocaine intraoperatively

GROUP	VAS					*p* value*
	None	Faint	Mild	Weak	Strong	
Articaine	14	8	1	1	1	$p > 0.994$
	28.0%	16.0%	2.0%	2.0%	2.0%	
Lignocaine	11	11	1	1	1	
	22.0%	22.0%	2.0%	2.0%	2.0%	

*Since Pearson chi-square p value is 0.994, there is no significant difference between the groups with respect pain

articaine and lignocaine [12]. Thus, the subjective-based evaluation for profoundness is reliable but the measurement is difficult to establish, because of multifactorial variance in perception of intensity, deficiencies regarding understanding and perception of VAS by the patient.

The intrinsic properties of the drug and the anesthetic technique employed influence the onset of action. But, latency is directly proportional to pKa value, with smaller pKa values being associated with shorter latency. Accordingly, 4% articaine (pKa = 7.8) would at least in theory present a shorter latency than 2% lidocaine (pKa = 7.9) [4]. In our study, the articaine group has early onset of 3.16 ± 0.55 min as compared to lignocaine 3.2 ± 0.48 min, though the data are statistically insignificant. Our results coincide with the study of Moore et al. who reported onset time for 4% articaine HCl with 1:100,000 as 4.2 ± 2.8 min but is slightly more than the study by Costa et al. who has found an early onset period of 2.07 min for articaine and 2.18 min for lignocaine when used in maxillary infiltration [4, 13, 14]. This is attributed to the deposition of local anesthetic close to the operative field by infiltration resulting in early onset due to rapid diffusion through bone and soft tissue unlike our study

Table 4 Comparison of duration of postoperative analgesia of articaine and lignocaine in different difficulty index group

Difficulty Idex[¥]	Gps	N	Mean (95% Confidence Interval)	SD	Std. Error Mean	*df*	t	Sig. (2-tailed) *p* value at 0.05
Very difficult	A[£]	4	240.5 ± 56	56.783	28.39	5	2.545	0.051
	B[€]	3	149 ± 30	26.514	15.3			
Moderately difficult	A[£]	4	236.25 ± 80	81.586	40.79	10	2.688	0.022*
	B[€]	8	152.86 ± 20	28.513	10.08			
Slightly difficult	A[£]	17	312.88 ± 52	109.09	20.42	29	5.738	0.000*
	B[€]	14	138.21 ± 18	35.006	9.3557			

*There is significant difference between two groups in case of MD and SD since $p < 0.022$ $p < 0.000$, respectively, which is $p < 0.05$

[¥]Difficulty index based on Pederson difficulty index scale

[£]Articaine group

[€]Lignocaine group

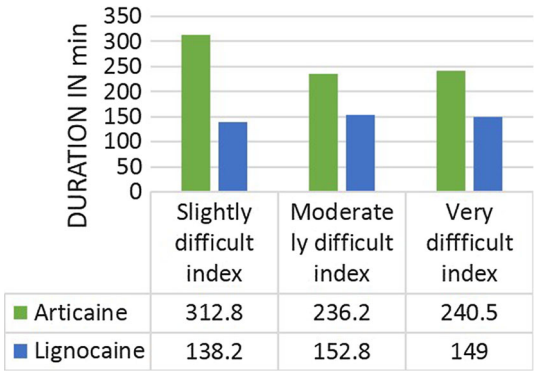

Fig. 4 Graph showing duration of postoperative analgesia in different difficult index subgroup

where the nerve block was assessed. According to other authors like Malamed et al., the reported latency for 4% articaine in mandibular block is 2–2.30 and 2–3 min in the case of lidocaine [15]. Rebolledo et al. reported 0.93 min for articaine versus 1.25 min for lidocaine. The recorded latency was longer in our case as we measured latency from the moment of needle insertion in contrast to investigators like Rebolledo et al. [11] who measured latency from the moment of needle withdrawal from the soft tissues.

The clinical studies suggest that articaine has a longer duration of action only surpassed by ultra-long acting anesthetic like bupivacaine, etidocaine and ropivacaine. Articaine has the greatest protein binding percentage implies to its longer duration of action [4].

In our study, we have a longer duration for articaine, i.e., 361.88 +40 min comparable to study by Costa et al. [14] who found mean duration of 4.28 h in comparison with 3.31 h of lignocaine. Few other studies Kambalimath et al. and Rebolledo et al. also supported the increased duration of anesthesia for articaine about 196.8 ± 57.3 and 220.8 min, respectively [4, 11]. Thus as per review of literature, articaine stands better in duration of action than lignocaine which was true in our study and was statistically evident. Further, the duration of anesthesia cited for each drug is an approximation which is affected by many factors, either prolonging or decreasing it. These factors include individual response to drug, accuracy in deposition of agent, status of tissue at the site of deposition, anatomical variation and volume of anesthetic used. Deposition of local anesthetic close to the nerve provides greater depth and duration of anesthesia as compared to depositing at a greater distance from the nerve to be blocked [6].

