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The effects of general and spinal anesthesia on systemic inflammatory response in patients undergoing total knee arthroplasty

Total diz artroplastisi uygulanan hastalarda genel ve spinal anestezinin sistemik inflamatuvar yanıt üzerine etkileri

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ABSTRACT

Objectives: This study aims to compare the systemic inflammatory responses (SIRs) developing after total knee arthroplasty (TKA) performed under general or spinal anesthesia.

Patients and methods: This prospective study included 40 patients (8 males, 32 females; mean age 67.15±9.27 years; range 51 to 89 years) who underwent TKA in our clinic between February 2014 and July 2014. Patients were grouped to receive general (group 1, n=20) or spinal anesthesia (group 2, n=20). Levels of pro-inflammatory markers [Interleukin-6 (IL-6), IL-8, IL-1β, tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP)] were studied from the venous blood samples obtained immediately before induction to anesthesia (T_1), immediately after closure of the operative wound (T_2), and at 24 hours postoperatively (T_3).

Results: In both groups, levels of CRP and IL-6 were significantly increased at T_3 compared to those achieved at T_1. Changes in the levels of TNF-α in both groups were similar. There were no significant differences between the groups in terms of the changes within the levels of the studied markers at the respective time intervals.

Conclusion: According to our study results, SIRs developing after TKA performed under general or spinal anesthesia are similar.

Keywords: General anesthesia; inflammatory response; spinal anesthesia; surgery; total knee arthroplasty.

ÖZ

Amaç: Bu çalışmada genel veya spinal anestezi altında uygulanan total diz artroplastisi (TDA) sonrasında ortaya çıkan sistemik inflamatuvar yanıt (SIY)'lar karşılaştırıldı.

Hastalar ve yöntemler: Bu prospektif çalışmaya Şubat 2014 - Temmuz 2014 tarihleri arasında kliniğimizde TDA uygulanan 40 hasta (8 erkek, 32 kadın; ort. yaş 67.15±9.27 yıl; dağılım 51-89 yıl) dahil edildi. Hastalar genel (grup 1, n=20) ve spinal (grup 2, n=20) anestezi alacak şekilde gruplandırıldı. Pro-inflamatuvar belirteçlerin [interlökin-6 (IL-6), IL-8, IL-1β, tümör nekroz faktör-alfa (TNF-α) ve C-reaktif protein (CRP)] düzeyleri anestezi indüksiyonunun hemen öncesinde (T_1), ameliyat yarasının kapatılmasından hemen sonra (T_2) ve ameliyat sonrası 24. saatte alınan venöz kan örneklerinden çalışıldı.

Bulgular: Her iki grupta CRP ve IL-6 düzeyleri T_1'de elde edilenlere kıyasla T_3'te anlamlı düzeyde arttı. Her iki grupta TNF-α düzeylerindeki değişiklikler benzerdi. İlgili zaman aralıklarında çalışılan belirteç düzeylerindeki değişiklikler açısından iki grup arasında anlamlı farklılıklar yoktu.

Sonuç: Çalışma sonuçlarımıza göre, genel veya spinal anestezi altında uygulanan TDA sonrasında ortaya çıkan SIY'lar benzerdir.

Anahtar sözcükler: Genel anestezi; inflamatuvar yanıt; spinal anestezi; cerrahi; total diz artroplastisi.

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Total knee arthroplasty (TKA), with its proven long-term success, constitutes the standard treatment of choice in end-stage gonarthrosis.[1] Total knee arthroplasty is a major surgery and it is well-known that the extent of surgical trauma may influence systemic inflammatory response (SIR). The SIR induced by TKA may lead to increased postoperative complication rates. Anesthesia, also, was reported to contribute to SIR.[2] Considering the extent of surgical trauma, the effect of anesthesia on SIR may be of importance following TKA.

