# Intravenous acetaminophen analgesia after cardiac surgery: A randomized, blinded, controlled superiority trial

Negmeldeen F. Mamoun, MD, PhD,[a,b] Peirong Lin, MD,[b] Nicole M. Zimmerman, MS,[b,c] Edward J. Mascha, PhD,[b,c] Stephanie L. Mick, MD,[d] Steven R. Insler, DO,[a,b] Daniel I. Sessler, MD,[b] and Andra E. Duncan, MD[a,b]

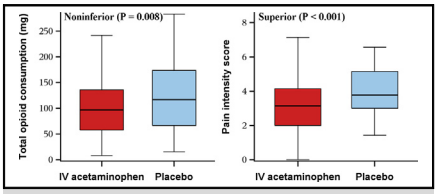
## ABSTRACT

**Background:** Pain after cardiac surgery traditionally has been controlled by intravenous opioids and nonsteroidal antiinflammatory drugs. An intravenous analgesic with fewer adverse effects is needed. Therefore, we tested the primary hypothesis that intravenous acetaminophen is more effective than placebo for pain management, which was defined a priori as superior on either pain intensity score and/or opioid consumption and not worse on either.

**Methods:** In this single-center, double-blind trial, 147 patients having cardiac surgery via median sternotomy were randomized to receive either 1 g of intravenous acetaminophen (73 patients) every 6 hours for 24 hours or comparable placebo (74 patients) starting in the operating room after sternal closure. Cumulative opioid consumption (in morphine equivalents) and pain intensity scores (on a 0-10 Numeric Rating Scale) were measured at 4, 6, 8, 12, 16, 20, and 24 hours after surgery. We estimated ratio of mean opioid consumption by using multivariable linear regression (noninferiority delta = 1.15) and pain score difference by using repeated measures regression (noninferiority delta = 1).

**Results:** Acetaminophen was superior to placebo on mean pain intensity scores and noninferior on opioid consumption, with estimated difference in mean pain (95% confidence interval) of −0.90 (−1.39, −0.42), $P < .001$ (superior), and estimated ratio of means in opioid consumption (90% confidence interval) of 0.89 (0.73-1.10), $P = .28$ (noninferior; not superior).

**Conclusions:** Intravenous acetaminophen reduced pain after cardiac surgery, but not opioid consumption. Intravenous acetaminophen can be an effective analgesic adjunct in patients recovering from median sternotomy. (J Thorac Cardiovasc Surg 2016;152:881-9)




IV acetaminophen was noninferior on opioid consumption and superior on pain scores.

**Central Message**

Intravenous acetaminophen significantly reduced pain, but not opioid consumption, after cardiac surgery done via median sternotomy.

**Perspective**

Pain after cardiac surgery traditionally has been controlled by intravenous opioids and nonsteroidal antiinflammatory drugs. Intravenous acetaminophen has fewer adverse effects and was found to significantly reduce pain intensity scores, but not opioid consumption, after cardiac surgery. Intravenous acetaminophen may be an effective component of a multimodal analgesic strategy after median sternotomy.

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Multimodal analgesic strategies depend on the synergistic effects of various classes of analgesics. Combining several agents thus permits reductions in individual drug doses and consequent adverse effects. The World Health Organization's Pain Ladder recommends administering nonopioid analgesics before adding opioids if warranted by the intensity of postoperative pain.[1] Similarly, the American Society of Anesthesiologists recommends stepwise

From the Departments of [a]Cardiothoracic Anesthesia and [b]Outcomes Research, Anesthesiology Institute, and Departments of [c]Quantitative Health Sciences and [d]Cardiothoracic Surgery, Cleveland Clinic, Cleveland, Ohio.

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The authors attest to having full freedom to explore the data and analyze the results. The authors had sole authority to make the final decision to submit the material for publication. The authors had no potential conflicts of interest and no financial interests with any commercial entity that would be affected by the publication.

The study had complex statistical methodology; therefore, 2 biostatisticians were needed to assist with the statistical design and analysis and were both included as authors.

Current affiliation of Dr Lin: Department of Anesthesiology, Beijing Anzhen Hospital.

This report describes a prospective randomized clinical trial. The author states that the report includes every item in the CONSORT checklist for a prospective randomized clinical trial.

The study was registered before patient enrolment at www.clinicaltrials.gov on March 28, 2013, registration number: NCT01822821.

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Address for reprints: Negmeldeen F. Mamoun, MD, PhD, Departments of Cardiothoracic Anesthesia and Outcomes Research, Anesthesiology Institute, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195 (E-mail: mamounn@ccf.org).

