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Alteration of Interleukin-4, Interleukin-6 Levels, and Post-operative Pain Intensity

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Abstract

INTRODUCTION: Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Pain can be both a symptom of tissue trauma associated with surgery or disease in itself. Surgical procedures may induce different alterations of interleukin (IL)-4 and IL-6 that affect the variation of pain intensity during surgery. Therefore, appropriate pain management during a surgical procedure may reduce postoperative morbidity caused by surgical pain.

METHODS: This prospective cohort study included patients by consecutive sampling from all general anaesthetic patients in Dr. M Djamil Hospital and Andalas University Hospital, Padang, West Sumatera. We collected data from early November 2021 until the end of January 2022 and got 90 patients that suit the criteria. All patients signed informed consent to check their interleukin level and pain intensity before and after surgery. We assessedIL-4 and IL-6 using the Sandwich-ELISA technique and pain intensity using the numeric rating scale (NRS). We also measured length of surgery and its correlation to IL-4, IL-6, and NRS score. Patients were anesthetized with General Anesthesia and received the same fentanyl range of dosage (3-5) mcg/kg Ketorolac 30 mg and Tramadol 100 mg intravenous were given for postoperative analgesia.

RESULT: We found a significant correlation between ΔIL-6 with surgical procedures, ΔNRS score, and length of surgery p = 0.039, p = 0.002, and p = 0.008, respectively). Whereas ΔIL-4 shows no significant correlation to surgical procedures, ΔNRS score, and length of operation (0.868, 0.195, and 0.112, respectively). Our result also found a significant correlation between ΔNRS and surgical procedures (p = 0.013).

CONCLUSION: Surgical procedures with severe tissue trauma may trigger high secretion of ΔIL6 and stimulate high pain intensity after the surgical procedure.

Introduction

According to the International Association for the Study of Pain (2020), pain is “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Pain is always a personal experience influenced by biological factors, psychological, and social in different levels [1]. Pain may last from hours to weeks and is associated with acute tissue damage or trauma, inflammation, a surgical procedure, or a straightforward disease process. Fentanyl is the potent synthetic opioid frequently used as an analgetic in intubated patients and severe cases of pain. Nevertheless, there is an individual’s variability in response to fentanyl that causes the dosage from one patient and others to be different [2].

Based on immunology theory, interleukin (IL)-6 as a pro-inflammation cytokine has a rule in pain modulation. The Janus-activated kinase/signal transducer activator of transcription (JAK/STAT) is the most well-studied pathway that is activated as a response to signal-transducing cytokine receptors. It can sensitize nociceptive receptors and reinforce pain stimulation [3]. Surgical procedures induce elevated IL-6 in the first 3 h and variations of surgical procedures and post-operative management may influence discrepancies in the magnitude of IL-6 elevation [4].

On the other hand, tissue trauma and destruction also release an anti-inflammation cytokine that has the opposite rule to IL-6. One of the anti-inflammation cytokine in pain modulation is IL-4 which acts as a pleiotropic regulator and neuroprotection. The beneficial effect of IL-4 is the inhibition of production and release of pro-inflammation cytokine, chemokine, protease, and reactive oxygen species [5]. IL-4 could induce macrophages M2 to produce endogen opioids and triggered peripheral opioid receptors to reduce pain sensation [6]. We, therefore, assessed the comparison between several surgeries on releasing IL4 andIL6 and count the numeric rating scale (NRS) to show the pain intensity experienced by the patient. Our aim in this research is to analyze the correlation between the alteration of IL-4 and IL-6 and the patient’s response to pain after surgery. We also analyze

between length of surgery and IL-4, IL-6, and NRS score among surgical procedures.

Patients and Methods

Patients

This prospective cohort study recruited patients by consecutive sampling method from all elective general anesthetic patients in Dr. M Djamil Hospital and Andalas University Hospital, Padang, West Sumatera, Indonesia. The patient must not routine consume opioid and don't have psychiatric, neurologic, or chronic pain issues and the range of age is between 16 and 65 years old. We collected data from all surgery that suit the criteria in early November 2021 until the end of January 2022 and got 90 patients. All patients signed informed consent to have their interleukin plasma level and the NRS score checked before and after surgery. Patients received the same fentanyl range of dosage (3–5 mcg/kg) when induction state and Ketorolac 30 mg and Tramadol 100 mg intravenous for postoperative analgesia.

