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Primary Knee

Is a Combination of Diosmin and Hesperidin Effective on Swelling, Pain, and Range of Motion After Total Knee Arthroplasty?

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ABSTRACT

Background: Swelling is one of the hindrances to functional recovery after total knee arthroplasty (TKA). The aim of this study was to investigate the effect of a diosmin and hesperidin combination on early rehabilitation of patients after TKA.

Methods: This randomized controlled study included patients who underwent unilateral primary TKA between October 2024 and June 2025. There were two groups that were determined as the diosmin and hesperidin group and the control group. The control group did not receive any placebo and only received standard postoperative treatment. The patients' extremity circumferences from the suprapatellar, patellar, and infrapatellar regions; visual analog scale scores at rest and during movement; knee joint range of motion; inflammatory markers in the blood at 24 and 48 hours, and 14 days postoperatively; and complications were compared.

Results: Flexion degrees were 78.8 on the first postoperative day, 86.7 on the second postoperative day, and 104.9 on the 14th postoperative day in the diosmin and hesperidin group, while they were 53.9, 65, and 91 degrees, respectively, in the control group ($P < 0.001$). Although there was a significant difference in suprapatellar and patellar circumference increases on postoperative days one and two between the two groups, there was a significant difference in suprapatellar, patellar, and infrapatellar circumference increases on day 14. There were no significant differences found between the two groups in terms of inflammatory markers.

Conclusions: Using a diosmin and hesperidin combination in the postoperative period after TKA surgery reduces extremity swelling and pain during rest and movement, increases the degree of knee flexion, and does not cause an increase in complications. Thus, it can be used to facilitate the rehabilitation of patients after TKA surgery.

The lifetime prevalence of symptomatic knee osteoarthritis is approximately 45% [1]. Thus, total knee arthroplasty (TKA) is one of the most frequently performed elective surgeries by orthopaedic surgeons worldwide [2]. Total knee arthroplasty significantly increases the quality of life of patients, as it provides a significant pain reduction and functional improvement. Although TKA surgery is generally a successful surgery, patients may be dissatisfied due to many factors. Patient dissatisfaction after TKA has been reported to be up to 20% [3,4]. Functional limitation after surgery is one of the most important reasons for this dissatisfaction. Swelling in the operated extremity is the primary cause of this functional limitation [5]. For this reason, many methods such as cryotherapy [6], compressive bandage application [7], and extremity elevation [8] are used to reduce lower extremity swelling after TKA. Since the predictive factors and mechanisms of postoperative lower extremity swelling are not fully understood, its definitive treatment is still controversial in the literature [9]. Additionally, there is no standard medical treatment to reduce postoperative lower extremity swelling.

Diosmin, a natural flavonoid, is known as a venoactive and venoprotective drug. It decreases the release of inflammatory mediators and thus decreases capillary hyperpermeability.

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Hesperidin, on the other hand, works by increasing the absorption of the diosmin molecule. Thus, the effect of diosmin increases [10,11]. Diosmin and hesperidin combination can be used effectively and safely in cases of venous insufficiency [12–14]. In this study, we aimed to investigate whether the diosmin and hesperidin combination reduces functional limitation by reducing lower extremity swelling in TKA patients in the postoperative period and to investigate its safety.

The hypothesis of this study was that the combination of diosmin and hesperidin would reduce postoperative swelling and pain in patients undergoing TKA and would also contribute to functional recovery by increasing knee flexion.

Materials and Methods

This randomized, controlled trial secured approval from the Clinical Trials and Biomedical Ethics Committee of the participating institution. All participants provided written informed consent. The study was registered in the NIH Clinical Trial Registry on December 30, 2024 (Registration number: NCT06753448).

Patient Selection

From October 1, 2024, to June 20, 2025, it was planned to include patients between 18 and 80 years who applied to a tertiary hospital due to symptomatic knee osteoarthritis, were prepared for surgery for unilateral primary TKA, and had an American Society of Anesthesiologists functional status of I, II, and III.

