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Evaluation of the Serum Level of Interleukin-6 in Patients Undergoing Surgical Removal of Impacted Mandibular Third Molars

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ABSTRACT

Aim: The aim of this study is to evaluate the changes in the serum levels of interleukin-6 after impacted third molar surgery and its relation with the degree of the operative difficulty.

Materials and methods: This prospective cohort study included patients who underwent surgical extraction of impacted mandibular third molar. Two blood samples were drawn from the patients; one before the operation and the second 48 hours postoperatively. The serum interleukin-6 levels were measured using the enzyme-linked immunosorbent assay (ELISA) and the differences between the pre and postoperative levels were assessed and correlated with the difficulty of surgical extraction determined by duration and technique of surgery and other variables.

Results: Thirty nine patients were included: 12 (30.8%) males and 27 (69.2%) females. The age range was from 20-38 years, with a mean ± SD of 29 ± 5 years. The level of interleukin-6 increased significantly following surgery in comparison with the level before operation, but there was no correlation between the change in the level of interleukin-6 pre and postoperatively with other variables namely; age, gender, indication of extraction, classification of impaction and difficulty of surgical extraction.

Conclusion: After surgical extraction of impacted mandibular third molar, there was a significant increase in interleukin-6 serum levels that does not correlate with the difficulty of surgical extraction and the other investigated variables.

Key words: Interleukin-6, Impacted third molars, Surgical difficulty

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INTRODUCTION

Impaction may be defined as the failure of complete eruption of a tooth into a normal functional position within normal time due to lack of space in the dental arch, obstruction by another tooth or development in an abnormal position [1]. The mandibular third molar is the most commonly impacted tooth in the mouth with a prevalence that may reach up to 70% of the population [2]. The surgical removal of impacted mandibular third molars produces a significant degree of tissue trauma that causes an inflammatory reaction. Cytokines mediate and regulate immunity, inflammation, and hematopoiesis [3]. There are many laboratory methods to evaluate the prognosis of inflammatory process. Usually the inflammatory markers are measured in frozen serum using standardized assays such as C-reactive protein (CRP), Tumor necrosis factor alpha (TNF-α), and Interleukin-6 (IL-6) [4]. Interleukin-6 is a soluble mediator with a pleiotropic effect, it is promptly and transiently produced in response to infections and tissue injuries and it contributes to host defense [5], and it has been found to be increased after surgical removal of impacted lower third molar [6,7].

There are relatively few studies that investigated the role of IL-6 as a marker for the inflammatory reaction following the surgical extraction of impacted mandibular third molars [6,8]. Therefore the aim of this study was to evaluate the changes in the serum levels of IL-6 after impacted third molar surgery and its relation with the degree of the operative difficulty.

MATERIALS AND METHODS

This prospective cohort study included patients who underwent surgical extraction of impacted

mandibular third molar under local anesthesia during the period from December 2018 to September 2019. The inclusion criteria were medically fit patients who were 18 to 40 years of age who had not taken any anti-inflammatory drugs within 7 days before surgery. Patients who were older than 40 years of age, had uncontrolled systemic diseases, or presented with impacted teeth associated with any pathology such as cysts or tumors were excluded from this study.

This study was approved by the institutional research ethics committee (protocol #062118), all patients were informed about the aim of this study and signed an informed consent to participate in the study. The preoperative radiographic evaluation using panoramic radiographs included the assessment of the angulation of the impacted tooth by winter's classification [9], position and depth of impaction by Pell, et al. classification [10], it also included the relation of the impacted teeth with the inferior alveolar canal and the presence of any pathology associated with the impacted teeth.

Prior to surgery a 4 ml blood was obtained from the patients for the assessment of the preoperative serum level of IL-6, the blood was centrifuged and the collected serum was stored at -20°C. All the surgical procedures were performed by the same operator under local anesthesia through inferior alveolar nerve block. After reflecting a traingular mucoperiosteal, the surgical extraction preceded using elevators with or without bone removal and tooth sectioning using surgical handpiece and bur under copious irrigation with normal saline. The duration of surgery was calculated in minutes from the first incision to the last suture.