Data and sample collecting procedures

The patient's history was collected through Medical records and direct dialogue with patients. We assessed pain intensity using the NRS score before the surgical procedure and excluded if the NRS score was >3. We collected 2 mL of blood just after induction of the anesthetic procedure and at the end of the surgery. Post-surgical NRS score assessed after patients wake in Post-Anesthesia Care Unit (PACU).

Measurement of cytokine level

Blood in EDTA tubes was centrifuged at 4000 rpm for 10 min. After the centrifugation, plasma was kept at -80^{0}C before measurement. The isolation of IL-4 and IL-6 was done in Andalas University Biomedic Laboratory and measure using the Sandwich-ELISA technique. Optical density (OD) was measured by spectrophotometric in 450 nm ± 2 nm wavelength. Human IL-4 and IL-6 can be counted by comparing OD samples with a standard curve

Statistics

We used SPSS Statistics 26 application to analyze all of the data. Wilcoxon test was performed to compare the levels of IL-4 and IL-6 before and after surgery. The correlation between interleukin with NRS score on each surgery was measured by Spearman's correlation analysis. The differences in variables between surgery groups were examined by Kruskal–Wallis test. Values of $p < 0.05$ were considered significant. Correlation between length of surgery and IL-4, IL-6, and NRS score measured using Pearson test. Several confounding variables were controlled by Spearman and Mann–Whitney analyses such as age and gender, respectively.

Ethical consideration

This research involves humans as research subjects. The ethical implications of this research follow the provisions of the Declaration of Helsinki and have passed the ethical test from the ethics committee of the Faculty of Medicine, Universitas Andalas Padang with number 574/UN.16.2/KEP-FK/2021. All medical matters relating to this research are confidential. Research subjects have the right to refuse to participate in the study if they do not agree.

Results

Out of 90 patients, 58 of them are females (64.4%) and 32 are males (35.6%) with ages ranging from 16 to 65 years old (mean 43.79 ± 14.8 years). Hypertension is the most frequent comorbidities of the subject (11.1%). The majority of patients' American Society of Anesthesiologists (ASA) score is 2. Laparoscopy and laparotomy are the most frequent surgery in this study (28.6% and 26.7%) (Table 1).

The highest ΔIL-4 level is on the removal tumor surgery followed by laparoscopy (0.6 and 0.4, respectively) (Figure 1). Meanwhile, ΔIL-6 was found highest in laparotomy and Open Reduction Internal Fixation operations (ORIF) as shown in Figure 2 (381.6 and 176.8, respectively). The alteration of NRS scores was found high in laparotomy followed by stabilization and decompression surgery (2.4 and 2.2, respectively) (Figure 3). Tympanomastoidectomy has the longest operation time (4.5 h) (Figure 4) and got the highest dosage of fentanyl (300 mg) (Figure 5).