Patients who had insufficient liver function, a history of surgery involving the same knee, a neuromuscular disorder that affects lower extremities, severe knee instability that could not be reconstructed with primary posterior stabilizing TKA, knee flexion deformity > 30 degrees, varus or valgus deformity > 15 degrees, active systemic or local infection findings, an allergy to either diosmin or hesperidin, or communication difficulties were not included in the study.

In total, 249 patients who underwent unilateral primary TKA surgery preparation between October 1, 2024, and June 20, 2025, were enrolled. There were 48 patients who did not meet the inclusion criteria, and 11 patients who did not consent to participate in the study were excluded. The remaining 190 patients were randomized and divided into two groups: as the diosmin and hesperidin group ($n = 95$) and the control group ($n = 95$). There were five patients from the diosmin and hesperidin group and nine patients from the control group who were lost to follow-up. As a result, the results of a total of 176 patients were analyzed, 90 in the diosmin and hesperidin group and 86 in the control group (Figure 1). The same clinical and demographic data were collected from all patients in the preoperative period.

Randomization

Patients were allocated to the control group or the diosmin and hesperidin group by using a stratified block randomization method to ensure that the number of patients in both groups was close, which relied on a computer-generated list of random numbers. The groups of patients were determined on the day of surgery. Postoperative outcome assessors were blinded to group allocation.

Surgical Technique

All patients received a standardized spinal anesthesia protocol. They underwent TKA surgery using the same technique. All surgeries were performed by five different senior arthroplasty surgeons in a single center. After administering spinal anesthesia, a pneumatic tourniquet was applied to the patients at a pressure of 250 to 300 mm Hg. A midline skin incision was made, and the knee was approached with a medial parapatellar arthrotomy. Following the necessary bone cuts and soft tissue procedure, a cemented posterior stabilizing total knee prosthesis was implanted. After the tourniquet was deflated and hemostasis was achieved, a drain was placed inside the knee joint, and the incision was closed. A compressive bandage was applied to all patients after the surgery.

Perioperative Management

After surgery, patients were transferred to the ward. Ice packs were applied around the incision for 20 minutes every hour. The study group was started on a combination of 450 mg diosmin and 50 mg hesperidin orally twice a day, starting from the eighth postoperative hour and continuing for 14 days. The control group did not receive any placebo and only received standard postoperative treatment. For pain control, patients received three $\times$ 1,000 mg paracetamol and three $\times$ 100 mg tramadol. Since inflammatory markers were also investigated as a secondary outcome in the study, nonsteroidal anti-inflammatory drugs, corticosteroids, or tranexamic acid were not given to the patients during their hospital stay in order not to affect the results.

The dosage of the diosmin and hesperidin combination was adjusted according to the recommendations given in the drug instructions and previous studies [15,16]. Diosmin and hesperidin were provided to patients as a prescription medication.

For venous embolism prophylaxis, patients received 4,000 anti-Xa IU/0.4 mL enoxaparin sodium subcutaneously daily, starting on the postoperative first day and continuing for one month.

All patients received the same physical therapy regimen in the postoperative period. On the first postoperative day, full weight-bearing mobilization and knee range of motion exercises were started.

Primary Outcome

The primary outcome was lower extremity swelling. The formula "[(postoperative lower extremity circumference) − (preoperative lower extremity circumference)]/(preoperative lower extremity circumference) $\times$ 100%" was used to measure the amount of postoperative swelling. Measurements were made in the preoperative morning before the surgery, at the 24th and 48th hours, and on the 14th day postoperatively. Circumference measurements were made using a tape measure, in accordance with the literature, from the thickest part of the calf (infrapatellar), from the upper pole of the patella (patellar), and 10 cm proximal to the upper pole of the patella (suprapatellar) in the operated extremity with the knee in full extension [17]. The patients' measurements were made by a blinded investigator and were repeated three times on the same patient, and the average value was recorded.

