

Effects of 15 mg meloxicam administered before odontectomy on pain, facial edema, trismus, and expressions of TNF- α following odontectomy of impacted mandibular third molar



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Abstract

Objective: To evaluate the effects of 15 mg meloxicam administered 60 minutes before odontectomy on pain, facial edema, trismus and expressions of TNF- α after odontectomy of impacted mandibular third molar.

Material and Methods: A total of 24 patients were randomized into treatment groups, each with 12 patients: Group A was administered with 15 mg of meloxicam; and Group B with placebo. Drugs were administered orally 60 minutes prior to surgery. Observation of pain (seen from VAS scores), facial edema (seen from swollen cheeks), trismus (seen from mouth opening) and expressions of TNF- α (measured from saliva by ELISA method), performed before odontectomy, H+1 (24 hours after odontectomy) and H+3 (72 hours after odontectomy).

Results: Patients who received 15 mg meloxicam 60 minutes before odontectomy showed less postoperative pain ($p=0.000$), less facial edema ($p=0.000$) and lower expressions of TNF- α ($p=0.000$). No differences were found in mouth opening between the meloxicam group and placebo group ($p=0.522$). The higher level of TNF- α level will lead to higher level of pain, greater facial edema and causes smaller mouth opening.

Conclusion: Oral administration of 15 mg meloxicam 60 minutes prior to odontectomy was found more effective in reducing pain, facial edema and expressions of TNF- α after odontectomy of impacted mandibular third molar compared with placebo.

Keywords: Facial edema, Meloxicam, Pain, Preodontectomy, TNF- α

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Introduction

Odontectomy is dental surgical removal performed with a mucoperiosteal flap and reduction of the jawbone.^{1,2} This surgery will cause injury and damage to soft and hard tissue, which trigger inflammatory responses leading to pain, facial edema or swelling and trismus. Short lasting, pain normally reaches the peak intensity within the first 24 hours after surgery while facial edema and trismus generally appear within 48-72 hours.^{3,4}

Pain, facial edema and trismus originate from the inflammatory process that results in the release of proinflammatory cytokines (tumor necrosis factor alpha, interleukin 1 and interleukin 6) thus activating the cyclooxygenase pathway and increasing prostaglandins in the wound area which will increase peripheral nociceptors and spur the appearance of inflammatory symptoms.^{5,6} Tumor necrosis factor alpha is the earliest and most powerful immune response mediator, making it a very sensitive parameter after surgical trauma.⁷

The intensity and severity of pain, facial edema and trismus can be controlled pharmacologically, among others by the use of nonsteroidal anti-inflammatory

drugs (NSAIDs). Anti-inflammatory drugs can inhibit or suppress the inflammatory responses, reduce the production of proinflammatory cytokines, also prevent and minimize clinical signs of inflammation.^{7,8} NSAID drugs, one of which is meloxicam, works to inhibit cyclooxygenase activity and the NF- β pathway in endothelial cells.⁹ Meloxicam has analgesic and anti-inflammatory activity with low toxic effects on the stomach and serves as a preferential COX-2 inhibitor used in the treatment of acute pain such as toothache and post-operative pain.^{10,11} The pharmacokinetic properties of meloxicam, characterised by a prolonged half-life and lack of accumulation, allow once-daily administration and translate into clinical advantages such as increased patient compliance.¹² Compared to 7.5 mg, 15 mg meloxicam is more effective in treating pain, facial swelling and trismus after odontectomy.¹¹

To overcome odontectomy-post discomfort, meloxicam was administered.^{13,14} Drug administered after surgery will work after wound injury and acute surgery-post inflammatory process thus unable to prevent the onset of acute inflammatory

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processes and discomfort along with the fading influence of local anesthesia, based on which some authors conducted studies of pre-odontectomy drug administration.^{4,15,16} Pain, facial edema and trismus occur as a result of the release of chemical mediators produced after tissue trauma, hence the administration of preoperative NSAIDs contributes to reducing the concentration of these mediators in the tissue and regulating release of prostaglandins and minimizing side effects of drugs compared to repeated postoperative drug administration.¹⁷⁻¹⁹

This far, no studies were conducted on the administration of 15 mg meloxicam before odontectomy to observe the clinical signs of inflammation and expressions of TNF- α . This study was aimed at identifying the effectiveness of oral administration of 15 mg meloxicam given 60 minutes before odontectomy on pain, facial edema, trismus and expressions of TNF- α following odontectomy of impacted mandibular third molar.

