

Influence of cytokines on the postoperative period

D. Jovanovic¹, D. R. Milovanovic², I. Jovanovic³, M. Folic², V. Jakovljevic^{4,5}

¹Department of Anesthesiology and Reanimatology, Clinical Centre "Kragujevac", Kragujevac

²Department of Clinical Pharmacology, Clinical Centre "Kragujevac", Faculty of Medical Sciences University of Kragujevac, Kragujevac

³Department of Immunology, Faculty of Medical Sciences University of Kragujevac, Kragujevac

⁴Department of Physiology, Faculty of Medical Sciences University of Kragujevac, Kragujevac (Serbia)

⁵University IM Sechenov, Department of Human Pathology, 1st MOSCOW State Medical, Moscow Russian Federation

Summary

Purpose of Investigation: The relationships between postoperative recovery and changes of circulating levels of pro- and anti-inflammatory cytokines. **Materials and Methods:** The study included prospectively a cohort of 51 females who underwent abdominal hysterectomy for benign diseases. Recovery was assessed with Quality of Recovery 40 (QoR-40) questionnaire and concentrations of four cytokines during the 72-hours period were measured using human sensitive enzyme-linked immunosorbent assay (ELISA) kits. **Results:** Total QoR-40 score significantly declined on the first and the second postoperative days and then returned to baseline ($p < 0.001$). Interleukin-17 serum levels had no significant trend ($p = 0.072$). Statistically significant patterns of concentration changes of interferon gamma ($p = 0.010$), interleukin-10 ($p < 0.001$), and transforming growth factor ($p = 0.016$) were found. There were no significant correlations between QoR-40 scores and concentrations of any cytokine, at prespecified study power for moderate relationships at least. **Conclusion:** Recovery after abdominal hysterectomy was rapid and complete and it was unrelated to serum concentration profiles of examined cytokines.

Key words: Hysterectomy; Postoperative recovery; Functional rehabilitation; Cytokines; Interleukins.

Introduction

A major surgery disturbs patient's quality of life during the period immediately after the intervention, known as postoperative recovery [1]. The researchers are intensively exploring pathophysiological basis of the postoperative recovery process as well as the measuring instruments in order to provide guidelines for practical implementation of those modalities of anesthesia, analgesia and surgery, which could improve it [2].

Surgical trauma activates several biological cascades collectively labeled as "host response to injury", including also the immune system pathways [3]. Inflammatory cascade, which consists of changes in cytokine levels and activity of various immune cells, is generally required for both the post-trauma repair of the tissue and the resolution of infections for post microbial invasions. On the other hand, tremendous fluctuations of cytokine levels, which appear after major surgery, have been associated with the emergence of serious postoperative complications, such as infections, sepsis, and delirium; for some cytokines, e.g. tumor necrosis factor- α (TNF- α) and interleukin-1b (IL-1 β), the association with disturbances of a patient's general well-being, inducing fatigue, malaise, insomnia, and irritability have also been documented [4,5]. However, the role of many other cytokines in different sickness

manifestations remains to be established during the postoperative period.

Many factors influence the balance between pro- and anti-inflammatory cytokines during the perioperative period, including the type and the extent of the surgery, anesthetics, and analgesics [6]. This opens the field for anesthesiologists to play an influential role in the patient's postoperative outcome, maintaining the most appropriate mode of analgesia and anesthesia for successful recovery [7, 8]. For example, it is known that opioid analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) exhibit the immunomodulatory activity, which also mirrors in changing cytokine concentrations with some differences between and within the pharmacological classes [9, 10]. The concentrations of interleukin-17 (IL-17), interferon- γ (IFN- γ), interleukin-10 (IL-10) or transforming growth factor beta (TGF- β) after abdominal hysterectomy, altogether with simultaneously investigating recovery (measured with Quality of Recovery 40, QoR-40) was insufficiently explored so far [11]. Therefore, the primary hypothesis of this study was that in women who underwent total abdominal hysterectomy, the recovery was rapid and that changes of circulating levels of two pro-inflammatory (IL-17, IFN- γ and two anti-inflammatory cytokines (IL-10, TGF- β) were markedly correlated with a QoR-40 total score, which

Table 1. — *QoR-40 total score and serum concentration of cytokines in the entire study population in different time points.*