Secondary Outcomes

The patients' pain was assessed using the visual analogue scale (VAS) [18]. Pain assessment was performed and recorded both when the patient was in a resting position and when the patient had the knee in maximum flexion. Pain assessment was performed preoperatively, at the 24th and 48th hours and on the 14th day, postoperatively.

Functional evaluation of the patients was performed by measuring the knee joint flexion degrees. The knee flexion of the patients was measured with a goniometer and recorded

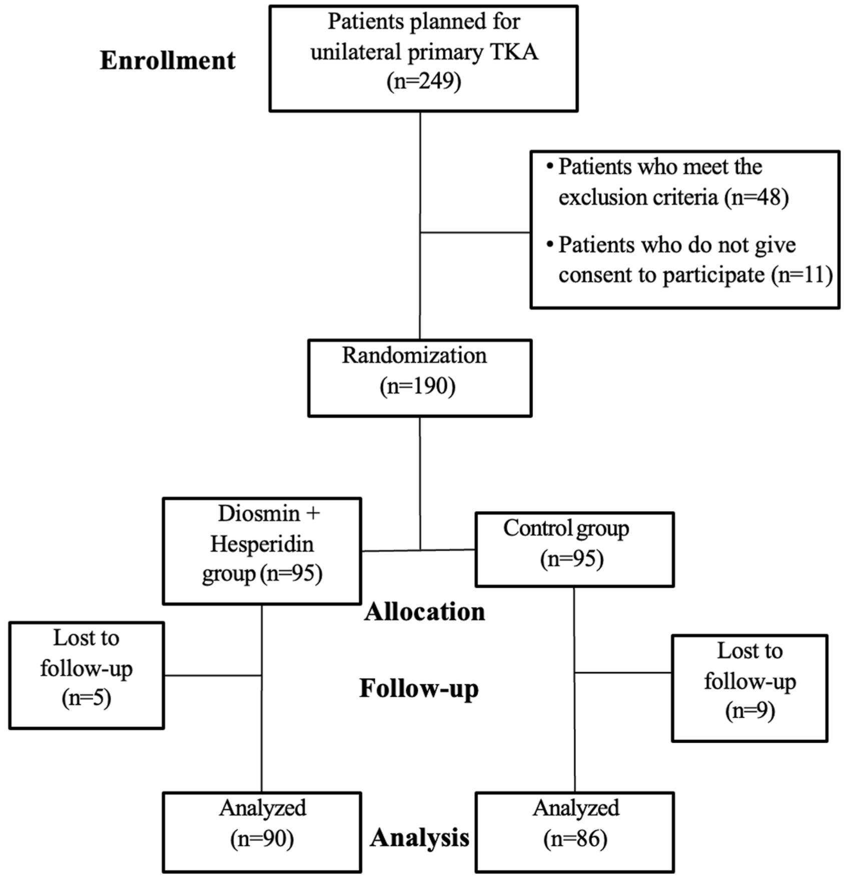

Figure 1. The flowchart of the study. TKA, total knee arthroplasty.

Table 1
Comparison of the Two Groups Regarding Demographic and Preoperative Characteristics of Patients.