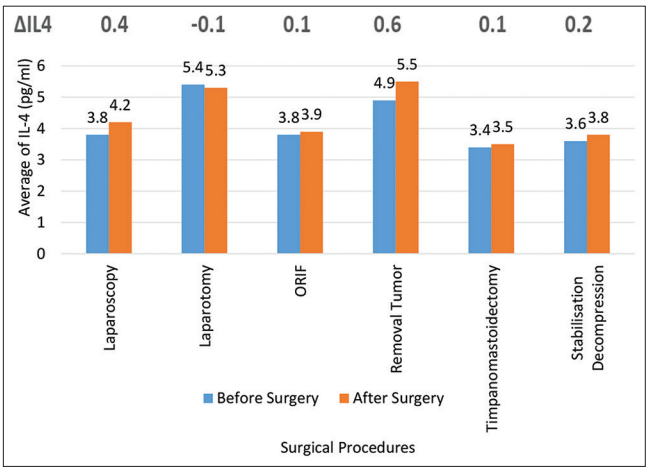

Figure 1: The average IL-4 value before and after surgery

Table 1: Demographic data

Characteristic	All patients N = 90
Gender (female-male)	32–58
Age (years), median (IQR)	**42.79 (16–65)**
ASA	
1	1 (1.1)
2	81 (90)
3	8 (8.9)
Surgical procedures	
Laparoscopy	**26 (28.6%)**
Laparoscopic cholecystectomy	15 (16.7)
Laparoscopic exploration	1 (1.1)
Laparoscopic adhesiolysis	3 (3.3)
Laparoscopic low anterior resection	2 (2.2)
Laparoscopic repair hernia	4 (4.4)
Laparoscopic hemicolectomy	1 (1.1)
Laparotomy	**24 (26.7%)**
Exploratory laparotomy	17 (18.9)
Laparotomy debulking	5 (5.6)
Relaparotomy repair fistula	1 (1.1)
Splenectomy	1 (1.1)
Open reduction internal fixation (ORIF)	**11 (12.1%)**
ORIF mandible	3 (3.3)
ORIF clavicle	3 (3.3)
ORIF humeral	2 (2.2)
ORIF radial	1 (1.1)
ORIF tibial	1 (1.1)
ORIF maxillofacial	1 (1.1)
Removal tumor	**22 (24.2%)**
Tumor excision	5 (5.6)
Hemimandibulectomy	1 (1.1)
Total thyroidectomy	4 (4.4)
Modified radical mastectomy	2 (2.2)
Wide excision	6 (6.7)
Tonsillectomy	2 (2.2)
Maxillectomy	1 (1.1)
Orchidectomy	1 (1.1)
Timpanomastoidectomy	**2 (2.2%)**
Stabilization and decompression	**5 (5.6%)**
Laminectomy	3 (3.3)
Spinal fusion	2 (2.2)
Comorbid	
Hypertension	10 (11.1)
Type 2 diabetes	4 (4.4)
Asthma	1 (1.1)
IL-4 before sugery (pg/mL), median (IQR)	3.61 (2.5–37.9)
IL-4 after surgery (pg/mL), median (IQR)	3.7 (3–34.7)
ΔIL-4 (pg/mL), median (IQR)	0.08 ([−3.2]– 8.4)
IL-6 before surgery (pg/mL), median (IQR)	148.05 (66.7–1255.4)
IL-6 after surgery (pg/mL), median (IQR)	207.34 (65.1–2246.4)
Δ IL 6 (pg/mL), median (IQR)	44.2 ((-417)– 2010.4)
NRS score before surgery, median (IQR)	1 (0–3)
NRS score after surgery, median (IQR)	3 (1–7)
Δ NRS, median (IQR)	2 (0–5)

*ASA: American Society of Anesthesiologists.

After analyzed correlation between confounding variables, like: Age and gender with IL-4, IL-6, and NRS score before and after surgery. We used spearman test for analyzed correlation between age with IL-4, IL-6 and NRS score (p > 0.05, among each variables). Mann–Whitney test we used to analyzed between

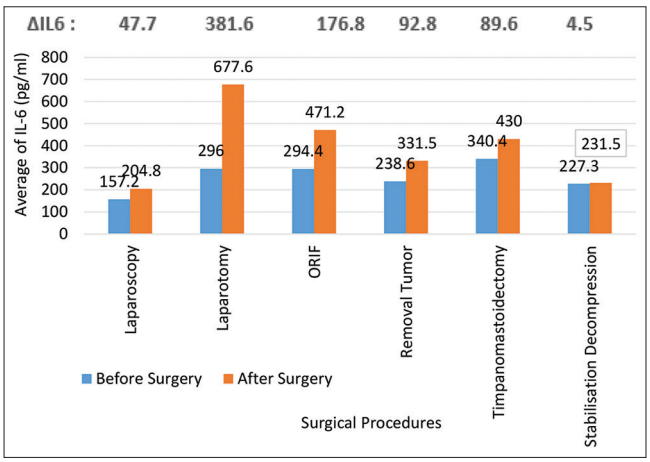

Figure 2: The average IL-6 value before and after surgery

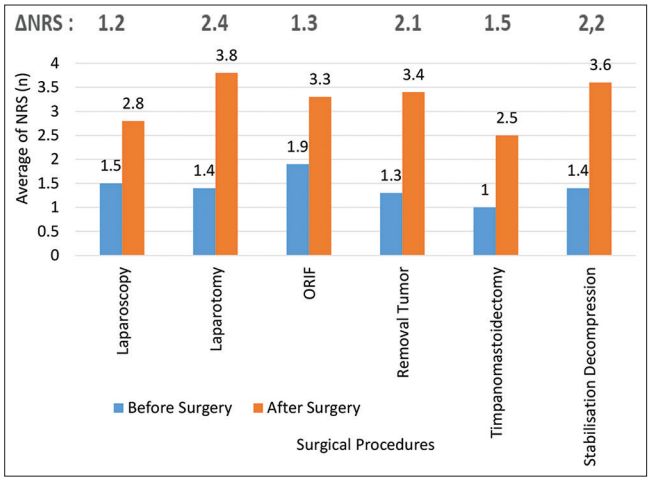

Figure 3: The average NRS value before and after surgery

gender with IL-4, IL-6, and NRS score (p > 0.05, among each variables).

