Pre-Emptive Analgesia with Ketamine for Relief of Postoperative Pain After Surgical Removal of Impacted Mandibular Third Molars

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Abstract

Purpose In this study we assessed the clinical efficacy of sub-mucosal injection of ketamine at sub-anesthetic dose of 0.5 mg/kg on post-operative pain, swelling and trismus following surgical extraction of impacted mandibular third molars.

Methods Forty bilaterally symmetrical impacted mandibular third molars in 20 patients who required surgical removal were included in the study. Within the same individual, one of the sites received a test medication whereas the other site was used as control. All patients received nerve blocks with local anesthetic (2 % lignocaine hydrochloride with 1:80,000 adrenaline); the Test group received sub-mucosal infiltration of 0.5 mg/kg of ketamine hydrochloride (without preservative) around the impacted mandibular third molar and along the incision line, while the Placebo group received normal saline infiltration, 10 min before placement of the incision.

Results The pain scores on VAS at 30 min, 1, 4, 12 h and 1 day post-operatively was significantly lower in the Test group than in the Placebo group ($p < .05$). With respect to facial swelling and mouth opening the Test group and

Placebo group showed overall no statistically significant difference ($p > .05$) on the 1st, 3rd and 7th post-operative days.

Conclusion The sub-mucosal injection of 0.5 mg/kg ketamine administered before surgical removal of impacted mandibular third molars was found to be effective in significantly reducing post-operative pain for the first 24 h.

Keywords Ketamine · Pre-emptive analgesia · Postoperative pain · Third molar surgery

Introduction

The surgical removal of impacted teeth is one of the most common procedures performed in the field of oral and maxillofacial surgery. Painless removal of impacted third molar, with least postoperative pain would be ideal situation in minor oral surgery, which most often is never completely achieved in spite of plethora of drugs being used. Postoperative pain can have a negative influence on wound healing. Different strategies have been employed to manage pain, one of which is pre-emptive analgesia.

The concept of pre-emptive analgesia minimizes post-operative pain by preventing central sensitization. Crile [1], who introduced pre-emptive analgesia, advocated the use of regional blocks in addition to general anesthesia to prevent intraoperative nociception caused by changes in the central nervous system during surgery. The revival of this idea was associated with a series of animal studies started by Woolf [2]. They suggested that the administration of opioids or local anesthetics before surgery might reduce the C-fiber-induced injury associated with incision and, thereby, the intensity of postoperative pain.

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Central sensitization due to tissue damage can be inhibited by the presurgical administration of an analgesic. To inhibit postsurgical peripheral sensitization, analgesia is administered again. This is considered to be a successful method for suppressing postoperative pain.

Ketamine is one of the most commonly used *N*-methyl-D-aspartate (NMDA) antagonists in practice which has a regulatory influence on central sensitization [3]. The purpose of the current study is to assess the clinical efficacy of sub-mucosal injection of ketamine, at sub-anesthetic dose of 0.5 mg kg^{-1} , on post-operative pain, trismus and swelling following surgical extraction of impacted mandibular third molars.

Methodology

Following review and approval from the ethical committee constituted in College of Dental Sciences, Davangere, the study was conducted after an informed consent was obtained from the patients. Forty bilaterally impacted mandibular third molars in 20 patients classified by American Society of Anesthesiologists as Grade I or II, requiring surgical removal were included in the study. Patients suffering from systemic diseases such as bleeding and clotting disorders, cardiovascular diseases, hypertension, uncontrolled diabetes mellitus, history of psychiatric illness etc., history of allergy to the drugs used in the study, pregnant or lactating females, patients who did not comply with the instructions and/or requirements of the procedure or missed follow up were excluded from the study.

Twenty patients having bilaterally impacted lower third molars, which were moderately difficult in removal according to Pedersen's difficulty index were included in this double-blind study. Participants were randomly selected, and all of them were assigned to 1 of 2 groups and underwent surgical removal in two sessions. The Test group received sub-mucosal infiltration of a sub-anesthetic dose of 0.5 mg kg^{-1} ketamine hydrochloride (without preservative) around the impacted mandibular third molar and along the incision line, while the placebo group received normal saline infiltration, 10 min before the incision. The syringe containing ketamine/saline was prepared by a nurse and the operator was unaware of what was being administered preoperatively. All surgical removals were performed by the same surgeon, thus providing calibration of the techniques and avoiding confounding discrepancies. The operator, who was blinded to the group assignments, evaluated all the patients.