Parameters	All Patients (n = 176)	Diosmin + Hesperidin Group (n = 90)	Control Group (n = 86)	*P*-Value
Sex, n (%)				
Women	145 (82.4)	73 (81.1)	72 (83.7)	0.650[a]
Men	31 (17.6)	17 (18.9)	14 (16.3)	
Age, years, mean (range)	67 (50 to 80)	68 (53 to 80)	65 (50 to 80)	**0.030**[b]
BMI, mean (range)	32.2 (21.5 to 50.8)	31.6 (21.5 to 43.9)	32.3 (22.7 to 50.8)	0.686[c]
Operated knee, n (%)				0.118[a]
Right	76 (43.2)	44 (48.9)	32 (37.2)	
Left	100 (56.8)	46 (51.1)	54 (62.8)	
Suprapatellar, cm, mean (range)	46.3 (35 to 59)	46.9 (36 to 59)	45.6 (35 to 58)	0.068[b]
Infrapatellar, cm, mean (range)	37.4 (29 to 54)	37.7 (29 to 50)	37.2 (29 to 54)	0.445[b]
Patellar, cm, mean (range)	42 (33 to 56)	42.1 (34 to 54)	41.9 (33 to 56)	0.774[b]
Flexion, degrees, mean (range)	123.4 (90 to 135)	122 (110 to 135)	124.8 (90 to 130)	**0.006**[b]
VAS at rest, mean (range)	2.6 (0 to 7)	2.4 (0 to 7)	2.8 (1 to 5)	**0.024**[c]
VAS movement, mean (range)	5.1 (1 to 8)	4.9 (1 to 8)	5.3 (3 to 8)	0.148[c]
CRP, mg/L, mean (range)	3.9 (0.2 to 45.2)	3.7 (0.3 to 17.4)	4 (0.2 to 45.2)	0.450[c]
ESR, mm/hour, mean (range)	13.9 (2 to 72)	14.9 (2 to 45)	12.9 (2 to 72)	0.074[c]
NLR, mean (range)	2 (0.8 to 5.7)	2.1 (0.9 to 3.8)	2 (0.8 to 5.7)	0.533[c]
PIV, mean (range)	328 (70 to 1,186)	315 (70 to 1,186)	341 (88 to 949)	0.147[c]
SII, mean (range)	569 (191 to 1,520)	554 (191 to 1,520)	585 (221 to 1,345)	0.264[c]
Platelet, mean (range)	283.2 (134 to 519)	269.7 (134 to 489)	297.4 (137 to 519)	**0.014**[c]

Bold values indicate statistical significance.
SD, standard deviation; VAS, visual analog scale; CRP, C-reactive protein; ESR, erithrocyte sedimantation rate; NLR, neutrophil/lymphocyte ratio; PIV, pan-immune-inflammation value; SII, systemic immune-inflammation index.
[a] *Chi*-square test.
[b] Independent groups *t*-test.
[c] Mann–Whitney *U*-test.

preoperatively, at the 24th and 48th hours, and on the 14th day postoperatively.

Blood samples were taken from the patients in the preoperative period and at the postoperative 24th and 48th hours, and on the 14th day. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), neutrophil/lymphocyte ratio (NLR) [19,20], pan-immune-inflammation value (PIV) [21], and systemic immune-inflammation index [22] values were measured.

Postoperative complications such as nausea, vomiting, deep vein thrombosis, pulmonary thromboembolism, and superficial wound infection that occurred during the follow-up period were recorded.

When the two groups were compared preoperatively, significant differences were found in terms of age, knee flexion degree, VAS at rest, and platelet count ($P = 0.03$, $P = 0.006$, $P = 0.024$, $P = 0.014$; respectively). Comparison of demographic and preoperative characteristics of patients between the two groups is given in detail in Table 1.

Data Analyses

Sample size was determined using *a priori* power analysis with G*Power 3.1 software (Heinrich Heine Universität, Düsseldorf). For a two-tailed independent samples *t*-test with an alpha level of 0.05, a power of 0.9, and a medium effect size (Cohen's $d = 0.5$), the required sample size was calculated as 140 participants (70 per group).

The research data were evaluated using the Statistical Package for the Social Sciences version 23 (IBM Corp., Armonk, New York, USA) statistical package program. In the descriptive statistics section, categorical variables were presented in tables and graphics by giving numbers and percentages, and continuous variables were presented with means ± standard deviations and medians. The conformity of continuous variables to normal distribution was evaluated using visual (histogram and probability graphs) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests). Independent groups *t*-tests were used in comparisons of continuous variables that conformed to normal distribution between two groups, and Mann–Whitney *U*-tests were used in comparisons of continuous variables that did not conform to normal distribution between two groups. Paired samples *t*-tests were used to compare the means of measurements of the same group at two different time points or in two different conditions. *Chi*-square tests were used in comparisons of categorical variables. The statistical significance level was accepted as $P < 0.05$.

