ORIGINAL ARTICLE

Anesthesia technique and serum cytokine concentrations in the elective cesarean section

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Background: Anesthesiologists should obtain the best technique for cesarean section (CS). This study designed to compare the effect of general anesthesia (GA) and spinal anesthesia (SA) on immune system function in elective CS. **Materials and Methods:** This descriptive study was performed on forty candidates for elective CS. They were randomly divided into GA and SA groups. The serum concentrations of interleukin (IL)-4, IL-6, IL-10, and IL-17 and interferon-gamma (IFN-γ) were measured using ELISA method prior to anesthesia (T0), immediately after the uterine incision (T1), 2 h post CS (T2), and 24 h post CS (T3). Data were analyzed using descriptive statistics and Chi-square, independent *t*-test, and repeated measures. **Results:** No significant differences were observed between the GA and SA groups regarding the serum levels of IL-4, IL-6, IL-10, IL-17, and IFN-γ. The serum levels of transforming growth factor beta (TGF-β) in the SA group were significantly ($P = 0.003$) more than that of the GA group at T3. **Conclusion:** According to the angiogenesis properties of TGF-β, it seems that SA probably affects the rate of recovery more than that of the GA.

Key words: Cesarean section, cytokine, general anesthesia, interleukin, spinal anesthesia

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INTRODUCTION

Currently, cesarean section (CS) is one of the most common and major surgeries.[1] Spinal anesthesia (SA) and general anesthesia (GA) techniques are used more commonly than other techniques for providing anesthesia for patients undergoing elective CS.[2] The condition of a newborn can be influenced by hypotension and uterine-peritoneal perfusion damage caused by the sympathetic block after SA. However, GA may induce neonatal depression, maternal aspiration, and difficulty in airway management.[2]

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Anesthesia and surgical tissue damage alter the function of the immune system.[3] Anesthesia causes metabolic and inflammatory changes and impedes the stress response, mainly by activating the pathway of cytokine production. Anesthesia may affect cytokine response through pharmacological effects or neurological and hormonal pathways.[4]

Interferon-gamma (IFN-γ) and interleukin 6 (IL-6) play important roles in hematopoiesis and immune response during stress and surgery.[5,6] IL-10 and IL-4 suppress the production of a variety of inflammatory cytokines, including IFN-γ and IL-6.[7,8]

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The IL-17 family plays a central role in the control of infections and directs many inflammatory factors against microorganisms in immune system-related diseases.[9] Transforming growth factor-beta (TGF-β) has multi-activities such as cell differentiation, inhibition of cell growth to modulation, and suppression of immune and inflammatory responses.[10]

Gu *et al*. compared the effects of preoperative epidural anesthesia (Group 1, n = 15) and postoperative epidural analgesia (Group 2, n = 15) on immune system functions. They reported that IL-17 concentration has significantly increased in the first group, whereas there was no significant difference in the second group.[11] Dermitzaki *et al*. compared the maternal serum level of TNF-α, IL-6, and IL-1 post CS using GA (n = 18) and neuraxial anesthesia (n = 18). The two groups had no significant difference in the serum concentration of the cytokines.[12] Considering that CS is the most common surgery in women, and the effects of surgery and anesthesia on immune system functions, the present study was designed to compare the effects of GA and SA on serum concentrations of IL-4, IL-6, IL-10, IL-17, IFN-γ, and TGF-β in elective CS. The result may provide a profound understanding of anesthetic aspects on immune system function.

MATERIALS AND METHODS

Subjects

This descriptive study was conducted on forty candidates for elective CS referred to the Nik-nafs hospital (Rafsanjan, southeast of Iran). The present study was approved by the research ethics committee of Rafsanjan University of Medical Sciences (IR. RUMS. REC.1395.125). Inclusion criteria were age between 20 and 40 years and singleton and uncomplicated pregnancy. Patients with contraindication to SA; those with a history of hypertension, diabetes, cardiovascular and immunodeficiency diseases, hepatitis B, and inflammatory diseases; those taking medicine during pregnancy; smokers; those with alcoholic consumption, and those with drug abuse were excluded from the study.

