

The effect of the Duration of Orthognathic Surgery on Plasma Concentration of Interleukin 6

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Abstract

Background: The cytokines have a major role in the inflammatory response to surgery and trauma. They have local effects of mediating and maintaining the inflammatory response to tissue injury, and also initiate some of the systemic changes which occur. IL-6 is one of the above mentioned cytokines, but it is not clear whether the duration of trauma or surgery has some effect on IL-6 level, so the aim of this study was to investigate the relationship between plasma levels IL-6 and duration of orthognathic surgery.

Materials and Methods: Twenty eight patients underwent orthognathic surgery were enrolled in this study. Blood samples were collected one day before and 4 hours after surgery for assessment the levels of plasma IL-6 which was measured by enzyme-linked immunosorbent assay.

Results: We found a significant elevation of plasma IL-6 level at 4 hours after surgery ($P<0.05$). Moreover, the elevation of plasma IL-6 level was correlated with the duration of surgery.

Conclusion: IL-6 is an important inflammatory mediator that its concentration is increased with the duration of surgery.

Keywords: Orthognathic surgery; Interleukin-6; Duration of surgery; Acute phase response

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Introduction

Orthognathic surgery is a surgery to correct conditions of the jaw and face related to structure, growth, sleep apnea, TMJ disorders, malocclusion problems owing to skeletal disharmonies, or other orthodontic problems that cannot be easily treated with braces. It is also used in treatment of congenital conditions like cleft palate (1). Bones can be cut and re-aligned, then held in place with either screws or plates. Orthognathic surgery can also be referred to as corrective jaw surgery (3). It was known that surgery at any location in the body leads to surgical stress response and alterations in normal body (2). Several studies demonstrated that pro-inflammatory cytokines such as IL-1 β (Interleukin-1beta), IL-6, IL-8, and TNF- α (Tumor necrosis factor-alpha) transiently increase in the serum or plasma of injured patients (3, 4). IL-6 is

a multifunctional cytokine that was originally identified as a B-cell growth factor-2 (BCGF-2). Since then, IL-6 has been found to have a wide array of additional activities, including effects on vascular endothelial cells, and neurons. In addition, IL-6 is closely related to other cytokines with diverse and, in some cases, redundant, activities, such as IL-1 and TNF (5). IL-6 is expressed at high levels in several inflammatory diseases, including systemic juvenile arthritis, systemic Lupus erythematosus, Crohn's disease, and rheumatoid arthritis (6).

One of the most important systemic actions of IL-6 is induction of the acute phase response and induction the synthesis of acute phase proteins (APPs) by liver (7-9). One of the other aspects of the acute phase response, which regulated at least in part by IL-6,

includes the induction of fever (8, 10). Inflammatory cytokines acts on the hypothalamus to induce fever within several hours of the onset of acute phase inflammatory response. The proinflammatory IL-1, IL-6 and TNF- α have been most investigated for their pyrogenic action, with most focus on IL-1 and TNF α (11). However, the concept was challenged when specific blockade of either IL-1 or TNF α activity did not diminish the febrile response to bacterial by-products such as LPS and it was suggested that during infection, fever could occur independently of IL-1 or TNF activity (12).

In other hand, it has been proved in the maxillofacial area that the level of IL-6 in plasma increases after different operations (13). Moreover, IL-6 has been thought to be associated with incidence of post-operative complications and the duration of surgery (14-17).

Granulocyte Macrophage Colony stimulating Factor (GM-CSF), interferon (INF), interleukin (IL)-1 β , IL-2, IL-6, IL-8, IL-10 and tumor necrosis factor (TNF)- α were detected in the synovial fluid from the temporomandibular joint (TMJ) spaces of temporomandibular disorder (TMD) patients (18). Since one of the aims of orthognathic surgery is to correct the temporomandibular disorders, it is not clear whether it can lower the IL-6 concentration or not. In addition, there is no study about the effect of duration of maxillofacial surgery on the level of inflammatory cytokines, so, the main objective of this study is to investigate the relationship between plasma level of IL-6 and duration of surgery, in patients undergoing orthognathic surgery.

Materials and Methods

Patients

28 patients (14 male and 14 female mean age, 23.7 \pm 7.94 years old) were enrolled in this study. Patients over 70 years old or less than 18 years old were excluded. No patients had apparent inflammatory conditions before surgery. None of them had any disorder of immune system or metabolism or endocrine or liver cirrhosis. Preoperative informed consent was obtained from enrolled patients. This study has been approved by the ethical committee of the research center of Dental school of Shahid Beheshti University of Medical Sciences. Fourteen of them underwent one jaw and the other fourteen patients underwent two jaw osteotomy. Operations were performed with ordinary general anesthesia and Bilateral Sagittal Split Ramus Osteotomy (BSSRO) and Lefort1 Osteotomy with down fracture for maxillae. The operation time was measured from intubation to extubation. All patients were routinely administered 8mg Dexamethasone and 1g Cephazolin intravenously 0.5h before and 3h after surgery.

