

Acetaminophen for Osteoarthritis of the Knee: Could the Guidelines Be Wrong?

Case JP, Baliunas AJ, Block JA. Lack of efficacy of acetaminophen in treating symptomatic knee osteoarthritis: a randomized, double-blind, placebo-controlled comparison trial with diclofenac sodium. *Arch Intern Med* 2003;163:169–78.

Study Overview

Objective. To determine if acetaminophen is as effective and of equal analgesic efficacy as nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of symptomatic knee osteoarthritis.

Design. Randomized, double-blind, placebo-controlled trial with an intention-to-treat analysis.

Setting and participants. Patients were enrolled through the section of rheumatology at a single, major academic medical center. Eligibility criteria included unilateral symptomatic idiopathic osteoarthritis of the knee diagnosed by radiographic and clinical criteria. Radiographic criteria included a modified Kellgren-Lawrence grade 1 or higher on radiograph, with possible or definite medial joint space narrowing or osteophytes. Clinical criteria included pre-enrollment ambulatory pain, moderate or increasing pain during a 2-week washout period following discontinuation of previous analgesic, and being able to ambulate without an assist device. Exclusion criteria included prior intolerance or allergy to study drug, functional class I or IV, history of peptic ulcer disease, significant hepatic abnormality, renal insufficiency, hematologic disease, joint disease other than osteoarthritis, history of joint replacement surgery, and the use of anticoagulants or any drug that might interfere with pain perception (tranquilizers, hypnotic agents, or excessive alcohol use).

Intervention. Patients were randomized to 75 mg of diclofenac sodium twice daily, 1000 mg of acetaminophen 4 times daily, or matching placebo.

Main outcome measures. Outcomes measures were assessed at screening, baseline, week 2, and week 12. The primary outcome measure included a clinical assessment performed by a physician, scores on the self-administered Western Ontario and McMaster Universities Osteoarthritis (WOMAC) survey, and the Lequesne Algofunctional Index for the Knees (Lequesne Index). The WOMAC survey assesses pain, stiffness, and function while the Lequesne Index assesses pain, walking, and function. Although both

scales were used, the authors had prospectively selected the WOMAC for the study's primary analysis. Pill counts were used to assess compliance.

Main results. 82 patients were randomized, with 25 to the diclofenac group, 29 to the acetaminophen group, and 28 to the placebo group. There were no significant differences in any of the measured characteristics (ie, age, sex, body mass index, prior use of osteoarthritis medications, baseline pain, and radiograph features) between the groups. Pill counts revealed greater than 90% compliance with the study drugs. Overall, 5 patients withdrew from the diclofenac group, 7 from the acetaminophen group, and 9 from the placebo group. The majority of the withdrawals from the diclofenac group (3/5) resulted from adverse events while the majority of withdrawals from the acetaminophen and placebo group resulted from inefficacy (5/7 and 4/9).

At week 2 and week 12, only improvements in the diclofenac group reached statistical significance ($P < 0.001$), with reductions in pain, stiffness, and function. No clinical or statistical significant differences were seen in the WOMAC scores for the acetaminophen and placebo groups. At week 2, there were statistically significant differences in the Lequesne Index for pain in the diclofenac group and functioning in all 3 groups. At week 12, no statistical differences were seen in any group on the Lequesne Index subscales. In subgroup analysis, after stratifying groups according to severity of baseline pain or radiographic severity, diclofenac efficacy was inconsistent and revealed no clear pattern of response. There were no statistically significant changes seen in the acetaminophen-treated or placebo groups in the subgroup analyses.

Conclusion. While diclofenac appears efficacious for the treatment of symptomatic osteoarthritis of the knee, acetaminophen does not and is not superior to placebo for this condition.

Commentary

Acetaminophen has been recommended as an initial treatment of choice in osteoarthritis of the knee [1,2]. These

guidelines are based on the superior safety and tolerability profile of acetaminophen over NSAIDs and the results of a major study that showed no clear benefit of ibuprofen over acetaminophen [3]. Despite these guidelines, patient surveys seem to suggest that NSAIDs are generally preferred over acetaminophen [4]. Furthermore, most of the evidence supporting acetaminophen over NSAIDs was based on trials that did not have placebo groups.

Case et al's well-designed trial overcomes many of the methodological shortcomings of prior studies. and acetaminophen's performance, when compared with placebo, was unimpressive. Acetaminophen's consistent lack of effect in this trial suggests practitioners should re-evaluate current recommendations for treatments of osteoarthritis of the knee. This study's strengths include the use of validated outcome measurements, an intention-to-treat analysis, and more than adequate power (98%) to detect meaningful differences among the groups (on post hoc power validation). The study, with only 82 participants, was relatively small, which might explain some of the lack of consistent findings in the subgroup analysis.

Applications for Clinical Practice

Despite clinical guidelines recommending acetaminophen in osteoarthritis of the knee, this treatment does not appear

to relieve pain, stiffness, or functional loss. When compared with placebo in this trial, acetaminophen's performance was unimpressive. Acetaminophen's consistent lack of effect in this trial suggests practitioners should re-evaluate current recommendations for treatments of osteoarthritis of the knee.

—Review by Harvey J. Murff, MD, MPH

References

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