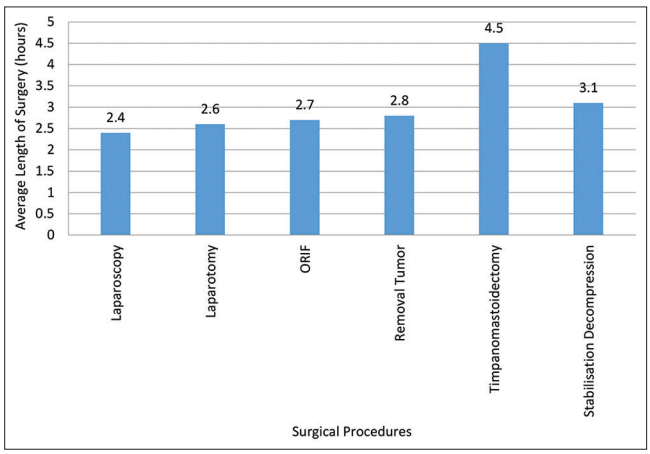

Figure 4: The average length of surgery for each surgical procedure

We analyzed the comparison between IL-4, IL-6, and NRS before and after surgery. The results showed that there was no significant difference between IL-4 before and after surgery in each surgical procedure (Table 2). But on the contrary, there were significant difference between IL-6 and NRS score before and after surgery in each surgical procedure except IL-6 for stabilization and decompression. Tympanomastoidectomy was not

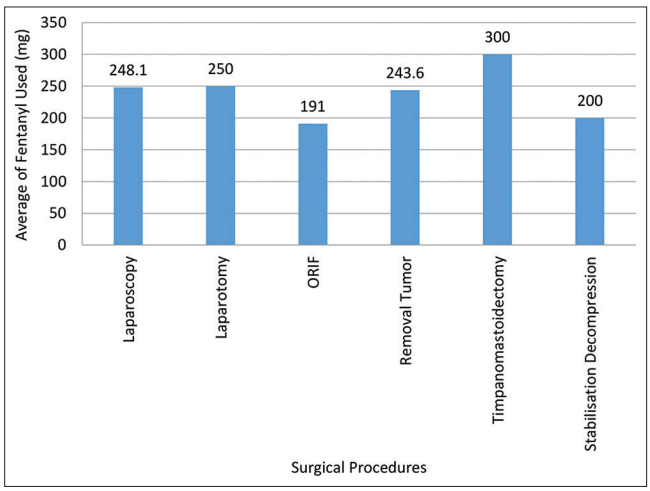

Figure 5: The average fentanyl used in each surgical procedures

Table 2: The comparison of IL-4 before and after surgery in each surgical procedures

IL-4 Before and After Surgery	Laparoscopy	Laparotomy	ORIF	Removal tumor	Stabilization and decompression
IL-4 before surgery, median (IQR)	3.68 (2.8–7.3)	3.56 (3.1–37.9)	3.44 (3–6.1)	3.71 (2.5–15.7)	3.61 (3.1–4.1)
IL-4 after surgery, median (IQR)	3.74 (3–7.5)	3.59 (3–34.7)	3.87 (3.2–5.3)	3.72 (3.1–24.1)	3.53 (3.1–4.5)
p	0.258	0.83	0.24	0.313	0.465

*Differences between before and after surgery groups in each surgical procedure were analyzed with Wilcoxon test. ORIF: Open reduction internal fixation, IL: Interleukin, IQR: Interquartile Range.

included because there were only two samples in the study (Tables 3 and 4).

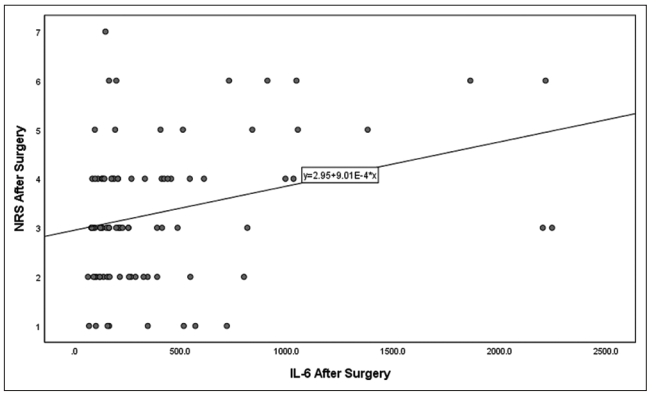

Figure 6: Linear correlation between IL-6 after surgery and NRS after surgery in all patients.