Material and Methods

This study approved by the Committee of Ethics of the Faculty of Dentistry, Gadjah Mada University (UGM). A double-blind randomized control trial study of patients undergoing odontectomy of impacted mandibular third molar at the Dental and Oral Hospital UGM Prof. Soedomo (RSGM).

Consecutive sampling was used with the inclusion criteria as follows: male or female subjects aged 18-30 years with Pell-Gregory class IB or IIB mesioangular class impacted mandibular third molar based on Panoramic; Willing to be a research sample; the operation was 60 minutes at the longest (duration for incision to suturing); no dental caries and periodontal disease were found; not under current orthodontic treatment and/or using prostheses; not pregnant, breastfeeding, or using contraceptive drugs; has no history of systemic disease; not smoking and/or consuming; and no history of allergy to the drugs such as meloxicam, amoxicillin and paracetamol.

Patients were excluded from the study if they met the following criteria: not showing up during control or withdrawing from the study; signs of post-odontectomy infection (pus in the socket used for odontectomy) was found; and experiencing severe post-odontectomy pain which Visual Analogue Score was unable to measure. All recruited individuals were informed about the objectives and study design, and those who consented to participate signed a written informed consent agreement and informed consent for odontectomy.

Double blind was used in drug administration and lottery cards were taken randomly. The pharmacists were responsible to give the drugs based on

the card number. Group A received a single oral dose of meloxicam 15 mg and Group B received a placebo (containing starch). The medications were administered 60 minutes before surgery.

All the patients underwent a standardized surgical procedures by a single operator. The odontectomy of impacted mandibular third molar was performed under local anesthesia with lidocain HCL 2% containing adrenaline 1:80,000, using as much 3 mL. A triangular full-thickness flap was raised, followed by peripheral osteotomy using round bur in low speed micrometer straight hand piece under copious irrigation. Tooth was sectioned if needed. Tooth elevated and delivered out of the socket in toto or in parts using elevators or suitable forceps. Sharp edges if remaining on the bone were smoothed using bone file then irrigated to remove bone debris. Flap repositioning and 3.0 silk thread suture were done with the simple interrupted technique. The surgery was accomplished along with completed suturing in which recording time was needed in odontectomy. Following the procedure, postoperative medication was prescribed: amoxicillin tablets 500 mg and paracetamol tablets 500 mg, to be taken at intervals of 8 hours for 5 days; and received educational sheets and post-operative instruction sheets; and were scheduled to come the clinic on the day 1st, 3rd, and 7th days after odontectomy.

Measurements of pain, facial edema, trismus and collecting saliva for TNF- α measurements were done by the same independent observer whose reliability was tested (ICC=0.8) on pre- and post-odontectomy periods (1st and 3rd days). The intensity of pain was measured using a visual analogue scale of 10 cm, with 0 representing the absence of pain or discomfort and 10 representing the maximum pain or discomfort. Research subjects marked themselves with a pencil on a scale value based on the intensity of pain felt.

The measurement of facial edema was done by the method described by Laskin,²⁸ that measures three facial lines and calculates the average of the lines. Three facial lines were defined by marking the distance from the tragus to the soft pogonion, the distance from the tragus to the labial commissure, and the distance from the mandibular angle to the external corner of the eye were measured by measuring tape. The maximum mouth opening was measured in centimeters the distance between the incisal edge of upper and lower central incisors using a vernier caliper.

Saliva was collected by the spitting method. The subjects is made to sit quietly with the head bent down for 5 minutes, saliva is allowed to accumulate in the floor of the mouth and the subject spits out it into the saliva container.