Inflammation is essential for tissue reconstruction. However, excessive SIR can have hazardous effects which lead to postoperative complications, such as postoperative infections, wound healing disturbances, prolonged hospital stay, increased health costs or organ dysfunctions.[2,3] Total knee arthroplasty might induce an increased SIR compared to some minor surgeries. Therefore, to prevent morbidity, it is important to reduce excessive SIR induced by TKA and anesthetic methods. The severity and duration of surgical trauma, patients' age, and anesthetic methods may influence perioperative stress response.[4-9] Anesthesia maintains homeostasis, makes the operation painless, reduces excessive response to surgery, and modulates immune responses.[10] In addition, anesthetics influence cellular (the functions of immune competent cells) and humoral (inflammatory mediator gene expression and secretion) inflammatory responses.[11] Different anesthetic methods may affect the cytokine response to surgery; e.g. addition of spinal block reduces neuroendocrinal response to surgery compared to general anesthesia alone.[2,12] Moreover, regional anesthesia was reported to have less adverse effects than general anesthesia.[2]

To the best of our knowledge, few studies in the literature investigated the effects of general vs. spinal anesthesia on the SIR induced by TKA. Therefore, in this study, we aimed to compare the SIRs developing after TKA performed under general or spinal anesthesia.

PATIENTS AND METHODS

This prospective study included 40 patients (8 males, 32 females; mean age 67.15±9.27 years; range 51 to 89 years) who underwent TKA in Medical Faculty of Afyon Kocatepe University between February 2014 and July 2014 with an American Society of Anesthesiologists score of 1-3. Patients were informed about the study procedure and provided written consent. The study protocol was approved by the Afyon Kocatepe University Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Appropriate patients were assigned to receive general (group 1, n=20) or spinal anesthesia (group 2, n=20). Patients with a history of metabolic or immunological diseases and use of immune suppressive drugs were excluded. All patients were operated by the same surgeon using the same surgical method and a tourniquet was used during the surgery.

In group 1, intravenous (IV) midazolam (2 mg), propofol (2 mg/kg), and fentanyl (1.5 μg/kg) were used for induction. Patients received IV rocuronium (0.8 mg/kg) to facilitate endotracheal intubation. After intubation, anesthesia was maintained with air and

TABLE I

Demographic and intraoperative data of general vs. spinal anesthesia groups

	Group 1			Group 2			
	Mean±SD	Median	Min.-Max.	Mean±SD	Median	Min.-Max.	*p*
Age (years)		64	51-89		66	57-88	0.420*
Weight (kg)		80	65-105		83	70-110	0.345*
Height (cm)	167.20±4.84			167.90±4.58			0.641**
Duration of anesthesia (minutes)		120	75-195		140	85-180	0.063*
Duration of surgery (minutes)		84	45-170		104	50-160	0.107*
Duration of tourniquet use (minutes)	56.70±24.98			69.60±30.19			0.102**
ASA score		2	1-3		2	1-3	0.547*

SD: Standard deviation; Min.: Minimum; Max.: Maximum; ASA: American Society of Anesthesiologists. * Mann-Whitney U-test was used for binary comparison between groups. ** Independent samples t-test was used for binary comparison between groups.

desflurane (6%) mixture and rocuronium (0.15 mg/kg) to maintain muscle relaxation. In group 2, 500 mL Ringer's lactate was given intravenously before spinal anesthesia. Spinal block was performed with the patients seated and bupivacaine 0.5% (3-4 mL) injected through L3-L4 intervertebral space using a 25 gauge spinal needle.

Patient characteristics and perioperative events (total blood loss, durations of anesthesia, surgery, and tourniquet use) were recorded. Routine monitorization was administered for all patients. Crystalloids were used for hydration when clinically needed. No patients required blood transfusion. All patients in both groups received the same analgesics postoperatively.

To evaluate the SIR, venous blood samples were obtained from all patients immediately before induction to anesthesia (T_1), immediately after closure of the operative wound (T_2), and at 24 hours postoperatively (T_3). Levels of interleukin-6 (IL-6), IL-8, interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) were studied. These pro-inflammatory markers were selected from previous studies in the literature because of rapid response.[13] Venous blood samples (4 mL) were centrifuged at 5000 rpm for 10 minutes immediately after collection and plasma aliquots were stored at -20 °C until assayed. Plasma concentrations of IL-6, IL-8, IL-1β, and TNF-α were measured using eBioscience Human Platinum enzyme-linked immunosorbent assay kits (Bender MedSystems GmbH, Vienna, Austria). Absorbance detection was performed using ChemWell® 2910 Analyzer (Awareness Technology, Inc. Martin Hwy. Palm City, USA). The results were given as pg/mL.

Values of CRP, IL-6, IL-8, IL-1β, and TNF-α were compared with the patients divided into subgroups of body mass index (<30 vs. >30), duration of anesthesia (<130 vs. >130 minutes), duration of surgery (<90 vs. >90 minutes), and patients' age (<65 vs. >65 years).

