Original Article - Comparative Study

Combination of Articaine and Ketamine V/S Articaine Alone After Surgical Extraction of Impacted Third Molars

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Abstract

Objective: Local anesthetics are the most effective drugs available for the management of pain while performing operative procedures. This study was performed to compare the clinical efficacy of treatment with local anesthetic articaine (4%) with ketamine and local anesthetic articaine alone (4%) for the relief or prevention of postoperative pain, swelling, and trismus after the surgical extraction of impacted mesioangular third molars. **Materials and Methods:** Sixty patients undergoing the extraction of impacted mesioangular mandibular third molars were included in the study. The patients were randomly divided into two groups: local anesthetic alone (LAA) and local anesthetic plus ketamine (LAK). **Results:** Facial swelling following surgery on postoperative days was significantly lower in the LAK group than in the LAA group on 3rd and 7th postoperative days ($P < 0.05$). Mouth opening on the postoperative days was significantly greater in the LAK group than in the LAA group on 3rd and 7th postoperative days ($P < 0.05$). The pain scores on the visual analog scale at 30 min and 1 h, 4 h, 12 h, and 24 h after the surgery were significantly higher in the LAA group than in the LAK group and there was no significant difference in heart rate, oxygen saturation, and blood pressure in both the groups. **Conclusion:** In this present study, the effect of articaine with ketamine in comparison with articaine alone intraoperatively and postoperatively was observed, and it revealed that the combination of articaine with ketamine produced good local anesthesia and provide good postoperative analgesia with less swelling and significantly less trismus.

Keyword: Mesioangular impaction, ketamine, articaine

Introduction

The removal of impacted teeth is one of the most common procedures performed by oral and maxillofacial surgeons. In fact, surgical removal of impacted third molars is associated with a moderate incidence of complications and side effects such as postoperative pain, swelling, and trismus. To increase patient satisfaction after third molar extraction, it is necessary to avoid the discomfort associated with the removal of the tooth and also to decrease the side effects associated with surgery.[1] Alleviation of discomfort postoperatively and efficient local anesthesia are imperative for the success in surgical practice. At suboptimal doses, ketamine has a noticeable analgesic action, which can be used to supplement local anesthesia with minimal side effects.[2] Postoperative pain followed by surgical extraction is one of the most undesirable experiences for a patient and to alleviate this prophylactically, deliberate action should be taken to treat the pain.

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Recently to alleviate postoperative pain, interest has focused on the use of *N*-methyl-D-aspartate (NMDA) receptor antagonists. In particular, ketamine has been thrust into the limelight both as a standalone drug and as an adjuvant to other analgesics (e.g., morphine, fentanyl, and tramadol).[3] Ketamine is an anesthetic agent which acts on the central nervous system and produces dissociative anesthesia. It has

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been found to produce profound analgesia. Local anesthetic combined with suboptimal dose of ketamine for the relief or prevention of postoperative pain, swelling, and trismus after the surgical extraction of third molars was studied, and it showed that this combination produced good local anesthesia while affording a comfortable procedure for the surgeon as well as for the patient and provides good postoperative analgesia with less swelling and significantly less trismus.[4] Ketamine has little impact on the cardiovascular and respiratory function in physiologically compromised populations,[5] but there are very fewer studies on the effect of low dose of ketamine after the removal of third molar.

Ketamine induced decrease in pain signaling systems may represent a common mechanism underlying reduced pain sensitization and opiate tolerance phenomenon. Therefore, ketamine is potentially promising in several perioperative strategies to prevent pathologic pain.[6]

Ketamine is a phencyclidine derivative that provides analgesia at subanesthetic doses. It can be administered intravenously and intramuscularly. Recent advances with respect to understanding the role of the NMDA receptor in the processing of nociceptive input have shown that ketamine is a potential antihyperalgesic that may inhibit C fiber activity, consequently decreasing the acute postoperative pain.[7]

