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RESEARCH ARTICLE

Effect of pre-operative 40 mg oral methylprednisolone on post- odontectomy facial swelling, intraoral redness, pain and level of TNF-α

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ABSTRACT

Odontectomy is the surgical removal of teeth by making a mucoperiosteal flap and reducing the jawbone. This procedure is likely to cause injury and damage to soft and hard tissues, stimulate inflammatory responses, and generate release of proinflammatory cytokines, one of which is TNF- α, resulting in the facial swelling, intraoral redness, and pain. This study was aimed at observing effects of 40 mg methylprednisolone, administered 1 hour before odontectomy on facial swelling, intraoral redness, and pain and level of TNF-α after odontectomy. The randomized placebo-control trial study involved 24 subjects who underwent odontectomy at the Oral Surgery and Maxillofacial clinic of Prof. Soedomo Dental Hospital, Universitas Gadjah Mada. To comply with the inclusion criteria, the subjects were divided into placebo group (12 patients) and methylprednisolone group (12 patients). The observation of facial swelling, intraoral redness, pain (VAS) and level of TNF-α (ELISA) was done before odontectormy, H+1 (24 hours after odontectomy) and H+3 (72 hours after odontectomy). The data gathered were analyzed using Repeated Measures ANOVA and post-hoc Bonferroni ($p < 0.05$). The results showed that those administered with methylprednisolone an hour before odontectomy experienced less postoperative facial swelling ($p = 0.000$), a lower score of intraoral redness ($p = 0.000$), a lower score of pain ($p = 0.000$) and a lower level of TNF-α ($p = 0.000$) compared to the placebo. The changes in TNF-α showed the strongest correlation with the changes in postoperative pain and intraoral redness compared with facial swelling. Oral administration of 40 mg methylprednisolone an hour before odontectomy is more effective in reducing facial swelling, intraoral redness, pain and level of TNF-α following odontectomy of mandibular third molar compared with the placebo.

Keywords: facial swelling; intraoral redness; level of TNF-α; methylprednisolone; pain; pre-odontectomy

INTRODUCTION

Odontectomy is the surgical removal of impacted teeth by making a mucoperiosteal flap and reducing the jawbone.[1,2,3] Odontectomy causes a wound in the tissue around the teeth and results in acute post-odontectomy inflammation. The clinical signs of inflammation include facial swelling, intraoral redness, pain, and an increased level of TNF-α. The pain usually lasts for a short term and peak intensity occurs in the first 24 hours after odontectomy followed by clinical signs of intraoral redness and facial swelling, usually appearing within 48-72 hours after surgery.[2,3,4,5]

Tumour necrosis factor-alpha (TNF-a) is the earliest and most powerful immune response mediator, which can be detected in saliva in both periodontitis and healthy conditions released during trauma. TNF-α reaches its peak in plasma 90 minutes after stimulation detected in saliva and gingival sulcus fluid (CSG) in both healthy and inflammatory conditions.[6] The content of TNF-α in healthy gingival sulcus fluid is more or less 88 pg/ml.[7]

The use of anti-inflammatory pre-odontectomy steroids drugs, including preemptive analgesia, refers to a treatment before surgery to prevent the formation of central sensitization caused by incision and inflammatory wound that occurs during surgery. Methylprednisolone is a systemic synthetic corticosteroid that is absorbed quickly through the digestive tract with immediate action that has an anti-inflammatory effect five times

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greater than hydrocortisone. Methylprednisolone has the same effect as its parent compound, without the presence of sodium retention and reduces the opposite effect on leukocyte chemotaxis, with a moderate action, having a half-life of 12 - 36 hours and five times stronger than hydrocortisone. The peak plasma concentration after oral administration is reached between 1.1 - 2.2 hours in humans with a good general condition. Methylprednisolone decreases or prevents tissue response to the inflammatory process, thereby minimizing inflammatory symptoms, not affected by the trigger factor.[8,9,10,11,12,13] The purpose of this study was to investigate the effects of a single dose of 40 mg of methylprednisolone given one hour before odontectomy on the amount of facial swelling, intraoral redness, pain, and level of TNF-α that occurred following odontectomy.