Based on Tables 3 and 4, it showed that mostly IL-6 concentration and NRS score always tend to increase significantly in each surgical procedure ($p < 0.04$).

We found significant difference of IL-6 after surgery, ΔIL-6 and ΔNRS score among each surgical procedures ($p = 0.003$ in three comparison test) (Table 5).

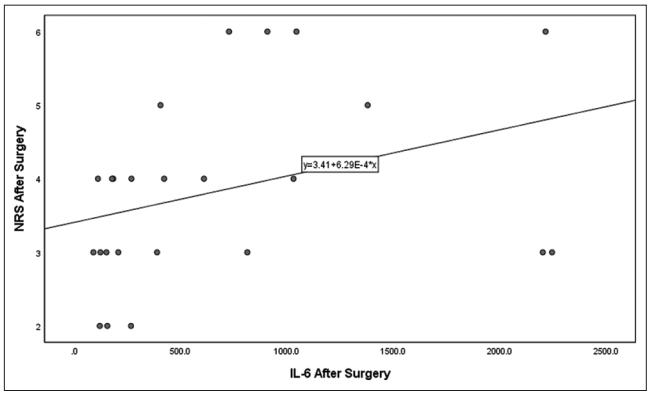

Figure 7: Linear correlation between IL-6 after surgery and NRS after surgery in laparotomy procedure

The correlation between IL-6 after surgery and NRS after surgery in all patients showed significant association ($r = +0.25$, $p = 0.01$), ΔIL-6 and ΔNRS also found significant ($r = +0.32$, $p = 0.002$). We also examined the correlation of Interleukins after surgery and NRS score in each surgical procedures. There were significant correlation between IL-6 after surgery and NRS after surgery in laparotomy procedure ($r = +0.47$, $p = 0.01$) (Table 5). Significant correlation also found between ΔIL-6 and ΔNRS in stabilization and decompression procedure ($r = +0.97$, $p = 0.01$) (Table 6).

We found positive linear correlation between IL-6 after surgery and NRS after surgery in all patients. ($r = +0.25$, $p = 0.01$) (Figure 6).

We found positive linear correlation between IL-6 after surgery and NRS after surgery in laparotomy procedure. ($r = +0.47$, $p = 0.01$) (Figure 7).

We found positive linear correlation between ΔIL-6 and ΔNRS in all patients. ($r = +0.32$, $p = 0.002$) (Figure 8).

We found positive linear correlation between ΔIL-6 and ΔNRS in stabilization and decompression ($r = +0.97$, $p = 0.01$) (Figure 9 and Table 7). The correlation between total fentanyl used and length of operation with ΔIL-4 and ΔIL-6.

We found positive linear correlation between Length of Operation and ΔIL-6. ($r = +0.27$, $p = 0.008$) (Figure 9).

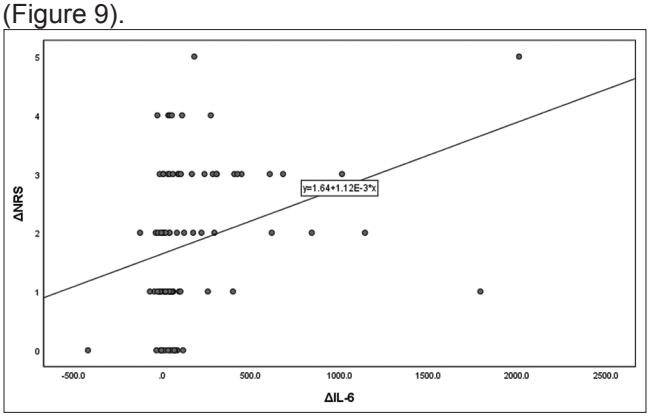

Figure 8: Linear Correlation Between ΔIL-6 and ΔNRS in all patients

Discussion

Our data showed a statistically significant difference of IL-6 after surgery, ΔIL-6 and ΔNRS among each surgical procedure. We noticed that the difference in surgical procedures could influence the degree of the inflammatory response, which in turn causes variations of cytokine secretion. To minimize the heterogeneity, we divided the surgical procedure into given groups (Laparotomy, Laparoscopy, Open Reduction Internal Fixation, Tympanomastoidectomy, and Removal Tumor) [Figure 10]. To minimize the heterogeneity of opioid usage, patients received the same fentanyl range of dosage