The sample size was estimated to be 15 people in each group based on the study of Dermitzaki *et al*.[12] and a significance level of 5%, a statistical power of 0.95, and using the $n=\frac{(Z_{1-\alpha/2}+Z_{1-\beta})^2\sigma^2}{(\mu_1-\mu_2)^2}$ formula. Further, σ was 0.1 in two groups, and μ1 was 0.17 in the GA and μ2 was 0.05 in the SA groups.

After arrival in the operating room, the researcher explained to the patients about the research procedure. After providing a written informed consent, the anesthesiologist randomly selected one of the forty sealed envelopes, twenty of which were marked G (GA) and twenty marked S (SA). Thus, the patient was placed in one of the groups. To remove confounding variables, in all CSs, the anesthesiologist and the gynecologist were considered the same.

In the SA group, the intravenous line was accessed with an 18G intravenous cannula at the forearm and 500-mL Ringer solution was administered. Electrocardiogram, noninvasive blood pressure, heart rate, and peripheral oxygen saturation were measured. SA was performed at the L3–L4 interspace in the sitting position using a 25G Quincke Spinal Needle (Japan) with the middle approach using 2.5 mL of 0.5% Marcaine (AstraZeneca, Sweden).[13] The sensory block level T4–T6 was induced.[2]

The GA was induced using 4–6 mg/kg sodium pentothal and 1–1.5 mg/kg succinylcholine. GA was maintained using a 50% O_2/N_2O mixture and 0.2–0.3 mg/kg atracurium.[2] After clamping the umbilical cord, 1–2 μg/kg fentanyl was injected intravenously.

The postcesarean pain relief protocol was similar for both groups. Patients received 50-mg pethidine I. M 4 h post cesarean and 2 h later, diclofenac sodium suppository was prescribed and repeated every 6 h for three times.[14]

Measurement of serum level of cytokines

To measure the serum level of cytokines, 5-mL venous blood was drawn before the anesthesia (T0), immediately after the uterine incision (T1), 2 h (T2), and 24 h post the CS (T3). The cytokine serum levels were measured using ELISA kits and according to the manufacturer's instructions (Karmania Pars Gene, Iran), and the final OD (optical density) was read by ELISA reader at 450-nm wavelength. In this study, the person who performed the laboratory tests was unaware of the grouping of patients.

Data were analyzed by SPSS version 18 (Chicago. SPSS Inc) using descriptive statistics, Chi-square test, and independent t-test. ANOVA's repeated-measures test was used to evaluate the changes of the serum cytokine concentration. In all tests, the significance level was <0.05.

RESULTS

In the present study, data of two participants in each group were outliers and thus were excluded from the analysis. The mean and standard deviation (SD) of the age of participants in the SA and GA groups were 32.83 ± 4.74 and 33.50 ± 4.87 years, respectively. The mean and SD of weight in the SA and GA groups were 83.72 ± 9.48 and

86.47 ± 12.99 kg and the mean and SD of duration of surgery were 36.11 ± 6.54 and 35.83 ± 8.09 min, respectively. There were no significant differences in age, weight, gestational age, and duration of surgery among the GA and SA groups. The mean ± SD serum concentration of IL-4, IL-6, IL-10, IL-17, TGF-β, and IFN-γ in the GA and SA groups is compared in Table 1.

Serum levels of interleukin-4 in general anesthesia and spinal anesthesia groups

Independent *t*-test revealed that the mean serum level of IL-4 at T0, T1, T2, and T3 was not significantly differing between the two groups [Table 1]. However, ANOVA's repeated-measures test showed that changes of mean serum level of IL-4 were significant in each group over time ($P < 0.001$) [Figure 1].

