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Surgical stress response following otolaryngology head and neck surgery as assessed by serum interleukin-6 level

Kenichi Takano, Naoki Hyakushima, Ryuta Kamekura, Fumie Ito, Tetsuo Himi

ABSTRACT

Aims: Various head and neck surgical procedures are performed in otolaryngology, which are associated with wide range of surgical stress. Currently, minimally invasive surgeries are preferred and widely accepted. The purpose of this study was to assess the postoperative stress response in order to determine surgical stress in head and neck otolaryngology. Methods: Serum interleukin-6 (IL-6) level of 59 patients who underwent otolaryngology surgery under general anesthesia was measured by enzyme-linked immunosorbent assay 24 h post-surgery. Patients were categorized into nine groups according to the surgery methods: (a) Ear, (b) Nose, (c) Larynx, (d) Tonsil, (e) Adenoid and tonsil, (f) Parotid gland, (g) Thyroid, (h) Head and neck tumors (HNT)-1, and (i) HNT-2. We analyzed the correlation between serum IL-6 level and the duration of surgery, blood loss, and C-reactive protein (CRP) level. Further, we investigated the postoperative serum IL-6 level of patients in each group. Results: There was a significant correlation between serum IL-6 level and the duration of surgery, blood loss, and CRP level. Serum IL-6 level was significantly higher in the HNT than any other groups. Conclusion: Serum IL-6 measurement is valuable to indicate degree of surgical stress associated with various otolaryngology head and neck surgical procedures.

Keywords: Interleukin-6, Head and neck surgery, Postoperative stress response, Surgical stress

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INTRODUCTION

The activation of the cytokine network is crucial for acute-phase response to stimuli such as surgical stress [1]. Surgical trauma can stimulate acute-phase response, which is thought to be mediated by cytokines including interleukin (IL)-6, IL-8, tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP). Serum IL-6 level was

identified as a sensitive early marker of tissue damage, and was found to be correlated with the severity of trauma, blood loss, and duration of surgical procedures [2–4]. Moreover, significant surgical trauma has been associated with increased IL-6 response [5]. Compared to other available markers, IL-6 showed better correlation with the magnitude of injury and systemic inflammatory response [6].

In head and neck otolaryngology, various surgical procedures are employed. These procedures have been associated with a wide range of surgical stress. For instance, laryngeal microsurgery (LMS) and endoscopic sinus surgery (ESS), which require no incision of the skin, may induce less inflammatory response when compared to head and neck cancer surgery using the microvascular free flap reconstruction technique. Currently, minimally invasive surgery techniques are preferred and widely accepted. However, to best of our knowledge, no studies have been performed to objectively compare surgical stress among various otolaryngology head and neck surgeries. In the present study, we evaluated serum IL-6 level at early postoperative period following otolaryngology head and neck surgery to investigate the postoperative stress response and assess surgical stress in head and neck otolaryngology.

MATERIALS AND METHODS

Patients

A total of 59 patients (median age of 48.0±23.1 years (± standard deviation); range 3–80 years) who underwent otolaryngology surgery under general anesthesia at Sapporo Medical University were included in the present study. Written informed consent was obtained from all patients, and the study was performed under a protocol approved by the hospital ethics committee. All patients had no inflammatory disease prior to surgery. As given in Table 1, patients were divided into nine groups according to the type of surgery performed (a) ear (tympanoplasty for cholesteatoma, cochlear implant, or stapes surgery for otosclerosis), (b) nose (ESS for chronic sinusitis), (c) larynx (LMS for polypoid or transoral laser microsurgery for early laryngeal cancer), (d) tonsil (tonsillectomy for recurrent tonsillitis or tonsillar focal infection), (e) adenoid and tonsil (adenoidectomy or tonsillectomy for obstructive sleep apnea syndrome), (f) parotid gland (superficial lobectomy of the parotid gland for benign tumor), (g) thyroid (hemithyroidectomy for adenomatous goiter), (h) head and neck tumors (HNT)-1 (neck dissection (ND) for neck lymph node metastasis, total laryngectomy and ND for laryngeal cancer, or total thyroidectomy and ND for thyroid cancer), and (i) HNT-2 (primary oropharyngeal cancer resection and reconstruction with radial forearm free flap or total pharyngolaryngeal resection for hypopharyngeal cancer using a jejunal flap).

Blood sample collection

Venous blood samples were obtained from patients upon admission and 24 h after surgery. Serum was isolated and stored at −80°C. Venous blood samples 24 h before surgery were also obtained from 15 patients.