Materials and Methods

After attaining ethical clearance from the institutional review board, a prospective, double-blind, randomized controlled trial was conducted in the Department of Oral and Maxillofacial Surgery of a dental college and hospital, from November 2016 to September 2018. After obtaining proper consent, 60 patients aged between 18 and 50 years with class II position B impacted mandibular third molar were considered for inclusion in the study. The patients were then randomly divided into two groups, namely local anesthetic alone (LAA) (articaine 4%) and local anesthetic (articaine 4%) plus ketamine (LAK) group having 30 patients in each group. All local anesthetic blocks and surgeries were performed by the same surgeon, who was experienced in performing third molar extractions under local anesthesia. Parameters used to appraise the study participants were divided into three types: (a) preoperative, (b) intraoperative, and (c) postoperative. The patients in the LAA group received 5 mL of a local anesthetic and saline combination which comprises 2 mL of local anesthetic and 3 mL of saline; and patients in the LAK group received 5 mL of a articaine, ketamine, and saline combination comprising 2 mL of articaine plus 0.3 mg/kg ketamine and saline. The efficacy of the local anesthetic was assessed by verbal contact and gentle probing of the buccal and lingual surfaces of the third molar. After surgery, the patients were asked to score overall pain on a 10-point visual analog scale (VAS: 0 – no pain; 10 – excessive pain) at 30 min and 1 h, 4 h, 12 h, and 24 h after the surgery. The level of facial swelling was determined by a modification of the tape-measure method described by Gabka and Matsumara preoperatively and 1, 3, and 7 days postoperatively, three measurements were made between five reference points: tragus, soft-tissue pogonion, lateral corner of the eye, angle of the mandible, and outer corner of the mouth. The sum of the three preoperative measurements was considered to be the baseline for that side of the face.

The difference between each postoperative measurement and the respective baseline value indicated the extent of facial swelling on that day. Trismus was evaluated preoperatively and 1, 3, and 7 days postoperatively by measuring the distance between the mesial-incisal corners of the upper and lower right central incisors at maximum opening of the jaws. The difference between the respective postoperative and preoperative measurements indicated the degree of trismus on that day. The level of sedation was also measured using the Ramsay Sedation Scale, cardiac changes were also recorded using electrocardiogram (ECG). Blood pressure (BP) was recorded using sphygmomanometer; heart rate (HR) and oxygen saturation were recorded using pulse oximeter.

Statistical analysis

The results of the clinical examination were recorded on a specific form. The data were subjected to statistical analysis using Chi-square test, repeated ANOVA, Turkey's *post hoc* analysis, independent *t*-test, and SPSS version 21 (Virginia, Newyork, US). The level of significance was concluded at $P < 0.05$.

Results

This study included 60 patients, 28 males and 32 females with a mean age of 31.60 ± 7.03. The mean age in the LAA group is 33.89 ± 8.335, whereas in the LAK group, the mean is 28.575 ± 6.1.

Pain score

Postoperative pain measured on the VAS scale was recorded on 30 min, 1 h, 4 h, 12 h, and 24 h, respectively. The mean VAS score at 30-min postoperative day in the LAA and LAK group was 0.36 ± 0.48 and 0.36 ± 0.48, respectively. Mean VAS score at 1 h in the LAA and LAK group was 0.00 and 0.00. Mean VAS score at 4 h in the LAA and LAK group was 0.04 ± 0.20 and 0.12 ± 0.33. Mean VAS score at 12 h in the LAA and LAK group was 0.72 ± 0.67. Mean VAS score at 24 h in the LAA and LAK group was 1.28 ± 0.67 and 0.80 ± 0.40. The VAS scores were compared using independent *t*-test. The difference reaches the level of significance at 12 h and 24 h where significantly less pain was reported in the group LAK as compared to the group LAA.

Mouth opening

Postoperative mouth opening was measured on the 1st, 3rd, and 7th day, respectively. The mean scores on the 1st day in the LAA and LAK group were 24.36 ± 8.15 and 27.44 ± 6.15, respectively. The mean scores on the 3rd day in the LAA and LAK group were 34.46 ± 5.42 and 39.06 ± 5.01, respectively.

The mean scores on the 7th day in the LAA and LAK group were 35.48 ± 4.02 and 40.18 ± 4.24, respectively. The mouth opening was compared using independent *t*-test. The difference reaches the level of significance at postoperative 3rd day and postoperative 7th day where significantly more mouth opening was reported in the group LAK as compared to the group LAA.

Swelling

Postoperative facial swelling was measured at 1st, 3rd, and 7th day, respectively. The mean scores on the 1st day in the LAA and LAK group were 3.96 ± 0.54 and 3.44 ± 3.66, respectively. The mean scores on the 3rd day in the LAA and LAK group were 2.16 ± 1.47 and 1.01 ± 0.21, respectively. The mean scores on the 7th day in the LAA and LAK group were 1.96 ± 1.43 and 0.9 ± 2.44, respectively. The swelling was compared using independent *t*-test. The difference reaches the level of significance at postoperative 3rd day and postoperative 7th day where significantly less swelling was reported in the group LAK as compared to the group LAA.