Blood samples

Blood samples were collected one day before and 4 hours after surgery. Blood was drawn into sterile tubes containing heparin. The plasma samples were separated by centrifugation at 1500g in 15min; the supernatant was stored at -80 °C until analysis.

IL-6 analysis

The plasma level of IL-6 was measured by enzyme – linked immunosorbent assay (ELISA) with a Human Interleukin-6 ELISA Kit (Biosource Inc. Belgium). The sensitivity for IL-6 was 2pg/ml.

Measurement of body temperature

Axillary's body temperature was measured 24hours before surgery. Classic mercury-in-glass thermometer was used for axillary recording.

Statistical Analysis

Descriptive statistics were followed by Pearson correlation coefficient and Multiple linear regression were used for comparison plasma level of IL-6 and body temperature; and plasma level of IL-6 and duration and type of surgery, and paired t test for assessing the difference in the level of IL-6 between before and after surgery.

Results

Table 1 shows the range, mean and standard deviation (SD) of age, and duration of surgery. 6 patients (20%) had post-operative fever.

Table 1. Descriptive statistics of age and duration of surgery. (n=28)

Variable	Range	Mean	SD
Age	18-59	23.7	7.94
Duration of surgery	3-7	4.8	1.21

Descriptive statistics of IL-6 levels are shown in table 2. Plasma level of IL-6 increased 4h after surgery, and it was statistically significant (P<0.05).

Table 2. Descriptive Statistics of plasma IL-6 before and 4 hours after the surgery. (n=28)

Variables	Range	Mean	SD	95% C I for mean		
				Lower	Upper	
IL-6*	Before	7-104	20.6	21.56	12.55	28.65
	After	52-345	134.54	85.02	102.78	166.28

*pg per ml

There was a significant elevation in IL-6 concentration after orthognathic surgery (P<0.05). Multiple regression (R²=0.238, P<0.05) showed that

duration of surgery having relationship with plasma IL-6, in other word, with increasing the duration of surgery, the level of IL-6 will be increased, but we could not find any relationship between IL-6 concentration and fever. We also found a positive correlation between postoperative level of IL-6 and fever.

Discussion

Acute-phase response (APR) is initiated in response to injury. The aim of this reaction is to prevent ongoing tissue damage, enhance body defense against pathogens and activate the repair process (19). APR is characterized by leukocytosis, fever, as well as induction of synthesis of various acute-phase proteins (APPs) which leads to changes in the plasma concentrations of them (20). The main stimulator of APP production is IL-6, produced during inflammatory processes and acts on hepatocytes in order to produce APPs (21). IL-6 is produced by various types of cells including T cells, B cells, monocytes etc, and plays a major role in host defense mechanisms, regulation of immune response and acute phase reactions (22). High level of this cytokine was found in sinovial fluids of patients with temporomandibular joint damage (18). Cytokine production reflects the degree of tissue trauma, so cytokine release is lowest with the least invasive and traumatic procedures (23, 24). We evaluated the plasma level of IL-6 and post operative fever only 4 hours after orthognathic surgery, rather than a longer term, because to exclude interfering factors such as post-operative infection of the surgical wound which may happen in the longer term. Furthermore, it was shown that the plasma level of IL-6 can be detected at 2 to 6 hours after incision (13). We found a significant elevation of plasma IL-6 level at 4 hours after surgery ($P < 0.05$). Moreover, the elevation of plasma IL-6 level was correlated with the duration of surgery ($P < 0.05$), which was similar to those observed in the previous studies (25, 26). The correlation of the IL-6 level with the duration of surgery is generally associated with this fact that IL-6 level is a marker reflecting the magnitude of surgical trauma (27-29).

Chachkhiani et al. reported a transient elevation in IL-6 concentration in plasma 12 hrs after resection of colorectal cancer but after 24 and 48hrs there was not any difference with the levels before surgery (30). We also found a significant increase in IL-6 level, but due to ethical considerations we cannot take any further samples after 4 hours.

We could not find any significant correlation between fever and IL-6 concentration in plasma, whereas Baigri et al. (15) and Miyawaki et al. (25) reported significant correlation between fever and IL-6 concentration. The difference between the results

may be due to the injection of corticosteroids before and immediately after the surgery in our study which in turn can decrease the production PGE2 and other arachidonic acid metabolites which act as pyrogen mediators. It is concluded that IL-6 is an important inflammatory mediator that its concentration is increased with the duration of surgery, in other word, there is a direct correlation between its concentration and the amount of the trauma during the surgery.

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