Assessment of IL-6 and CRP levels

Interleukin-6 level was analyzed using a commercially available solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) kit with an IL-6 monoclonal antibody (R&D Systems Co, Minneapolis, MN, USA). Serum CRP level was measured and analyzed at the Department of Laboratory Diagnosis, Sapporo Medical University. Furthermore, duration of surgery was recorded and intraoperative blood loss was evaluated.

Table 1: Clinical characteristics and operative surgical procedures in each patient groups.

	n	Age (years)	Operative time (minutes)	Amount of bleeding (ml)	Operative procedures
Ear	8	27.8 ± 20.1	204.0 ± 145.3	45.0 ± 85.0	Tympanoplasty, cochlear implant, stapes surgery
Nose	7	48.0 ± 20.4	111.3 ± 62.2	165.7 ± 247.5	Endoscopic sinus surgery
Larynx	4	66.3 ± 13.0	39.5 ± 31.2	Not Detectable	Laryngeal microscopic surgery
Tonsil	13	38.8 ± 14.4	66.8 ± 18.3	15.4 ± 37.6	Tonsillectomy
Adenoid and tonsil	5	5.2 ± 1.3	77.6 ± 11.5	80.0 ± 18.7	Adenoidectomy + tonsillectomy
Parotid gland	5	57.2 ± 12.8	147.0 ± 85.3	78.0 ± 41.5	Superficial lobectomy of the parotid gland
Thyroid	4	64.5 ± 9.7	146.3 ± 105.0	60.0 ± 46.2	Hemithyroidectomy
Head and neck 1	7	54.7 ± 27.2	261.9 ± 165.4	342.9 ± 250.7	Total laryngectomy, neck dissection
Head and neck 2	5	60.4 ± 6.7	566.6 ± 283.1	734.0 ± 710.1	Oropharyngeal or hypopharyngeal cancer with free-flap reconstruction
					Not Detectable

Statistical analysis

Statistical analysis was performed using SPSS version 22 (IBM Analytics, Armonk, NY, USA). Differences between groups were assessed using the Tukey–Kramer method. Correlations between variables were evaluated using the Spearman's rank correlation coefficient. Data are expressed as the mean ± standard deviation. p values of < 0.05 were considered statistically significant.

RESULTS

Patient background

Clinical characteristics, mean surgery duration, and amount of blood loss of patients in each group are given in Table 1. The HNT-2 group had the longest surgery duration (566.6±283.1 min) and the greatest amount of blood loss (734.0±710.1 ml). In contrast, the larynx group had the shortest surgery duration and the least amount of blood loss.

Correlation between the serum interleukin-6 level and surgery duration or blood loss

There was a significant correlation between the duration of surgery and serum IL-6 level (Figure 1; Spearman's rank correlation test: rs = 0.611; p < 0.01). Blood loss was also significantly correlated with serum IL-6 level (Figure 2), Spearman's rank correlation test: rs = 0.742, p < 0.01.

Correlation between serum interleukin-6 and C-reactive protein levels

C-reactive protein has been widely used as an early marker for inflammatory response. The correlation between serum CRP level and IL-6 concentration 24 h after surgery is shown in Figure 3. There was a significant correlation between serum CRP and IL-6 levels (Figure 3; Spearman's rank correlation test: rs = 0.496; p < 0.01).

Interleukin-6 level in various otolaryngology head and neck surgical stress

The preoperative serum IL-6 level obtained from 23 patients was 0.85±0.77 pg/ml. The postoperative serum IL-6 level at 24 h post-surgery for each patient group is shown in Figure 4. Serum IL-6 level in the ear, nose, and larynx group was 8.6 ± 5.9, 32.4±20.2, and 4.6±3.9 pg/ml, respectively. Interleukin-6 level for the tonsil group was 12.2±8.5 pg/ml, whereas the level for the Adenoid and tonsil group was 24.8±24.7 pg/ml. Interleukin-6 level for the parotid gland and thyroid groups was 18.5±12.4 and 25.9±21.9 pg/ml, respectively. Serum IL-6 level was significantly higher in the HNT than other groups, with the HNT-1 and HNT-2 groups displaying 100.5±86.7 and 285.8 ± 187.1 pg/ml of serum IL-6, respectively. No

