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DO PREOPERATIVE IL-1BETA, IL-6 AND TNF-ALPHA LEVELS OF PATIENTS WHO UNDERWENT TOTAL KNEE ARTHROPLASTY SURGERY AFFECT THE POSTOPERATIVE FUNCTIONAL AND STRUCTURAL RESULTS?

ORIGINAL ARTICLE

ABSTRACT

Purpose: Serum cytokines were associated with symptoms and progression of osteoarthritis. It is unknown whether these cytokines have a predictive role on the severity of symptoms after total knee arthroplasty (TKA) or not. This study was performed to investigate the effect of preoperative Serum Cytokine Levels (SCL) on length of stay in hospital (LOS), postoperative pain intensity, functional status, joint position sense, and change in X-ray.

Methods: Twenty-nine patients with Grade 4 osteoarthritis degeneration level were included in the study. SCL (IL-6, TNF-alpha, IL-1beta) were assessed before surgery. Pain intensity at rest/activity and lower limb alignment were evaluated preoperative, postoperative 72nd hour and 6th week. Functional status and joint position sense were assessed before surgery and 6 weeks after surgery. Length of stay in hospital was also recorded.

Results: The mean age of the participants was 67.55±6.55 years. The length of stay in the hospital mean was 6.48±3.06 day (min:3, max:16 days). Preoperative IL-6 and TNF-alpha level negatively correlated with functional status in the 6th week after surgery (r=0.46; p=0.01, r=0.39; p=0.03). Also, there was a positive correlation between preoperative TNF-alpha and the lower limb alignment at the 6th week after surgery (r=0.39; p=0.04).

Conclusion: Patients with osteoarthritis who had lower preoperative IL-6 and TNF-alpha levels had better functional status and better lower limb alignment in the postoperative period. So in order to decide TKA surgery timing, primarily decreasing SCL might be caused better biomechanical development after surgery. Preoperative SCL was not directly related to the length of stay in the hospital.

Keywords: Arthroplasty, Cytokine, Osteoarthritis, Preoperative

TOTAL DİZ ARTROPLASTİ CERRAHİSİ GEÇİREN HASTALARIN CERRAHİ ÖNCESİ IL-1BETA, IL-6 VE TNF-ALPHA SEVİYELERİ CERRAHİ SONRASI FONKSİYONEL VE YAPISAL SONUÇLARINI ETKİLER Mİ?

ARAŞTIRMA MAKALESİ

ÖZ

Amaç: Serum sitokinleri osteoartritin semptomları ve progresyonu ile ilişkilidir. Bu sitokinlerin Total Diz Artroplastisi (TDA) sonrası semptomların şiddeti üzerinde tahmin edici bir etkisinin olup olmadığı bilinmemektedir. Bu çalışma cerrahi öncesi serum sitokin seviyelerinin (SSS) hastanede kalış, cerrahi sonrası ağrı şiddeti, fonksiyonel durum, eklem pozisyon hissi ve X-ray deki değişim üzerine etkisini göstermek amacıyla gerçekleştirildi.

Yöntem: Evre 4 osteoartriti olan yirmi dokuz hasta çalışmaya dahil edildi. Cerrahi öncesi SSS (IL-6, TNF-alfa, IL-1beta) değerlendirildi. İstirahat/aktivite ağrı şiddeti ve alt ekstremite dizilim düzgünlüğü cerrahi öncesi, cerrahi sonrası 72. saat ve 6. haftada değerlendirildi. Fonksiyonel durum ve eklem pozisyon hissi cerrahi öncesi ve cerrahi sonrası 6. haftada değerlendirildi. Hastanede kalış süresi kaydedildi.

Sonuçlar: Bireylerin yaş ortalaması 67,55±6,55 yıldı. Hastane kalış süresi ortalaması 6,48±3,06 gündü (en düşük:3, en yüksek:16). Cerrahi öncesi IL-6 ve TNF-alfa seviyeleri 6. haftada fonksiyonel durum ile negatif yönde koreleydi (r=0,46; p=0.01, r=0,39; p=0,03). Ayrıca, cerrahi öncesi TNF-alfa ve alt ekstremite dizilim düzgünlüğü arasında pozitif korelasyon vardı (r=0,39; p=0,04).