All patients received nerve blocks with local anesthetic (2 % lignocaine hydrochloride with 1:80,000 adrenaline). To prevent confounding effects, long-acting agents were not used. The surgery was performed by raising full

thickness mucoperiosteal flap, buccal bone guttering followed by odontectomy to deliver the tooth. After extraction of third molar, toileting of the cavity was done and sutured. All patients were kept in the ward for 4 h post operatively and were followed up on the first, third and seventh post-operative day to record the level of discomfort. All the patients were under standard antibiotic coverage for 5 days and were prescribed paracetamol 500 mg thrice daily routinely after surgery as a rescue analgesic. Both the test and placebo group were standardized with same dosage and timing of analgesics post operatively to fulfill the criteria of research methodology. Information regarding following of postoperative instructions and consumption of analgesics was extracted from patients; however the record was taken only verbally. Within the same individual, one of the sites received a test medication whereas the other site was used as control approximately 6 weeks later.

Pain was recorded with Visual Analogue Scale (VAS), 100 mm in length; extreme scores being 'no pain' and 'worst pain imaginable'. Pain was assessed pre-operatively and 30 min, 1, 4, 12 h after surgery and on the 1st, 3rd and 7th postoperative day. This scale was further subdivided into four intervals 0–25 = no pain, 26–50 = mild pain, 51–75 = moderate pain, 76–100 = maximum pain [4, 5].

As no published method satisfies all criteria for assessing facial swelling, we decided to use a measuring tape to measure facial swelling in one-dimension only. Facial swelling was measured using a measuring tape on the 1st, 3rd and 7th postoperative days by a modification of the tape-measure method as described by Schultze-Mosgau et al. [6–8]. Two measurements were made between three reference points: the tragus, pogonion and corner of the mouth. The preoperative sum of the two measurements was considered as the baseline for that side.

Mouth opening i.e. trismus (inter incisal distance) was recorded in millimeters, using a metallic scale preoperatively and on the first, third and seventh postoperative days. The data thus obtained was tabulated and subjected to statistical analysis using SPSS software (version 12; SPSS Inc, Chicago, IL, USA). Unpaired 't' test/ Paired 't' test were used.

Results

This study consisted of 13(65 %) male and 7(35 %) females, age range of patients being 18–31 years. In the Test group, pre-operative mean pain score of 8 ± 11.5 was noted. At 30 min post operatively the mean pain score on VAS was seen to be 8.5 ± 8.1 which corresponds to 'no pain'. At all other times of measurement the difference was statistically significant ($p < .05$). The mean VAS score at 1 and 4 h post operatively was 12 ± 5.2 and 18 ± 6.1

respectively, which relates to ‘no pain’. The mean VAS score at 12 h post operatively and 1st post-operative day was 57.5 ± 5.5 and 64.5 ± 5.1 respectively indicating ‘moderate pain’ and at 3rd post-operative the mean was found to be 30 ± 3.2 relating to ‘mild pain’ (Table 1).

In the Placebo group, pre-operative mean pain score was 6.5 ± 8.1 . At all other times of measurement the difference was statistically significant ($p < .05$). The mean VAS score at 4 h post operatively was 37.5 ± 4.4 pointing to ‘mild pain’; at 12 h post-operatively and 1st post-operative day was 76 ± 5.0 and 80 ± 3.2 respectively showing ‘maximum pain’. 3rd post-operative day showed mean of 31.5 ± 3.6 relating to ‘mild pain’ (Table 2).

On comparison of pain in both the groups it was found that there was statistically significant difference ($p < .05$) at 30 min, 1, 4, 12 h postoperatively and on 1st post-operative day. On the 3rd and 7th post-operative day the difference was not statistically significant ($p > .05$). Thus the Test group showed significantly better results in reduction of post-operative pain when compared to Placebo group at 30 min, 1, 4, 12 h and 1 day post-operatively (Table 3; Fig. 1).