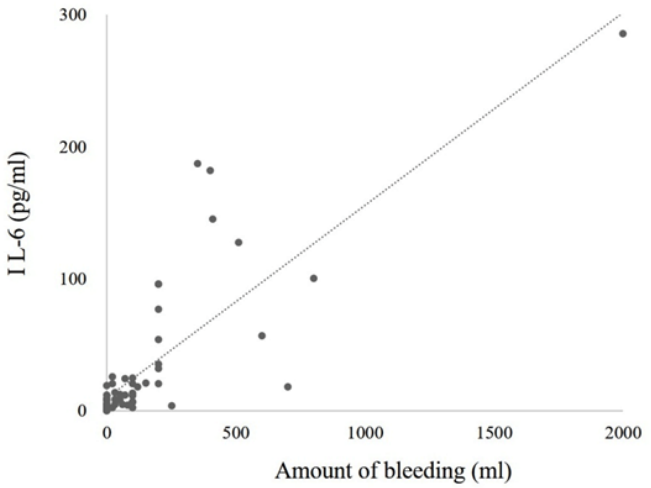

Figure 1: Correlation between the duration of surgery and serum IL-6 level.
(Spearman's rank correlation test: rs = 0.611, p < 0.01)

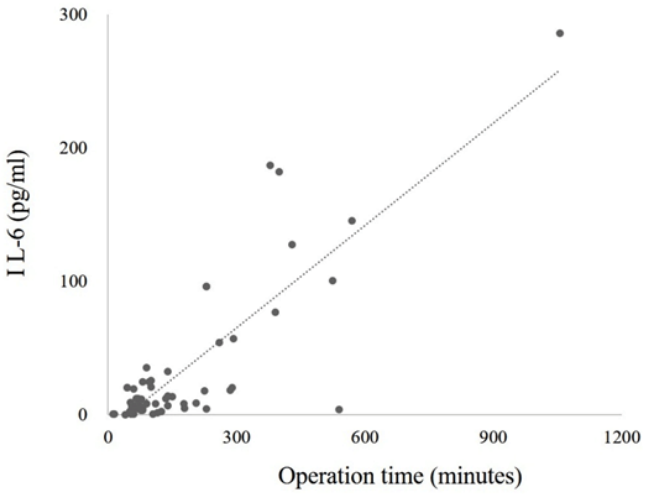

Figure 2: Correlation between the amount of blood loss and serum IL-6 level.
(Spearman's rank correlation test: rs = 0.742, p < 0.01)

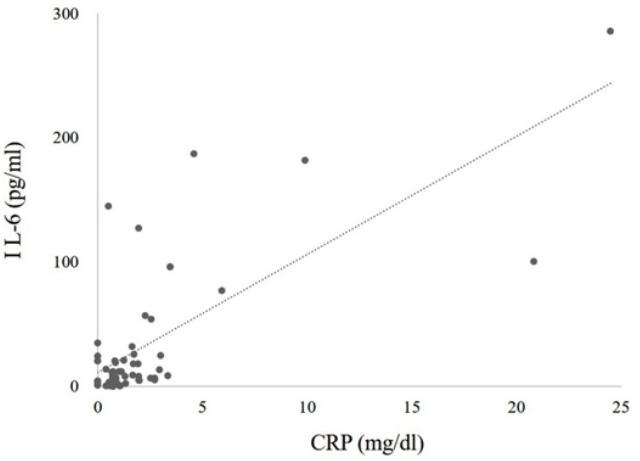

Figure 3: Correlation between serum CRP and IL-6 levels.
(Spearman's rank correlation test: rs = 0.496, p < 0.01)

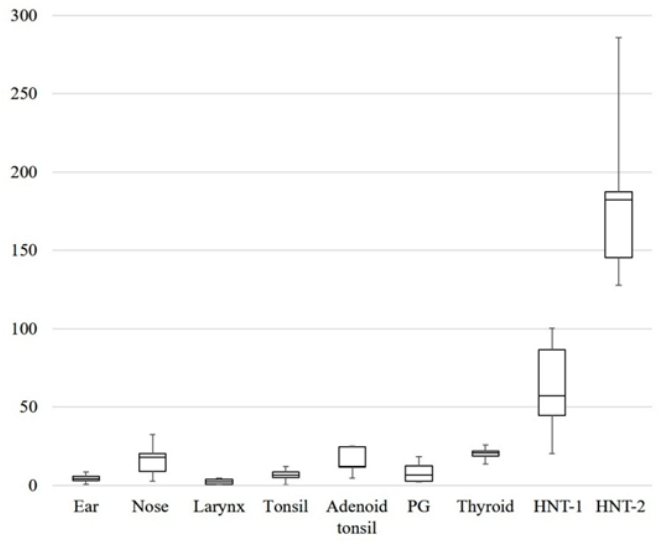

Figure 4: Interleukin-6 level in various otolaryngology head and neck surgical stress. The level of serum IL-6 was determined for each otolaryngology head and neck surgery group at 24 h post-surgery. Serum IL-6 level was significantly higher in the HNT-1 and HNT-2 groups when compared to other groups evaluated in the study. Abbreviations: PG: Parotid gland, HNT: Head and neck tumor

significant differences in serum IL-6 level were observed between groups, except for the HNT-1 and -2 groups.