Statistical analysis

We estimated the sample size regarding the power analysis. For two tailed α value of 0.05 (sensitivity: 95%) and a β value of 0.20 (study power: 80%),

TABLE II

Comparison of changes in studied parameters within groups at three different time points

	T_1	T_2	T_3	*p*
C-reactive protein				
Group 1	0.68 (0.46)	0.67 (0.76)	11.29±6.20^{†,‡,a,b}	<0.001
Group 2	0.34 (0.65)	0.54 (0.47)	12.20±4.13^{†,‡,a,b}	<0.001
P value inter-group	0.27*	0.85*	0.59**	
IL-1 beta				
Group 1	1.96 (3.67)	1.90 (2.65)	2.66 (2.54)†,‡	0.09
Group 2	1.8 (2.02)	1.68 (2.31)	2.08 (1.91)†,‡	0.11
P value inter-group	0.19*	0.94*	0.93*	
IL-6				
Group 1	2.97 (3.84)	2.06 (2.29)	63.54±30.32$^{\dagger,\ddagger a,b}$	<0.001
Group 2	2.22 (3.37)	3.05 (4.59)	70.86±27.21$^{\dagger,\ddagger a,b}$	<0.001
P value inter-group	0.39*	0.56*	0.43**	
IL-8	11.7 (7.44)	9.8 (18.65)	17.24 (19.35)†,‡	0.52
Group 1	10.66 (13.08)	12.66 (26.55)	22.23 (19.24)†,‡	0.14
Group 2				
P value inter-group	0.18*	0.78*	0.84*	
TNF-alpha				
Group 1	2.12 (4.11)	2.86 (4.09)	2.08 (3.17)†,‡	0.19
Group 2	2.38 (2.82)	1.56 (3.39)	1.49 (2.71)†,‡	0.39
P value inter-group	0.48*	0.29*	0.40*	

* Mann-Whitney U test was used for binary comparison between groups. Data are given as median (minimum-maximum). ** Independent samples t-test was used for binary comparison between groups. Data are given as mean ± standard deviation.† Friedman test was used to compare values obtained within same groups at T_1, T_2 and T_3. ‡ Wilcoxon test was used for binary comparisons within same group. The data are given as median (min.-max.) unless otherwise stated. Bold *p* values define significant difference between two groups (p<0.05), (a; p<0.05 vs. T_1, b; p<0.05 vs. T_2) IL: Interleukin; T_1: Immediately before induction to anesthesia; T_2: Immediately after wound closure; T_3: 24 hours postoperatively; TNF: Tumor necrosis factor.

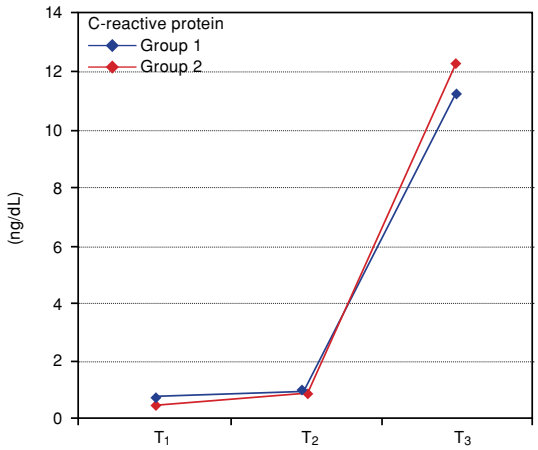

Figure 1. Mean levels of C-reactive protein in two groups achieved at three different time periods (T_1, T_2, and T_3).

we detected that at least 20 patients were needed for each group.

The IBM SPSS software version 20.0 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. The distribution of variables was evaluated with the Shapiro-Wilk test. Variables with normal distribution were expressed as mean (±) standard deviation and the ones without normal distribution were expressed as median (minimum-maximum). Student's t test was used to compare parametric variables between the groups. Friedman test was used to compare the values obtained within the same groups at T_1, T_2, and T_3. Wilcoxon signed ranks test was used to evaluate continuous variables with normal distribution for the same groups. *P* value of <0.05 was considered statistically significant.