Table 3: The comparison of IL-6 before and after surgery in each surgical procedure

IL-6 Before and After Surgery	Laparoscopy	Laparotomy	ORIF	Removal Tumor	Stabilization and Decompression
IL-6 before surgery, median (IQR)	112 (66.7-522.5)	167.7 (81.1-1103.5)	155.1 (89-1255)	149.5 (86-829)	156.5 (102-572)
IL-6 after surgery, median (IQR)	160 (65.1-515.2)	397.8 (90.4-2246.4)	197.8 (102-1862)	254.9 (82.8-1051)	163.7 (90-546)
p	**0.007**	**0.001**	**0.006**	**0.006**	0.893

*Differences between before and after surgery groups in each surgical procedure were analyzed with Wilcoxon test. Bold figures indicate statistical significance. ORIF: Open Reduction Internal Fixation, IL: Interleukin, IQR: Interquartile range.

Table 4: The comparison of NRS before and after surgery in each surgical procedure

NRS Before and After Surgery	Laparoscopy	Laparotomy	ORIF	Removal Tumor	Stabilization and Decompression
NRS before surgery median (IQR)	1 (0-3)	1.5 (0-2)	2 (1-3)	1 (0-3)	1 (1-3)
NRS after surgery median (IQR)	3 (1-6)	4 (2-6)	3 (1-6)	3 (1-7)	3 (2-6)
p	**0.001**	**0.001**	**0.01**	**0.001**	**0.04**

*Differences between before and after surgery groups in each surgical procedure were analyzed with Wilcoxon test. Bold figures indicate statistical significance. ORIF: Open reduction internal fixation, IL: Interleukin, IQR: Interquartile range, NRS: Numeric rating scale.

(3–5 mcg/kg) when induction state. Some patients received additional dose of fentanyl in condition of increased blood pressure and heart rate due to pain stimulation during surgery with total fentanyl limitation up to 400 mcg.

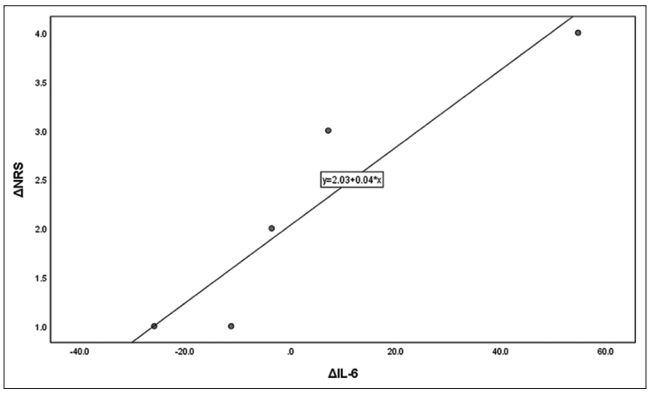

Figure 9: Linear correlation between IL-6 after surgery and NRS after surgery in laparotomy procedure

Our study showed that mostly all surgical procedures resulted in a significant increase in IL-6 after surgery compare to IL-6 before surgery. In the contrary, there was no significant difference between IL-4 before surgery and IL-4 after surgery. Our data showed that the elevation of IL4 after surgery was not as high as IL6. The phenomenon might happen because IL4 is not fully secreted just after the surgery. Instead, it takes 24 h to be secreted to the entire body and 14 days for the optimal elevation [7]. The secretion of IL-4 performs as an anti-inflammatory response to the location of surgery. The variations of its level during each surgery are caused by different aggregation of the macrophages and other pro-inflammatory mediators residing in the surgical spot. The severity of tissue trauma from the surgery is in line with the IL-4 secretion [8].