Tartışma: Cerrahi öncesi daha düşük IL-6 ve TNF-alfa seviyesi olan osteoartritli hastalar cerrahi sonrası dönemde daha iyi fonksiyonel durum ve alt ekstremite düzgünlüğüne sahiptiler. Bu nedenle TDA cerrahisi zamanlamasına karar verebilmek için öncelikle SSS'nin azaltılması, cerrahi sonrası daha iyi bir biyomekanik gelişime neden olabilir. Cerrahi öncesi SSS hastane kalış süresi ile direk bağlantılı değildir.

Anahtar Kelimeler: Artroplasti, Sitokin, Osteoartrit, Cerrahi Öncesi

INTRODUCTION

Total knee arthroplasty (TKA) is one of the most common surgical approaches in the final stage of knee osteoarthritis (OA). The main purpose of this treatment is to decrease pain intensity and improve functional status (1). It is also a cost-effective treatment. The annual prevalence of TKA is expected to enhance in the next several decades due to the gradually increasing elderly population and this situation results in a dramatically incremental cost of TKA (1). Increased LOS also brings many hospital costs (2).

Patients with TKA encounter several symptoms in the early postoperative period including increased pain intensity, functional disability, alteration in the perception of proprioception (3,4). Increased pain intensity is a risk of arthrofibrosis, adversely affects the rehabilitation process and decreases patient satisfaction (3). Early postoperative pain is also a significant risk factor for long-term persistent pain and delayed recovery (4). Proprioception is important for providing patients to feel their knees better and preventing falls by ensuring postural stability. Moreover, impaired proprioception contributes to non-specific pain and results in functional disability (5,6). TKA surgery targets to reduce symptoms through correcting varus/valgus angle and malalignment of the knee.

Understanding of predictive factors affecting symptoms after TKA is important for improving therapy options in the preoperative period as well as postoperative period in order to reduce symptoms and thus obtain better surgery results due to preoperative status is the strongest determinant of outcomes following knee surgery (7). In the preoperative period, OA, common reason of TKA, is considered as a non-inflammatory form of arthritis whereas the systemic inflammation role on symptoms and progression of the disease are gradually understood in OA pathogenesis (8- 10). The mostly studied cytokines in OA are IL-6, TNF-alpha and IL-1beta (8- 10). IL-6 has been related to the progress of radiographic knee OA and IL-1beta linked to cartilage destruction (9, 10). TNF-alpha have been initiated in the inflammatory cascade (10). Cytokine-mediated inflammation leads to various symptoms including pain, knee joint effusion, alteration of proprioception, cartilage degradation, functional limitation and ultimately progression of disease in patients with OA (8-12). There were some studies indicating that preoperative symptoms had a predictive role and a better clinical outcome was obtained after TKA if symptoms improved before surgery (13,14). It was wondered whether cytokines, have an important role in the pathogenesis of OA, have a predictive value on the severity of symptoms or not after TKA (15-17). However, the current studies were limited to the effect of the preoperative SCL on LOS and pain intensity during this period (16,17). In these studies, the relationship between SCL and pain did not give similar results and also this topic was not investigated in period after discharge (16,17). In the related literature, there was no study examining the correlation between preoperative SCL, functional status, joint position sense and X-ray in early postoperative period as well as after discharge. So, this study was conducted to demonstrate the effect of preoperative SCL on hospital stay, postoperative pain intensity, functional status, joint position sense, and change in X-ray in patients with OA.

METHODS

The descriptive clinical trial was conducted between May 2018 and January 2020 in Karadeniz Technical University Application and Research Center (Farabi Hospital). Patients were informed about the study. Laboratory health and safety procedures complied with in the course of conducting this study.

Patients

Patients were informed about all appropriate warnings on any hazards that may be involved in the study. Informed consent was obtained from the study participant. This study was conducted with 29 OA patients in Karadeniz Technical University, Faculty of Medicine, Department of Orthopedic and Traumatology and Faculty of Health Science, Department of Physiotherapy and Rehabilitation, in Trabzon. This study registered with the number "NCT04487535". The registry name and URL of the study was https://clinicaltrials.gov/ct2/show/NCT04487535?cond=NCT04487535&draw=2&rank=1.

Patients included if they 1) aged between 55-75

years, 2) were scheduled for unilateral or bilateral TKA, 3) were diagnosed of OA with a severity Grade 4 according to the Kellgren-Lawrence (KL) classification. Exclusion criteria were 1) neuropathic pain, 2) pre-surgery for same lower extremity, 3) vascular disease, 4) any chronic disease related to kidney, heart, liver 5) cancer 6) chronic inflammatory disease.