Variable	Baseline	Visit 1	Visit 2	Visit 3	Visit 4
QoR-40 total score	188.6 ± 9.6 (165-200)	n.a.	170.6 ± 11.1* (146-189)	180.4 ± 11.2* (152-195)	187.7 ± 6.0 (174-200)
IL-17 (pg/mL)	25.0 ± 21.4 (7.0-159.0, 23.1)	20.4 ± 12.1* (4.4-71.0, 17.9)	20.3 ± 14.1* (7.1-66.8, 15.5)	22.8 ± 21.9 (3.7-151.0, 16.5)	22.4 ± 18.7 (3.8-129.3, 17.9)
IFN-γ(pg/mL)	740.6 ± 1846.9 (0-11394.8, 60.7)	646.3 ± 1826.6* (0-10302.7, 71.8)	591.7 ± 1956.5 (0-12845.6, 49.6)	739.8 ± 1845.8 (0-11634.3, 127.6)	255.0 ± 671.8* (0-3759.2, 38.4)
IL-10 (pg/mL)	77.2 ± 126.4 (0-557.7, 27.7)	88.5 ± 108.7 (10.2-690.8, 56.9)	47.0 ± 91.8* (0-540.1, 19.4)	58.7 ± 81.4 (0-330.5, 28.1)	45.5 ± 57.5 (0-296.6, 12.1)
TGF-β (pg/mL)	34.4 ± 13.6 (14.3-67.8, 32.8)	32.7 ± 14.5 (14.5-80.6, 30.1)	30.5 ± 11.1 (14.2-63.7, 28.8)	29.7 ± 11.6* (14.8-74.6, 27.8)	27.3 ± 12.8* (14.0-70.0, 25.7)

Numbers represent the mean ± standard deviation (minimal value, maximal value, median); baseline-preoperatively; visit 1, 2, 3, 4 - 3h, 24h, 48h, and 72h after surgery, respectively; * $p < 0.05$ in comparison with baseline (see text for details of statistic calculations); n.a.: not applicable.

was considered to be a measure of patient's postoperative improvement. The secondary objectives were to investigate the changing pattern of serum concentrations of different cytokines, their mutual relationships, and possible influence of some patients characteristics and analgesics on outcome measures during postoperative recovery.

Materials and Methods

The study was designed as interventional, time-series, non-therapeutic trial including the women who underwent abdominal hysterectomy successively, in the period from October 2011 to February 2013, up to the number of the pre-calculated total sample size. Eligible subjects met the following criteria: females, total abdominal hysterectomy due to benign disease (leiomyoma), American Society of Anesthesiologists physical status classification system (ASA) I or II, administration of morphine and ketoprofen, ketorolac or paracetamol. The patients with previous chronic use of anti-inflammatory drugs and opioids, recognized previous hypersensitivity to the study drugs and the history of medically important kidney or liver diseases were not included in the study. The study approval was obtained from the Institutional Ethics Review Board and all study participants were informed and signed their written consent.

The patients had general anesthesia. Analgesics had been prescribed independently of study researchers, at the discretion of anesthesiologist who was in charge in the intensive care unit during the patient's recovery, according to his or her clinical judgment and using the postoperative pain assessment tools [12].

Study data included the patient's age, ASA physical class, smoking habits, duration of surgery, and used analgesics modes. The postoperative recovery was the primary study outcome and it was assessed using the researcher-assisted, QoR-40 which was designed and validated to measure a patient's health status at post-surgery and anesthesia [2]. The sum of the individual items (grouped within five dimensions) generated a total score, considered to be the primary study variable, ranging from 40 (the worst) to 200 (the best) points. Venous blood samples (5-10 mL) were collected before saline infusion (V0), and 3 (V1), 24 (V2), 48 (V3) and 72 (V4) hours after the surgery. The samples were centrifuged and sera immediately separated and stored at -20°C until concentrations (pg/mL) of IL-17, IFN-γ, IL-10 and TGF-β were determined using human sensitive enzyme-linked immunosorbent assay (ELISA) kits and microplate reader (set to 450 nm), as previously described [13]. The cytokine concentrations were considered as primary independent variables.