Serum levels of interleukin-6 in general anesthesia and spinal anesthesia groups

Statistical analysis showed that the mean serum level of IL-6 at T0, T1, T2, and T3 was not significantly differing between the groups [Table 1]. However, changes of mean serum level of IL-6 were significant in each group over time [Figure 2].

Status of interleukin-10 serum levels in general anesthesia and spinal anesthesia groups

Independent *t*-test showed that the mean serum level of IL-10 at T0, T1, T2, and T3 was not significantly differing between the two groups [Table 1]. The mean serum level difference of IL-10 was significant in both groups over time [Figure 3].

Status of interleukin-17 serum levels in general anesthesia and spinal anesthesia groups

Statistical analysis showed a significant decrease in the mean serum level of IL-17 in the SA and GA groups at

Table 1: The mean plasma concentrations of interleukin-4, interleukin-6, interleukin-10, interleukin-17, interferon-gamma, and transforming growth factor-beta in the studied groups in different times

Variable	Mean±SD		*P*
	SA (*n*=18)	GA (*n*=18)	
IL-4 (pg/mL)			
T0	15.67±0.73	15.79±0.54	0.558
T1	16.24±0.74	16.05±0.69	0.404
T2	16.50±0.68	16.93±0.70	0.063
T3	19.19±0.89	19.15±1.50	0.930
IL-6 (pg/mL)			
T0	9.96±1.40	8.93±2.01	0.068
T1	12.53±3.48	12.31±2.86	0.836
T2	17.12±4.95	16.85±4.60	0.858
T3	15.80±2.67	14.62±3.55	0.252
IL-10 (pg/mL)			
T0	16.05±6.13	18.69±4.33	0.861
T1	18.20±10.70	17.91±14.45	0.781
T2	22.26±3.99	27.33±11.21	0.064
T3	21.85±4.00	22.79±2.00	0.373
IL-17 (pg/mL)			
T0	29.08±13.22	31.45±16.03	0.631
T1	18.29±10.70	17.91±14.45	0.929
T2	8.28±7.95	8.42±8.06	0.959
T3	13.46±12.73	13.69±10.39	0.953
TGF-β (pg/mL)			
T0	8.85±5.99	13.25±7.77	0.066
T1	30.20±21.99	27.49±27.37	0.747
T2	33.95±22.21	35.00±24.82	0.895
T3	56.92±24.58	30.68±24.27	0.003*
IFN-γ (pg/mL)			
T0	69.14±35.50	66.04±32.40	0.780
T1	75.51±46.78	59.10±38.82	0.263
T2	142.20±103.79	125.59±104.24	0.626
T3	375.96±256.99	411.58±196.20	0.646

**P*<0.05. T0=Prior anesthesia; T1=Immediately postuterine incision; T2=2 h postsurgery; T3=24 h postsurgery; SA=Spinal anesthesia; GA=General anesthesia; SD=Standard deviation; IL=Interleukin; TGF-β=Transforming growth factor-beta; IFN-γ=Interferon-gamma

