Diosmin + Hesperidin for Swelling, Pain, and ROM After TKA

Girgin AB, Duman E. Is a Combination of Diosmin and Hesperidin Effective on Swelling, Pain, and Range of Motion After Total Knee Arthroplasty?

Citation: J Arthroplasty 2026;41:2043–2050 (PMID 41161507). doi:10.1016/j.arth.2025.10.058.

Study type / level of evidence: Therapeutic study — single-center randomized controlled trial, open-label, no placebo. 176 analyzed (90 vs 86). Level II (RCT downgraded for lack of blinding/placebo).

Part 1 — Leopold Five-Minute Critical Appraisal

1. What kind of study and what design?

A therapy RCT: patients undergoing unilateral primary cemented PS TKA were randomized (stratified block) to a diosmin 450 mg/hesperidin 50 mg combination twice daily for 14 days versus standard care with no placebo. Outcome assessors were blinded; 176 of 190 randomized were analyzed.

2. Does it study an important question?

Moderately. Postoperative swelling impedes early rehabilitation and there is no standard pharmacologic anti-edema treatment, so a cheap, safe oral venoactive that accelerates flexion recovery would be attractive for ASC rapid-recovery pathways. The endpoints, however, are short-term surrogates (limb circumference, VAS, 14-day ROM).

3. To whom does it apply, and to whom not?

Applies to standard primary unilateral cemented PS TKA under spinal anesthesia, ASA I–III, age ≤80, without hepatic insufficiency or flavonoid allergy. It does not speak to long-term function or to bilateral, revision, or severely deformed knees, and the 14-day horizon limits any durability claim.

4. Describe the methods — anything to watch for?

The control group received nothing (no placebo), creating strong expectation and performance bias for subjective endpoints (VAS, ROM), only partly offset by blinded assessors. Importantly, randomization did not balance key prognostic baselines: groups differed significantly in age, baseline flexion, resting VAS, and platelet count — and lower baseline flexion in controls inflates the between-group flexion delta. NSAIDs, steroids, and TXA were withheld to keep inflammatory markers clean, which is internally tidy but not real-world. Multiple endpoints across several timepoints introduce multiplicity.

5. Were hypotheses clearly stated?

Yes — the combination was hypothesized to reduce postoperative swelling and pain and to improve knee flexion.

6. Key results — any counterintuitive findings?

Flexion was markedly higher with diosmin/hesperidin (78.8/86.7/104.9° at day 1/2/14 vs 53.9/65/91°, P<0.001), circumference increases were lower (all three regions by day 14), and resting and movement VAS were lower. Nausea (42% vs 66%) and vomiting (13% vs 26%) were less frequent. Strikingly, inflammatory markers (CRP, ESR, NLR, PIV, SII) did not differ except CRP/ESR on day 1 — so the benefit does not appear to act through systemic anti-

inflammation, and the antiemetic effect is unexplained. The very low day-1 control flexion (53.9°) is itself a flag for measurement/expectation effects.

7. Strengths?
Randomized design with an adequate a priori power calculation, a clinically meaningful functional endpoint (ROM), an inflammatory-marker panel, deliberate withholding of NSAIDs to isolate the drug effect, and reasonable sample size.

8. Weaknesses?
No placebo and open-label control (major threats to subjective endpoints), baseline imbalance in prognostic variables, a 14-day horizon, surrogate swelling measures of uncertain clinical relevance (the authors concede this), single center, unknown optimal dose/timing, and a large early flexion gap that invites expectation-bias concern.

9. How does it fit with what is known, and what remains?
It builds directly on Wang 2024 (JBJS), a multicenter RCT of diosmin alone after TKA that reduced swelling and pain, and is consistent with the broader micronized purified flavonoid fraction (MPFF) venous-disease literature and post-trauma edema RCTs. It diverges from Wang on ROM (Wang found no flexion difference). Open questions: placebo-controlled, blinded confirmation; dose-finding; clinical/PROM relevance of the swelling reduction; longer follow-up; and DVT-safety surveillance.