Sample size calculation assumed statistically significant correlation coefficient (r) of at least 0.50 (moderate-to-very high) between QoR-40 total scores values and serum concentrations of any cytokine (IL-17, IL-10, TGF-β, IFN-γ) during the study period, with $\alpha=0.05$, $b=0.2$ and two-sided approach. The assumption was based on available data from similar studies investigating the QoR-40 scores (their changes and correlations) during post-operative periods [2, 11, 14]. The estimated sample size was 29 study subjects, initially, but approximately for a half more patients was finally included in order to decrease the influence of possible heterogeneity of study data and to increase the power of secondary analyses [15]. Statistical analysis included description methods, analysis of variance (one-way and repeated measures pairwise comparisons), Friedman test, Kruskal Wallis test, Wilcoxon Signed Rank test, and correlations (Pearson, Spearman's rho). All statistical tests were performed two-sided and the differences were considered statistically significant at the level of $p < 0.05$.

Results

The final study population included 51 females with the average age of 51.6 ± 7.8 years (the mean ± standard deviation), the youngest being 39 and the oldest 69 years. Among them, 76.5% were ASA I ($n=39$), 23.5% ASA II ($n=12$), and 43.1% were smokers ($n=22$). The average duration of surgery was 74.8 ± 26.4 (35-120) minutes. The four analgesic drug protocols had been identified, which were based on morphine, either as single therapy (19 subjects, 37.3%) or in combination with ketoprofen (14, 27.5%), ketorolac (6, 13.7%) or paracetamol (7, 13.7%). Principal drug doses and administration routes were as following: morphine 0.15 mcg/kg or 0.075 mcg/kg *iv*, ketoprofen 100 mg *iv inf*, ketorolac 30 mg *iv inf*, and paracetamol 1000 mg *iv inf*. The five women had the same analgesics but with some differences in dosing schedules and mutual combinations.

The total QoR-40 score decreased during early postoperative period and returned to preoperative values after three days (Table 1). In general, the scores during the study changed significantly ($p < 0.001$; ANOVA-repeated measures) with significantly lower values on the first two post-surgical days ($p < 0.05$; ANOVA-repeated measures, pairwise comparisons).

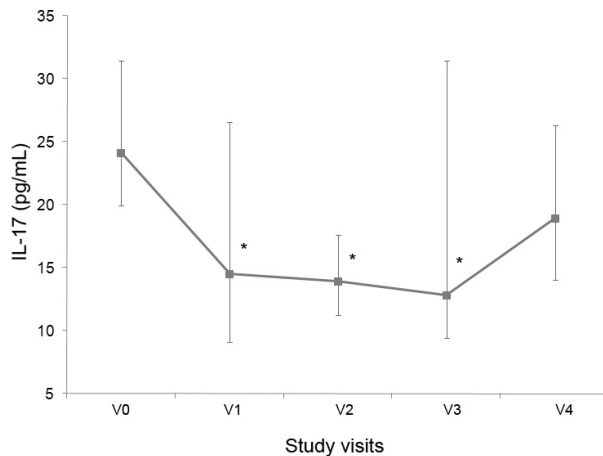


Figure 1. — Serum concentrations of IL-17 (pg/mL) in 14 patients receiving morphine plus ketoprofen analgesia at different time points; squares represent medians and vertical bars represent the 25th and 75th percentiles, respectively * $p < 0.05$.

There were no significant differences in IL-17 concentrations across the study visits (V0, V1, V2, V3, and V4) in the entire study population ($p = 0.072$; Friedman test). On the other hand, IL-17 concentrations were significantly different comparing the pairs of values from V0 and V1 ($p = 0.016$; Wilcoxon Signed Rank test), as well as from V0 and V2 study visits ($p = 0.007$; Wilcoxon Signed Rank test) (Table 1).

IFN- γ serum concentrations changed significantly throughout time points in the entire study population ($p = 0.010$; Friedman test). IFN- γ concentrations expressed the most pronounced within-subjects variability and across-visits fluctuations among other cytokines, but the general trend was a decrease. Absolute concentrations of IFN- γ made significant difference comparing to the pairs of values measured at V0 and V1 ($p = 0.020$; Wilcoxon Signed Rank test), V0 and V4 ($p = 0.004$; Wilcoxon Signed Rank test), V1 and V3 ($p = 0.023$; Wilcoxon Signed Rank test), V1 and V4 ($p = 0.046$; Wilcoxon Signed Rank test), V2 and V3 ($p = 0.018$; Wilcoxon Signed Rank test), and V3 and V4 study visits ($p = 0.005$; Wilcoxon Signed Rank test) (Table 1).