All patients were evaluated for pain intensity, SCL (IL-6, TNF-alpha, IL-1beta), functional status, knee joint position sense and X-ray. Surgery performed by same experienced orthopedic surgeon who also measured valgus angle on X-ray Pain intensity, functional status and knee joint position sense were assessed by the same experienced physiotherapist.

The sample size was estimated based on a previous study considering primarily outcome as relation between serum IL-6 and postoperative pain intensity (16). A total of 27 patients was detected to provide 80% power with an 0.05 alpha error and 40% effect of the correlation size.

Outcome Measurements

Serum Cytokine Level Measurement: Venous blood sample was collected 2 weeks before surgery. Five-milliliter (ml) blood samples from each individual were placed into vacutainer tubes without anticoagulant. These were then centrifuged at 1800 g for 10 minutes. Serum samples were stored at -80°C until being used for measurements. Serum IL-6, TNF-alpha and IL-1beta levels were determined using commercial sandwich-ELISA kits (DIASource, Ref No: KAP1261, Lot: 1812-1824, Ref No: KAP1751, Lot: 1812-1785, Ref No: KAP1211, Lot: 1901-1992, Louvain-la-Neuve–Belgium, respectively) in line with the manufacturer's instructions. The absorbance of the samples was measured at a 450 nm wavelength on a VERSA (designed by Molecular Devices in California, USA) micro plate reader. The results were expressed as pg/ ml. The coefficients of variation (CV) of this ELISA method were 6.69% for IL-6, 6.62% for TNF-alpha and 6.72% for IL-1beta.

Pain Intensity Assessment: Rest and activity pain intensity were evaluated 2 weeks before surgery, 72 hours and 6 weeks following surgery using by 100 mm vertical line Visual Anolog Scale (VAS). 0= no pain, 10=unbearable pain (18).

Functional Status: Functional status was assessed before surgery and 6 weeks after surgery using the Turkish Version of Western Ontario McMaster University Osteoarthritis Index (WOMAC). The WOMAC is a self-reported functional assessment scale consisting of 24 items which responded on likert type scale (0= none, 1= mild, 2= moderate, 3= severe, 4= extreme), with higher score indicating more difficulty (19).

Joint Position Sense (JPS): Joint position sense was evaluated by using a digital goniometer (Baseline Digital Absolute-Axis Goniometer Model, Enterprises, Inc. PO Box 1500, White Plans, Newyork), before surgery and 6 weeks after surgery under non-weight bearing condition according to the protocol used before Baker et al (20). Each patient was asked to sit in an erect pack position on the chair with knee relaxed in 90 º flexion noticing that the popliteal fossa was not in contact with the end edge of the chair. Patients were allowed to wear loose short. The patients' eyes were closed to prevent visual cues. A digital goniometer was placed at the lateral aspect of the knee, with a moveable arm in the course of the midline of the lateral malleolus and a stationary arm along the midline of the femur.The knee was moved passively by the examiner slowly from the initial position (90º flexion) to the final predetermined three angles (35º, 55º, 70º), hold final position for 5 seconds, and then returned to the initial position with the same speed. After instruction the procedure, patients were asked to extend the knee actively for each angle. This procedure was repeated three times for each angle. Absolute angular error which represent accuracy without directional bias was determined by calculating difference between test and response position for each angle. The averaged absolute angular error was considered as joint position sense error.

X-ray Evaluations: X-ray evaluated before surgery, 72 hours after surgery and 6 weeks after surgery. To measure valgus angle, standard anteroposterior (AP) X-ray view was obtained from patients in standing position without shoes. The angle between femoral axis which indicate a line drawn from femoral head to femoral intercondylar notch

and tibial axis which describe a line from the center of the talus bone to the center of the tibial spine was measured by the same orthopedics (21).

Statistical Analysis

Data were analyzed using SPSS version 21.0 (Statistical Package of Social Sciences, Chicago, IL, USA) for Windows program. Descriptive statistics were used to describe demographic characteristics. Shapiro Wilk test was used for determination of the normal distribution of the data. The Mann-Whitney U test for non-normally distributed data was used to compare SCL between groups which are LOS ≤5 or LOS>5 days. The significance of correlations was determined by Spearman's rank correlation test. The magnitude of correlation was classified as the low=0.26–0.49; moderate=0.50–0.69; high=0.70–0.89; very high=0.90–1.00 for interpretation of the correlation coefficient (22). Differences with p value less than 0.05 were considered significant.