MATERIALS AND METHODS

This double-blind randomized placebo-controlled trial study was conducted at the Oral and Maxillofacial Surgery clinic of Prof. Dr. Soedomo Dental Hospital, Universitas Gadjah Mada, within 2 months involving 24 patients as samples. Patients were selected according to inclusion criteria, underwent general physical examination, filled out information sheets and signed the informed consent for odontectomy and took the random number. Measurements of facial swelling, intraoral redness, pain, and TNF-α level were performed before odontectomy, H + 1 (day 1) and H + 3 (day 3). Measurement of facial swelling refers to the Laskin method, which measures three lines and calculates the average of three lines, the distance from the tragus to pogonion soft tissue, tragus to the lateral point of the corner of the mouth, the most inferior point of the mandibular angulus to the lateral angle of the eyes using a measuring tape.

Intraoral redness assessment before odontectomy, day 1 and day 3 after odontectomy in 5 scores is presented as follows: 1 = redness surrounds along the suture along 1 cm; 2 = 1-5 cm-long redness; 3 = redness < 5 cm and induration; 4 = the presence of spontaneous purulent drainage or with a drainage incision; and 5= the presence of fistulas.[14] Measurement of pain was done preoperatively, day 1 dan day 3 following odontectomy. Pain intensity was measured using a visual analog scale on a scale of 0-10, in which scale 0 represents the absence of pain or discomfort and a scale of 10 marks the maximum pain or discomfort as stated by the subjects.[15]

Salivary sampling for measuring TNF- α was performed preoperatively, and day 1 and day 3 postoperatively. Saliva collection in patients used the spitting method, where the subjects sat quietly while bowing their heads. The process was carried out for 5 minutes, after which they were asked to spit the saliva collected in the mouth into a container, which was then stored in a 1.5 ml-sized save lock tube and labeled A or B. Save lock tube was labeled after sampling, then taken to Integrated Research Laboratory, Faculty of Medicine, Public Health and Nursing (FKKMK), Universitas Gadjah Mada, Yogyakarta with a cold box. Samples were stored at -80 °C until TNF-α concentration was tested.

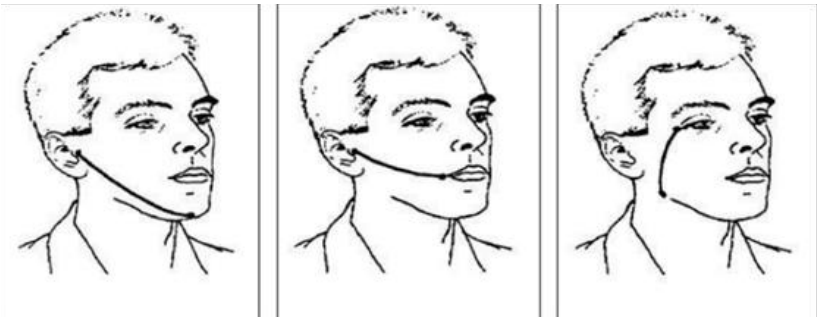

Figure 1. Measurement of facial swelling based on the Laskin method[12]

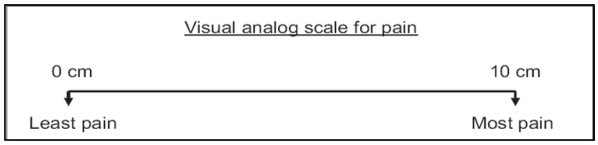

Figure 2. Measurement of pain scale[15]

Figure 3. Collection of saliva by the spitting method.[16]

All subjects received post-odontectomy drugs, 500 mg amoxicillin, taken immediately aftersuturing and then every 8 hours for 5 days and 500 mg paracetamol, administered after the effects of local anesthetics disappeared and subsequently every 8 hours for 5 days. Statistical calculations were use to assess differences and interaction between groups based on the result of this investigation, using Repeated Measures ANOVA. To establish some significant differences between the groups, researchers used a post hoc Bonferroni test. Statistical significance was defined as a p-value of < 0.05.

