Original Investigation

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Effect of Combination of Paracetamol (Acetaminophen) and Ibuprofen vs Either Alone on Patient-Controlled Morphine Consumption in the First 24 Hours After Total Hip Arthroplasty

The PANSAID Randomized Clinical Trial

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Visual Abstract

Key Points

Question Does paracetamol (acetaminophen) combined with ibuprofen reduce postoperative morphine usage relative to the use of each drug alone in patients undergoing total hip arthroplasty (THA), and does ibuprofen increase the incidence of serious adverse events (SAEs)?

Findings In this randomized clinical trial that included 556 patients who underwent THA, morphine usage in the first 24 hours was statistically significantly lower for the combination of paracetamol 1000 mg and ibuprofen 400 mg than for either alone; however, the combined medications did not meet the prespecified threshold for clinically important postoperative morphine reduction (10 mg) compared with ibuprofen alone. The percentage of pa-

tients with SAEs for those in any of the ibuprofen groups vs paracetamol alone was 15% vs 11%, which was not statistically significant.

Meaning Although the combined use of paracetamol and ibuprofen reduced immediate postoperative morphine consumption compared with paracetamol alone in patients undergoing THA, ibuprofen alone resulted in comparable pain control without increasing SAEs, suggesting that ibuprofen alone may be a reasonable option.

Abstract

Importance Multimodal postoperative analgesia is widely used but lacks evidence of benefit.

Objective Investigate beneficial and harmful effects of 4 nonopioid analgesics regimens.

Design, Setting, and Participants Randomized, blinded, placebo-controlled, 4-group trial in 6 Danish hospitals with 90-day follow-up that included 556 patients undergoing total hip arthroplasty (THA) from December 2015 to October 2017. Final date of follow-up was January 1, 2018.

Interventions Participants were randomized to receive paracetamol (acetaminophen) 1000 mg plus ibuprofen 400 mg (n = 136; PCM + IBU), paracetamol 1000 mg plus matched placebo (n = 142; PCM), ibuprofen 400 mg plus matched placebo (n = 141; IBU), or half-strength paracetamol 500 mg plus ibuprofen 200 mg (n = 140; HS-PCM + IBU) orally every 6 hours for 24 hours postoperatively, starting 1 hour before surgery.

Main Outcomes and Measures Two co-primary outcomes: 24-hour morphine consumption using patient-controlled analgesia in pairwise comparisons between the 4 groups (multiplicity-adjusted thresholds for statistical significance, $P < .0042$; minimal clinically important difference, 10 mg), and proportion of patients with 1 or more serious adverse events (SAEs) within 90 days (multiplicity-adjusted thresholds for statistical significance, $P < .025$).

Results Among 559 randomized participants (mean age, 67 years; 277 [50%] women), 556 (99.5%) completed the trial and were included in the analysis. Median 24-hour morphine consumption was 20 mg (99.6% CI, 0-148) in the PCM + IBU group, 36 mg (99.6% CI, 0-166) for PCM alone, 26 mg (99.6% CI, 2-139) for IBU alone, and 28 mg (99.6% CI, 2-145) for HS-PCM + IBU. The median difference in morphine consumption between the PCM + IBU group vs PCM alone was 16 mg (99.6% CI, 6.5 to 24; $P < .001$); for the PCM-alone group vs HS-PCM + IBU, 8 mg (99.6% CI, −1 to 14; $P = .001$); and for the PCM + IBU group vs IBU alone, 6 mg (99.6% CI, −2 to 16; $P = .002$). The difference in morphine consumption was not statistically significant for the PCM + IBU group vs HS-PCM + IBU (8 mg [99.6% CI, −2 to 16]; *P*

=.005) or for the PCM-alone group vs IBU alone (10 mg [99.6% CI, −2 to 16]; *P*=.004) after adjustment for multiple comparisons and 2 co-primary outcomes. There was no significant difference between the IBU-alone group vs HS-PCM+IBU (2 mg [99.6% CI, −10 to 7]; *P* =.81). The proportion of patients with SAEs in groups receiving IBU was 15%, and in the PCM-alone group, was 11%. The relative risk of SAE was 1.44 (97.5% CI, 0.79 to 2.64; *P* =.18).

Conclusions and Relevance Among patients undergoing THA, paracetamol plus ibuprofen significantly reduced morphine consumption compared with paracetamol alone in the first 24 hours after surgery; there was no statistically significant increase in SAEs in the pooled groups receiving ibuprofen alone vs with paracetamol alone. However, the combination did not result in a clinically important improvement over ibuprofen alone, suggesting that ibuprofen alone may be a reasonable option for early postoperative oral analgesia.

Trial Registration ClinicalTrials.gov Identifier: NCT02571361

Full Text

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