Saliva was then put into a 1.5 ml safe lock tube, coded and stored at -80°C until TNF- α determination. The collected saliva homogenized in a room temperature ($18-25^{\circ}\text{C}$, 15 minutes) and followed by centrifugation (1000 g, 20 minutes, $2-8^{\circ}\text{C}$). The supernatant was used to determine the expressions of TNF- α by ELISA method, using a commercial kits (Human TNF- α ELISA Kit (catalogue EH0302); Wuhan Fine Biological Technology, China). The assays were performed in accordance with the manufacturer's instructions. The expressions of TNF- α was recorded in a picogram per deciliter (pg/dl).

Results

The subjects consist of 24 people (10 men, 41.7%; 14 women, 58.3%), who went to two groups equally. The average age was 23.8 years and 22.5 years for the placebo and meloxicam group respectively, while the BMI mean of the placebo and meloxicam group was

21.74 and 21.35 respectively. The classification of Pell and Gregory impaction of placebo group (6 IB classes, 6 classes IIB) and meloxicam (5 IB classes, 7 class IIB). The average duration of surgery for the placebo group was 33.67 minutes while meloxicam group was 32.08 minutes. Characteristics of the subjects based on sex, mean of age, mean of BMI, impaction classification and mean of surgical duration showed no significant difference ($p>0.05$).

Pain scores increased significantly on 1st day after odontectomy in both the placebo group (3.6 ± 0.6) and the meloxicam group (1.3 ± 0.5). Pain was significantly reduced in both groups on 3rd day following odontectomy (placebo 2.8 ± 0.7 ; meloxicam 0.1 ± 0.3). The meloxicam group showed lower pain changes compared to the placebo group on day 1 and day 3 after odontectomy ($p<0.000$) table 1.

Measurement of facial edema showed a significant increase in the placebo group (13.0 ± 1.0 cm) and meloxicam group (12.3 ± 0.5 cm) on 1st day after odontectomy, followed by a significant decrease in the placebo group (12.4 ± 0.7 cm) and the meloxicam group (11.9 ± 0.5 cm) on 3rd day after odontectomy. Changes in facial edema were significantly lower in the meloxicam group compared with placebo on 1st day after odontectomy ($p=0.000$) table 2.

The meloxicam group showed a maximum mouth opening value of 2.4 ± 0.3 cm on day 1 after odontectomy, with a significant improvement on day 3 after odontectomy (3.1 ± 0.6 cm). The placebo group showed maximum mouth opening value on day 1 after odontectomy (2.1 ± 0.8 cm) and increased slightly on day 3 after odontectomy (2.5 ± 0.5 cm). Mouth opening was significantly greater in the meloxicam group when were compared to the placebo group but statistically insignificant both on day 1 and day 3 after odontectomy ($p>0.05$) table 3.

TNF- α expressions increased on 1st day after odontectomy (placebo 558.3 ± 360.1 pg/dl, meloxicam 108.6 ± 42.3 pg/dl), and decreased on 3rd day following odontectomy (placebo 107.8 ± 59.6 pg/dl, meloxicam 47.4 ± 21.1 pg/dl). There was a significant difference in changes in TNF- α expressions between the two groups on day 1 and day 3 after odontectomy ($p<0.05$) table 4.

TNF- α changes showed the strongest correlation with the changes in pain compared to facial edema and trismus. Changes in TNF- α was strong in correlation with changes in pain on day 1 ($r=0.748$) and day 3 after odontectomy ($r=0.630$). Changes in TNF- α were of a moderate correlation with changes in facial edema on day 1 ($r=0.490$) and day 3 after odontectomy ($r=0.459$). The correlation between TNF- α changes and trismus changes was weak, both on day 1 ($r=0.399$) and day 3 after odontectomy ($r=0.324$) table 5.