RESULTS

The research subjects amounted to 24 patients. Based on gender, age average, BMI average, the Impacted classification, and the length of the surgical average, there was no significant difference in the data ($p > 0.05$) (Table 1). The normality test of Shapiro-Wilk indicated that facial swelling in both groups showed normal undistributed data ($p < 0.05$). The test was followed by transformation 1/square root resulting in normally distributed data ($p > 0.05$), and thus the data were analyzed using parametric analysis. The average difference in facial swelling in both groups with Repeated Measures ANOVA test revealed a meaningful value ($p < 0.05$) (Table 2 and Figure 4).

There was a significant difference in facial swelling between the condition before odontectomy to the condition three hours after odontectomy in both the placebo group ($p = 0.000$) and methylprednisolone ($p = 0.000$). The difference of facial swelling between the time of observation in both groups with the post hoc test of Bonferroni (Table 5) indicates a significant difference in the average swelling between all-time observations in the placebo and methylprednisolone groups ($p < 0.05$). (Table 3).

The results showed that the maximal intraoral redness in the Metilprednisolone group (score 1) was lower than that of the placebo group (score 2) in both the an hour and three hours after odontectomy. Intraoral redness was analyzed with a non-parametric test using the Friedman test, and obtained a value of $p = 0.000$. This result showed a meaningful intraoral redness between the condition before odontectomy and the condition of an hour in the placebo and methylprednisolone groups (Table 4, Figure 5).

Post hoc test of Wilcoxon results revealed a significant intraoral redness between the days before odontectomy with an hour after odontectomy, before odontectomy with three hours post odontectomy in the placebo group and the Metilprednisolone Group ($p = 0.001$), while an hour with three hours after odontectomy did not show any significant differences in both groups ($p = 1.000$). (Table 5).

The normality test of Shapiro-Wilk and the homogeneity test of Levene's test data pain in both groups were found to result in non-distributed normal data (Methylprednisolone H+3) and not homogeneous (H+3) ($p < 0.05$). The data remained to be not normally distributed even after the data transformationx. The pain difference in both groups with Friedman's test had a significant value ($p < 0.05$) between the days before odontectomy to three hours after odontectomy

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after odontectomy in both the placebo group (p = 0.000) and methylprednisolone (p = 0.000). (Table 6, Figure 6).

The pain test difference between the time of observation in each group with a Wilcoxon post hoc test (Table 7) indicated a significant pain difference between all observation times in the placebo group (p < 0.05), and Methylprednisolone group (p < 0.05). Results of the normality test of Shapiro-Wilk and the homogeneity test of Levene's test data TNF-α in both groups were found to be non-normally distributed (placebo before odontectomy, an hour and three hours after odontectomy) and not homogeneous (p < 0.05), (praodontectomy and an hour after). Afterwards, the data transformation was carried out but the data remained non-normally distributed, so the data were analyzed using a non-parametric method. The TNF-α difference between the two groups with Friedman's test had a significant value (p < 0.05) between the days before odontectomy to three day post-odontectomy both in the placebo group (p = 0.000) as well as in the methylprednisolone group (p = 0.000), and it appeared to increase the expression of the real TNF-α in the placebo group an hour after odontectomy (Table 8 and Figure 7).

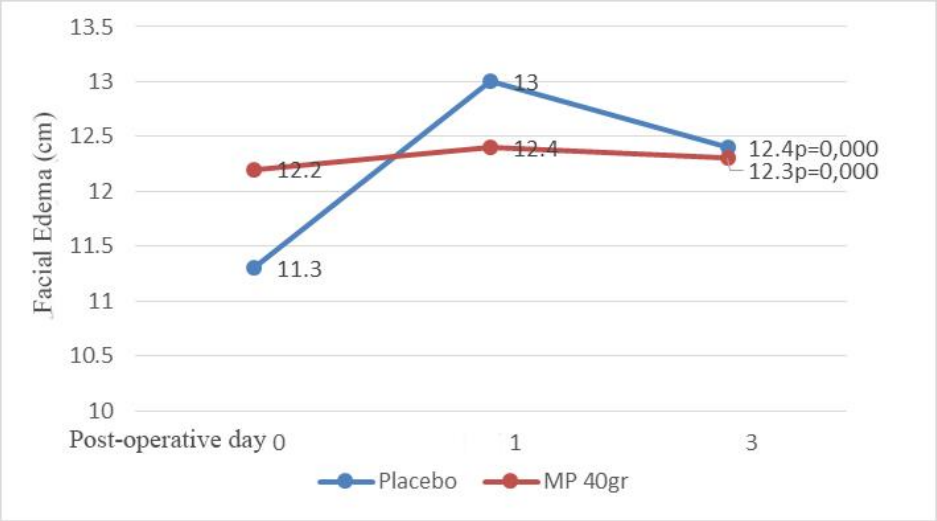
Table 1. Characteristics of subjects by sex, average age, average BMI, impaction classification and average surgical duration (n = 12)