Lidocaine, a relatively old local anesthetic, with side effects and safety well documented as compared to articaine. In our study, no systemic adverse reaction observed with both the solution except for local complications, which correlates with the conclusions derived from Kambalimath et al., Shruthi et al., Wenwen et al. who demonstrated that lidocaine followed by bupivacaine was the most often involved local anesthetics in adverse drug reactions with incidence 43.17 and 16.32%, respectively, as compared to 4% articaine which is 3.32%. [4, 6, 16]. Because of insufficient evidence it is hard to believe that the underlying cause for local complication in our study is the type of anesthetic used and hence it could be associated with the operative procedure.

Postoperative pain being an important factor in clinical practise could even discourage patient from seeking treatment. In theory, pain in the perioperative period is due to 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. Dirks et al. [17] suggested that central neuronal sensitization plays an important role in postoperative pain. Gordan et al. [18] 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 postoperative pain.

With peaks of postoperative pain occurring in first 8 and 12 h, the use of local anesthetic solutions with long duration is justified, in an effort to reduce the consumption of analgesic in the postoperative period. In the present study, patients who received articaine experienced a statistically significant longer period of analgesia about 289.40 + 40 min than lignocaine which was 144.2 + 12 min which is comparable to study of Colombini et al. [19] for articaine (198 + 28.86 min) although he compared it with mepivacaine. In the work of Rebolledo et al. [11], it was observed that postoperative pain control was better and satisfactory with articaine. In a comparative study of articaine with lignocaine by Chawla et al. [20], the onset of postoperative pain with 4% articaine was after 223.3 ± 29.44 min which was comparable to our study.

Noxious intraoperative inputs that arise from cutting of mucosa and bone, the inflammatory response, contribute to peripheral and central sensitization. Several studies have found that more difficult procedures were more painful due to the release of more inflammatory factors and proximity to the nerve [21]. Thus, peripheral afferent neuronal barrage from the tissue injury produces central nervous system hyperexcitability inducing early postoperative pain. In the present study, relation of postoperative analgesia with the difficulty index of the extracted tooth was studied. In slightly difficult and moderately difficult index subgroup articaine experienced longer period of analgesia about 312.88 ± 52 and 236.25 ± 80 min, respectively, as compared to lignocaine which was 138.21 ± 18 and 152.86 ± 20 min. Therefore, it was observed that except in very difficult index subgroup articaine has a statistically significant longer analgesia as compared to lignocaine. Although the result was not statistically significant in very difficult index group which was attributed to the lower sample size, the duration of analgesia was more with articaine about 240 ± 56 min when compared to lignocaine which was 149 ± 30 min. To our knowledge, no other studies have demonstrated the relation of difficult index of the tooth to be extracted with postoperative analgesia, so comparison with other studies is not possible.

Articaine being considered as one of the long lasting anesthetic there are others, such as bupivacaine, etidocaine or ropivacaine, with more extended anesthetic effects. Bupivacaine is often chosen in prolonged surgery due to its extensive anesthetic period and reduced analgesic requirements in the early postoperative hours. To our knowledge, only a couple of clinical trials have compared bupivacaine with articaine for lower third molar removal of which study by Gregorio et al. and Puchades et al. stated that in comparison with 0.5% bupivacaine, 4% articaine provided a shorter time of onset and comparable hemostasis and postoperative pain control with a shorter duration of soft tissue anesthesia in lower third molar removal [22, 23]. Puchades et al. observed the longer duration of soft tissue anesthesia of 621.2 min for bupivacaine and 289.6 min for articaine. Therefore, bupivacaine seems to be a valid alternative to articaine, particularly in the prevention of early postoperative pain. But the extended anesthetic effect entailed, nevertheless, prolonged periods of soft tissue numbness, which may be a nuisance posing a greater risk of soft tissue trauma.

Conclusion

In the present study, it was noted that 4% articaine is more potent and has a longer duration of anesthesia and better postoperative analgesia when compared to 2% lignocaine, hence could be considered as an alternative to lignocaine in clinical practice. Research based on these pain control parameters is difficult to standardize, due to the pain threshold of each patient, as well as degree of difficulty of patients to understand the instructions for filling out the questionnaire. Thus, we suggest that further researches with larger samples and double blind studies in other surgical procedures, as well as in medically compromised patients are recommended to demonstrate a satisfactory difference between both the solutions with respect to onset and the relation of postoperative analgesia corresponding to the difficulty index of the tooth extracted so that a newer protocol is developed to provide greater authenticity of this drug in clinical use. The superiority of articaine is most significant and well documented when used during local infiltration anesthesia of maxillary teeth. Hence, studies are to be considered for its use as nerve block in attaining anesthesia for third molar removal.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Standard Ethical approval taken by the Institutional Review Board (IRB No. 2013/P/OS/22).

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