Table 1 Average pain scores between groups

		Pain		p value
		Placebo	Meloxicam	
Pre-odontectomy		0.0 \pm 0.0	0.0 \pm 0.0	
Post-odontectomy	1st	3.6 \pm 0.6	1.3 \pm 0.5	0.000
	3rd	2.8 \pm 0.7	0.1 \pm 0.3	0.045

Table 2 Average facial edema between groups

		Facial Edema		p value
		Placebo	Meloxicam	
Pre-odontectomy		11.3 \pm 0.8	11.6 \pm 0.4	
Post-odontectomy	1st	13.0 \pm 1.0	12.3 \pm 0.5	0.000
	3rd	12.4 \pm 0.7	11.9 \pm 0.5	0.173

Table 3 Average trismus between groups

		Trismus		p value
		Placebo	Meloxicam	
Pre-odontectomy		3.7 \pm 0.2	3.9 \pm 0.3	
Post-odontectomy	1st	2.1 \pm 0.8	2.4 \pm 0.3	0.522
	3rd	2.5 \pm 0.5	3.1 \pm 0.6	0.134

Table 4 Average of TNF- α expressions between groups

		TNF- α		p value
		Placebo	Meloxicam	
Pre-odontectomy		26.5 \pm 12	29.4 \pm 16.6	
Post-odontectomy	1st	558.3 \pm 360.1	108.6 \pm 42.3	0.000
	3rd	107.8 \pm 59.6	47.4 \pm 21.1	0.001

TNF- α : tumour necrosis factor alpha

Table 5 Analysis of correlation between TNF- α expressions and clinical data for pain, facial edema and trismus

Variable		TNF- α	
		1st day	3rd day
Pain	r	0.748	0.630
	p-value	0.000	0.001
Facial Edema	r	0.490	0.459
	p-value	0.015	0.024
Trismus	r	-0.399	-0.324
	p-value	0.047	0.049

TNF- α : tumour necrosis factor alpha; r: correlation coefficient; p<0.05, pearson correlation

Discussion

This study was aimed at identifying the effects of 15 mg oral meloxicam administered before odontectomy on pain, facial edema, trismus and expressions of TNF- α after odontectomy of mandibular third molar. Meloxicam is an analgesic and anti-inflammatory agent that works as a COX-2 preferential inhibitor responsible for converting arachidonic acid to prostaglandin H₂ and inhibiting TNF-sintesis synthesis by suppressing NF- κ B.^{20,21} Onset of the work of meloxicam was about 30 minutes, the maximum plasma concentration was 2.5-7 hours and half-life was 20-24 hours.^{9,12,22,23} Inhibition of peroxidase enzymes by meloxicam provides better gastrointestinal tolerance compared to other NSAIDs.^{10,24}

Assessment of post-odontectomy pain intensity in this study used Visual Analogue Scale (VAS) because this method is sensitive to identify changes in pain intensity, more reliable, valid and appropriate.²⁵ The results of pain measurements in two observations indicated the maximum pain intensity occurred on day 1 after odontectomy. Post-odontectomy pain can be categorized as short to moderate duration, and peak intensity occurred within the first 24 hours after surgery.¹³

The administration of meloxicam before odontectomy is effective in reducing post-odontectomy pain based on the previous studies.^{4,16} Meloxicam used for premedication reduced postoperative pain compared with control in oral surgery.¹⁶ Patients receiving preoperative meloxicam had a better postoperative analgesia and anti-trismus effect compared with who were given diclofenac after third molar extractions.⁴ Meloxicam is a inhibitor COX-2 which prevent peripheral sensitization by reducing prostaglandin synthesis at the site of surgery thus preventing the main mechanism of central sensitization.^{16,19,26} There were significant differences in pain changes between the meloxicam and placebo groups on day 1 and day 3 after odontectomy (p<0.05). Pre-odontectomy drugs reduce