Analysis by comparing the difference between the average of IL-6 before and after surgery (ΔIL6) confirmed that the laparotomy procedure had a higher degree of change in ΔIL-6 than other procedures. Several authors compared laparotomy with laparoscopy procedures in the digestive field. The comparison showed higher ΔIL-6 in laparotomy surgery due to more severe trauma to the tissue. Higher postoperative IL-6 values found in the laparotomy group correspond to greater surgical stress. Laparoscopy surgery incites less stress response and therefore is associated with a lesser tissue injury than laparotomy surgery. The evaluation between laparoscopic and laparotomy colorectal resection patients found higher IL-6 elevation in the laparotomy group due to more severe trauma to the tissue. [9] However, Dunker *et al*. did not find significantly different IL-6 or CRP concentrations between the laparoscopic and laparotomy surgery groups in patients undergoing ileocolic or colonic resection for regional enteritis or colectomy for ulcerative colitis or familial adenomatous polyposis.[10] Factors that may have affected the disparity in IL-6 measurements include heterogeneity of the patient populations, ie malignant versus benign diseases (such as regional enteritis), the complexity of the procedure performed, and the occurrence of perioperative complications [11].]

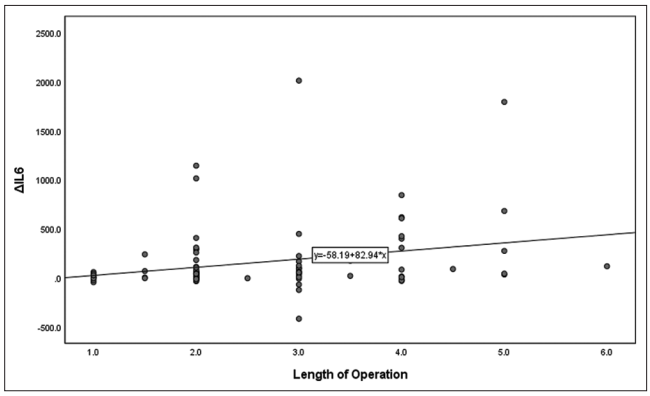

Figure 10: Linear correlation between length of operation and ΔIL-6

Table 5: The comparison of interleukins after surgery, NRS score, total fentanyl used, and length of surgery with surgical procedures

Interleukins, NRS, Fentanyl Dosage and Lenght Of Surgery	Laparoscopy	Laparotomy	ORIF	Removal Tumor	Stabilization and Decompression	Tympanomastoidectomy	p value
IL-4 after surgery, median (IQR)	3.74 (3–7.5)	3.59 (3–34.7)	3.87 (3.2–5.3)	3.72 (3.1–24.1)	3.53 (3.1–4.5)	3.5 (3.3–3.7)	0.95
IL-6 after surgery, median (IQR)	160 (65.1–515.2)	397.8 (90.4–2246.4)	197.8 (102–1862)	254.9 (82.8–1051)	163.7 (90–546)	429.9 (142.2–717.8)	**0.03**
NRS after surgery, median (IQR)	3 (1–6)	4 (2–6)	3 (1–6)	3 (1–7)	3 (2–6)	2.5 (1–4)	0.175
ΔIL-4, median (IQR)	0.09 ([−0.8]–3.7)	0.00 ([−3.2]–1.2)	0.14 ([−0.8]–0.7)	0.09 ([−1.8]–8.4)	0.00 ([−0.7]–0.9)	0.05 ([−0.1]–0.2)	0.88
ΔIL-6, median (IQR)	42.4 ([−417]–399.4)	103.6 ([−26.6]–2010.4)	41.7 ([−3.2]–843.1)	43.5 ([−123.6]–448)	−3.5 ([−25.9]–54.7)	89.6 (61.1–118.1)	**0.03**
ΔNRS, median (IQR)	1 (0–4)	2 (0–5)	1 (0–3)	2 (0–4)	2 (1–4)	1.5 (0–3)	**0.03**
Total fentany used (mg)	200 (100–500)	250 (250–250)	200 (100–400)	205 (100–400)	200 (100–300)	300 (300–300)	0.24
Length of surgery (h)	2 (1–5)	2 (1.5–5)	2 (1–5)	3 (1–5)	3 (2–4)	4.5 (3–6)	0.13

*Differences between Interleukin, NRS, Total fentanyl used, and length of surgery in every surgical procedure were analyzed with Kruskal–Wallis test. Bold figures indicate statistical significance. ORIF: Open reduction internal fixation, IL: Interleukin, IQR: Interquartile range.