Results

Significant differences were found between the groups on the first postoperative day (Table 2) in terms of suprapatellar and patellar circumference increase, knee flexion degree, VAS at rest, VAS during movement, CRP, ESR, and NLR ($P = 0.002$, $P = 0.002$, and $P < 0.001$, $P < 0.001$, $P < 0.001$, $P < 0.001$, $P = 0.020$, $P = 0.021$; respectively).

Significant differences were found between the groups on the 2nd postoperative day (Table 3) in terms of suprapatellar, patellar circumference increase, knee flexion degree, VAS at rest ($P < 0.001$), VAS during movement, and systemic immune-inflammation index ($P < 0.001$, $P = 0.016$, $P < 0.001$, $P < 0.001$, and $P < 0.001$; respectively).

Significant differences were found between the groups on the 14th postoperative day (Table 4) in terms of suprapatellar and patellar, infrapatellar circumference increase, knee flexion degree ($P < 0.001$), VAS at rest, VAS during movement, and platelet count ($P < 0.001$, $P < 0.001$, $P = 0.043$, $P < 0.001$, $P < 0.001$, and $P = 0.009$; respectively).

In the diosmin and hesperidin group, 38 (42.2%) patients had nausea, 12 (13.3%) had vomiting, three (3.3%) had superficial wound infection, and one (1.1%) had pulmonary thromboembolism. In the control group, 57 (66.3%) patients had nausea, 22 (25.6%) had vomiting, and three (3.5%) had superficial wound infection as postoperative complications (Table 5). When the two groups were compared, nausea and vomiting were found to be significantly higher in the control group ($P = 0.001$, $P = 0.040$, respectively).

The mean preoperative platelet count of the patients was 283.2 (range, 134 to 519) and 427.1 (range, 217 to 994) on the 14th postoperative day. The mean preoperative platelet count in the control group was 297.4 (137 to 519), and on the 14th postoperative day, it was 471.6 (219 to 1015), while in the diosmin and hesperidin group, they were 269.7 (range, 134 to 489) and 427.1 (range, 217 to 994). When platelet counts were compared between the two groups, a significant difference was

Table 2
Comparison of the Two Groups Regarding Postoperative First Day Results of Patients.

Parameters	Diosmin + Hesperidin Group (n = 90)	Control Group (n = 86)	*P*-Value[a]
Suprapatellar, % increase, mean (range)	6.8 (0 to 17)	9.1 (1.9 to 20.7)	**0.002**
Patellar, % increase, mean (range)	7.3 (0 to 32.4)	9.2 (0 to 23.8)	**0.002**
Infrapatellar, % increase, mean (range)	6 (0 to 19.4)	7 (0 to 17.6)	0.260
Flexion, degrees, mean (range)	78.8 (40 to 110)	53.9 (30 to 90)	**<0.001**
VAS at rest, mean (range)	1.7 (0 to 6)	2.8 (1 to 5)	**<0.001**
VAS movement, mean (range)	4.1 (1 to 8)	5.1 (3 to 7)	**<0.001**
CRP, mg/L, mean (range)	21.7 (6 to 212)	63.4 (8 to 212.4)	**<0.001**
ESR, mm/hour, mean (range)	17.8 (2 to 90)	21.3 (3 to 64)	**0.020**
NLR, mean (range)	10.3 (0.9 to 50)	8.2 (1.7 to 20.7)	**0.021**
PIV, mean (range)	1,506 (62 to 6,927)	1,655 (166 to 6,253)	0.270
SII, mean (range)	2,499 (145 to 15,560)	2,102 (319 to 6,130)	0.100
Platelet, mean (range)	238.7 (61 to 373)	246.8 (124 to 449)	0.565

Bold values indicate statistical significance.
SD, standard deviation; VAS, visual analog scale; CRP, C-reactive protein; ESR, erithrocyte sedimantation rate; NLR, neutrophil/lymphocyte ratio; PIV, pan-immune-inflammation value; SII, systemic immune-inflammation index.
[a] Mann–Whitney *U*-test.

Table 3
Comparison of the Two Groups Regarding Postoperative Second Day Results of Patients.

