# Intravenous Acetaminophen as an Adjunct Analgesic in Cardiac Surgery Reduces Opioid Consumption But Not Opioid-Related Adverse Effects: A Randomized Controlled Trial

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***Objectives:*** **The authors hypothesized that intravenous acetaminophen as an adjunct analgesic would significantly decrease 24-hour postoperative opioid consumption.**

***Design:*** **Double-blind, randomized, placebo-controlled trial.**

***Setting:*** **A single academic medical center.**

***Participants:*** **The study was comprised of 68 adult patients undergoing cardiac surgery.**

***Interventions:*** **Patients were assigned randomly to receive either 1,000 mg of intravenous acetaminophen or placebo immediately after anesthesia induction, at the end of surgery, and then every 6 hours for the first 24 hours in the intensive care unit, for a total of 6-1,000 mg doses.**

***Measurements and Main Results:*** **The primary outcome was 24-hour postoperative opioid consumption. The secondary outcomes included 48-hour postoperative opioid consumption, incisional pain scores, opioid-related adverse effects, length of mechanical ventilation, length of intensive care unit stay, and the extent of wound hyperalgesia assessed at 24 and 48 hours postoperatively. The mean ± standard deviation postoperative 24-hour opioid consumption expressed in morphine equivalents was significantly less in the acetaminophen group (45.6 ± 29.5 mg) than in the placebo group (62.3 ± 29.5 mg), representing a 27% reduction in opioid consumption (95% CI, 2.3-31.1 mg; p = 0.024). There were no differences in pain scores and opioid-related adverse effects between the 2 groups. A significantly greater number of patients in the acetaminophen group responded "very much" and "extremely well" when asked how their overall pain experience met their expectation (p = 0.038).**

***Conclusions:*** **The administration of intravenous acetaminophen during cardiac surgery and for the first 24 hours postoperatively reduced opioid consumption and improved patient satisfaction with their overall pain experience but did not reduce opioid side effects.**



***KEY WORDS: intravenous acetaminophen, cardiac surgery, analgesia***

THE OPTIMAL MANAGEMENT of acute pain after cardiac surgery is challenging and important, considering that poor pain control may lead to worse outcomes.[1] Pain management in cardiac surgery patients usually is achieved with parenteral and oral opioids. Even though opioids are effective analgesics, a number of adverse effects are common. In addition, there is a growing concern about overuse of prescription opioids with attendant serious safety issues and associated mortality and morbidity,[2] including opioids administered postoperatively.[3] To reduce the need for opioids and associated wound hyperalgesia,[4] several multimodal analgesia strategies[5] are available for surgical patients, but many are not suitable for use in cardiac surgery patients. Acetaminophen is a relatively safe nonopioid analgesic that can be used as part of a multimodal analgesia approach in cardiac surgery patients, and unlike nonsteroidal anti-inflammatory drugs, it has minimal impact on platelet and renal function.

In the immediate postoperative period, acetaminophen often is administered via the rectal or oral route. However, oral acetaminophen absorption may be poor due to decreased gastrointestinal motility and gastric emptying after surgery,[6] concurrent opioid administration, perioperative fasting state, and the prolonged supine position,[7-10] and rectal absorption may be poor due to gastrointestinal hypoperfusion.[11] Because intravenous (IV) acetaminophen results in earlier and higher peak plasma levels[12] and decreases opioid consumption in cardiac surgery patients compared with oral acetaminophen,[13] IV acetaminophen may be better suited for cardiac surgery patients for achieving therapeutic plasma concentration levels.

The IV formulation of acetaminophen has an established role in postoperative pain management in noncardiac surgery patients.[14] However, previous studies of IV acetaminophen use in cardiac surgery patients were equivocal.[15,16] Because IV acetaminophen is an expensive drug in the United States, the aim of this study was to determine whether the analgesic efficacy of IV acetaminophen in cardiac surgery patients is sufficient to consider its routine use. The authors performed a prospective, randomized, double-blind, placebo-controlled trial to determine whether perioperative IV acetaminophen administration to patients undergoing cardiac surgery would decrease cumulative 24-hour postoperative opioid consumption.

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*This study was supported by an investigator-initiated research grant from Cadence Pharmaceuticals, Inc (San Diego, CA), which was acquired subsequently by Mallinckrodt Pharmaceuticals, Inc (St. Louis, MO), and did not have any involvement in the design, study conduct, data collection or analysis, or manuscript preparation.*

*Preliminary data were presented as a poster at the International Anesthesia Research Society 2014 Annual Meeting and International Science Symposium, Montréal, Canada, on May 18, 2014.*

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*1053-0770/2601-0001$36.00/0*

*http://dx.doi.org/10.1053/j.jvca.2016.02.010*

## METHODS

After study approval by the Human Subjects Division at the University of Washington, informed written consent was obtained between July 2012 and December 2013. The study was registered with ClinicalTrials.gov under identifier NCT01544062. Mallinckrodt Pharmaceuticals, Inc. (St. Louis, MO) donated the IV acetaminophen, but had no role in the design or conduct of the study, the analysis of the data, or the preparation of the manuscript. Inclusion criteria were English-speaking patients between the ages of 18 and 75 years undergoing elective sternotomy for cardiac surgery. Exclusion criteria included a history of chronic or neuropathic pain, chronic use of opioids, poorly controlled psychiatric disorder that would interfere with postoperative assessment, allergy to acetaminophen, severely impaired liver or kidney function, and history of previous sternotomy.