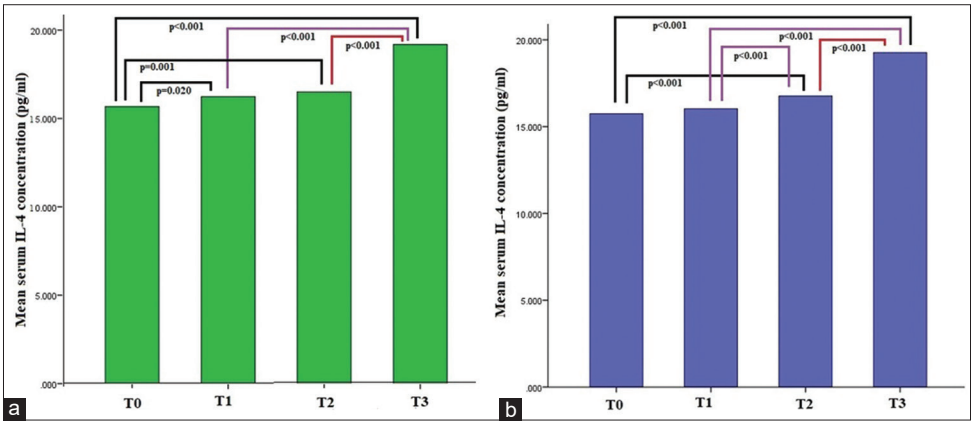

Figure 1: The serum levels of interleukin-4 in the SA and GA groups at different time points. (a) Spinal anesthesia, (b) general anesthesia. T0: Prior anesthesia, T1: immediately post uterine incision, T2: 2 h post CS, T3: 24 h post CS

T1, T2, and T3 compared to T0. The mean serum level of IL-17 at T2 had also significantly decreased compared with that at T1 in both groups [Figure 4]. Independent *t*-test revealed that the mean serum level of IL-17 at T0, T1, T2, and T3 was not significantly differing between the two groups [Table 1].

Serum levels of interferon-gamma in general anesthesia and spinal anesthesia groups

The difference in the mean serum level of IFN-γ at T0 was not significant in any of the groups compared to that at T1 and T2. However, this difference was significant in both groups compared to that at T3. The mean serum level of IFN-γ was

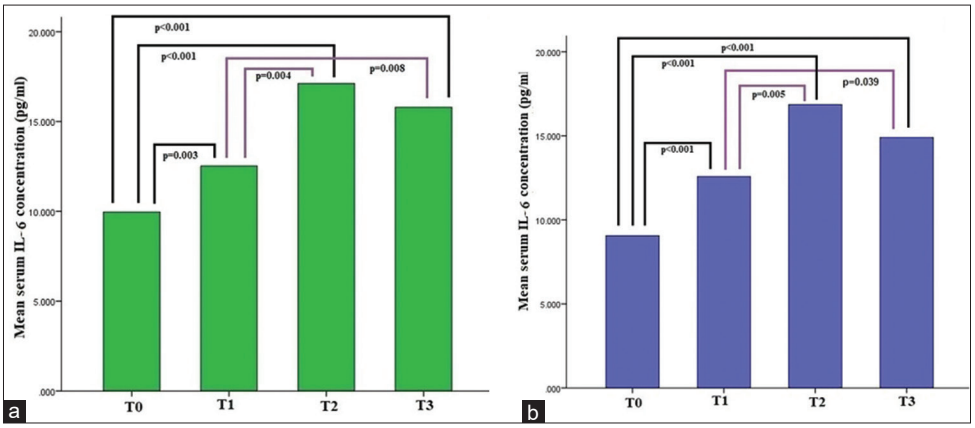

Figure 2: The serum levels of interleukin-6 in the SA and GA groups at different time points. (a) Spinal anesthesia, (b) general anesthesia. T0: Prior anesthesia, T1: immediately post uterine incision, T2: 2 h post CS, T3: 24 h post CS