Parameters	Diosmin + Hesperidin Group (n = 90)	Control Group (n = 86)	*P*-Value[a]
Suprapatellar, % increase, mean (range)	7.8 (0 to 20.5)	10.4 (0 to 20.7)	**<0.001**
Patellar, % increase, mean (range)	8.8 (0 to 28.6)	10.5 (0 to 26.2)	**0.016**
Infrapatellar, % increase, mean (range)	7.7 (0 to 21.9)	8.6 (0 to 21.6)	0.146
Flexion, degrees, mean (range)	86.7 (30 to 110)	65 (35 to 100)	**<0.001**
VAS at rest, mean (range)	1.1 (0 to 3)	2.2 (1 to 4)	**<0.001**
VAS movement, mean (range)	3.4 (1 to 7)	4.6 (3 to 7)	**<0.001**
CRP, mg/L, mean (range)	142.4 (12.1 to 338)	151 (29 to 342.7)	0.456
ESR, mm/hour, mean (range)	33.4 (4 to 91)	37.2 (10 to 96)	0.094
NLR, mean (range)	6.1 (1.6 to 23.3)	5 (1.1 to 11.2)	0.241
PIV, mean (range)	1,202 (128 to 4,452)	1,191 (13 to 3,542)	0.748
SII, mean (range)	1,396 (291 to 5,113)	648 (1 to 2,970)	**<0.001**
Platelet, mean (range)	219.5 (96 to 370)	238.4 (111 to 477)	0.117

Bold values indicate statistical significance.
SD, standard deviation; VAS, visual analog scale; CRP, C-reactive protein; ESR, erithrocyte sedimantation rate; NLR, neutrophil/lymphocyte ratio; PIV, pan-immune-inflammation value; SII, systemic immune-inflammation index.
[a] Mann–Whitney *U*-test.

found between the values on the preoperative and postoperative 14th day ($P = 0.014$, $P = 0.009$, respectively). It was also observed that the platelet count on the postoperative 14th day was significantly higher than the preoperative value ($P < 0.001$). The change in mean platelet count over time in the entire group is shown in Figure 2.

Discussion

In this study, it was found that the diosmin and hesperidin combination reduced lower extremity swelling and pain at rest and during movement, increased the degree of knee joint flexion, decreased postoperative nausea and vomiting, and did not change the other complication rates in the early postoperative period in TKA patients.

Various factors affect the recovery process after TKA surgery. Swelling in the operated extremity is one of the main factors that slows down the recovery process [3,4,9,23,24]. There is no routine, effective, and safe medical treatment to reduce lower extremity swelling after TKA. There are studies in the literature on the use of oral or intravenous corticosteroids and periarticular cocktail injections containing local anesthetics or steroids [25–29]. In this study, it was found that the diosmin and hesperidin combination significantly reduced lower extremity swelling, and there was no difference in early complications compared to the control group. Similar results were found in a recent prospective study using diosmin alone after TKA [15]. In studies where the combination of diosmin, coumarin, and arbutin was used in patients who have hand and ankle edema after trauma or surgery, it was observed that the edema regressed more rapidly [30,31]. This result is thought to occur because diosmin increases microcirculation and lymphatic drainage, and reduces capillary permeability, and has venoprotective and anti-inflammatory effects [12,14,16,32,33]. Hesperidin increases the absorption of diosmin, making it more effective [11].

It is uncertain whether the anti-edema effect of diosmin and hesperidin is related to their anti-inflammatory effect. Although the patients did not receive nonsteroidal anti-inflammatory drugs postoperatively, no significant difference was found between the inflammatory marker levels of the diosmin and hesperidin group and the control group, except for the CRP and ESR values on the first postoperative day. This situation, which could not be clearly evaluated in a previous study [15] because anti-inflammatory drugs were also received by patients, was found to have the same result in this study, although no anti-inflammatory drugs were given to patients.

Table 4
Comparison of the Two Groups Regarding Postoperative 14th Day Results of Patients.