post-odontectomy pain by preventing nerve sensitization before surgery so no hyperalgesia occurs.²⁷ Absorption of pre-odontectomy drugs would have begun before the onset of pain and therapeutic blood level will be achieved at the time of pain onset.^{17,19} Meloxicam is able to limit peripheral sensitization by reducing prostaglandin synthesis in the the location of the operation so as to prevent the main mechanism of central sensitization.^{19,26} Low VAS values in the meloxicam group can also be affected by the administration of paracetamol postodontectomy every 8 hours, although there are significant differences in VAS values between the meloxicam group and the placebo. The placebo group did not get anti-inflammatory preodontectomy so the starting point of prostaglandins was higher than meloxicam, causing a higher degree of pain and hyperalgesia, with a sustained pain effect. The administration of meloxicam before odontectomy contributes to reducing the initial production of prostaglandins and the release of TNF- α in tissues so as to prevent peripheral nerve sensitization in the surgical area thereby reducing pain.

Assessment of post-odontectomy facial edema in this study used an objective method with craniometric measurement described by Laskin (1987) which Calvo et al used,¹¹ it is the average measurement of three facial lines including the distance from the tragus to the soft tissue of pogonion, tragus to the lateral point of the corner of the mouth, lateral corner of eye to the most inferior point of the mandibular angulus.²⁸ The measurement results of facial edema showed the average size of facial edema in the meloxicam group was smaller than the one in the placebo group. Meloxicam is an analgesic and anti-inflammatory agent works by inhibiting COX; therefore, it can prevent the prostaglandin production which triggers classic signs of inflammation such as edema, redness, pain and fever.²¹ Meloxicam can suppress inflammation at a single dose for a long time.²⁹

Further, the administration of meloxicam before odontectomy effectively reduces facial edema following odontectomy. A single dose of pre-odontectomy drug can reduce inflammatory mediators compared to post-odontectomy drugs.³⁰ The presence of COX inhibitors in the surgery areas can inhibit the production of prostaglandins associated with hyperalgesia and edema.^{17,19} There were significant differences in facial edema changes between the meloxicam and placebo groups on day 1 (p=0.000). The half-life of meloxicam is 20-24 hours so that the drug works as an anti-inflammatory until 24 hours after administration, thus the level of biochemical mediators causing post-odontectomy facial edema in the wound area becomes lower in meloxicam group than in placebo group leading to smaller size of facial edema in the

meloxicam group than in placebo group. There were no significant differences in facial edema changes between the meloxicam and placebo groups on day 3 ($p=0.173$) because meloxicam had lost its effectiveness as an anti-inflammatory after 24 hours of drug administration. The peak time of facial edema is 24-48 hours after surgery and the size of the edema will decrease on day 3 and 4 after odontectomy.^{1,2,31} The administration of pre-odontectomy meloxicam contributes to reducing the initial production of prostaglandins and the release of TNF- α in tissues to prevent the accumulated fluid in the soft tissue of the face which may result in facial edema.

Trismus measurement used maximum interincisal opening distances, by measuring the distance between the maxillary incisors and mandibular incisors using a vernier caliper. The measurement results of trismus in two observations showed that the minimum mouth opening size was found on day 1 after odontectomy, corresponding to the study by Orozco-Solis et al.⁴ and Albuquerque et al.⁶ which showed the peak of post-odontectomy trismus occurred 24 hours after surgery.

Meloxicam administered before odontectomy can reduce post-odontectomy trismus. The subjects in meloxicam group were able to open mouth wider than those of in the placebo group but there were no statistically significant differences in 1st and 3rd day after odontectomy ($p>0.05$). The pain scores and the size of facial edema in the meloxicam group was smaller those of placebo group. Post-odontectomy pain can cause a reduced ability to open the mouth after surgery.^{32,33} Berge's (1988) study showed trismus was correlated with facial pain and edema.³³ A smaller pain score makes subjects feel comfortable to open and close mouth and the smaller size of facial edema will reduce the disruption of the movement.