RESULTS

There were no statistically significant differences between demographic and intraoperative data of both groups (Table I). Comparison of the changes in the studied parameters within and between the groups at three different time points (T_1, T_2, and T_3) are given in Table II. In groups 1 and 2, levels of CRP and IL-6 increased significantly and in parallel at T_3 when compared to values achieved at T_1 ($p<0.001$). Although the increase from T_1 to T_2 was not significant, the increase from T_2 to T_3 was (Table II) (Figures 1 and 2). Changes in the levels of IL-1β, IL-8, and TNF-α were similar in both groups with no statistically significant differences ($p>0.05$) (Table II). Mean level of IL-1β from T_1 to T_2 was observed to decrease in group 1 and to increase in group 2. However, the difference between the groups was not significant and final levels of IL-1β at T_3 were similar with no differences ($p>0.05$) (Table II) (Figure 2). Level of IL-8 gradually increased

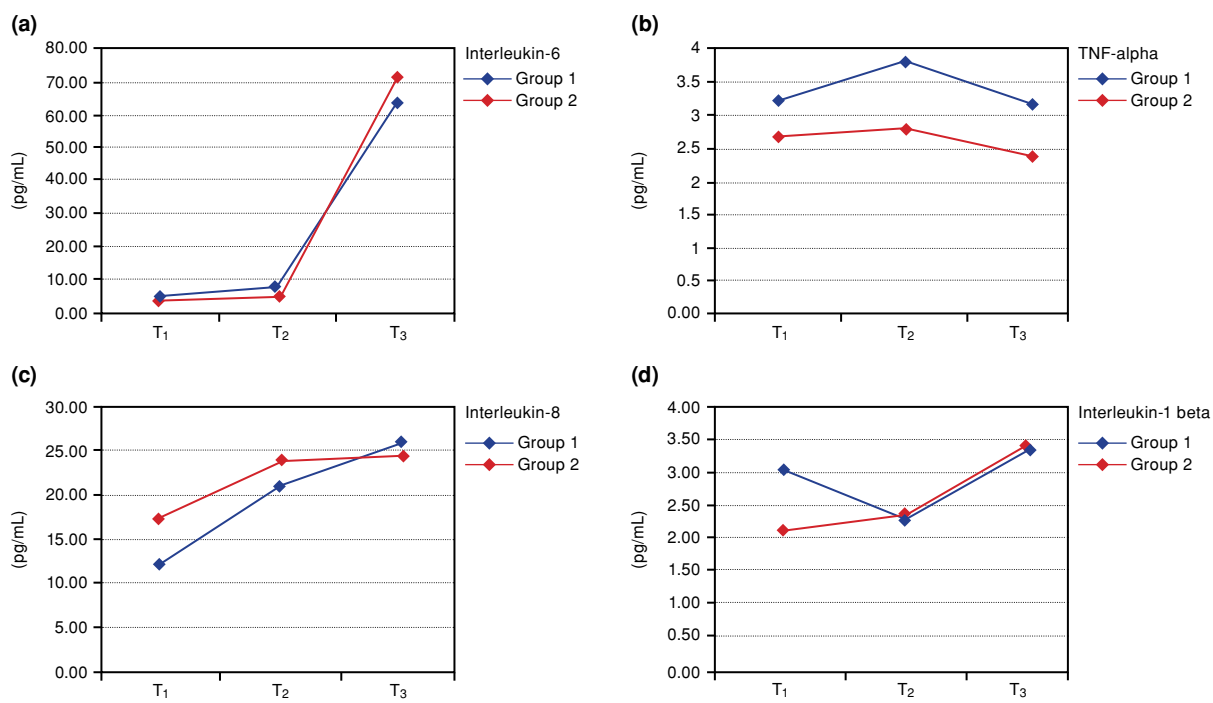

Figure 2. Mean levels of interleukin-6 **(a)**, tumor necrosis factor-alpha **(b)**, interleukin-8 **(c)**, and interleukin-1 beta **(d)** in two groups achieved at three different time periods (T_1, T_2, and T_3). TNF: Tumor necrosis factor.

TABLE III

Comparison of results between subgroups regarding body mass index and duration of anesthesia and surgery