DISCUSSION

Various surgical procedures are utilized in otorhinolaryngology. Interleukin-6 activation is known to play a role during acute response to operative trauma [2–4]. The present study is the first to evaluate surgical stress associated with otolaryngology head and neck surgeries by analyzing serum IL-6 level during early postoperative period.

Serum IL-6 level has been acknowledged as an indicator of surgical stress [7–9]. Although TNF-α and IL-8 were also thought to mediate acute-phase response due to surgical trauma, they were not detected in significant amount or their levels were below the limit of detection by ELISA in the present study. Interleukin-6 is produced by activated monocytes, macrophages, T cells, B cells, epithelial cells, and fibroblasts as an acute phase protein during operative damage [10]. Interleukin-6 production at surgical wound site has been reported and its level increased rapidly and peaked at 24 h after surgery [11, 12]. Elevated serum IL-6 level resulting from local production was thought to reflect the degree of surgical damage and cause a systemic immunological effect [13]. Thus, serum IL-6 level can be utilized as an early and sensitive marker of surgical tissue damage [7, 14].

Interleukin-6 and CRP were described to correlate with the severity of trauma, blood loss, and the duration of surgery [2]. Our results demonstrated a significant correlation between serum IL-6 and CRP levels. IL-6 induces the maturation of B-cell lymphocytes and synthesis of acute phase proteins including CRP in the liver [15]. Duration of surgical procedures and amount of blood loss were also shown to influence the degree of surgical damage [16]. Although changes in CRP or IL-6 levels may be induced by blood loss only, the amount of bleeding is generally thought to be proportional to surgical invasion. Indeed, in the present study, serum IL-6 level was also significantly correlated with blood loss and duration of surgery, and the extent of surgical stress was affected by these parameters. Our data revealed that serum IL-6 level can be used as a marker for surgical stress associated with otolaryngology head and neck surgery.

Otolaryngology head and neck surgeries comprise various surgical procedures that may be associated with surgical stress. As expected, the larynx group (LMS) showed the lowest serum IL-6 level, whereas the two HNT groups showed significantly higher IL-6 level when compared to other groups. Although low serum IL-6 level was also observed in the Tonsil group, adenoidectomy increased the IL-6 level approximately two-folds. No significant difference in surgery duration was observed between the HNT-1 and ear groups; however, the HNT-1 group displayed 7.6-fold increase in blood loss when compared to the ear group. In addition, the HNT-2 group showed approximately two-fold increase in surgery time and blood loss when compared to the HNT-1 group. The degree of surgical stress is known to be affected by surgery length and blood loss [16], which was reflected by the level of IL-6. Microvascular free flap reconstructions, which are considered more invasive, were included in the HNT-2 group. Elevated concentration of serum inflammatory cytokines has been reported in major and invasive surgical procedures. This revealed a close relationship between the invasion of cavities and severity of tissue damage [17–19]. Surgical procedures in the HNT-2 group may cause more extensive tissue injury and consequently a greater release of IL-6.

CONCLUSION

Measurement of serum interleukin-6 level is a valuable indicator to evaluate the degree of surgical stress in otolaryngology head and neck surgeries, because it is measurable and can be observed as a single peak of induction at early times following surgery.

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Author Contributions

Kenichi Takano – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Naoki Hyakushima – Substantial contributions to

conception and design, Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Ryuta Kamekura – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
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Tetsuo Himi – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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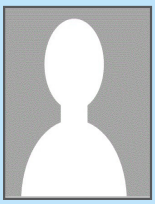

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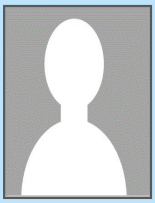

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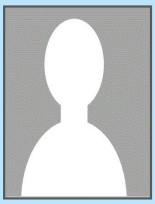

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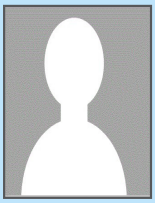

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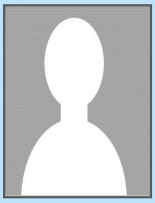

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