Similarly, other parameters, that is, HR, BP, oxygen saturation, and ECG failed to reach the level of significance in both the groups.

Discussion

The key to good oral health is prevention, that is, prevention of problems before they arise. Unfortunately, people who suffer from dental anxiety fail to visit the dentist in time because of fear from surgical removal of an impacted third molar because the surgery is associated with pain and swelling during the postoperative period. Therefore, to increase the patient satisfaction after third molar extraction, it is necessary to avoid the intraoperative and postoperative discomfort associated with surgical removal a tooth.[1]

The addition of ketamine to local anesthetic improves or prolongs pain relief postoperatively because ketamine binds noncompetitively to the phencyclidine binding site of NMDA receptors and modifies them through allosteric mechanisms. When studied at suboptimal doses, its analgesic efficacy correlates well with its inhibitory action on NMDA receptor-mediated pain facilitation and the decrease in activity of brain structures that respond to noxious stimuli.[8] Ketamine also blocks peripheral and human central nervous system sodium channels, as it interacts with mu (m), delta (d), and kappa (k) opioid receptors. Taking into account the beneficial effects of ketamine, this study was conducted to evaluate the postoperative response after the third molar surgery in 6° mesioangular impacted mandibular third molars. Carlton and Coggeshall[9] in their study demonstrated that NMDA and non-NMDA glutamate receptors exist on primary afferent axons and are increased after the induction of inflammation. Low doses of ketamine do not delay regaining consciousness; therefore, low-dose intervenous administration of ketamine in children undergoing tonsillectomy under general anesthesia reduces the postoperative pain.[10]

In the present study, combination of local anesthesia (articaine 4%) with ketamine versus local anesthesia alone (articaine 4%) was used. The age of patients in the study ranges from 18 to 56 years. The mean age was 31.60 ± 7.50 years [Table 1]. Postoperative pain was assessed in both groups using visual analog scale, results evaluated the pain on VAS score during postoperative time at 30 min, 1 h, 4 h, and 12 h; 24 h results suggested pain in the LAA group at 30 min (0.36), at 1 h (0.00), at 4 h (0.04), at 12 h (0.72) in LAA group, at 24 h (1.28) in LAA group and in the LAK group at 30 min (0.36), at 1 h (0.00), at 4 h (0.12), at 12 h (0.44), and at 24 h (0.80) [Table 2]. Difference in pain among both groups was found to be statistically significant. Ketamine group showed less pain at 12 h and 24 h postoperatively as compared to the LAA group ($P < 0.05$). According to the study conducted by Satilmus *et al*.[1] and Hadimane *et al*.,[11] pain was comparatively less with administration of LAK compared to LAA. Postoperative facial swelling was assessed in both the groups using tape-measure method, results suggest that the swelling on the 3rd (1.01 ± 0.21) and 7th day (0.9 ± 2.44) postoperatively was significantly reduced in the LAK group as compared to the LAA group (2.16 ± 1.47) and (1.96 ± 1.43) [Table 3]. Difference in swelling is statistically significant in the LAK group ($P < 0.05$), and the results of our study were in accordance to the study conducted by Gupta *et al*.,[8] Satilmus *et al*.,[1] Gopalraju *et al*.,[12] Garip *et al*.[13] and Yuasa *et al*.[14] and Yildrim *et al*.[15] Explanation for decreased swelling after the administration of ketamine was given by

Table 1: Mean±standard deviation age of study population according to gender

	Mean±SD		
	Group LAA	Group LAK	Total
Males	32.73±9.04	28.67±8.17	30.70±8.61
Females	35.05±7.63	28.48±4.03	31.77±5.83
Mean age (total)	33.89±8.335	28.575±6.1	31.60±7.03

SD=Standard deviation; LAK=Local anesthetic plus ketamine; LAA=Local anesthetic alone

Table 2: Mean and standard deviation of the presence of pain in two groups at different time intervals

Presence of pain	Mean±SD		
	Group LAA		Group LAK
T=30 min	0.36 (0.48)		0.36 (0.48)
t, *P*[b]		0.00, 1.0	
T=1 h	0.00 (0.00)		0.00 (0.00)
t, *P*[b]		-	
T=4 h	0.04 (0.20)		0.12 (0.33)
t, *P*[b]		−1.00, 0.327	
T=12 h	0.72 (0.67)		0.44 (0.58)
t, *P*[b]		−2.281, 0.03*	
T=24 h	1.28 (0.67)		0.80 (0.40)
t, *P*[b]		−4.303, 0.00*	