	Body mass index						Duration of anesthesia						Duration of surgery					
	≤29			>29			≤130 minutes			>130 minutes			≤90 minutes			>90 minutes		
	General	Spinal	*p*	General	Spinal	*p*	General	Spinal	*p*	General	Spinal	*p*	General	Spinal	*p*	General	Spinal	*p*
	Mean±SD	Mean±SD		Mean±SD	Mean±SD		Mean±SD	Mean±SD		Mean±SD	Mean±SD		Mean±SD	Mean±SD		Mean±SD	Mean±SD	
CRP T_1	0.48±0.37	0.78±0.88	0.316	0.46±0.38	0.67±0.33	0.218	0.47±0.37	0.76±0.82	0.285	0.46±0.38	0.68±0.37	0.285	0.50±0.39	0.78±0.85	0.322	0.46±0.36	0.65±0.35	0.278
CRP T_2	2.49±2.72	0.84±0.83	0.135	2.74±2.56	0.98±0.45	***0.038***	2.49±2.72	0.84±0.78	0.133	2.75±2.56	1.04±0.45	***0.045***	2.76±2.83	0.87±0.80	0.130	2.58±2.53	0.95±0.48	***0.042***
CRP T_3	14.30±2.64	13.16±5.32	0.536	19.55±6.28	8.49±6.69	***0.002***	14.30±2.64	13.64±5.57	0.714	19.55±6.28	5.80±3.67	***<0.001***	13.95±2.65	12.96±5.14	0.574	19.33±6.07	8.21±7.17	***0.005***
IL-6 T_1	2.68±2.51	3.12±1.93	0.681	3.41±2.69	3.12±2.04	0.785	2.68±2.51	3.01±1.92	0.751	3.41±2.69	3.37±2.07	0.973	2.87±2.64	3.19±1.86	0.784	3.25±2.64	2.98±2.16	0.811
IL-6 T_2	4.57±4.17	2.25±1.61	0.171	4.96±4.90	3.89±2.82	0.543	4.57±4.17	2.61±2.20	0.248	4.96±4.90	3.59±2.45	0.443	5.04±4.28	2.72±2.25	0.217	4.68±4.80	3.27±2.40	0.393
IL-6 T_3	60.21±28.80	59.78±32.47	0.976	77.95±24.77	69.15±27.90	0.482	60.21±28.80	57.69±31.28	0.851	77.95±24.77	77.17±25.10	0.951	63.91±28.98	60.15±31.11	0.791	74.59±26.63	69.81±30.07	0.731
TNF T_1	2.46±1.77	2.79±2.56	0.736	2.81±1.73	3.83±3.43	0.457	2.46±1.77	2.99±2.70	0.584	2.81±1.73	3.71±3.54	0.579	2.57±1.88	3.14±2.75	0.594	2.72±1.69	3.33±3.38	0.667
TNF T_2	2.33±1.74	3.84±3.16	0.187	3.11±3.32	3.74±3.28	0.681	2.33±1.74	4.17±3.50	0.116	3.11±3.32	2.94±1.99	0.893	2.46±1.84	4.36±3.57	0.132	2.98±3.21	2.76±1.88	0.847
TNF T_3	3.27±2.98	3.05±2.87	0.873	1.84±1.66	3.34±3.76	0.316	3.27±2.98	3.56±3.62	0.840	1.84±1.66	2.24±1.53	0.618	3.40±3.19	3.74±3.71	0.835	1.88±1.59	2.10±1.45	0.755
IL-8 T_1	7.99±5.05	13.24±6.27	0.055	23.93±19.37	10.36±4.63	***0.037***	7.99±5.05	13.57±5.83	0.064	23.93±19.37	8.63±3.93	***0.021***	8.48±5.26	13.47±6.06	0.076	22.44±19.30	9.53±4.31	***0.037***
IL-8 T_2	11.61±6.86	26.87±37.74	0.196	31.56±35.21	12.00±13.75	0.102	11.61±6.86	24.80±35.19	0.195	31.56±35.21	11.88±15.79	0.121	13.03±6.01	25.29±36.58	0.259	29.26±34.71	12.81±14.62	0.156
IL-8 T_3	20.59±13.44	32.13±37.35	0.343	26.79±12.85	16.24±9.80	0.053	20.59±13.44	31.00±34.61	0.330	26.79±12.85	13.59±8.74	***0.022***	22.32±13.51	32.12±35.76	0.392	25.38±13.31	13.99±8.05	***0.029***
IL-1B T_1	1.39±1.19	3.41±3.16	0.063	2.62±1.13	2.40±1.47	0.724	1.39±1.19	3.24±2.99	0.055	2.63±1.13	2.46±1.49	0.816	1.55±1.19	3.43±3.02	0.065	2.45±1.25	2.23±1.49	0.746
IL-1B T_2	2.30±2.91	2.58±1.66	0.808	2.38±1.42	1.89±1.43	0.462	2.30±2.91	2.61±1.69	0.790	2.39±1.42	1.61±1.06	0.295	2.57±3.03	2.74±1.68	0.896	2.23±1.47	1.51±1.00	0.211
IL-1B T_3	4.90±4.38	3.37±2.22	0.385	2.43±0.91	3.31±3.03	0.451	4.91±4.38	3.82±2.84	0.543	2.43±0.91	2.26±0.86	0.693	5.56±4.29	3.93±2.92	0.392	2.27±1.05	2.27±0.79	0.997