IL-10 concentrations were significantly different across the time points in the whole study population ($p < 0.001$; Friedman test). Statistically significant differences of serum concentrations of IL-10 were found among the values measured at V0 and V2 ($p = 0.007$; Wilcoxon Signed Rank test), V1 and V2 ($p < 0.001$; Wilcoxon Signed Rank test), V1 and V3 ($p = 0.006$; Wilcoxon Signed Rank test) and V1 and V4 study visits ($p < 0.001$; Wilcoxon Signed Rank test) (Table 1).

TGF- β serum concentrations were significantly different across study visits in the entire study population with a prominent trend towards decrease ($p = 0.016$; Friedman

test). The serum concentrations of TGF- β were significantly different comparing impaired values from V0 and V3 ($p = 0.023$; Wilcoxon Signed Rank test), V0 and V4 ($p = 0.001$; Wilcoxon Signed Rank test), and those from V1 and V4 at study visit ($p = 0.042$; Wilcoxon Signed Rank test) (Table 1).

There were no statistically significant correlations between QoR-40 total scores and serum concentrations of any cytokine (IL-17, IL-10, TGF- β , IFN- γ) during the study period ($p > 0.05$; Pearson correlation). Among all measured cytokines, the consistent, positive correlation (Spearman's rho) was found between IFN- γ , on one side, and IL-10 and TGF- β on another side.

Taking into account the changes (absolute differences) of cytokine concentrations from one study visit to the another one, there were positive, mainly low-to-moderate correlations between IFN- γ and IL-10 from V0 to V1 ($r = 0.301$, $p = 0.038$), V0 to V2 ($r = 0.366$, $p = 0.010$), V0 to V3 ($r = 0.453$, $p = 0.001$), V0 to V4 ($r = 0.458$, $p = 0.001$), V1 to V2 ($r = 0.583$, $p < 0.001$), V1 to V3 ($r = 0.449$, $p = 0.001$), V1 to V4 ($r = 0.305$, $p = 0.037$), V2 to V3 ($r = 0.454$, $p = 0.001$), V2 to V4 ($r = 0.321$, $p = 0.028$), and from V3 to V4 study visits ($r = 0.321$, $p = 0.028$). Similarly, there were positive, low correlations between absolute changes of IFN- γ and TGF- β serum concentrations from V0 to V1 ($r = 0.340$, $p = 0.018$), V0 to V2 ($r = 0.347$, $p = 0.016$), V0 to V3 ($r = 0.483$, $p = 0.001$), V0 to V4 ($r = 0.431$, $p = 0.002$), V1 to V3 ($r = 0.431$, $p = 0.002$), V1 to V4 ($r = 0.384$, $p = 0.08$), V2 to V4 ($r = 0.442$, $p = 0.002$), and from V3 to V4 study visits ($r = 0.442$, $p = 0.002$).

The observed changes of QoR-40 total scores across the study visit were not significantly associated with other study variables (age, ASA status, smoking status, duration of surgery, and analgesic protocol). In addition, there were no significant connections between cytokine serum concentrations and these variables, except for analgesic modes and IL-17.

Statistically significant suppression was found for IL-17 concentrations but analgesics did not influence IFN- γ , IL-10 and TGF- β serum concentrations. The patients receiving morphine plus ketoprofen had lower IL-17 serum concentrations in comparison with the subjects receiving other analgesic protocols. In these patients (but not in the others), a significant decreasing trend of IL-17 concentrations across the entire study period appeared ($p = 0.018$; Friedman test) and the absolute changes of IL-17 concentrations were significant comparing the pairs of values from V0 and V1 ($p = 0.016$; Wilcoxon Signed Rank test), V0 and V2 ($p = 0.003$), V0 and V3 ($p = 0.041$; Wilcoxon Signed Rank test), and V2 and V4 study visits ($p = 0.041$; Wilcoxon Signed Rank test) (Figure 1). Furthermore, significant differences of absolute changes of IL-17 serum levels from V0 to V1 visits ($p = 0.031$; Kruskal Wallis test), as well as from V0 to V3 at study visits ($p = 0.030$; Kruskal Wallis test) appeared in women receiving