Parameters	Diosmin + Hesperidin Group (n = 90)	Control Group (n = 86)	*P*-Value[a]
Suprapatellar, % increase, mean (range)	4.9 (0 to 16.3)	8.3 (0 to 22.4)	**<0.001**
Patellar, % increase, mean (range)	5.5 (0 to 18.6)	8.7 (0 to 23.8)	**<0.001**
Infrapatellar, % increase, mean (range)	5.5 (0 to 27)	6.7 (0 to 20.4)	**0.043**
Flexion, degrees, mean (range)	104.9 (75 to 125)	91 (60 to 120)	**<0.001**
VAS at rest, mean (range)	0.8 (0 to 4)	1.8 (1 to 4)	**<0.001**
VAS movement, mean (range)	2.5 (1 to 7)	3.5 (2 to 6)	**<0.001**
CRP, mg/L, mean (range)	12.9 (1.1 to 129.5)	12.2 (0.5 to 58.4)	0.533
ESR, mm/hour, mean (range)	31.7 (7 to 61)	30.9 (6 to 63)	0.751
NLR, mean (range)	3.4 (1.2 to 13.4)	3.1 (1.1 to 6.7)	0.150
PIV, mean (range)	859 (111 to 3,392)	940 (116 to 3,732)	0.316
SII, mean (range)	1,435 (445 to 5,525)	1,444 (437 to 3,279)	0.782
Platelet, mean (range)	427.1 (217 to 994)	471.6 (219 to 1,015)	**0.009**

Bold values indicate statistical significance.
SD, standard deviation; VAS, visual analog scale; CRP, C-reactive protein; ESR, erithrocyte sedimantation rate; NLR, neutrophil/lymphocyte ratio; PIV, pan-immune-inflammation value; SII, systemic immune-inflammation index.
[a] Mann–Whitney *U*-test.

Table 5
Comparison of the Two Groups Regarding Postoperative Complications.

Complications	Diosmin + Hesperidin Group (n = 90)	Control Group (n = 86)	*P*-Value[a]
Nausea, n (%)	38 (42.2)	57 (66.3)	**0.001**
Vomiting, n (%)	12 (13.3)	22 (25.6)	**0.040**
Superficial wound infection, n (%)	3 (3.3)	3 (3.5)	0.955
Pulmonary thromboembolism, n (%)	1 (1.1)	0	

Bold values indicate statistical significance.
[a] *Chi*-square test.

Another important factor that reduces patients' comfort and makes rehabilitation more difficult after TKA is pain. After surgery, patients have serious pain both at rest and during movement. Inadequate pain control delays the recovery process [34,35]. In this study, the mean VAS values of the diosmin and hesperidin group were found to be significantly lower than the control group in the postoperative period, both at rest and during movement. This may be due to the analgesic effect of diosmin on the central and peripheral nervous systems. It has been shown in the literature that diosmin has an analgesic effect through different mechanisms [12,13,32]. Also, diosmin and hesperidin may indirectly reduce pain by reducing swelling of the extremity.

Knee range of motion is frequently used in the literature to evaluate functional outcomes after TKA [36–38]. In this study, postoperative knee flexion degree was used as a secondary outcome. In the diosmin and hesperidin group, the degree of knee joint flexion was found to be significantly higher on postoperative days one, two, and 14. Thanks to the anti-edema effect of diosmin and hesperidin, patients can flex their knees more as lower extremity swelling and pain are reduced. This shortens the postoperative recovery period and increases the patient's compliance with the rehabilitation process. In a previous study, no significant difference was found in terms of knee flexion degree between the diosmin-receiving and non-receiving groups [15].

In this study, fewer patients in the diosmin and hesperidin group had complications of nausea and vomiting than in the control group, and this difference was found to be significant. In a previous study, less nausea and vomiting were observed in the diosmin group, but this difference was not found to be significant [15]. The mechanism of this effect of diosmin and hesperidin is unknown since there is no study explaining the mechanism in the literature. This may be the direct effect of the medication, or it may be due to reducing patients' pain and decreasing the need for opioids, and therefore it may reduce opioid-related nausea and vomiting. Future studies are needed to investigate and explain the mechanism of this effect.