No	Subject Characteristics	Group		Total	Sig (p)
		Placebo	Methylprednisolone		
1.	Sex				1.000[a]
	Male	5 (41.7%)	5 (41.7%)	10 (41.7%)	
	Female	7 (58.3%)	7 (58.3%)	14 (58.3%)	
	Total	12	12	24 (100%)	
2.	Average Age ± SD	23.8 ± 1.5	22.5 ± 1.8		0.075[b]
3.	Average BMI ± SD	21.74 ± 1.15	21.36 ± 1.37		0.461[b]
4.	Impaction Classification				1.000[a]
	I B MA	6 (50.0%)	6 (50%)	12 (50%)	
	II B MA	6 (50.0%)	6 (50%)	12 (50%)	
	Total	12	12	24 (100%)	
5.	Average Surgery Duration	33.67 ± 7.23	37.28 ± 3.68		0.159[b]

Description: p: significance based on (a) Chi-Square test; (b) independent T-test, BMI: body mass index

Table 2. Results of measurements of the mean of facial swelling by day of observation in both groups with the Repeated Measures Anova.

Group	N	Facial swelling			p_1
		Pre-odontectomy	Post-odontectomy		
			H+1	H+3	
		mean	mean	mean	
Placebo	12	11.3	13.0	12.4	0.000
Methylprednisolone	12	12.2	12.4	12.3	0.000



Description: p_1 = significance of each treatment group based on the Repeated Measures Anova

Figure 4. Linear graph of facial swelling measurements in the placebo and methylprednisolone group (n = 12)

Table 3. Differences in facial swelling in the placebo and methylprednisolone group between observation time in both groups

Difference	the p-value of Placebo	the p-value of 40 mg MP
Pre-odontectomy vs H+1	0.000*	0.000*
Pre-odontectomy vs H+3	0.000*	0.0013
H+1 vs H+3	0.004	0.000*

Description: *: significant p < 0.05

Table 4. Observation results of intraoral redness by day of observation in both groups with the Friedman test

Group	N	Intraoral redness			p_1
		Pre-odontectomy	Post-odontectomy		
			H+1	H+3	
		mean	mean	mean	
Placebo	12	0	2.0	2	0.000
Methylprednisolone	12	0	1.0	1.0	0.000

Table 5. Differences in intraoral redness after odontectomy in the placebo and methylprednisolone group between observation time

Difference	Placebo p-value	MP 40 mg p-value
Pre-odontectomy vs H+1	0.001	0.001
Pre-odontectomy vs H+3	0.001	0.001
H+1 vs H+ 3	1.000	1.000

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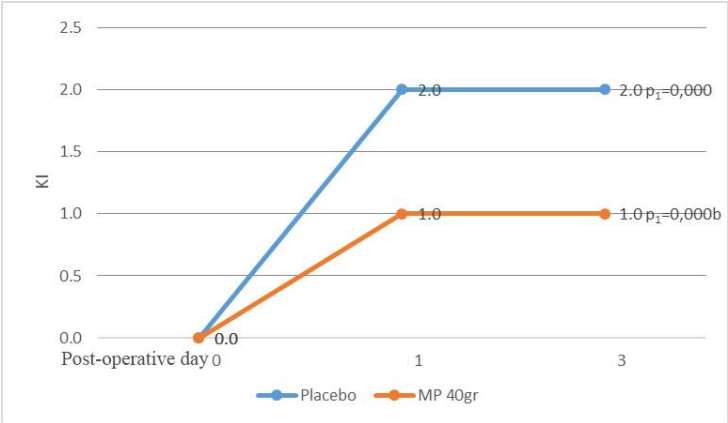
Table 6. VAS scores based on days of observation in both groups with Friedman test