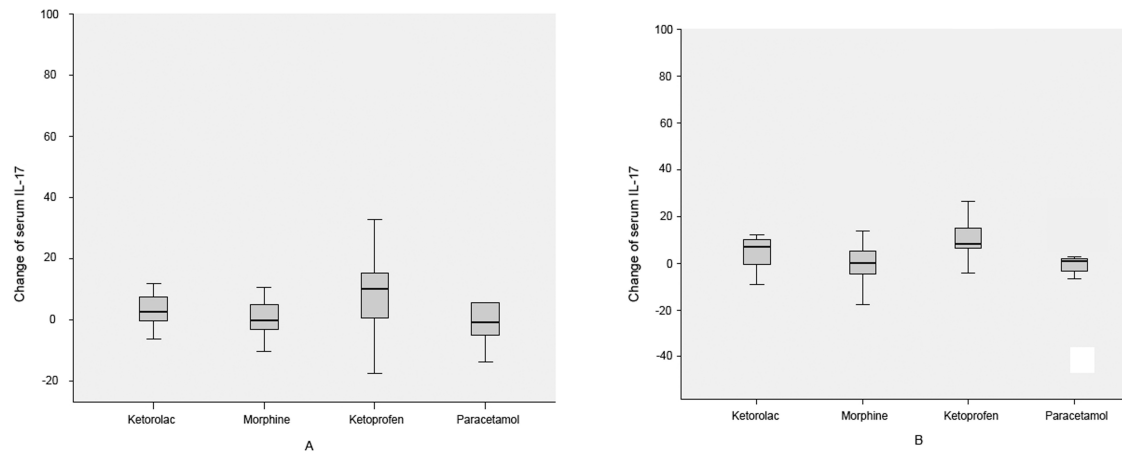


Figure 2. — Changes (absolute differences) of IL-17 concentrations from V0 to V1 (panel A) and from V0 to V2 study period (panel B) in different patient subgroups receiving morphine plus ketorolac (ketorolac), morphine (morphine), morphine plus ketoprofen (ketoprofen) and morphine plus paracetamol (paracetamol), excluding five subjects with numeric pain rating scale score of four at the final visit; the boxplots represent medians with interquartile ranges and whiskers.

different analgesic modes. The median of such changes of IL-17 concentrations from V0 to V1 study visits were significantly higher (e.g. more decrease in absolute concentrations) in patients who received morphine plus ketoprofen, in comparison to those with morphine alone ($p = 0.012$; Mann-Whitney-Wilcoxon test), and especially in comparison with the morphine plus paracetamol ($p = 0.014$; Mann-Whitney-Wilcoxon test) (Figure 2-A). In addition to this, the median of absolute changes of IL-17 concentrations from V0 to V2 study period were significantly higher (e.g. decreased more in absolute concentrations) in the patients who received morphine plus ketoprofen in comparison the subjects who received morphine alone ($p = 0.007$; Mann-Whitney-Wilcoxon test) and morphine plus paracetamol ($p = 0.031$; Mann-Whitney-Wilcoxon test) (Figure 2-B).

Discussion

The results of this study showed rapid recovery after abdominal hysterectomy, which was not significantly correlated with serum concentrations of the examined cytokines. Significant changes of IL-17 serum levels were not detected but serum concentrations of IFN- γ , IL-10 and TGF- β significantly fluctuated. The patients who received different analgesics had similar trends of postoperative recovery. Those females receiving morphine and ketoprofen had higher suppression of IL-17 in comparison with the patients receiving morphine, either as monotherapy or in combination with ketorolac or paracetamol. Similar previous research usually measured postoperative recovery with narrow-focused domains like those concerning drug adverse reactions (e.g. postoperative nausea and vomiting), patient's motor activ-

ity (e.g. mobilization speed) or healthcare performance indicators (e.g. hospital stay duration). To the present authors' knowledge (including the most recent search of available literature), there is only one study with a design similar to the present, but it focused on two anesthesia modalities, not on cytokine patterns [11].