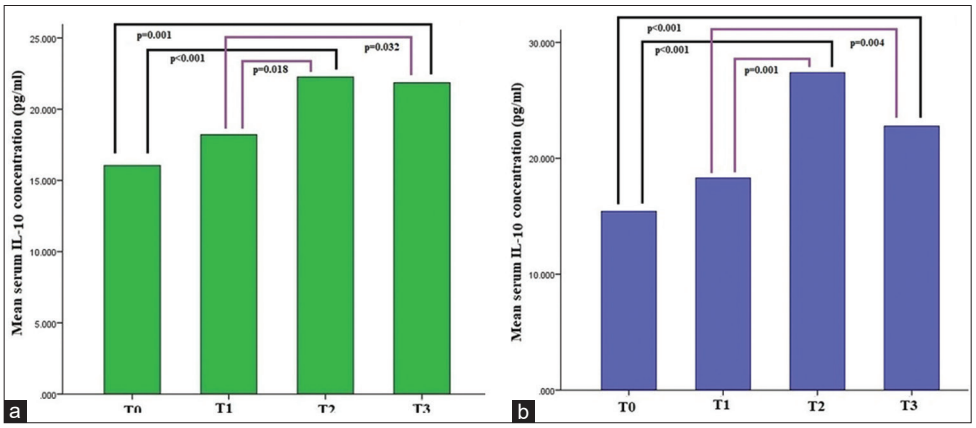

Figure 3: The serum levels of interleukin-10 in the SA and GA groups at different time points. (a) Spinal anesthesia, (b) general anesthesia. T0: Prior anesthesia, T1: immediately post uterine incision, T2: 2 h post CS, T3: 24 h post CS

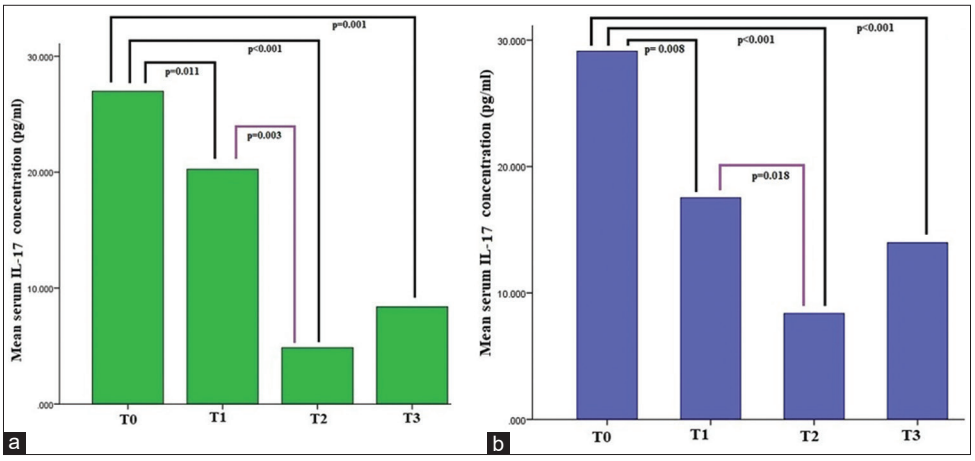

Figure 4: The serum levels of interleukin-17 in the SA and GA groups at different time points. (a) Spinal anesthesia, (b) general anesthesia. T0: Prior anesthesia, T1: immediately post uterine incision, T2: 2 h post CS, T3: 24 h post CS

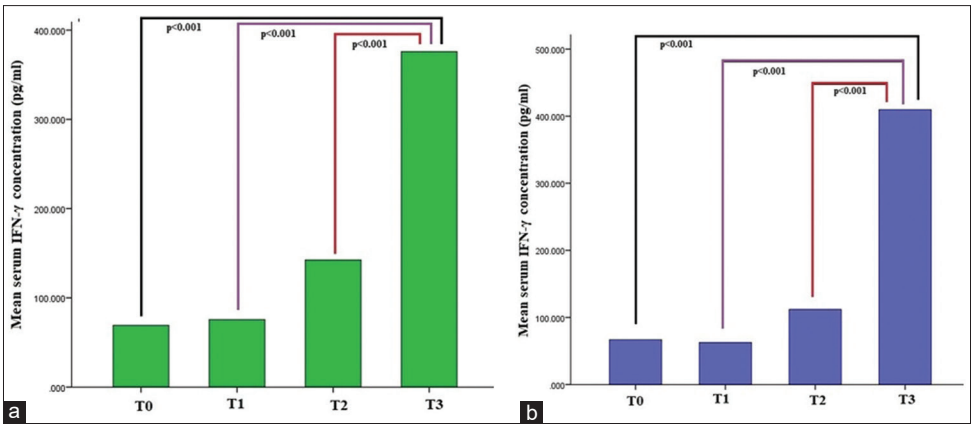

Figure 5: The serum levels of interferon gamma in the SA and GA groups at different time points. (a) Spinal anesthesia, (b) general anesthesia. T0: Prior anesthesia, T1: immediately post uterine incision, T2: 2 h post CS, T3: 24 h post CS