Group	N	Mean of VAS			p_1
		Pre-odontectomy	Post-odontectomy		
			H+1	H+3	
Placebo mean ± SD	12	0.0 ± 0.0	3.6 ± 0.6	2.8 ± 0.7	0.000
Methylprednisolone mean ± SD	12	0.0 ± 0.0	0.5 ± 0.3	0.2 ± 0.2	0.000

Description : SD = standard deviation
p_1 = significance of each treatment group based on the Friedman test



Description: p_1 = significance of each treatment group based on the Friedman test

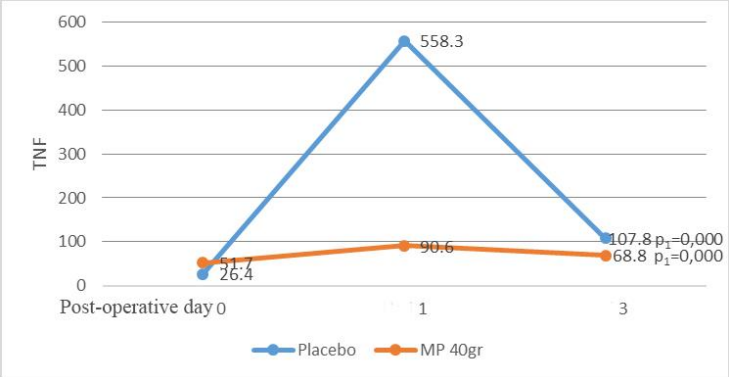
Figure 6. Linear graph of pain measurement results in the placebo and methylprednisolone group (N = 12)

Table 7. Differences in pain between the placebo and methylprednisolone group between observation time

Difference	the p-value of Placebo	the p-value of MP 40 mg
Pre-odontectomy vs H+1	0.002	0.002
Pre-odontectomy vs H+3	0.002	0.003
H+1 vs H+3	0.002	0.003

Table 8. Measurement results, the mean and standard deviation of TNF-α level based on days of observation in both groups by the Friedman test

Group	N	TNF-α			p_1
		Pre-odontectomy	Post-odontectomy		
			H+1	H+3	
		mean	mean	mean	
Placebo	12	26.4	558.3	107.8	0.000
Methylprednisolone	12	51.7	90.6	68.8	0.000



Description: p_1 = the significance of each treatment group based on the Friedman

Figure 7. Linear graph of pain measurement results in the placebo and methylprednisolone group (n = 12)

Table 9. Differences in TNF-α in the placebo and methylprednisolone group between observation time

Difference	Placebo p-value	MP 40 mg p-value
Pre-odontectomy vs H+1	0.002	0.000
Pre-odontectomy vs H+3	0.012	0.026
H+1 vs H+3	0.002	0.000

Table 10. Correlation between TNF-α level and facial swelling, intraoral redness, and pain after odontectomy

Variable	Correlation Result	TNF-α	
		H+1 Post-odontectomy	H+3 Post-odontectomy
Facial swelling	r	0.663	0.729
	p	0.000*	0.000*
Intraoral redness	r	0.867	0.795
	p	0.000*	0.000*
Pain	r	0.867	0.795
	p	0.000	0.000*

Description: r: correlation coefficient
p: Spearman correlation test
*: significant correlation (α=96%)

TNF-α difference test between observations time in both groups with the Posthoc Wilcoxon Test (Table 9) indicated a significant TNF-α difference between all observation times in the placebo and methylprednisolone groups ($p < 0.05$). The Spearman's correlation test between the decline of TNF-α expression with the reduction of swelling, intraoral redness and post-operative pain indicated a significantly positive (+) correlation ($p < 0.05$) (Table 10). A decrease in TNF-α against the reduction of post-odontectomy face edema had a strong correlation to an hour after ($r = 0.663$) and three hours after odontectomy ($r = 0.729$). The decrease in TNF-α against intraoral

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redness reduction had a very strong correlation with the condition an hour after odontectomy (r = 0.867) and a strong correlation with the condition three hours after odontectomy (r = 0.795). The reduced TNF-α levels of pain reduction had a very strong correlation to the condition an hour after odontectomy (r = 0.867) and a strong correlation with the condition three hours after odontectomy (r = 0.795).