RESULTS

Forty-one patients were included in the study. 11 patients were excluded for contact problems and 1 was excluded due to hepatitis C virus in the follow-up period. This study was completed with 29 patient consisting of 24 (82.8%) female and 5 (17.2%) male. The mean age of the participants was 67.55±6.55 years and body mass index was 31.72±3.79 kg/m^2.

Baseline and postoperative values of pain, functional status, JPS and valgus angle was shown in (Table 1).

Preoperative IL-6, TNF-alpha and IL-1beta level were not correlated with activity and rest pain both in 72 hours and 6 weeks after surgery (p>0.05) (Table 2).

Mean LOS was 6.48±3.06 (3.00-16.00) days. There were no correlations between LOS and IL-6 (r=0.087, p=0.655), TNF-alpha (r=0.143, p=0.459) and IL-1beta (r=0.020, p=0.920). In terms of cytokine levels, there were no differences between LOS≤5 or LOS>5 (Table 3).

WOMAC score was positively weakly correlated with IL-6 (r=0.467, p=0.011) and TNF-alpha (r=0.392, p=0.036) (Figure 1). No correlation was found between WOMAC score and IL-1beta (r=0.142, p=0.463) (Figure 1).

There were no correlations between JPS (35°) and IL-6 (r=0.004, p=0.983), TNF-alpha (p=0.134, p=0.495) and IL-1beta (r=0.212, p=0.279). There were no correlations between JPS (55°) and IL-6 (r=0.192, p=0.319), TNF-alpha (r=0.034, p=0.861) and IL-1beta (r=0.101, p=0.600). There were no correlations between JPS (70°) and IL-6 (r=0.182, p=0.355), TNF-alpha (r=0.266, p=0.171) and IL-1beta (r=0.002, p=0.990).

There were no correlations between valgus an-

Table 1. Pain, Functional Status, Joint Position Sense and Valgus Angle Before and After Surgery

	Pre-operative Mean±SD	Post-operative 72nd Hour Mean±SD	Post-operative 6th Week Mean±SD
SCL			
IL-6 (PG/ML)		395.75±53.88	161.04±30.71
TNF-alpha(PG/ML)	54.54±73.76	94.46±12.59	52.18±4.65
IL-1beta (PG/ML)	113.14±11.17	257.19±196.57	114.45±14.43
Pain Intensity (VAS)			
Rest	4.04±2.87	3.28±2.45	1.26±1.35
Activity	6.88±2.09	4.53±2.14	2.10±1.69
WOMAC	72.72±13.13		27.92±14.24
JPS			
35°	6.11±6.06		
55°	6.08±4.04		
70°	10.40±9.21		
Valgus Angle	184.23±7.31	176.33±2.73	176.26±2.91

SCL: Serum Cytokine Level, VAS: Visual Analog Scale, WOMAC: Western Ontario McMaster University Osteoarthritis Index, JPS: Joint Position Sense.

Table 2. Correlation Between Pre-Operative Serum Cytokine Level and Pain

SCL	Pre-operative Pain Intensity (VAS)				Post-operative 72nd Hour Pain Intensity (VAS)				Post-operative 6th Week Pain Intensity (VAS)			
	Rest		Activity		Rest		Activity		Rest		Activity	
	r	p	r	p	r	p	r	p	r	p	r	p
IL-6 (PG/ML)	0.211	0.250	0.340	0.070	0.126	0.522	-0.058	0.766	-0.198	0.312	-0.093	0.632
TNF-alpha (PG/ML)	0.022	0.900	0.151	0.410	0.185	0.347	0.044	0.822	-0.143	0.467	-0.194	0.312
IL-1beta (PG/ML)	0.100	0.580	0.032	0.850	-0.013	0.946	0.172	0.373	-0.145	0.461	0.012	0.951

*p<0.05, Spearman correlation, SCL: Serum Cytokine Level, VAS: Visual Analog Scale, point.