10. Would it change your practice?
Promising, inexpensive, and low-risk as an adjunct in an ASC rapid-recovery protocol — but the absent placebo and baseline imbalance mean I would want placebo-controlled, blinded confirmation before routine adoption. It is reasonable to consider given the safety profile; it is not yet standard of care.

Validity and Bias

Internal validity: Weakened principally by the absence of a placebo (performance and detection bias on subjective outcomes) and by baseline prognostic imbalance (susceptibility bias) that randomization failed to control, which directly affects the headline flexion result.

External validity (generalizability): Standard primary cemented PS TKA under spinal anesthesia at a single Turkish center; short-term only.

Principal biases: Performance/detection bias (open-label, no placebo), susceptibility bias (baseline imbalance in age, flexion, VAS, platelets), and multiplicity from repeated endpoints/timepoints.

Part 2 — Comparison to the Existing Literature

Search method: PubMed searched across three windows — the past 20 years (2006–2026), the past 2 years (2024–2026), and the trailing 30 days (29 May–29 June 2026). Citations below include DOIs (source: PubMed).

Foundational / landmark context (20-year window)

Background rests on the MPFF/venoactive literature (Lyseng-Williamson 2003 review; Nicolaides 2020) and on non-pharmacologic swelling measures after TKA — cryotherapy (Wyatt 2023 systematic review), compression bandaging (Liu 2020 meta-analysis), and elevation — none of which is definitive. Post-trauma/post-surgical edema RCTs of diosmin-containing

products (Cacchio 2019, 2023) established a plausible anti-edema, lymphatic-drainage mechanism.

Past two years (2024–2026)

The pivotal comparator is Wang Q, et al. (JBJS 2024;106:492–500), a randomized controlled multicenter trial of diosmin alone for lower-extremity swelling and pain after TKA, which this study extends to the diosmin+hesperidin combination and corroborates for swelling and pain. Serra 2021 (Nutrients) provides contemporaneous placebo-controlled RCT support for diosmin in chronic venous disease.

Trailing 30 days

A targeted PubMed search returns only this article (PMID 41161507) for diosmin+hesperidin in TKA, with no additional on-topic study indexed in the trailing 30 days. This is effectively the first RCT of the diosmin+hesperidin combination (as opposed to diosmin alone) in the TKA setting.

Where this paper sits in the literature

This is the second RCT of a venoactive flavonoid in TKA and the first of the combination. It reproduces Wang's swelling and pain benefit and adds an antiemetic signal, but is methodologically weaker than the multicenter Wang trial because of the missing placebo and baseline imbalance — so it advances the hypothesis without settling it.

Key comparator references

1. Wang Q, Jin Q, Cai L, et al. Efficacy of diosmin in reducing lower-extremity swelling and pain after total knee arthroplasty: a randomized, controlled multicenter trial. J Bone Joint Surg Am 2024;106:492–500. doi:10.2106/JBJS.23.00847
2. Serra R, et al. Efficacy of a low-dose diosmin therapy on symptoms and quality of life in chronic venous disease: randomized, double-blind, placebo-controlled trial. Nutrients 2021;13:999. doi:10.3390/nu13030999
3. Wyatt PB, et al. The role of cryotherapy after total knee arthroplasty: a systematic review. J Arthroplasty 2023;38:950–956. doi:10.1016/j.arth.2022.12.004
4. Liu P, et al. Should compression bandage be performed after total knee arthroplasty? A meta-analysis of RCTs. J Orthop Surg Res 2020;15:52. doi:10.1186/s13018-019-1527-9
5. Cacchio A, et al. Efficacy and safety of diosmin/coumarin/arbutin (Linfadren) for persistent post-trauma/surgery hand edema: RCT. Clin Rehabil 2019;33:904–912. doi:10.1177/0269215519829797