In this study, all patients were operated on under spinal anesthesia. Similar results were obtained when patients were operated on under general anesthesia in a previous study [15]. Therefore, the type of anesthesia does not change the postoperative effect of diosmin.

In the study, it was observed that the platelet value tended to decrease on the first and second postoperative days, but was significantly higher than the preoperative value on the 14th postoperative day. It is known that the platelet count decreases in the first four days after surgery and then increases, peaking on the 14th day. This situation is explained by the presence of postoperative dilutional thrombocytopenia and subsequent physiological overshoot in the platelet count due to delayed thrombopoietin response [39,40]. In the past, the relationship between this condition and complications after colorectal [41], urologic [42], and orthopaedic surgeries [43] has been investigated, but the results were controversial. It was also found in this study that there is no significant association between postoperative thrombocytosis and complications. Larger studies on this topic are needed to draw meaningful conclusions.

A potential limitation of the study is that it is not known when and at what dose the optimal effect will be achieved when diosmin and hesperidin are administered after TKA. The drug dose was determined based on past studies, but it is not known whether the dose used is the most effective dose. More studies are needed to determine the optimal drug dose and timing of administration. Not using a placebo is another limitation, as it increases the risk of bias and limits internal validity. Another limitation of the study is the short follow-up period. Since the patients were followed for only 14 days, long-term results are unknown. However, the diosmin and hesperidin combination can be used safely and effectively for longer periods in the treatment of different diseases such as chronic venous insufficiency and hemorrhoids. Longer follow-

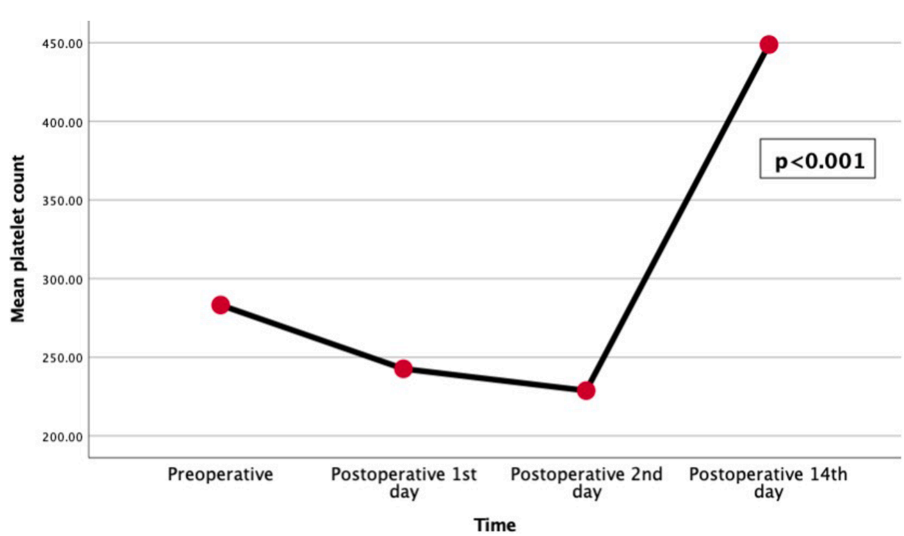

Figure 2. The change in mean platelet count of the patients over time.

up studies are needed to determine the safety of diosmin and hesperidin in TKA. Furthermore, it is unclear whether the reduction in swelling is clinically relevant or not.

Conclusion

The diosmin and hesperidin combination reduces lower extremity swelling and pain at rest and during movement, increases knee joint flexion degree, and decreases nausea and vomiting complications in early postoperative TKA patients. In this respect, a diosmin and hesperidin combination may be an option to facilitate the rehabilitation of early postoperative TKA patients. However, more studies are needed to reveal the long-term outcomes.

CRediT authorship contribution statement

Ahmet B. Girgin: Writing – original draft, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Evrim Duman:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

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