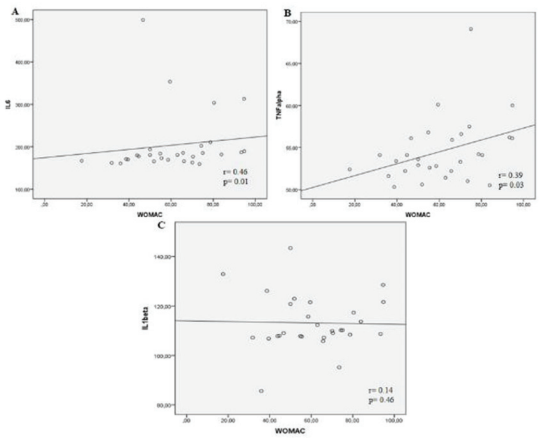

Figure 1. Correlation Between WOMAC and IL-6, TNF-alpha, IL-1beta

gle with IL-6 in 72 hours (r=0.178, p=0.356) and 6 weeks after surgery (r=0.126, p=0.539) as well as IL-1beta in 72 hours (r=0.027, p=0.890) and 6 weeks after surgery (r=0.075, p=0.717). There was no correlation between TNF-alpha and valgus angle and in 72 hours after surgery (r=0.269, p=0.158). However, there was weakly correlation between valgus angle and TNF-alpha in 6 weeks after surgery (r=0.396, p=0.045).

DISCUSSION

It is important to know predictive factors which effect the symptoms after TKA in order to reduce symptoms by taking precautions against these factors. This study indicated that preoperative IL-6 and TNF-alpha were effected in postoperative functional status. While higher TNF-alpha level might affect valgus angle in postoperative term no association occurred between valgus angle and IL-6 and IL-1beta levels. Also there was no relationship between preoperative IL-6 and IL-1beta levels with valgus angle.

In the related literature the effect of LOS is ambiguous in patients who underwent TKA. Our study is the first research which examined the effect of preoperative TNF-alpha and IL-1beta in addition to IL-6 on LOS and it was found that there was no association among any of them. This result was similar to the only study, performed by Zhang et al.(23) which investigated the effect of only IL-6 level on LOS, found that preoperative serum IL-6 level was not associated with LOS but increased serum IL-6 level on postoperative day 1 leads to enhanced LOS in patients who underwent primary

Table 3. Comparison of Serum Cytokine Level According to Length of Stay in Hospital (LOS)

SCL	LOS<5 Mean±SD	LOS>5 Mean±SD	z	p
IL-6 (PG/ML)	201.75±61.63	206.53±89.07	-0.658	0.511
TNF-alpha (PG/ML)	53.86±2.61	55.37±4.93	-0.768	0.442
IL-1beta (PG/ML)	113.36±14.38	112.86±5.67	-0.505	0.614

*p<0.05, Man Whitney U test, SCL: Serum Cytokine Level.

TKA (23). There was not enough research to discuss the relationship between SCL and LOS. It might be affected by other factors.

Higher SCL that exceed their normal limits in peripheral blood might enter brain through blood-brain barrier and cause various cascade of inflammation and ultimately contribute to the development of persistent pain, reduced mood, sleep quality, increased depression, cortisol level (24). Although higher SCL was shown in patient with OA compared to healthy participants and had a positive association with pain intensity, there was inconsistent results for their effect on postoperative pain (8,16,17). As similar to our results Si et al. (16) and Azim et al. (17) showed that preoperative serum IL-6 and TNF-alpha level were not associated with rest pain intensity in 72 hours after surgery. Si et al.(16) demonstrated that activity pain intensity was correlated with preoperative serum IL-6 but not TNF-alpha level. Taken together, these may suggest that IL-6 had no influence on rest pain in 72 hours. However, this result should be implemented carefully due to three cytokines IL-6, TNF-alpha and IL-1beta activate neural pathways and enhance cortisol in adrenal cortex and thus, leads to reduced mood, increased depression, stress, anxiety, cortisol level and sleep quality, all the variables that may threaten the life but we did not control (24). The differences between the studies in terms of activity pain and IL-6 relation may be stemmed from those variables. Zietek et al. (15) reported that patients who had preoperative higher level synovial TNF-alpha demonstrated greater reduce in rest pain and activity pain intensity during gait at the 6th week after TKA surgery. Gandhi et al. (25) reported that patients who had higher preoperative IL-6 and TNF-alpha level, felt significant decrease on pain intensity two years after surgery (25). Zietek et al. (15) and Gandhi et al. (25) concluded that patients who underwent surgery in a high inflammatory state had more reduction in joint inflammation after surgery, leading to a further reduction in pain intensity. In our study, it was demonstrated that preoperative SCL had no correlation with reduction in pain intensity in 72 hours and 6 weeks after surgery. Synovial and serum cytokine levels may have different predictive roles on pain. There is needed more study which investigate preoperative SCL on pain in the long term period.