DISCUSSION

Several studies on administration of methylprednisolone before odontectomy compared with controls have been carried out, among others by the Alcantara, et al., which found that orally administered 8 mg dexamethasone 1 hour before odontectomy is more effective to reduce swelling and trismus than 40 mg methylprednisolone, but both are equally effective against post-odontectomy pain.[10] The study by Kocer, et al, shows that intramuscularly injected 20 mg methylprednisolone, intravenously injected 20 mg methylprednisolone immediately after odontectomy and orally administered 20 mg methylprednisolone 1 hour before odontectomy can reduce post-odontectomy swelling, while intramuscularly injected 20 mg methylprednisolone immediately after suturing works more effectively to reduce swelling and trismus.[11]

The measurement results of facial swelling showed that the mean size of facial swelling in the methylprednisolone group was significantly smaller than that of a placebo. This study showed that methylprednisolone is more effective in reducing intraoral redness than a placebo. There is a statistically significant difference between the days of pre-odontectomy with day, between preodontectomy and day 3 while between day 1 and day 3, no significant difference was found. Intraoral reddish color occurs because the arteries that circulate blood to the area of trauma dilate, thus increasing blood flow to the site of injury. Assessment of post-odontectomy pain intensity used VAS for post-odontectomy pain on day 1 and day 3. It was found that there was a significant effect of drug administration on VAS in the 40 mg methylprednisolone group. This study showed that methylprednisolone is more effective in reducing post-odontectomy pain. Significant VAS difference between methylprednisolone versus placebo was found on day 1 and day 3 and day 3 after odontectomy as the pain reduction graph shows.

The measurement results of TNF-α level in both treatment groups showed the maximum level on day 1 after odontectomy. Increased level of TNF-α was found in inflammatory conditions.[9] The highest TNF-α level was found 12-12 hours after injury and returned to the normal level after the proliferation phase of wound healing completed.[17,18,19] Preemptive analgesia before odontectomy is effective in reducing the level of TNF-α after odontectomy, as stated by Albuquerque et al., that steroid administration before odontectomy can reduce TNF-α level after odontectomy.[6] Measurements at the different observation times showed a significant difference in TNF-α level in the methylprednisolone and placebo group on day 1 and day 3 after odontectomy.

There was a significant positive correlation between a decrease in TNF-α level and a reduction in facial swelling, intraoral redness and pain. The decrease in TNF-α level to the reduction of facial swelling after odontectomy has a strong positive correlation on day 1 and day 3. The decrease in TNF-α level to the reduction in intraoral redness has a very strong positive correlation on day 1 and a strong positive correlation on day 3. Decreased TNF-α level to reduced pain has a very strong positive correlation on day 1 and a strong positive correlation on day 3.

The higher the level of TNF-α the greater the stimulation of facial swelling, while the higher the intraoral redness score, the higher the pain score. The TNF-α level is correlated more strongly with post-odontectomy intraoral pain and redness than facial swelling. The administered methylprednisolone before odontectomy prevents peripheral nerve sensitization in the wound area thereby inhibiting and preventing fluid buildup in the facial soft tissue, which will result in facial

swelling, inhibiting blood vessels dilatation, and ends up with intraoral redness and reduces pain. Among the weaknesses of this study is the fact that the assessment of TNF- α was derived from saliva. On the other hand, the saliva obtained from the subjects was not confirmed to originate from local or systemic inflammation.

CONCLUSION

The oral administration of 40 mg methylprednisolone 1 hour before odontectomy was considered effective in reducing facial swelling, intraoral redness pain and decreased the level of TNF-α after odontectomy of mandibular third molars. Further studies of other acute inflammatory biochemical mediators in the wound areas are deemed necessary, and detailed studies with short time observation after odontectomy of mandibular third molars are worth conducting.

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