In the Test group the baseline facial measurement was 254.7 ± 10.2 mm. There was increase in mean of swelling size to 292.7 ± 9.1 mm on 1st post-operative day, which gradually decreased to 271.4 ± 8.5 and 248.3 ± 9.7 mm on the 3rd and 7th post-operative days respectively. In the Placebo group the baseline facial measurement was 255.9 ± 10.3 mm. There was increase in mean of swelling size to 296.1 ± 8.4 mm on 1st post-operative day which gradually decreased to 271.2 ± 7.6 and 249.9 ± 17.7 mm on the 3rd and 7th post-operative days respectively.

On comparison of facial measurements in both the groups, though there was less facial swelling in the Test group with a mean difference of 3.4 and 1.6 on the 1st and 7th post-operative days respectively, it was not statistically nor clinically significant ($p > .05$). Thus the Test group and Placebo group showed overall no statistically significant difference ($p > .05$) on the 1st, 3rd and 7th post-operative days (Fig. 2).

Baseline mouth opening in Test group was 32 ± 6.4 mm. There was decrease in mean mouth opening to 17.7 ± 2.5 mm on 1st post-operative day which gradually increased to 23.4 ± 1.9 and 35.5 ± 2.8 on the 3rd and 7th post-operative days respectively. In the Placebo group, baseline mouth opening was found to be 35 ± 5.7 mm. There was decrease in mean mouth opening to 18.2 ± 2.9 mm on 1st post-operative day which gradually increased to 26 ± 3.7 and 35.5 ± 2.5 on the 3rd and 7th post-operative days respectively.

On comparison of mouth opening in both the groups it was found that, though there was better mouth opening in the placebo group with a mean difference of 0.5, 2.6 and 0.3 on the 1st, 3rd and 7th post-operative days respectively, it was not statistically nor clinically significant ($p > .05$). Thus the Test group and Placebo group showed overall no statistically significant difference ($p > .05$) on the 1st, 3rd and 7th post-operative days (Fig. 3).

No drug related complications were noted in the subjects. Except for one patient who had an episode of vomiting post operatively, none of the patients complained of nausea, vomiting, hallucinations, dreams, nystagmus, excitation, and photophobia.

Discussion

Pre-emptive analgesia is an anti-nociceptive treatment that prevents establishment of altered processing of afferent input, which amplifies postoperative pain. It is defined as treatment that prevents establishment of central sensitization caused by incisional and inflammatory injuries; it starts before incision and covers both the period of surgery and the initial postoperative period [9].

There is considerable evidence that pain associated with peripheral tissue or nerve injury involves NMDA receptor (NMDAR) activation [10]. Consistent with this, NMDAR antagonists have been shown to effectively alleviate pain related behavior in animal models as well as in clinical situations [11, 12]. Although central NMDARs, especially

Table 1 Pain scores (VAS)—Test group

Time of assessment	Mean $\pm$ SD	Mean difference	t value	p value
Pre-operative	8 ± 11.5			
30 min post-operatively	8.5 ± 8.1	0.50	0.252	.804
1 h post-operatively	12 ± 5.2	4.00	2.179	.042
4 h post-operatively	18 ± 6.1	10.00	4.359	.000
12 h post-operatively	57.5 ± 5.5	49.50	20.142	.000
1st post-operative day	64.5 ± 5.1	56.50	18.738	.000
3rd post-operative day	30 ± 3.2	22.00	8.543	.000
7th post-operative day	1 ± 3.1	7.00	3.036	.007

Paired student ‘t’ test for intra group variations

Table 2 Pain scores (VAS)—Placebo group

Time of assessment	Mean $\pm$ SD	Mean difference	t value	p value
Pre-operative	6.5 $\pm$ 8.1			
30 min post-operatively	18.5 $\pm$ 4.8	12.000	5.64	.000
1 h post-operatively	22.5 $\pm$ 5.5	16.000	9.49	.000
4 h post-operatively	37.5 $\pm$ 4.4	31.000	15.203	.000
12 h post-operatively	76 $\pm$ 5.0	69.500	29.600	.000
1st post-operative day	80 $\pm$ 3.2	73.500	35.219	.000
3rd post-operative day	31.5 $\pm$ 3.6	25.000	14.694	.000
7th post-operative day	1 $\pm$ 3.0	5.500	2.979	.008