### Intervention

Seventy patients were assigned to receive placebo or acetaminophen. Only the research pharmacists had access to the securely stored randomized group allocation list, which remained blinded until statistical analysis was completed. A research pharmacist prepared 100-mL normal saline infusion bags, which contained either 1,000 mg of IV acetaminophen or placebo. Identical in appearance, the bags then were delivered to either the operating room satellite pharmacy or intensive care unit (ICU).

The patients received a total of 6 doses of 1,000 mg IV acetaminophen or placebo over 15 minutes at the following time points: (1) immediately after anesthesia induction but before the incision and (2) at the end of surgery; (3) 4 additional doses were administered postoperatively in the ICU every 6 hours for the first 24 hours. The first ICU dose was administered 6 hours after the patient arrived in the ICU.

### Intraoperative Care

All study participants underwent cardiac surgery under general anesthesia. General anesthesia was induced with lidocaine (1-1.5 mg/kg), fentanyl (25-50 μg/kg), etomidate (0.2 mg/kg), and rocuronium (0.6-1 mg/kg) and was maintained with sevoflurane while targeting a bispectral index between 40 and 60. The cardiac surgery procedures included standard midline sternotomy, and in cases involving coronary artery bypass grafting, harvesting of the saphenous vein and internal mammary artery grafts. Cardiopulmonary bypass was performed using membrane oxygenation. The intraoperative analgesia consisted of fentanyl boluses, and some patients received additional hydromorphone boluses, which were administered at the discretion of the anesthesia provider. At the end of the surgery, patients were transferred to the ICU while intubated and sedated by a propofol infusion. The propofol infusion was started at 25 μg/kg/min and continued until extubation. None of the study participants received postoperative nausea and vomiting prophylaxis.

### Postoperative Pain Management

Postoperative pain management consisted of IV fentanyl boluses administered by nurses while patients were sedated and mechanically ventilated. The ICU nurse assessed the level of analgesia every 30 minutes based on the hemodynamics (presence of hypertension and/or tachycardia), facial expressions, and compliance with mechanical ventilation and administered 50-to-100 μg of IV fentanyl, if appropriate. After extubation, patients received oral oxycodone, 5 to 15 mg every 3 hours, either at a patient's request or if the patient's pain score was above the individually stated tolerable pain score. IV hydromorphone, 0.2 to 0.4 mg, or morphine 1-to-2 mg boluses, were administered every hour if needed for breakthrough pain. The time of arrival to the ICU was considered time 0 for the purpose of postoperative study drug dosing and further evaluations.

### Outcome Measures

The primary outcome was 24-hour opioid consumption, for which data were obtained from the electronic medication administration record and expressed in morphine equivalents per standard opioid conversions (Supplementary Table 1). Similar to the 24-hour opioid consumption, the 48-hour postoperative opioid consumption data were obtained from the electronic medication administration record and converted to morphine equivalents as a secondary outcome. Other secondary outcomes included incisional pain scores at rest and with coughing, opioid-related adverse effects, the extent of wound hyperalgesia, length of mechanical ventilation, length of ICU stay, and a short patient satisfaction survey (Supplementary Appendix A), which were assessed at 24 and 48 hours postoperatively by one of the investigators (SJ or PR). Pain assessments were recorded using an 11-point (0-10) numeric rating scale. Opioid-related adverse effects (nausea, pruritus, sedation, respiratory depression, and dizziness) were recorded using a numeric scale (0 = no adverse effects, 1 = mild adverse effects not requiring treatment, 2 = moderate adverse effects requiring treatment, and 3 = severe adverse effects refractory to treatment). The responses to the extent to which patients' overall pain experience met their expectations were recorded using a Likert scale (1 = not at all, 2 = a little, 3 = a fair amount, 4 = very much, and 5 = extremely well).

In addition, the ICU nursing staff were trained to complete the "extubation criteria" checklist for each 2-hour period until extubation[17] and the "ICU discharge criteria" checklist for each 4-hour period until discharge from the ICU (Supplementary Appendix B).[18,19]

Wound hyperalgesia was measured using a method previously described by Stubhaug et al.[20] Wound hyperalgesia was determined by testing the right side of the chest along 5 horizontal lines vertically separated by 2 cm at right angles to the incision (Fig 1). Only the right side of the chest was chosen to avoid confounding skin sensation changes from the left internal mammary artery harvesting. The distance (in cm) from the incision to the point where sensations changed was measured along 5 horizontal lines, and the average distance was used as the extent of wound hyperalgesia.

### Statistics

A power analysis determined that 35 patients in each group were needed to achieve an 80% chance to detect a 30%