In the related literature, there was very few study which examined the effect of preoperative SCL level on functional status after TKA. In our study, greater functional status was seen in patients with lower preoperative serum IL-6 and TNF-alpha in 6 weeks after surgery whereas preoperative IL-1beta level was not associated with postoperative functional status. Zietek et al.(15) reported that there was a greater improvement of functional status was seen in patients with higher preoperative synovial TNF-alpha level. They comment that patients with higher local inflammation in the preoperative period had more functional improvement after surgery (15). Our study demonstrated that there was minor improvement in the function in patients with higher preoperative systemic inflammation. This may indicate that preoperative local and systemic inflammation have different effects on postoperative function in the postoperative period. In contrast to TNF-alpha and IL-1beta, which are both inflammatory cytokines, IL-6 has an inflammatory and anti-inflammatory effect (25-29). Circulating IL-6 is involved in the regulation of TNF-alpha and IL-1beta by inhibiting the production of them depends on exercise intensity and duration. Regular exercise training reduces plasma IL-6 concentration whereas untrained people have high circulating IL-6 level. Patient who are more active on preoperative period may have better functional status in postoperative period (25-29).

Systemic inflammation may lead to alterations in electrophysiological properties of joint mechanoreceptors and induce abnormal afferent discharge affecting joint proprioceptive acuity (11). In contrast to our result the only study which investigated the relation between systemic inflammation and proprioception performed by Cudejko et al. who concluded that systemic inflammation as determined by measuring erythrocyte sedimentation rate was associated with decreasing in proprioception via causing muscle weakness in patients with knee OA (11). IL-6, TNF-alpha and IL-1beta may have a different role on erythrocyte sedimentation rate.

Serum inflammatory markers has been known to affect joint alignment and progression of OA (9, 30).

Livshits et al.(9) concluded that higher serum IL-6 level was associated with the progression of OA in patients with knee OA after 15 years follow up period. Stannus et al.(30) showed that serum IL-6 is associated with narrowing of the joint space and loss of knee cartilage and proposed IL-6 plays a predictive role in presuming medial and lateral tibial cartilage loss. In our study, only TNF-alpha low level affects the valgus angle low level at postoperative 6th week. There is needed more study which investigate the mechanism behind the TNF-alpha influence on the valgus angle.

The first limitation of the study was that repeated catheter utilization and sleep deprivation were not recorded. The second limitation was that postoperative exercise effects weren't considered. IL-6 exerts an anti-inflammatory effect with exercise and ceases to be pro-inflammatory. The exercise level of the subjects affects the release of cytokine. Correlation between SCL and CRP was ignored in the study since CRP values were within normal limits in the preoperative period. It was the third limitation of the study. The final limitation was cytokines samples were taken from blood serum. However synovial and serum cytokine levels may have different predictive roles on pain.

This study indicated that preoperative SCL affected in postoperative biomechanical and physical changes. Patients with OA who had lower preoperative IL-6 and TNF-alpha levels had better functional status and better lower limb alignment in the postoperative period. Although preoperative SCL was not directly influencing pain, LOS and JPS, it should be in consideration to obtain better functional status and lower limb alignment in the early postoperative period. So in order to decide TKA surgery timing, primarily decreasing SCL may cause better biomechanical development after surgery. Preoperative SCL was not directly related to the LOS. Preoperative TNF-alpha was positively related with incremented lower limb alignment after surgery. There was no relationship between SCL and, LOS, pain, and joint position sense. Cytokines might have a predictive role on severity of symptoms after TKA. It is an important contribution in terms of drawing attention to the importance of lowering the SCL level before TKA surgery.

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Conflict of Interest The authors have no relevant financial or non-financial conflict of interest.

Ethical Approval This study was approved by the ethical committee of Karadeniz Technical University at 25.05.2018 (2018/91).

Informed Consent Written informed consent was obtained all patients who were willing to participate in the study.

Peer-Review The authors will comply with the editor's decision on this matter.

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KAYNAKLAR

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