Paired student 't' test for intra group variations

Table 3 Comparison of pain scores (VAS) between Test group and Placebo group

Time of assessment	Mean $\pm$ SD		Mean difference	t value	p value
	Test group	Placebo group			
30 min post-operatively	8.5 $\pm$ 8.1	18.5 $\pm$ 4.8	10.0	4.714	.000
1 h post-operatively	12 $\pm$ 5.2	22.5 $\pm$ 5.5	10.5	6.185	.000
4 h post-operatively	18 $\pm$ 6.1	37.5 $\pm$ 4.4	19.5	11.487	.000
12 h post-operatively	57.5 $\pm$ 5.5	76 $\pm$ 5	18.5	11.103	.000
1st post-operative day	64.5 $\pm$ 5.1	80 $\pm$ 3.2	15.5	11.461	.000
3rd post-operative day	30 $\pm$ 3.2	31.5 $\pm$ 3.6	1.5	1.371	.178
7th post-operative day	1 $\pm$ 3	1 $\pm$ 3	0.00	.000	1.0

Unpaired student 't' test for inter group variations

Fig. 1 Comparison of pain scores (VAS) between Test group and Placebo group **Fig. 2** Comparison of facial swelling measurement between Test group and Placebo group

ones located in the spinal cord, still receive a great deal of attention, evidence is accumulating that suggests that NMDARs located in peripheral somatic tissues and visceral pain pathways play an important role in nociception. With the recognition of peripheral somatic and visceral NMDARs, it is now apparent that the role of NMDARs in pain is much greater than thought previously [3].

Ketamine, a NMDA antagonist, is a rapidly acting intravenous anesthetic and analgesic agent, from phencyclidine family which has been used for more than 40 years in general anesthetic practice. It is clear that high dose ketamine is an intravenous anesthetic and low dose ketamine is an analgesic. The presence of ionotropic glutamate receptors, such as NMDA receptors on peripheral sensory

Fig. 3 Comparison of mouth opening between Test group and Placebo group

axons could be the basis of peripheral ketamine induced analgesia [13].

Several studies have shown the effects of sub-analgesic doses of ketamine on postoperative pain and opioid consumption. In humans, the peripheral administration of ketamine enhanced the local anesthetic and analgesic actions of bupivacaine used for infiltration [9]. Schmid et al. [14] reviewed the use and efficacy of low-dose ketamine in the management of acute postoperative pain and the evidence suggested that low-dose ketamine may play an important role in postoperative pain management when used as an adjunct to local anaesthetics, opioids, or other analgesic agents.

Corticosteroids and NSAIDs are two other large groups of drugs that are widely used for the prevention of postoperative inflammatory complications and to diminish unwanted effects such as pain or trismus following third molar surgery. NSAIDs have been reported to be effective in pain relief, while corticosteroids are effective in diminishing edema. Grossi et al. [7] evaluated submucosal administration of 4 and 8 mg dexamethasone and showed a statistically significant reduction in facial edema on the second postoperative day in both dexamethasone doses compared with the control group, but no statistically significant differences were observed between the two dosage regimens. Vegas-Bustamante et al. [15] showed that local injection of a single 40-mg dose of methylprednisolone into the masseter muscle on completion of the extraction of impacted lower third molars decreased swelling, trismus, and pain. Guillen et al. [16] compared the efficacy of tramadol given before or immediately after surgical extraction of an impacted mandibular third molar under local anesthesia. The analgesic efficacy measured as complete relief of pain at 24 h was 86 % in the preemptive tramadol compared with 70 and 36 % for postoperative tramadol administration and control group.

Many investigators have combined corticosteroids and NSAIDs. Schultze-Mosgau et al. [6] studied the combined usage of oral ibuprofen and revealed that combined usage of these two drugs decreased the edema by 56 % and pain by 67 % compared with the control group. Buyukkurt et al. [17] determined that the intramuscular injection of a single dose of the combination of prednisolone and diclofenac immediately after surgery was well suited to treat postoperative pain, trismus, and swelling, and they recommended that it be used when extensive postoperative swelling of soft tissue is anticipated. Santos et al. [18] investigated the effect of preemptive analgesia with a combination of tramadol + dexamethasone or tramadol + diclofenac sodium and found that patients treated with tramadol + dexamethasone showed lower pain scores and inflammation compared to the tramadol + diclofenac sodium combination. Bamgbose et al. [19] illustrated enhanced effects of co-administered dexamethasone and diclofenac K on short-term post-operative pain and swelling, compared to diclofenac potassium alone in third molar surgery.