Table 6: The correlation of IL-4 and IL-6 after surgery with NRS score after surgery in each surgical procedure

Interleukins	All patients	NRS after surgery				
		Laparoscopy	Laparotomy	ORIF	Removal tumor	Stabilization and decompression
IL-4 after surgery						
r	0.03	0.01	0.38	−0.11	−0.35	0.05
p	0.73	0.97	0.06	0.73	0.87	0.93
IL-6 after surgery						
r	**0.25**	−0.01	**0.47**	0.25	0.22	−0.10
p	**0.01**	0.93	**0.01**	0.45	0.31	0.87

*Correlation between Interleukin after surgery and NRS after surgery in each surgical procedure were analyzed with Spearman test. Bold figures indicate statistical significance. Δ: Delta, ORIF: Open reduction internal fixation, IL: Interleukin, NRS: Numeric rating scale.

We found that IL-6 after surgery and ΔIL-6 showed a significant correlation with the NRS after surgery and ΔNRS. The power of those coefficient correlations were strong enough with a positive trend, which means the elevation of IL-6 after surgery and ΔIL-6 influences the elevation of NRS after surgery and ΔNRS, respectively We also found that ΔNRS had a significant correlation with surgical procedures. Laparotomy had the highest ΔIL-6 level and highest ΔNRS value than other procedures. This result implies that high ΔIL6 may contribute to high ΔNRS in the laparotomy procedure. Sarah *et al*. found on chemotherapy-treated prostate cancer patients with (NRS 3) exhibited significant elevation of several pro-inflammatory cytokines, particularly IL-6. These findings suggest that the cytokines (IL-6, IL-8, Eotaxin, VEGF, and IP-10) that exhibited significant increases, particularly IL-6, are involved in the pathophysiology of chemotherapy-induced pain [12]. IL-6 is a powerful pro-inflammatory cytokine produced in response to peripheral nerve injury that mostly happens in a surgical procedure. It continues with the recruitment of other cytokines, promoting infiltration of T cells and then maintaining pain sensation [13].

Table 7: The correlation of ΔIL-4 and ΔIL-6 with ΔNRS score after surgery in each surgical procedure

Δ Inerleukins	All patients	ΔNRS				
		Laparoscopy	Laparotomy	ORIF	Removal tumor	Stabilization and decompression
ΔIL-4						
r	−0.12	−0.16	0.15	0.42	−0.14	−0.66
p	0.23	0.43	0.46	0.19	0.53	0.21
ΔIL-6						
r	**0.32**	0.14	0.27	0.30	0.41	**0.97**
p	**0.002**	0.48	0.18	0.35	0.053	**0.01**

*Correlation between ΔInterleukin and ΔNRS in each surgical procedure were analyzed with Spearman test. Bold figures indicate statistical significance. Δ: Delta, ORIF: Open reduction internal fixation, IL: Interleukin, NRS: Numeric rating scale.

We also found that the length of surgery significantly correlates with ΔIL-6. Duration of surgical procedure may affect IL-6 release. Our data form comparing ΔIL-6 and length of surgical procedures showed a strong enough coefficient correlation and positive trend. The study reported by Leung *et al*. reveals a similar elevation of IL-6 postoperative level during 48–72 h. The data suggest an elevation of IL-6 in every period of surgery [14]. Tzu-Chi Hsu also found there was an elevated trend of IL-6 concentration two hours after surgery and declined to baseline 48 hours after surgery [4]. Trauma caused by surgery will lead to an increased level of IL-6 during the 3 hours of surgery and will probably increase until 72 h [15].

Table 8: Correlation between Total Fentanyl Used and Length of Operation with ΔIL-4 and ΔIL-6

Total Fentanyl and Operation Length Factors	ΔIL-4 (pg/mL)	ΔIL-6 (pg/mL)
Total fentanyl used		
r	0.093	−0.069
p	0.381	0.519
Length of operation		
r	−0.169	**0.279**
p	0.112	**0.008**

Correlation between total fentanyl used and length of operation with ΔIL-4 and ΔIL-6 were analyzed with Spearman test. Bold figures indicate statistical significance. Δ: Delta, IL: Interleukin

Limitation

This study was conducted on samples that underwent different types of surgery. We also did not follow serial interleukin and NRS changes from the beginning and after surgery.

Conclusions

We conclude that every surgery could influence different responses to produce IL-6. The variation of IL-6 concentration may contribute to the ΔNRS discrepancy. Laparotomy procedures with high tissue stress may trigger the elevation of ΔIL-6 and stimulate high pain intensity.

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