The operative difficulty was evaluated according to the surgical technique and duration [11]. According to the surgical technique the degree of operative difficulty was categorized as low when the extraction was performed by elevators alone, moderate when bone removal was needed and high when bone removal and tooth sectioning was required to complete the extraction. According to duration of surgery, the difficulty was categorized as low when the duration of surgical extraction was less than 15 minutes, moderate when the duration was 15-30 minutes and high when the surgery lasted more than 30 minutes.

Forty eight hours postoperatively another blood sample was obtained from the patients to assess the postoperative serum level of IL-6 in the same manner described earlier. The assessment of the pre and postoperative serum IL-6 levels was performed using the enzyme-linked immunosorbent analysis (ELISA) kit for quantitative determination of serum IL-6 (Demeditec Diagnostics Gmbh, Germany).

The outcome (dependent) variable was the postoperative serum IL-6 level measured 48 hours after the surgical extraction of the impacted mandibular third molar. The predictor (independent) variables were the preoperative serum IL-6 level, the difficulty of surgical extraction assessed by technique and duration, in addition to the classification of impacted mandibular third molars according to winter, et al. and Gregory classifications. Other variables included age and gender.

The statistical analysis was performed using GraphPad Prism version 6 for Windows (GraphPad Software, La Jolla, CA, USA). Descriptive analysis included percentages or mean ± standard deviation (SD). The investigated variables were analyzed statistically using the D'Agostino-Pearson omnibus normality test, Wilcoxon matched-pairs signed rank test, unpaired t-test, Mann-Whitney test, one way ANOVA test and Pearson Correlation Coefficient. The differences were considered significant at $P<0.05$.

RESULTS

Forty six patients participated in this study, 7 were lost to follow up, so they were excluded from the study. The Remaining 39 patients were 27 (69.2%) females and 12 (30.8%) males. Their age range was 20-38 years, with a mean ± SD of 29 ± 5 years. The indications for extraction of the impacted mandibular third molars were pericoronitis in 14 (35.9%) patients, periodontitis in 11 (28.2%) patients, dental caries in 10 (25.6%) patients and for orthodontic treatment in 4 (10.3%) patients. The classification of impacted mandibular third molars according to Winter's and Pell and Gregory classifications is summarized in Table 1.

The distribution of the operative difficulty of the surgical extractions according to technique and duration of surgery is shown Table 2. The mean ± SD preoperative serum level of IL-6 was 22.7 ± 11.88 pg/ml with a range of 3.4 to 55 pg/ml, the mean ± SD postoperative serum level of IL-6 was

37.3 ± 17.58 pg/ml with a range of 4.3 to 75.3 pg/ml. The difference between the preoperative and the postoperative levels of IL-6 was statistically significant (p<0.0001). The correlation of different variables with the differences between the pre- and postoperative serum IL-6 levels is shown in Table 3.

Table 1: Classification of impacted teeth according to Winter's and Pell and Gregory classifications.

Classification	Number (%)
Winter's classification	
Vertical	19 (48.7)
Mesioangular	14 (35.9)
Horizontal	6 (15.4)
Distoangular	0 (0)
Pell and Gregory classification	
Position A	30 (76.9)
Position B	9 (23.1)
Position C	0 (0)
Class I	31 (79.5)
Class II	8 (20.5)
Class III	0 (0)

Table 2: Distribution of operative difficulty according to technique and duration of surgery.

Operative difficulty	Number (%)
According to technique	
Low	25 (64.1)
Moderate	4 (10.3)
High	10 (25.6)
According to duration	
Low	25 (64.1)
Moderate	9 (23.1)
High	5 (12.8)

Table 3: The correlation of different variables with the differences between the pre- and postoperative serum IL-6 levels.