Postoperative recovery results in re-establishment of the patient's health and social activities by mitigating "sickness behavior" symptoms and other side effects of surgery and anesthesia. In recent decades, it is recognized as an important clinical outcome. Nowadays, strong efforts to develop valid instruments for measurements of the phenomenon and creation of its biological basis are more relevant [16, 17]. For example, the concentrations of some cytokines correlated with "sickness behavior" (TNF- α , IL-1 β), fatigue (TGF- β), and depressive symptoms (IL-10, IFN- γ), all being important for domains of postoperative recovery [17, 18]. On the other hand, studies that attempted to verify the link between IL-17, depression, and fatigue showed negative results [19]. To the present authors' knowledge, no published research investigated the role of cytokines in postoperative recovery after abdominal hysterectomy, measured by using QoR-40 questionnaire, making these findings a novelty in the field.

Although many studies reported an IL-10 increase in the early postoperative period, one research group found no correlation between its levels and QoR-40 scores after a major spinal surgery [20]. In the present study, IL-10 finally declined below the baseline level probably because of the immunomodulating action of sevoflurane and the sudden drop of estrogen levels due to oophorectomy [21]. The studies evaluating IL-17 and TGF- β after surgery are rare, and no reports were found related to hysterectomy. One rare study included IFN- γ and postoperative recovery,

but it had a difference concerning the cytokine measurement methods [22].

In the present study, pro-inflammatory and anti-inflammatory cytokines were activated during postoperative recovery, but with oscillations within signaling pathways depending on the particular cytokine activity. Consistent interplay was found between IFN- γ and IL-10 and, in some to a lesser extent, IFN- γ and IL-10 fluctuations. Although no study investigated the same cytokine pattern in the similar clinical settings, there is evidence of the similar switch in cytokine dynamics concerning IL-6, TNF- α and IL-8, which indirectly supported the present findings [23]. The present results might suggest that immune signals depending on IL-17, IL-10, IFN- γ , and TNF- β activities are not included in major biological pathways of postoperative recovery after abdominal hysterectomy. Similarly, the increase in some other proinflammatory cytokines has not been correlated with the variation in postoperative recovery of women who had total laparoscopic hysterectomy [24].

Alternatively, the use of different analgesic modalities could modulate the response of examined cytokines and quicken postoperative recovery. For example, a study reported that opioid-based analgesia modes (pethidine, morphine, sufentanil) had immunomodulatory effects, significantly influencing serum IL-17 and IL-10 levels in women who underwent cesarean delivery [25]. In addition, some non-steroidal anti-inflammatory drugs (ketoprofen, ibuprofen) changed IL-17 mediated responses and improved postoperative recovery given either experimentally or during surgical treatment [26-28]. Therefore, synergistic action of analgesic drugs could contribute to the observed outcomes in the present study. These results provide solid theoretical basis for designing and conducting future studies, focusing particularly on the role of IL-17 activity in postoperative recovery and possibilities for putative therapeutic modulation.

Several limitations of the present study should be included when extrapolating its results to wider clinical context, such as limited sample size and the absence of placebo-control group, blinding, and randomization of patients to particular analgesic modality. The effects of unmeasured confounders (e.g. preoperative patients' health conditions and habits, body mass index, menopausal status, cycle of the day in premenopausal women, and initial diagnosis) should also be considered. However, the present believe that these constraints did not undermine the conclusion about primary study objective, but rather influenced the study power relating the analysis of the influence of confounding factors. The recent introduction of major technological advances, such as robotic surgery, strongly challenged conventional approaches and the current knowledge about mutual relationships between cytokine and metabolic response, treatment strategies, and patients' postoperative recovery [29]. Therefore, future extensive research is warranted, focusing on specific postoperative recovery domains, cytokines, analgesic modalities, and other factors with putative influence on postoperative quality of life, particu-

larly those ones that are suitable for modulation by clinicians' interventions.

Conclusion

The recovery after abdominal hysterectomy was rapid and complete and not significantly associated with fluctuations of blood concentrations of the examined cytokines. More prominent decline of IL-17 concentrations and higher QoR-40 scores in the patients receiving morphine and ketoprofen were however noticed.

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Corresponding Author:
D. JOVANOVIĆ, M.D., PH.D.
Department of Anesthesiology and Reanimatology
Clinical Centre "Kragujevac"
Zmaj Jovina 30
34000 Kragujevac (Serbia)
e-mail: danijeladrjovanovic@gmail.com