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**Abbreviations and Acronyms**

ALT = alanine aminotransferase
ASD = absolute standardized difference
AST = aspartate aminotransferase
CI = confidence interval
CV = coefficient of variation
ICU = intensive care unit
IV = intravenous
LOS = length of stay
PCA = patient-controlled analgesia
PONV = postoperative nausea and vomiting
RASS = Richmond Agitation Sedation Scale
SD = standard deviation

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multimodal analgesic regimens for postoperative pain control via round-the-clock nonopioid analgesics as the initial treatment.[2]

Oral acetaminophen usually is used as an initial treatment of acute pain because of its high therapeutic index.[3] The Food and Drug Administration approved an intravenous (IV) formulation of the drug in 2010, which brought new potential to this century-old drug. Although IV acetaminophen might not offer a clear benefit over the oral formulation in patients who can tolerate oral intake,[4] it may be more helpful in patients who remain intubated postoperatively or those who develop delayed gastric emptying or postoperative nausea and vomiting (PONV). Further, IV acetaminophen avoids variable first-pass elimination that accompanies oral administration, and thus has a faster onset[5] and a greater peak plasma concentration.[6] There is consequently greater cerebrospinal fluid penetration with the IV preparation, along with more predictable pharmacokinetic behavior and bioavailability.[7]

Pain after cardiac surgery traditionally has been controlled with IV opioids and nonsteroidal antiinflammatory drugs, which have significant adverse effects.[8] Therefore, there is an unmet need for a safer IV analgesic, such as IV acetaminophen.[9] IV acetaminophen has been used effectively to control acute pain after various surgeries,[10-14] but the extent to which it might help after cardiac surgery remains unclear. We therefore tested the primary hypothesis that IV acetaminophen is more effective than placebo for pain management after cardiac surgery. We defined a priori that acetaminophen would be considered more effective than placebo if it was superior on pain intensity score and/or opioid consumption and noninferior on both. We also tested the secondary hypotheses that IV acetaminophen reduces opioid-related adverse effects (PONV, sedation, and respiratory depression), reduces the duration of mechanical ventilation, and reduces intensive care unit (ICU) and hospital length of stay (LOS).

## METHODS

This prospective, single-center, randomized, parallel-group, double-blind trial was approved by the Cleveland Clinic Institutional Review Board and registered before patient enrollment at www.clinicaltrials.gov on March 28, 2013, registration number: NCT01822821, Principal investigator's name: Negmeldeen Mamoun. Written consent was obtained from each participating patient.

We screened adults 18 years of age or older who were scheduled for elective cardiac surgery performed via a median sternotomy at the Cleveland Clinic. Exclusion criteria included complex cardiac surgery such as multiple valve replacements or aortic arch surgery. Other exclusion criteria included previous cardiac surgery, moderate or severe right ventricular dysfunction, left ventricular dysfunction with ejection fraction $\leq$35%, severe tricuspid regurgitation, severe lung disease requiring home oxygen therapy, preoperative renal insufficiency (creatinine >2.0) or hemodialysis, history of active liver disease or liver cirrhosis, chronic pain conditions that required daily preoperative opioid administration, pregnancy, weight less than 50 kg, and allergy to fentanyl or acetaminophen.

### Protocol

Patients were randomized (1:1) without stratification to IV acetaminophen or placebo. Allocations were concealed by a password-protected Web site. Randomization codes were computer-generated by using the PLAN procedure in SAS statistical software (SAS Institute, Cary, NC), using block randomization with a block size of either 2 or 4 patients. After enrollment, the Cleveland Clinic Investigational Drug Pharmacy blinded the designated study drug by repackaging acetaminophen or placebo (normal saline). Study drugs were labeled with codes that remained locked until completion of patient enrollment.

Anesthetic induction involved the administration of etomidate or propofol, fentanyl, midazolam, and a depolarizing or nondepolarizing muscle relaxant to facilitate intubation. Fentanyl, isoflurane, and nondepolarizing muscle relaxants were given for maintenance of anesthesia. Routine strategies for heparinization and initiation and separation from cardiopulmonary bypass were followed.

Four doses of IV acetaminophen (1 g each) or an equal volume of identical-looking placebo were given over 15 minutes every 6 hours ($\pm$30 minutes) starting in the operating room after sternal closure, with subsequent doses given in the ICU. All patients were also offered patient-controlled analgesia (PCA). Fentanyl was the default drug (PCA settings: no basal rate, demand bolus dose of 20 $\mu$g, bolus interval every 6 minutes); however, hydromorphone was substituted (PCA settings: no basal rate, demand bolus dose of 0.2 mg, bolus interval every 6 minutes) if clinically indicated, that is, fentanyl was ineffective in decreasing pain intensity scores <4/10 on the Numeric Rating Scale, where 0 is no pain and 10 is the worst possible pain.[15] Similarly, rescue analgesia included IV fentanyl or hydromorphone boluses, or oral oxycodone if PCA was ineffective in decreasing pain intensity scores <4/10. IV meperidine was given as needed for shivering. Wounds were not infiltrated with local anesthetics. No other form of acetaminophen was permitted, nor were topical lidocaine patches or nonsteroidal antiinflammatory drugs allowed.