Assessment of the inflammatory response caused by proinflammatory cytokines (TNF- α) used saliva as diagnostic fluid as Franco-Molina et al.³⁴ used in their study. Saliva is representative fluid originating from the local environment around the surgical area. Procedures for salivary collection are less invasive, easy, require no special equipment and / or trained staff, and are more convenient for patients than those of blood samples.^{34,35} The measurement results of two observations showed the TNF- α expressions were found maximum on day 1 after odontectomy. Elevated serum and tissue levels of TNF- α are found in inflammatory conditions.³⁶ Due to the breach of the protective barrier, the underlying tissue becomes vulnerable to pathogens and the risk of infection increases. Immune cells such as monocytes and neutrophils are triggered to travel to the wound via the aforementioned

cytokine and chemokine signaling. This signaling, along with receptor gene expression, is just one of many avenues in which miRNAs regulate the inflammatory phase. Macrophages are regulated by miR-146a and miR-155, which promote production of cytokines and growth factors.³⁷ In the wound healing process, the highest TNF- α level was seen 12-24 hours after injury and returned to normal level after the proliferation phase of healing the lesion was completed.^{38,39} Very high post-operative levels of cytokine and the maintenance of those high levels after the 4th day may indicate potential complications and post-operative infection.⁴⁰

The administration of meloxicam before odontectomy was found effective in reducing the expressions of TNF- α after odontectomy. This results correspond with the study done by Albuquerque et al.⁶ that the administration of NSAIDs prior to odontectomy reduces the expressions of post-odontectomy TNF- α . Meloxicam inhibits TNF- α synthesis by suppressing NF- κ B activity. Inhibition of COX-2 pathway by pre-operative COX inhibitors will reduce the level of TNF- α .^{6,20} There were significant differences in TNF- α level changes between the meloxicam and placebo groups on day 1 and day 3 after odontectomy ($p<0.05$). The TNF- α level of the meloxicam group was lower than that of placebo group. Pre-operative drug contributes to reducing the concentration of proinflammatory mediators in tissues, because the drugs in the bloodstream can inhibit its initial production.¹⁸

There was a significant correlation between the changes in TNF- α with pain, facial edema and trismus. Strong positive correlation was found between TNF- α changes with pain, moderate positive correlation was seen with facial edema, while weak negative correlation was seen between TNF- α changes with trismus. The higher level of TNF- α level will lead to higher level of pain and the greater facial edema causes smaller mouth opening. Changes in TNF- α expressions were found stronger in correlation with pain than facial edema and trismus. TNF- α was directly associated with hyperalgesia produced by inflammation under two mechanisms: (1) induction of COX-2 and prostanoicid synthesis by releasing IL-1 β , (2) induction of sympathomimetic amine production through IL-8.^{6,41} Administered meloxicam prior to odontectomy contributes to minimizing the concentration of biochemical mediators in tissues because the presence of drugs in the bloodstream will inhibit its initial production, thus resulting in lower concentration of prostaglandins and the release of TNF- α in the tissue leading to lower inflammatory response. Peripheral nerve sensitization in the surgical area was then inhibited for reducing pain,

inhibiting and preventing the accumulated fluid in the facial soft tissue prone to facial edema and overcoming the risk of trismus.

This study used the whole saliva containing local and systemic inflammatory biomarkers. Systemic disease tracking that influenced TNF- α in this study using a Review of system found no systemic disease and the TNF- α preodontectomy average expression value was still within normal limits (26.5 pg/dl and 29.4 pg/dl). Saliva TNF- α levels in healthy individuals are below 67.37 pg/dl.⁴² The increased expression of TNF- α in saliva that occurred in this study can be ascertained to be a local inflammatory product of postodontectomy, but comparative study is deemed necessary involving gingival sulcus fluid or gingival tissue samples around the surgical area to be more specific to assess the local inflammatory response following odontectomy of impacted mandibular third molar.

Conclusion

The administration of 15 mg meloxicam before odontectomy was found to be more effective in reducing pain, facial edema, and expressions of TNF- α after odontectomy of mandibular third molars compared with placebo. The higher level of TNF- α level will lead to higher level of pain, greater facial edema and causes smaller mouth opening.

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Conflict of Interest

The authors report no conflict of interest.

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