Variable	Serum IL-6 level (pg/ml)		P value
	Preoperative	Postoperative	
Gender			
Female	22.2 ± 12.95	37.0 ± 17.72	0.8982[a] [NS]
Male	23.8 ± 9.47	37.9 ± 18.02	
Indications of extraction			
Pericoronitis	21.24 ± 11.30	35.1 ± 19.93	0.8458[b] [NS]
Periodontitis	26.1 ± 16.17	43.56 ± 15.69	
Dental caries	24.2 ± 7.25	36.4 ± 18.36	
Orthothodontic treatment	14.8 ± 7.85	30.02 ± 11.04	
Winter's classification			
Mesioangular	22.8 ± 7.27	39.5 ± 19.81	0.6312[b] [NS]
Vertical	25.3 ± 14.25	39.7 ± 16	
Horizontal	14.3 ± 8.78	24.6 ± 13.4	
Pell and Gregory classification			
Position A	22.2 ± 11.85	36.1 ± 18.44	0.4143[a] [NS]
Position B	24.2 ± 12.59	41.2 ± 14.6	
Class I	23.9 ± 10.16	39.9 ± 16.54	0.1965 c [NS]
Class II	18 ± 17.1	27.1 ± 18.83	
Operative difficulty			
Technique			
Low	24.1 ± 11.06	39.6 ± 17.21	0.5910[b] [NS]
Moderate	18.4 ± 11.07	26.3 ± 11.52	
High	20.9 ± 14.73	36.0 ± 20	
Duration			
Low	24.1 ± 10.97	39.6 ± 17.22	0.5670[b] [NS]
Moderate	20.8 ± 15.48	31.2 ± 17.46	
High	19.2 ± 10.16	36.7 ± 20.78	

[a]Mann Whitney U test, [b]One way ANOVA, [c]Unpaired t-test, [NS] Non-significant

DISCUSSION

The surgical removal of impacted mandibular third molars produces tissue trauma that causes an inflammatory reaction, the latter produces the usual postoperative signs and symptoms such as pain, facial edema, and limited mouth opening [3]. Cytokines mediate and regulate the inflammatory response and they generally act over short distances and short time spans and at very low concentration [12]. IL-6 is a critical cytokine in the cascade of host response to inflammation [13]. There are relatively few studies of the use of the IL-6 as a marker in surgical removal of mandibular third molars [6,8].

The mean level of IL-6 48 hours postoperatively was significantly higher than the preoperative level which is in line with many studies that showed that IL-6 is an early and sensitive marker of tissue injury that is particularly informative in the early postoperative period [14,15].

In general there was no correlation between the differences in the pre- and postoperative serum IL-6 levels and other variables namely; age, gender, indication of extraction, classification of impaction and the difficulty of surgical extraction of impacted third molars. The difficulty levels assessed by duration and technique of surgery did not affect the IL-6 levels which is in agreement with Sainz de Baranda et al. [16] who demonstrated that IL-6 concentration varied considerably after the operation but were not influenced by the degree of surgical difficulty, although the authors attributed this finding to the fact that the postoperative evaluation of IL-6 level was confined to a single measurement made 1 week after surgery which might not be sufficient.Miyawaki et al. [17], on the other hand, observed that the level of IL-6 peaked within 6 hours after the end of surgery and it correlated significantly with the duration of surgery and they demonstrated that radical surgeries for oral cancer that lasted more than 8 hours resulted in the highest elevation of IL-6 levels among the other types of oral and maxillofacial surgeries and they suggested that the magnitude of tissue damage in oral and maxillofacial surgery may be similar to that of minor abdominal surgeries such as cholecystectomy. Other studies that evaluated IL-6 level in patient with other major surgical procedures such as hip surgery, colorectal surgery and vascular surgery found that there were significant correlations between IL-6 level and duration of surgery [18].

The main limitations of this study are small sample size and the evaluation of postoperative IL-6 level in one time interval (48 hours); evaluation of IL-6 serum levels at earlier time intervals and extending the evaluation period for more than 48 hours can provide a better picture of the postoperative changes in the serum levels of IL-6.

CONCLUSION

Surgical extraction of impacted mandibular third molar results in a significant increase in IL-6 serum levels that does not correlate with age, gender, indication of extraction, classification of impaction and difficulty according to duration and technique of surgical extraction.

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