Ketamine has been used to reduce post-operative pain following various surgical procedures like herniorraphy [20], abdominal hysterectomy [21], thoracotomy [22], circumcision [23], cesarean section [24], open cholecystectomy [25], appendectomy [26], tonsillectomy [27–31]. Recently ketamine has been used in oral and maxillofacial surgical practice as well [14, 32–36].

In various studies done by Satilmiş et al. [32], Garip et al. [33], Gupta et al. [36] ketamine has shown to reduce postoperative pain and swelling in patients undergoing surgical removal of third molars and also provide a comfortable procedure for the surgeon and patient. But in contrast Lebrun et al. [35] concluded that there was no benefit to pre-emptive administration of ketamine 300 µg/kg iv whether administered pre- or postoperatively after assessing the effect on 84 patients scheduled for third molar surgical removal.

Different administration routes used for ketamine include intramuscular intravenous and sub mucosal. Many studies have evaluated the effectiveness of ketamine administered locally to the peri-tonsillar region following tonsillectomy for postoperative pain management [27–31]. Tan et al. [23] gave a subcutaneous ring infiltration of ketamine at the incision site before circumcision surgery and showed that the time interval until first analgesic demand was longer and the incidence of pain-free status during movement and erection was significantly higher than for the saline-treated analogs. Atashkhoyi et al. [24] evaluated the efficacy of pre-incisional subcutaneous infiltration of low-dose ketamine at the site of incision after cesarean section and reported decreased postoperative pain scores with a significant decrease of analgesics consumption. Safavi et al. [25] concluded that a 2 mg/kg dose of

subcutaneous infiltration ketamine or 1 mg/kg dose of intravenous ketamine given at approximately 15 min before surgery provides an adjunctive analgesia for 24 h after surgery in patients undergoing cholecystectomy surgery. In contrast to these reports Pedersen et al. [37] examined the analgesic effect of local ketamine infiltration, compared with placebo and systemic ketamine, in a human model of inflammatory pain induced by a burn and showed that though local ketamine infiltration reduced pain during the burn injury compared with systemic treatment and placebo, no difference between local ketamine and placebo could be detected 1 and 2 h after the burn and hence concluded that a clinically relevant effect of peripheral ketamine in acute pain seems unlikely.

Few studies have compared the efficacy of ketamine administered through different routes and the results have been varying [25, 38]. Dal et al. [28] compared same dose of peritonsillar infiltration of ketamine with iv ketamine and found no statistically significant difference in pain scores in both the groups of patients undergoing adenotonsillectomy. Various sub-anesthetic doses of ketamine have been used by different authors. Siddiqui et al. [31] compared two doses 0.5 or 1 mg/kg of peritonsillar infiltration of ketamine and found that both the groups had comparable pain scores. Tverskoy et al. [20] showed that ketamine acting via a peripheral mechanism can profoundly enhance anaesthetic and analgesic actions of a local anaesthetic administered for infiltration anaesthesia. Though the mechanism is not clear, it can be related to the blockade of NMDA receptors. Satilmiş et al. [32] used a combination of local anaesthetic and ketamine locally before surgical extraction of third molars. In our study though we did not combine the local anesthetic and ketamine solutions together, they were used locally around the third molar. After the local anesthetic nerve block and infiltration, 0.5 mg/kg ketamine was infiltrated locally around the third molar and incision line to enhance the anesthetic and analgesic actions of local anesthetic.

In oral and maxillofacial surgery, Mathisen et al. [33] examined analgesic effect of racemic ketamine and its 2 enantiomers in 16 female patients who had their 3rd molar teeth surgically removed on prophylactic indications, under local anaesthesia. The patients received ketamine by intramuscular injection and all three forms of ketamine consistently relieved postoperative pain. Gupta et al. [36] assessed the clinical efficacy of premedication with a combination of oral midazolam (0.25 mg/kg) plus low-dose ketamine (5 mg/kg) prior to surgical removal of third molars resulting in significantly low pain scores at 30 min and 24 h post operatively. Satilmiş et al. [32] assessed the clinical efficacy of combined treatment with local anesthetic and sub-anesthetic ketamine (0.3 mg/kg) during surgical extraction of third molars. The VAS scores at

30 min and 1, 4, 12 and 24 h post operatively were significantly higher in the local anesthetic alone group than in the combined treatment with local anesthetic and sub anesthetic dose of 0.3 mg/kg ketamine. Garip et al. [34] assessed the clinical efficacy of midazolam (0.03 mg/kg) plus low-dose ketamine (0.3 mg/kg) conscious intravenous sedation on relief from or prevention of postoperative pain, swelling, and trismus after the surgical extraction of third molars and concluded that patient compliance to procedure increased and significant post-operative decrease in parameters considered.