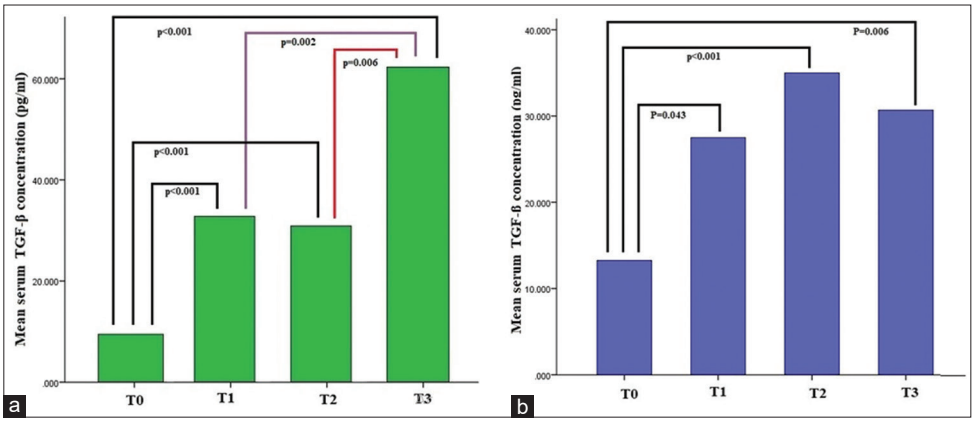

Figure 6: The serum levels of transforming growth factor-β in the SA and GA groups at different time points. (a) Spinal anesthesia, (b) general anesthesia. T0: Prior anesthesia, T1: immediately post uterine incision, T2: 2 h post CS, T3: 24 h post CS

significantly different at T3 with that at T1 and T2 in both groups [Figure 5]. The difference in the mean serum level of IFN-γ between the groups was not significant [Table 1].

Serum levels of transforming growth factor beta in general anesthesia and spinal anesthesia groups

The mean serum levels of TGF-β considerably increased in the SA group at T1, T2, and T3 compared to that at T0. The increased level of TGF-β at T3 was also significant compared to that at T1 and T2. Our results showed a considerable elevation in the mean serum level of TGF-β at T1, T2, and T3 compared to that at T0 in the GA group [Figure 6]. Independent *t*-test showed that the mean serum level of TGF-β at T3 was significantly differing between the two groups [Table 1].

DISCUSSION

The current study was designed to compare the effect of GA and SA on the serum concentrations of IL-4, IL-6, IL-10, IL-17, TGF-β, and IFN-γ in elective CS.

Our results demonstrated that the serum levels of IL-4, IL-10, and TGF-β increased in both groups. The serum level differences of IL-4 and IL-10 between the two groups were not significant. However, in the SA group, the serum level of TGF-β was significantly more than that of the GA group at T3. Immunocompetent cells release different cytokines and effector molecules, such as IL-4, IL-6, and IL-10, which mediate body stress reaction to the operation.[15,16] The sympathetic block that is induced by SA can prevent or suppress inflammatory stress through blocking the afferent impulses, thereby reducing the complications and improving the surgical outcome.[17] The pivotally important anti-inflammatory cytokines, such as TGF-β, regulate the Th17 differentiation and thereby IL-17 production.[18] Since 24 h after cesarean, the elevated levels of TGF-β in the SA group were significantly higher than the GA group, the protective effects of this technique against the severe inflammatory reactions could be important to investigate. In the present study, the serum levels of IL-4, IL-10, and TGF-β in the GA and SA groups significantly increased at 2 and 24 h post CS compared to that of before inducing anesthesia. IL-4 and TGF-β participate in the tissue repair and play pivotal roles in the regulation of pro-inflammatory cytokine functions.[19,20] Therefore, increasing the level of these cytokines after CS is necessary to begin tissue