SD: Standard deviation; CRP: C-reactive protein; IL: Interleukin; TNF: Tumor necrosis factor.

from T_1 to T_3 in both groups and decreased from T_2 to T_3 (Figure 2). However, the change patterns were similar with no significant differences between the groups ($p>0.05$).

Level of TNF-α slightly increased from T_1 to T_2 and decreased from T_2 to T_3 in both groups. However, there were no significant differences between the groups (Table II).

Overall, no significant difference between the groups was observed in regard to the levels of CRP, IL-1β, IL-6, IL-8, and TNF-α within the studied time period.

The groups were also divided into subgroups regarding body mass index (≤29 vs. >29) and duration of anesthesia (≤130 minutes vs. >130 minutes) and surgery (≤90 minutes vs. >90 minutes). Comparison of the subgroups indicated similar results. However, the only statistically significant differences between the subgroups were observed for CRP values obtained at T_1 and T_3 and for IL-8 values obtained at T_0 and T_3, with higher values in group 1 (Table III).

DISCUSSION

The results of this study suggest that the level of SIR does not differ in terms of the anesthetic method after TKA. Any insult to the organism causes the host response including both local and systemic components. Anesthetic techniques used during perioperative period result in a SIR and suppression of cell-mediated immunity.[14]

Tissue damage emerging during surgery is the main factor in determining the level of SIR.[12] It was previously reported that the changes in SIR were not different in regard to anesthetic method between the groups undergoing minor surgery.[15] However, the effect of anesthetic methods on SIR following major surgeries have not been clarified. Decreasing excessive SIR after major surgeries, such as arthroplasty, by using appropriate anesthetic methods may provide clinical benefits. Although several studies investigated the effect of anesthetic methods on the SIR following various surgeries,[16-18] to our knowledge, there are few studies to evaluate the effect of general and spinal anesthesia on SIR following TKA.[13]

Regional anesthesia, alone or in combination with general anesthesia, is used to provide satisfactory postoperative analgesia following major surgeries. However, the benefits of it regarding perioperative morbidity and mortality reduction and later outcomes (patients' rehabilitation and return to preoperative situation) are not fully clarified. Although the effect of regional anesthesia on the SIR was studied in some experimental models, there are few clinical studies with inconclusive results. Nonetheless, regional anesthesia can modulate SIR via various mechanisms at different levels following tissue injury.[14] Hogevold et al.[13] studied the effect of regional and general anesthesia in hip arthroplasty and, similar to our results, they reported that although the inflammatory markers (IL-6 and TNF-α) increased postoperatively compared to the preoperative levels, there were no significant differences between the groups. Conrick-Martin et al.[19] investigated the effect of spinal and epidural anesthesia vs. general anesthesia on natural killer T-lymphocytes and reported that the anesthetic methods seem not to effect postoperative natural killer T-lymphocyte functions.[19]

Tourniquet use may result in skeletal muscle ischemia-reperfusion injury, and thus increase the SIR to surgery.[20,21] However, the mean time for tourniquet use were similar between the groups in this study.

Anesthetic methods used for minor and major surgeries would probably induce SIR of different levels. In a group of patients undergoing minor surgery, the levels of IL-2 were increased more in patients receiving general anesthesia compared to spinal anesthesia. However, no statistically significant difference was found in the levels of other pro- or anti-inflammatory cytokines after surgery under general or spinal anesthesia.[22] The results of the present study revealed that the SIR was also similar following a major surgery.

This study has several limitations. First, only the pro-inflammatory cytokines were studied. Thus, we cannot comment on the changes in the levels of anti-inflammatory cytokines. Second, we studied the levels of the cytokines only within 24 hours postoperatively. A longer study period might show different results.

In conclusion, this study indicated that TKA induces a postoperative SIR. Considering the levels of pro-inflammatory markers studied, the SIR is affected by the surgery itself and not by the drugs used in spinal or general anesthesia. Thus, we believe that the anesthesia method may not be used to overcome the adverse effects related to SIR following TKA.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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