Significance of *and [b]statistically significant value (P<=0.05) and probability SD=Standard deviation; LAK=Local anesthetic plus ketamine; LAA=Local anesthetic alone

Mazar *et al*.,[16] and he stated that the anti-inflammatory effects of ketamine were mediated by the release of adenosine and adenosine through A2AR reduces the systemic inflammatory response by the inhibition of secretion of pro-inflammatory cytokines as well as leukocyte activation and recruitment. Postoperative trismus was assessed in both the groups, before the surgery and postoperatively on 1st, 3rd, 7th day, results suggest that trismus was significantly reduced on 3rd day (39.06 ± 5.01) and 7th day (40.18 ± 4.24) in group LAK as compared to group LAA [Table 4]. Difference in trismus was statistically significant with *P* value at 3rd day (*P* = 0.048) and 7th day (*P* = 0.006). There is a strong correlation between postoperative pain and trismus, indicating that pain may be one of the principal reasons for the limitation of opening after the removal of impacted third molars.[13] Hence, decreased pain in the ketamine group could be the reason for less trismus postoperatively. A similar study was conducted by Satilmis *et al*.[1] 2009 on 50 patients and found that pain on VAS score, facial swelling and trismus reduced postoperatively significantly after the administration of ketamine, and our results were in accordance to this study. The mouth opening on the postoperative days was significantly greater in the ketamine group than in the local anesthetic group. Postoperative and intraoperative oxygen saturation was assessed in both the groups using pulse oximeter, but no statistically difference was obtained. Postoperative and intraoperative systolic and diastolic BPs were assessed in both groups using sphygmomanometer, but results were inconclusive. Sheth *et al*. 2018[17] studied the effect of ketamine on HR and BP during Rapid Sequence Intubation (RSI) and found that higher doses (>200 mg) and moderately high doses (151–200 mg) of ketamine was more associated with hypertension than lower doses. Patients who received ketamine doses >150 mg were 1.3 times more likely to develop hypotension or hypertension after ketamine administration when compared to patients who received doses <150 mg; However, the results of this study are similar to the results of present study. Therefore, we can conclude that ketamine at lower doses does not alter hemodynamic stability. According to the study conducted by Jaikaria *et al*.[18] 2018, low dose of ketamine has mild effect on HR, oxygen saturation, and BP and as compared to our study, suboptimal dose of ketamine has very low effect on HR, BP, and oxygen saturation. In this study, almost all the vital parameters had been taken into considerations, and the findings shows that the combination of local anesthetic and ketamine enhances the duration of action and reduces the pain on 12 h and 24 h significantly and also facial swelling, and trismus also reduced on the 3rd and 7th day postoperatively without any major influence on cardiovascular system when used as an adjunctive to articaine while disimpaction of mandibular third molars.

Table 3: Mean and standard deviation of mouth opening in two groups

	Mean±SD		*t*	*P*[b]
	Group LAA	Group LAK		
1st postoperative	24.36±8.15	27.44±6.15	0.698	0.492
3rd postoperative	34.46±5.42	39.06±5.01	−0.62	0.048*
7th postoperative	35.48±4.02	40.18±4.24	−0.133	0.006*

*Statistically significant value (*P*<=0.05). SD=Standard deviation; LAK=Local anesthetic plus ketamine; LAA=Local anesthetic alone

Table 4: Mean and standard deviation of swelling in two groups

	Mean±SD		*t*	*P*[b]
	Group LAA	Group LAK		
1st postoperative	3.96±0.54	3.44±3.66	−1.00	0.298
3rd postoperative	2.16±1.47	1.01±0.21	1.093	0.013*
7th postoperative	1.96±1.43	0.9±2.44	−2.094	0.041*

*Statistically significant value (*P*<=0.05) SD=Standard deviation; LAK=Local anesthetic plus ketamine; LAA=Local anesthetic alone

Conclusion

In the present study, we compared the effect of LAK in combination with LAA intraoperatively and postoperatively, and it showed that the combination produced good local anesthesia while affording a comfortable procedure for the surgeon and patient and providing good postoperative analgesia with less swelling and significantly less trismus. Similarly, no effect was observed on HR, BP, and oxygen saturation after the administration of low dose of ketamine.

Hence, the use of low dose ketamine along with local anesthesia is advantageous in all ways, and no side effects were seen when used at a lower concentration.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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