repair and reduce inflammation. The significant elevated TGF-β level 24 h after CS in the SA group.[21] Surgical incisions and tissue damage shift the balance of cytokines toward pro-inflammatory factors and increase the serum levels of IL-1, IL-6, and TNFα.[22] Inflammatory response induced by immune cells can increase the incidence of postoperative complications such as delayed surgical wound healing, systemic inflammatory response syndrome, cognitive impairment, progression of malignancies, severe hemodynamic disorders, and multiple organ failure (compared to GA group may partly be attributed to modulation of inflammation and faster tissue repair). This issue needs further studies.

The present study showed that the serum levels of IL-6 and IFN-γ increased in both groups post CS; however, the differences between the groups were not significant. A previous study found that anesthetic techniques did not affect the concentrations of IL-6 in women undergoing elective CS.[12] These results revealed that serum levels of the cytokines have followed a similar pattern and their levels have increased following surgery with minor differences. These findings are in consistent with those of previous studies that have suggested that surgical trauma plays a more important role in postoperative release of inflammatory cytokines than the type of anesthesia.[23] Recent publications have shown that CS increases the risk of asthma and allergic disease in childhood.[24-26] A recent study showed CS to be associated with decreased pro-inflammatory cytokine, increased risk of bacterial colonization in the airway, and infantile wheezing.[27] Hogevold *et al*. compared the effect of RA and GA on TNF-α and IL-6 serum levels in orthopedic surgery. They have shown that IL-6 and TNF-α level in two groups had been elevated; however, these differences were not significant.[27]

Graham introduced results that point to the effects of anesthesia on the immune system for the first time. In fact, local anesthesia is believed to suppress the immune system to a lesser extent than GA.[28] However, Dermitzaki *et al*. observed no differences in the serum levels of cytokines in the two groups similar to that of the present study. They examined the serum levels of IL-6 and TNF-α in patients undergoing CS under GA and epidural anesthesia.[16] Hogevold *et al*., who examined the effects of local and GA on the concentration of IL-6 and TNF-α in patients undergoing orthopedic surgery,[21] obtained similar results too.

The mean serum IL-17 levels at T1, T2, and T3 in both groups decreased significantly compared to that at T0. Thus, decreased IL-17 levels can probably be predominantly attributed to the surgical procedures, rather than anesthesia technique. It has also been proven that factors such as surgical and hospitalization stresses, tissue damage, and changes in blood circulation can cause a reliable change in cytokine levels.[23] Major surgeries reduce the immune system activity, whereas minor surgeries may stimulate the immune response,[29] which is confirmed by the results of the present study because CS is classified within major surgeries. Due to the requirement of body tissues to angiogenesis in healing processes and the inhibitory nature of the IL-17 against angiogenesis, the decreased serum levels of this cytokine is reasonable.

In the present study, the repeated-measures test showed significant changes in the mean serum levels of IL-17 within the groups. Dietz *et al*. reported that GA, local anesthesia, and other anesthetic methods have significant effects on immune cell function after surgery.[30] On the other hand, it is believed that the potential moderating effects of anesthesia can be useful in reducing the likelihood of the systemic inflammatory response syndrome that occurs during high-risk surgeries.[31]

CONCLUSION

Overall, according to the results of the current investigation, it seems that surgery plays important roles in the attenuation of immune responses independent of cesarean procedures. However, SA may be associated with a higher rate of tissue recovery, due to the increased levels of TGF-β. The present results may also reconfirm the roles of cytokines in response to surgery in both GA and SA techniques.

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Conflicts of interest

There are no conflicts of interest.

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