These results coincide with that of our study where the Test group showed significantly better results in reduction of post-operative pain when compared to Placebo group at 30 min, 1, 4, 12 h and 1 day post-operatively. On the 3rd and 7th post-operative days the difference was not statistically significant. Thus sub-mucosal infiltration of 0.5 mg/kg ketamine was found to be effective in significantly reducing postoperative pain for the first 24 h following surgical removal of impacted third molars.

Reduction of postsurgical swelling leads to concomitant reduction of postsurgical discomfort, soreness, trismus and unsightly discoloration of the patients face. Post-surgical facial swelling is difficult to quantify accurately, as it requires a three-dimensional measurement of an irregular, convex surface and can manifest itself internally as well as externally. Several researchers have tried various techniques in an effort to objectively measure edema, most of which are indirect assessments of the altered contours of skin surface. Measurement tools mentioned in the literature have included visual analog scales, trismus recordings, standardized stereo-radiographic or photographic measurements, computerized tomography, modified face bow devices, ultrasonography, facial plethysmographs, or various other means of taking direct facial measurements. In the present study, a modification of the tape-measure method as described by Schultze-Mosgau et al. [6–8], two measurements were made between three reference points: the tragus, pogonion and corner of the mouth. The preoperative sum of the two measurements was considered as the baseline for that side. It is noteworthy to mention that the cheek swelling following third molar surgery is diffuse in different planes and is very difficult to measure accurately.

Several experimental and clinical studies have shown that, in addition to its anesthetic activity and analgesic effects, ketamine exerts anti-inflammatory properties by inhibiting the release of pro inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6 [39–43]. Beilin et al. [40] used small doses of ketamine before induction of anaesthesia in patients undergoing abdominal surgery and showed that there was attenuation of secretion of the proinflammatory cytokines IL-6 and TNF alpha, and in preservation of IL-2 production at its preoperative level.

They also suggested that ketamine prevented immune function alterations in the early postoperative period. Mazar et al. [41] suggested that the sepsis-protective anti-inflammatory effects of ketamine are mediated by the release of adenosine acting through the A2A receptor. In contrast, based on the inflammatory and stress response markers measurement, low-dose infusion of ketamine did not exert any apparent anti-inflammatory effect in patients undergoing on-pump coronary bypass graft surgery in studies done by Cho et al. [42] and Akhlagh et al. [43].

Satılmış et al. [32] found significantly lower facial swelling and greater mouth opening on postoperative days 1, 3 and 7 in the combined treatment with local anesthetic and ketamine than in local anesthetic alone group. Gupta et al. [36] checked postoperative swelling 24 h after surgery; out of 30 patients, only 5 patients showed slight swelling when oral midazolam plus low-dose ketamine was used, whereas 12 patients showed swelling when placebo was used. Garip et al. [34] found that facial swelling on postoperative days 1, 3 and 7 was significantly lower in the midazolam plus ketamine group than in midazolam plus placebo group and also mouth opening was significantly better on postoperative days 1 and 3 in the midazolam plus ketamine group.

Contrary to these studies [32, 34, 36]; in our study comparison of facial measurements and mouth opening in both the groups showed overall no statistically significant difference on the 1st, 3rd and 7th post-operative days. Thus sub-mucosal infiltration of 0.5 mg/kg ketamine did not seem to be effective in reducing postoperative swelling or trismus.

Conclusion

In conclusion, sub-mucosal infiltration of 0.5 mg/kg ketamine around the impacted third molar has significant effectiveness in reducing post-operative pain for the first 24 h following surgery but not post-operative swelling nor trismus. Our results are nevertheless interesting in light of the possible clinical application of small doses of pre-emptive ketamine as an adjunct to post-operative analgesics in significantly reducing post-operative pain after third molar surgery and various other oral and maxillofacial surgical procedures in the future. From what is evident in our study and numerous other studies, sub-anesthetic dose of ketamine administered pre-operatively is effective in reducing post-operative pain.

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